BSE Safety Standards: An Evaluation of Public Health Policies of Japan, Europe, and USA

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Abstract

Since the advent of bovine spongiform encephalopathy (BSE) in the United Kingdom in 1986, new BSE cases have recently become rare. However, in Japan and the United States, positive cases have started to be seen recently. The rise in BSE cases paved the way for the human form of this disease, the variant Creutzfeldt-Jakob disease (vCJD). The observed trends in the UK may be attributed to effective implementation of public health policies coupled with increased vigilance through advancement in science and technology, or they may well be a reflection of the natural disease progression. We aim to discuss the BSE chronology of events, and compare examination methods, costs and cost-efficiency, management, and public policies of Japan, Europe, and the USA.

Key words: bovine spongiform encephalopathy, transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease, public health policy, mad cow disease

Introduction

The first case of Bovine Spongiform Encephalopathy (BSE) was diagnosed in 1986 in the United Kingdom, and because of the long incubation periods that are characteristic of the transmissible spongiform encephalopathies (TSE)—scrapie, for example, has an incubation period of about three years—the moment of infection can be assumed to have occurred years earlier (1). The second phase of the BSE story is its passage from bovines to humans in the form of variant Creutzfeldt-Jakob Disease (vCJD). In cattle with BSE the only tissues outside the central nervous system that have been shown to be infectious are the retina, the trigeminal and paraspinal ganglia, the distal ileum and (perhaps) the bone marrow (2).

Creutzfeldt-Jakob Disease (CJD) is a human spongiform encephalopathy whose clinical picture can involve weekly deterioration into blindness and epilepsy as one's brain becomes riddled with tiny holes (Table 1) (3).

It is sometimes forgotten that in the story of BSE and vCJD there is but one incontestable fact, that BSE is the cause

of variant Creutzfeldt-Jakob disease (1). The incidence of sporadic or classical CJD (cCJD) in human populations appears to be approximately one in a million worldwide. It has been hypothesized that other spongiform encephalopathies also might occur in the host populations at the same rate. Although averaging only 10–15 cases a year since its first appearance in 1994 in the UK, its future magnitude and geographic distribution (in countries that have imported infected British cattle or cattle products, or have endogenous BSE) cannot yet be predicted. The possibility that large numbers of apparently healthy persons might be incubating the disease raises concerns about iatrogenic transmissions through instrumentation (surgery and medical diagnostic procedures) and blood and organ donations (Table 1) (4).

Genetic CJD is a very rare illness. In this form, an inherited abnormal gene causes CJD. The illness is therefore not caught in any way and there is no causal relationship between this form and BSE. In most cases, the illness is known within the family because of the family history. Occasionally, genetic cases are seen in which no previous family history is identified. The definitive test in relation to genetic CJD is a blood test in order that the gene can be analyzed to see whether there is any genetic abnormality (5).

Iatrogenic CJD is also very rare. This is the CJD which has been accidentally transmitted during the course of medical or surgical procedures. The most important example of this is in the UK where CJD is known to have been transmitted via human growth hormone treatment in childhood (5).

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Table 1 Differing characteristics of sporadic CJD and variant CJD*

Characteristics	Sporadic CJD	Variant CJD
Discovery	Identified by German psychiatrists Hans Gerhard Creutzfeldt and Alphonse Maria Jakob in the 1920s	First documented in March 1996
Incidence	Affects one person per million	Affects one person per million
Prevalence	Affects approximately one person per million worldwide each year, representing an average over time that increases with age Usually strikes people over the age of 55 (median age of death is 68 in the US)	Disease has stricken almost exclusively people under the age of 55, a number of whom were teenagers
Median age at death (years)	68	28
Transmission	Unknown origin and accounts for 85% of all CJD cases	Research from the UK supports an association between BSE and vCJD [†] in that vCJD [†] likely developed as a result of people consuming with nervous system tissue from BSE-infected cattle
Clinical presentation	Dementia associated with neurologic signs	Psychiatric or sensory symptoms; delayed appearance of neurologic signs
Median illness duration (months)	6	13
Diagnosis	Sharp-wave complexes present in EEG [‡] results Neuropathological features include spongiform change, neuronal loss, and astrocytosis	Lack sharp-wave complexes in EEG [‡] results Amyloid plaques are extensively distributed throughout the cerebrum and cerebellum Plaques typically have a dense center surrounded by spongiform change that give the plaque a daisy-like floral pattern
Periodic short waves on EEG [‡] tracings	In approximately 75% of patients	Absent
Symmetrical pulvinar high signal on MRI [§]	Not reported	In over 75% of patients
Codon 129 genotype	Polymorphic	Methionine/Methionine
Numerous 'florid plaques' on neuropathology	Absent	In all patients
Immunohistochemical analysis of brain tissue	Variable	Marked accumulation of PrP-res
Increased glycoform ratio on Immunoblot analysis of PrP-res	Not reported	In all patients
Presence of infective agent in lymphoid tissues	Not readily detected	Readily detected

Modified from: Belay E and Schonberger L, 2002 (Reference No. 64) and Beghi E, Gandolfo C, Ferrarese C, Rizzuto N, et al., 2004 (Reference No. 65).

* Creutzfeldt-Jakob disease

[†] Variant CJD

[‡] Electroencephalogram

[§] Magnetic Resonance Imaging

Optimists can take heart in the latest case predictions for vCJD, which have plummeted from 100,000 or more cases originally suggested as a maximum estimate. Based on the yearly incidence of vCJD in the UK through 1999, and assuming an average incubation period of between 20 and 30 years in patients presently incubating the disease, mathematical modeling now predicts an eventual upper limit of not more than about 3,000 cases, and only about 600 cases if, as seems entirely reasonable, the average incubation period is less than 20 years (6).

The infectious agent that causes scrapie in sheep crossed the species barrier to bovines to cause BSE. Changes in the rendering of livestock carcasses allowed infectivity to survive and contaminate meat and bone meal (MBM) in livestock feed, amplifying infection to epidemic proportions. Export of contaminated MBM and live cattle incubating the disease caused the spread of BSE to other countries. BSE caused vCJD, most probably through adulteration of cooked meat products with mechanically recovered meat (MRM) contaminated by compressed spinal cord and paraspinal ganglia. International regulatory measures are limiting the further spread of BSE, its entry into the human food chain, and potential secondary human-to-human spread of vCJD, so that both diseases should gradually disappear (1).

To our knowledge this is the first review of its kind where the BSE histories, management and policies of Japan, Europe, and the United States were discussed altogether in one paper. Our objectives are to show the BSE chronology of events; compare the examination methods, costs, the number of cases; the management; and the public health policies of Japan, Europe, and the United States.

Methods

Reference list of retrieved literature were searched electronically in Pub Med, Hokkaido University Medical Library, and serial online BSE websites; and manually, including journals and newspapers. The search terms used were: bovine spongiform encephalopathy, BSE, Creutzfeldt-Jakob disease, and CJD. For instance, there were 1,900 articles available for review if the keyword BSE were searched in Pub Med. In order to limit the number of articles for evaluation, we used more specific keywords such as BSE Japan, BSE Europe or BSE USA. Twenty-eight articles were available for review when more detailed keywords, in this case BSE Japan, were used.

The process of following up references from one article to another sometimes referred to as purling, the ancestry

approach, or citation chasing was done also.

Inclusion criteria

We included relevant articles dating from 1998 to the most recent available literature written either in Japanese or English. We also included articles from recently reported updates in symposia and proceedings.

BSE History

Japan (Table 2, Fig. 1 and Appendix)

The Japan Ministry of Agriculture, Forestry, and Fisheries

(MAFF) reported its first suspected case of BSE to the Office International des Epizooties (OIE) on 10 September 2001. The suspected case was a five-year old Holstein cow from a dairy farm in Chiba prefecture. A Prionics check test was negative, two histopathological (HP) tests were positive, and one immunohistochemical (IHC) test was positive. To control the suspected outbreak, the herd was placed under quarantine by the prefecture veterinary inspector immediately after BSE was suspected, widespread inspection of livestock operations by numerous health officials for animals with signs of BSE was undertaken, and the use of MBM in feed products for cattle was banned in September 2001 (Appendix A) (7). A test has shown

Table 2 Comparison of BSE cases and management of Japan, Europe, and USA

	Japan	Europe	USA
Total no. of cattle	45,000,000	40,600,000 (adult cows)	100,000,000
First confirmed BSE case	September 2001	September 1985	December 2003
BSE cases	19*	187,623 [†] Europe: 3,412* UK: 184,211*	2*
No. of cows examined	3,159,408 (100% of all slaughtered) [‡]	7,551,131 ^{†‡}	20,453 (<2% of all slaughtered) [‡]
Testing methods	RT [§] WB or IHC [¶] +HP ^{**}	RT [§] WB or IHC [¶] +HP ^{**}	1) RT [§] +IHC 2) RT [§] +WB 3) IHC [¶] only
Testing age of cattle	All cattle are examined	Over 30 months	Over 30 months
Testing cost per cow	US\$ 15–50		US\$ 20–50
Testing cost total	US\$ 13–16 million	US\$ 1.2 billion	US\$ 6–12 million
Testing duration	4 hours		5 days

* Japan—as of 7 June 2005; Europe—as of 26 July 2005; USA—as of 27 June 2005

[†] Include France, Germany, Ireland, Italy and Switzerland.

[‡] As of March 2004

[§] Rapid Test

^{||} Western Blot

[¶] Immunohistochemistry

^{**} Histopathology

Fig. 1 Bovine spongiform encephalopathy cases in Japan, UK, and USA*.

* Adapted from Brown P, et al., 2001. (Reference No. 4)

Japan—As of 7 June 2005. UK—As of 29 July 2005. USA—As of 29 July 2005.

that a Japanese animal slaughtered in August 2001 carried BSE, confirming the first known case of the brain-wasting illness in Asia and the first case outside of Europe in native-born cattle (8, 9). Three BSE cases (one clinical case and two cases detected as a result of screening at the abattoir) were uncovered in 2001 and the annual incidence was 1.44 indigenous cases per million bovines aged over 24 months (10, 11). Meanwhile, there were two more BSE cases in 2002 and its incidence rate became 0.97 indigenous cases per million bovines aged over 24 months (10, 11).

A Holstein cow aged six years and 11 months, born in Hokkaido Prefecture, and then transferred to a dairy farm in Wakayama Prefecture, which was slaughtered at the abattoir on 17 January 2003 was confirmed to have BSE on 20 January 2003. A Holstein cow aged six years and nine months, born and kept in a dairy farm in Hokkaido Prefecture was slaughtered at an abattoir on 21 January 2003, and was initially detected to have BSE on 23 January 2003 (12). An atypical case of BSE was detected on 06 October 2003 in a Holstein bullock aged 23 months slaughtered at an abattoir on 29 September 2003 in Ibaraki Prefecture (13). There were four BSE cases as of 05 November 2003 and the ninth case was a bullock aged 21 months (10). As of 23 November 2004, there were five additional BSE cases, making a total of 19 cases since 2001 (10).

Europe (Table 2, Fig. 1 and Appendix)

The first confirmed BSE case was in September 1985 (14). From the time of BSE discovery until 1987, a total of 446 cases were reported in the UK (15). Four herds had been affected when the Central Veterinary Office alerted the Ministry of Agriculture, Fisheries, and Food (MAFF) in June 1987 (14). In 1988, the government set up a working party to investigate BSE and any implications for human health. The government banned the feeding of cattle with protein derived from other cattle and sheep. Epidemiological studies done by MAFF scientists had pinpointed this cannibalism as being the only plausible cause of BSE. The total BSE cases in the UK in 1988 increased to 2,514 (15). The Southwood committee reported in February 1989, recommending a ban on the use of bovine offal in baby foods. The British government went further, and in November 1989, banned the use of specified bovine offals (SBO) in all human food (14). The total BSE cases in the UK tripled to 7,228 in 1989 (15).

In 1990, scientists showed that BSE could be orally transmitted to mice (14). Total BSE cases in 1990 doubled to 14,407 and further augmented to 25,359 in 1991. Cases of BSE peaked between 1992 and 1993, with three in every 1,000 cows affected. Total BSE cases in UK spiked at 37,280 in 1992 (15). In 1993, total BSE cases in the UK decreased to 35,090 and further dipped to 24,437 cases in 1994 (15). Research in 1994 showed that cattle could contract BSE orally (14).

It was in 1995 that the human tragedy began. In May, a 19-year-old man died after an illness resembling CJD. Two other deaths occurred that year, showing similar symptoms. The National CJD Surveillance Unit discovered that the brains of these patients showed unusual spongiform symptoms and named it vCJD. By 1996, there had been a total of eight cases

of vCJD, mostly in young people (14). There have been 150 confirmed and probable vCJD cases in the UK as of 1 July 2005 (5). Total BSE cases in the UK decreased in 1995 to 14,562 and declined further to 8,149 in 1996 (15).

Spain reported its first case of BSE to the OIE on 22 November 2000. A second case was reported to the OIE in 07 December, and additional two suspected cases were reported in 2 January 2001. Germany announced in 26 November 2000 the first BSE case in a native-born cow. Until this time, Germany had declared itself free of BSE, despite the fact that it had reported six prior cases of BSE between 1992 and 1997. However, all previously reported cases were in imported animals (16). After Germany reported its first case of BSE in a native-born animal in November 2000, a total of seven cases were confirmed in 2000 (17). Other countries that reported their first BSE case in a native animal included Denmark (March 2000) (16). Total BSE cases further tapered to 1,443 (15). In 17 January 2001, Italy announced its first native case of BSE. The infected animal was found through mandatory testing at slaughter. As of late February 2001, a total of five native-born infected animals had been found in Italy (16, 17). Total BSE cases decreased to 1,202 in 2001 (15).

In 2002, total BSE cases in UK were 1,144 and annual incidence was 228.24 indigenous cases per million bovines aged over 24 months. In 2003, total BSE cases in UK were 612 and annual incidence 122.44 indigenous cases per million bovines aged over 24 months (15, 18). In 2004, total BSE cases in UK further declined to 242 (10).

United States (Table 2, Fig. 1 and Appendix)

In 1986, BSE was identified as a new and a separate disease, and in 1987, it was made a reportable disease. USA agreed with UK that no cattle with meat on the bone should be imported to the USA (19). In 1988, the USDA established a BSE Working Group to review available science and recommend appropriate regulatory controls (20). In 1989, the USDA banned the importation of live ruminants (cattle, sheep, goats, etc.) and most ruminants from UK and other countries where BSE was diagnosed (19, 20).

In 1990, the USDA began educational outreach of veterinarians, cattle producers, laboratory diagnosticians, etc. about the clinical signs and diagnosis of BSE. In 1991, the USDA conducted risk assessment and the results showed that conditions in the US and UK were different in regards to amount of sheep rendered. In 1993, the surveillance was expanded to include examination of the brain tissue from "downer cows". In 1994, the surveillance was expanded to incorporate new technology (immunohistochemistry) of testing brains for the partially resistant form of the prion protein that is indicative of the TSEs (20). In 1997, the USDA prohibited the importation of live ruminants and most ruminant products from all of Europe and supported FDA regulations to prohibit the feeding of most mammalian proteins to ruminants (19, 20). In December 1997, the USDA enacted regulations that prohibited the importation of live ruminants and ruminant meat from all European countries including Germany. These import restrictions also applied to bone meal, blood meal, meat meal, offal, fat, glands, and serum from ruminants (16). In October 1998, in consultation

with USDA, the State of Vermont quarantined two flocks of sheep imported from Belgium and the Netherlands due to the risk of being exposed to BSE contaminated feed (16, 19, 20). In October 1999, the USDA expanded the surveillance of fallen stock (downer cows) as evidence in Switzerland supported this population as an effective target. In November 1998, the USDA published proposed rules to strengthen efforts for scrapie eradication (20).

In March 2000, the US placed a ban on imports of any ruminant or swine, or any fresh (chilled or frozen) meat of any ruminant or swine from Japan due to an outbreak of foot-and-mouth disease (FMD) in Japan (7). In 25 December 2003, the first BSE case was confirmed after it was slaughtered for food in Washington State (21). The USDA's traceback investigation indicated that the affected cow was likely imported from Canada in 2001.

In 8 January 2004, the USDA's FSIS submitted three rules and one notice for publication in the Federal Register on 12 January. The rules and notice were: 1) an interim final rule declared that the Specified Risk Materials (SRMs), the skull, brain, trigeminal ganglia, eyes, vertebral column, spinal cord, and dorsal root ganglia (DRG) of cattle 30 months of age or older, and the small intestine of all cattle are SRMs, and prohibited in the food supply. Tonsils were already excluded. In 12 January 2004, a declaration of extraordinary emergency was published in the Federal Register. This declaration of extraordinary emergency authorized the Secretary to 1) hold, seize, treat, apply other remedial actions to destroy (including preventative slaughter), or otherwise dispose of, any animal, article, facility, or means of conveyance if the Secretary determines the action is necessary to prevent the dissemination of BSE; and 2) prohibit or restrict the movement or use within the State of Washington, or a portion of the State of Washington, of any animal or article, means of conveyance, or facility if the Secretary determines that the prohibition or restriction is necessary to prevent the dissemination of BSE. In 20 January

2004, senior US government officials continued talks with trading partners and met with officials in Japan, the Philippines, Hong Kong, and South Korea to discuss BSE related cases (22).

BSE Management

Japan

A. Management History (Table 2 and Appendix)

Japan adopted universal testing in 2001 after it found its first case of BSE (23, 24). Identification of all animals that were kept with the infected cow was done, as well as epidemiological investigation of the feed used on the farm as a possible source of infection. The dairy farm in Hokkaido Prefecture where the infected cow was born and kept was placed under movement control by Abashiri Livestock Hygiene Service (25).

B. Specific Risk Materials (Table 3 and Appendix)

Japanese officials grind up small amounts of brain tissue and wash them in chemicals, which can detect the presence of prions. If the test is positive, the cow is isolated and subjected to a test like the one used in the US (25). Japan removes and incinerates the following portions of all cows: heads, spinal cords, spines, and ileum.

Based on Article 6 of the Abattoirs Law and Section 2, Article 7 of the Law Concerning Special Measures for Bovine Spongiform Encephalopathy, owners or managers of abattoirs are required to retain bovine heads (except for tongues and cheek meat), spinal cords and distal ileum (2 meters from connection to caecum) in a special waste container for incineration (24).

In 22 July 2004, the Japan-US BSE working group (24) reported that the two countries agreed on the following points: 1) removal of SRMs is extremely important for protecting public health; 2) the scientific foundation of initiatives for determining SRMs implemented by both Japan and the US is

Table 3 Specified risk materials

Specified risk materials	Japan	Europe	USA
Head	Yes	Yes	Yes
Head meat			No
Brain	Yes	Yes	Yes
Eyes		Yes	Yes
Tongue	No		No
Tonsils		Yes	Yes
Cheek meat	No		No
Trigeminal ganglia		Yes	Yes
Thymus		Yes	
Spinal cord	Yes	Yes	Yes
Spine	Yes		
Vertebral column	Yes		Yes
Dorsal root ganglia		Yes	Yes
Transverse process of thoracic & lumbar vertebrae	No		No
Sacral wings & vertebrae of tail	No		No
Intestines		Yes*	Yes†
Ileum	Yes		Yes
Spleen		Yes	

* Duodenum to rectum

† Entire small intestine is removed

based on pathogenesis studies performed in the UK; and 3) as per international guidelines, the tissues and ages of SRMs will be determined by the BSE risk in the respective country.

However, there were divergent views on the following points: 1) regarding pathogenesis studies test data from the UK, Japan stated that since a relatively small number of animals were tested, the data were insufficient and therefore, removal of SRMs should be implemented for cattle of all ages. The US stated that since the risk of BSE in the US is low, removal should be implemented only for cattle 30 months of age and older as per international guidelines; 2) SRMs are excluded from the food chain in both Japan and the US. Japan excludes their use in all animal feed while the US excludes them from use in ruminant feed; and 3) the US stated that as a result of pathogenesis studies conducted in the UK and the reaffirmation of this laboratory data on the age distribution of clinical cases in the UK, 30 months of age is appropriate for SRM removal for a low prevalence country like the US (24).

C. BSE Testing (Table 2 and Appendix)

In Japan, 3.16 million cows have so far been examined as of 8 May 2004 (24, 26). It takes about four hours to complete a single BSE test that costs US\$15 to 50 per animal (26). With a total of 45 million cattle (27), Japan needs to expend US\$13 to 14 million (1.5 billion yen) in total cost to test all its cattle (28).

Positive cases from the BSE screening test are diagnosed conclusively based on the results of confirmation tests. The criterion for positive BSE diagnosis consists of a positive confirmatory result by either Western Blot (WB) or immunohistofluorescence (IHF) examinations. Furthermore, histopathological (HP) tests are also conducted in the confirmation test (24).

D. Feed Ban Implementation (Appendix)

As of October 2001, a complete ban was implemented on the use of MBM as feed. All MBM originating from ruminant animals and produced through rendering is to be disposed off through incineration. Dedicated feed manufacturing lines are to be introduced by the end of March 2005 (24).

In FY 2002, on-site inspections of 667 manufacturers were conducted, and 1,618 samples of feed and feed additives were tested with only one case of animal protein-related violations recorded (chicken substance in imported fish flour) (24).

E. Surveillance modalities (Appendix)

Japan asserted that its BSE testing is implemented for all cattle in abattoirs (launched in 18 October 2001) and on all dead cattle at farms (launched in April 1996, with its scope gradually expanded to eventually cover all dead 24 months of age and older as of April 2004). The test results are incorporated into the surveillance data (24).

Since testing in Japan is implemented in a comprehensive and almost all-inclusive manner, it is possible to accurately keep track of the status of BSE. In the three-year period from FY 2001, the nine cases of BSE-positive cattle were detected through abattoir inspections of approximately three million animals, and two cases of BSE-positive cattle were detected through the testing of fallen stock or CNS suspects at farms. Five cases of nine BSE-positive cattle detected through abattoir

inspections were otherwise healthy cattle, and it is thought that they would not have been detected through surveillance applied only on “BSE high-risk” cattle populations (24).

Europe

A. Management History (Table 2 and Appendix)

In 1988, the government set up a working party to investigate BSE and any implications for human health. The government instituted a mass slaughter program for all cows suspected of having BSE (14).

In May 1990, the SEAC set up spot checks on abattoirs. The British government introduced new measures in an attempt to contain BSE, such as selective cull of cattle reared alongside those with BSE between 1989 and 1993 (14). The “over 30 months” (OTM) rule was introduced in 1996, when scientists realized that eating BSE-infected cattle caused the lethal human disease vCJD. The British government compensated farmers and disposed off the carcasses at a cost of US\$746 million (£420 million) per year. Britain could drop its expensive ban on eating cattle over 30 months old without significantly raising the risk of vCJD in people, according to a newly published epidemiological analysis (29, 30).

In 2003, all older British cattle were being incinerated to stop BSE from entering the human food chain. In contrast, in the rest of Europe, cattle are tested for BSE at slaughter. The epidemiologists calculate adopting this approach in Britain would probably cause no extra vCJD deaths over the next 60 years (31). The incidence of BSE in British cattle has fallen steadily since 1996, leading UK Food Standards Agency (FSA) to start reviewing the OTM rule in 2002 (30, 31).

In March 2003, a “core stakeholder group” of scientists, consumers and farmers recommended that the OTM rule be dropped, either completely or for those cattle born after 1996. This recommendation was based on the best estimate calculated by “independent experts” that switching to testing at slaughter would lead to insignificant number of additional deaths over the next 60 years. Using the most pessimistic assumptions, the figure rose to 1.6 deaths. The stakeholder group also noted that dropping the OTM rule would reduce costs by 93% (30). The EU enacted regulations, effective 1 January 2001, requiring that all cattle over 30 months of age be tested for BSE at slaughter (32).

B. Specific Risk Materials (Table 3 and Appendix)

In 1988, shortly after setting up a party to investigate BSE, the government banned the feeding of cattle with protein derived from other cattle and sheep. The British government went further, and in November 1989, banned the use of specified bovine offals (SBO) in all human food (14).

In 1 January 2001, the EU amended the policy on specified risk portions to: 1) the skull including the brains and eyes, the tonsils, the spinal cord of bovine animals aged over 12 months, and the intestines from the duodenum to the rectum of bovine animals of all ages; and 2) the skull including the brains and eyes, the tonsils and the spinal cord of ovine and caprine animals aged over 12 months or that have a permanent incisor erupted through the gum, and the spleen of ovine and caprine animals of all ages (33).

C. BSE Testing (Table 2 and Appendix)

Of the total 40.6 million adult cattle (34) in Europe, 4.1 million were slaughtered in the UK alone. All the 20 million cows that entered the food chain were tested in Europe (35, 36). The OTM scheme currently costs around US\$650 million (£360 million) a year compared to around US\$108 million (£60 million) a year for the proposed replacement of testing. To date, the OTM scheme has cost more than US\$5.4 billion (£3 billion) (37). Total BSE testing cost amounts to US\$1.2 billion (38).

United States

A. Management History (Table 2 and Appendix)

The US mandates labeling of cattle of domestic origin. The brain and spinal cord, which harbor most of the infection, are not removed from most cattle on slaughter. US studies revealed in 2002 that 35% of mechanically recovered meat (the bits sluiced off carcasses and used to make processed meats such as hot dogs) contain such tissue (39). The US will, in the future, introduce the mandatory labeling of individual cows. Crippled cattle are to be banned from human consumption (21).

B. Specific Risk Materials (Table 3 and Appendix)

USDA scientists examine slices of brain or spinal cord tissue from cows under a microscope to look for prions (26). There is no removal and no incineration at present. The brain and spinal cord, which harbor most of the infection, are not removed from most cattle on slaughter (39). The USDA announced additional safeguards to bolster the US protection system against BSE and to further protect public health: 1) downer cattle and SRM and tissues will immediately be banned from the human food chain (skull, brain, trigeminal ganglia, eyes, vertebral column, spinal cord, and DRG of cattle of more than 30 months of age and a portion of the small intestine of cattle of all ages are now considered SRMs and are prohibited from entering the human food supply; 2) any normal cattle, if they are targeted for BSE surveillance testing at slaughter, will no longer be marked as "inspected and passed" until confirmation is received that the animals have, in fact, tested negative for BSE; 3) DRG, clusters of nerve cells connected to the spinal cord along the vertebral column, were added to products already prohibited in labeled meat; 4) the air-injection stunning of cattle will be prohibited; 5) mechanically separated meat in human food will be prohibited; 6) a verifiable system of national identification will be immediately implemented (40).

In the future, the US will implement the removal of the following portions from cows more than 30 months of age: crania, brain, trigeminal ganglion, eye, spinal cord, spines, dorsa, all bowels and tonsils (21).

After considering the internationally validated scientific factors known, the US decided to designate the brain, skull, trigeminal ganglia, eyes, spinal cord, DRG, and vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum) of cattle 30 months of age and older, and the tonsils and distal ileum of all cattle as SRMs, declare them inedible, and prohibit their use for human food. To ensure effective removal of the distal ileum, in the US the entire small intestine shall be

removed (24).

C. BSE Testing (Table 2 and Appendix)

Of the 36.9 million cows slaughtered in the US, only 20,453 cows (less than 2 percent) were tested (36). On the other hand, according to APHIS, over 72,500 cow brains have been examined for BSE or another form of TSE in cattle as of 30 April 2004 (34). According to USDA (22), BSE testing cost per animal will amount to US\$20 to 40, however, according to the official journal of the European communities (26), it costs around US\$50 per animal. With a total of 45 million adult cows (41), the total amount, though, is US\$6 to 12 million and the duration of testing is about 5 days (26). In the future, the total testing cost will be US\$70 million (42).

The definition of BSE in US laboratories is fulfillment of one of the following criteria (Table 2): 1) positive results by rapid test and IHC; 2) positive results by rapid test and WB (the UK version), in the event that a sample is not suitable for IHC or the brain stem architecture is not evident, or 3) positive result by IHC only, in the event that no appropriate fresh brain tissue is available to employ either a rapid or WB test (24).

The US also provided information on how BSE-specific diagnostic tests are employed for surveillance of cattle for the presence of the BSE agent. Testing will be completed by use of the USDA-approved rapid tests as well as a confirmatory WB reference or IHC method. The IHC is considered the method of choice for the detection of the abnormal prion protein (PrP^{Sc}) in the central nervous system (CNS) of affected cattle. According to the World Animal Health Organization (OIE) Manual of Standards for Diagnostic Tests and Vaccines, IHC is the method of choice for both confirmatory diagnosis and surveillance in countries with low BSE incidence (24).

D. Feed Ban Implementation (Appendix)

The US issued guidance to industry in 1994 regarding not using ruminant products from BSE countries in FDA regulated products. In 1997, the US issued a legally binding regulation imposing the current feed ban that meets or exceeds OIE recommendations. The effectiveness of the feed ban is based on 1) enforcement mechanisms supported with legal penalties; 2) methods for monitoring compliance that include inspection by state and Federal authorities on a regular basis; 3) sampling products for the presence of prohibited material; 4) an extensive training program for Federal and State inspectors that perform the feed ban inspections; 5) outreach and education efforts to assist industry; and 6) the publication of all inspection results and the availability of these results to all interested parties (24).

E. Surveillance modalities (Appendix)

The US reemphasized the goals of BSE surveillance. These goals do not include the use of BSE testing as a food safety test, on the basis that 1) SRM removal is keeping the US beef supply is safe; 2) there is currently limited scientific evidence to suggest the time at which the various diagnostic tests are effective in detecting BSE infection in cattle; and 3) BSE surveillance since 1990 has not detected BSE in US native cattle (24).

These surveillance samples include field cases of cattle

exhibiting signs of neurologic disease, cattle condemned at slaughter, rabies negative cattle, neurological cases submitted to diagnostic laboratories, and samples of nonambulatory cattle and adult cattle dying on farms (24).

As a result of the detection of the BSE agent in North America, as of 1 June 2004, the BSE surveillance program in the US has been significantly enhanced over the last 12–18 months in the “high-risk for BSE” cattle populations over 30 months of age in order to estimate the magnitude of the problem, if it exists. Surveillance systems targeting these high-risk sub-populations have been shown to be the most efficient at identifying BSE cases. Laboratory diagnostics will consist of decentralized laboratory screening with rapid diagnostics and confirmatory testing at USDA (24).

Calculated Risks

Projections of both the short- and long-term course of the vCJD epidemic in the UK have demonstrated great uncertainty due to the lack of knowledge of key aspects of the biology and epidemiology of this new disease. Such projections are sensitive to assumptions made regarding the pattern of exposure to BSE-infected animals, the effectiveness of control measures introduced in 1989 and 1996 in reducing this exposure, the functional form of the incubation period distribution and patterns of age-dependent susceptibility/exposure (43).

From 1985 to 1996, Nakamura et al. noted an increase in the incidence of CJD in Japan (44). The percentage of females with developed CJD was higher among the patients having iatrogenic CJD and the incubation period of female patients was statistically shorter than that of male patients (45). The Food Safety Commission estimated the risk in Japan to be 0.1 to 0.9 (46).

Since the French population was much less exposed to the BSE agent than the UK population, the France/UK ratio of vCJD incidence was approximately 0.05 (47). Although Ireland has the second highest incidence of BSE worldwide, estimates of future vCJD cases remain low (48). Back-calculation analysis of vCJD epidemic in the UK indicates that the current case data are compatible with numbers of infections ranging from a few hundred to several millions. In the latter case, the model suggests that the mean incubation period must be well beyond the human lifespan, resulting in disease epidemics of at most several thousand cases (49).

Discussion

The epidemic of BSE in the United Kingdom, which began in 1986 and has affected nearly 200,000 cattle, is probably coming to an end (Fig. 1), but leaves in its wake an outbreak of human Creutzfeldt-Jakob disease, most probably resulting from the consumption of beef products contaminated by central nervous system tissue (4).

Within weeks of identification of the first case of BSE, concern was expressed about human risk (50–56), and as the epidemic unfolded, a series of measures was taken to eradicate BSE and prevent potentially infected tissues from reaching the human food chain (Appendix). Then, in 1995, Lancet reported three cases of CJD in patients 16, 19, and 29 years of age in the UK (57, 58). On neuropathologic examination, all three patients

had amyloid plaques, which was unexpected in view of their occurrence in only 5–10% of sporadic cases of CJD. In Japan, the health ministry confirmed its first case of vCJD on 4 February 2005 in a Japanese man who died in December 2004. The MHLW suspected the man, who was in his fifties, contracted the disease during his month-long stay in Britain in 1989 (59).

If CJD in young patients was not being obscured by misdiagnosis, perhaps it reflected increased physician awareness through publicity surrounding BSE and iatrogenic CJD in recipients of contaminated growth hormone, or the active CJD surveillance program instituted in the UK, or the availability of genetic and proteinase-resistant protein (PrP) immunohistochemistry. Although all these factors may have contributed to ascertainment bias, most of the excess cases were in older age groups, in which CJD was now being diagnosed more often than in earlier decades (4).

Recognition of this source of infection has led to a series of countermeasures taken by the UK and other countries to break the cycle of cattle reinfection, restrict the geographic spread of disease, and eliminate potential sources of new infections. Probably the single most important measure in the UK was the imposition in 1988 of a ruminant protein feed ban that by 1992 began to bring the epidemic under control (4).

Several governments have implemented policies to minimize the risk for human-to-human disease transmission through blood donations from apparently healthy persons who may be in the incubation phase of vCJD. In the UK, where whole blood or blood products from some persons who later died of vCJD have been administered to others, all plasma is imported and all blood from UK donors is filtered to eliminate leukocytes, which are the most likely carriers of infectivity in blood (60–62). In the United States, a blood donor policy excludes donations from anyone who has lived in or visited the UK for a cumulative period of 6 months or more during 1980 to 1996. The 6-month period was based on the fact that more than 80% of total US person-years in the UK would be excluded and that the 2–3% deficit of blood donors resulting from the deferral could be absorbed by the blood banking industry without undue shortages. Several countries (Canada, Australia, New Zealand, Switzerland, Japan and Germany) have since applied these criteria and formulated similar policies (4). Japan is considering a tough new rule to prevent the spread nvCJD. If the rule passes, it would ban anyone who spent even a single day in Britain or France between 1980 and 1996 from donating blood (63).

Because of the possibility of widespread infection in the UK, concern extends beyond blood and organ donors to the safe use of medical and surgical instruments, particularly those used in neurosurgery and ophthalmic surgery. Similar considerations apply to invasive medical and surgical procedures: sound medical practice cannot be suspended on the basis of a theoretical risk for vCJD, and it would be unethical to deny needed procedures to persons suspected of having CJD (4).

We believe that with continued advances in the medical and technological fields coupled with legislative and executive actions, the risk of BSE will taper down and thereby decrease the risk of the variant form of CJD.

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Appendix

Table A: Measures taken to prevent the spread of bovine spongiform encephalopathy to animals*

Precautions	Japan	UK†	EU†	USA
BSE made a notifiable disease		Jun 1988	Apr 1990	Nov 1987
Universal BSE testing	Oct 2001			
BSE surveillance, with histologic examination of brains	Sept 2001	Jun 1988	May 1990	May 1990
BSE testing on all dead cattle at farms	Apr 1996			
Ban on ruminant protein in ruminant feed	Apr 1996	Jul 1988		
Ban on export of UK cattle born before July 1988 feed ban			Jul 1989	
Ban on import of live ruminants and most ruminant products from all BSE countries				Jul/Nov 1989
Ban on export of UK cattle >6 months of age			Mar 1990	
Ban on SBO for use in animal nutrition, ban on export of SBO and feed containing SBO to EU countries		Sept 1990		
High-risk waste to be rendered at 133°C/3 bar/20 min (or other approved procedure)	Oct 2001		Nov 1990	
Ban on export of SBO and feed containing SBO to non-EU countries		Jul 1991		
Ban on MBM from SBO in fertilizer		Nov 1991		
After 1 Jan 1995, rendering methods must sterilize BSE			Jun 1994	
Ban on mammalian MBM in ruminant feed	Sept 2001		Jul 1994	
BSE surveillance includes immunohistologic features of brains	Sept 2001			Oct 1993
Ban on mammalian protein in ruminant feed‡	Apr 1996/ Sept 2001	Nov 1994		Aug 1997
Ban on import of live ruminants and most ruminant products (including meat products) from all countries of Europe				Dec 1997
Immunologic testing for ruminant protein in animal feed	2002		Jul 1995	
Mammalian MBM prohibited from all animal feed/fertilizer	Oct 2001	Mar/Apr 1996		
Slaughtered cattle >30 months old (except certain beef cattle >42 months old) ruled unfit for animal use (hides for leather excluded)		Mar 1996		
Mammalian MBM and MBM-containing feed recalled		Jun 1996		
Feed for ruminant animals is separated from other types of feed and specialized handling is implemented‡	Oct 2001			
All mammalian waste to be rendered at 133°C/3 bar/20 min (or other approved procedure)			Jul 1996	
Cattle tracing system improved	Sept 2001	Sept 1998		
Slaughter businesses required to process bovine heads (except tongue and cheek meat), spinal cords, and distal ileum)	Oct 2001			
Quarantine of 3 sheep flocks imported from Europe with possible exposure to BSE (4 animals die with atypical TSE)				Oct 1998
BSE surveillance of fallen stock (downer cows) is intensified	Sept 2001			Oct 1998
Proposal to eradicate scrapie is rejuvenated				Nov 1999
Allow export of deboned beef from cattle >30 months old born after July 1996		Aug 1999		
Prohibit use of animal protein, including MBM and blood meal (but excluding milk, or fish meal for nonruminants) in feed for any farmed animal species (effective 1 Jan 2001)			Dec 2000	
Prohibit importation of rendered protein and rendering wastes originating or processed in Europe				Dec 2000
Use of vertebral column (excluding transverse process of thoracic and lumbar vertebrae, wings of sacrum and vertebral tail) for food in meat processing prohibited	Feb 2004			

* Adapted from Brown P, et al., 2001. (Reference No. 4)

† In Northern Ireland and Scotland, dates of implementation sometimes differed from those shown for England and Wales; in addition, individual European Union countries often adopted different measures on different dates.

‡ Some exemptions, e.g., milk, blood, and gelatin.

§ Dedicated manufacturing lines are to be introduced by the end of March 2005.

BSE, bovine spongiform encephalopathy; EU, European Union; MBM, meat and bone meal (protein residue produced by rendering); SBO, specified bovine offals (brain, spinal cord, thymus, tonsil, spleen, and intestines from cattle >6 months of age); TSE, transmissible spongiform encephalopathy.

Table B: Measures taken to prevent the spread of bovine spongiform encephalopathy to humans*

Precautions	Japan	UK†	EU†	USA
Compulsory slaughter of BSE-affected cattle		Aug 1988		
Destroy milk from affected cattle (except for milk fed to cows' own calves)		Dec 1988		
Ban on import of UK cattle born after Jul 1988 feed ban			Jul 1989	
Ban on SBO for domestic consumption		Nov 1989		
Ban on export to EU of SBO and certain other tissues, including lymph nodes, pituitaries, and serum		Apr 1990	Apr 1990	
Ban on export of live UK cattle (except calves <6 months old)		June 1990	June 1990	
Ban on use of head meat after skull opened	Oct 2001	Mar 1992		
FDA recommends use of BSE/scrapie-free sources for materials used in manufacture of regulated products be restricted to BSE-free countries				Dec 1993
Bone-in beef only from farms with no BSE for 6 years, if not BSE-free, must be deboned with visible nervous and lymphatic tissue removed			July 1994	
FDA requests that bovine-derived materials for animal use or for cosmetics and dietary supplements not be sourced from BSE countries				Aug 1994
Thymus and intestines from calves <6 months old made SBO		Nov 1994		
Import of beef only from UK cattle 1) >30 months, or 2) from herds BSE-free for 6 years, or 3) if not BSE-free, deboned with visible nervous tissue and lymph nodes removed			Jul 1995	
SBO ban broadened to include whole skull (SBM)		Aug 1995		
MRM from bovine vertebral column banned and export prohibited		Dec 1995		
Removal of lymph nodes and visible nervous tissue from bovine meat >30 months exported to EU		Jan 1996		
Ban on export of all UK cattle and cattle products except milk			Mar 1996	
SBM ban broadened to include entire head (excluding uncontaminated tongue)	Oct 2001	Mar 1996		
Slaughtered cattle >30 months (or certain beef cattle >42 months) ruled unfit for animal or human use (hides excepted)		Mar 1996		
FDA urges manufacturers of FDA-regulated human products to take steps to assure freedom from BSE agent			May 1996	
Partial lifting of export ban on tallow and gelatin			Jun 1996	
SBM ban broadened to include certain sheep and goat heads, spleens, and spinal cords (SRM)		Sept 1996		
FDA recommends withdrawal of plasma and plasma products made from pools to which persons who later died of CJD had contributed	1996 (?)			Dec 1996
CNS tissues excluded from cosmetic products for use in EU			Jan 1997	
BSE cohort cattle in UK ordered slaughtered and destroyed		Jan 1997		
Proposed ban on SRM in cosmetics for use in EU (effective October 2000)			Jul 1997	
SBM controls for cosmetics and medicinal products		Mar 1997		
FDA request to manufacturers that no bovine gelatin from BSE countries be used in injectable, implantable, or ophthalmic products, and that special precautions be applied to gelatin for oral and topical use				Sept/Dec 1997
Ban on marketing cosmetic products containing SRM prepared before 1 April 1998			Mar 1998	
Allow export of beef and beef products from cattle >30 months in certified BSE-free herds from Northern Ireland			Mar 1998	
Importation of all plasma and plasma products for use in UK		Aug 1998		
FDA limits plasma product withdrawals to pools at risk for contamination by vCJD donors				Sept 1998
Slaughter and destruction of offspring born to BSE-affected cattle after July 1996		Jan 1999		
FDA guidance to defer blood donors with >6 months cumulative residence in UK during 1980–1996				Nov 1999
Leukodepletion of whole blood donations from UK residents		Jul/Nov 1999		
Public FDA discussion about possible risk associated with vaccines produced with bovine-derived materials from BSE countries				Jul 2000
Withdrawal and destruction of a potentially tainted 1989 lot of polio vaccine from one manufacturer		Oct 2000		
SRM ban implemented (effective 2000)			Jul 2000	
Ban on slaughter techniques that could contaminate cattle carcasses with brain emboli (e.g., pithing or pneumatic stun guns), effective Jan 2001			Jul 2000	
All cattle >30 months old must have brain examinations for proteinase-resistant protein (PrP) before entering the food chain (effective Jan–Jun 2001)			Dec 2000	

* Adapted from Brown P, et al., 2001. (Reference No. 4)

† In Northern Ireland and Scotland, dates of implementation sometimes differed from those shown for England and Wales; in addition, individual European Union countries often adopted different measures on different dates.

CNS, central nervous system; EU, European Union; MRM, mechanically recovered meat; SBM, specified bovine materials (SBO plus entire head, including eyes but excluding tongue); SBO, specified bovine offals (brain, spinal cord, thymus, tonsils, spleen, and intestines from cattle >6 months old); SRM, specified risk materials (SBM plus sheep and goat heads and spleens from animals of any age, and spinal cords from animals >1 year old).