



SEAC No: 77/4

OFFSPRING CULL: PAPER FOR SEAC MEETING ON 11th FEBRUARY 2003

Issue

1. The EU TSE Regulation requires all Member States *“to cull the last progeny of a female animal in which [BSE is] confirmed born within two years prior to, or after, clinical onset of the disease in its dam”*.

The same provisions regarding the culling of offspring that are in the TSE Regulations also apply in the OIE Code^a. In addition, the UK operates a comprehensive offspring cull. This requires the compulsory slaughter of *all* offspring born in the UK after 1 August 1996; the date from which the UK reinforced feed ban is considered fully effective. This wider cull was seen as necessary to secure the agreement of other EU Member States to the resumption of UK beef exports, eventually agreed in September 1998, even though no risk was apparent in offspring born more than two years before the onset of clinical symptoms in their dams.

Previous SEAC advice

2. In 1997, SEAC considered a seven-year cohort study (1) on maternal transmission. The study showed that offspring of clinical BSE cases have an enhanced risk of developing BSE. The risk difference for offspring from BSE dams was estimated at 9.6% compared to non-BSE cases. An additional analysis of this study concluded that maternal exposure was estimated to be most important in animals born within 150 days of disease onset in their dams (2).
3. A separate analysis of the dam-calf pairs from the BSE database reported that the BSE risk was highest in offspring born after the onset of clinical symptoms in the dam (3). For offspring born before the onset of clinical symptoms, the risk was highest in the six

^a The OIE International Animal Health Code contains standards, guidelines and recommendations to prevent the import of infectious agents and diseases pathogenic to animals and humans during trade in animals, animal genetic material and animal products. This is done through detailed recommendations on sanitary measures to be used by OIE member countries in establishing the health regulations applying to the import of animals, animal genetic material and animal products.

months before onset but diminished as the interval between birth and onset increased. No transmission was detected in offspring born more than two years before the onset of clinical symptoms.

4. SEAC concluded that the research provided some evidence for low level, direct maternal transmission, however they acknowledged that the contribution of variation in genetic susceptibility to a feed-borne infection could not be ruled out as an additional factor.
5. SEAC confirmed that the evidence on maternal transmission did not call into question existing measures and it was satisfied that the controls in place (SRM, and OTM supported by the then reinforced feed ban) to protect the consumer were adequate.
6. SEAC considered the issue of an offspring cull and concluded that a cull of offspring from BSE affected dams would have only a small effect both on the incidence of BSE and the duration of the epidemic. Nevertheless SEAC suggested that Government consider the possibility of an offspring cull and its effects on the epidemic. SEAC issued a statement on maternal transmission on 16th April 1997. This is attached at Annex A
7. Although SEAC had advised that existing consumer health protection measures were appropriate, the Government decided to introduce an offspring cull in support of DBES. A cull of all offspring began on a voluntary basis in August 1998 and the BSE Offspring Slaughter Regulations 1998, which made it compulsory, came into effect on 4th January 1999.

Advice sought from the Committee

8. The UK continues with a comprehensive offspring cull in which all offspring (born after August 1996) from BSE cases are culled. To meet the EU TSE regulations, as applied in other Member States, the UK would only have to implement an offspring cull with regard to offspring born 2 years prior to the onset of BSE, or offspring born at any time after the development of BSE in the dam. Offspring born outside the two-year period would go into the food chain.

In view of this,

Does the Committee agree that this change to the existing UK offspring cull would not result in significant additional risk to consumers?

Background

Background information is provided in Annexes A-E

- [Annex A](#) SEAC and Epidemiological sub-group statements from 1997.
- [Annex B](#) The progress of the BSE epidemic.
- [Annex C](#) Research on maternal transmission since the previous SEAC consideration in 1997.
- [Annex D](#) The impact of the offspring cull on disease eradication
- [Annex E](#) Update on cases of BSE born after the real ban (BARBs)

ANNEX A

Statement, 16th April 1997

On 29 July 1996, the Spongiform Encephalopathy Advisory Committee (SEAC) issued a statement on maternal transmission of BSE following its consideration of an interim report on a study conducted by the Epidemiology Department, Central Veterinary Laboratory, Weybridge to investigate the occurrence and incidence of dam to calf transmission of BSE (the cohort study).

SEAC established an Epidemiology Subcommittee to consider the final results from the cohort study. The Subcommittee was chaired by Professor Peter Smith (London School of Hygiene and Tropical Medicine), a member of SEAC. It included two further members of SEAC, Dr Richard H Kimberlin (SARDAS) and Professor Will Hueston (University of Maryland). The Subcommittee also included Professor Roy Anderson (Oxford University), Professor Robert Curnow (Reading University), Dr Peter Goodfellow (SmithKline Beecham Pharmaceuticals), Professor Dr. Ir. Aalt Dijkhuizen (Wageningen Agricultural University, the Netherlands) Professor Nicholas Day (Medical Research Council Biostatistics Unit), Dr John Williams (Roslin Institute), Dr Rosalind Ridley (Cambridge University) and Mr John Wilesmith (Central Veterinary Laboratory). The Subcommittee was assisted by Dr Sheila Gore (Medical Research Council Biostatistics Unit), Dr Neil Ferguson (Oxford University), Dr Christl Donnelly (Oxford University), Dr John Woolliams (Roslin Institute), and Ms Judith Ryan (Central Veterinary Laboratory). The Subcommittee met on four occasions, and submitted its final report on maternal transmission of BSE to SEAC on 11 April 1997.

At its meeting on 15 April 1997, SEAC considered and accepted in full the report from the Epidemiology Subcommittee.

SEAC noted that the results of the cohort study were not inconsistent with those of the case control study published in 1995 by Hoinville and others of the Epidemiology Department, CVL. That study, which involved cases of BSE born after the ruminant feed ban, did not identify significant evidence of maternal transmission, but the statistical confidence interval included a risk of up to 13 per cent (Veterinary Record (1995) 136, 312-318).

The cohort study provides no information on the mechanism of direct maternal transmission of BSE. We recommend that further research should be undertaken to shed light on the mechanism.

Some research has already been carried out into potential routes of transmission from dam to calf, by testing the infectivity of tissues from BSE-affected animals, including placenta, embryos, blood and milk: no evidence of infectivity has been found. However, given that the rate of transmission is probably low, some of these negative results may be due to the practical difficulties of detecting low levels, or a low prevalence, of infectivity. SEAC recognises that a low level of transmission would make research on mechanisms difficult, and that it would be complemented by a better understanding of the mechanisms of scrapie transmission in sheep.

Any cull based upon the slaughter of calves born to cows in which BSE has been confirmed will have only a small effect on the incidence of BSE and the duration of the epidemic. Nevertheless, Government should consider the possibilities for such a cull, and its effects.

SEAC noted that, in its statement of 29 July 1996, it had concluded that the evidence on maternal transmission did not call into question existing measures to protect public health. In the light of the Subcommittee's report, SEAC reconsidered the existing measures.

With respect to consumption of bovine products the measures currently in place to protect the consumer are considered appropriate. In particular, the Committee considered the possibility of milk being a vehicle of transmission. SEAC concludes that no evidence has been found to suggest that milk from any species affected by transmissible spongiform encephalopathies is infectious. This concurs with the opinion of the Scientific Veterinary Committee, which advises the European Commission.

With respect to occupational exposure, responsibility for assessing whether any amendments are needed to the existing Health and Safety Executive guidance rests with the Advisory Committee on Dangerous Pathogens.

Epidemiology subcommittee statement to SEAC on maternal transmission of 11 April 1997

In July 1996 SEAC issued a statement on maternal transmission of BSE following an interim analysis of data from an ongoing study (called the "cohort study") being conducted by the Epidemiology Department, Central Veterinary Laboratory (CVL). The study was intended to determine whether maternal transmission occurred, and if so, to inform policy makers with respect to animal health implications.

The study involved over 300 "matched-pairs" of calves. One calf in each pair was the offspring of a confirmed case of BSE and the other an animal born in the same herd in the same calving season whose dam had reached the age of 6 years without developing clinical signs of BSE. The two groups of animals were born between August 1987 and November 1989, and were taken from their natal herds between July 1989 and February 1990, aged between 2 and 24 months. They were kept on one of three experimental farms until they reached the age of 7 years or were culled at an earlier age with BSE or another disease. All animals surviving to the age of 7 years were then slaughtered and their brains were examined pathologically for evidence of BSE.

The preliminary results of the study, when most but not all of the animals had been followed to the age of 7 years, suggested that the offspring of BSE cases had an incidence of BSE that was about 10% greater than that of control animals, with statistical confidence limits (95%) ranging from 5-15%, the range reflecting the limited numbers of animals that developed BSE in the study.

By November 1996 the last of the animals in the study had reached the age of 7 years, and by January 1997 the last of their brains had been examined. As had been anticipated, the final results were not markedly different from those on which the interim analysis had been based in 1996. Of the 301 offspring of BSE cases, 42 (14.0%) developed BSE. Among the 301 offspring of the "control" dams without BSE, 13 (4.3%) developed BSE. The difference between the two risks was thus 9.6%, and was highly statistically significant with a confidence interval ranging from 5.1% to 14.2%. A paper giving the results of the study will be published shortly in the *Veterinary Record* by the Epidemiology Department of CVL.

The cohort study was set up to investigate the occurrence of maternal transmission, but interpretation of the results was confounded by the likely exposure of some of the experimental animals to contaminated feed. The results could be explained by two hypotheses, acting alone or in combination, namely direct maternal transmission of infection or inherited genetic variation in susceptibility to BSE via contaminated feed. Although most of the animals involved in the study had been born after the ruminant feed ban in July 1988, feed-borne transmission is thought to have continued beyond that date. This is consistent with the observation that the BSE risk in both of the groups was greater among animals born before the introduction of the feed ban than among animals born later. However, the difference in risk between the two groups

was also greater in those born earlier, and this would not be expected if direct maternal transmission was the sole route of infection of the calves in the study. Such an effect might be apparent if cattle vary in their susceptibility to contracting BSE from infected feed. It is possible that the offspring of BSE cases may inherit, from their dams, genes associated with increased susceptibility to disease and that at least some of the difference in BSE risk between the offspring of BSE affected and non-affected dams in the study may be due to inherited factors, rather than because of direct transmission of BSE from dam to calf.

The subcommittee has reviewed the evidence for variation in genetic susceptibility to BSE in cattle. There is variation in the risk of TSEs according to genotype in some species. For example, polymorphisms of the PrP gene are associated with substantial variation in susceptibility to infection with the scrapie (and in incubation period) in sheep and mice and with differences in risk of CJD in humans. The subcommittee notes, however, that the limited research so far completed has failed to identify genetic factors as a major component in the epidemiology of BSE.

To assist the CVL Epidemiology Department in the interpretation of the results of the cohort study, independent analyses of the data were conducted by three additional groups with expertise in statistical analysis (based in the Wellcome Trust Centre for the Epidemiology of Infectious Disease, University of Oxford; the MRC Biostatistics Unit, Cambridge; and the Department of Applied Statistics, University of Reading). In so far as was possible, they tried to evaluate the contributions to the risk difference between the animals in the two groups from inherited differences in susceptibility to disease caused by infected feed and from direct transmission of BSE from dam to calf. In the absence of detailed information on the genetic make up of the animals in the study, the possible genetic contribution could only be assessed by statistical modelling.

The analyses by the three groups have been submitted for publication later this year. These analyses reached broadly the same conclusions. That there was a highly significant difference in risk between the two groups of animals was clear. The findings did not definitively establish direct maternal transmission as the sole explanation for the difference in risk. The statistical model which fitted the data best involved contributions from both direct maternal transmission and inherited susceptibility. The main evidence for direct maternal transmission is that the risk of BSE in the calf of an affected dam was greatest for calves born close to the onset of BSE in the dam. However, the power of the study to detect differences

related to the time between BSE onset and the date of birth of a calf was limited by the design of the study which resulted in 83.4% of the calves being born within the six months prior to onset of clinical disease in the dam.

Further investigation was necessary of the possible variation in the risk of BSE associated with the time between the birth of an animal and the onset of BSE in the dam. This was undertaken mainly by the group from the Wellcome Centre for the Epidemiology of Infectious Diseases, University of Oxford through analyses of data on all cases of BSE born after the ruminant feed ban, which are recorded on the BSE database held by the Epidemiology Department at the CVL. The findings will be submitted for publication shortly. Evidence was found that the subsequent BSE-risk was greatest in calves born after the date of BSE onset in the dam. For calves born before onset, the risk was lower, and diminished as the interval between birth and onset increased, and no risk was apparent more than two years before onset (see next paragraph). Thus, although possibly subject to some biases, these analyses also suggested that enhanced BSE-risk in the offspring of BSE dams involves a low level of direct maternal transmission in the late stages of the incubation period.

In view of the findings of the analyses that are summarised above, the subcommittee concludes that there is some evidence for direct maternal transmission of BSE at a low level, but some variation in genetic susceptibility to BSE following feed-borne exposure may occur. The risk of transmission of BSE from dam to calf is likely to be less than 10%, and appears to be confined to animals born after the onset of BSE in the dam or up to two years beforehand. This level of transmission is not sufficient, by itself, to perpetuate BSE in the cattle population and is likely to have only a minor effect on the rate at which the incidence of BSE declines. It is inevitable that cases infected via animal feed will continue to appear in diminishing numbers for several years. Therefore, although the number of cases infected maternally will be small, they may represent an increasing proportion of the remaining cases detected.

Given the evidence that variation in genetic susceptibility may have contributed to the results of the cohort study, and of the importance of genetic factors in TSEs in other species, the subcommittee considers that further research is necessary to clarify whether or not variations in the PrP gene or other genes may be influencing the transmission of, or susceptibility to, BSE in cattle. Research should seek to identify polymorphisms of the PrP gene which may be associated with BSE susceptibility, including stored samples from

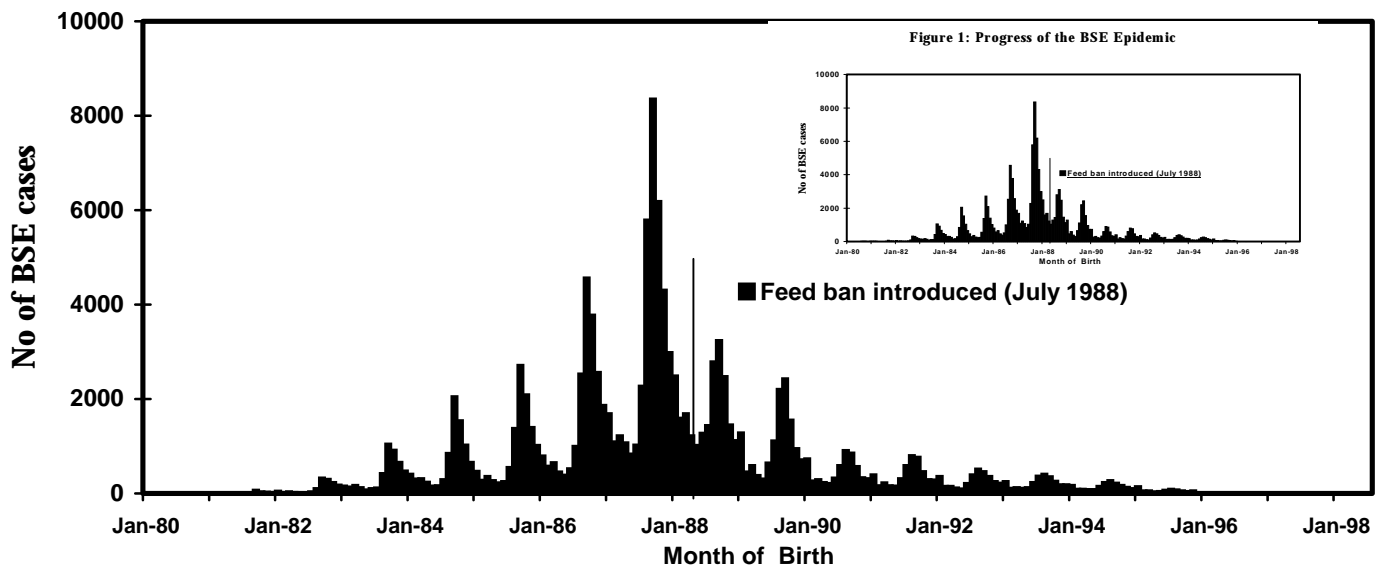
the cohort study. There should also be a search [AVMC1] for other genetic markers, outside the PrP gene, which may be associated with an increased BSE risk in.

Annex B

The BSE Epidemic

The number of cases, month and year of birth of BSE cases is shown in figure 1. The inset shows the numbers of BSE cases born after the reinforced feed ban became fully effective on 1 August 1996 (BARB cases). One set of analyses (4) has indicated that the BSE control measures introduced in 1988, mainly the ruminant derived protein ban, resulted in a 67% reduction in the risk of contracting the disease for animals born in the first 12 months after the introduction of the ban in July 1988. The subsequent SBO ban of 1990 reduced the risk of the disease (in animals born in the first 12 months after introduction) by a further 46%. There is evidence of a further marked reduction in risk for animals born after 31 July 1996, but this not yet quantifiable using the same method as for the earlier control measures.

Figure 1: Progress of the BSE Epidemic



ANNEX C

Research on maternal transmission since the previous SEAC consideration and the 1997 cohort study

A paper published by Donnelly *et al* in 2002 (4) based on the BSE survey and clinical incidence data estimated maternal transmission at 0.5% (0 - 2.8%). When the effects of the offspring cull were taken into account, the estimate increased to 0.7% (0- 4.0%). These estimates are substantially lower than the 9.6% estimated in the 1997 cohort study.

These analyses are based on data from Defra's BSE database, which provides information on the relationship between cases, and from modelling itself. The figures are derived from cumulated data from the whole epidemic and therefore provide estimates of the average. More specifically they have relatively large confidence bounds, which include zero. The estimated rates do not therefore apply to the more recently born animals, as the evidence suggests that maternal risk has declined over time.

It has been suggested that the evidence to date support a maternally associated risk factor rather than direct maternal transmission *per se*. That is, offspring of dams that develop clinical BSE are more susceptible to BSE infection than offspring of dams that do not develop clinical BSE. Defra has adopted a working hypothesis that as the feedborne risk declines so does the apparent risk for offspring. The results of the 1997 cohort study supports this hypothesis as it showed that the maternal risk declined in successive cohorts born after the feed ban.

In November 1999, SEAC was asked to advise on a proposal to investigate possible mechanisms of maternal transmission using offspring of BSE affected cattle (that would otherwise have been slaughtered). SEAC agreed that the offspring were valuable animals. However, SEAC concluded that in view of the revised predictions of the decline of the epidemic and the long-term nature of the experiment, such a study would not yield results within a useful time frame. As such SEAC did not consider such research as high priority. Members agreed that although maternal transmission would not sustain the epidemic, it was important that further studies exploring this route of transmission were undertaken.

No further research has been commissioned on maternal transmission to date. This is due to a combination of limited resources and competing priorities within Government. Additionally,

the offspring cull has destroyed potential research animals. However, the continued monitoring of the epidemic and associated analyses has indicated that the rate of maternal transmission predicted after the original cohort study (9.6%) has not occurred in the later born cohorts. That is, the incidence in animals born after 31 July 1996 is considerably less than would have been expected if maternal transmission of BSE was taking place from dams that did not live long enough to develop clinical signs.

Annex D

Impact of the offspring cull on disease eradication

As at 13th January 2003 13,809 offspring have been culled since August 1998. The peak of the potential contribution of the offspring cull to the decline in the incidence of BSE would have passed by now.

The transmission rate of 9.6% derived from the 1997 cohort study is an estimate derived from animals born from August 1987 to November 1989, with the majority born at the peak of exposure, between July to December 1988. This essentially represents field data and the results were in agreement with the dam-calf pairs analyses conducted by Defra and previous analyses by the Imperial Group (1996/97 and earlier work).

TSE Testing

As at 15 January 2003, 1,402 offspring aged over 30 months have been tested for BSE. All animals tested negative.

Table: Age distribution of Offspring tested for BSE
September 2001 - 15 January 2003

Age Group	Number tested in GB	Number tested in NI
Data pending	76	4
Under 30 months	11	335
30-35 months	162	34
3 years	325	20
4 years	252	26
5 years	138	6
6 years	12	1
Total tested	976	426

BARB cases

Data on the first 16 BARBs born in GB was presented to SEAC in September 2002 by Professor Wilesmith (VLA). This data has subsequently been published in the Veterinary Record (SEAC/INF/75/24). An update for the first 27 BARBs born in GB has

been provided by Professor Wilesmith and is attached at Annex E. The author suggests that the observations do not provide evidence that any of these cases are maternally associated.

Other Data

The data and information from SSC opinions and other EU member states do not provide support for the hypothesis that a maternally associated factor plays a role in transmission of the disease. This may be due to the generally low risk of exposure from feed.

ANNEX E

SUMMARY OF INITIAL EPIDEMIOLOGICAL FINDINGS OF 27 CASES OF BSE BORN AFTER 31 JULY 1996 IN GREAT BRITAIN AS AT 31 DECEMBER 2002

1. The following provides a summary of the initial epidemiological findings, from routine investigations, of the first 27 BARB cases born in Great Britain. Complete information has so far been received for all but two purchased cases, for which the questionnaires for the natal (breeder) herds have not been received.

METHOD OF DETECTION

2. The method of detection is summarised in Table 1.

Table 1

METHOD	NO. CASES
Clinical suspects	9
Casualty slaughter	12
Fallen stock	2
OTM survey	4

It is notable that only one third of the cases to date were detected as clinically suspect animals. All of the cases found as a result of the screening of casualty slaughtered animals had, however, exhibited clinical signs associated with BSE, as had one of the two positive cases detected in the fallen stock survey. Of the four cases detected in the OTM survey, two animals had exhibited clinical signs of BSE, one was an apparently healthy animal and one was a member of a herd that was slaughtered as a result of the death of the owner.

DATES OF BIRTH

The distribution of the 27 cases by their month and year of birth is shown in Table 2.

Table 2

MONTH AND YEAR OF BIRTH	NO. CASES
August 1996	3
September 1996	2
October 1996	1
November 1996	1
December 1996	1
January 1997	2
February 1997	4
March 1997	1
April 1997	2
May 1997	1
June 1997	1
July 1997	2
September 1997	1
November 1997	1
February 1998	1
March 1998	1
July 1998	2

AGE AT ONSET OF CLINICAL SIGNS/SLAUGHTER

The age at onset of clinical signs or at slaughter ranged from 46 to 72 months, with a mean of 58 months. This remains greater than for the first 20 confirmed cases in the previous BAB cohorts and preliminary analyses indicate that this is a statistically significant increase. The three oldest animals (70m, 71m and 72 months of age) were detected in the OTM survey.

HERD TYPE

Twenty-three of the 27 cases were in dairy herds and four were in beef suckler herds. This is not remarkable in that it does not represent a change in the incidence in the two herd types. All four

of the cases occurring in the suckler herds had received commercial concentrates in their early life.

GEOGRAPHICAL DISTRIBUTION

Seven of the cases were in purchased animals. From the time spent in the natal herds and ultimate herds, and taking account of the apparent i.p. distribution, it is most likely that these seven animals were infected in their natal herds. The distribution of the 27 cases by the county in which they were most likely exposed is given in Table 3.

Table 3

Region	County	No. Cases
Northern England	Cumbria	1
	Lancashire	1
	S. Yorkshire	1
	Greater Manchester	1
	Cheshire	3
Mid and West England	Staffordshire	1
	Shropshire	1
	Leicestershire	1
East England	Cambridgeshire	1
South-East England	Oxfordshire	1
	Buckinghamshire	2
	Hampshire	2
South-West England	Somerset	1
	Dorset	2
	Devon	2
	Gloucestershire	1
Wales	Gwynedd	1
	Pembrokeshire	1
	Carmarthenshire	1
	Powys	1
Scotland	Dumfriesshire	1

This geographical distribution remains different from the major part of the epidemic, comprised of cases born before the initial feed ban in 1988, during which the incidence was greatest in the southern part of England. It is also notably different from the geographical distribution of BAB cases, which was concentrated in the eastern region of England. The distribution of BARB cases is consistent

with the major risk factor being simply the number of cattle dairy herds per county. The only apparent “cluster” of cases are the three animals in the Buckinghamshire/Oxfordshire area.

PREVIOUS INCIDENCE OF BSE IN BARB AFFECTED HERDS

The owners of seven of the 20 natal herds, in which homebred cases occurred, have not reported any suspect cases in their herds previously and no confirmed cases are associated with these herds. The other BARB-affected herds do not represent the high within-herd incidence BSE-affected herds nor those herds with, numerically, the greatest number of cases.

BSE STATUS OF THE DAMS

None of the dams of the cases, or the other offspring of these dams, has developed clinical signs of BSE. The survival of the dams is summarised in Table 4.

Table 4

	Age (yr.) of Dams Alive At Time Of Investigation Of BARB				Survival Time (mths), Post Birth of BARB, of Dams That Were Dead or Untraceable						
	6	8	11	NK	<3	3-5	6-11	12-23	24-35	>36	N
No.Cases	1	2	2	1	2	2	2	7	2	2	5

* BSE 1 questionnaires for the breeders not yet received for two purchased cases.

OTHER POSSIBLE SOURCES OF INFECTION

For one case, there was a possibility of it being accidentally fed dog food.

SUMMARY

This updated analysis has not indicated any change in the basic epidemiological picture compared to the examination of the first sixteen BARB cases that were born in Great Britain. There is some additional evidence of a prolonged incubation period for the BARB cases and the geographical distribution of the cases is indicative of a wide-scale distribution of a low risk of exposure.

J.W.W.

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References

- (1) WILESMITH JW, WELLS GAH, RYAN JBM, GAVIER-WIDEN D, SIMMONS MM (1997) A cohort study to examine maternally associated risk factors for bovine spongiform encephalopathy. *Veterinary Record* 141, 239-243.
- (2) DONNELLY CA, GHANI AC, FERGUSON NM, WILESMITH JW, ANDERSON RM. (1997) Analysis of the Bovine Spongiform Encephalopathy Maternal Cohort Study: Evidence for Direct Maternal Transmission. *Applied Statistics* 46, (3) 321-344.
- (3) DONNELLY CA, FERGUSON NM, GHANI AC, WILESMITH JW, and ANDERSON RM. (1997) Analysis of dam-calf pairs of BSE cases: confirmation of a maternal risk enhancement. Proceedings of the Royal Society of London, Series B. 264, 1647-1656.
- (4) STEVENSON MA, WILESMITH JW, RYAN, JBM, MORRIS, RS, LOCKHART, JW, LIN, D and JACKSON, R. (2000) Temporal aspects of the bovine spongiform encephalopathy epidemic in Great Britain: individual animal-associated risk factors for the disease. *Veterinary Record* 147, 349-354