Bovine spongiform encephalopathy and food safety

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Bovine spongiform encephalopathy (BSE) is a fatal disease of cattle, caused by infective proteins known as prions. A prion (PrP^{Sc}) is a mis-folded isoform of the glycoprotein PrP^{C}, which is highly expressed in the nervous system. Prions replicate by coercing PrP^{C} to refold into PrP^{Sc}. The BSE epidemic was propagated by rendering dead cattle to produce meal which was then included in cattle feed. Consumption of BSE PrP^{Sc} from contaminated beef resulted in over 200 human cases of variant Creutzfeldt-Jakob (vCJD) disease, which is invariably fatal. There were rare cases of person-to-person vCJD transmission by blood transfusion. Variant CJD is now very rare, due to adoption of measures that prevent the feeding of ruminant protein to ruminants and the contamination of beef with the tissues that harbour PrP^{Sc}. Beef from countries with these control systems are safe for human consumption.

The infectious agent

Bovine Spongiform Encephalopathy (BSE) is one of a number of diseases known collectively as Transmissible Spongiform Encephalopathies (TSEs) of which scrapie of sheep, chronic wasting disease (CWD) of deer and elk and Creutzfeldt-Jakob disease (CJD) in humans are also members. TSEs are caused by a mis-folded isoform of the prion glycoprotein (PrP). The mis-folded pathogenic isoform is known as a 'prion', a contraction of the words 'proteinaceous' and 'infectious'[1]. By convention, normal PrP is represented as PrP^{C}, while the prion is represented as PrP^{Sc}. Prions replicate themselves by binding to PrP^{C} and acting as a template that coerces PrP^{C} to refold into PrP^{Sc}[2,3].

In mammals, PrP^{C} is present in a wide variety of tissues but is highly expressed in the nervous system[2,4,5]. The physiological function of PrP^{C} remains obscure and mice modified to express no PrP^{C} show only subtle, non-lethal differences to wild-type mice[3,6].

Three strains of BSE exist, which exhibit differences in prion distribution, histopathology, incubation time and clinical signs[7] as well as the appearance of the prions on western blots. Only one strain, classical BSE, was responsible for the BSE epidemic and the associated epidemic of vCJD[8]. The atypical H-type and L-type strains typically occur in cattle over eight years of age, and appear to arise spontaneously[9,10].

Diseases

Cattle

The incubation period of BSE is estimated to be from 30 months to 8 years and clinical disease usually occurs in cattle of four to five years of age. The course of clinical disease is generally less than 6 months[11]. Clinical signs in cattle include abnormal posture, incoordination, and changes in temperament[9,11].

Humans

Consumption of BSE prions in contaminated beef resulted in over 200 human cases of variant CJD (vCJD)[7]. The great majority of patients were residents in the United Kingdom (UK) during the period 1985-1996[12]. Patients ranged in age from 17–42 years[5]. Variant CJD is distinct from the most common human prion disease, sporadic CJD (sCJD), which occurs spontaneously in people,

including lifelong vegetarians[8], between 55 and 70 years old[12]. Both forms of CJD are fatal.

Pathogenesis

The first tissues in which PrP^{Sc} can be detected in BSE are those of the nervous system supplying the intestine[13] although it is not clear how infection reaches the nerves from the intestinal lumen. Infection ascends to the brain via the autonomic nerves[2]. The routes of spread of prions from cell to cell within the nervous system are not fully understood[14,15], and the mechanisms of cerebral damage are unknown. Depletion of PrP^{C} does not appear to be a factor. On the contrary, depletion of PrP^{C} in mice has been shown to reverse early degeneration and prevent progression to clinical disease[7].

Transmission and incidence of disease

Animals

The epidemic of BSE was first recognized in 1986 in the UK and was propagated by the rendering of dead cattle to produce meat-and-bone meal (MBM) which was then included in feed for cattle[8]. The infection was spread elsewhere in the world by exports of cattle and contaminated MBM[9]. There is no evidence that BSE can be transmitted between living cattle. This is in marked contrast to the horizontal infectivity of scrapie in sheep and CWD in deer[16–18].

More than 184,000 cases of BSE have been diagnosed in cattle. At the peak of the epidemic 1,000 cases were being diagnosed each week in the UK[18]. The feeding of MBM to cattle was banned in the UK in 1988, but because of the long incubation period and initially ineffective implementation of the feed ban, clinical incidence continued to rise, peaking in 1992. The incidence has steadily declined since, and the disease is now very rare[19].

A number of zoo animals, including *Bovidae*, *Felidae* and non-human primates, developed TSEs at the same time as the BSE epidemic[20]. Cases of TSE were also diagnosed in two domestic goats[20] and a number of domestic cats[8,18]. All these cases were attributed to ingestion of BSE prions in beef or processed feed.

The epidemic is believed to have been amplified from a single common source[7], which remains unknown. Sporadic cases of BSE occur in cattle, although to date only the atypical L- and H-type strains have been found. It is possible that classical BSE may also occur spontaneously. Although it has sometimes been suggested that BSE arose from rendering of scrapie-infected sheep, encephalopathy induced in cattle by intracerebral inoculation with scrapie prions does not resemble BSE, and experimental BSE in sheep does not resemble scrapie. Furthermore, cattle are resistant to oral infection with scrapie or CWD[8].

Humans

Since the first ten cases were reported in April 1996, over 200 vCJD cases have been identified[7,21]. The epidemic of vCJD is attributed to consumption of beef contaminated with central nervous system tissue containing BSE PrP^{Sc}. BSE PrP^{Sc} and vCJD PrP^{Sc} have identical biochemical properties and cause identical lesions in mice, and on a country-by-country basis the incidence of vCJD in humans generally correlates with the prevalence of BSE in cattle[7]. The infective dose of bovine PrP^{Sc} to human beings is unknown[12].

Four cases of person-to-person vCJD transmission by blood transfusion have been reported in the UK[13]. Iatrogenic transmission of vCJD remains a concern because retrospective analysis of tonsil and appendix specimens suggests that up to 1 in 4000 persons exposed during the UK epidemic may be a sub-clinical carrier[8,22]. Internationally, blood donations are generally not accepted from people who lived in the UK between 1980 and 1996, or who received a blood transfusion in the UK since 1980. These precautions are in place in Australia[23] and in New Zealand[24].

A polymorphism at position 129 of the PrP^{C} amino acid sequence has been identified in humans, which appears to affect susceptibility to TSEs. Approximately 40% of Caucasians are homozygous for methionine (Met) at position 129, 10% are homozygous for valine (Val) and 50% are Met/Val heterozygotes. To date, all confirmed clinical cases of vCJD have been Met/Met homozygotes[12]. However, PrP^{Sc} was found in the spleen of a Met/Val heterozygote who died of unrelated causes five years after receiving a blood transfusion from a person incubating vCJD[2,12], and PrP^{Sc} was also found in anonymous postsurgical samples of appendices from two Val/Val homozygotes. Thus, lymphoid tissue of all three genotypes may become infected[8,12,25]. It is not yet clear whether the Met/Val and Val/Val genotypes prevent or only delay neurological infection with vCJD[12]. Besides vCJD, the only other orally acquired TSE known in humans is kuru, a historical disease of some communities in Papua New Guinea who practiced funerary cannibalism. The mean incubation period of kuru is 12 years, but the incubation period has exceeded 50 years in some individuals[13]. Retrospective analysis of samples has shown that the majority of those with unusually long incubation periods were Met/Val heterozygotes[12]. Some authors have predicted a late peak of vCJD cases affecting Met/Val heterozygotes[7,25].

Food safety and controls

A key component of prevention of both BSE in cattle and vCJD in humans is the prohibition on feeding mammalian-derived protein to food animals. Feeding of mammalian-derived proteins, other than dairy proteins, to livestock has been prohibited in the UK since 1996

and throughout the European Union since 2001[26,27]. Numerous other countries worldwide have enacted similar legislation. Enforcement of this ban includes[27]:

- Registration and regular auditing of feed producers
- Mandatory physical separation of ruminant feed production, storage and transport from production, storage and transport of non-ruminant feed that may contain animal proteins
- Testing of raw materials and finished feeds for presence of mammalian proteins
- Warning labels on feed bags
- Education of livestock keepers.

Throughout the EU, cattle are individually and permanently identified, and each country has an electronic database recording the details, locations, movements and fate of all cattle. Cattle that die or require emergency slaughter on farms are rendered and then incinerated to ensure that infective material is destroyed[27] and cannot be used in animal feed.

As a result of these measures (also see Figure 1 for a summary of the critical BSE control points) the BSE epidemic was controlled, and classical BSE is now very rare [19]. Surveillance programs for BSE are in place in many countries throughout the world, and occasionally detect isolated cases of atypical BSE[28].

The risk of oral infection of humans with vCJD can be eliminated by preventing contamination of the food supply with the animal tissues know to harbour infectivity, which are known as specific risk materials (SRM). SRM include the brain, spinal cord, eyes, palatine tonsils and gastrointestinal tract. Slaughter and processing procedures have been implemented throughout Europe and other countries to prevent contamination of beef with SRM. Following removal, SRM are transported to rendering plants under strict controls, and are rendered and incinerated under conditions known to destroy infectivity[27]. Beef and beef products from countries with these control systems are safe for human consumption.

Australia and New Zealand are among eleven countries internationally recognized as being at 'negligible risk' for BSE. Live cattle may not be imported into Australia from BSE-affected countries. A ban on the importation of MBM from countries other than New Zealand was in place almost two decades before the UK BSE outbreak, as a measure to prevent importation of anthrax spores. Should infected material enter Australia, propagation to the national cattle herd would not occur, because the feeding of ruminants with MBM is prohibited. Information on Australia's approach to BSE may be found on the website of the Department of Agriculture, Fisheries and Forestry[29].

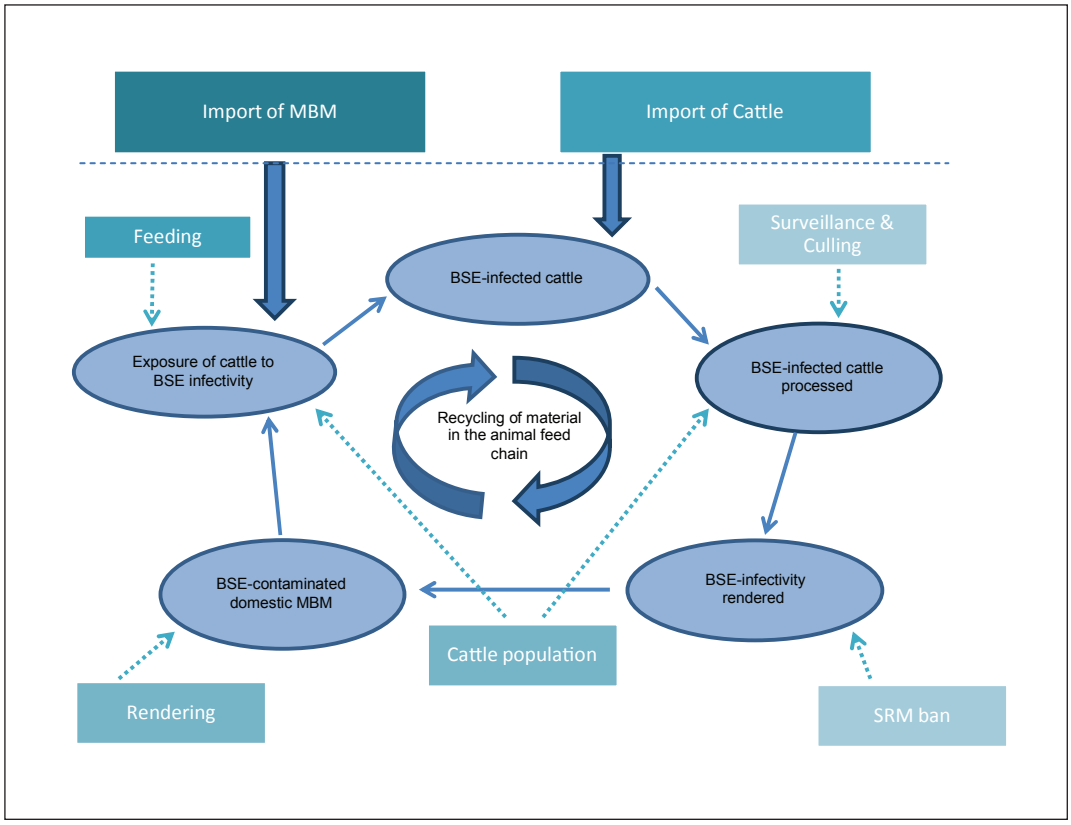

Figure 1. The critical points within the cattle production system that BSE controls need to be implemented to prevent introduction and recycling of the BSE agent.

With respect to the importation of beef products, Australia implemented a revised policy in 2010 whereby any country wishing to export beef to Australia must undergo a rigorous risk assessment of their BSE-related control measures[30]. The risk assessment, consistent with the principles outlined by the World Organisation for Animal Health, is undertaken by Food Standards Australia New Zealand who also visits each country to verify the effectiveness of the control measures. Countries are given a BSE category that establishes the conditions under which they may import beef products into Australia[31].

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Biographies

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