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# The epidemiology of BSE in cattle herds in Great Britain. I. Epidemiological processes, demography of cattle and approaches to control by culling

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## SUMMARY

This paper explores the key epidemiological processes and demographic factors that determined the pattern of transmission of the aetiological agent of bovine spongiform encephalopathy (BSE) in cattle herds in Great Britain (GB). The analyses presented utilize data from published and unpublished experimental studies and from the GB central database of confirmed BSE cases.

We review the experimental and epidemiological evidence that has both confirmed indirect horizontal transmission via the consumption of infectious material as the major transmission route and provided information on the duration and variability of the dose-dependent incubation period of BSE in cattle. The epidemiological and genetic data pertaining to the possible existence of maternal transmission and/or genetically variable susceptibility to infection is discussed.

The demography of British cattle is characterized and the impacts of key demographic features on the observed epidemic profile are discussed. In the main BSE case database, analyses reveal that BSE cases cluster significantly at both the holding and county scale. Furthermore, analysis of longitudinal patterns reveal substantial temporal within-holding correlation. Such clustering of cases suggests a highly heterogeneous infection process.

The paper ends with a discussion of how analyses of spatio-temporal clustering inform the design of targeted culling programmes aimed at reducing future disease incidence. We show how the retrospective implementation of culling policies on the BSE case database allows the qualitative evaluation of policy performance, but that model predictions of future trends in case incidence are required to estimate the precise impact of any current or future programme.

## 1. INTRODUCTION

The disease termed bovine spongiform encephalopathy (BSE) was first identified in November 1986 following clinical and pathological investigation of a cow referred to the Central Veterinary Laboratory (CVL) of the Ministry of Agriculture, Fisheries and Food (MAFF) at Weybridge, Surrey (Wells *et al.* 1987). The disease in cattle is thought to have 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 transmissible spongiform encephalopathy (TSE) agents has been demonstrated experimentally (Barlow & Middleton 1990; Fraser *et al.* 1992; Middleton & Barlow 1993; Wells *et al.* 1994; MAFF 1996). Subsequent epidemiological investigations undertaken in 1988 and 1989 revealed that the consumption of MBM from infected cattle was the probable cause of the rapid development of the epidemic in the cattle population within Great Britain (GB)

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(Wilesmith *et al.* 1988, 1991). The disease was made notifiable in June 1988 and in July 1988 a ban on the use of ruminant-based MBM in cattle feed came into force (Statutory Instrument 1988). Despite this ban, however, cases of BSE have arisen in animals born after 1988, indicating that the ban was not fully effective for a number of years after its introduction (Anderson *et al.* 1996).

The impact of the BSE epidemic on the agricultural industry in the UK and in Europe has been great. Public confidence in meat products has declined and relations between member states of the European Union have become strained as a result of differences of opinion on how best to eradicate BSE from the UK in particular, and Europe in general. The urgency of dealing with this epidemic has been heightened recently by scientific results that suggest a link between BSE infection in cattle and a new variant of Creutzfeldt–Jacob Disease (CJD) in humans (Collinge *et al.* 1996).

The progression of the BSE epidemic in cattle in GB has been described by the staff of the CVL (Wilesmith *et al.* 1991, 1992*a,b*) via surveillance based on the notifiable disease and the construction of an extensive epidemiological database recording the demographic details of diseased animals. Such detailed data can provide precise estimates of the temporal and spatial trends of the epidemic. In parallel, a series of studies has been conducted to assess various epidemiological processes such as incubation periods and maternal transmission.

Given the long incubation period of BSE (typically around five years (Bradley 1991)) and the small fraction of animals surviving beyond three years of life (Anderson *et al.* 1996), it is clear that the number of cattle infected with BSE is much greater than the number of confirmed cases of the disease. Various mathematical and statistical techniques can be used to estimate past trends in the incidence of infection given knowledge of cases of disease over time and the distribution of the incubation period (Brookmeyer & Gail 1986; Bacchetti *et al.* 1993). However, such models are best constructed and applied against a thorough understanding of the key epidemiological processes influencing the observed pattern. Moreover, the interpretation of trend also requires a detailed knowledge of the demography of the host population.

We begin in § 2 by describing the CVL database of confirmed cases of BSE which we use in the later sections of the paper to examine past, present and possible future trends in the epidemic in GB. Section 3 reviews experimental and observational studies that address the key processes influencing the transmission and spread of the aetiological agent of BSE. These include possible modes of transmission, biological and genetic factors influencing susceptibility and estimates of the incubation-period distribution. In addition, we present new data on animal feeding practices from the Institute for Animal Health (IAH) farm at Compton, Berkshire. This is followed by a review and analysis of the demography of the British cattle population in § 4. In § 5 we present a detailed

investigation of epidemiological trends in BSE incidence over time and space, in particular focusing on the clustering of cases. Section 6 explores the possible impacts of different culling policies on future trends in BSE incidence. By implementing different culling policies retrospectively on the case database, we explore trends in their effectiveness without recourse to statistical models. Such an analysis, while unable to predict future effectiveness, allows us to provide a template for the assessment of the possible impact of different culling policies. Given this analysis, we then use the predictions in the accompanying paper (Ferguson *et al.* 1997*a*) to evaluate the relative performance of the different culling policies.

## 2. THE CVL DATABASE OF CONFIRMED BSE CASES

All confirmed BSE cases arising in GB have been entered into a database maintained at the CVL. The information recorded is obtained from the questionnaire completed by a veterinary officer. Post-mortem diagnosis of BSE is based on the pathological examination of brain tissue. The variables considered in the following analyses include herd, holding and county of diagnosis, holding and county of origin, date of birth, date of onset of the clinical signs of BSE and adult herd size for herd of diagnosis. From 21 June 1988, all BSE suspects were required to be reported to CVL (Statutory Instrument 1988); before this time reporting was not compulsory.

It should be noted that where dates were reported as a month and year, the dates were entered into the database as the first day of the month. Figure 1*a* shows the loading of dates on the first day of the month for reported dates of birth, onset and purchase due in part to these approximations. There appears to be no other trend in the dates of birth and purchase suggesting that the person reporting either knew the date precisely or estimated it as the first of the month. For the date of onset, however, date estimation is evident from the increased proportion of dates reported as days 7 (one week into the month), 10, 15, 20, 25 and 30. This is not surprising in light of the difficulty in precisely identifying the day on which clinical signs of disease onset. Similarly, age loading is apparent for the reported age at onset, with a substantial bias towards reporting in whole years (figure 1*b*). These biases complicate the analysis and modelling of the data on a fine time-scale (Ferguson *et al.* 1997*a*).

As with any data set of such magnitude, some variables are missing for some cases. Where the date of birth was missing, its value was estimated from the age and date at onset if these values were available. Similarly missing dates of onset were estimated from the date of birth and age at onset. If date and age of clinical onset were both missing, the date of clinical onset was estimated to be one month before the completion of the BSE preliminary report by the veterinary officer.

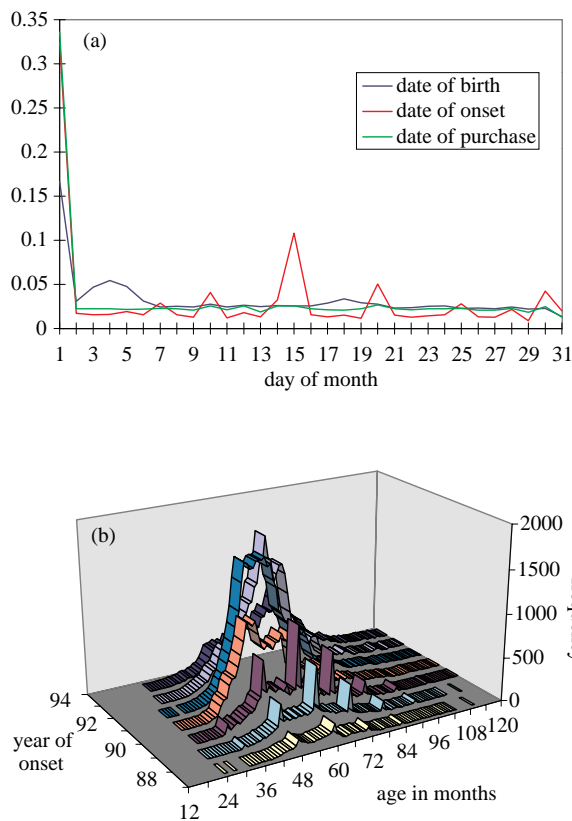


Figure 1. Illustration of biases in: (a) reported dates by day of month; and (b) reported age at the onset of clinical signs of BSE by year of onset.

### 3. EPIDEMIOLOGICAL PROCESSES

BSE is one of a number of TSEs which manifest as neurodegenerative diseases in their mammalian hosts. The aetiological agents of these diseases are believed to be an abnormal form of a cellular sialoglycoprotein PrP<sup>C</sup> coded by the host *PrP* gene. The transition to the abnormal isoform (PrP<sup>SC</sup>) is a post-translational event and its presence in the host reflects the presence of infection (the prion hypothesis) (Prusiner *et al.* 1996). Of the known TSEs, scrapie, a disease of sheep, has been most intensively studied. The disease was first discovered in England in 1730 (Stamp 1962). Despite the long period over which the disease has been recognized in sheep, relatively little is clearly understood concerning its epidemiology and the main routes of transmission. Its endemic persistence in sheep flocks argues for an element of horizontal transmission. Maternal transmission is also reported to occur but the evidence for this is very limited to date.

#### (a) Non-feed-borne transmission of BSE

In the case of BSE, horizontal transmission by routes other than the consumption of contaminated feed has not yet been identified. While it cannot be excluded, the time course of the epidemic following the introduction of the ban on the use of

ruminant-based protein in feed suggests that if horizontal transmission does occur, it is a rare route of transmission and that its overall contribution to transmission is on its own insufficient to maintain BSE endemically within the cattle population (Ferguson *et al.* 1997a). However, no experimental studies have been carried out to date to test for the existence of horizontal transmission via contaminated pasture or cow-to-cow contact.

In contrast, a pair-matched cohort study by staff at CVL to test for the presence of maternal transmission has recently been completed. Offspring of BSE-confirmed dams were recruited into the study as maternally 'exposed' animals. For each exposed animal, a matched control animal was selected which was born in the same herd in the same calving season and whose dam had reached at least six years of age without developing clinical signs of BSE (but was not necessarily six years of age when the calf was born). Animals recruited into the study were born as early as 1987 and as late as 1989. Most of the maternally exposed animals were born within the last five months of the incubation period in the dam; however, some animals were born after disease onset in their dams. Study animals were followed until suspected of BSE, until they had to be culled for reasons unrelated to BSE, or until they reached seven years of age. The brain of each animal was examined for histological signs of BSE.

Interim results were released from this study in July 1996 by the Spongiform Encephalopathy Advisory Committee (SEAC). Full results are reported in Wilesmith *et al.* (1997), Donnelly *et al.* (1997a), Gore *et al.* (1997) and Curnow *et al.* (1997). In brief, the study reveals an enhanced risk of disease in maternally 'exposed' animals of 9.6% (with 95% confidence limits of 5.1–14.2%). Unfortunately, however, disease also occurred in the control arm of the study due to animals being exposed to contaminated feed. As a result, it is not possible to say from the summary results whether the enhanced risk is due to maternal transmission of an aetiological agent, genetic predisposition to disease (inherited from the dam) or some combination of both factors. Under the hypothesis that the enhanced risk is due to genetic predisposition, the risk ratio of the exposed to the control group is 3.2 (with 95% confidence limits of 1.8–5.9). In an attempt to resolve the question of whether maternal transmission exists, detailed analyses of the study outcomes for individual animals have been performed (Donnelly *et al.* 1997a). These analyses, using a variety of models and taking careful account of the manner in which the risk is related to the timing of the birth of the calf in relation to when the dam develops BSE, suggest that the most likely explanation of the observed pattern is a combination of direct maternal transmission of the aetiological agent plus genetic predisposition (Donnelly *et al.* 1997a; Ferguson *et al.* 1997b). Most importantly, the cohort study data suggest that the risk of developing BSE in the offspring increases for calves born closer to the date of disease onset in the dam. This is thought to be a signature of maternal transmission, given the hypothesis that



infectivity rises greatly in the late stages of pathogenesis (as in the nervous system of mice following their parenteral inoculation with scrapie (Dickinson & Outram 1979)). Indeed, it is difficult to envisage a genetic mechanism that might give rise to the same effect.

Further information on the magnitude of the maternally enhanced risk of disease comes from the main BSE database. Recent analyses of the dams of confirmed BSE cases born after the introduction of the ruminant feed ban reveal an enhanced risk similar to that observed in the cohort study (Donnelly *et al.* 1997b). Equally important, however, is the observation that the enhanced risk is greatest in the 12 month period before the onset of BSE (and higher still if the calf is born at or after the onset of the clinical signs of BSE in the dam). This trend is again suggestive of a component of direct maternal transmission. In the absence of a second experimental study in which no exposure of the study animals to contaminated feed is ensured, or examination of the genetic backgrounds of all animals in the completed study (sequencing the *PrP* gene and flanking regions), it is unlikely that much new information will emerge on this issue as the epidemic decays over the next few years.

#### (b) *Exposure to feed*

If contaminated feed is the main source of BSE infection, then exposure to infection may be related to feed consumption. The profile of feed consumption with age is believed to be highly variable between holdings and regions, but it is likely that almost all cattle born in GB in the 1980s were fed protein supplements that included MBM at some point during their lives. Although the composition of feed varies according to the age of the animal, feed for animals of all ages contained MBM before the ruminant feed ban. Calves are first given protein supplements shortly after birth, with feeding patterns thereafter being seasonal and so dependent on the month of birth. A minority of animals are not given supplementary feed as adults, but the feed intake of dairy cows is substantially increased at the time of first lactation and is maintained thereafter. The profiles of feed intake for cows on one dairy farm are shown in figure 4 for animals born in December (*a*), March (*b*), July (*c*) and September (*d*). The main point emerging from these observations is that the majority of cattle were exposed to potentially contaminated feed throughout their lives and that the degree of exposure was commonly highest in adult cows. Thus, all age classes were at risk of infection. Mathematical models of the transmission dynamics of BSE (Anderson *et al.* 1996; Ferguson *et al.* 1997a) suggest that age-dependent changes in the susceptibility of cattle to BSE infection play a far more significant role than age variation in feed intake.

#### (c) *Age-dependent susceptibility and the age-at-infection distribution*

The amount and type of manufactured feed consumed by cattle varies as a function of age, season of the year, milk production of the animal and other factors. It was initially assumed that all infection with the aetiological agent of BSE occurred very early in life. However, recorded BSE cases in animals born as early as 1974 with late ages at BSE onset suggest that animals may be infected as adults. In addition, Wilesmith *et al.* (1992a) observed that some BSE cases had not been fed feed containing meat and bonemeal during the first two years of life.

The collection of information on the age-specific prevalence of infections by the aetiological agent of BSE is complicated by the fact that at present infection can only be detected in the very late stages of disease. In most birth cohorts (those born in the past 12 years), the peak in the age at onset of BSE (after adjusting for survival) remains at approximately six years of age (figures 2*c, d*). As in Anderson *et al.* (1996), annual birth cohorts were defined so that, for example, the 1989 cohort consists of cattle born between 1 July 1988 and 30 June 1989. With an average incubation period of approximately five years, this pattern indicates that the peak age at infection is around one year of age.

Additional evidence that the peak age at infection is not at birth is revealed by examining the incidence of BSE by birth quarter adjusted for calving seasonality (see § 4*d*). Specifically, the incidence estimates are adjusted to reflect the number of cases expected were cattle equally likely to be born in each quarter. This distribution, shown in figure 3, shows a strong seasonal pattern, with animals born in the first two quarters generally having higher risk than those born in the last two quarters (note that little can be learned from the pattern after 1988, due to the rapidly decreasing and potentially more sporadic risk of feed-borne infection (Anderson *et al.* 1996; Ferguson *et al.* 1997a)). If the majority of infections are feed-borne and calves are fed on the same regimen for the first six months of life regardless of month of birth (see previous section and figure 4), then this finding indicates that susceptibility is not greatest at birth. At the IAH farm at Compton, Berkshire, cows are also fed similarly from their first lactation, indicating that it is the feeding practices during the ages 6–24 months that determine relative exposure. The relative amounts of feed consumed in that 18 month period (compared to animals born in the fourth quarter of the year) are 1.4, 1.4 and 1.0 for animals born in quarters one, two and three, respectively. Between ages 6 and 12 months, the relative amounts are 2.3, 2.2 and 1.1. These relative feed consumption rates are similar to the relative incidence rates observed in figure 3, suggesting increased susceptibility in this latter age range.

In the absence of experiments in which animals are challenged with BSE-infected material at various ages, estimates of the relative susceptibility to infection as a function of age can only be estimated

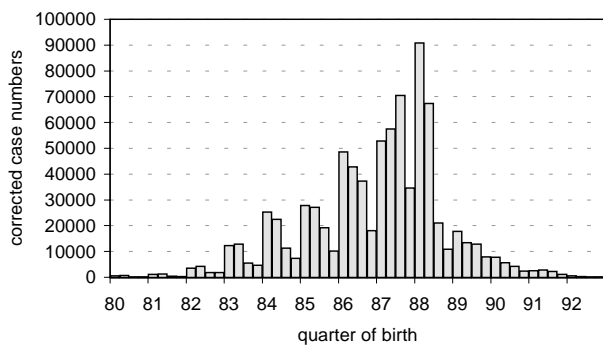


Figure 3. The number of confirmed cases by quarter of birth corrected for birth seasonality.

from mathematical and statistical models incorporating the available information on the incubation period. In the absence of detailed data on feed intake by age, however, the function obtained by fitting the model to age-specific incidence data is the distribution of ages at infection given a constant feed infectivity level. The results of an examination of the fit of such models to the data on disease incidence with differing assumptions on how susceptibility changes with age (Ferguson *et al.* 1997a) indicate a strong trend with age, with highest susceptibility occurring between 6 and 18 months of age.

#### (d) Incubation period

Genetic studies of scrapie infection have identified two genes, the *Sip* and *Sinc* genes, which have a major influence on the duration of the incubation period (Dickinson *et al.* 1968; Hunter *et al.* 1992; Bruce *et al.* 1994; Farquhar *et al.* 1994). Experimental studies of scrapie have also indicated that some host genotypes appear to be resistant to infection (Davies & Kimberlin 1985; Foster & Dickinson 1988). However, in similar studies conducted to look for genetic determinants for susceptibility to BSE in cattle, no evidence has been found to date for differences in either susceptibility or the length of the incubation period (Wijeratne & Curnow 1990; Curnow *et al.* 1994; Curnow & Hau 1996; Hau & Curnow 1996).

Interim results are available from a recent experimental study on the oral dosing of cattle with brain from cattle affected by BSE. Each of four dose regimens (a single dose of 1, 10, 100 g or three doses of 100 g) was applied to ten cattle. The first animal to show clinical signs of disease did so 34 months after infection; it had received three doses of 100 g. Following 52 months of observation, there have been 28 BSE cases in the exposed cattle (four in the 1 g group, seven in the 10 g group, seven in the 100 g group and ten in the  $3 \times 100$  g group). Kaplan–Meier curves based on these data are given by Anderson *et al.* (1996).

For the BSE-affected animals from the maternal cohort study, the mean age at the onset of clinical signs of BSE was 63.1 and 64.4 months for maternally exposed and control arms, respectively. Although the ages at infection for these animals are

unknown, these figures provide an approximate upper bound for the mean duration of the incubation period.

#### (e) Strain variation

There is much evidence to suggest the existence of distinct strains of the scrapie agent (Bruce *et al.* 1991). These are distinguishable by their varied incubation periods and pathological indications in sheep and mice when host genetic background is controlled for. In experiments similar to those undertaken for scrapie, BSE was transmitted to mice from seven unrelated and geographically distant cattle hosts. The consistency of the pathology and incubation period observed for all seven BSE sources suggests that all seven were infected with the same strain of BSE (Fraser *et al.* 1992; Bruce *et al.* 1994; Bruce 1996).

The experimental work to date is of limited scale and hence is likely to miss rare strains. However, the consistency of the observed pathology of BSE in cattle throughout the current epidemic supports the hypothesis that, as yet, strain variation is limited for BSE (Wells *et al.* 1992). A more recent study compared samples of suspected BSE cases reported in the period 1992–1994 to a similar sample of confirmed BSE cases with the onset of clinical signs of disease in the period 1987–1989 (Simmons *et al.* 1996). This study found no change in the distribution and severity of the vacuolation in diseased animals, again supporting the hypothesis that the BSE epidemic arose from a single stable strain of the aetiological agent. However, given the significance of strain variation in the epidemiology of scrapie, more intensive study is needed in the case of BSE, particularly in the latter stages of the epidemic where sufficient time may have elapsed to favour the evolution of different strain types.

## 4. DEMOGRAPHY

#### (a) Cattle herds and holdings

The lowest level of aggregation of recorded BSE cases in the main database is the herd. The mean size of a herd with at least one BSE case is 81 adult animals. This average is biased upwards compared with the national average herd size because, given identical per capita feed risk, large herds are more likely than smaller herds to generate at least one BSE case.

Herds are organized into holdings, a unit which most often corresponds to the farm. These are the basic units of analysis used in census data (MAFF 1992–1995) and are often classified into dairy and beef holdings. It is possible to estimate minimum holding sizes in the CVL database of confirmed BSE cases by summing the sizes of herds within holdings. This gives a mean holding size of 94 animals, with an average of 1.17 herds per holding. As not all herds within a holding will generate at least one BSE case, these are clearly minimum estimates.

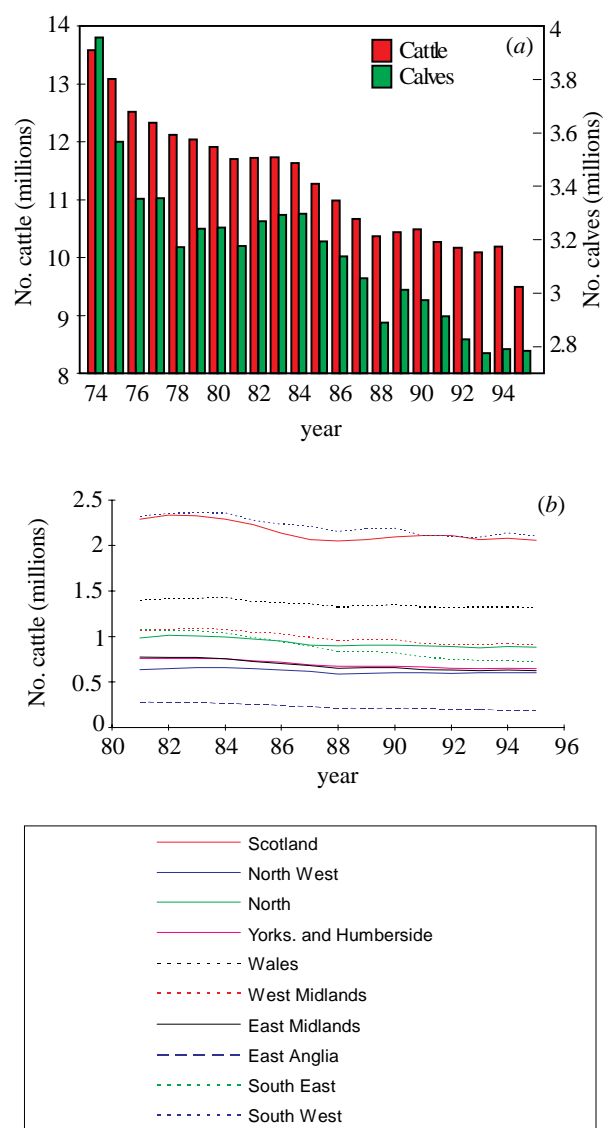


Figure 5. The total number of cattle by year: (a) in GB; and (b) in each MAFF region. The number of calves by year: (a) in GB.

For animals which experienced BSE onset in a holding other than their natal holding, the CVL database records this natal holding (the natal herd was not recorded). The size of natal holdings could be estimated for those which also appeared in the database as BSE-onset holdings. Hence, if a natal holding experienced at least one onset case of BSE, we have an estimate of its size. We were able to estimate the natal holding size for 88% of cases.

It should be noted that all incidences calculated for natal holdings are based on the estimated adult holding size as described above. In some analyses holding size categories (up to 29 adult cattle, 30–49, 50–99 and 100 and over) were used.

#### (b) Trends

The annual cattle census data provide some information about the age distribution and beef/dairy classification of the national herd (MAFF 1975–1990,

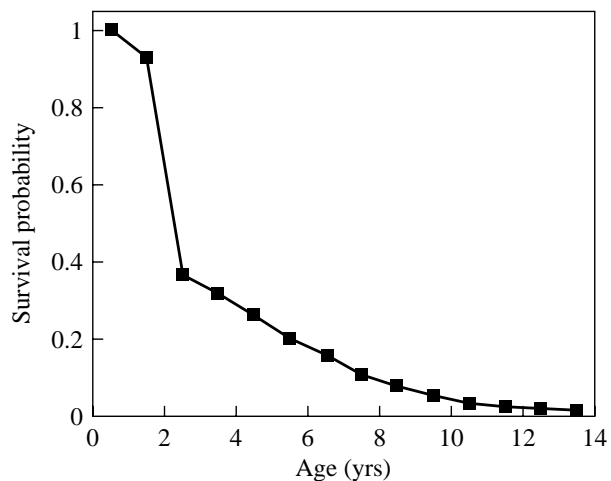


Figure 6. Estimated survival probability of cattle with age.

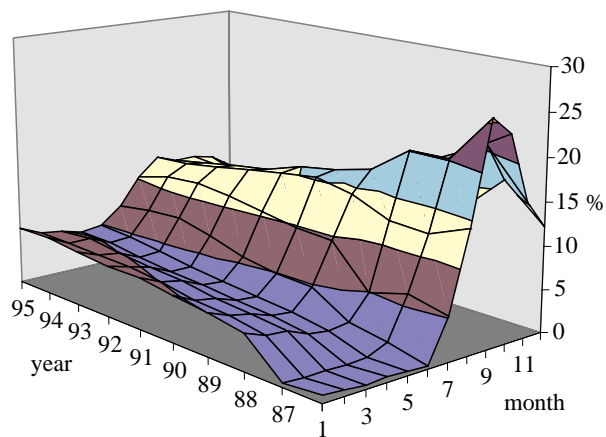


Figure 7. The observed seasonality of births in cattle recorded in National Milk Records from 1986 to 1995.

1992–1995; Department of Agriculture and Fisheries for Scotland 1975–1980; The Scottish Office 1991–1995). The census records, at June 30 each year, the number of cattle in the age classes 0–6, 6–12, 12–24 and over 24 months for each county in Britain. Over the period 1974–1996, these data show that the national herd has declined from 13.6 to 10.2 million cattle (figure 5a) and that the number of calves under 12 months old (a measure of annual recruitment) has declined from 4.0 to 2.8 million (figure 5a). These trends were also examined at the level of the individual county and are presented for the ten MAFF regions in figure 5b. There are eight MAFF regions in England (South-West, South-East, East Anglia, East Midlands, West Midlands, Yorkshire and Humberside, North and North-West) in addition to the regions of Wales and Scotland.

#### (c) Age-specific survival

The annual census does not provide information on the age structure of the cattle population over two years old. More detailed age profiles were obtained from the National Milk Records (NMR) for a subset of dairy herds in each of the years 1982, 1988, 1989, 1991 and 1994 with a minimum sample size of 2000

cattle. Note that these records ignore males (which make up a negligible fraction of the population over two years of age) and do not include beef herds (the age distribution of breeding beef cattle gives mean ages typically up to six months older than for dairy cattle; however, the majority of BSE cases occur in dairy herds).

The ages of cattle in the NMR surveys are estimated from the number of lactations. Data on calving intervals (Esslemont 1992) give the average age of first lactation at 26 months with an average lactation interval of 12.5 months. This allowed the age structure to be rescaled to one-year intervals by linear interpolation and numbers in each class in each year weighted to give total number of cattle over two years recorded in the annual census for that year.

This procedure generated five age distributions. These were used for standard life table analysis (Southwood 1978). Survivorship to age  $x$ , ( $l_x$ ), was calculated as the ratio of numbers in age class  $x$  to  $x + 1$  years to the size of the corresponding birth cohort (0–1 years). There was no indication of temporal trends in  $l_x$  values, therefore mortality rates per age interval ( $q_x$ ) were calculated for each age distribution. Geometric mean  $q_x$  values were used to provide an overall survivorship function for the period of interest (figure 6). As sufficient data were available only for cattle up to 12–13 years old,  $q_x$  values for older cattle (up to 17–18 years) were obtained by extrapolation of the linear trend from age classes 3–4 to 12–13 years. As the birth cohort is defined as the age class 0–1 year, some mortality of calves up to one year old is ignored by this analysis. In practice, there is significant mortality of young calves (natural deaths, disposal of unwanted animals, slaughter or export as veal) but these animals are of limited relevance to interpretation of the BSE epidemic pattern.

The resulting demographic model has a constant survivorship function but a variable recruitment rate, taken as the numbers of 0–1 year old calves from annual census data. The survivorship function shows a substantial loss of cattle between 1–2 and 2–3 years old (figure 6), corresponding to the age at which many animals are slaughtered for beef. The mean life expectancy at birth is 3.0 years, but the mean life expectancy of cattle which are to be kept for milk production is 5.8 years. The model predicts culling rates of cattle over two years old of 22–23% per year, in good agreement with observed culling rates (Esslemont 1992). Over the period of the BSE epidemic, the model predicts the total cattle population over two years old in Britain to within  $\pm 4\%$  of observed values and predicts the mean age of this population to within  $\pm 0.2$  years.

#### (d) Calving patterns

Data on the seasonality of calving are available from NMR records, giving the month of birth for each calf over the period 1986 to 1995, based on a minimum sample size of 5000 births. The data show that calving patterns are highly seasonal and that

the degree of seasonality has changed significantly over the last ten years (figure 7). Seasonality in calving reflects differences in calving interval (Esslemont 1992; Kafidi *et al.* 1992) and calving rates also vary with climate, herd, breed and sire (Kafidi *et al.* 1992; Ray *et al.* 1992).

To account for this seasonality in the back-calculation model presented in Ferguson *et al.* (1997a), recruitment was partitioned into four quarters of each year, each weighted according to the relative calving rate in that quarter in that year. The survivorship function was rescaled to quarter years by geometric interpolation, but the survivorship function itself was not taken to be seasonal.

#### (e) Movement between herds, counties and regions

Approximately two-thirds of the confirmed BSE cases are reported to experience the onset of clinical signs of disease in the same herd in which they were born. The remainder were purchased before the reported onset of clinical signs. This proportion varied over time and within regions (figure 8). The average age at purchase was  $2.99 \pm 0.01$  years.

The distances which cattle were moved could be ascertained by comparing the county and region of birth to that at BSE onset in purchased cattle. Of the purchased cases for whom information on the natal holding county was available (62%), around half (49%) onset in the same county as birth, while a third (33%) onset in a different region from that of birth. However, more detailed data on movement is required to properly assess the spatial disaggregation of cases.

### 5. EPIDEMIOLOGICAL PATTERNS IN BSE INCIDENCE

#### (a) Population incidence by age and time

The age at disease onset for confirmed BSE cases was known for 97% of the total reported BSE cases in the main database. The distribution of age at onset differs by birth cohort, as shown in figure 2. It is well known that as the force of infection increases over time, the average age at infection decreases and thus the average age at onset of clinical signs decreases (Anderson & May 1991). Such patterns can thus arise even in the absence of a time-varying incubation period, given that in the early phases of the epidemic the volume of infected material entering cattle feed was rising up to the end of 1989. However, such a mechanism relies on the variation in susceptibility with age being minor, an assumption that is unlikely to be valid for BSE. This is further discussed in the companion paper (Ferguson *et al.* 1997a).

#### (b) County and regional incidence

In the following analyses, we use two geographical scales: county and MAFF region. Information on natal county was available for 88% of the total confirmed BSE cases. The distribution of cases by



county must be examined using the incidence per head of cattle to avoid spurious identification of high risk areas that have more BSE cases simply because they have more cattle. The annual incidence maps presented by Anderson *et al.* (1996) were based on county of diagnosis. Examination of the annual incidence by natal county reveals similar patterns.

Highly significant heterogeneity was seen between counties. The number of cases observed by natal county differed considerably ( $\chi^2_{66} = 72\,948$ ,  $p < 0.0001$ ) from the number expected under the assumption that case numbers were proportional to the number of cattle in each county (taken from the 1988 census). Six counties (Dorset, Hampshire, Norfolk, Somerset, West Sussex and Wiltshire) with significantly more cases than expected each contributed more than 3000 to the  $\chi^2$  value, as did two counties with significantly fewer cases than expected (Grampian and Strathclyde).

Figure 9 records the longitudinal pattern of BSE incidence by MAFF region in which the diseased animal was born. Thus, while the number of cases per head of cattle varied both between regions and over time, a striking degree of similarity is observed in the overall temporal pattern of infection in different regions.

### (c) Incidence within holdings

Given a constant rate of exposure to infection and a constant survival distribution over time, we would expect the BSE incidence per head of cattle to be constant over all holding sizes. In this section we therefore examine the per head incidence of BSE by the size of the natal holding. As noted in § 4*a*, the number of adult cattle in each natal holding giving rise to a BSE case can only be given a minimum bound through analysis of the BSE case database. In addition, for 29% of the natal holdings identified, we were unable to obtain any estimate of the holding size. Our analyses therefore explore the sensitivity of the results to these uncertainties.

In figure 10, we present the estimated per head incidence of BSE by natal holding size category (up to 29 adult cattle, 30–49, 50–99, and 100 and over). To assess the sensitivity of the results to assumptions about missing data on natal holding size, we present analyses based on three assumptions about the missing data. At the two extremes, for each holding size category, we can either assume that all holdings with missing data belong to this category or that none do. Figures 10*a–d* show the resulting temporal patterns of incidence by natal holding size for these two extremes. The results show larger per head BSE incidence rates in the largest holdings. It should be noted that the underestimation of holding sizes may result in the mis-allocation of some holdings with one or more BSE cases to lower holding size categories. Thus our observation that larger natal holdings have higher incidence can only be strengthened by the collection of additional holding size data.

Figure 10*e* shows the average cohort incidence per head by natal holding size. In addition to the two extreme assumptions regarding missing size data outlined above, we also consider the case where the size category is missing at random conditional on the number of cases. Under all three assumptions, cattle born in larger holdings appear to be at increased risk of disease. Figure 10*f* shows that this effect is greater in England than in Wales or Scotland. Although such a finding could arise due to the presence of some form of direct horizontal transmission, caution should be exercised in reaching such a conclusion without more detailed analysis. In particular, data are required on how the use of MBM feed varies with holding size; it is possible that larger holdings use more intensive farming methods. Alternatively, holding sizes may be geographically correlated with county-scale spatial variability in incidence. To interpret these findings, more information is therefore required on the regional distribution of holdings of various sizes and on the feeding practices of different holdings.

Figure 11 shows the frequency distribution of cases per holding by natal holding size category. Alongside this distribution we plot the expected values assuming a Poisson (random) distribution. Again, we consider the two extreme assumptions regarding missing data. Thus figures 11*a, c, e, g* assume that none of the missing data belongs to the relevant natal holding size category, while figures 11*b, d, f* assume that all of the missing data belong to the relevant size category. For the largest size category, the number of holdings with one or more BSE cases exceeds the total number of holdings, if it is assumed that all holdings with missing data belong to this category, and so we are unable to make the latter assumption for this size category. In every case, the results indicate significant deviation from the Poisson assumption indicating aggregation of cases within natal holdings.

We further examine the clustering of cases within holdings by considering the relationship between the mean and variance in numbers of cases within holding size categories and cohorts. Under a Poisson distribution, the mean is equal to the variance, while the mean and variance conditional on at least one case are given by

$$E(x|x \geq 1) = \frac{\lambda}{1 - e^{-\lambda}}$$

and

$$\text{Var}(x|x \geq 1) = \frac{\lambda^2 + \lambda}{1 - e^{-\lambda}} - \frac{\lambda^2}{(1 - e^{-\lambda})^2},$$

where  $\lambda$  is the unconditional mean of  $x$ . At the upper and lower limits of  $\lambda$ , the conditional mean minus 1 is therefore approximately equal to the conditional variance. Figures 12*a–d* show the relationship between the unconditional mean and variance stratified by natal holding size category under the two extreme assumptions regarding missing holding size data, while figures 12*e, f* combine the data for the four holding size categories, ignoring the missing

data, for the unconditional and conditional cases, respectively. In all cases, the results again show a deviation from the Poisson distribution which increases with an increasing mean number of cases. The conditional means and variances show a more defined deviation from the Poisson distribution and are likely to be more reliable since they do not depend on the estimation of the number of holdings with no BSE cases.

The patterns underlying the observed clustering of cases within holdings were examined by studying the incidence per holding by year of onset and birth cohort. Assuming stationarity, for each time separation (lag), a single correlation estimate can be obtained. Thus, the correlation functions  $\rho_Y(l)$  and  $\rho_C(l)$  are defined to be the correlations within holdings between the incidence in years  $i$  and  $i+l$  and between the incidence in birth cohorts  $j$  and  $j+l$ , respectively. The years of onset for which complete data are available are 1986–1995, so time-lags from 1 to 9 years were examined. Although cases have been recorded during that time from animals from birth cohorts 1974–1993, very few cases arise from the early cohorts. The correlations were therefore examined for time lags of 1–12 years for the 1981–1993 birth cohorts.

These sample correlation functions are displayed in figure 13a. The correlations were calculated using the data from all 90 584 GB holdings. Confidence intervals were calculated using the transformation from  $r$  to the approximately normally distributed quantity  $z = 0.5(\ln(1+r) - \ln(1-r))$  (Snedecor & Cochran 1989). The approximate standard error of  $z$  is  $1/\sqrt{n-3}$ . Since  $n = (13 - \text{lag})N$  for the cohort correlations and  $n = (10 - \text{lag})N$  for the year of onset correlations, where  $N = 90\,584$ , the number of holdings, the confidence intervals are so narrow as to be invisible on the graph.

The results show a substantial positive correlation in incidence for lags up to three years for cohorts and up to five years for years of onset. These results illustrate the clustering of infection within holdings. The higher correlations between years of onset may reflect point infections yielding clinical onsets in more than one calendar year. In figure 13b we present the sample correlation functions by cohort stratified by cohorts born before and after the introduction of the ruminant feed ban. The results show significantly less correlation in the number of cases in consecutive cohorts following July 1988. These results suggest that the infection process was more sporadic in these later cohorts.

## 6. CONTROL STRATEGY DESIGN

Since 1988, the British government has passed many regulations designed to monitor and curb the BSE epidemic. The disease became notifiable on 21 June 1988 for British cattle, and from 18 July 1988 ruminant protein was banned from ruminant feed (Statutory Instrument 1988). On 25 September 1990, the use of specified bovine offals was banned from

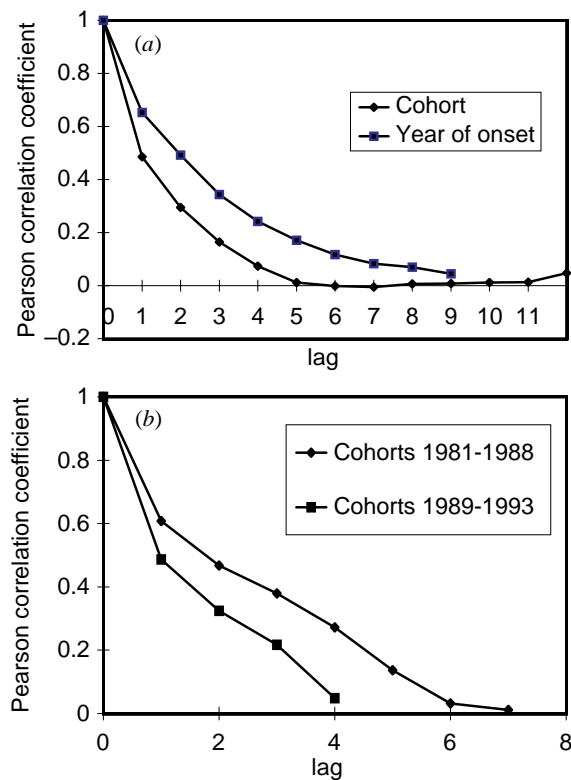


Figure 13. The Pearson correlation coefficient of the incidence within holdings: (a) over various cohort and year-of-onset lags; and (b) over various cohort lags stratified by cohorts born before and after the introduction of the ruminant feed ban.

all animal feed (Statutory Instrument 1990). Finally, in June 1994 the feeding of mammalian protein to ruminants was prohibited throughout the European Union (other than Denmark) (EC Decision 1994).

In addition to these interventions, which focus on the sources of feed-borne infection, the implementation of a targeted culling programme has the potential to reduce the number of BSE cases arising in the future. Given evidence for an enhanced risk to calves born to infected dams, a targeted cull would also act to reduce the number of maternally infected calves in the future. In May 1996, MAFF described a planned selective culling policy targeting approximately 80 000 cattle identified to be at high risk from BSE (MAFF 1996). In the following sections we consider the performance of different control strategies.

### (a) Aims

Strategies for the control of BSE infection should be designed to maximize the number of BSE cases prevented, while minimizing the costs in terms of the number of animals culled and the number of herds involved. A culling programme can be described in terms of its effectiveness (proportion of future cases prevented), efficiency (number of cases prevented per animal culled) and scale (number of cattle culled). The goal of any culling eradication programme must be clearly identified in terms of such measures, with possible implementation constraints (i.e. the costs involved in identifying or visiting herds that have re-

ported cases or tracing offspring born to dams who developed BSE) considered in parallel.

Given these aims, in this section we evaluate a range of culling policies: age targeted—slaughtering all animals born between dates  $y$  and  $y'$ ; holding targeted (cases)—slaughtering all cattle born in herds from which at least one case has arisen; holding targeted (incidence)—slaughtering all cattle in herds with greater than a specified incidence level (if the critical level is specified to equal zero, then this is equivalent to the previous policy); and maternally targeted—slaughtering animals born within  $x$  months of onset of BSE onset in the dam. To evaluate the future effectiveness of these culling policies, assumptions need to be made about how the fraction of cases predicted to arise from the targeted animals in the absence of culling varies with time. To characterize this fraction as a function of the number of years after implementation, we used the CVL case database to determine the effect of these culling policies had they been implemented in the past (§ 6*b*). For example, to examine the performance of the policy of culling all animals born before the ban on ruminant feed initiated on 18 July 1988, we determine the number of cases that would not have arisen had such a policy been implemented on 1 January 1989, or on 1 January 1990, and so on.

This retrospective implementation of culling policies on the BSE case database allows the evaluation of policy performance without the need for modelling. However, to evaluate any culling policy implemented now or in the future, model predictions are required for the number of cases expected to arise in future years from both targeted and untargeted animal groups. In § 6*c* we utilize the model predictions presented in Ferguson *et al.* (1997*a*). Such methods were used to evaluate targeted culling policies in Anderson *et al.* (1996). In making these predictions, we assume that currently implemented culling policies would follow similar trends to those observed in our retrospective analysis.

Animals over 30 months of age are currently excluded from human food as agreed by the EU Council of Agriculture Ministers on 2 April 1996. These animals are currently slaughtered when put forward by the owner under the ‘over thirty month slaughter’ (OTMS) scheme. The number of animals slaughtered per week under this scheme has varied from approximately 25 000 to 50 000. By 14 March 1997, there had been 1 120 822 animals slaughtered under this scheme in GB. In § 6*d* we present an analysis of the effects on the predicted number of future BSE cases if OTMS slaughtering were optimally targeted.

### (b) Retrospective implementation of culling policies

#### (i) Age-targeted policies

We evaluated the retrospective implementation of one age-targeted policy, namely culling all animals born before the ban on ruminant feed initiated on 18 July 1988. BSE cases did arise in animals born after

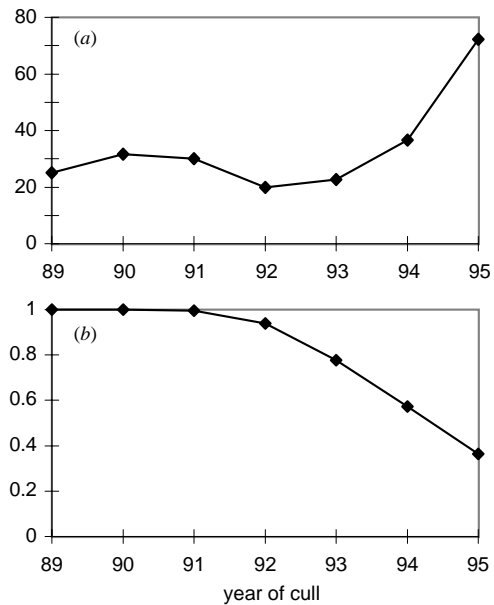


Figure 14. The results of age-targeted culling policies in: (a) the number of animals culled per case prevented in the year following the cull; and (b) the fraction of cases prevented in the year following the cull. (Note that efficiency increases as the number of animals culled per case prevented decreases.)

this time; however, these were a small proportion of the total number of cases observed.

Figure 14*a* shows the first-year efficiency of this culling policy (in terms of the number of animals culled per case prevented) by year of initiation. To avoid differences over time due simply to cases not observed to date, we consider only the number of cases prevented in the year following the cull. Hence, while these values cannot be compared to estimates of true efficiency (based on the number of cases prevented in all future years), they provide an efficiency profile of the culling policy were it initiated at different time points.

The results indicate a higher efficiency for this strategy had it been implemented early in the epidemic. From 1994 onwards, while a significant number of uninfected cattle from these cohorts are still alive, few cases are observed, and so the efficiency of this culling policy decreases dramatically.

Figure 14*b* shows the fraction of all cases prevented in the year following the cull. This fraction predictably declines over time. In the early years, a large proportion of cases arise from cohorts before the ban, while in later years this proportion decreases. In particular, cases born after the ban are not affected by this culling policy. The trends observed are similar for other retrospectively implemented age-targeted culling policies.

#### (ii) Holding-targeted (case) policies

The analyses presented in § 5*c* showed a significant clustering of cases within holdings (figures 10–12). These results suggest that a more efficient culling policy might be to target holdings from which one or



more cases have already arisen. We refer to this type of culling as holding-targeted (case).

Through retrospective implementation in the CVL database, we evaluated a policy to cull all cattle in holdings within a selected cohort from which at least one case had been recorded. Figure 15*a* shows the effectiveness of this policy for a range of possible implementation years (with culls implemented on 1 January of the specified year) and two cohorts (1987 and 1988). Within a cohort we consider the number of animals culled per case prevented in the year following the cull. The results show a substantial decrease in efficiency as the year in which the culling is introduced moves closer to the present time. This is due to the epidemic pattern in these cohorts—the decline in cases arising from these cohorts is greater in later years than the decline in the number of cattle surviving.

Figure 15*b* shows the fraction of total cases within the targeted cohort prevented in the year following the cull. This appears to follow a logistic pattern, with a small proportion of cases prevented if the cull is implemented early on. This is due to lack of information early on in the cohort epidemic; that is, few cases have yet arisen at early ages in these cohorts, making targeting of holdings difficult.

Of particular interest is whether the fraction of cases prevented for a given cohort is predictable through time. A predictable pattern would facilitate estimation of the fraction of cases to be prevented in the future if the culling policy were to be implemented at the present time. Figure 15*c* shows a slight but stable decline in this fraction, suggesting that estimates of the future efficiency of this policy can be reliably deduced.

#### (iii) *Holding-targeted (incidence) policies*

The analyses of incidence within holdings in consecutive years presented in § 4*c* showed a strong correlation between years which decreased with increasing time-lag (figure 13). This result suggests that future cases are more likely to arise in holdings which have already experienced a high incidence of infection. In this scenario, culling policies which target high-incidence holdings may be more efficient than those targeting all holdings from which cases have arisen to date.

In this analysis, we consider three holding-targeted incidence policies. These policies target animals within a selected cohort from holdings with an incidence in the top 20% of all recorded incidences (among holdings with at least one BSE case), with an incidence above one case per 27 cattle and with an incidence above one case per 50 cattle. The results are presented in figure 16 for the 1987 and 1988 cohorts.

Figure 16*a* indicates that beyond four years of age as the cohorts age, the implementation of an incidence-targeted culling policy becomes increasingly less efficacious; that is, the number of animals culled per case prevented increases. This is due to a steep decline in the numbers of cases observed

in older animals. All three holding-targeted (incidence) policies are more efficacious than the holding-targeted (case) policy.

The pattern of the fraction of cases prevented as a function of when the cull was implemented again appears to follow a logistic curve (figure 16*b*). Clearly, the future fraction of cases prevented will be lower than that of holding-targeted (case) policies.

Finally, figure 16*c* again shows a gradually decreasing fraction of cases prevented for a given cohort and cull date through time. Thus, estimates of the future efficiency of holding-targeted (incidence) culling policies can be estimated from the efficiency of such policies to date.

#### (iv) *Maternally targeted and combined policies*

Evaluation of the effectiveness of maternally targeted policies in the case database requires information linking dams and their calves. While some information is available linking cases born following the introduction of the feed ban in July 1988 to BSE affected dams, there was insufficient information to accurately describe the past effectiveness of maternally targeted policies and so such an analysis was not attempted. However, given estimates of maternal transmission calculated in the maternal cohort study (see § 3), we were able to estimate the future effectiveness of these policies. These results are given in § 6*c* (iv).

#### (c) *Future effectiveness of culling policies*

##### (i) *Age-targeted policies*

While the culling of all animals born between October 1990 and June 1993 by 1 January 1997 is predicted to prevent 56% of the cases predicted to arise in the years 1997–2001 (table 1), the efficiency of this policy, like that of other age-targeted culling policies (Anderson *et al.* 1996), is very low. The significant clustering of cases within herds means that age-targeted policies perform poorly compared to herd-targeted policies. (In this context it should be noted that maternally targeted policies are also herd-targeted.)

##### (ii) *Holding-targeted (case) policies*

We consider a policy targeting cattle in the 1990–1993 birth cohorts in herds from which a case originated in the corresponding cohort between January 1991 and December 1995. The implementation of this policy by 1 January 1997 is predicted to prevent 24% of cases predicted to arise in the years 1997–2001 (table 1). Such policies are considerably more efficient than non-targeted and age-targeted culling, but are less efficient than policies based on a non-zero incidence threshold since targeting all holdings with a case in the time period of interest penalizes larger holdings where the chance of a single case is larger.

##### (iii) *Holding-targeted (incidence) policies*

Culling cattle born in the July 1989–June 1992 cohorts in herds from which more than one case per



Table 1. *Comparison of possible culling policies*

policy	culling policy description	cases prevented		total cattle culled		number of natal holdings	cattle culled per case prevented
		number	%	number	%		
1	<i>non-targeted</i> all cattle	6900	100	9 360 000	100	111 000	1357
2	<i>age-targeted</i> all cattle born 10/90–6/93	3881	56	2 030 000	22	≤ 111 000	523
3	<i>holding targeted (case)</i> cattle born in the cohorts 1990–1993 in holdings from which a case originated in the corresponding cohort during 1/91–12/95	1678	24	127 000	1.4	6 240	76
4	<i>holding targeted (incidence)</i> cattle born in 7/89–6/92 in holdings with more than one case per 27 cattle in the cohort range during 1/91–12/95	734	11	21 300	0.23	638	29
5	as policy 4 but with a threshold of one case per 50 cattle	1508	22	71 900	0.77	2 000	48
6	<i>maternally targeted</i> cattle born after 10/90 within 6 months of BSE case in the dam	581	8.4	< 22 000	0.24	≤ 22 000	38
7	<i>combined maternally and incidence targeted</i> incidence (one per 27) and maternally targeted policy (policies 4 and 6 combined)	1315	19	< 44 000	0.47	≤ 25 500	33
8	incidence (one per 50) and maternally targeted policy (policies 5 and 6 combined)	2089	30	< 94 000	1.0	≤ 26 800	45

Table 2. *Optimal cohort culling orderings*

programme (ordering of targeted cohorts)	time required (months)	% cases prevented in 1997–2001	
		10% maternal transmission (6800 cases total)	no maternal transmission (10 400 cases total)
(1) (92, 91, 90, 93, 94, 89, 88)	37.4	39	43
(2) (92, 90, 91, 89, 93, 88, 94)	26.0	53	58
(3) (88, 92, 90, 91, 93, 89, 94)	16.6	66	73
(4) (88, 92, 90, 91, 93, 89, 94)	16.6	67	73

27 cattle originated in the cohort range during January 1991–December 1995 on 1 January 1997 is predicted to prevent 11% of cases predicted to arise in the years 1997–2001 (table 1). A similar policy with an incidence threshold of one case per 50 cattle is predicted to prevent 22% of cases in the same five-year period, though the latter policy is less efficient than the former. It should be noted that the latter prevents a similar number of cases to the examined holding-targeted (case) policy with a greater efficiency (i.e. a lower number of cattle culled per case prevented).

Culling policies targeted on the basis of incidence become increasingly efficient as the incidence threshold increases. This benefit is offset, however, by the corresponding decrease in the effectiveness.

(iv) *Maternally targeted and combined policies*

The model predictions (Ferguson *et al.* 1997a) provide sufficient information to predict the effect of culling cattle born to dams confirmed with BSE, while a retrospective implementation of maternally targeted culling on the database of confirmed BSE cases would be limited since while the majority of the dams of confirmed BSE cases among cattle born after the introduction of the ruminant feed ban have been identified, data on the identities of dams of other confirmed BSE cases were not available.

Culling cattle born after October 1990 within six months of the onset of the clinical signs of BSE in the dam is predicted to prevent 8% of cases predicted to arise in the years 1997–2001, assuming that maternal transmission occurs at the rate of 10% over the last

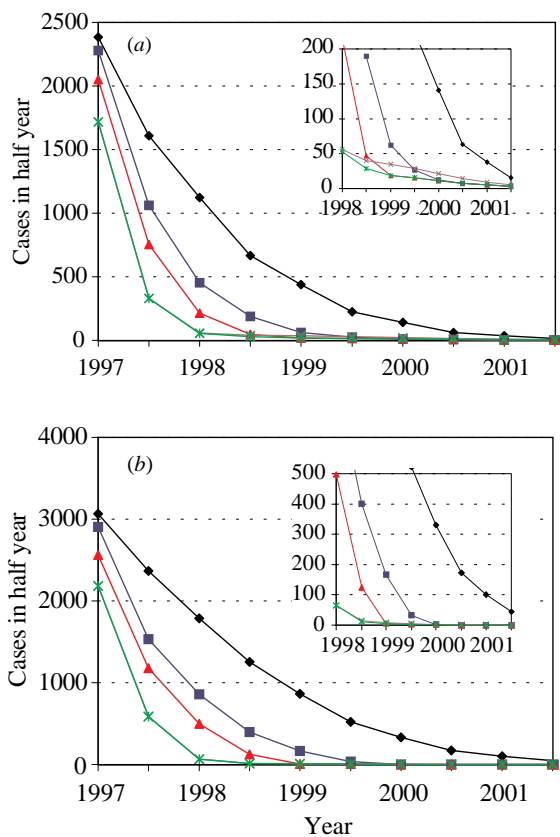


Figure 17. The predicted number of BSE cases in the years 1997–2001 under three culling policies and with no culling, assuming: (a) 10% maternal transmission over the last six months of the maternal incubation period; and (b) no maternal transmission. Both models assumed no horizontal transmission. Inset graphs show detail for 1998–2001.

◆ No targeting  
 ■ 15000 p.w. cohort targeted cull (in addition to standard 25000 p.w. slaughter rate)  
 ▲ 25000 p.w. cohort targeted cull (in addition to standard 25000 p.w. slaughter rate)  
 × 50000 p.w. cohort targeted cull (no extra culling to remove backlog)  
 \* 50000 p.w. cohort targeted cull (+ extra year of culling to remove backlog)

six months of the incubation period in the dam. Maternal targeting is very efficient, but a large number of holdings would be affected by the cull.

Combining maternal targeting with a holding-targeted policy based on incidence is predicted to achieve high levels of efficiency and effectiveness, in terms of the number of cattle culled per case prevented and the number of cases prevented (table 1).

**(d) Optimal culling of animals over 30 months of age**

All possible orderings of the seven cohorts (1988–1994) with highest expected incidence (over the period 1997–2001) were considered, making allowance for the time required for clearance of each cohort and the cases arising from the targeted but not yet slaughtered animals. Culling affects the overall de-

mography of the GB cattle herd and hence influences the expected case numbers. This is allowed for in calculations.

Four types of programmes have been considered: (1) the existing baseline slaughtering of 25 000 cattle per week over 30 months with an additional cohort-targeted culling of 15 000 per week; (2) as in (1) but with the additional cohort-targeted culling of 25 000 per week; (3) cohort-targeted culling of 50 000 per week with no other culling of OTMS-eligible animals while the targeted cohorts are being eliminated, after which the pre-OTMS pattern of slaughtering is resumed; and (4) as in (3) but once the targeted cohorts have been culled, the pre-OTMS slaughter pattern is resumed together with clearance (at a maximum rate of 25 000 animals per week) of the backlog of animals which would have otherwise been slaughtered while the elimination programme was ongoing.

We considered the cases of no maternal transmission and 10% maternal transmission over the last six months of the maternal incubation period. In both cases, the programmes targeting 50 000 animals per week are clearly seen to prevent more cases than those which target 15 000–25 000 OTMS animals slaughtered per week (figure 17 and table 2). However, programme (3) is rather less effective in later years due to the increase in life expectancy in animals from non-targeted cohorts caused by the cessation of their slaughter during the implementation of the programme. The increased number of such animals left after completion of programme (3) can be seen partly compensating for any reduction in dairy production caused by elimination of targeted animals. In reality, therefore, the end result of any targeted programme utilizing all available slaughter capacity is likely to lie somewhere between programmes (3) and (4).

Note that by the time any of the policies have been completed, infection prevalence is reduced by at least 90% compared with what it would have been without targeted culling. Targeting within OTMS would have been less effective if implemented after January 1997.

**7. CONCLUSIONS**

In the absence of more complete biological data on the nature and pathogenesis of the BSE aetiological agent than that available (and described here), thorough analysis and modelling of the epidemiological pattern of reported cases become vital to gain insight into the epidemic process and the transmission dynamics of the aetiological agent. Such insight is essential for the design and evaluation of control strategies and for estimating past patterns of infection and predicting future trends in case incidence. Detailed statistical analysis of the underlying heterogeneities present in the case database is a necessary prerequisite for an understanding of key epidemiological determinants and therefore the design of robust mathematical models. This paper has presented a comprehensive statistical description of case data, together with an analysis of available demographic

information. These lay the foundation for the back-calculation models presented in the companion paper (Ferguson *et al.* 1997a), inform control strategy design and highlight priority areas for future research.

The nature of the information contained in the BSE case database presents a nearly unique opportunity to examine the detailed spatio-temporal structure of an epidemic, but before such analyses are performed, it is essential to quantify any systematic biases and missing values. There are two main types of missing values. Only 70% of the confirmed BSE cases can be traced to their natal holding and dates of birth are not available for all cases. In many instances, the date of birth can be estimated from the approximate age of the animal at onset, but doing this exposes one of the major sources of bias in the data—an over-representation of cases with an integer age at disease onset. Overall, however, of the 163 450 confirmed cases of BSE, 97% had adequate information recorded to identify the birth cohort. The limited missing data give us confidence that the patterns we observe—at least at the yearly birth cohort level—will be very similar to those that would be obtained from the complete data. The second main bias in the case data is an apparent seasonality in the distribution of onset dates. Methods are being developed to correct for these biases, but at present they pose major problems for the construction of models that attempt to fit case data which are more finely stratified than by year of birth and age at onset.

A thorough understanding of the demography of the GB cattle population is the second prerequisite for understanding the pattern of cases observed. Here, we have derived a simple survivorship model, drawing on published recruitment data, and longitudinally sampled age distributions from a variety of individual herds. The epidemiological relevance of survivorship lies in the long incubation period of BSE; most cases are thought to have been infected in the first two years of life, but disease onset typically occurs at age six, by which time the majority of animals have been slaughtered. Two further demographic features are of interest; the national herd declined by 30% from 1974 to 1995 and there have been significant temporal changes in the degree of calving seasonality seen in the GB herd.

The key aim of the descriptive analyses presented here was to identify the major heterogeneities that affect the pattern of BSE cases observed. A key feature of the epidemic to date is the clustering of cases on large and small geographical scales. While the temporal incidence pattern is strikingly similar for all ten MAFF regions, the magnitude of the epidemic differs significantly. At the county level, considerable heterogeneity in incidence was observed. These results reflect a highly heterogeneous infection process, possibly at a finer spatial scale. This is reflected in holding-level analyses, where the distribution of BSE incidence rates is highly overdispersed—indicating strong clustering effects. In addition, cattle born in larger holdings appear to be at increased risk for disease, although this result requires further information on the regional distribution of cattle and on

feeding practices before any causal effect can be hypothesized. In contrast to the high degree of spatial heterogeneity observed, within-herd temporal variation in incidence seems relatively minor, with a high degree of correlation in observed yearly incidences and birth cohorts.

These features are highly favourable for the design of small to medium scale selective culling policies, enabling use of both cohort and holding-incidence targeting to maximize the number of future cases prevented while minimizing the number of animals culled. Targeting for large-scale policies is more problematic, however, since the over dispersion of the herd-incidence distribution causes rapidly diminishing returns for policies utilizing low incidence thresholds. We have also demonstrated in this paper that the effectiveness of culling policies depends critically on the timescale over which they are implemented and the ordering of animals targeted for slaughter. Accurate evaluations of culling scheme effectiveness should therefore be designed with careful reference to the epidemiological pattern (in age and time) of infections to date. This necessitates the use of mathematical models to estimate past and future trends in infection incidence (Ferguson *et al.* 1997a).

Beyond the data available to date in the main case database, a number of other variables would considerably enhance the analyses presented in this paper. To determine more precisely the relative contributions of direct maternal transmission and enhanced genetic susceptibility to the observed maternal-risk enhancement (Donnelly *et al.* 1997a,b), it would be particularly useful to have life history data for all calves born to dams diagnosed with BSE, with analogous records for the offspring of a matched dam who remained unaffected by BSE. This would considerably enhance the power of any analysis of dam-calf pairs to describe the maternal-risk enhancement as a function of the time from birth of the calf to onset of clinical signs in the dam. Precise information on natal herd and holding sizes and on the spatial demography of the national herd would remove much of the uncertainty in our estimates of incidence presented in §5. In particular, our ability to interpret the observation that cattle in larger holdings appear at higher risk for disease is limited by these uncertainties. In addition, detailed information on feeding practices within holdings would allow an exploration of possible between-holding variation, a factor which could in part explain this observation. Given such data, detailed holding-based models could be constructed to further explore the observed spatial and temporal clustering of cases. Such models can aid our understanding of the dynamics of the infection process, thereby allowing a fuller exploration of the factors determining the statistical associations presented in this paper.

Finally, of critical importance in the future will be the use of the epidemiological methods presented in this and the companion paper (Ferguson *et al.* 1997a) to refine estimates of past human exposure to BSE infected material over time. In order to accurately characterize the relative risk to humans from the

consumption of beef and beef products from BSE infected animals, it is necessary to characterize a number of factors. These include the number of infected animals slaughtered by time and incubation stage, the concentration of the infectious agent in infected animals as a function of incubation stage and the effectiveness of regulations at preventing human exposure. However, the current rapid decline in the BSE epidemic and the absolute ban on the use of cattle over 30 months of age in food production, together with the earlier SBO ban, are likely to have greatly reduced any human exposure to BSE in recent years and in the coming final stages of the epidemic in cattle.

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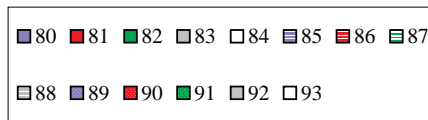
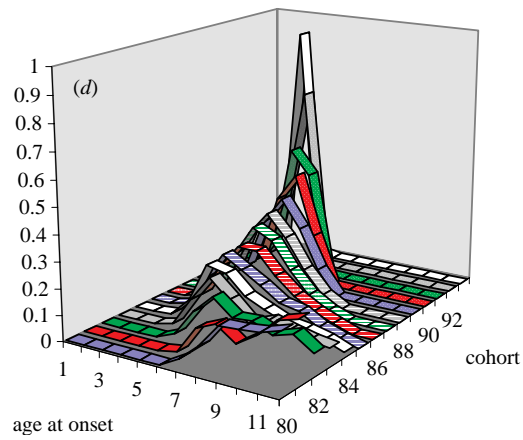
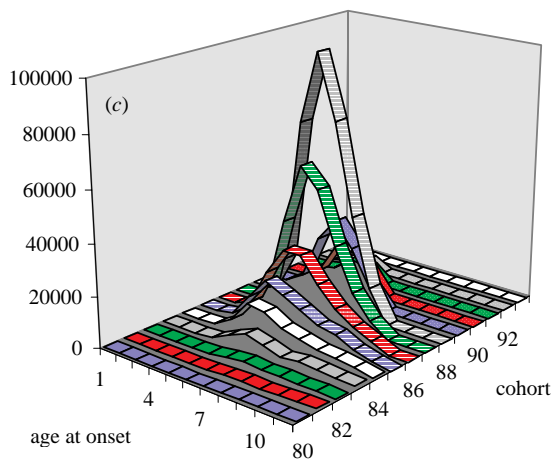
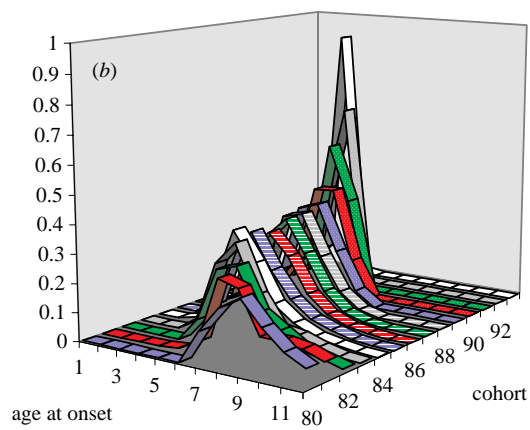
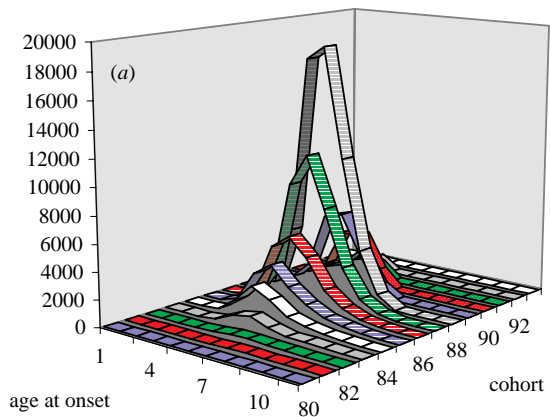
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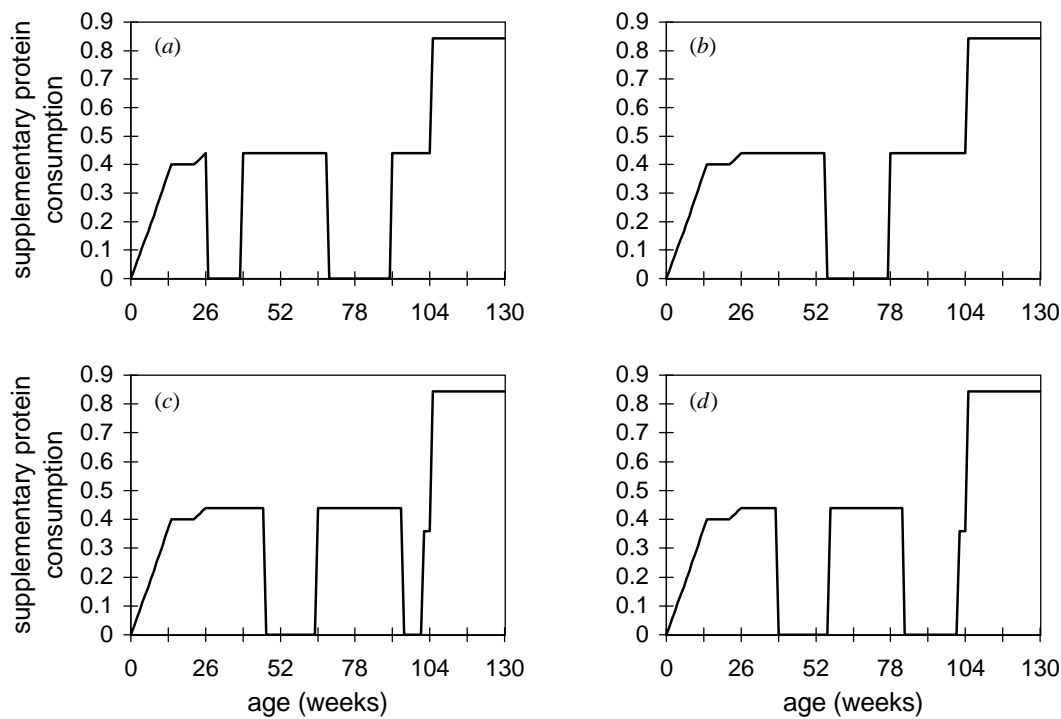


Figure 4. The relative amounts of supplementary protein consumed by dairy cattle on the IAH farm at Compton, Berkshire for animals born in (a) December, (b) March, (c) July, and (d) September. For cattle less than two years of age, the profile gives an average intake reflecting a combination of seasonality in feed consumption and seasonality in birth dates.

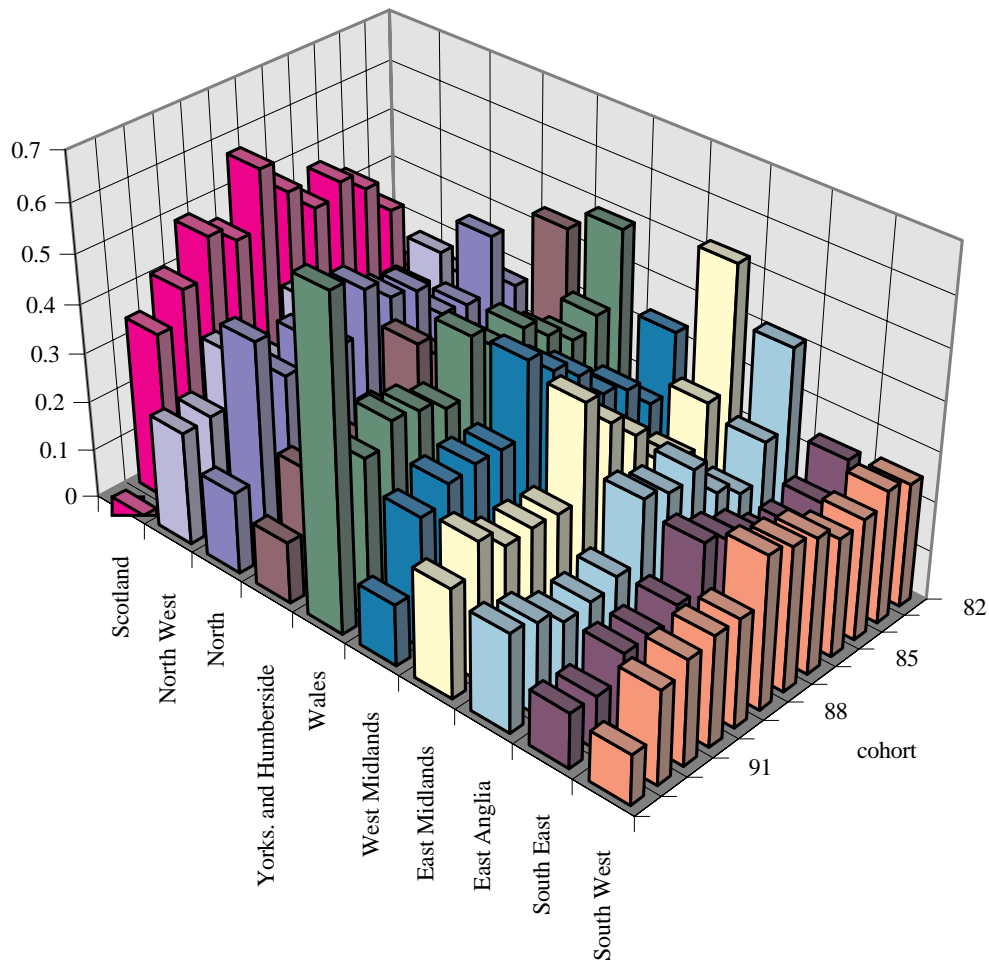


Figure 8. The proportion of confirmed BSE cases which experienced disease onset in a herd other than that into which it was born by MAFF region and birth cohort.



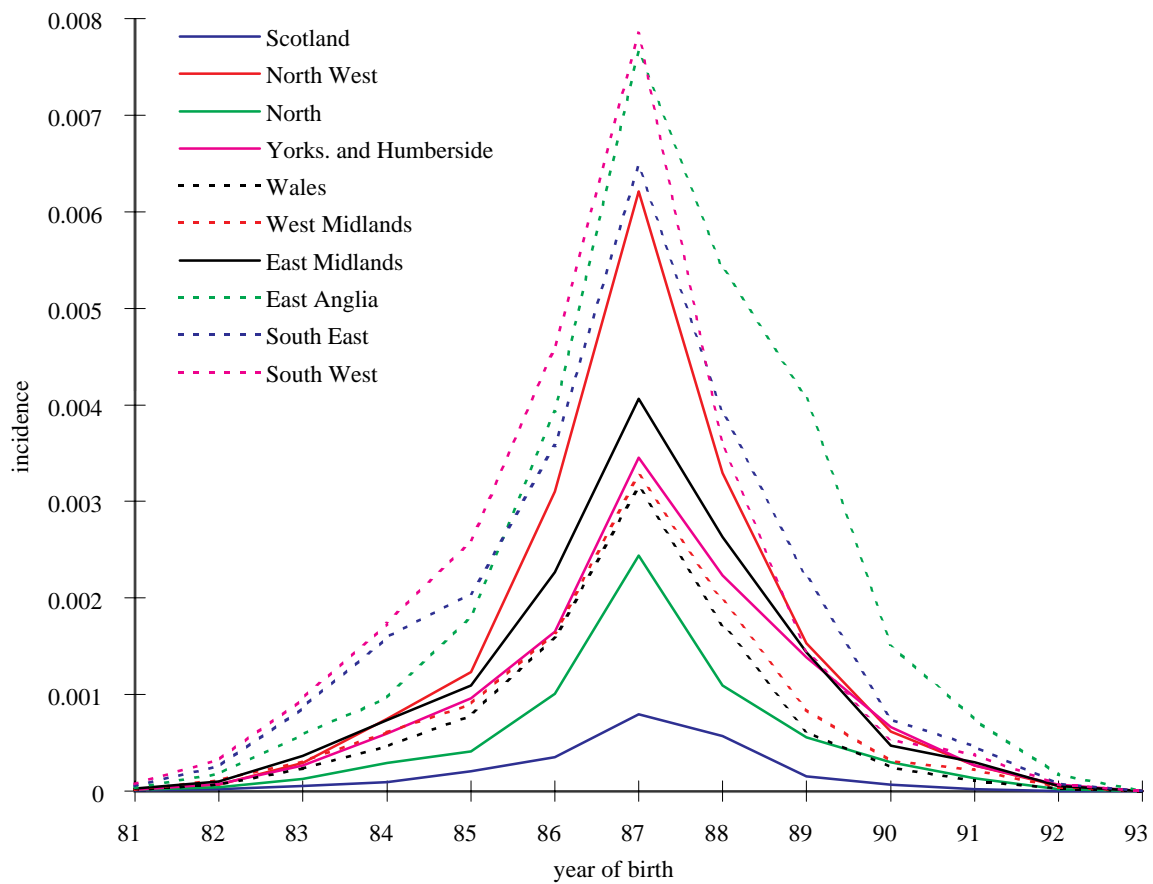


Figure 9. BSE incidence by natal MAFF region by year of birth.

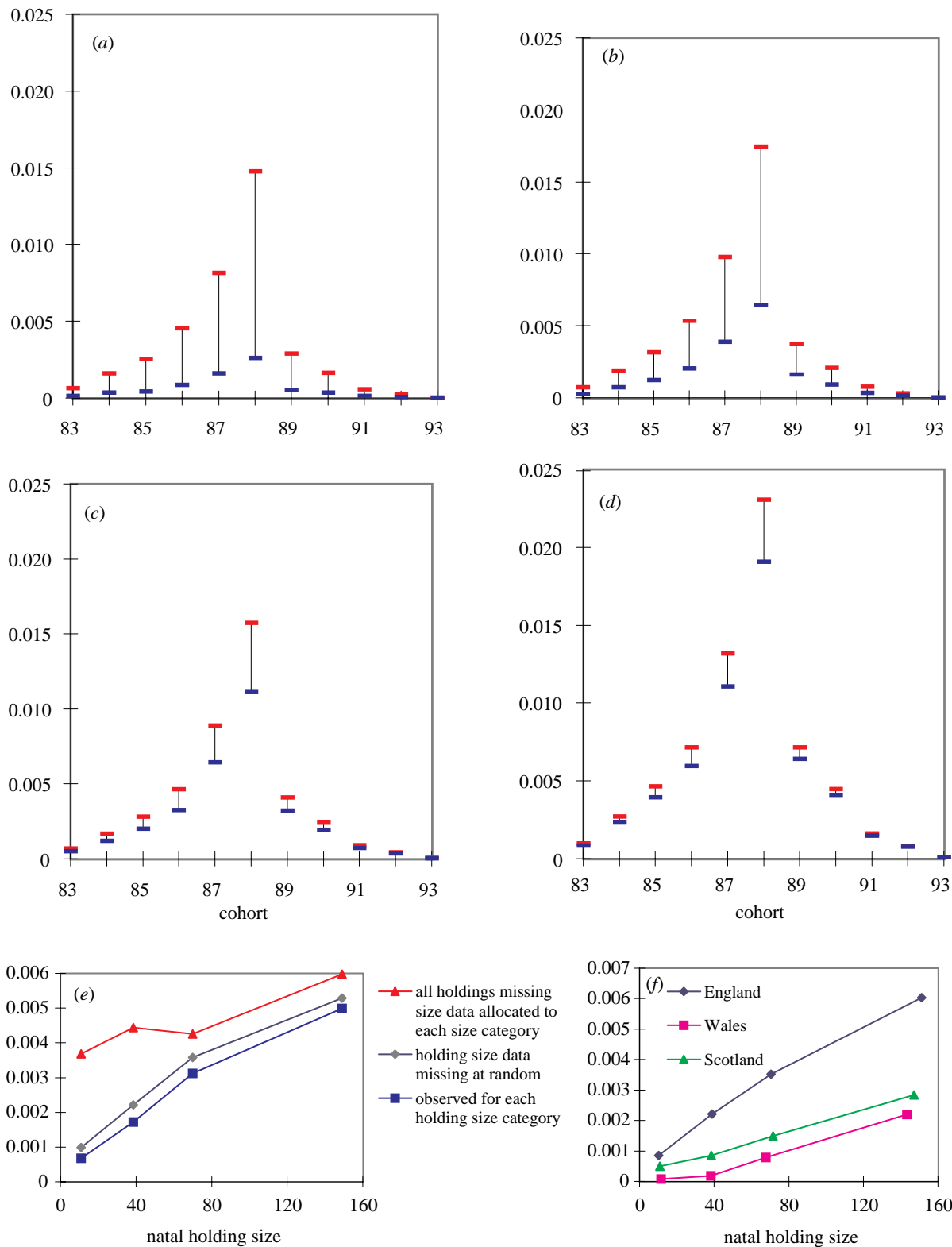


Figure 10. BSE cohort incidence by natal holding size category: (a) up to 29 adult cattle; (b) 30–49 adult cattle; (c) 50–99 adult cattle; and (d) 100 and over adult cattle. Upper and lower bounds are obtained from the two extreme assumptions that all and none of the observations with missing data arose from the category concerned, respectively. The average cohort incidence (for the 1983–1993 cohorts) is presented in (e) by holding size category under the two extreme assumptions and under the assumption that the size category data are missing at random conditional on the number of cases, and in (f) by country and holding size category, ignoring missing data.

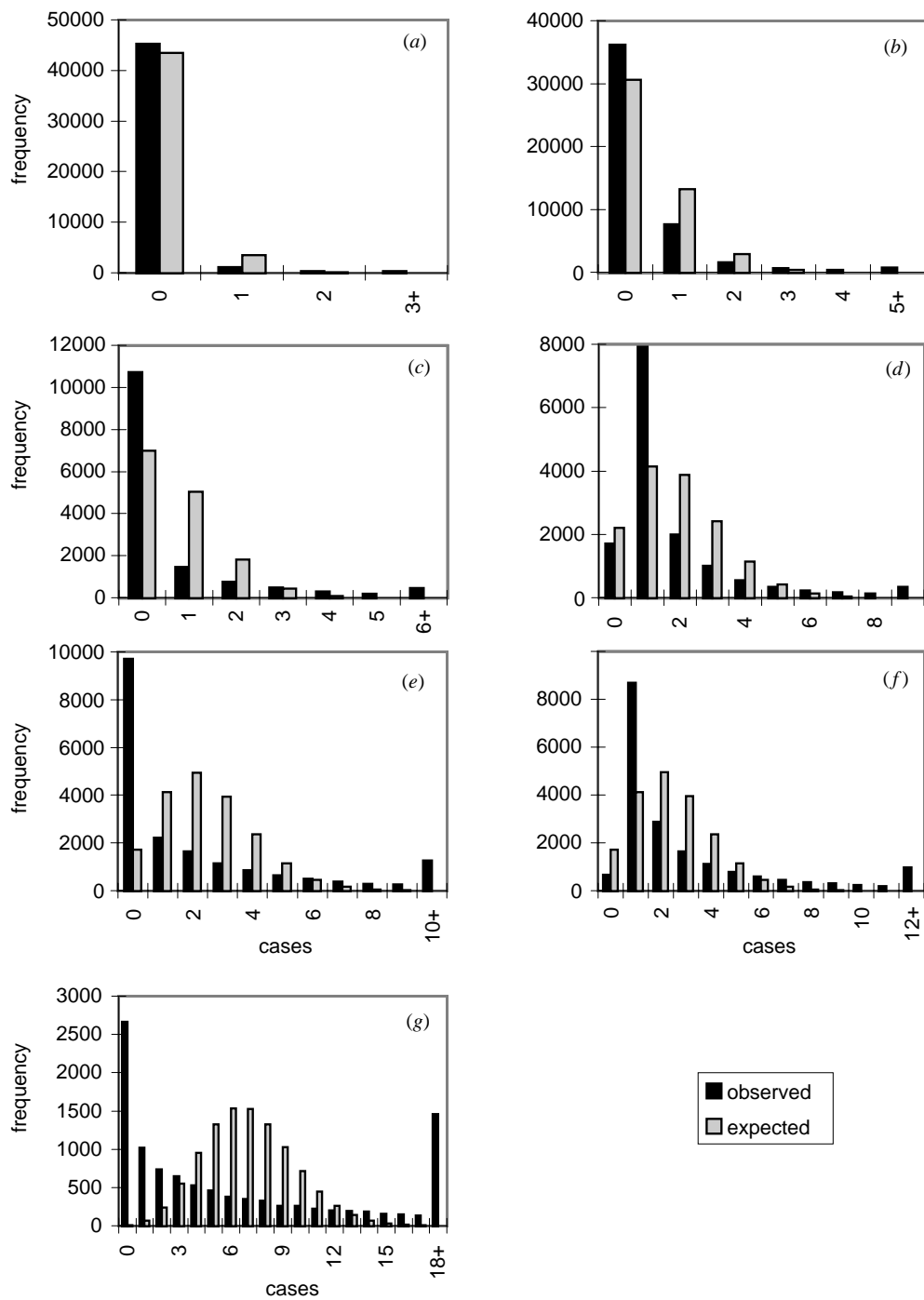


Figure 11. The observed frequency distribution of cases per holding by natal holding size category is plotted along with the expected frequency distribution assuming a Poisson distribution assuming that none of the missing data belongs to the relevant natal holding size category ((a) up to 29 adult cattle; (c) 30–49 adult cattle; (e) 50–99 adult cattle; (g) 100 and over adult cattle) and that all of the missing data belong to the relevant size category ((b) up to 29 adult cattle; (d) 30–49 adult cattle; (f) 50–99 adult cattle).

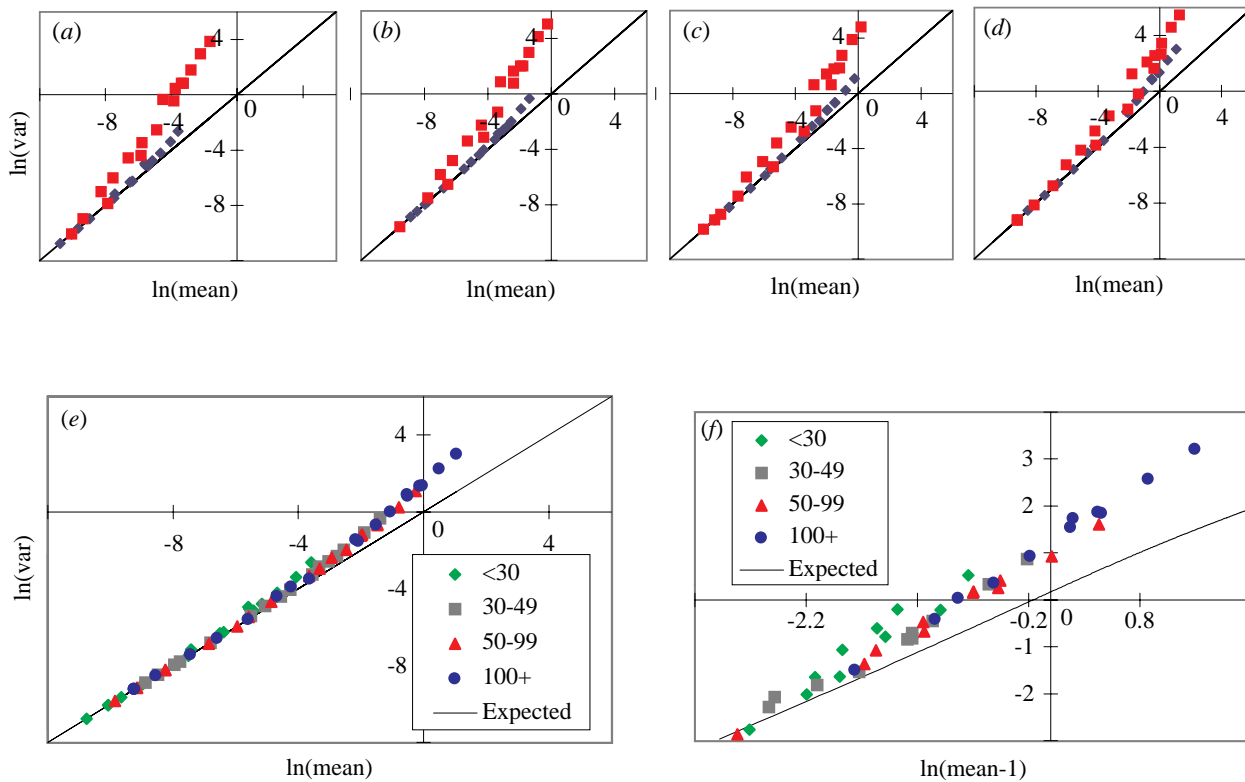


Figure 12. The logarithms of the mean and variance of the number of cases in a cohort in a natal holding are presented, stratified by natal holding size category ((a) up to 29 adult cattle; (b) 30–49 adult cattle; (c) 50–99 adult cattle; (d) 100 and over adult cattle). Results are shown assuming that none of the missing data belongs to the relevant natal holding size category (blue) and that all of the missing data belong to the relevant size category (red). (e) and (f) show the unconditional and conditional mean–variance relationship, respectively, for the combined data for the four holding size categories ignoring the data with missing natal holding size category. In all cases, the expected relationship under a Poisson distribution is given by the solid black line.

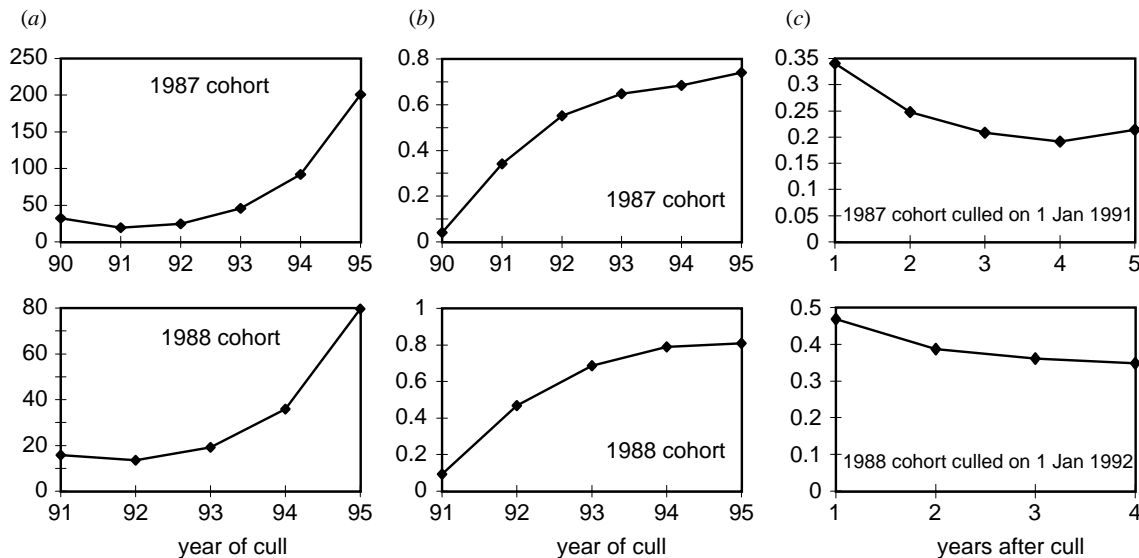


Figure 15. The results of holding-targeted (case) culling policies in: (a) the number of animals culled per case prevented in the year following the cull; (b) the fraction of cases arising in the targeted cohort prevented in the year following the cull; and (c) the fraction of cases arising in the targeted cohort prevented in the years following the cull. (Note that efficiency increases as the number of animals culled per case prevented decreases.)



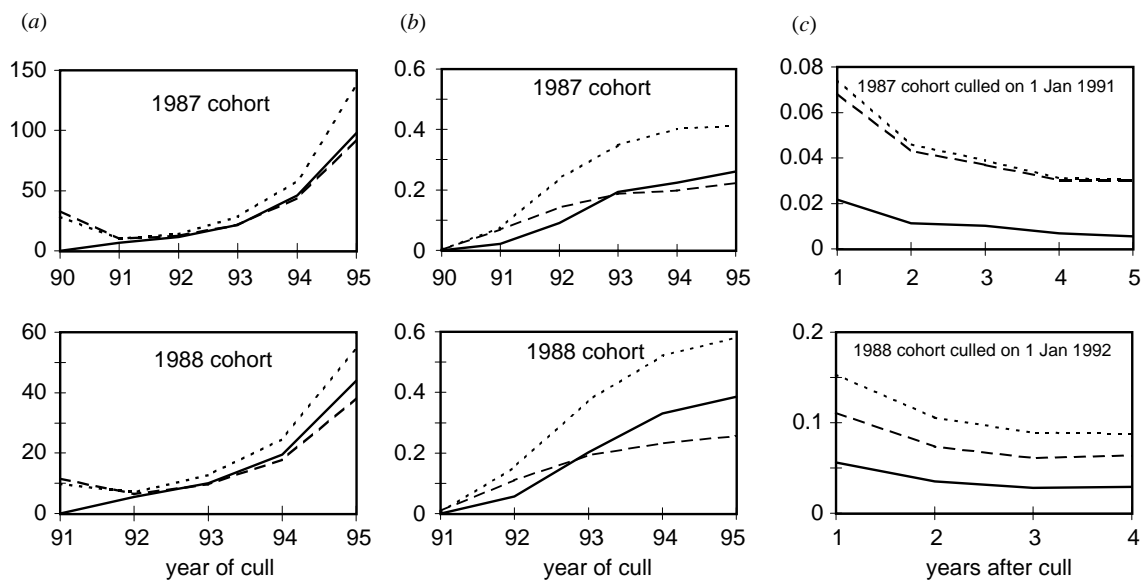


Figure 16. The results of holding-targeted (incidence) culling policies in: (a) the number of animals culled per case prevented in the year following the cull; (b) the fraction of cases arising in the targeted cohort prevented in the year following the cull; and (c) the fraction of cases arising in the targeted cohort prevented in the years following the cull. (Note that efficiency increases as the number of animals culled per case prevented decreases.) Lines: dashed, holdings with top 20% incidence; solid, holdings with greater than one case per 27 cattle; dotted, holdings with greater than one case per 50 cattle.