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Bovine spongiform encephalopathy: A review of current knowledge and challenges

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ABSTRACT
Bovine spongiform encephalopathy (BSE), also referred to as mad cow disease, is a chronic degenerative disease that affects the central nervous system. BSE is caused by a misfolded isoform of the prion protein, a widely expressed glycoprotein. The illness is referred to as Variant Creutzfeldt-Jakob disease (vCJD) in humans. In the United Kingdom (UK), BSE in cattle was first discovered in 1986. Based on epidemiological data, it appears that animal feed containing tainted meat and bone meal (MBM) as a source of meat protein is the common cause of the BSE outbreak in the UK. Clinical indicators in cows include irregular body posture, incoordination, difficulty in standing, weight loss, and temperamental changes, including agitation and hostility. Feeding livestock MBM obtained from BSE-infected livestock contaminated with BSE prions is the only known risk factor for BSE development. Strong evidence linking BSE to human transmission and a variant type of CJD has brought the disease to the attention of many countries. Screening living animals for BSE is challenging. In most cases, suspected animals are usually killed. Typically, the central nervous system is examined for prions to diagnose this illness. There is currently no robust treatment for BSE. The prevention of BSE can be achieved by avoiding the feeding of susceptible animals with ruminant tissues that might carry prions.
Keywords: BSE, Cattle, Prion, Public health, vCJD.

Introduction

Bovine spongiform encephalopathy (BSE), also referred to as mad cow disease, is a chronic degenerative disease that affects the central nervous system (Haley and Richt, 2023). This is caused by a misfolded isoform of prion protein (PrPSc) that deviates from its normal cellular isoform, PrPC. The alternative form of BSE in humans is the variant Creutzfeldt-Jakob Disease (vCJD). BSE is a member of the transmissible spongiform encephalopathies (TSE) disease family (Brown and Abee, 2005; EFSA, 2022). The infectious agent of the disease is believed to be a misfolded protein known as a prion. The disease has a lengthy incubation period, spanning 30 months to

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8 years (Poggiolini *et al*., 2013). The brain and spinal cord develop spongy degeneration as a result of the misfolding and aggregation of additional native prion proteins (PrPs) in the brain caused by these malformed prions (Kumagai *et al*., 2019). The consumption of tainted meat and bone meal (MBM) in cattle feed results in cattle-to-cattle transmission (Islam *et al*., 2022). This illness is deadly, and there is currently no known cure.

Beginning in the mid-1980s, a cattle outbreak in the United Kingdom (UK) was caused by a novel form of prion disease known as BSE. In 1986, the UK identified the first cases (Lee *et al*., 2013). Around 200,000 cases of BSE have been confirmed in cattle, nearly all of which occur in the UK (Columbus, 2004). During the UK outbreak in 1992, 37,280 cases were recorded in 1 year (Watson *et al*., 2021). Native cattle in the majority of European nations, Japan, the US, Canada, and Brazil have been reported to have lower occurrences (EFSA *et al*., 2017). The BSE epidemic has far-reaching economic repercussions. Trade restrictions on beef commodities were accompanied by a sharp decline in consumer confidence in beef products in countries where BSE cases were prevalent (Jin and Koo, 2003).

The traits of BSE-affected cows include altered body posture, decreased milk output, abnormal weight loss, altered temperament (nervous or aggressive), and loss of appetite (Hamir *et al*., 2011). Typically, symptoms do not appear for 3 to 6 years following the original illness. Typical pathogenic alterations include astrocyte growth, neuronal loss, and gray matter spongy degeneration in the absence of signs of an inflammatory response (Soto and Satani, 2011). Through the use of Western blotting techniques, aberrant prions can be used to diagnose this condition (Olech, 2023). Postmortem identification can be used to diagnose BSE if clinical indications are present. A postmortem examination may show overall neuronal degeneration and microscopic vacuolization of the gray matter of the brain (Rech *et al*., 2018). While the animal is alive, diagnostic tests are not available.

At present, it is recognized that humans can contract BSE by eating contaminated beef or coming into contact with other items made from the diseased cattle's nerve tissue (Pritzkow *et al*., 2021). The illness is referred to as vCJD in humans. All age groups are susceptible to this disease, which is extremely difficult to diagnose until almost completely cured (Brandel and Knight, 2018). Early nervous system symptoms, such as depression and loss of coordination, are experienced by those with vCJD. These symptoms eventually lead to dementia (Kelemen *et al*., 2022). However, in the later phases of the illness, magnetic resonance imaging can identify additional brain abnormalities. Typically, 13 months after the onset of symptoms, vCJD is fatal. This has raised the question of whether and to what extent eating certain foods or other exposures can expose people to prions.

The number of cases of BSE disease has increased dramatically in recent decades, ranking among the main health issues. The link between BSE and vCJD in humans has raised awareness of the possible risks associated with BSE. The purpose of this review is to explain the etiology, history, epidemiology, pathogenesis, pathology, clinical symptoms, diagnosis, transmission, host range, risk factors, public health importance, economic impact, and control of BSE.

History

Before the identification of BSE, sheep scrapie was the first disease of its kind to be documented, having been present for more than 200 years (Ness *et al*., 2023). In the UK, BSE in cattle was first discovered in 1986. Although the exact cause of the outbreak is unknown, there is strong evidence linking the use of MBM in cattle feed tainted with an agent similar to scrapie (Nathanson *et al*., 1997). Regardless of the underlying cause, the epidemic persisted and expanded as a result of the recycling of BSE-contaminated cow material to additional animals starting in the mid-1980s. Since the 1920s, MBM has been used in the UK to manufacture feed supplements for cattle and other livestock (Islam *et al*., 2022). Modifications made to these processing methods in the 1970s and 1980s may have permitted the infectious agent to endure the manufacturing process.

The UK has been the site of most BSE cases. In April 2005, 180,780 BSE cases were confirmed in over 36,000 cattle herds as of April 2005. Almost a thousand probable cases were recorded every week during the height of the pandemic in January 1993 (Alarcon *et al*., 2023). As of 2005, there have been two documented BSE cases in the US as of 2005. In October 2001, an adult dairy cow was imported from Canada for the first BSE occurrence. In June 2005, a second case was verified (Holman *et al*., 2010). BSE surveillance found 22 cases in North America as of February 2011: 3 in the US and 19 in Canada (one imported from the UK) (EFSA *et al*., 2017). Other than BSE, known animal TSEs include transmissible mink encephalopathy, chronic wasting disease (CWD) in deer and elk, and scrapie in sheep and goats (Otero *et al*., 2021). Feline spongiform encephalopathy (FSE), which has been reported in domestic cats and several wild cat species in zoos (Bencsik *et al*., 2009), as well as spongiform encephalopathy in several African ruminant species in zoos, is thought to result from infection with the BSE agent (Cunningham *et al*., 2004).

TSEs in humans include Kuru, Gerstmann-Straussler-Scheinker syndrome, Creutzfeld-Jakob disease (CJD), and fatal familial insomnia (Collins *et al*., 2001). There is compelling evidence that humans can acquire vCJD by consuming by-products from infected cattle, as the same prion strain that causes BSE also causes vCJD in humans (Ritchie *et al*., 2021). The primary sources of prion-contaminated material from diseased cattle include the brain and spinal cord, as well as some intestines (Hedlin *et al*., 2012). There are no other

animal TSE agents known to cause illness in humans, besides BSE. Between October 1996 and March 2011, 175 cases of vCJD were recorded in the United Kingdom and Northern Ireland (UK), and 49 cases were recorded abroad (Diack *et al*., 2012). Since 2000, the number of vCJD cases in the UK has decreased following the containment of the BSE pandemic in cattle.

Based on the EU TSE annual report, out of 1,021,252 cattle that were tested, 66,121 cattle were tested in eight non-EU reporting countries, with two cases of H-BSE in France and Spain and four cases of L-BSE in France, Germany, and Spain were recorded (EFSA, 2022). Additionally, out of the 311,174 sheep and 118,457 goats that were tested, 551 cases of scrapie, 448 classical scrapie (CS), and 103 atypical scrapie (AS) were reported in sheep. In the other non-EU reporting countries, 55 CS and 1 AS in Iceland, and 8 AS in Norway were reported out of the 27,594 sheep that were tested. In goats, 224 cases of scrapie (219 CS and five AS) were reported (EFSA, 2022).

Epidemiology

Based on epidemiological data, it appears that animal feed containing prion-tainted MBM as a source of meat protein was the common cause of the BSE outbreak in the UK (Nathanson *et al*., 1997; Amin *et al*., 2023; Betancor *et al*., 2023). The cause of BSE is the subject of multiple scientific theories. Feeding processed proteins to livestock derived from carcasses of sheep or cattle infected with scrapie with previously undisclosed TSEs may have been the cause of BSE in the UK (Greenlee and Greenlee, 2015; Amin *et al*., 2023; Betancor *et al*., 2023; Kaifa *et al*., 2023). For many years, the use of meat, bone meal, and other similar items was a source of protein in cattle diets. It is possible that modifications to processing procedures in the late 1970s and early 1980s contributed to disease onset (Alarcon *et al*., 2023). There is no proof that mature cattle that are unrelated to one another or that animals that come into contact with other species transfer BSE horizontally.

An infectious agent exposure in 1981–1982 led to an outbreak in the UK, which was correlated with a sharp decline in the usage of organic solvents in the production of MBM (Kumagai *et al*., 2019). Between 1987 and 1992, the number of BSE cases reported in the UK rose from 446 to 37,280, and after 2010, it decreased to less than 10 (Kumagai *et al*., 2019). In several European countries, with the exception of the UK, the numbers peaked in 2001–2002 and in Japan in 2006 (Houston and Andréoletti, 2019). The prevalence of BSE was effectively decreased by "feed bans," which were implemented in nations plagued by BSE to prohibit the recycling of BSE agents (Kao *et al*., 2003; Amin *et al*., 2023; Global Times, 2023).

The UK resumed surveillance for CJD in 1990 in an effort to track any changes in CJD patterns linked to the BSE outbreak (Will *et al*., 1996). Concerns regarding the connection between this human disease and BSE were raised when a new vCJD was identified, characterized by a unique neuropathological profile and atypical inclusions at a young age (Ritchie *et al*., 2021; Amin *et al*., 2023; Kaifa *et al*., 2023). A connection between the two diseases is supported by a comparison of Western blot (WB) glycoform patterns and artificial BSE transmission in experimental animals, such as monkeys. A World Health Organization consultation conducted on 2–3 April 1996, determined that although no clear relationship had been identified between BSE and vCJD, exposure to the BSE agent was probably the most likely cause of vCJD. The consultation suggested avoiding animal-to-human BSE transmission and limiting human exposure to BSE. In the UK, France, and other countries, 177, 27, and 25 confirmed instances of definite and probable vCJD occurred from 1995 to 2014, respectively. Two additional cases were reported in 2016 (Chen and Dong, 2016).

At necropsy, the tonsils, spleen, and lymph nodes of vCJD patients were shown to have disease-associated PrPSc (Head *et al*., 2004; Kaifa *et al*., 2023). Additionally, appendix tissue from vCJD patients was collected 8 months before the commencement of the disease. According to a comprehensive study of appendix samples obtained during surgery in the UK, 16 out of 32,441 samples tested positive for the aberrant PrP, indicating that the prevalence of vCJD in the country is 493 per million (Gill *et al*., 2020).

Before the discovery of the new atypical BSE, prions isolated from BSE cattle were believed to be a strain of TSE prion (Kamali-Jamil *et al*., 2021). Bovine amyloidotic spongiform encephalopathy (BASE, later also called L-type BSE (L-BSE) and H-type BSE (H-BSE), are two atypical types of BSE that were identified by active surveillance in 2004 in Italy and France (Kumagai *et al*., 2019). These types of BSE differed from previous cases in terms of neuropathological and molecular features. To differentiate it from atypical BSE, the BSE strain that has been identified as the cause of epidemics in the UK and other countries has since been dubbed classical BSE (C-BSE). The unglycosylated disease-associated isoform (PrPd) from H-BSE and L-BSE animals had a greater molecular mass than that of PrPd produced from C-BSE animals (Hamir *et al*., 2011). As of November 2018, the Food Safety Commission of Japan reported 135 atypical BSE cases globally, primarily through active surveillance programs for fallen livestock and normal and emergency animal slaughter. Overreaction to external stimuli, unexpected startle response, panic, anxiety, difficulty awakening, and lethargy are examples of atypical clinical symptoms of BSE identified in intraspecies transmission trials. These symptoms are difficult to differentiate from C-BSE (Costassa *et al*., 2016).

Etiology

BSE is caused by a misfolded isoform of the PrP, a widely expressed glycoprotein. PrP is encoded by the PrP gene PRNP and is a typical component of vertebrate cell membranes (Castle and Gill, 2017). An abbreviation for misfolded pathogenic protein isoforms is "prion," which was coined as a combination of the words "proteinaceous" and "infectious" (Aulić *et al*., 2013). Conventionally, PrPC is used to indicate the normal cellular isoform of PrP. The cellular form is represented by the superscript C. The prion form, denoted as PrPSc, shares the same amino acid sequence as the normal form (Baldeschi *et al*., 2022). The superscript in question Sc refers to the classic animal prion disease, scrapie, which afflicts sheep (Imran and Mahmood, 2011). To proliferate, prions attach to the healthy PrPC protein and use it as a template to refold the PrPC molecule into the aberrant PrPSc form (Westergard *et al*., 2007).

PrPC is found in fish, amphibians, birds, mammals, fish, and yeast (Pastore and Zagari, 2007). The protein is highly expressed in the neurological system and is expressed in a wide range of organs in animals, including the spleen, lymph nodes, kidney, pancreas, salivary glands, adrenal glands, liver, thymus, and bone marrow (Tichopad *et al*., 2003). Nonetheless, the physiological role of PrPC is still unknown, and several mouse strains that have been produced to lack PrPC expression exhibit only minor, non-fatal variations in their physiological and locomotor activities in contrast to wild-type mice (Nico *et al*., 2005). Some strains of prion disorders, such as scrapie and BSE, have distinct disease characteristics. The protein deposition patterns in the brain and lymphoid tissues, the length of time an animal must incubate following experimental infection, histology, and clinical symptoms are among the differences among the strains. For instance, in the case of scrapie, certain strains are characterized by significant infectivity in lymphoid organs, whereas others preferentially grow in the central nervous system (Scialò *et al*., 2019). There are three known strains of BSE known to exist. The human vCJD epidemic that accompanied the BSE epidemic that started in the UK and expanded to other nations was caused by a single strain of the prion, known as classical BSE (Ritchie *et al*., 2021). Atypical strains, referred to as H (high)-BSE and L (low)-BSE, are uncommon and typically found in cattle aged between 8 and 20 (Masujin *et al*., 2016). They seem to emerge randomly and spontaneously.

When it comes to the inactivation of prions, standard sterilizing techniques used to prepare surgical instruments and supplies are infamously ineffective (Sakudo *et al*., 2022). PrPSc can withstand 70% alcohol treatment, gamma irradiation, UV irradiation at 254 nm, and traditional autoclaving (121°C for 20 minutes). PrPSc can be inactivated by a range of procedures, including harsh autoclaving conditions (134°C for 8–18 minutes) combined with detergents and hydrogen peroxide gas plasma treatment (Sakudo *et al*., 2020). The infectiousness of prions can be decreased by various processes that alter or hydrolyze proteins. PrPSc has a protease-resistant core and is insoluble in detergents, whereas PrPC is protease-sensitive and soluble in nondenaturing detergents (Yuan *et al*., 2006).

Pathogenesis

Although the pathophysiology of BSE in cattle has been well investigated, there are still many unanswered questions. PrPSc was initially observed in Peyer's patches in the ileum after calves were orally exposed to contaminated material. It was also found in gut-associated lymphoid tissue (GALT) at the ileocecal junction and jejunum (Stack *et al*., 2011). Infection occurs in follicular dendritic cells (FDCs) and macrophages. Subsequently, infection can be detected in the enteric nervous system; however, the mechanism by which infection moves from lymphoreticular cells to nervous system cells remains unclear (Natale *et al*., 2011). Prion infections may occur when they come into contact with thin nerve fibers located just beneath the intestinal mucosa following their passage through the intestinal mucosal barrier (Sigurdson *et al*., 2019). Once the neurological system is compromised, the infection proceeds to the brain through the sympathetic and parasympathetic nervous systems, which include the vagus and splanchnic nerves, respectively (Ackermann *et al*., 2021). The involvement of GALT is less in BSE than in scrapie in sheep (Press *et al*., 2004).

It has been proposed that bloodstream infections caused by oral-acquired prion disorders could possibly affect the brain; however, infectious agents were not found in the blood of cattle infected with BSE (Gallardo and Delgado, 2021). In contrast, GALT showed significant infectivity, whereas blood samples were reported to contain prions in experimental BSE in sheep and human vCJD (Mabbott, 2017). It is unknown how PrPSc replication in splenic FDCs contributes to the transmission of agents and may differ throughout animals. According to scrapie research, neuroinvasion can be prevented or delayed by FDC depletion, delayed or prevented by splenic denervation, and promoted by augmenting the spleen's nerve supply (Mohan *et al*., 2005). In mice infected with BSE and expressing sheep PrP, splenic PrPSc was detected (Espinosa *et al*., 2007). Only one of the three cows that were halted at the advanced clinical stage of BSE had splenic PrPSc.

Once cells become infected with PrPSc, membrane microparticles harboring PrPSc can disseminate the infection to nearby cells (Fevrier *et al*., 2004). It has been demonstrated that PrPSc and exosomes can be released from infected cells *in vitro*, supporting this theory. Exosomes are tiny, membrane-bound vesicles that cells can produce and merge with other cells to form new vesicles (Zhang *et al*., 2019). Exosome production by lymphoid cells has been demonstrated,

but it has not been demonstrated that neurons make exosomes. Another way that PrPSc can spread between neighboring cells is by tunneling nanotubes, which are very thin membrane bridges that can form between cells and facilitate the movement of pathogens, cytoplasmic chemicals, organelles, and parts of the plasma membrane (Gousset and Zurzolo, 2009).

Additional suggested routes of propagation inside the nervous system consist: lymph flow around neurons, axonal transport, and successive infection of Schwann cells, which nourish and insulate peripheral nerves (Oliveira *et al*., 2023). Although some suggestions have been made, the chemical mechanisms responsible for brain injury remain mostly unclear. Given that genetically designed mice with no PrPC at all and mice whose expression of PrPC is turned off in maturity do not exhibit clinical indications of TSE, PrPC depletion does not appear to be the etiology (Lakkaraju *et al*., 2022). It has been demonstrated that depleting PrPC in mice with prion infection can reverse early spongiform degeneration and prevent disease progression to a clinical stage (Mallucci *et al*., 2003). These results imply that several PrPC-dependent mechanisms are necessary for PrPSc toxicity. It has been proposed that the conversion of PrPC to PrPSc impairs this neuroprotective effect and promotes neurodegeneration (Mahabadi and Taghibiglou, 2020). An alternative explanation could be that the binding of PrPSc to PrPC initiates a signal transduction cascade that damages nerves (Panes *et al*., 2021). Based on the *in vitro* data, further suggestions regarding the pathogenicity of PrPSc include diminished proteasome system degradation, overexpression of genes related to endoplasmic reticulum function, and poor lysosomal breakdown of cellular waste (Goold *et al*., 2015).

Pathology

BSE microscopic alterations are pathognomonic and extremely specific. The alterations manifest as bilateral, symmetrical, and degenerative lesions that affect multiple regions of the brain stem's gray matter (Zerr, 2022). There are two manifestations of neuronal vacuolization. "Sponic encephalopathy" is the term used to describe the presence of 20 μm-sized vacuoles in the neurites of the neuropil. Larger vacuoles (30–40 μm), either single or multiple, in the neuronal pericardium are another presentation. These vacuoles cause the pericardium to expand, resulting in a bloated neuron with only a thin rim of cytoplasm remaining (Kumagai *et al*., 2019). The primary requirement for a valid histological diagnosis of BSE is the existence of vacuoles in the gray matter neuropil and the neuronal perikaria and cortex (Olech, 2023).

Clinical symptoms

In cattle

According to field data, cattle's vulnerability to BSE infection peaks at approximately 12 months of age, yet cases of BSE have been reported in cattle that were not fed MBM until they were more than 2 years old (Nathanson *et al*., 1997). Cattle are thought to take between 30 months and 8 years (on average, 4.5–5.5 years) to fully incubate; nevertheless, the clinical course is brief from the moment clinical indications appear, with most animals dying or necessitating euthanasia within 6 months (EFSA *et al*., 2017). The age at which clinical indications first appeared was known for 124,000 British cattle, of which 7% were aged 3 years, 31% were aged 4 years, 33% were aged 5 years, and 29% were aged 6 years or older. Clinical indicators in cows include irregular body posture, incoordination, difficulty in standing, weight loss despite continuous eating, and temperamental changes, including agitation and hostility (Saegerman *et al*., 2004).

In humans

There have been > 200 documented incidences of vCJD in people. The age of patients was 17–42. Most patients lived in the UK between 1985 and 1996 (Alarcon *et al*., 2023). The variant CJD usually manifests 18 months after the onset of symptoms and is always fatal (Maheshwari *et al*., 2015). Problems with cognition and movement are examples of clinical symptoms and indicators. Patients typically present with psychological or sensory symptoms when the disease first manifests. Psychiatric symptoms that have been reported include anxiety, hostility, recklessness, paranoid delusions, melancholy, apathy, agitation, sleeplessness, poor concentration, and withdrawal (Wall *et al*., 2005). Approximately one-third of patients experience unpleasant, unusual, and persistent sensory sensations. As the illness worsens, neurological symptoms such as involuntary movements, muscle spasms, and cerebellar ataxia appear. Urinary incontinence, akinetic mutism, and increased immobility are examples of late-onset symptoms (Barnwal *et al*., 2022). Typically, opportunistic infections result in death. Sporadic CJD is the primary cause of most human cases of prion disease (Tam *et al*., 2023). In contrast to vCJD, sCJD often affects individuals aged 55–70 years. Unlike vCJD, cerebellar ataxia or progressive dementia is more common in the early stages of sCJD (Cooper *et al*., 2006). Moreover, vCJD has a unique histopathology. Other than conventional BSE, the only other TSE that has been known to spread orally to humans is the now-extinct illness known as "kuru", which only affected a limited number of cannibalistic natives in Papua New Guinea (Liberski *et al*., 2012).

Diagnosis

Early, accurate, and rapid diagnosis is vital for the prevention and control of the spread of BSE, especially in the absence of effective treatment strategies and vaccines. Arrays of approaches and methods have been explored and implemented to improve the detection of BSE in cattle; however, each technique has its own drawbacks and strengths. Due to this limitation, several methods and approaches are usually combined to increase the odds of eliminating the disadvantage of using a single method (Olech, 2023).

No BSE testing was performed on living animals. The CNS is typically examined for prions to diagnose this illness (Watson *et al*., 2021). Although the brainstem may occasionally be sampled through the foramen magnum, whole brain sampling is typically performed at the level of the obex (e.g., for surveillance with fast testing) (Olech, 2023). The most precise assays are immunohistochemistry and immunoblotting. There are also some quick diagnostic methods that rely on lateral flow assays, automated immunoblotting WB, and enzyme-linked immunosorbent assays (ELISA). Rapid tests are frequently employed in surveillance and slaughter testing because they enable the screening of large quantities of samples (EFSA *et al*., 2018). Immunohistochemistry or immunoblotting is the conventional method for confirming positive samples in fast tests (Cooley *et al*., 2001). However, according to the World Organization for Animal Health (WOAH, 2008), in certain situations, confirming a positive result with a second BSE rapid test may be acceptable. Using electron microscopy, the BSE causative agent can also be identified by observing distinctive prion fibrils known as scrapie-associated fibrils; however, the sensitivity of this test is limited (Simon *et al*., 2008). While a histological examination of the brain is usually not the only confirmatory test, it can be very helpful in the diagnosis process, as some animals in the early stages of infection exhibit little to no spongy alterations (Olech, 2023).

The majority of BSE diagnostic tests are comparatively insensitive and only identify prions in the brain three to 6 months before the manifestation of clinical symptoms. Prion identification can be accelerated by highly sensitive assays, such as real-time quaking-induced conversion (QuIC) and protein misfolding cyclic amplification (PMCA) (Kaelber *et al*., 2019). The capacity of these methods to transform PrPc, a typical cellular protein, into prions *in vitro* allows the identification of minute concentrations of prions. Although these methods have not been properly assessed for surveillance programs, they are being investigated for diagnostic purposes. The rodent bioassay, which involves inoculating rats with BSE, is another method for detecting the disease; however, due to the lengthy incubation period, this method is not feasible for routine diagnosis. Because antibodies are not produced against BSE, serology is useless (Corda *et al*., 2015).

The same assays used to diagnose conventional BSE can also be used to detect atypical prions, such as H-BSE and L-BSE. Although these prions can also be identified in obesity, the distribution patterns of H-BSE and L-BSE in the brain differ slightly from those of classical BSE and from one another (Orge *et al*., 2021). Atypical prions can be identified in immunoblotting tests by their characteristics similar to classical BSE prions. Compared with classical BSE, H-BSE has fragments with larger molecular masses (Moore *et al*., 2016). Additionally, following proteinase K cleavage, H-BSE interacts with monoclonal antibodies against an N-terminal epitope absent from classical BSE (McCutcheon *et al*., 2014). The molecular mass of L-BSE is lower than that of the classical BSE prion. It has a unique deposition pattern in the brain, which is marked by amyloid plaques, and its glycosylation pattern is different from that of classic BSE (Fast *et al*., 2023).

It is important to differentiate between BSE in small ruminants and scrapie, a prion disease that affects these animals far more frequently. In most cases, this can be done using a conventional prion test. However, it is difficult to distinguish BSE from other scrapie prions (CH1641) (Gough *et al*., 2014). The latter two agents can be distinguished from one another using a restricted set of tests, such as PMCA, specific types of specialized immunoblots, PrPSc profiling, and epitope mapping (Elezgarai *et al*., 2017).

The lack of tests with the potential to identify asymptomatic BSE-infected animals that could be employed in screening healthy cattle populations, such as whole herds or specific animals for import or export purposes, represents a major challenge in the effective prevention and control of BSE. *In vitro* prion techniques, such as PMCA and RT-QuIC, which have the capability to detect minute amounts of prions in various tissues and body fluids, have not been fully evaluated for use in legal BSE surveillance programs, even though they help in the development of systems for antemortem TSE diagnosis (Olech, 2023).

Transmission

There is little evidence that BSE can spread among animals in ways other than feeding tainted with specific tissues from animals that have the disease (Gallardo and Delgado, 2021). This stands in sharp contrast to deer's chronic wasting disease (CWD) and sheep's horizontal spread of scrapie (Madsen-Bouterse *et al*., 2016). Saliva, urine, feces, placentas, and decomposing carcasses are also sources of CWD prions (Saunders *et al*., 2008). In a previous report, PrPSc was discovered in milk, saliva, placental tissue, nasal secretions, and excrement from sheep with scrapie infections (Vascellari *et al*., 2007); however, there is no proof that BSE can spread among cattle through this method or through contact with excrement or secretions. However, prions associated with scrapie and CWD persist in the environment, attaching to soil particles or other fomites (EFSA *et al*., 2019). There is also no proof of vCJD human-to-human vCJD transmission other than through medical procedures such as blood transfusions.

It seems that animals can become infected with each other by consuming less than 1 mg of infected brain material. Oral injection of 5 g of infective brain homogenate has been shown to transmit BSE to monkeys; nevertheless, the infective dose of bovine PrPSc for humans remains unknown (Lasmézas

et al., 2005). According to current prion theory, the BSE agent, also known as PrPSc, is an abnormally folded isomer of a normal cell surface protein, also known as PrPc. It can cause a conformational change in PrPc, leading to increased production of PrPSc in the central nervous system (CNS) of infected cattle (Thackray *et al*., 2005). This process culminates in neurological abnormalities typical of BSE after a protracted incubation period. Strong evidence suggests that people who consume offal (particularly the brain and spinal cord) from infected cattle develop vCJD, a neurodegenerative illness that is identical to that of cattle and develops after a protracted incubation period (Houston and Andréoletti, 2019). Consequently, vCJD is the only zoonosis associated with TSEs. Similar to BSE, vCJD is lethal and typically results in months of crippling neurological illness before death (Belay *et al*., 2005).

Dead cattle due to BSE infection, which were processed for MBM and subsequently added to animal feed, were first identified in the UK in 1986 (Kumagai *et al*., 2019). The transmission pathway of BSE in cattle (Fig. 1) starts with prion infection through contaminated animal feed. The misfolded prions induce the conversion of normal proteins to CNS proteins, leading to neurodegeneration. The sole method of agent transmission between cattle currently known to exist is the ingestion of infectious material in MBM made from animals exposed to BSE (Islam *et al*., 2022). Human cases of vCJD have also been linked to the consumption of steak tainted with infected cow CNS tissue (Maheshwari *et al*., 2015). It also becomes clear how contaminated beef products consumed by humans act to cause vCJD (Fig. 1). Four incidences of human-to-human transmission of vCJD through blood or plasma transfusion have been reported in the UK, despite the fact that the majority of cases are caused by the ingestion of tainted beef (McManus *et al*., 2022). In rare instances, dura mater grafts, growth hormone injections, and corneal transplants have resulted in the transmission of sickle cell disease (sCJD) between individuals (Heath *et al*., 2006). Because the disease can occur in lifelong vegetarians as well, there is no evidence that sCJD is a TSE of animal origin (Davanipour *et al*., 2014).

Host range

Through intracerebral (IC) inoculation, the following species have been experimentally exposed to BSE: rats, sheep, goats, mink, pigs, marmosets, and macaques (Baron, 2002). There have been failed attempts at IC transmission in hamsters. Cattle, sheep, goats, rodents, and mink have all been successfully exposed to BSE through oral transmission (Tamgüney *et al*., 2009). Pigs have not been proven to be good subjects for oral transmission. In chickens, parenteral and oral transmission has also been attempted; thus, far, no signs of illness have been reported (Moore *et al*., 2011). In addition to eight captive wild ruminant species, exotic cats (cheetahs, pumas, tigers, and ocelots) and domestic cats have been found to have TSE (Orge *et al*., 2021). FSE has been reported in approximately 81 domestic cats in the UK and in one domestic cat in each of Norway, Northern Ireland, and Liechtenstein

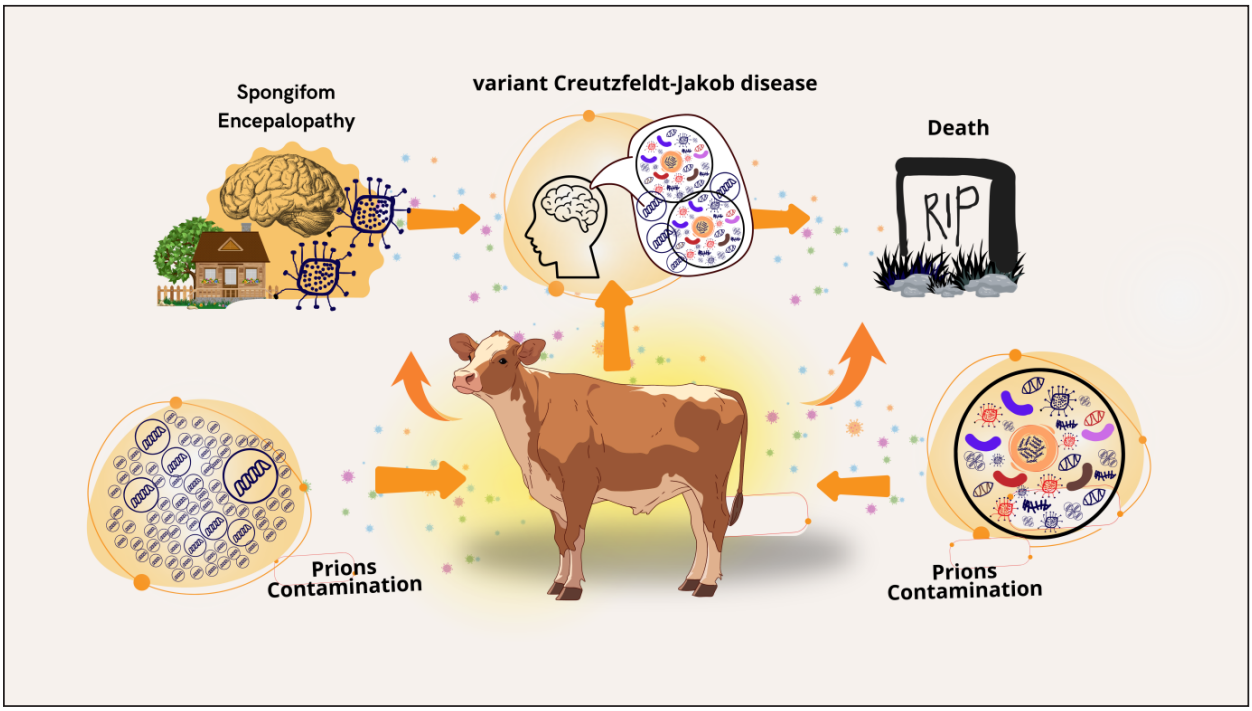

Fig. 1. Understanding BSE transmission: from prion contamination to neurological disease.

(Iulini *et al*., 2008). The agent recovered from several of these instances using strain typing in mice was indistinguishable from BSE in cattle, demonstrating that FSE is indeed BSE in exotic and domestic cats. It seems that this also applies to other ruminants. According to epidemiological data, feed tainted with BSE is the primary cause of BSE infection in this species (EFSA *et al*., 2017).

There have also been reports of spongiform encephalopathy in kudu, eland, nyala, gemsbok, and some exotic cats (Orge *et al*., 2021). It is believed that tainted feed is also connected to this. It has also been proposed that exposure to BSE prior to the implementation of a ban on certain beef offal (SBO) at slaughterhouses in 1989 may have contributed to 23 cases (up to 31 January 1998) of the variant form of CJD (nvCJD) (human disease) in the (UK Department of Health, 2 March 1998) and 1 case in France (Sanchez-Juan *et al*., 2007). Finally, a ban on the consumption of brains, spinal cords, and other tissues that could potentially transmit BSE.

Risk factors

Animals cannot contract BSE from one another, and it is not a contagious illness. In addition, milk and other dairy products do not contain BSE. According to research, feeding livestock MBM obtained from BSE-infected livestock contaminated with BSE prions is the only known risk factor for the development of BSE (Islam *et al*., 2022). Specified risk material refers to specific animal tissues that are likely to contain and consequently spread BSE prions (Shui *et al*., 2023). The WOAH Terrestrial Animal Health Code lists the brain, spinal cord, eyes, spine, tonsils, skull, and distal ileum as examples of these tissues (WOAH, 2008). BSE prions are not entirely eliminated by processing methods and are resistant to common inactivation techniques like heat and disinfectants (Giles *et al*., 2008).

Public health importance

Strong evidence linking BSE to human transmission and a variant type of CJD has brought the disease to the attention of many countries. British researchers suspected that the cases might reflect the advent of a new form of CJD stemming from human-to-human BSE transmission because of the relatively young age of the victims and their clinicopathological uniformity (Ritchie *et al*., 2021). Approximately 9 years after BSE was discovered in the UK, the appearance of this variant form of CJD (vCJD) was reported in 1996 (Zou and Gambetti, 2009). The causative link between vCJD and BSE is further supported by the lack of similar instances in other nations with comparable monitoring systems, the fact that it still occurs almost exclusively in the UK, and more laboratory research studies.

Human cases of vCJD are increasing as a result of eating meat tainted with central nervous system tissue from diseased cattle (Maheshwari *et al*., 2015). Four incidences of human-to-human transmission of vCJD through blood or plasma transfusion have been reported in the UK, despite the fact that the majority of cases are caused by the ingestion of prion-tainted beef (McManus *et al*., 2022). A retrospective study of tonsil and appendix specimens has led to estimates that up to 1 in 4,000 people exposed during the UK outbreak may have been asymptomatic carriers of vCJD, raising concerns about similar transmission (Gill *et al*., 2020; Ironside *et al*., 2000). Nonetheless, infectious agents are present in nearly every tissue in the body, including the blood, despite being mostly concentrated in nerve tissue (Brown, 2001). Before regulations on high-risk offal were introduced in 1989, between 460,000 and 482,000 BSE-infected animals had entered the human food chain (Supervie and Costagliola, 2006).

In the United Kingdom, the first 10 cases of vCJD were reported in April 1996 (Diack *et al*., 2014). As of November 1, 2004, there have been 151 recorded instances of vCJD in the UK as of November 1, 2004 (Ritchie *et al*., 2021). Furthermore, eight cases of vCJD from France and one case from Italy have been detected, along with three cases (one from each of Canada, Ireland, and the United States) among individuals who may have been exposed to BSE in the United Kingdom as a result of their prior residency there. There have been 227 recorded cases of vCJD as of December 2012 (Watson *et al*., 2021). Most cases (176) occurred in the UK.

Economic impact

The global beef sector has been severely damaged by the BSE outbreak. Not only are BSE-affected nations unable to export live ruminants, beef, or beef products, but they also incur financial losses as a result of having to kill livestock that is either afflicted or thought to be infected (Onodera and Kim, 2006). Before the discovery of a potential connection between vCJD and BSE in 1995, the UK exported 77,000 metric tonnes of beef and veal to other countries (Beisel and Morens, 2004). In the month following the 1996 announcement, household consumption of beef had decreased by 26% from the previous year's level, while domestic sales of beef products in the United Kingdom had declined by 40% (Alarcon *et al*., 2023). The total economic damage caused by BSE to the UK in the first year of the crisis (1996) was estimated to be between £740 million and £980 million (Nura and Lelisa, 2018). It is anticipated that the UK will export less than 2000 metric tonnes in 2000 because exports will probably stop as more BSE cases are reported (Alarcon *et al*., 2023).

The European Union outlawed the use of substances derived from cows in nonfood goods in 1996. Processed beef by-products, including collagen, elastin, gelatin, and derivatives of beef fat, are used in many of these goods. Historically, byproducts from cows' hearts, kidneys, spleens, lungs, and brains have been used as food supplements and medications (Latoch *et al*., 2024). More than 800 medications are on the market that may pose a risk of vCJD (Ponte, 2006). Oral polio

vaccination had to be discontinued in the UK in the fall of 2000 due to the discovery that it possibly contained contaminated serum (Sanchez-Juan *et al*., 2007). The food business has experienced losses as a result of BSE. In Europe, restaurants are cutting back on their beef offerings or completely eliminating them. The demand for European meat distributors, who frequently supply restaurants, has decreased by up to 40%. Almost every aspect of the European food business has been affected by BSE (Meijer *et al*., 2023).

As BSE spread outside Europe to Japan and, in mid-2003, to Canada, USDA enhanced its surveillance efforts and increased funding for BSE-related research. Regulatory efforts to counter the disease were further strengthened when, on December 23, 2003, a dairy cow in Washington State tested positive for BSE. Within days of the Washington state BSE announcement, 53 countries, including major markets, such as Japan, Mexico, South Korea, and Canada, banned imports of U.S. cattle and beef products. The potential impacts of additional BSE measures regarding the ban on animal feed were estimated to have associated costs of $2.16 per head for fed slaughter and $6.77 per head for non-fed slaughter. Additionally, it was estimated that a complete ban on feeding ruminant-derived proteins would cost $14.01 per fed animal and $12.35 per non-fed animal, in addition to adding $4.50 per head to feed costs for a fed animal (Kansas Department of Agriculture, 2005).

In 2003, U.S. beef exports totaled $3.95 billion, accounting for 9.6% of U.S. commercial beef production. The import bans caused U.S. beef exports to plummet, and although some important markets, including Mexico and Canada, reopened during 2004, export quantities for the year declined by 82% below 2003's level (Kansas Department of Agriculture, 2005). A market model that incorporated assumptions about the elasticity of demand for beef and offal to estimate the price impact of additional supplies on the market estimated that the total U.S. beef industry losses arising from the loss of beef and offal exports during 2004 ranged from $3.2 billion to $4.7 billion (Kansas Department of Agriculture, 2005).

Control

There is no treatment for BSE. In most cases, suspected animals are put to death so they can be tested. When a veterinarian comes across or suspects BSE, reports on the illness are usually made in accordance with local or national protocols (Saegerman *et al*., 2004). Most countries require reports on this condition. In the United States, notification of state or federal veterinary authorities is required immediately (Charatan, 2001).

Some nations utilize tests conducted at slaughterhouses to identify BSE cases in cattle and occasionally in sheep and goats. Tests on small ruminants and healthy cattle meant for human consumption are often conducted on animals older than a particular age. Japan tested all cows, regardless of age (Onodera and Kim, 2006). High-risk animals usually have stricter testing criteria (such as cattle that have neurological indications or are unable to move) (EFSA *et al*., 2018). Only high-risk animals are tested in certain countries. Nations that formerly tested most or all cattle have lowered their testing criteria as the prevalence of BSE has decreased (Olech, 2023).

Following the identification of diseased animals, the afflicted herd is typically placed under quarantine while the infection's cause is investigated (Simon *et al*., 2008). Groups of animals that are infected (such as those that were born or raised in the same herd during their first year of life) are frequently tested and put to death because they are most likely to have shared feed during the peak of their vulnerability (Kumagai *et al*., 2019). These animals may also be euthanized because the progeny of affected cattle have an elevated risk of BSE.

Preventing BSE can be achieved by avoiding feeding vulnerable species with ruminant tissues that might carry prions (EFSA *et al*., 2017). Because prions cannot be completely inactivated by cooking or processing, complete avoidance is usually required (Lee, 2023). Nowadays, the use of ruminant or mammalian proteins in animal feed is prohibited in many nations, with the exception of specific foods like milk and blood (Ferreira *et al*., 2019). The specific types of prohibited and banned sources of protein differ among nations. In several nations, fertilizer and other types of animal feed are also prohibited. By taking these last measures, it may be possible to avoid cross-contamination and unintentional exposure of cattle to BSE prions (Kumagai *et al*., 2019). Feed restrictions have the potential to curb the spread of the BSE epidemic, but because the illness has a protracted incubation period, there may be a delay in the number of cases. Moreover, the importation of live cattle and specific ruminant proteins from impacted nations may be prohibited under trade agreements (Onodera and Kim, 2006).

Countries that meet specific criteria (e.g., feed bans, laboratory support, and BSE awareness programs for people working with livestock) and have surveillance and traceability programmes that comply with WOAH standards are recognized as being at "negligible risk" or "managed risk" for BSE (WOAH, 2008). Countries classified as controlled risk have had more recent cases of BSE, whereas countries under negligible risk have not reported any cases of classical BSE in local animals or contaminated animals born more than 11 years ago (EFSA *et al*., 2017). "Undetermined risk" refers to nations that do not fit the criteria for insignificant or controlled risk.

Most countries with cases of BSE are implementing certain stringent measures, such as bans on live animals (especially cattle), meat products, and some animal feedstuffs, disease surveillance programmes, restrictions on feeding some suspected prion-infected animal tissues to ruminant animals, and restrictions

on blood donations from individuals who previously resided in BSE-affected countries, in a way to drastically curtail/eliminate the spread of BSE and its risk materials from the food chain (Boujon *et al*., 2016; Amin *et al*., 2023). For example, Brazil, one of the world's top exporters of beef, especially to China, has already announced a reduction in beef shipment to China due to concerns arising from the spread of BSE (Global Times, 2023).

Conclusion

A transmissible neurological disease known as BSE affects cattle and is caused by misfolded proteins. The main route of BSE transmission among cattle is through the ingestion of infectious material found in MBM made from diseased animals. This illness has an influence on the economy and public health. The main route of contracting the virus is through eating beef contaminated with tissue from diseased cattle's central nervous system. There is no known cure for BSE. Reared cattle tissues that may contain prions should not be fed to vulnerable species to prevent BSE.

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Conflict of interest

The authors declare no conflict of interest.

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Author's contributions

TDL, ARK, BWKW, and SW drafted the manuscript. ZAB, DAAK, WW, and IBM revised and edited the manuscript. KAF, RZA, EFL, TH, and RD participated in the preparation and critical checking of the manuscript. IF, SU, SM, RR, and MKJK edited the references. All authors have read and approved the final manuscript.

Data availability

All references are open-access, so data can be obtained from the online literature.

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