What Can We Learn From BSE?

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Bovine Spongiform Encephalopathy was first identified in the United Kingdom in 1986 as a result of the routine surveillance of animal diseases by the State Veterinary Services (Wells and others 1988). Epidemiological studies were initiated in May 1987. These had a number of objectives: (i) To obtain more detailed descriptions of the clinical signs to improve the ascertainment of suspect cases; (ii) to determine whether BSE was a new disease or not; (iii) to obtain sound descriptive epidemiological data and (iv) to investigate aetiological hypotheses. With respect to the last of these, hypotheses were not restricted to BSE being a member of the Transmissible Spongiform Encephalopathies (TSEs). They can be summarized as BSE being the result of infection with a scrapie-like agent, the result of an intoxication or a purely genetic disease. For the first of these the possible source or vehicles of infection were investigated as far as was possible. These were imported cattle, contact with sheep, contact with wildlife and contaminated biological products, including feedstuffs.

An in depth cases study was adopted for the initial study and this began by farms being visited to determine the available sources of documented information, the development of a questionnaire and lines of questioning for some aspects. Veterinary practices were made aware of the need for the then voluntary notification of suspect cases via colleagues in Veterinary Investigation Centres. A target of 200 cases was set for this initial phase. This was achieved in December 1987 and revealed a number of interesting aspects. Cases of BSE had occurred in herds which had not purchased cattle for a number of years and which had had no contact with sheep and goats. The observed incidence of the disease was considerably greater in dairy herds compared with beef suckler herds. Also, although cases of BSE appeared simultaneously throughout Great Britain there was a notable greater incidence in the southern counties of England (Wilesmith 1991). This study eliminated all of the potential aetiological hypothesis except BSE being due to infection with a scrapie-like agent with the vehicle of infection being most likely meat and bone meal included in cattle rations as a source of protein (Wilesmith and others 1988).

Relatively, simple simulation studies indicated that effective exposure of the cattle population had started in 1981/82. In examining possible reasons for this apparently sudden phenomenon, a number of explanations were eliminated. The main ones were a marked increase in the prevalence and incidence of sheep scrapie and the use of meat and bone meal commencing in 1981/82; meat and bone meal had been used in commercial feedstuffs for some decades before this. An examination of rendering practices indicated that changes had occurred in the industry. **A survey of rendering plants in the autumn of 1988 revealed that the suggested onset of effective exposure was coincident with a dramatic reduction in the use of hydrocarbon solvents for the extraction of tallow (fat) such that only two plants, both in Scotland, were still using this method at the time of the survey (Wilesmith and others 1991).**This survey also revealed possible reasons for the geographical variation in the risk of infection. First the low incidence in Scotland and the north of England was likely to be associated with the fact that the majority of meat and bone meal produced in Scotland had been produced using a hydrocarbon solvent extraction process. Secondly, it was realized that there had been a re-processing of greaves, resulting in a double heat treatment having been applied in the production of a significant proportion of meat and bone meal, but with a geographical variation in this proportion which matched the regional incidence of BSE. This was considered to be of epidemiological importance because meat and bone meal tended to be sold and used locally.

As a result of the findings from these initial studies, legislation was introduced in June 1988 making the disease notifiable and the ban on the feeding of ruminant derived protein to ruminants was introduced in July 1988. The first of these pieces of legislation allowed un-

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biased epidemiological analyses because of the eventual complete ascertainment of cases. Additional epidemiological studies reinforced the meat and bone meal hypotheses. The main finding was the difference in the incidence of BSE between the two main Channel Islands of the British Isles, Guernsey and Jersey. Proprietary cattle feedstuffs have only been purchased from mainland Great Britain, but there was a difference in the principal manufacturer of cattle rations imported. The main supplier to Guernsey was found to use meat and bone meal relatively more frequently, whereas, by chance, that for Jersey had not considered meat and bone meal as nutritionally/economically valued ingredient in the formulation of the majority of their cattle rations. However, a formal analytical epidemiological approach, a case-control study, had been initiated in the first half of 1988. The first phase was to identify potential control herds before the meat and gone meal hypothesis had become widely known in order to minimize bias from this source. This case-control study had the objective of examining for any association between the feeding of meat and bone in calfhood rations and the occurrence of BSE. The analyses of data collected for this study, which included obtaining the details of the rations fed from the herds and manufacturers, were completed in 1991. The results of these were that there was a positive association between the inclusion of meat and bone meal in feedstuffs consumed in the first year of life and the occurrence of BSE in later life (Wilesmith and others 1992). The original hypothesis was therefore supported. One of the original objectives of this case-control study was to determine whether there was any evidence of a dose response effect in terms of the inclusion rate of meat and bone meal. This proved to be impossible because of a lack of complete records of the feedstuffs' manufacturers, and to a lesser extent because more than one type, often from different manufactures, was fed to individual animals in their first year of life.

The positive association found in this case-control study tended to support the initial finding that the majority of cases seen in the course of the epidemic became infected in calfhood (Wilesmith 1991). This is not because of an age dependent susceptibility, for which there is no evidence in any species, but because the majority of animals infected as adults would not outlive the mean incubation period which is of the order of 60 months, and there was a greater inclusion rate of meat and bone meal in proprietary calf feeds.

One aspect which had been considered in the initial study was the possibility of a genetic influence on the incubation period analogous to that known for sheep (Hunter and others 1992). This has been the subject of further research by both molecular genetic studies and biometrical analysis. Neither has provided any evidence of a significant genetic influence on the susceptibility of cattle to BSE (Hunter and others 1994). This was suspected from the uniform incubation period and 100% attack rate in cattle parenterally exposed to BSE (Dawson and others 1990). Also the constancy of the distribution of lesions in the brains of affected cattle was suggestive of an absence of a host genetic factor (Wells and Wilesmith 1989; Wells and others 1992). This has remained constant throughout the epidemic (Simmons and others 1996) and strain typing studies of isolates of the BSE agent in in-bred strains of mice have indicated that throughout the epidemic cattle have succumbed to a single strain of agent (Bruce and others 1994).

Other epidemiological aspects which provided supporting evidence for the feedborne hypothesis included the very large difference in the incidence of affected dairy herds compared with beef suckler herds. Currently 59% of the 36,090 dairy herds in Great Britain have had at least one case and 15.3% of the 57,515 beef suckler herds have had at least one case. The low incidence in the latter herd type, with in excess of 48,000 unaffected herds, is consistent with the fact that the feeding of concentrate rations is relatively uncommon in beef suckler herds, in which nutrition during the winter period is largely based on conserved grass and home-grown cereals. In addition, investigations of the cases of spongiform encephalopathy in a nyala in 1986 and a gemsbok in 1987 in one zoological collection in the south of England were of interest. These cases had been identified in the course of normal surveillance of animal diseases. At the time, thoughts on the aetiology centered on a solely genetic origin. However, following the identification of BSE in cattle, further investigations revealed that the nutrition of the collection of these two species had included chimerically produced feedstuffs. For reasons not related to any concerns about the risk of infection with a scrapie-like agent, meat and bone meal had been specifically excluded from the ingredients at the request of the keepers. Begetable proteins, such a soya had been used, but when the price of this commodity increased markedly, meat and bone meal was used for economy for a very short period of time. This finding and that of an association between feeding cattle feedstuffs to other exotic ungulates, such as greater kudu and arabian oryx, reinforced the hypothesis.

The detailed monitoring of the epidemic through the completion of a standard epidemiological questionnaire for all suspect cases reported has allowed the effects of the ban on the feeding of ruminant derived protein to ruminants to be observed. The first of these, a reduction in the incidence of BSE in two year old animals (Wilesmith and Ryan 1993). In subsequent years the incidence in the older age groups has successively reduced (Wells and Wilesmith 1995). Analysis of the annual age specific incidences within affected herds indicated that

the reduced incidence in the younger age groups in 1991 and 1992 could not have an effect on the national incidence of BSE as the incidence in the older age groups over this time was increasing. This was because the majority of cases in the epidemic are the result of infection from recycled cattle tissues via meat and bone meal. The risk of exposure therefore was greatest at the time of the feed ban. However, in 1993 when the incidence in four year old animals was reduced a decline in the national incidence occurred. The peak incidence was therefore at the end of 1992/beginning of 1993 when some 1000 suspect cases were begin reported each week. Since then the number of suspect cases reported each week has declined such that in recent (May 1996) weeks the number has been approximately 230 per week, of which at least 16% will not be confirmed as BSE. Since the peak of the epidemic there has been a reduction of approximately 40% in successive years. As would be expected, there has been a coincident decline in the incidence of newly affected herds. However, it should be noted that in 1995 there were 1.152 newly affected herds in the total of 8,545 herds with at least one case in the year. The within-herd incidence has remained low and was 2.7% of adult animals in affected herds in 1992 at the peak of the epidemic. This low incidence is consistent with a low average exposure to infection in feedstuffs, analogous to bio-assays of scrapie infectivity at limiting doses when cases occur infrequently and unpredictably (Kimberlin and Wilesmith 1994). This phenomenon is also evident from the fact that currently 41.9% of all affected herds have experienced only one case and 50.2% of affected herds have only experienced cases of BSE in a single birth cohort, **indicating that BSE is not a herd problem.**

Clear effects of the feed ban are evident from the close monitoring of the epidemic. However, cases of BSE in animals "Born After the Ban" (BABs) have occurred. These currently account for 60% of the total confirmed cases and this proportion will continue to increase. Following the occurrence of the first 1988 born BAB cases, additional epidemiological investigations were instituted for each. These were to determine whether there was any evidence of maternal or horizontal transmission and examine the possibility of a continued exposure from feedstuffs. These revealed no evidence of maternal or horizontal transmission, but did indicate that exposure form the feedborne source was highly likely. This was simply because at the time of the feed ban there were feedstuffs containing meat and bone meal in the supply chain and on farms which could not be identified and would have been fed to cattle.

At this time analyses were initiated to identify changes in the risk of exposure for animals born in successive years since the feed ban. Two approaches have been used to assess this. One is an age-period-cohort model which is referred to later and the second is the calculation of what is akin to standardized morbidity rations (SMR) and their 95% confidence intervals (Hoinville 1994). The use of the latter technique, and the modelling approach, indicated that there has been a declining risk since July 1988. These analyses showed that there was an immediate effect of the ban in that the risk of infection for animals born in August 1988 was 65% of that for animals born in August 1987. Thereafter the risk of infection declined such that the risk of infection for animals born in December 1990 was 10% of that for animals born in December 1987. The absence of any evidence for a further decline in risk of infection is discussed below. The continued occurrence of BAB cases born in 1989 and later stimulated the design of a case-control study to determine whether they could be explained by maternal or horizontal transmission. This was a within herd study with a match design involving 300 cases and up to four control animals per case. The conclusions from this study were that neither maternal nor horizontal transmission could explain the majority of the BAB cases (Hoinville and others 1995).

As a result, the possibility of a continued exposure from the feedborne source was examined. An analysis of the regional distribution of homebred cases by 12 monthly (July to June) birth cohorts indicated a change in the proportion of cases per region. Homebred cases were used for this analysis as feedstuffs and produced and distributed locally and the hypothesis was that there could have been cross-contamination of cattle feedstuffs in mills producing both ruminant and monogastric rations; meat and bone meal derived from any bovine tissue could have been legitimately used in pig and poultry feedstuffs until September 1990 when the ban on the use of specified bovine offals was introduced. The results of this analysis indicated that there had been a relative increase in the incidence of BSE in animals born after the feed ban in the northern and eastern regions of England. This was of interest because the national pig and poultry populations are largely concentrated in these regions. As a result, the correlation of the incidence of BAB cases born after 30 October 1988 with the ratio of both pigs to cattle and poultry to cattle in each country of England and Wales was examined. This revealed statistically significant correlations suggesting that in areas where there are large populations of either pigs or poultry relative to cattle, the risk of infection for cattle born after July 1988 was increased.

Subsequent investigations of feed mills and the examination of finished cattle feedstuffs, using an ELISA which detects species specific (bovine, ovine and porcine) protein, as part of a systematic national survey have revealed that accidental cross-contamination of cattle feedstuffs was possible in some feed mills and this has occurred. Such cross-contamination should have been

precluded after September 1990 because of the ban on the inclusion of specified bovine offals (SBO) in the food of any animal. However, it became apparent in 1995 that there had been incomplete compliance with this ban. This therefore provides an explanation for the absence of a reduction in risk of infection for animals born after 1990. In this context it is important to appreciate that the prevalence of infected cattle increased until the early months of 1993. It would therefore not be until the 1993 autumn calving season that the risk of infection for cattle from the recycling of cattle tissues would be further reduced in the absence of an incomplete compliance of the legislation. Therefore, as the non compliance with the SBO ban was clearly not 100%, the risk of infection for animals born in 1993 and subsequently would have naturally declined.

In order to obtain a fuller understanding of the epidemiology of BSE and, more pragmatically to estimate the future number of suspect cases requiring expenditure for compensation to herd owners and for the incineration of the carcasses of cattle slaughtered, a number of modelling approaches have been used (Wilesmith and others 1988; Richards and others 1993). In recent years a standard age-period-cohort approach (see for example, Holford 1992) has been used with good precision routinely. By definition this method, and indeed any other, can only use data from already affected birth cohorts. The application of this methodology allows not only an estimate of the number of confirmed cases in each coming year, but also an estimate of a number of cases occurring in each year in each birth cohort. The central estimates for each year 1996 to 1998 are currently 8000, 5000 and 2,800, respectively. These are in remarkably close agreement with recently published independent analyses of data from the main BSE database provided to the epidemiology group at Oxford University (Stekel and others 1996). The conclusions from all of these analyses is that if no further measures are instituted the incidence of BSE in the UK cattle population will be very low by the turn of the millennium. However, there have been additional control measures which no model can currently take into account. These include the enhancements to the current rendering processes to conform with the results of the collaborative study of the potential inactivation of the BSE agent by rendering processes used in EU member states (Taylor and others 1995). These were instituted in 1994. There was also the strengthening of the legislation controlling the separation and disposal of the specified bovine offals in April and July 1995. Moreover, in 1996 the feeding of meat and bone meal to any farm livestock species, horses and farmed fish was totally banned. It is not possible to institute any more stringent controls to preclude the exposure of cattle from the feedborne source.

This does, however, leave the question of whether cattle to cattle transmission, notable maternal transmission, can occur at all. At present, the evidence points unanimously to the fact that this form of transmission, on its own, cannot perpetuate the epidemic of BSE indefinitely. On this basic epidemiological concept, the probability that an infected cow will produce a female offspring which will become a breeding animal capable of producing a female offspring which will in turn produce a breeding female, and so on, lies between 0.5 and 0.7. Therefore the contact rate is less than 1 and therefore whether or not the epidemic could be prolonged by the occurrence of maternal transmission. All of the available epidemiological evidence for the occurrence of maternal transmission points in one direction. That is, if this means of transmission occurs it will be at a low rate. This is based on a number of facts: (i) there has been a decline in the within herd incidence, not an increase; (ii) the case-control study of animals born after 30 October 1988 provided no evidence for a significant rate of transmission by either a maternal or horizontal means and (iii) routine analyses of the difference between the expected incidence of BSE in the offspring of confirmed cases of BSE and that observed during the course of the epidemic have not revealed any excess risk for offspring of confirmed cases.

Although all of this evidence has accumulated, a cohort study was initiated in July 1989 to examine the question of the risk of maternal transmission. The study population comprises a proportion of animals born before the feed ban (in July 1988), a majority of animals born in the autumn calving season immediately after the ban and a small proportion of animals born subsequently. They are being kept until seven years of age, unless death or the need to slaughter intervenes and the youngest animal will reach this terminal age in November 1996. This study is kept under review by members of the Spongiform Encephalopathy Advisory Committee and it is unlikely that the final result will be available before the end of 1996.

There is therefore considerable evidence that the number of cases will continue to decline as a result of the feed ban on the feeding of any mammalian protein to any agricultural animal, horses and farmed fish will prevent any accidental exposure. The national survey of finished feedstuffs using an ELISA to detect species specific mammalian protein is currently being altered to a survey of raw ingredients to ensure that this ban is maintained.

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The Outbreak Of Akabane Virus Disease In Korea

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Abstract

An epizootic of Akabane virus disease of cattle, an infectious disorder causing congenital abnormalities in calves, was studied in Korea from 1983 through 1995. Congenital abnormalities of calves and the main clinical signs were investigated. Antibody titer to Akabane virus was determined by the virus neutralization test. 2094 (77.3%) of 2709 sera had neutralizing antibody to Akabane virus. The positive rate were 86.8% in 1983 and 82.6%, 95.6 % in 1988 and 1989 respectively.

Of the 9,354 samples, 3,537 of sera (37.7%) showed positive to Akabane virus by virus naturalization test. In 1995 the positive rate was 62.2% and 26.8% 22.7% in 1994 and 1995 respectively. According to the areas, the highest positive rate was 89.1% in Kangwon province in 1993. In 1994, distribution of the positive rate in all areas was not different from average positive rate.

From 1984 through 1995, of 881 submitted calves aborted or stillborn, 81 were diagnosed as Akabane disease. The types of abnormalities were arthrogryposis and hydranencephaly, 71.9% and 18.1% respectively. Ten percent of the calves had arthrogryposis and hydrancencephaly simultaneously.

The results indicated that Akabane disease was widespread among the cattle population in Korea since 1983 and cause the congenital abnormalities of calves, and abortion, stillbirth in cattle at 5 year intervals.

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