

Transmission dynamics and epidemiology of BSE in British cattle

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A comprehensive analysis of the bovine spongiform encephalopathy (BSE) epidemic in cattle in Great Britain assesses past, present and future patterns in the incidence of infection and disease, and allows a critical appraisal of different culling policies for eradication of the disease.

In March 1996 the Spongiform Encephalopathy Advisory Committee (SEAC) of the Department of Health (DoH) and Ministry of Agriculture, Fisheries and Food (MAFF) in the United Kingdom reported to government that the most likely explanation at present for the occurrence of 10 cases (now 12 confirmed cases)^{1,2} of an apparently new variant of the rare but lethal Creutzfeldt-Jakob disease (CJD) in humans was exposure to the aetiological agent of BSE (believed to be an abnormal form of the prion protein (PrP)³) before regulations were introduced to prevent any part of cattle with clinical signs (1988) and specified offal from all cattle entering the human food chain (1989)^{4,5}. This announcement triggered a crisis in Europe, both in consumer confidence in beef and beef products, and in relations between the member states of the European Union.

An analysis is presented of the key epidemiological processes that have shaped the pattern of the BSE epidemic in Great Britain, and of the demography of the cattle population, using new data on the incubation period of the disease and the rate of maternal transmission from infected dam to a new-born calf⁶. Mathematical models are used to derive estimates of the age-stratified incidence of infection in cattle over time and the likely impact of various culling policies⁷ on the incidence of BSE in the coming years.

Origins and time course of the epidemic

Current evidence suggests that the disease originated from supplementary feed containing meat and bone meal (MBM) contaminated by a scrapie-like agent derived from sheep or cattle (the oral route of infection for scrapie-like agents has been demonstrated experimentally^{8,9}). Infectivity is thought to be facilitated by changes in the early 1980s in the method of rendering of offal into meat and bone meal¹⁰. Legislation was introduced in June 1988 to make BSE a notifiable disease. Shortly afterwards a statutory ban on the feeding of ruminant-derived protein to ruminants and regulations for the compulsory destruction of all animals exhibiting signs¹¹ were introduced. By June 1996, 161,412 confirmed cases of BSE had been reported in Great Britain. The pattern of the epidemic remains consistent with the hypothesis that the vast majority of cases arose by infection with contaminated feed (feed-borne hypothesis)¹²⁻¹⁶. It remains possible, however, that other routes of transmission may occur infrequently, in particular maternal transmission from dam to calf⁶.

In contrast to studies of transmissible spongiform encephalo-

pathies (TSEs) in rodent models¹⁷, sheep and goats¹⁸⁻²⁰, to date there is no evidence that cattle genotype influences the susceptibility or average duration of the incubation period of BSE²¹⁻²³, although this remains a possibility. There is much geographical heterogeneity in the incidence of BSE per head of cattle in Great Britain (Fig. 1g), probably because of variation in the past use of meat and bone meal in supplementary feedstuffs, geographical variation in the proportion of meat and bone meal produced by rendering plants, and variation in the use of hydrocarbon-solvent extraction procedures (the use of which is thought to reduce the likelihood of agent survival)¹⁰.

The observed epidemic pattern is influenced by under-reporting before the disease became notifiable in June 1988 (a degree of under-reporting may have continued for one or two years after this) and the short average reporting delay (approximately 3 months) which influences the most recent records (Fig. 1e). Our analyses exclude recent reports influenced by the delay. The rapid growth of the epidemic from 1986 to 1991 is consistent with recycling of contaminated material in the ruminant feed chain fuelling transmission before July 1988. The lag after this period before the incidence of disease decays is consistent with the hypothesis of a long average incubation period (4-6 years)^{24,25} (Fig. 1a). Examination of the age distribution of the incidence of disease in cohorts of animals of defined birth years, under the assumption that most animals acquire infection soon after birth, suggests a mean incubation period of approximately 5 years, with marked variation around the average but little variation between cohorts (Fig. 2a). An inspection of the cohort data on proportional incidence by age (Fig. 2b) reveals a trend for the average age at clinical onset to decrease within the cohorts born in 1977 to those born more recently. This pattern provides evidence that infection of older animals (>5 years of age) is possible through contaminated feed²⁶. It is also consistent with the hypothesis of recycling fuelling the pace of the epidemic, where a raised transmission intensity reduces the average age at infection²⁷.

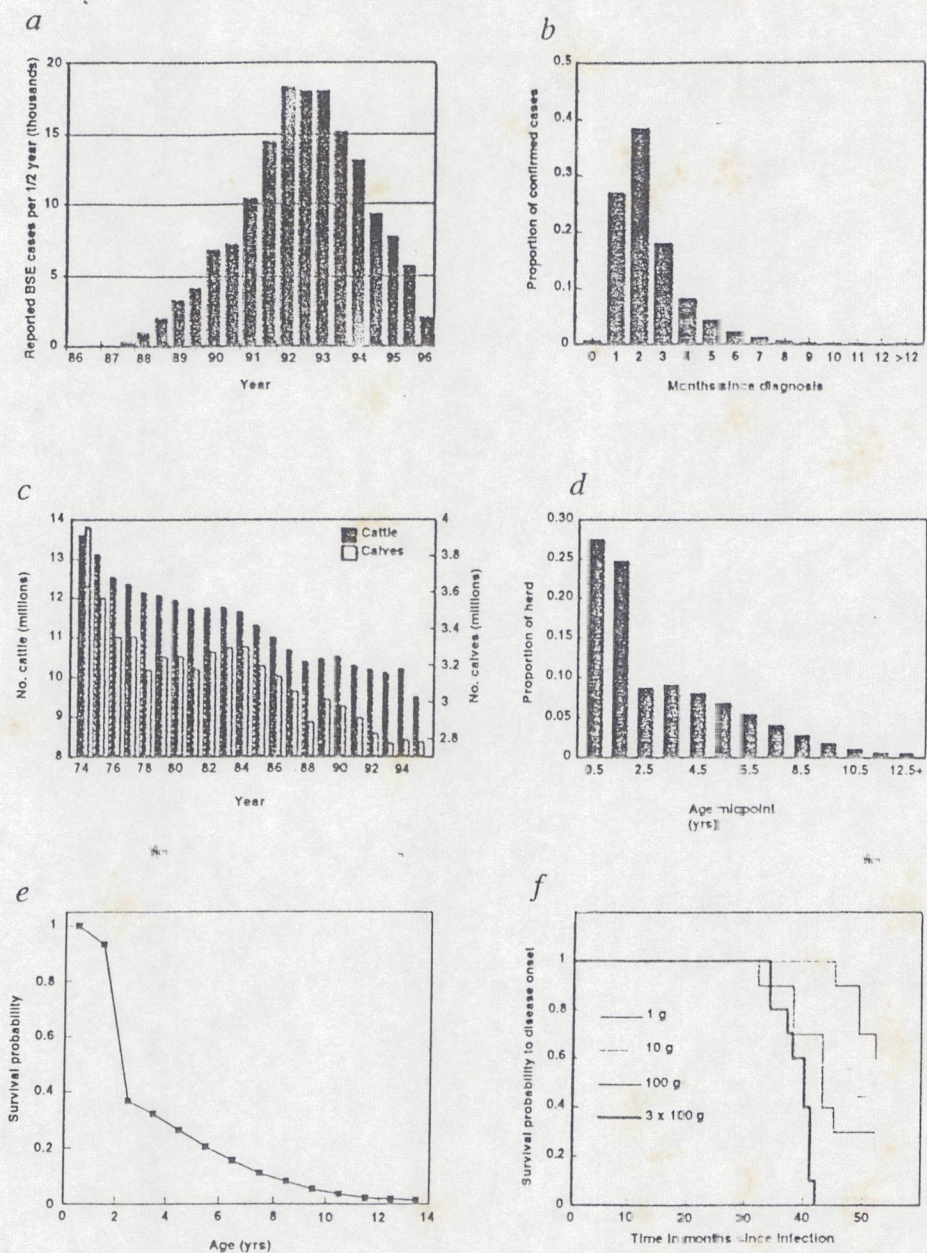
Epidemiological parameters

To estimate longitudinal trends in the incidence of infection (as opposed to disease, when clinical signs are exhibited), a series of key epidemiological parameters must be determined and their relationship with demographic variables ascertained. We exclude consideration of the influences of host genotype and changes in the nature of the infectious agent over time. In rodent models,

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FIG. 1 a, Longitudinal trend in the incidence of confirmed BSE cases per half year from 1986 to the first half of 1996. Note that the number for the first half of 1996 will rise once reporting delays are taken into account (see b). b, Distribution of the reporting delay from diagnosis to entry on the Central Veterinary Laboratory BSE database for confirmed cases (mean, 3.1 months). c, Number of cattle (all ages) and calves up to 12 months old in Great Britain from 1974 to 1995 (data from MAFF^{49,50} and The Scottish Office⁵¹⁻⁵³ for 30 June each year; these data exclude small holdings). Numbers of calves are used as inputs for the demographic model. d, Estimated survivorship function for cattle showing probabilities of survival to each age, $S(u)$, estimated using standard methods⁵⁴ with data on age structure for 1982, 1988, 1989, 1991 and 1994 (e) and correcting for declining herd size by scaling by the size of the birth cohort (data from MAFF^{49,50}, The Scottish Office⁵¹⁻⁵³ and Milk Marketing Board⁵⁵, assuming average inter-calf interval of 12.5 months⁵⁶). Estimated $S(u)$ values do not vary significantly through time, and geometric mean values (shown here) are used throughout. e, Estimated age structure of the British cattle herd in 1994. Note the substantial loss through slaughter between ages 2 and 3 years. Data are the same as in d. f, Kaplan-Meier curves based on unpublished research on the duration of the incubation period of BSE in cattle dosed orally with a range of varying quantities of brain from animals exhibiting clinical signs (sample sizes: 10, 1g; 9, 10g; 10, 100g; 10, 3 x 100g). g, Spatial distribution of the incidence of BSE per head of cattle from 1986-95 by county.



where scrapie prions passed in one species are inoculated into another, recycling of infection can act to reduce the incubation period of the disease^{24,28}.

Age-dependent exposure and susceptibility. Changes in the incidence of infection over time, and by host age, depend on the age-dependent rates of exposure and susceptibility (together given by probability density function $g(a)$), weighted by time-dependent levels of exposure (dose of aetiological agent), $K(t)$. The latter is influenced by recycling of BSE-infected tissues in MBM before 1988 and the degree to which the feed ban was effective after 1988. The age-dependent rate of exposure reflects the age-dependent intake of supplementary feed containing MBM. Supplementary feed is used in both dairy and beef herds, although management practices vary considerably between the two (over 90% of BSE cases originate in dairy or mixed herds). In herds where supplementary feed is given to calves, intake rises with age for the first two years, although it varies according to season and is highest during the winter. In many herds, intake is highest in cows over two years old. However, the epidemiological data on clinical onset

by age, taking account of the long incubation period of BSE, suggest that most, but not all, infection occurs during the first two years of life. Thus there may be age-dependent susceptibility to infection. For TSEs in rodent models, some experimental data hint at decreasing susceptibility with age²⁹, although other data show an opposite effect³⁰; experimental evidence for BSE in cattle is not yet available. The major changes in the immunology and physiology of the intestinal tract that occur in cattle as they age^{31,32} may well lead to (perhaps complex) age-related changes in susceptibility. **Incubation period.** Interim results from recent experimental studies involving the oral dosing of cattle of known age with varying doses of brain from cattle affected with BSE (1g, 10g, 100g and 3 x 100g) (Fig. 1f) point to a dose-dependent incubation period, with a relatively small variance which also depends on dose. Across all doses, a range of 3-5 years is apparent, which will be increased once the surviving animals with longer incubation periods are included. The degrees to which animals at different stages of the incubation period are infectious to cattle through contaminated feed, to offspring born to infected dams, and



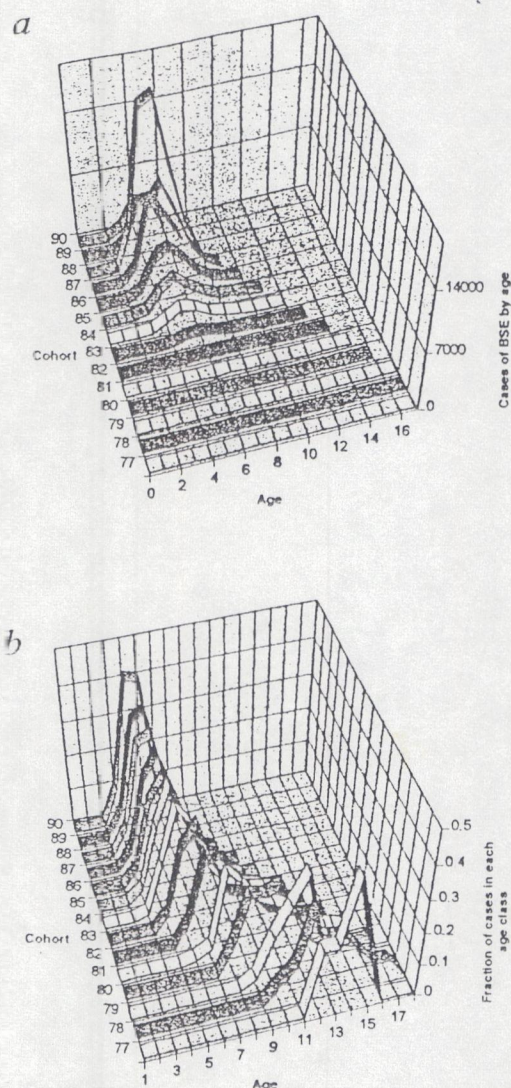


FIG. 2 a, Age distribution of confirmed cases of BSE by birth year cohort, b, Fraction of BSE cases in each age class for birth cohorts 1977–1990.

humans through contaminated food are key questions. Unlike scrapie in mice, where both spleen and brain are infectious, detectable titres of abnormal prion seem to be limited to brain, cervical spinal cord, terminal spinal cord, retina and possibly distal ileum in cattle^{17,33,34}. Experimental studies of TSEs in animal models, however, suggest the possibility, that infectivity will change markedly over the incubation period. Detectable titres of replicating abnormal prion in the brain might rise exponentially in the second half of the incubation period (these plateau much earlier in spleen and lymph nodes^{5,35}, and may decline subsequently³⁶), with very high levels after clinical signs have developed³⁷. For BSE in cattle, therefore, high infectivity may be restricted to the latter stage of the incubation period with a peak when clinical signs of disease appear.

Demography of cattle in Great Britain. The number of cattle in Great Britain has steadily fallen from 13.6 million in 1974 to 9.5 million in 1995 (Fig. 1c), and will decrease further as a result of new culling measures to control BSE. Recruitment has also declined during this period (Fig. 1c). From the age structure of the herd in different years it is possible to estimate the age-specific survivorship function (Fig. 1d), which gives an estimated life expectancy at birth of 3.0 years. Overall, these demographic patterns have caused a small increase in the mean age of the

national herd during the BSE epidemic. Between the ages of 2 and 3 years, a large fraction of animals are slaughtered for consumption (Fig. 1e). Those not slaughtered at that time are kept for breeding and/or milk production until, on average, they are 5–6 years old. Almost all cattle slaughtered (including those from dairy herds) provided beef and beef products for human consumption until the recent ban on cattle aged over 30 months. Age-specific slaughter rates are essential to the interpretation of the BSE epidemic and any associated risks to humans of infected animals entering the human food chain. Given an incubation period of 5 years, an average age of infection of about 1 year, and a life expectancy at birth of 3 years, it can be seen that most animals acquiring infection do not survive long enough for BSE to develop. Given that infectivity of tissues from animals infected with the BSE agent may depend on time since infection, any risk assessment for humans must include the distribution of slaughtered infected animals by time since infection and any changes therein over the course of the epidemic.

Maternal and horizontal transmission. To date no evidence exists to support the notion that the BSE agent can be transmitted horizontally either through close contact between susceptible and infected animals or through contaminated pasture¹⁶. This route cannot be eliminated, given evidence for the clustering of cases in individual herds, but the overall epidemiological pattern of infection and the pattern of decay in the epidemic after the feed ban argue against its occurrence at a level high enough to influence materially the course of the epidemic. Maternal transmission is thought to occur in scrapie³⁸, and horizontal transmission must also occur owing to the long-term persistence of the disease, and so this relevance to the interpretation of the British BSE epidemic has long been recognized⁴. A recent cohort study that monitored calves born to infected dams provided clear evidence of maternal transmission with a probability of 10.6% and a 95% confidence interval of 5.7–15.6 ($n = 546$)⁶. The infection rate for calves born to dams over the entire incubation period (5 years on average) may be lower (for example, if the rate is 10% over the last half-year of incubation and close to zero before that time, the average rate over a five-year incubation period is 1% if the birth rate is constant). The results of the cohort study provide no evidence that the incubation period following maternal transmission is different to that arising following feed-borne infection (the mean period from the maternal study is 5 years; ref. 6).

Trends in the incidence of infection

In the absence of an *in vivo* diagnostic test to detect infection, back-calculation methods using observed trends in the incidence of disease, and a knowledge of the distribution of the incubation period^{39,40}, provide the only methods available to estimate trends in the incidence of new infections. They should take into account the demography of the host species (age-specific survivorship of cattle and changes in recruitment over time), the maternal and feed-borne transmission routes, and the age-dependent exposure/susceptibility to infection. Simple projection methods can be used to predict future trends in cases of BSE^{25,41}, based on past trends in yearly cohorts, but this approach does not provide information on the pattern of infection, which is crucial to the full assessment of the current and future pattern of the epidemic. Our analyses are based on a model of the following structure, where $c(u, t_0)$ defines the probability density function (PDF) for the onset of BSE at age u for an animal born at time t_0 :

$$c(u, t_0) = \rho(t_0 + u)S(u) \times \left\{ [1 - \pi(t_0)] \int_{a=0}^u K(t_0 + a)g(a)f(u - a)da + \pi(t_0)f(u) \right\}$$

where $\pi(t_0)$ is the probability that an animal born at time t_0 is maternally infected, $S(u)$ is the age-dependent cattle survivorship function, $g(a)$ is the PDF for age at infection, $K(t)$ is the time-

dependent feed-risk function, $f(i)$ is the PDF for the incubation period, and $\rho(t)$ is the probability that a case diagnosed at time t was reported (to take account of under-reporting) (see legend to Fig. 3 for more detail). The probability $\pi(t_0)$ can be expressed as

$$\pi(t_0) = \left\{ \left[\sum_{n=1}^{\infty} \epsilon^{n-1} (F - G)^{n-1} \right] \cdot \epsilon G \cdot 1 \right|_{t_0} \right\}$$

where ϵ is the probability that a calf born to an infected dam is itself infected, F and G (see legend to Fig. 3) are two operators used to calculate maternal infection from a dam infected by feed and maternal infection by a dam herself maternally infected, respectively, and n is the generation number for successive rounds of maternal infection. (In the time scale of the epidemic and for $\epsilon \ll 1$, the effect of second- or higher-order generation terms in the maternal transmission function are likely to be negligible). Maximum-likelihood methods are used to estimate the variance of the incubation period (but not the mean), the age-dependent infection rate, and the time-dependent feed-risk function

(see legends to Figs 3 and 4). Unfortunately, many parameters must be estimated in connection with the likelihood of feed-borne infection, using the age-structured notification records over time (data arise from a multinomial distribution when viewed by cohort and divided into yearly age classes). Thus the likelihood was maximized for various assumptions about the functional forms of $K(t)$, $g(a)$ and $f(i)$, given information on $S(t)$, ϵ and the mean of $f(i)$, using direction set^{42,43} and Latin hypercube sampling⁴⁴ along with simulated annealing methods⁴⁵⁻⁴⁷. A wide range of functional forms was examined for the age at infection distribution, Weibull and gamma distributions were considered for the incubation period, and the feed-risk profile was fitted using linear splines with optimized knot locations. Based on the minimization of the likelihood ratio χ^2 for all yearly cohorts, the model including 10% maternal transmission ($\epsilon = 0.1$) for the last half-year of the incubation period, with the functional form for $f(i)$ and $g(a)$ shown in Fig. 3c, d, provided the best fit ($\chi^2_{219} = 482$) to observed trends of BSE cases in yearly cohorts of animals (illustrated in Fig. 4b). The fit to the observed changes in the age distribution of cases through time is consistent with there being no

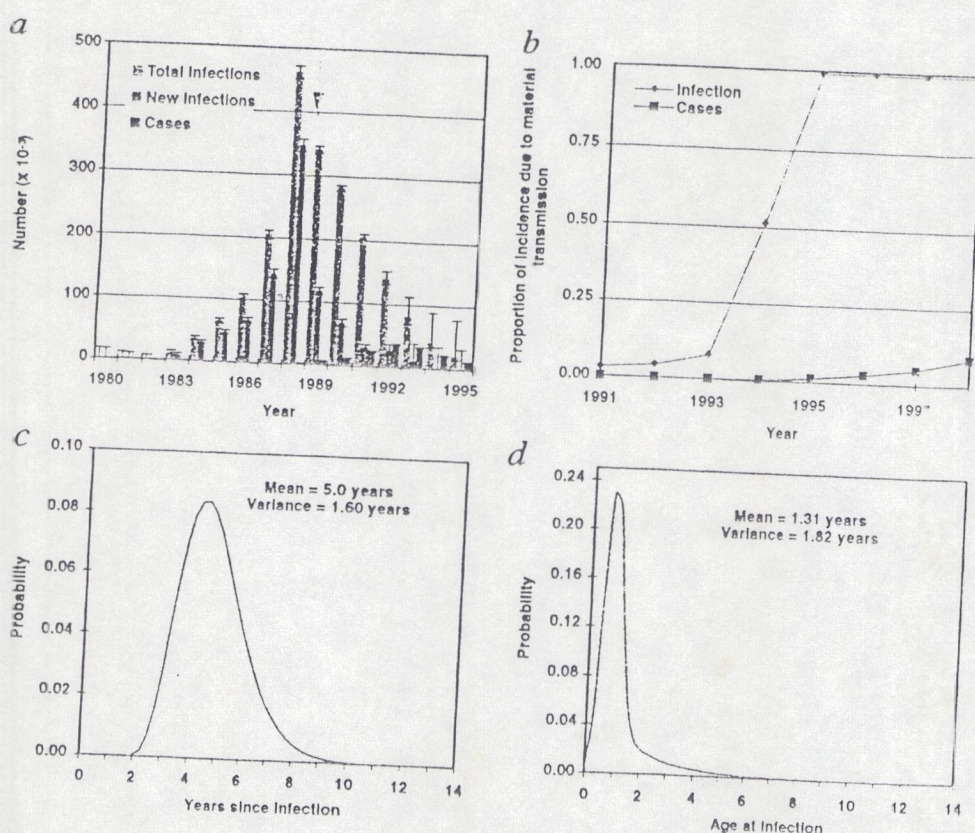


FIG. 3 a, Estimated trends in the incidence of infection, disease (per year) and the total number of infected cattle at the year end for Great Britain. The 95% confidence intervals (shown) were calculated from the hypercube obtained from the bounds of the univariate likelihood ratio confidence intervals, under the assumption that feed risk drops to zero by July 1996. (The arrow indicates the year of the statutory ban of the feeding of ruminant-derived protein to ruminants and the introduction of legislation making BSE a notifiable disease, with compulsory destruction of all animals exhibiting signs¹¹.) b, The proportions of infections and cases of BSE that are predicted to arise from maternal transmission (a rate of 10% over the last half year of the incubation period). The operators F and G used in the definition of $\pi(t_0)$ (see text) are defined as follows (y being any univariate function, $y(z)$):

$$(F \cdot y)(t_0) = \left\{ \frac{\int_{x=0}^{t_0-2} B(x) S(z-x) \left[\int_{i=z-x}^{t_0-x+1} f(i) di \right] y(x) dx}{\int_{x=0}^{t_0-2} B(x) S(z-x) dx} \right|_{z=t_0} \right\}$$

$B(x)$ is the birth rate of cows at time x , and T is the length of time before case diagnosis for which cows are assumed to be infectious to offspring (assumed to be 6 months or 1 year). Other quantities are defined elsewhere in the text. c, The estimated probability density function (PDF) $f(i)$, of the incubation period of BSE (gamma form). d, The estimated FDF of the age at infection distribution, $g(a)$. The cumulative distribution function has the form $g(a) = [1 - \exp(-(a/x_1)^6)][1 - \exp(-(a/x_2)^{6.7})]$.

$$(G \cdot y)(t_0) = \left\{ \frac{\int_{x=0}^{t_0-2} B(x) S(z-x) \left[\int_{a=0}^{t_0-x} K(x+a) g(a) \left[\int_{i=x+a}^{t_0-x+1} f(i) di \right] y(x) da dx}{\int_{x=0}^{t_0-2} B(x) S(z-x) dx} \right|_{z=t_0} \right\}$$

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change in the mean incubation period *per se*. Rather, these changes are in line with standard epidemiological theory: as the risk of infection increased up to 1989, the average age of infection declined and, as the risk of infection decreased after 1989, the average age of infection increased²⁷. Bearing in mind the problems raised by estimating many parameters from a single age- and time-structured data set, the goodness of fit provides a degree of confidence in the resulting incidence pattern (Fig. 3a). A large number of situations were examined, including: one in which maternal transmission is assumed to occur at a rate of 10% over the last year of the incubation period ($\chi^2_{219} = 492$); the best-fit case, in which a 10% maternal transmission rate is restricted to the last half-year ($\chi^2_{219} = 482$); and one in which maternal transmission is zero, with all transmission resulting from the consumption of contaminated feed ($\chi^2_{219} = 492$). These χ^2 values rise signifi-

cantly, regardless of model, if underreporting is excluded; when included, the estimated number of cases not reported before July 1988 is 3,240. The predicted pattern of maternal infection in recent years is shown as a proportion of total cases and infections in Fig. 3b. Examining predictions on a finer timescale (less than half-yearly) demonstrates evidence of seasonality in contaminated feed intake (Fig. 4c). If the period over which maternal transmission takes place is increased, the goodness of fit of the model decreases (for example, $\chi^2_{219} = 740$, for transmission allowed for 3 years before BSE in the dam).

Back-calculations of trends of infection incidence suggest that the feed ban introduced in mid 1988 had an immediate and lasting impact. Infection is predicted to have continued through this route, although at a much reduced level, before falling to negligible levels by mid 1994, after which new infections arose entirely

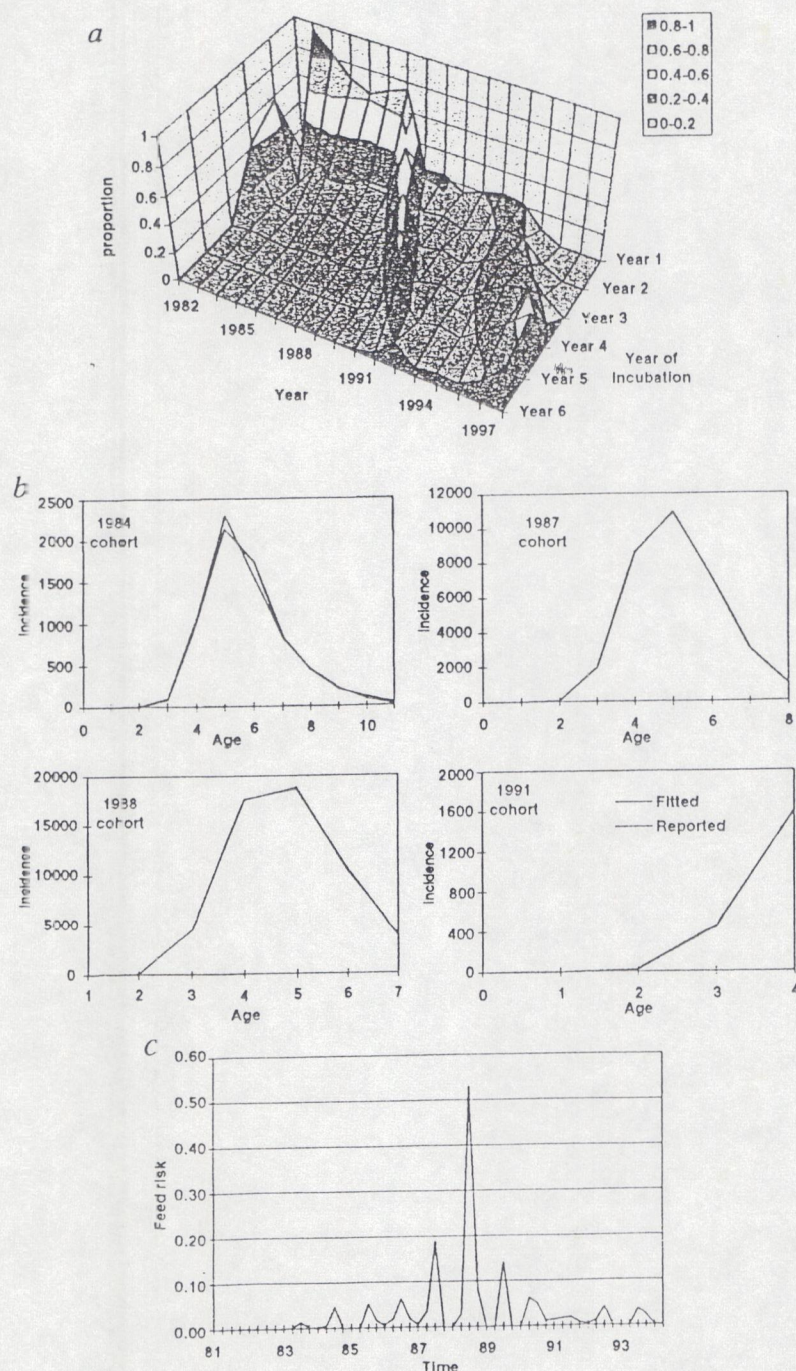


FIG. 4 a, The predicted proportion of infected animals in each age class by birth-year cohort using the model with 10% maternal transmission in the last half year of the incubation period of the dam. Although the proportion of older infected animals increases in recent years, the number of infected animals declines over the plotted time period. b, The observed and expected number of cases of BSE by age in a series of birth cohorts for the model with 10% maternal transmission in the last half year of the maternal incubation period (overall $\chi^2_{219} = 482$). c, The estimated time series of the risk of infection through contaminated feed over time ($K(t)$), illustrating the high risk during the winter months and the effect of the 1988 feed ban.

from the maternal route (318–352 in 1995) (Fig. 3b). The large difference between numbers infected and numbers of cattle diagnosed with BSE reflects the short life expectancy of cattle relative to the average incubation period, such that most infected animals were slaughtered before exhibiting disease. We estimate that approximately 446,000 (440,000–580,000) infected animals entered the human food chain before the specified bovine offal ban at the end of 1989 (ref. 48), with approximately 283,000 (270,000–330,000) more before the end of 1995. The estimated total number of animals infected over the period 1974 to the end of 1995 is 903,000 (840,000–1,250,000). Of these the estimated number of infections arising through maternal transmission is 5,100 (4,970–6,250) to the end of 1995, and 340 (240–1,270) in the period 1996–2001. It may take many years before an accurate assessment can be made of whether or not there is an epidemic of an apparently new variant of CJD, but if the postulated association between the new variant of CJD in humans and BSE is proved correct², then the numbers of infected animals that are culled and have entered the food chain, and the distribution of such numbers by stages of the incubation period in infected cattle (associated with a possible higher risk later in the incubation period), are of considerable public health significance. Maternal transmission is not predicted to lengthen or increase the scale of the epidemic (Fig. 5).

In the rising stage of the epidemic, most culled infected animals were in the early stages of incubation, although as the epidemic moves into the declining phase a growing fraction are in the late stages (note, however, that the total number of cases is declining at this stage) (Fig. 4a). At first sight the predictions plotted in Fig. 4a might be interpreted as the risk to humans being greater in recent years (1991–1995) than at the peak of the epidemic of infection (1987–1990). This is unlikely to be the case because, before August 1988, animals showing clinical signs (and hence with very high levels in the CNS of the BSE agent) could enter the food chain. The specified offal ban came into force in 1989, and over the following years infected brain and spinal cord should have been eliminated from the human food chain.

FIG. 5 Predictions of future trends in the incidence (per year) of cases of BSE and infections for the model with no maternal transmission (a), 10% maternal transmission in the last half year of the maternal incubation period (b), and 10% maternal transmission in the last year of the maternal incubation period (c). In fitting the trend to data on cases before 1996, the best fit was achieved by the model b. Error bars denote 95% prediction intervals calculated as described in Fig. 3.

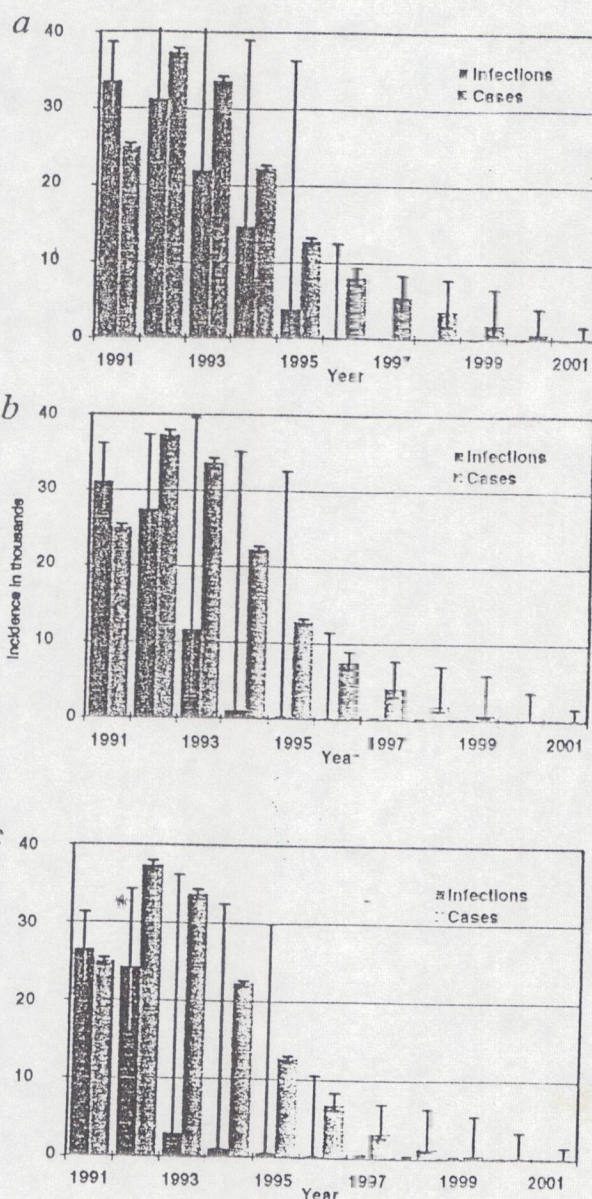


TABLE 1 Predicted trends in the incidence (by year) of BSE infections (a) and cases (b) from 1996 to 2001 under different assumptions

(a)	No maternal transmission		6 months, 10% maternal trans.		1 year, 10% maternal trans.	
	Expected value	95% Prediction interval	Expected value	95% Prediction interval	Expected value	95% Prediction interval
1996	0	(0–12,500)	189	(155–11,300)	270	(224–10,500)
1997	0	(0–0)	95	(63–236)	102	(75–435)
1998	0	(0–0)	38	(21–214)	31	(20–389)
1999	0	(0–0)	12	(5–162)	8	(5–276)
2000	0	(0–0)	3	(1–86)	2	(1–136)
2001	0	(0–0)	1	(0–33)	0	(0–49)
(b)	No maternal transmission		6 months, 10% maternal trans.		1 year, 10% maternal trans.	
	Expected value	95% Prediction interval	Expected value	95% Prediction interval	Expected value	95% Prediction interval
1996	7,988	(7,044–9,306)	7,386	(6,541–8,856)	6,740	(6,085–8,291)
1997	5,573	(3,774–8,369)	4,111	(3,006–7,664)	3,145	(2,559–6,904)
1998	3,644	(1,654–7,762)	1,864	(1,153–7,025)	1,247	(960–6,365)
1999	1,896	(560–6,545)	682	(388–5,909)	456	(357–5,417)
2000	744	(152–4,042)	221	(128–3,660)	172	(140–3,388)
2001	225	(34–1,728)	72	(45–1,592)	68	(56–1,499)

Note that for the case of 10% maternal transmission (trans.) over 6 months, the predicted number of cases in the period 1997–2001 is 6,950. See text and legends to Figs 3 and 5.

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The future

Extrapolation of the longitudinal trends in incidence of new infections (ignoring for now the impact of culling) from 1996 to 2001 gives the pattern of infections and cases of disease detailed in Table 1. This includes the appropriate prediction intervals for models with no maternal transmission but continued risk from feed, contaminated feed plus 10% maternal transmission rate for the last half-year of maternal incubation, and contaminated feed plus 10% maternal transmission for the last year of maternal incubation. In the last two models the risk from contaminated feed is estimated to have fallen to zero by mid 1994; it is likely that all of the new infections since then have arisen through maternal transmission (Fig. 3b).

In analyses to discriminate between different culling policies, optimization is based on the criteria of maximizing the number of BSE cases prevented and minimizing both the number of animals culled and the number of herds involved in the cull. In such calculations, several factors are important: the number of infected animals when the policy is implemented; the age distribution of infected animals; and the distribution of infection between herds. The first two factors can be assessed from the output of the models (Figs 5 and 6a, b). The predicted age distributions provide a means of assessing the expected impact of a cohort-targeted culling policy. Similarly, by distinguishing cases arising through feed or through maternal transmission (Fig. 3b), the expected impact of a maternally targeted policy can be assessed. A disease-case-herd-targeted policy involves identification of BSE cases over a defined period, and slaughtering cattle born on the same farms. A variant

of this policy is to define an incidence of BSE (number of cases in defined cohort per head of cattle in the holding) above which the cohort is culled; this is a herd-incidence-targeted policy.

The likely success of herd-targeted policies depends on the degree to which future cases are clustered in cohorts within herds where animals diagnosed with BSE have originated. There is an important distinction to be made here between the distribution of infected animals and the distribution of diagnosed cases of BSE. In roughly one-third of those herds in which BSE-diagnosed cattle were born, no cases have been reported resulting from movement of incubating cattle from those herds. Whether or not cattle movements are related to the detection of early signs of disease (before firm diagnosis) is difficult to assess, but the distribution of the time interval between when an animal is moved between herds and the date of diagnosis shows an unusual bimodal pattern with an early peak. This may suggest that perhaps 1% of the total animals with BSE had been moved between herds close to the point of disease diagnosis. However, animal movement may result in a stress-induced acceleration of the appearance of clinical signs. Another important factor in cohort-based herd-targeted culling (on the basis of diagnosed cases of disease) is the clustering of cases by herd size. If the distribution is clustered within all herd size categories then targeting is more likely to be successful in removing infected (but not yet diseased) animals. There is clustering, with the distribution of case numbers in each herd size category (<50 to >200) being overdispersed with variances significantly greater than the respective means. This acts to enhance the likelihood of removing infected animals by a disease-herd-

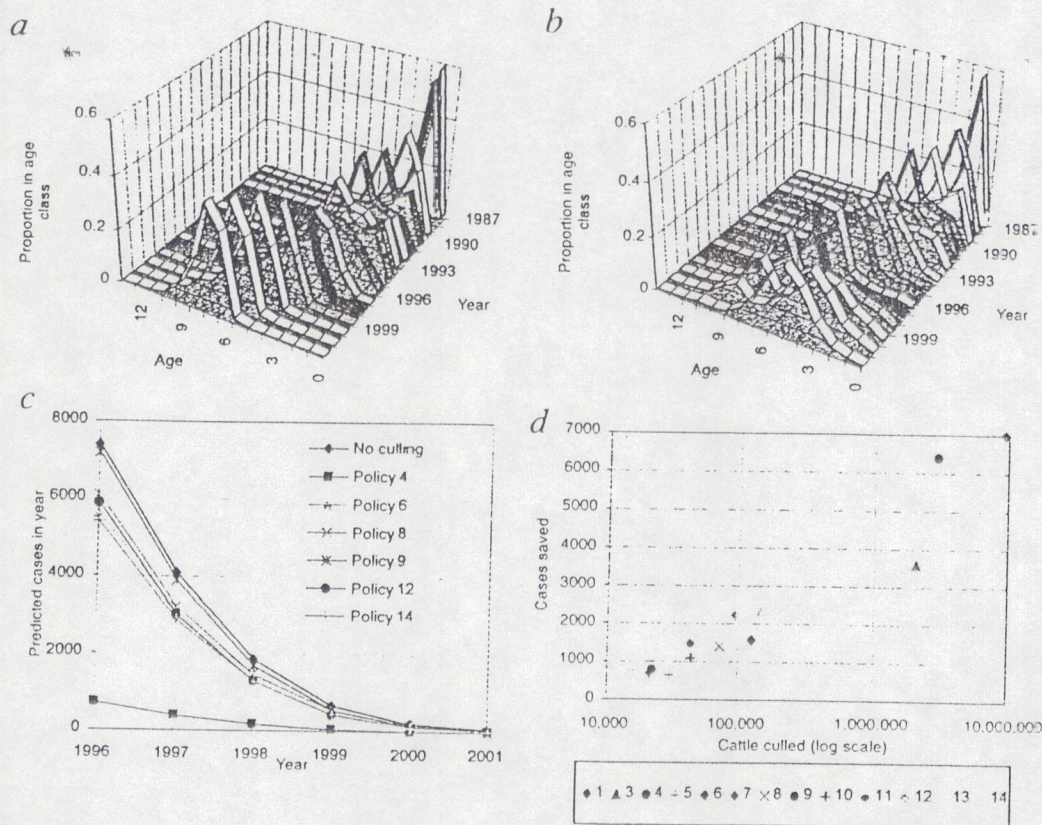


FIG. 6 a, b, The predicted age distribution (proportion in age class) of infected animals after 1995 for two of the three models described in Fig. 5. a, No maternal transmission; b, 10% maternal transmission in the last six months of the maternal incubation period. Note that proportions are plotted; the numbers of cases are small as detailed in Table 1. c, Predicted effect of selected culling policies on the future incidence of BSE cases, 1997–2001 (policies numbered as in Table 2). d, Comparison of the number of BSE cases saved and the number of cattle slaughtered (log

scale) for the different culling policies listed in Table 2. This comparison is relatively robust to uncertainty as to the number of future cases, but is sensitive to the estimated distribution of those cases in different herds and age classes. The overall pattern is one of diminishing returns across all culling policies, because, as the number of cattle slaughtered increases the number of cases increases much less rapidly. The numbers identify the policies detailed in Table 2.

targeted policy, over that which would pertain if the distribution was random. For herd-targeted policies, calculation of the fraction of cases captured by a defined policy cannot be precise owing to uncertainties in the future degree of clustering. The analyses are based on the calculation of the fraction of cases in the targeted age range captured by a given policy in 1995, 1994 and 1993, as if the policy had been implemented in those years, and extrapolating forwards. Estimates of the number of cases saved are therefore approximate. Most emphasis should be placed on the ranking of the relative efficiencies of different policies given that estimates of the number of holdings affected and cattle culled are fairly precise.

Working on the basis of a maternal transmission rate of 10% for the last half-year (the best-fit model to the data), predicted

impacts of a range of possible culling policies are compared in Table 2. One measure of the efficiency of any given policy is provided by the ratio of the number of animals culled to the predicted number of cases saved over the period from 1997 to 2001. This ratio must be considered in parallel with the number of herds affected by the cull and the total number of BSE cases (Table 2). The predicted total number of cases yet to be diagnosed in the absence of culling is 6,950 (see Table 1 for prediction intervals). Herd-targeted policies are by this measure significantly better than other options (Table 2), with a herd-incidence-targeted policy predicted to be most 'efficient'. For the latter approach, a threshold incidence of 1 case in the July 1989 to June 1992 cohort, per 27–50 cattle in the holding as a whole is most efficient and also affects the smallest number of herds. In light of

TABLE 2 Comparison of possible culling policies

No.	Culling policy description	Cases saved		Total cattle culled		No. of origin holdings	Cattle culled per case saved
		Number	%	Number	%		
Non-targeted							
1	All cattle	6,950	100	9,360,000	100	111,000	1,300
Age-targeted							
2	All cattle born before 7/88	250	4	352,000	3.8	≤ 111,000	1,400
3	All cattle born 10/90–6/93	3,600	51	2,030,000	22	≤ 111,000	564
Herd-targeted (case)*							
4	All cattle born in herds from which a case originated during 1/91–12/95	6,300	90	2,870,000	31	28,500	455
5	Cattle born in the 10/90–6/91, 7/91–6/92 or 7/92–6/93 cohorts in herds from which a case originated in the corresponding cohort during 1/91–12/95 (govt policy)	650	9	30,100†	0.32	1,460	46
6	As 15), but extended to include 7/89–9/90 cohort (govt compulsory + voluntary policy).	1,580	23	127,000†	1.4	6,240	80
Herd-targeted (incidence)*‡							
7	Cattle born in 7/89–6/92 in herds with more than 1 case in that cohort range (during 1/91–12/95) per 27 cattle in the holding as a whole.	691	10	21,300†	0.23	638	31
8	As 7) but with a threshold of 1 case per 50 cattle	1,420	20	71,900†	0.77	2,000	51
Maternally targeted§							
9	Cattle born after 10/90 within six months of BSE case in the dam	797	11	<22,000	0.24	≤ 22,000	28
10	Cattle born after 10/90 within 12 months of BSE case in the dam	1,100	22	<44,000	0.47	≤ 35,600	40
Combined herd-targeted and maternally targeted policies							
11	* Incidence (1 per 27) + § maternally targeted policy = policies 7 and 9 combined	1,490	21	<44,000†	0.47	≤ 25,500	30
12	* Incidence (1 per 50) + § maternally targeted policy = policies 8 and 9 combined	2,220	32	<94,000†	1.0	≤ 26,800	42
13	* Govt compulsory + maternally targeted policy = policies 5 and 9 combined	1,450	21	<53,000†	0.57	≤ 26,300	37
14	* Govt inc. voluntary + maternally targeted policy = policies 6 and 9 combined	2,380	34	<150,000†	1.6	≤ 31,000	63

Projections are made using the model with 10% maternal transmission over 6 months (unless otherwise stated) and refer to cases saved over the period 1997 to 2001 achieved by a culling policy implemented at the end of 1996. Values are to 3 sig. figs, percentages to 2 sig. figs.

* These projections require estimates of the fraction of cases captured by a diseased-herd-targeted policy. These estimates were obtained by calculating the appropriate fraction for the years 1995, 1994, and 1993 (had the policy been implemented in those years) and extrapolating to 1996. In cases where the exact date of birth of a case was not listed in the database, this was calculated from the estimated age.

† Using age structure of BSE-infected herds calculated from lactation data collected by CVL.

‡ Incidence is calculated from cases in specified cohort range, but using the total number of all animals on each holding as estimated from the BSE case database, since reliable estimates of total numbers of animals in the targeted cohort on each holding are not available. For holdings with multiple herds, the estimated size is the sum of the sizes of the constituent herds that appear in the database, so if herds within a holding have not reported a case, they are not included in the estimate of holding size. Two representative policies are shown here, illustrating that by lowering the incidence threshold for culling, more cases are saved, but at the cost of disproportionately more animals culled.

§ Running policy (culling until 2001). Other policies involve one-off cull in 1996.

|| Assuming 6 month infectious period for maternal transmission.

¶ Assuming 10% maternal transmission occurs in the last 12 months of incubation period and calculated from corresponding model (predicting 5,100 cases total in 1997–2001).

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recent evidence for maternal transmission⁶, consideration must be given to augmenting policies by culling cattle in given cohorts born to dams who subsequently developed BSE (a maternally targeted policy). Maternal targeting is very efficient and is predicted to reduce to almost zero the number of new infections arising over the period 1997 to 2001, but a large number of herds would be affected by the cull. Combining a herd-incidence-targeted policy with a maternally targeted policy is predicted to maximize efficiency.

Conclusions

The epidemic of BSE in British cattle seriously affected both animal health and Europe's agricultural industry. However, the epidemic is well past its peak, and seems to be in a phase of rapid decline. New infections from contaminated feed are predicted to be close to zero by the end of 1994, with all new cases of infection arising from maternal transmission. However, the numbers are small (Table 1) and this route of infection by itself cannot sustain the epidemic. To accelerate the rate of decline of the epidemic (Fig. 6c) without the slaughter of a very large number of animals

(Fig. 6d) is very difficult in the absence of an *in vivo* diagnostic test. Bearing in mind both this and the prediction that the epidemic is likely to fade close to extinction by the year 2001 in the absence of culling, the calculated optimal culling policy (maximizing cases saved, minimizing animals culled) is a combination of herd-incidence targeting (with a threshold for culling of one BSE case in cattle born July 1989 to June 1992 per 27 cattle in the holding as a whole) plus a maternally targeted policy. However, the practicalities of such an approach, given that roughly 25,500 herds would be affected, need careful consideration.

We believe eradication to be possible, but the history of the epidemic in cattle will continue to be of great importance as attempts are made to formalize risk assessments to determine the likely degree of past exposure of the human population to the BSE agent, and therefore the likelihood of an association between BSE and the apparently new variant of CJD². Whether or not the 12 reported cases of the new variant are the beginning of an epidemic remains uncertain, and will continue to be so for the next few years.

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