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MATHEMATICAL MODELS FOR ESTIMATING THE RISKS OF BOVINE SPONGIFORM ENCEPHALOPATHY (BSE)

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When the bovine spongiform encephalopathy (BSE) epidemic first emerged in the United Kingdom in the mid 1980s, the etiology of animal prion diseases was largely unknown. Risk management efforts to control the disease were also subject to uncertainties regarding the extent of BSE infections and future course of the epidemic. As understanding of BSE increased, mathematical models were developed to estimate risk of BSE infection and to predict reductions in risk in response to BSE control measures. Risk models of BSE-transmission dynamics determined disease persistence in cattle herds and relative infectivity of cattle prior to onset of clinical disease. These BSE models helped in understanding key epidemiological features of BSE transmission and dynamics, such as incubation period distribution and age-dependent infection susceptibility to infection with the BSE agent. This review summarizes different mathematical models and methods that have been used to estimate risk of BSE, and discusses how such risk projection models have informed risk assessment and management of BSE. This review also provides some general insights on how mathematical models of the type discussed here may be used to estimate risks of emerging zoonotic diseases when biological data on transmission of the etiological agent are limited.

Transmissible spongiform encephalopathies (TSE) are a group of animal and human neurodegenerative disorders that are induced by abnormal infective proteins called prions. Infective prions (PrPSc) are misfolded forms of the normal prion protein (PrP) that are expressed in different tissues, particularly the central nervous system (CNS). Bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, was first detected in the United Kingdom in the mid 1980s, and has now been reported in globally (World Organization for Animal Health–OIE, 2013). The disease, spread by contaminated supplementary feed, has been largely brought under control after implementation of feed bans and other preventive measures.

The oldest known TSE is scrapie in sheep, which has been recognized in Europe since the mid-18th century. Other animal TSE include chronic wasting disease (CWD) in deer and elk populations in the United States and Canada, transmissible mink encephalopathy (TME) of mink, and other sporadic cases in domestic cats and zoo animals (Vandevelde, Zurbriggen, and Fatzer, 1992; Williams and Miller, 2003). A rare

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occurrence of TSE in avian species was reported in a flock of ostriches in Germany (Sigurdson and Miller, 2003). The origins of TSE in cats and zoo animals have been linked to BSE; however, the causes of CWD and TME remain unknown. An important form of human TSE diseases, the new variant Creutzfeldt–Jackob disease (vCJD), makes prion diseases zoonotic diseases.

The origin of the first case of BSE remains disputed. The most widely believed and plausible hypothesis is that BSE resulted when contaminated meat and bone meal (MBM) prepared from scrape-infected sheep was given to cattle as supplementary feed (Narang, 1987). Another hypothesis on the origin of BSE suggests that sporadic BSE infections appeared in a small number of cattle that were rendered into MBM (Narang, 2001). The most common form of transmissible encephalopathy in humans occurs sporadically at a low incidence in elderly individuals. Similarly, the kuru epidemic in New Guinea is thought to have resulted from a sporadic case of CJD that appeared in the tribe around 1900, such that an infective prion agent was transmitted to other members of the tribe through the ritual of funeral cannibalism (Mathews, Glasse, and Lindenbaum, 1968). Recent identification of BSE cases associated with gene mutation (Richt and Hall, 2008) supports this hypothesis.

Epidemiological evidence supports the "feed-origin" hypothesis of BSE. Careful examination of the UK BSE epidemic during the 1980s reveals that significant exposure to a scrapie-like agent most likely occurred around 1980 or 1981 (Bradley, 1991; Smith, 2003). This exposure coincided with changes in MBM rendering practices (Taylor and Woodgate, 2003), specifically the cessation of hydrocarbon solvent extraction of fat from meat and bone meal. This change may have allowed the BSE agent to contaminate the feed protein supplement and infect cattle (Nathanson, Wilesmith, and Griot, 1997; Wilesmith, Ryan, and Atkinson, 1991). The early and rapid spread of the disease was augmented by the recycling of infected bovine tissue into MBM before recognition of BSE as an epidemic. The decline in the clinical cases in the United Kingdom after the use of MBM in ruminant was banned further supports this hypothesis (Brown et al., 2001; Nathanson, Wilesmith, and Griot, 1997; Smith and Bradley, 2003; Taylor and Woodgate, 1997). Accumulation of extensive epidemiological data implicated MBM as playing the dominant role in propagating BSE disease (Groschup, 1999; Narang, 1996; Taylor and Woodgate, 2003; Wilesmith et al., 1988; Wilesmith, Ryan, and Hueston, 1992).

The outbreak of BSE in the United Kingdom and several European countries, and subsequently worldwide, produced enormous economic losses and severe psychosocial and public health impacts (Baker and Ridley, 1996; Ridley and Baker, 1999). Concerns over the magnitude of the epidemic prompted the enactment of trade policies and regulations that initiated changes in animal agricultural industries globally (Bradley and Liberski, 2004; Kimball and Taneda, 2004; Wales, Harvey, and Warde, 2006; Walton, 2000).

This review provides in-depth discussion of mathematical models that have been used to predict important parameters affecting risk of BSE transmission. These models are based on the demography of cattle herds and occurrence of clinical BSE in the herd, as well as results from animal studies on prion growth in tissues and disease pathogenesis. These models are based on the fact that consumption of prion-contaminated MBM is the main route of BSE transmission, while transmission from affected dams to offspring (maternal transmission) and direct, animal-to-animal (horizontal transmission) are presumed to be minor transmission routes (Ferguson et al., 1997; Wilesmith et al., 1997).

QUANTITATIVE RISK MODELING

One of the most prominent features of prion diseases is the long and variable incubation period. The outbreaks of such disease are typically observed through the occurrence of a small number of reported clinical cases representing a fairly weak and delayed signal of a potentially impending epidemic.

A major challenge in the face of this uncertainty is the prediction of the future course of the epidemic. With zoonotic diseases such as BSE, it is also necessary to assess the extent and degree of human exposure to the BSE agent, raising uncertainty in the prediction of human health risk. Adding to the difficulty in characterizing the outbreaks is the possibility that effectiveness and suitability of disease control measures may not become apparent until several years after an epidemic has begun after control measures have been implemented. Risk modeling therefore becomes an essential tool in assessing the risks of prion diseases, and in evaluating the effectiveness of risk management and intervention intended to control such diseases.

Although there are many possible objectives for constructing risk models for BSE, the focus here is on two conceptually different motivations for such models, broadly labeled as data assimilation/risk estimation and predictive modeling. Data assimilation and risk estimation address the need to compile and make sense of noisy and uncertain data. Quantitative models provide estimates of the extent of infection in the population of interest based upon potentially weak signals from case observations and surveillance data and uncertain epidemiological and etiological knowledge. Perhaps, more importantly, such models attempt to identify and report uncertainties in a coherent and consistent manner. Models that estimate BSE infection rates retrospectively are the prime example of such data assimilation. Predictive modeling offers means of projecting the evolution of disease, and the impact of different disease control interventions based on disease-transmission dynamics. The modeler may provide a clearer picture of the dependence of outcomes (level of infectivity) on important risk factors (like consumption of MBM) and disease control variables, and in some cases may address questions regarding optimal allocation of resources to reduce risk of infection. An examples of this analyses are by Cohen et al. (2003), who evaluated the effect of hypothetical BSE exposure through importation of cattle infected with the BSE agent, and by Schwermer et al. (2006), who developed expressions for the basic reproduction number (usually referred to as R_0) in terms of the disease control measures.

PURPOSE AND STRUCTURE OF THIS REVIEW

Understanding of BSE involves collecting information from a broad spectrum of disciplines, ranging from molecular biology and protein science to epidemiology and veterinary medicine. This complex web of knowledge, which is subject to a number of uncertainties, needs to be reduced in an intelligent and coherent manner for presentation to a varied audience of scientists contributing to BSE risk assessment, regulatory officers responsible for risk management, and the interested public. The risk modeler plays a critical role in this knowledge synthesis process.

Although data summarizing the state of prion disease science and risk management are available (Crozet and Lehmann, 2007), few investigations focused in particular on mathematical models for prion disease risks. The purpose of this review is twofold: First is to provide an overview of different modeling approaches that have been used to estimate parameters of prion disease risk and how risk models data contribute to BSE risk management. As an example, estimates of the trends of BSE infection during the epidemic in the United Kingdom and other countries helped in evaluating the effectiveness of control measures—especially those related to feed bans—and provided insight into implementing more efficient and comprehensive measures to mitigate health and economic impact of the disease. Second is provide some general insights for risk modelers and veterinary scientists on how to estimate the risks of emerging zoonotic diseases by mathematical representation of disease indices. This modeling approach is particularly useful when biological data on pathogenesis of etiological agent are lacking.

The following sections describe different types of risk models that have been used to estimate the risk of BSE. The mathematical basis

of each model is briefly presented along with the most integrated quantitative indicators of risks derived from these models. Estimation of BSE infection rates in countries that have a moderate to high number of BSE cases was predominantly conducted using back-calculation models that are used to estimate the number of infections retrospectively and future infection rates in the near future. The back-calculation model requires extensive data on cattle demography, detailed records of cases by birth date, age at diagnosis, and region of diagnosis. Another type of risk model is needed for countries with low case numbers or even countries without cases. The most prominent model of this type is the BSurvE, which uses demographic information with respect to national cattle population and BSE surveillance data of a given country to determine the true prevalence of BSE infection in a standing cattle population. The two main components of BSE risk models reviewed in this article are summarized in Table 1.

ESTIMATION OF THE EXTENT OF BSE INFECTION

The incubation period of BSE may be similar to, or even exceed, the life span of the animal (Arnold et al., 2007). Therefore, a substantial number of infected animals might die of other causes (including slaughter) before clinical onset. Consequently, the number of reported clinical cases of BSE represents a minor fraction of the actual number of animals carrying the infection. Allowance for survival patterns including deaths due to causes other than BSE (competing risks) is therefore a critical factor in the analysis of BSE incidence data. Indeed, mathematical modeling adjusts for competing risks and takes into consideration the predicted incubation period such that past and current patterns of disease onset are employed to construct the past pattern of infection incidence rates (Anderson et al., 1996; Donnelly, Ferguson, Wilesmith, et al., 1997; Ferguson et al., 1997, 1999; Supervie and Costagliola, 2004).

Another factor that contributes to underestimating the true prevalence of BSE is underreporting. This is a key parameter since in many countries the disease was only made notifiable several years after the appearance of the first cases (Bradley, 1998; Bradley and Liberski, 2004; Brown et al., 2001). At the beginning of the epidemic, many countries instituted passive surveillance systems, making it mandatory for farmers and veterinary practitioners to report cases clinically diagnosed with BSE. However, such passive surveillance constituted an ineffective monitoring system since, being a new disease at that time, clinical diagnosis of BSE cases was difficult (Braun et al., 1999; Brown et al., 2001). In addition, the economic and public health impacts of the disease were not recognized until several years later, when BSE became an epidemic, and a link between BSE and vCJD was suspected (Brown et al., 2001; Ricketts, 2004).

Consequently, the reporting rate of BSE clinical cases was low in the early years of the epidemic and increased as awareness of the disease grew. Introduction of active-surveillance systems in several countries in the early 2000s confirmed that underreporting in the early years

TABLE 1. The Two Major Components of Estimating the Risk of BSE

Indicator of risk	Quantities estimated	Modeling approach	Data requirements	Other model inputs
Estimation of the extent of BSE infection	Past incidence and current prevalence of BSE infection	Back-calculation binomial models	Number of reported cases, incubation period, case reporting rate, survival distribution	Time-dependent risk of infection, age-dependent susceptibility to infection
BSE spread in the cattle population	The basic reproduction number R0	Back-calculation	Infection hazard, cattle age distribution, relative susceptibility of an animal, age at slaughter	ID50, relative infectivity at certain time from the disease onset, transmission coefficient

of the epidemic was appreciable (Heim and Kihm, 2003).

BACK-CALCULATION METHOD

The back-calculation method is one of the approaches to estimate trends in the incidence of infection for diseases with long incubation periods (Becker and Marschner, 1993; Brookmeyer and Gail, 1987; d'Aignaux, Cousens, and Smith, 2003; Deuffic et al., 1999; Karon, Dondero, and Curran, 1988; Marion and Schechter, 1993; Schechter et al., 1992). The method was originally developed to determine the number of HIV infections based on AIDS incidence data (Bacchetti et al., 1993; Brookmeyer and Damiano, 1989; Gail and Brookmeyer, 1988; Hellinger, 1990), and later extended to estimate BSE infection patterns using clinical incidence data (Anderson et al., 1996; Donnelly et al., 2003; Ferguson et al., 1997; Stekel, Nowak, and Southwood, 1996; Supervie and Costagliola, 2004; T. Oraby, M. Al-Zoughool, S. Elsaadany, and D. Krewski, personal communication). The fundamental premise of the back-calculation model is straightforward: Given knowledge of the incubation-period distribution for infected animals, past and future pattern of infection incidence can be reconstructed by determining past and current disease incidence patterns.

The idea of back-calculation is described from a queuing theory point of view as an M/G/∞ queue (Baccelli and Bremaud, 2003). Susceptible individuals get infected as a nonhomogeneous Poisson process incidence rate $\lambda(t)$ and are immediately assigned an incubation period that follows a probability density function f and is independent of the arrival time. The process of becoming a clinical case is a nonhomogeneous Poisson process (Mirasol, 1963) that is given by

$$\nu(t) = \int_0^t t\lambda(s) f(t-s)\, ds \qquad (1)$$

Several key epidemiological parameters affecting disease dynamics and transmission, including age susceptibility, survival rates, and disease-reporting rates, may be also included in the general model shown in Eq. (1). A more specific model that relates these parameters to the number of clinical cases is given by

$$E(C(a,t)) = F(t) \int_0^t E(N(a, t-a+s)) f(a-s)\, S(a|s)\, ds \qquad (2)$$

(Supervie and Costagliola, 2004), where $C(a,t)$ and $N(a,t)$ are random numbers of clinical cases among animals and newly infected animals of age a at time t, respectively. Assuming that the incubation period distribution has a density $f(t)$, $S(a|a')$ represents the probability that an animal will survive to age a, given that it was alive at age a', and $F(t)$ is a time-dependent probability that a given clinical case is actually reported at or by time t.

Evidently, as the number of infected animals is described by a Poisson process, the number of cases, conditional on a Poisson number of infected animals, is also a Poisson process. The unknown time- and age-specific number of infections can be modeled as

$$E(N(a,t)) = \pi(a)\, Q(a,t),$$

where $\pi(a)$, determined from demographic data, is the proportion of animals in the population that are of age a, and $Q(a,t)$ is the infection rate. The parameter $Q(a,t)$ can be factored into the product $Q(a,t) = r(t)g(a)$ of two univariate functions: the time-dependent risk of infection/exposure $r(t)$ and the age-dependent susceptibility distribution $g(a)$ (Donnelly, 2002; Ferguson et al., 1997). The former function reflects changes in the intensity of infection and extent of exposure over time, while the latter describes how susceptibility to infection varies with age.

Parametric or nonparametric functions may be used to represent the time-dependent risk of infection (mainly feed-borne risk profile). While straightforward predictions can be made using

a parametric form of $r(E)$, assumptions must be made about the form of this function in order to predict future feed risk (Ferguson et al., 1997). The latter, nonparametric functions require no prior assumptions to make similar predictions and to describe the temporal course of the epidemic.

Expressing the preceding parameters in terms of the number of BSE clinical cases gives the overall model:

$$E\left(C(a,t)\right) = F(t)\int_0^t \pi(s)\, g(s)\, r(t-a+s)\, f(a-s)\, S(a|s)ds.$$

It should be emphasized that this is a simplified form, which for clarity assumes transmission only through consumption of contaminated feed. Supervie and Costagliola (2007b) incorporated surveillance and detected asymptomatic cases of BSE into the model. The mean number of detected asymptomatic cases is given by

$$E\left(C(a,t)\right) = \int_0^a \int_0^\infty \pi(s)\, g(s)\, r(t-a+s)\, f(a-s+u)\, \psi(u)\, \alpha(a)\, S(a|s)ds\, du$$

Here, $\psi(u)$ is the probability of detecting BSE at time u before the onset of clinical signs using tests, $\alpha(a)$ is the death rate, and the remaining functions are as already described.

Another approach depends on the assumption that the time to infection is independent of the incubation period (Ferguson et al., 1997), implying that the probability density function of the disease-onset time is the convolution of their corresponding probability density functions. In other words,

$$p(t) = \int_0^t \phi(s)\, f(t-s)\, ds, \tag{3}$$

where p, φ, and f are the probability density functions (pdfs) of the onset time, time to infection, and incubation period, respectively. The pdf φ can be written in terms of the hazard function h as

$$\varphi(t) - h(t)\exp\left(\int_0^t h(u)du\right).$$

Again, additional parameters can be incorporated into the general model (Eq. (3)), such as susceptibility, survival, and case underreporting. Adding in both $F(t)$ and $S(a\,|a')$, the probability of a cow becoming a case at time t and age a is given by

$$p(a,t) = F(t)\int_0^a g(s)r(t-a+s)\, exp\left(\int_a^s g(u)r(t-a+u\right)du)\, f(a-s)S(a|s)ds. \tag{4}$$

Here, t falls within a fixed time window $[t_0, t_1]$ and a is in the cow's age spectrum.

Let the birth cohort be given as $c = t-a$ and assume, for simplicity, that the birth rate is homogeneous over time, for simplicity. Thus, the size of the birth cohort c, N_c-Na, is fixed over c. Split the range of ages at disease onset in birth cohort c into subintervals $I_1, I_2, \ldots, I_{k(c)}$. The number of infected animals in birth cohort c out of N with ages falling in $I_1, I_2, \ldots, I_{k(c)}$, denoted by $\left\{X_i(c)\,; i = 1, 2, \ldots, k\right\}$, can be jointly modeled by a multinomial distribution with probabilities $\left\{P_i(c)\,; i = 1, 2, \ldots, k\right\}$ where $P_i(c) = \int_{I_i} p(a, c+a)\, da$ for $i = 1, 2, \ldots, k$. Notice that $X_i(c)$ are independent over c for all i. Maximum likelihood can be used to estimate the different parameters that are incorporated in the model.

A more complex model involving several other factors and other possible routes of

transmission is discussed in detail in Anderson et al. (1996), Donnelly (2002), and Ferguson et al. (1997).

INPUT PARAMETERS OF THE BACK-CALCULATION METHOD

Incubation Period

Epidemiological data and experimental studies provided useful data for estimating the incubation period of BSE. Epidemiological data indicated that the mean incubation period for cattle infected in the field is in the order of 5–5.5 years (Arnold and Wilesmith, 2004; Wilesmith et al., 1988). Arnold et al. (2007) examined the effect of dose attack rate on the incubation period of BSE in cattle exposed orally to four different dose levels of brain homogenate from affected cattle. Data showed mean incubation time between 37 and 72 mo, with mean incubation period decreasing with increasing dose.

Further information regarding the incubation period for BSE may be derived from a mechanistic model of disease pathogenesis that assumes that prion density increases at a certain rate following initial exposure to the BSE agent, with disease onset occurring when the prion density reaches a certain critical level (Ferguson et al., 1997). Under this assumption, it is possible to describe the variability in incubation period within a population as function of variation in initial dose. This approach is further supported by Castilla et al. (2004) using transgenic mice expressing different levels of prion protein genes. In that study, incubation times were inversely related to the level of expression of prion protein genes and the amount of prions in the inoculum. In another model, M. Al-Zoughool et al. (personal communication) described incubation period density function that ranged from 30 to 40 mo depending on the initial dose of the infected material. Alternatively, variations in the incubation period might be attributed to variations in rate of prion growth within animals. However, there are no apparent biological data available to support this hypothesis at this time (Hunter et al., 1994; Masel, Genoud, and Aguzzi, 2005).

Based on the prion density model, it was postulated that the average incubation period in the early years of the UK epidemic was shorter than in later years because animals were exposed to a high infectious dose in the initial phase of the BSE epidemic (Ferguson et al., 1997). The decline in infectious dose as the epidemic progressed was thought to be due to implementation of MBM feed bans in Europe. This hypothesis is further supported by results from serial passage experiments of TSE in rodents (Kimberlin, 1993; Weissmann, 1991), which demonstrated that incubation periods of BSE might change dramatically due to alterations in feed exposure profiles. Further, back-calculation analysis of the French BSE cases taking into account BSE surveillance data in that country showed that the mean age of cases found increased if the force of infection fell in the past (Supervie and Costagliola, 2007b). Evidence indicated that a lengthening of the incubation period (from 5 years to 6.3 years), rather than rise in age at infection, provided most realistic description of the data.

Time-Dependent Risk of Infection

The risk of infection is the first component of the infection rate term in the back-calculation model. The time-dependent risk of infection can be segregated into three transmission routes: indirect transmission via MBM, maternal transmission, and direct horizontal (animal-to-animal transmission). Since studies demonstrated that maternal and horizontal transmission occur at such low rates that they cannot sustain the epidemic (Braun et al., 1998; Donnelly, Ghani et al., 1997), most BSE risk models considered only feed-borne transmission (Anderson et al., 1996; Donnelly, 2002; Donnelly, Ghani et al., 1997; Ferguson et al., 1999).

A wide range of plausible patterns of feed exposure may be postulated from constant exposure levels with age, to a doubling of exposure once animals move into dairy herds at

2 yr of age. Another pattern postulates exposure peaking in the first year of life and decrease slowly thereafter. Analysis of these and other exposure patterns in the context of the UK epidemic revealed a flexible distribution with exposure doubling at 2 yr of age best fitting the observed data. Exposure to infectivity associated with MBM varied over time, depending on feed practices, MBM and import of live cattle, bans and regulations, and recycling of infectivity (Clauss et al., 2006; Morley, Chen, and Rheault, 2003; Sellier, 2003; Yamamoto et al., 2006). It is expected that exposure was greatest at the beginning of the epidemic in the United Kingdom in the early 1980s, and fell in subsequent years after the 1988 ban on ruminant protein in ruminant feed. However, a low level of infection risk remained, largely due to cross-contamination between ruminant feed and feed intended for monogastric species (poultry and pigs) (Nathanson, Wilesmith, and Griot, 1997; Stevenson et al., 2000, 2005). Noncompliance may have also contributed to persistence of infection after the ban (AFFSSA, 2001). The additional reduction in exposure observed in post-1990 birth cohorts may be attributed to the effect of the specified bovine offal (SBO) ban introduced in September 1990, and to the ban on the use of mammalian MBM in all animal feed and fertilizers in 1996. Cases born after the feed ban in the United Kingdom and France were most probably induced by highly infectious animal feed potentially contaminated by tissues from cattle dying at the end of their incubation period (Saunders et al., 2007; Savey et al., 2000).

Feed infectivity is related to several factors, including pattern of MBM use and manufacture conditions (temperature, pressure, time), recycling of BSE-infected carcasses in MBM, regional differences in exposure (indicated by differences in the number of cases), and effectiveness of MBM feed bans (Braun et al., 1999; Hagenaars et al., 2000). In other countries, feed infectivity involves other factors, such as importation of infected material from the United Kingdom (Hornlimann, Guidon, and Griot, 1994; Kamphues et al., 2001), variation in the reprocessing of greaves to produce MBM (Wilesmith, Ryan, and Hueston, 1992), and changes in rendering practices over time (Taylor and Woodgate, 2003). Yamamoto et al. (2006) constructed a simulation model to estimate the potential BSE infectivity to cattle in Japan via MBM derived from one BSE-infected animal at the clinical stage, and compared infection risks associated with exposure to MBM before and after feed restrictions had been put in place. The model revealed that the median total infectivity fed to dairy cattle via MBM derived from one infected animal was approximately 0.49 ID50 (the oral infectious dose for cattle results in 50% infection). This value was reduced by 55% after the addition of MBM to cattle concentrates was restricted in 1996. Changes in the risk of infection following implementation of control measures in a given country followed roughly similar patterns in the United Kingdom, France, and other countries in which BSE was endemic. It is reasonable to assume that a residual risk of infection remained after implementation of a ruminant-to ruminant feed ban due to cross-contamination of feed. Such cross-contamination was an important factor that produced continued BSE infections in most, if not all, BSE-affected countries (Jarrige et al., 2006, 2007; Paul et al., 2007; Savey et al., 2000; Schwermer et al., 2006; Yamamoto et al., 2006). The degree of cross-contamination and rate of noncompliance are critical factors in estimating the risk of infection after various feed bans.

One method of determining the amount of cross-contamination is to estimate the amount of MBM of cattle concentrates contaminated from pig/chicken concentrates based upon experimental trials on the carryover of antibiotics at feed plants (Conference on the Improvement of Animal Feed [CIAF], 1989). Noncompliance is evaluated by analysis of government surveillance data to estimate probabilities for mislabeling and contamination in MBM and feed-production facilities. Mislabeling occurs when a rendering plant or feed manufacturer incorrectly labels prohibited product as non-prohibited. Contamination occurs when MBM or feed not labeled as

containing a prohibited product is tainted with prohibited product.

Import of infectivity from the United Kingdom or any other country with BSE in the form of MBM and live cattle was an important pathway for the spread of BSE infectivity into several countries (Hornlimann, Guidon, and Griot, 1994; Jarrige et al., 2007; Kaaden et al., 1994; Kamphues et al., 2001; Morley, Chen, and Rheault, 2003; Sugiura et al., 2003; Sugiura, 2004; Wahlström et al., 2002; Zentek et al., 2002). In France, importation of MBM increased significantly after it was banned in the United Kingdom, thereby contributing to the rapid rise in number of infected animals in the French cattle herd in the early 1990s (Jarrige et al., 2006; Savey, Belli, and Coudert, 1993; Savey and Baron, 1994; Savey and Moutou, 1996). A reliable source of data on importation of materials that may have been contaminated with the BSE agent is provided by Heim et al. (2006). The sensitive period during which both items were probably most infectious in the United Kingdom was between 1984 and 1990, when BSE infections peaked between 1984 and 1990, while the risk of infection herein was largely negligible outside that period (Schreuder et al., 1997; Sugiura, 2004; Wahlström et al., 2002). Fitting feed-risk profiles in the United Kingdom resulted in a best fit model that estimated the time of maximum risk to be mid 1988 (Ferguson et al., 1997).

Age-Dependent Susceptibility

Age-dependent susceptibility is the second component of the infection-rate term ($Q(a,t)$) in the back-calculation model. The first epidemiological datum on clinical onset by age suggested that calves are at higher risk of infection than adult cattle (Wilesmith et al., 1988; Wilesmith, Ryan, and Hueston, 1992; Anderson et al., 1996). A more recent study (Arnold and Wilesmith, 2004) suggested that susceptibility to infection was highest in the first 6 mo of life. Analyses of the French epidemic indicated that approximately 99% of infections occurred between 6 mo and 1 yr of age (Supervie and Costagliola, 2006, 2007b). Further, experiments with TSE on rodent models suggested decreasing susceptibility with age (Mckinley et al., 1989). In humans, susceptibility of vCJD infection is highest in younger age groups (Boëlle et al., 2003). Since exposure to contaminated feed is the major source of BSE infection, it may be postulated that age dependency in the risk of BSE infection is related to higher feed consumption and thus higher exposures to the BSE agent during the early years of life. However, data on feeding patterns showed that intake of feed rises with age for the first two years of life and that, in most herds, intake was highest for animals over 2 yr of age (Anderson et al., 1996; Donnelly, Ferguson, Wilesmith et al., 1997).

The models assuming maximal susceptibility to infection in the first year of life predict relatively high numbers of total infections, since younger infected animals have a lower probability of survival to the typical age of clinical onset. This low mean age at infection is consistent with empirically observed incubation period distribution (Ferguson et al., 1997).

The assumed age at infection of less than 1 yr also implies that it will take several years (equivalent to the average incubation period) to observe a decrease in the clinical disease incidence following implementation of feed bans and other preventive measures to reduce the risk of infection (Calavas et al., 2007), and might only reduce infection in animals born after the feed ban. Otherwise, if animals of all ages were equally susceptible, then the risk of infection would also be reduced in birth cohorts born before the feed ban.

Reporting Rate

The time-dependent BSE case reporting function used in the back-calculation relies on time-dependent reporting probability. However, in the absence of independent data on reporting rates, it is difficult to fit a time-dependent probability of reporting across the entire epidemic, as the reporting rate is confounded with time-varying risk of infection (Donnelly, 2000; Supervie and Costagliola,

2006). Data from a scrapie survey in the United Kingdom showed that only 13% of scrapie cases were reported (Hoinville et al., 1999, 2000). Several differences between the two diseases make this rate an unreliable estimate of the BSE case-reporting rate. Therefore, an extremely flexible case reporting function for BSE is assigned, whereby temporal changes in these probabilities are estimated for different periods of the epidemic, depending on the surveillance system (passive or active) in place at the time.

Relying on passive surveillance to provide estimates of reporting rates is subject to substantial uncertainty, since it is difficult to estimate the efficiency of the passive surveillance systems for BSE initially deployed (Doherr et al., 2002). The recent development and application of postmortem BSE screening tests (Adkins, Simons, and Arnold, 2012) may be used to estimate the odds of finding a case in different BSE risk categories such as fallen stock and emergency slaughtered cows. These data may also be used retrospectively to measure the number of potential cases that escaped detection through the passive surveillance. Data from BSE testing at the abattoir and screening of healthy cattle data were used to estimate case reporting rates in the United Kingdom (Donnelly, 2002; Ferguson and Donnelly, 2003). The results revealed significant case underreporting. In addition, analysis of data derived from testing of preclinical BSE cases requires adjustment for the proportion of infected animals still alive by the age at which the animal was tested, as well as the sensitivity of the test as a function of the incubation period for BSE.

Although estimation of the reporting rates for BSE clinical cases is difficult, it is reasonable to assume that reporting was low, especially in the early years of the BSE epidemic (Ferguson et al., 1999). For subsequent years, a progressively increasing reporting rate can reasonably be assumed, due to a variety of factors, including increasing awareness of the disease. More complete reporting may be assumed following the introduction of active surveillance.

CATTLE DEMOGRAPHY AND SURVIVAL RATES

Reliable inferences with respect to cattle survival rates requires detailed data on the number and type of cattle herds in the country of interest, the cattle age structure of the herds, and slaughter rates. Unfortunately, for some countries like Canada, these data often have to be pooled from several sources, which usually contain incomplete information. Most of these data are available for dairy cattle, rather than beef cattle. The age distribution of breeding beef cattle gives a mean age approximately 6 mo older than for dairy cattle (Ghani et al., 2002). The age structures and management systems for dairy and beef cattle are quite different, with the prevalence of BSE being higher in dairy cattle (Ducrot et al., 2003; Stevenson et al., 2000). In addition, the number, age, and type of cattle slaughtered need to be analyzed to describe the seasonality of slaughter rates (Donnelly, 2002). However, several countries across Europe recently developed national animal databases which are rich sources of information on cattle demography.

A convenient method of fitting a survival function (for animals older than 1 yr) is to determine the age-specific numbers of cattle alive in two consecutive years and the age-specific numbers of cattle sent to the abattoir and rendered in the same two years. Other parameters that are estimated through analysis of these data include age distribution of cattle, the age-specific death rate, and the age-specific proportion of mortality attributed to slaughter. However, relying on snapshots of the age distribution and slaughter rates of cattle within time intervals may result in either over- or underestimation of the actual survival rates, since slaughter patterns undergo substantial changes in response to BSE risk management interventions. In the United Kingdom, the ban on slaughter of cattle over 30 mo of age resulted in an abrupt end to the slaughter of cows and adult bulls for consumption as food (Donnelly, 2002). Another factor that complicates the characterization of cattle survival

rates is the lack of information on other causes of death, such as death-on-farm, emergency slaughtered, or emergency euthanized. These causes of death may not be accounted for in the analysis of cattle survival, leading to overestimation in the survival rates. Changes in survival distributions generally lead to different estimates of certain parameters, such as the mean incubation period, reporting rate for clinical cases, and, most importantly, the number of infected cattle (Supervie and Costagliola, 2004). In the United Kingdom, the longer the survival time, the smaller is the number of infections needed to produce the reported number of clinical cases.

For countries with little data on cattle demography, data on the number of calves born each year and age category of slaughtered animals may be used to model survival distribution (Donnelly et al., 1999). These limited data usually yield different survival curves than complete demographic data. In addition, changes in a country's national herd size in the period of interest affects estimates of the number of infections over time. It is necessary in some country profiles to compare birth rates, age distributions, and slaughter rates observed in two consecutive years to determine whether or not these demographic parameters are stationary. An alternative approach to characterizing the survival distribution of cattle from data given for a number of birth cohorts is to apply a method used in the United Kingdom, whereby survivorship to age x is calculated as the ratio of number of animals in age class x to $x + 1$ years to reflect the size of the corresponding birth cohort aged 0 to 1 yr; the geometric mean of mortality rates over the different birth cohorts is then used to estimate survivorship function for the period of interest (Donnelly, Ferguson, Ghani, et al., 1997).

PARAMETER ESTIMATION AND UNCERTAINTY IN THE BACK-CALCULATION MODELS

Due to the substantial uncertainties inherent in epidemiological parameters affecting the age- and time-specific infection risk of BSE, flexible functions need to be used to describe the uncertainty in these parameters and then a sensitivity analysis needs to be conducted to select the best model (Supervie and Costagliola, 2004). Two distributions for the incubation period of BSE were explored in the analysis of the British and the French BSE epidemics: the gamma distribution, and a distribution based on a mechanistic model of disease pathogenesis (Ferguson et al., 1997; Supervie and Costagliola, 2006). Since the gamma distribution does not reproduce the observed lag of 2 yr from infection to disease onset, a time-delay variable needs to be introduced into the functional form for the source distribution. By varying the parameters of this distribution, a range for mean and variance of incubation period is obtained. Supervie and Costagliola (2006) noted that a gamma distribution with an average incubation period of about 5.6 yr provided a good fit to the available data.

The mechanistic model of the incubation period assumes that prion density grows exponentially at a certain rate depending upon initial dose. The onset of clinical symptoms occurs when prion density reaches a certain critical level. This distribution describes the observed 2-yr time delay from initial infection to appearance of clinical signs in the British epidemic (Arnold et al., 2007). Different values of prion growth rate and initial dose yielded different values of mean and variance of the incubation period.

Other parameters affecting BSE risk, such as age-dependent susceptibility to infection, time-dependent risk of infection/exposure, survival distributions, and probability of reporting, are not directly estimable but may be determined by using the expectation–maximization (EM) algorithm. The EM algorithm is a technique for obtaining maximal likelihood estimates in situations when only incomplete data are available but where it is possible to define a set of complete data for which straightforward maximal likelihood estimates exist (Dempster, Laird, and Rubin, 1977; Dempster, Selwyn, and Patel, 1978). Since these maximal likelihood estimates may be unstable, a smoothing

step may be needed (Silverman et al., 1990). The smoothing step consists of calculating a weighted average over the components of one or more of the estimates (Becker and Marschner, 1993).

Sensitivity analysis of time-dependent risk of infection/exposure is particularly intricate, since limited biological or epidemiological data are available regarding this parameter. Ferguson et al. (1997) examined a wide range of functional forms for age-dependent exposure; some of the forms assumed constant exposure with age, while others presumed exposure doubles as animals move into the dairy herd after 2 yr of age. BSE risk models suggested maximal susceptibility at 1 yr of age and decreasing thereafter (Anderson et al., 1996; Ferguson et al., 1997; Supervie and Costagliola, 2006).

Given the lack of information on reporting rates, quantifying underreporting of BSE is difficult. One approach would be to select a reporting profile that takes into account changes in disease surveillance following implementation of first passive and then active surveillance systems. The reporting profile assumes zero reporting before the disease was made notifiable and a time-dependent BSE case reporting function for subsequent years (Ferguson et al., 1997). The logistic reporting function depends on two parameters: the shape parameter β, and, a parameter, θ, determining the reporting probability after introduction of passive surveillance (Supervie and Costagliola, 2007a). By varying β, a wide range of reporting pattern may be explored, from constant reporting throughout the epidemic ($\beta - 0$) to low reporting in the early stages of the epidemic and an abrupt increase in the recent past ($\beta - 1$). The parameter θ determines the reporting probability. By varying this parameter, a range of reporting rates that best fits the data for the BSE epidemic in a certain period in a given country is selected.

After flexible functions have been attributed to the parameters already described and appropriate sensitivity analyses have been conducted, the model that best fits the data may be selected, based on Akaike's information criterion (AIC) (Anderson, Burnham, and White, 1998). The AIC is given by

$$AIC\,(model)—2\log L + 2p,$$

where L is the likelihood of the model and p is the number of estimated parameters. The AIC takes into account both statistical goodness of fit and the number of parameters that have to be estimated to achieve this particular degree of fit by imposing a penalty for increasing the number of parameters.

APPLICATIONS OF THE BACK-CALCULATION METHOD

Back-calculation models have been applied to determine the magnitude of BSE epidemics in several countries across Europe (Ducrot et al., 2010), including the United Kingdom (Anderson et al., 1996; Ferguson et al., 1997, 1998), France (Donnelly, 2000, 2002; Supervie and Costagliola, 2004, 2006, 2007a), Portugal (Donnelly et al., 1999), and Canada (M. Al-Zoughool, personal communication). Because of the causative link between BSE and vCJD, estimates of the number of animals that were infected with BSE agent throughout the epidemic are of considerable public health relevance. Those estimates may be utilized to evaluate the extent of human exposure to infected beef and beef products by determining the number of animals that entered human food chain and the distribution of such numbers according to the stage of the incubation period associated with maximal human infectivity (Ferguson and Donnelly, 2003; Ghani et al., 1998; Supervie and Costagliola, 2006).

Analysis of clinical BSE data by back-calculation modeling showed that the majority of infected animals were not detected because they were slaughtered or died before clinical onset. It has been estimated that some 900,000 cattle were infected over the course of the epidemic in Great Britain (Anderson et al., 1996; Ferguson et al., 1997), with an additional 10,000 infected animals in Northern Ireland (Ferguson et al., 1998). Estimates of the number of infected animals helped to assess the impact and efficiency of feed regulations and other policies introduced to control the spread

of BSE and protect human health. Predictions in the United Kingdom suggested that the 1988 ruminant-to-ruminant feed ban and the 1990 ban on the use of specified bovine offal (tissues that harbor the BSE agent) in animal feed exerted a significant impact on risk of infection: the Number of infected animals fell significantly in the early 1990s, subsequently declining to negligible levels after the complete feed ban in 1996 (Ducrot et al., 2010).

Another example demonstrating the impact of BSE control measures is illustrated in Figures 1 and 2. The implementation of a passive surveillance system in France in 1991 led to detection of the first few cases of BSE, following which the number of detected cases continued to rise (Figure 1). This surveillance program was apparently somewhat inefficient, since there was a notable elevation in the number of detected cases after the program was replaced by the systematic screening system implemented in 2000, under which every slaughtered cow older than 30 mo was tested for BSE. Back-calculation models estimated the extent of under-reporting of cases under the passive surveillance program. The time lag between implementation of the complete feed ban in 2001 and decline in the rate of occurrence of clinical cases corresponds roughly to the incubation period of the disease (Figure 1). Ducrot et al. (2010) found that a ban on feeding of meat and bone meal (MBM) to cattle

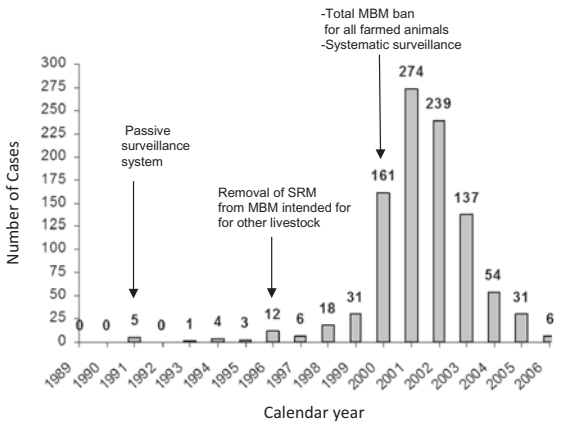

FIGURE 1. Number of reported BSE cases in France, 1989–2006. The major control measures taken at different times are indicated by vertical arrows.

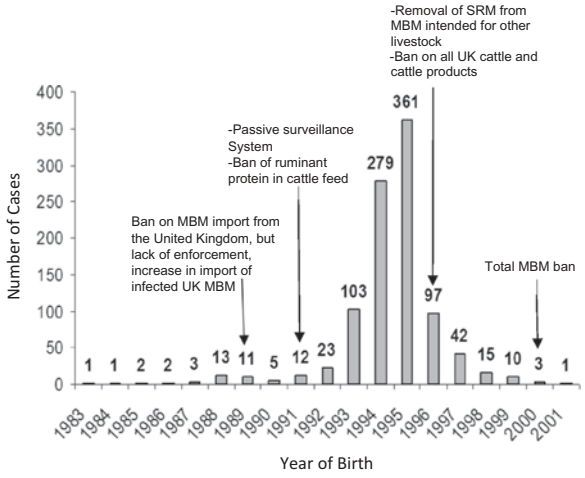

FIGURE 2. Time course of BSE cases (by year of birth) detected in France until 2001 and major control measures implemented in the same period.

alone was not sufficient to eliminate BSE in European countries. The fading out of the epidemic started shortly after the complementary measures targeted at controlling the risk in MBM.

Looking at the epidemic in terms of year of birth provides another perspective on the effectiveness of the BSE control measures implemented in France (Figure 2). As shown in Figure 2, BSE infection rate increased steadily in France in the early 1990s and started to decline in 1996. This pattern is consistent with the timing of the introduction of BSE infectivity from the United Kingdom in the form of MBM and live cattle, and removal of infectivity after excluding specified bovine offal (SBO) from MBM used as feed for other species. The removal of SBO from feed intended for other species prevented cross-contamination, and significantly reduced the entry of the infectious agent into cattle feed. However, it required some time for the infectious agent to completely disappear from the feed system, with infection persisting for several years after the ban in 1996 that mandated the removal of SBO from MBM intended for other livestock.

Another important finding of the back-calculation analysis is the short-term prediction of future cases of BSE. Predictions of

the numbers of cases in the United Kingdom through to 2000 using back-calculation models (Anderson et al., 1996; Ferguson et al., 1997) were similar to the actual numbers subsequently reported (Ghani et al., 2002), indicating the reliability of those models in making future predictions. Table 2 shows the results of different models used to determine the size of the epidemics in the United Kingdom, France, Portugal, Northern Ireland, and Japan. It is clear from the numbers presented in the table how mathematical models revealed that actual extents of epidemics in those countries were in fact multiples of what was really discovered.

BSurvE MODEL

The BSurvE model was developed to estimate prevalence of BSE status in a given country. BSurvE is a probabilistic model in which cattle are born, become infected early in life with a certain probability, and then are slaughtered and tested for BSE at a later age. The model is based on demographics of cattle herd and BSE surveillance data with assumptions about how well the surveillance system works (European Food Safety Authority [EFSA], 2004). Scientific knowledge regarding etiology of BSE, such as the incubation period for the disease, is also considered.

TABLE 2. Major Findings of BSE Risk Models in Different Countries

Country	Models Used	Reported number of BSE cases (time period[1])	Estimated number of BSE infections (time period[2,3])	Ratio of estimated BSE infections/ number of reported	Estimated number of infected animals slaughtered for human consumption
Great Britain	Back-calculation (Ferguson et al., 1997, Anderson et al., 1996)	168,688 (1988–1996)	900,000 to 1, 130,3000 (1974–1996)	6.0	460,000 to 482,000 were slaughtered before the specified bovine offal ban in 1989
	Back-calculation (Donnelly et al., 1997)	191,042 (1988–2005) 191,209 total	1.05 to 3.5 million (–1999)	11.9	0.87 to 2.9 million infected cases
France	Back-calculation (Supervie and Costagliola 2004)	103 (1991–2000)	301,200 (July 1980–June 1997)	2924	47,300 slaughtered before the SBO ban in 1996
	Back-calculation: Updated analyses (Supervie and Costagliola, 2006)	31 (1987–1997)	44,800 (July 1987–June 1997)	1445	2078–5980 were slaughtered before 1996 and 1500 between July 1996 and June 2004
	Back-calculation: Updated analyses that included clinical surveillance (Donelly et al., 2000)	939 (July 1994-June 2004)	8000 (July 1994–June 2001)	8.5	
Portugal	Back-calculation (Donnelly et al., 1999)	94 (1989–1996)	9 per 1000		
Northern Island	Back-calculation (Ferguson et al., 1998)	1766 (1988–1998)	11,300–12,300 (prior to 1997)	6.7	9500 to 10,300
Japan	Sugiura and Murray model (Sugiura and Murray, 2007)	11 (1992–2004)	225 (1992–2004) if infectivity was introduced in 1995	20.5	116
			905 if infectivity was introduced in 1992	82.27	694

[1]Data were reported in the cited reference. If the data for the specific period was not available they were obtained from the World Organisation for Animal Health–OIE website for the indicated period.

[2]The upper limit of the time period was chosen to be about 3 yr less than the upper limit of the time period of reported clinical cases (in the previous column) since infected cases take a minimum of 3 yr to become detectable.

[3]Although time periods of reported clinical cases and infected cases do not match, the ratio roughly estimates the degree of under ascertainment of cases in a certain time period. When a range of values is given, the midpoint of the range is used in calculating the ratio.

The model provides a means of evaluating surveillance programs in different countries according to criterion set out by the World Organization for Animal Health–OIE (2013). According to the World Organization for Animal Health–OIE standards, animals leaving the national herd are categorized into one of four surveillance streams (Powell, Scott, and Ebel, 2008): healthy slaughter (healthy cattle slaughtered for human consumption), fallen stock (animals that died on farm), casualty slaughter (animals that are injured or abnormal, but eligible for slaughter under special restrictions), and clinical suspects (animals showing neurological signs that may be due to BSE). Because the selection of animals for BSE testing is not random, relying on surveillance testing to obtain estimates of BSE prevalence is unreliable. In addition, each of testing streams just listed is biased by the age distribution of the cattle herd, misclassification of animals into the four streams, and testing capability of the country. Older animals are more likely to be identified as BSE positive and are more likely to leave the herd as fallen stock or casualty slaughter. In addition, screening tests are unable to detect infections with the BSE agent until late in the incubation period.

The BSurvE model converts the test results in each of the four testing streams into a probability of BSE infection in animals that are still on farm, thereby providing an estimate the prevalence of BSE in the standing cattle population (Prattley, Cannon, et al., 2007; Prattley, Morris, et al., 2007). The model uses four sets of data: age distribution of culled animals; incubation period of BSE; conditional age-stream exit probabilities for clinically infected animals; and conditional age-stream exit probabilities for other animals (Prattley, Cannon, et al., 2007). The BSE infection prevalence estimate in a given cohort is found by equating the observed number of animals testing positive for BSE with the expected number of positives. The same calculation is applied for each cohort in the national cattle herd for which sufficient data are available.

Because of the difficulty in detecting BSE early in its long incubation period, a major limitation of the BSurvE model is its inability to provide precise estimates of BSE prevalence in younger cohorts, while the probability of detecting BSE in the last 3 mo of the incubation period is $>.99$, and this probability is $<.01$ during the first 12 mo (EFSA, 2007). Consequently, the model does not provide an indication of recent changes in the evolution of an epidemic. Another complication of this model is requirement for extensive data inputs, including age distribution of the standing population, stratified by beef and dairy cattle, and age distribution of infected cattle showing clinical signs at the time of exit in each stream (healthy slaughter, fallen stock, casualty slaughter, or clinical suspect). These inputs may not be readily available in some countries (EFSA, 2004). Other inputs, such as country-specific exit probabilities for infected and uninfected animals, are subjective and may differ for high- versus low-risk countries. Probabilities for infected animals would be more easily obtained for a high-prevalence country than for a low-prevalence country (Prattley, Cannon et al., 2007).

Despite these limitations, the BSurvE model has been used to assess national BSE surveillance programs, and to improve surveillance strategies in both BSE-affected and nonaffected countries. In this application, a point value for each test in the four surveillance streams may be calculated. The point value represents the relative likelihood of detecting BSE in an animal of a certain age leaving a particular stream, thereby providing an indicator of the merit of testing such an animal (Prattley, Cannon et al., 2007). Prattley, Cannon, et al. (2007) examined both types of analyses (BSE prevalence estimation and evaluation of surveillance testing) in a hypothetical example country with typical European input data. Model validation was conducted by comparing predictions provided by the BSurvE model with those from other validated models (usually the back-calculation model) using the same data set. Model robustness to the main assumptions was assessed by conducting a series of sensitivity analyses. The main assumptions underlying the BSurvE model are the unchanging size and age structure of the national herd and the binomial distribution

for the number of infected animals detected in each surveillance stream. Application of the BSurvE model to the Netherlands BSE surveillance data revealed difficulties in drawing clear distinctions in prevalence among birth cohorts (Heres, Elbers, and Van Zijderveld, 2007).

HARVARD SIMULATION MODEL

The Harvard Center for Risk Analysis developed a probabilistic simulation model for the U.S. Department of Agriculture (USDA) to evaluate the impact of allowing additional cattle imports from countries designated as BSE minimal-risk regions (Cohen et al., 2003). The simulation model (1) predicts the likelihood that BSE-infected cattle will be imported into the United States given regulations and other preventive measures in place at the time of analysis, (2) determines the extent to which disease might spread among U.S. cattle, and (3) characterizes the resulting impacts on humans (in terms of exposure to cattle ID50). The model also evaluates the impact of other sources of infectivity to the U.S. cattle herd, such as spontaneous BSE; the import of 1 to 500 BSE-infected cattle; the import of contaminated feed; domestic scrapie; CWD; TSE in domestic mink, pigs, and chickens; and recycled food waste.

To account for the possibility that cattle feed containing the BSE agent was introduced to the country, Cohen et al. (2003) evaluated a scenario in which the contaminated feed came from five infected animals, each of which is at an advanced but preclinical stage of BSE (an average of 2000 ID50s per animal). The Harvard simulation model predicted that approximately 6.5% of the original infectivity in a slaughtered animal would be administered to other cattle, prior to the implementation of the feed ban. After the implementation of the feed ban, this value fell to 0.25%. Cattle are exposed only to this small fraction of overall infectious dose because the rendering process eliminates some of the BSE infectivity, and because MBM is also used in feed for other animal species.

One of the strengths of the model is inclusion of several factors affecting the risk of BSE by feed recycling, and their implications for human exposure to the BSE agent present in infected beef. Those factors are incorporated into the model within the context of various components of transmission of infectivity. The first component characterizes cattle population dynamics with respect to age, gender, and type of cattle (beef or dairy); these factors affect the rate of infection due to consumption of MBM and age-dependent susceptibility. The first component also quantifies the probability that an exposed animal might become infected with BSE as a function of dose, and characterizes the disposition of infected animals with respect to the types of tissues rendered and distribution of infectivity within tissues of an infected animal. The second component describes different slaughter practices and chances of spreading infectivity by those practices specifically: exsanguination; stunning; and disposition of the brain and spinal cord, in addition to efficiency of antemortem and postmortem testing. The third component characterizes the rendering process and its effects on inactivation of BSE infectivity. The probabilities of misfeeding (intentional or accidental use of ruminant MBM in cattle feed) and cross contamination are also considered. The final component quantifies human exposure to the BSE agent through consumption of high-risk material (the brain and spinal cord) or consumption of processed meat products contaminated with high-risk material.

In Cohen et al. (2003) and in order to calculate the possible number of ID50s in the imported cattle from the United Kingdom to accomplish this, the probability that a cow was infected at some age I before exportation (at age e) to the United States is derived. It was given as the product of the probability that it was ever infected, the probability that it was infected at age I conditional on the event that it is infected, the probability that it did not show symptoms at the age of infection, and a normalizing constant. However, the resulting probabilities provided do not add up to 1, which might lead to inaccurate results. The reason is that the normalizing constant needs to be the probability that the cow displays

symptoms after the time when it was examined for BSE.

Sensitivity Analysis in the Harvard Model

Sensitivity analyses were conducted to identify the most important sources of uncertainty in the Harvard simulation model. This involved evaluation of the extent to which each assumption or parameter individually influences model predictions of two cumulative outcomes over a 20-year period: the total number of cattle that became infected after the introduction of 10 infected animals at the beginning of the period, and the amount of BSE infectivity (quantified in terms of the number of oral ID50s) in food available for human consumption over that period. Sensitivity analyses were conducted by running the base case simulation 5000 times and recording the distribution of outcomes for each of the two outcomes of interest (total additional cattle infected, and total potential human exposure to BSE infectivity). To evaluate the contribution of an individual parameter or assumption to the uncertainty of these two outcomes, each assumption was then altered, one at a time, setting all other assumptions to their base case values.

Recent advances using the Harvard simulation model include assessing the impact of importation of older cattle from Canada into the United States following the ban on the import of Canadian cattle older than 30 mo of age, and additional analysis of model sensitivity to other assumptions that might enhance the risk associated with importing cattle from Canada (Cohen et al., 2003). Those factors include mislabeling and contamination, misfielding, proportion of poultry litter used in cattle feed, and the prevalence of BSE in Canada.

COMPARISON OF RESULTS OF THE MAIN BSE RISK MODELS

Table 3 provides a comparative summary of the three main discussed models, focusing on the purpose of the model, its mathematical basis, and underlying assumptions: what countries the model is applied to, source of data, parameter estimation, and sensitivity analysis. From the comparison, it becomes clear that back-calculation provides the most robust analysis of the BSE epidemic since it incorporates many of the factors that influence BSE infection risk. The model has also been applied to epidemics in the United Kingdom and France, and has been continuously revised since it was originally developed to determine the number of HIV infections based on AIDS incidence data (Brookmeyer and Damiano, 1989). The problem with BSurvE model is the inability to provide estimates for the younger cohorts (Prattley, Morri,s et al., 2007). In addition, recent changes in the epidemic trends may not be captured by the model. Despite the inclusion of several factors that affect the transmission of BSE, the Harvard model relies on assumptions to derive values and ranges of these factors.

OTHER RISK MODELS

Other approaches to estimate the risk of BSE have been developed, especially for countries with a low number of BSE cases or those with no cases. These approaches do not require detailed mathematical modeling such as the application of the back-calculation method. Such models were developed in Japan, where only 36 cases were detected to date.

The first case of BSE in Japan appeared in September 2001. Shortly afterward, several BSE control measures were implemented, including enhancement of the BSE surveillance system to include testing of all cattle slaughtered for human consumption. Sugiura and Murray (2007) developed a model to describe the outbreak in Japan. In that model, dairy cattle are divided into four subgroups—clinical suspects, fallen stock, sick laughter, and healthy slaughter—and are assigned different independent probabilities of infection, detection, and BSE testing. The model denotes the observed number of BSE cases by a binomial distribution with probability determined by infection prevalence, probability that infection is detectable, and probability that it is tested. The estimation methods used by Sugiura

TABLE 3. Comparison of BSE Risk Models

Criterion	Risk projection model		
	Back-calculation	BSurvE	Harvard Simulation
Purpose	Determines, retrospectively, the number of BSE infections based on the current reported clinical cases.	• Evaluates BSE status in a given country. • Evaluates the effectiveness of BSE detection in surveillance streams.	• Estimates the likelihood that BSE-infected cattle are imported to the United States. • Determines the extent to which the disease might spread in the cattle. • Finds the potential of human exposure to BSE-contaminated beef products.
Mathematical basis	Deconvolution of probability density functions and survival analysis.	• A probabilistic simulation model.	A probabilistic simulation model.
Underlying assumptions	• Infection time and incubation period are statistically independent. • A multiplicative form of the age-dependent susceptibility/exposure and time-risk profile.	• The removal profile is assumed to be the same for all member states. • The expression of clinical disease in BSE-infected animals follows a lognormal distribution. • The detectable preclinical stage precedes the onset of clinical signs by 1 yr. • The latent stage (infected animals that are not detectable) precedes the preclinical phase. • The sensitivity and specificity of surveillance test are both assumed to be 100%.	• Import of infected cattle. • Import of contaminated feed that comes from five infected animals at an advanced but preclinical stage of the disease (average 2000 ID50s per animal). • Rendering process eliminates the majority of infectivity, with only 6.5% of the original ID50 ultimately administered to cattle.
Countries in which model was applied	• The United Kingdom, France, Ireland, Portugal.	• A hypothetical example country and typical European input data were used to estimate BSE infection. The model was also used to estimate the prevalence in the United States.	The United States and Switzerland.
Source of data	• Data for cases: country clinical BSE case reports and surveillance testing results. • Demographic data of type and number of cattle herds in a given country.	• Demographic information about national cattle population of a country. • BSE surveillance data for that country. National cattle age structure, BSE surveillance streams and testing results.	• Information about imported cattle from the United Kingdom and Europe. • Cattle population demographic data classified by age, gender, and type. Other information about bypass protein consumption and probabilities of rendering cattle.
Parameter estimation	• Age-dependent exposure: EM algorithm was used to obtain this parameter based on other variables (e.g., feeding patterns and exposure rates). • Age-dependent susceptibility: Assuming and average incubation period of five years and given that, in the majority of cases clinical onset appears at the age of 5 yr.	• Age-specific removal probabilities for each industry sector are estimated after pooling surveillance data from European Union member states. • Proportion of preclinical detectable cattle that exit via a certain surveillance stream.	• Sensitivity analyses were conducted to identify the most important sources of uncertainty on the two major model out- puts: total additional animals infected and total potential human exposures to BSE infectivity (cattle ID50s). • Underreporting: was difficult to determine at the beginning

(*Continued*)

TABLE 3. (*Continued*)

Criterion	Risk projection model		
	Back-calculation	BSurvE	Harvard Simulation
	• Incubation period: The incubation period distribution was derived from the mechanistic model of the disease pathogenesis assuming that animals are infected with some initial dose and that prion density grows exponentially with time such that disease onset occurs when the prion density reaches some critical level.		of the epidemic, but recent integration of data on clinical incidence and results from screening of clinically unaffected cattle allowed the reporting rate to be estimated.
Comments	• This method incorporates as inputs most of the factors influencing the risk of BSE infection. Those factors include differential mortality, incubation time, age-dependent susceptibility, time- dependent feed risk, case reporting rate.	• BSurvE model cannot give precise estimates for younger cohorts because there is only a limited probability of detecting BSE during the usually long incubation period of BSE. • The model cannot provide an indication of recent changes in the trend of an epidemic. • Some of the input variables, such as removal probabilities of the different subgroups and number expected to leave the herd in each of those age groups via the four streams, are user defined and therefore subjective.	• The model included several factors affecting the risk and dynamics of transmission of BSE and infectivity by feed recycling route, and the consequence on human exposure to beef infectivity. • The model is simulation based and does not rely on actual data. • The major limitation of the model is that several assumptions and factors affecting import and recycling of BSE infectivity are associated with substantial uncertainty, due to the lack of proper documentation to quantify those factors.

and Murray (2007) are efficient with sparse data characteristic of the BSE epidemic.

In another study, Sugiura (2006) sought the goal to estimate the incidence of BSE in the 1996 birth cohort, adjusted for the age distribution of the cohort. This allowed comparison with incidence risks in Europe, where only fallen stock over 30 mo of age and slaughter cattle over 30 mo of age were tested. The age-adjusted incidence risk of infection may be inferred by first estimating the prevalence $R(s)$. However, the confidence intervals for $R(s)$ given by (Sugiura, 2006) are uncertain, since a sample size of eight for each s is not sufficient to ensure the asymptotic normality assumed for the maximum-likelihood estimates.

Two other models-an exit model and a BSE epidemic model were introduced by (Sugiura et al., 2008). These models were used to assess the administrative guidance on BSE issued by the Japanese government in 1996 and to estimate the number of secondary infections for primary-culled infections. Sugiura et al. (2008) split the infected population into three groups according to the cause of death: BSE ($s = 1$), non-BSE ($s = 2$), and slaughter ($s = 3$). The exit model uses simulation pathways to estimate the probability that infected cattle leave the population at age a due to cause s, the level of infectivity that exits the population at age a due to cause s, and the probability that an infected animal has reached the last stage of the incubation period at age a, when the infection would be detectable by rapid tests. The BSE epidemic model uses the outputs of the exit model to reconstruct the BSE epidemic

and assumes that the only route of transmission is via feed. The model expresses the number of infected animals, quantity of actual (but possibly unobserved) cases, and number of observed cases in terms of a set of equations in which the quantity of infected animals is convoluted with different parameters, including the probability that an infected cow exits the population, the probability of rendering a cow from subgroup *s*, and the level of infectivity. This model uses conditional simulations to find the best values of the probability that MBM derived from infected cattle was fed back to cattle for each year of the epidemic. Simulations were used to obtain predictions of the number of BSE cases (Sugiura and Murray, 2007). The model suggests that the probability of feeding infected MBM to cattle decreased by a factor of over 100-fold (estimated range 104–141) after administrative guidance was issued.

Other BSE risk assessments have been based on the age-period-cohort (APC) model (Dahms, 2003). The APC model has traditionally been used to estimate time trends in chronic disease incidence and mortality rates (Robertson and Boyle, 1998; Ducrot et al., 2010). For example, the model was used on mesothelioma mortality data and to make predictions with respect to future mortality rates from this disease (Price, 1997). The age factor in the model represents the biological effect of age on disease incidence rates, adjusting for the effects of cohort and period. The cohort factor accounts for the possible birth cohort effects on disease incidence. The period factor accounts for changes affecting all individuals of a given age, such as changes in disease reporting rates. In the context of BSE, the model was used to determine the time of origin of the epidemic, before BSE was made notifiable (Cohen and Valleron, 1999). In addition, it was used to describe trends in BSE occurrence in France and Italy and to estimate the effect of control measures on such trends (Sala et al., 2009; Sala and Ru, 2009). The major strength of APC-based models is their simplicity and utility in understanding the many factors affecting trends in disease incidence. Further, this class of models does not require extensive data on BSE dynamics. However, inferences regarding certain epidemiological aspects of BSE need to rely on further assumptions that cannot be validated simply in terms of model fit (Dahms, 2003).

A deterministic model was developed and applied to data from Norway (a country of low prevalence) (Hogasen and de Koeijer, 2007). The model is a discrete-time model with yearly increments of time. The model allows external and internal challenges to be examined. It assumes that the infection was imported into the country in the form of either infected cattle or contaminated MBM, and recycled in the cattle feed production cycle. A number of parameters are required for the model, including BSE prevalence in source countries, the number of imported cattle, the amount of imported MBM, the quantity of cattle equivalent to 1 ton of MBM from each country, and basic reproduction number R_0. It was found that there were two peaks of 0.13 and 0.06 cases per year in 1989 and 1993–1994, respectively. Importation of live cattle from the United Kingdom accounted for 99% of the first peak and for 92% of the second peak. Imported MBM accounted for 17% of the BSE cases predicted by the model in 1996.

Another quantitative model was presented by Hutter and Kihm (2010) to evaluate the risk of BSE in a given country. The model estimates the potential risk if one BSE-infected animal is introduced into the production cycle. The input information in the model might be varied to suit country with a BSE risk profile. The analysis in the model considers level of regulatory implementation over a given period of time.

A stochastic model was recently developed to estimate risk of BSE as a result of importation of cattle and MBM from high-risk countries (T. Oraby, personal communication). The model simulates a number of factors affecting BSE risk of infection, including the amount of imported infectivity and its recycling and propagation through rendering and feeding processes. The main outputs of the model are the distribution of the yearly number of newly infected animals (infection incident) and the yearly cumulative number of infected cattle (prevalent cases), as well as the yearly number of cattle slaughtered

for human consumption. Model predictions suggest that the actual number of cases of BSE in Canada is about 40-fold as high as the number of clinically diagnosed cases.

Barnes and Lehman (2013) recently developed a basic ecological disease model that examines the role feedback loops that may play in the spread of BSE and related diseases. This model considers a form of feedback in which prions are amplified in one species (mainly cattle) and then fed to a secondary species in which they may or may not be decreased before being fed back to the first species (cattle). This cross contamination as previously described is the main factor of infections that appeared after the ruminant-to-ruminant feed ban.

Yamamoto et al. (2008) developed a simulation model to obtain the year of death and the final disposition of infected cows born in each year from 1996 to 2001. The main purpose of the model was to estimate the number of BSE-infected cattle that are the source of infection to other cattle and humans. Using this model, the total number of infected cattle in each birth year was estimated by maximal likelihood estimation using data on number of detected cases from 2002 to 2006. It was estimated that the majority of infected cattle that might have been sources of infection before 2001 were born in 1996.

DESCRIPTION OF THE SPREAD OF BSE IN CATTLE

The fundamental parameter that describes the transmission potential of an infectious disease is called the basic reproduction number (R_0). This parameter was used extensively to characterize a variety of infectious diseases and evaluate efficiency of preventive measures used to control them (Bacaeer et al., 2007; Britton, Nordvik, and Liljeros, 2007; Chen and Liao, 2008; Dejong, Diekmann, and Heesterbeek, 1994; Hartemink et al., 2007; Heffernan, Smith, and Wahl, 2005; Ngwa, 2006; Roberts and Heesterbeek, 2007; Satou and Nishiura, 2007; van Den and Zou, 2007). The basic reproduction number is defined as the expected number of secondary infections produced in an entirely susceptible population by a typical infected host (Anderson, 1991; Heffernan, Smith, and Wahl, 2005). If $R_0 > 1$, the infectious agent has the potential to persist indefinitely; however, if $R_0 < 1$, then incidence of infection will die out and the epidemic will fade out. R_0 is an indicator of how swiftly an infection will spread in a population previously unexposed to that pathogen, and of the total proportion that will be infected once the infection becomes endemic (Ferguson et al., 1999).

In the context of BSE, estimates of the basic reproduction number have been used in the BSE epidemic to (1) describe transmission dynamics (Anderson and May, 1991), (2) determine whether the disease will persist in a host population, (3) evaluate the effect of control measures (de Koeijer et al., 2004; Schwermer et al., 2006), and (4) determine infectivity of feed products prepared from recycling of infectious BSE material (Zentek et al., 2002). The basic reproduction number has also important implications on vCJD risk assessment. After allowing for bovine-to-human species barrier, infectivity estimates throughout the incubation period are used to assess the extent of human exposure to the infectious material.

Calculation of R_0 assumes that animals are infectious only prior to disease onset, which implies that only reported cases are included in the analysis. This assumption is not entirely valid since, early in the epidemic, carcasses of many undiagnosed/unreported cases may have been recycled for animal feed (Ferguson et al., 1999). Including unreported cases in the model would require more complicated expressions that would be subject to considerable uncertainty.

The explicit expression of the basic reproduction number is derived in terms of several variables that describe cattle demography, disease pathogenesis, and route of transmission routes. Briefly, R_0 (the expected number of infections via a type route j produced by an animal that was itself infected via a type i route) is given by the following equation:

$$\left[R_0\,(t)\,{}^{\infty}_{0}\right] ij = \int \int_{0}^{\infty} gi(a)\sigma \mathrm{i}\,(\mathrm{t},\mathrm{a})\,\beta \mathrm{j}\,(\mathrm{t}+\tau)$$

$$\psi \mathrm{i}\,(\tau)\,\mathrm{d}\tau\,\mathrm{da}.$$

Here, t is the time of infection of the primary host, $g_i(a)$ is the relative susceptibility of an animal of age a, $\beta_j(t)$ is the transmission coefficient for horizontal transmission from a maximally infectious host at time t, and $\psi_i(\tau)$ is the relative infectivity of a host at time τ after infection (here standardized to have a maximum value of 1 of a host at time τ after infection) (Ferguson et al., 1999). The function $\sigma_i(t,a)$ is the probability density function (pdf) of the age at slaughter for animals slaughtered at time t when $i = F$ (feed route of transmission), the pdf of the age at giving birth at time t when $i = M$ (maternal route of transmission), and the fraction of animals alive at time t when $i = H$ (horizontal route of transmission). This simplified expression assumes that birth rate and survivorship are independent of time; otherwise, a more complex expression of R_0 is needed that involves other risk factors such as the probability of culling and the fraction of the infectious load of an infected animal entering the rendering process.

Since calculation of R_0 involves the three transmission routes, a 3×3 matrix $[R_0(t)]ij$ is obtained, and a summary value of R_0 is obtained by averaging over transmission routes (Heesterbeek, 2002). Assuming that infectivity peaks at the onset of clinical symptoms, it would be more useful to express infectivity as a function of the time remaining until clinical onset of BSE rather than as a function of the time since infection. The relative infectivity of bovine tissue $\psi_i(\tau)$ is now given by

$$\psi_i\,(\tau) = \int_{0}^{\infty} fi\,(v+\tau)\,\Omega i\,(v)\,dv,$$

where $fi(v + \tau)$ is the incubation period distribution and Ω_i is the infectivity at time v prior to disease onset (Ferguson et al., 1999).

The results of modeling the BSE epidemic suggested relatively constant and highly infectious BSE prior to introduction of the first feed ban in 1988, with R_0 estimates to be in the range of 10–12. This value provided insight into the infectiousness of late-incubation-stage animals and indicated that a maximally infectious animal could infect up to 400 other animals in order to generate number of BSE cases seen in the United Kingdom (Ferguson et al., 1999). The values of R_0 decreased significantly after that date, ranging from 0 to 0.25, depending on the transmission coefficient and infectivity of an infectious animal. Both parameters are given arbitrary values and therefore are subject to a wide range of uncertainty (Ferguson et al., 1999).

Those results were based on the feed-borne transmission route alone. In the absence of horizontal transmission and limited information on relative contribution of maternal transmission, those projections were uncertain. In another analysis of the UK epidemic, Ferguson et al. (1997) examined the potential impact of direct horizontal transmission after the 1988 partial feed ban on the projected number of cases in the period 1997–2001. This analysis also produced R_0 values in the range 0–0.25. Data also demonstrated that a value of $R_0 = 0.15$ predicted that about 85% of projected cases in the same period are attributable to horizontal transmission. Further analysis of the British BSE epidemic revealed that the BSE agent possessed the potential to infect 90% of cattle exposed to MBM feed (Woolhouse and Anderson, 1997). In another study, de Koeijer et al. (2004) estimated the upper bound transmission routes other than feed transmission, resulting in low values of R_0 equal to 0.06. Therefore, it is reasonable to conclude that these transmission pathways are hypothetical and may not be relevant.

One of the principal determinants of the basic reproduction number R_0 is the relative infectivity of cattle at different stages of incubation. Limited information available in this regard was derived from studies using bovine, mouse, or primate animal models (Foster et al., 1996; Fraser et al., 1994; Herzog et al., 2004;

Lasmézas et al., 1996, 2005; Wells et al., 1998). Different assumptions regarding this parameter have an appreciable effect on estimates of R_0. Ferguson et al. (1999) presented the results of two infectivity models based on feed-borne transmission alone. The first assumes infectivity rises exponentially throughout the incubation period until being infectious in the last 6 mo of the incubation period. The assumption of maximal infectivity in the last 6 mo of the incubation period is in agreement with experimental data (Curnow, Hodge, and Wilesmith, 1997; Donnelly, Ferguson, Ghani et al., 1997; Gore, Gilks, and Wilesmith, 1997; Wells et al., 1998; Wilesmith et al., 1997). Pathogenesis studies suggest that infectivity in the CNS increases rapidly in the last few months of the incubation period and remains low in other tissues (Bellworthy et al., 2005; Espinosa et al., 2007; Wells et al., 2005). The second model assumes that animals are equally infectious throughout their incubation period.

Data from both models show that the value of R_0 values fell significantly following the 1988 feed ban. These two models have different implications for vCJD risk assessment when estimating the effect of different bovine tissue infectivity scenarios on past levels of human exposure to the BSE agent. In addition, the assumptions underlying both models reflect different generation times for BSE and hence have different implications for theories on when BSE originated. The exponential growth of the infectivity model, which assumes that animals are infectious in the last 6 mo of the incubation period, implies a 3- to 4-yr generation time (the time between when the animal was infected and when it infects other animals). Data suggest that infections in the 1988 cohort were generated by small levels of infection in the 1978–1979 birth cohorts. The constant infectivity model, on the other hand, implies a shorter generation time, with infections of the 1982 cohort predominantly generated by infections in the 1981 cohort (Ferguson et al., 1999). Current models for estimating R_0 assume homogeneous mixing of cattle to infectivity. However, this might not be entirely accurate, since significant clustering of cases was observed (Hagenaars et al., 2000).

Other potential outputs, such as the proportion of infected animals, transmission via the horizontal route, relative infectivity of infected cattle and infectivity at a certain time prior to disease onset, and estimated average of the expected number of infections per maximally infectious slaughtered cattle in an entirely susceptible population, are modeled during the derivation of R_0. Those outputs are directly related to BSE and vCJD risk assessment, since they help estimate infectivity recycling through feed and potential human exposure to infectious material.

CONCLUSIONS AND FUTURE DIRECTIONS

The emergence of prion diseases in animals with minimal knowledge regarding their pathogenesis or transmission created enormous pressure on the scientific community to (1) understand their biological and epidemiological features, (2) determine the way they propagate, and (3) evaluate the possibility of their transmission to humans. Extensive quantitative analyses have been conducted over the last two decades to address different aspects of BSE risk, including the BSE case-reporting rate, the incubation period distribution, and estimation of the number of infected animals during an outbreak, age-dependent susceptibility/exposure to MBM infectivity, and relative infectivity of an infected animal. This body of work substantially reduced a number of uncertainties pertaining to prion disease infectivity and transmission.

Implementation of effective preventive and control measures to minimize the risk of prion diseases is contingent upon quantitative knowledge of the magnitude of infection risk and the projected persistence of the disease in the host population. Risk modeling therefore becomes an essential tool for prion disease risk management. Indeed, BSE risk models helped in estimating, with reasonably narrow confidence

bounds, the number of animals infected in the past; these models were also useful in projecting the future course of the epidemic and permitted an assessment of the effect of implementing control measures. Risk models describing time trend of BSE infections in the United Kingdom showed that infectivity remained in the feed system, as new cases continued to appear in animals born after the ruminant-to-ruminant feed ban. Spatiotemporal analysis of feed practices implicated cross-contamination as the source of infection in animals born after the ruminant-to-ruminant feed ban. Risk models showing that the number of infected animals far exceeded the number of reported clinical cases pointed to some limitations of the passive surveillance systems, implemented at the beginning of the epidemic, and led to surveillance being intensified in the European Union in 2000.

Projections from these same risk models indicated that the BSE epidemic is on decline, and produced predictions that were similar to the actual number of cases reported later. After the link between BSE and vCJD was established in 1996, new models focusing on the risk of contracting vCJD from consumption of BSE-contaminated beef products were developed. For example, risk estimates derived from back-calculation models provided information on the number of infected animals slaughtered for human consumption, and were of critical importance in projecting future trends in vCJD infection in the United Kingdom.

Although the incidence of BSE is declining in many countries in Europe, some countries such as Spain and Poland reported a small number of cases within the past few years. BSE risk models may still be valuable tool to inform sound risk management policies in those countries. An example in this regard is the Cattle TSE Monitoring Model (C-TSEMM) developed to evaluate different transmissible spongiform encephalopathy (TSE) monitoring regimes in cattle by estimating the trend of the current BSE epidemic within European Member States (MSs) (Adkins, Simons, and Arnold, 2012).

Future research efforts in prion disease risk assessment may be directed toward studies of the possibility of modification of prion infectivity and adaptation to new hosts. Especially important in this respect is to determine whether the BSE agent can back-cross species and infect sheep. This is critical, since it is postulated that scrapie prevailed for about 200 years without posing risk to humans, supporting the view that BSE may not be transmissible to other animals. This reasoning is not valid, since after crossing the species barrier the behavior of infective prions in the host is unpredictable (Vidal et al., 2013).

Another potential area of investigation is modeling the risk of atypical BSE. The recent identification of atypical cases of BSE raises concerns about the existence of new types of animal prion diseases that differ from classical TSE with respect to risk factors, pathogenesis, and clinical symptoms. Experimental studies on inbred mice showed that atypical BSE may evolve naturally to BSE (Capobianco et al., 2007). Other studies suggested other possible types of pathogenesis of atypical BSE (Comoy et al., 2008) and a possible link between atypical BSE and one subtype of human sporadic CJD (Casalone et al., 2004). Even though such studies are preliminary, these investigations call for caution against relaxing current measures that have been put in place to control BSE and vCJD.

Most of the models described in the preceding did not include analysis by industry sector (beef vs. dairy). Since feeding practices and management differ between the two sectors (dairy beef are given more supplementary feed), results may underestimate the infection risk in dairy cattle while overestimating the infection risk for beef cattle. Future risk analysis methods needs to be directed toward analyzing the risk separately in dairy and beef cattle, given that data on cattle demography provide feeding patterns and culling rates for both cattle types. Another alternative would be to include sector in any BSE modular approach and allow for different feeding management and age structure profiles.

In conclusion, BSE risk projection models that were developed by different investigators to date have made an important contribution

toward understanding the etiology of this new zoonotic disease. In particular, these models have been useful in (1) estimating the latency of BSE; (2) gauging the infectivity of BSE at different stages of its development with the host; (3) evaluating the relative importance of different modes of transmission; (4) projecting the future course of the BSE epidemic; (5) evaluating the effectiveness of BSE risk control measures (both before and after implementation; and (6) assessing the risk of interspecies transmission, particularly from cattle to humans. The insights afforded by careful interpretation of the risk predictions obtained from such models have also been useful in guiding BSE risk management policy development, including the selection of the most appropriate BSE control measures. Although the BSE epidemic has been declining worldwide, continued vigilance is warranted to prevent a resurgence of the epidemic. BSE risk models continue to play an important role in the ongoing assessment and management of this critical prion disease.

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