B S E : CULL POLICIES AND THE DISEASE

- *Modelling the disease in cattle*
- *Implications for cull policy*
- *Latest implications for human health*

Scientific understanding of the factors affecting the spread of BSE among UK cattle has advanced since the last POST review[1]. More information is available on the **incubation period** and on the extent of **maternal transmission** between infected dams and their calves, and epidemiologists at Oxford University have refined **mathematical models** to project the shape of the epidemic in the years to come, assess the likely impact of different culling options, and estimate the numbers of infected cattle which have entered the food chain.

This note describes these developments and examines the policy implications that arise.

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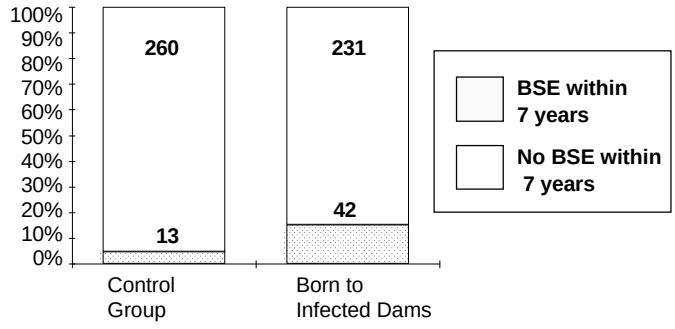
MATERIAL TRANSMISSION

One area of uncertainty regarding the BSE epidemic was whether maternal transmission occurred between dam and calf. Some scientists had argued that since this took place with scrapie in sheep, the likelihood was that it could also occur with BSE in cattle. MAFF vets maintained that the number of BSE cases could be explained on the basis of exposure to infected feed, indicating that if cows were able to pass the disease on to their offspring, it was occurring at a "*very low and undetectable frequency*"[2] .

An experiment to resolve this question was set in train at the Central Veterinary Laboratory (CVL) in 1989 to follow two groups of cattle, each containing over 300 pairs of calves - one of each pair (the 'control') had been born to a dam which had not developed BSE (by age 6); the other had been born in the same herd and season, but from a BSE-affected dam. The original intention was to keep all animals for 7 years (i.e. to Nov 1996), or until they developed BSE (or another disease). However, due to the importance of the study, preliminary results were released up to July 1996, by which time data were available from 273 animals in each group.

The findings are shown in **Figure 1** which shows that calves born to infected dams did have a 10% 'excess' risk of contracting BSE. However, the fact that 5% of calves in the control group developed BSE shows that they must have been exposed to contaminated feed before they entered the study. This complicates interpretation, since the results could (in whole or part) be due to calves sharing with their mothers a genetic predisposition to catch BSE from feed[3]. **This experiment has thus not resolved the question of maternal transmission.** It may be possible to pin down the cause more precisely using the expertise at Oxford University, if access can be given to the original experimental data from the CVL study.

Figure 1 **PRELIMINARY RESULTS FROM THE CVL MATERNAL TRANSMISSION STUDY**



If it turns out that maternal transmission is direct however, we need to know how far the risk is related to the state of the dam's infection. According to the Spongiform Encephalopathy Advisory Committee (SEAC), the detail of the CVL study provides some evidence that the **risk of maternal transmission is greatest in the 6 months** before dams develop actual BSE symptoms. Since most of the infected dams in the CVL study were in this category, MAFF suggest that the 10% figure should apply only to dams about to develop clinical symptoms. If it is assumed that the 6 month period is a 'cut-off', with calves born before it being at little risk of infection and those born after facing a 10% transmission rate, then SEAC estimates that the overall risk of a calf acquiring BSE from an **infected** mother would be nearer 1%.

1. BSE and CJD: Science, Uncertainty and Risk, POST Rpt 78, April 1996.

2. SEAC 1994 (A Summary of Present Knowledge and Research), p39.

3. MAFF analysis suggests that the risk of BSE is higher in the calves born before the 1988 ruminant feed ban than after, which would not be expected if the transmission were direct from infected cow to calf, but would be consistent with a genetic susceptibility component.

INCUBATION PERIOD

The shape of the BSE epidemic in the UK from the mid-1980s to the current day suggests that the disease has an incubation period of several years between infection and the onset of BSE symptoms. Thus the first BSE cases were not diagnosed until 1986, some years after the first widespread exposure of cattle to infected meat and bone meal (MBM) in cattle feed in the late 1970s and early '80s. Similarly, it took several years before the effects of the first ban on recycling ruminant-derived MBM into cattle-feed (in 1988) had any noticeable impact on the number of new BSE cases (which started declining in 1993 / 4 - see Figure 1, POST report 78).

More detailed insights have recently emerged into how the average incubation period varies within the cattle population, and according to dose or route of transmission. In one study, four groups of cattle were fed with infected brain tissue (doses of 1g, 10g, 100g and 3x100g respectively). The experiment is on-going, but interim results for the first 52 months suggest that BSE signs first develop after 3 years or so- first in those cattle receiving the highest doses (100 g or 3x100g), subsequently in the cattle receiving the lower doses (from 44 months on). While all animals receiving the 3x100g dose had contracted BSE, some given 1 or 10g are still disease-free after 52 months.

The CVL study of maternal transmission found an average age of onset of 5 years. Taken together, the studies suggest that the incubation period:

- lasts an average of around 5 years, with most animals developing BSE 3 to 7 years after infection;
- varies according to the dose received (higher doses = shorter incubation period).

MODELLING THE BSE EPIDEMIC

Much attention has been given recently to the results of a computer model of the BSE epidemic in British cattle developed at The Wellcome Centre for the Epidemiology of Infectious Disease at Oxford University. This explains the pattern of the epidemic to date, projects the possible future shape of the epidemic, and can be used to assess the potential impact of culling options.

Mathematical models to project the future course of a disease epidemic have been in use in medical circles for many years and much work has gone into their refinement in order to inform public health policy (e.g. on vaccination campaigns), as well as predicting the possible course of the spread of HIV / AIDS. As discussed in **Box 1**, these models describe the course of the disease by calculating the number of uninfected, infected and diseased individuals, and include the factors that influence the 'flow' of the disease (transmission rates, incubation periods, etc.). Where full information is avail-

Box 1 APPLYING EPIDEMIOLOGICAL DISEASE MODELS TO BSE

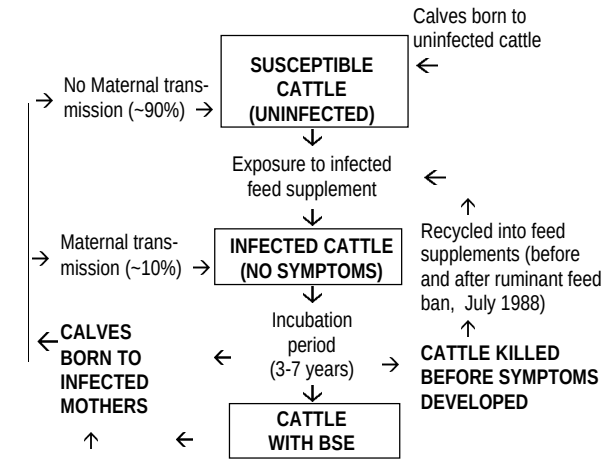
Epidemiological models apply knowledge of the course of a disease in individuals to the study of its transmission within a population. The first step in constructing such a model is to split the population up into different categories depending on their disease status. This idea is illustrated in the Figure, which shows a simplified model of the various factors relevant to the BSE epidemic. The three main categories within the cattle population (depicted as boxes in the Figure) are:

- susceptible cattle (those not infected);
- infected cattle (which carry the infectious agent but do not yet display signs of BSE);
- cattle with clinical signs of BSE.

In principle, modelling the progression of a disease within the population is achieved by calculating the numbers in each category over time. This requires two further steps. Firstly, mathematical equations must be devised to describe the flow of the disease from one category to another (depicted as arrows in the Figure). In the case of BSE these would have to take account of changing birth-rates over the course of the epidemic, feed-borne transmission rates (which vary with time and with age), maternal transmission rates, slaughter rates (most infected animals will be killed before they develop clinical signs of BSE) and the characteristics of the incubation period.

Secondly, basic data on the number of individuals in each category are required, in order to define the state of the epidemic at the start, from which point the number of affected individuals in each category over successive periods of time can be calculated, and the likely future course of the disease projected. Such approaches have been succesfully used to model a range of diseases in humans (e.g. to inform public health policy regarding vaccination programmes). However, the case of BSE presents particular problems, since the lack of a diagnostic test means that there is no way of distinguishing uninfected (i.e. susceptible) animals from those which have the infection but which have not yet developed BSE symptoms. In the event, valuable experience had been accumulated in developing epidemiological models for infection by HIV and progression to AIDS, and it was possible to build on this in developing techniques of back-calculation to model the BSE outbreak.

Figure A SIMPLIFIED MODEL OF BSE IN CATTLE



able, the model can both explain the current position and project the disease's likely future course.

Information is available on the numbers with signs of BSE, the incubation period, maternal transmission, the effects of slaughter patterns in removing animals before developing BSE, and on other factors. Due to the lack of a diagnostic test for infection however, no direct information on the number of **infected** (but asymptomatic) animals is available. Instead, the pattern of infection throughout the epidemic has to be deduced by **back-calculation,** developed from methods used to model the progress of the HIV / AIDS epidemic. In this way, the number and age of infected animals in the cattle population at any given time is 'reconstructed' by working backwards from MAFF and Scottish Office (SO) records of the number and age of confirmed BSE cases throughout the epidemic.

Several factors in the model are known only approximately - e.g. the extent of under-reporting of actual BSE cases (most likely in the early stages of the epidemic), how many infected animals were slaughtered before they had time to develop BSE signs[4], the exact variation in the incubation period, the variation in risk of feed-borne infection with age and time, and the maternal transmission rate. The scientists thus ran a large number of different 'versions' of the model, each making different assumptions to find which set best explained the historical pattern of confirmed BSE cases and their age. The best 'fit' was found with a model that assumed:

- an incubation period with a mean of 5 years, but ranging from 2 to 9 years;
- the susceptibility to feed-borne infection peaks at age one, and declines rapidly thereafter;
- a maternal transmission rate of 10%, but only in the last 6 months of the dam's incubation period.

This model gives the trends in the incidence of infection shown in **Figure 2**. This has the first infection starting to develop by 1983, after which the number of new infections and the total number of infections rose steeply until the feed ban was introduced in 1988. After the ban, **new** infections declined rapidly, accompanied by a slower tail-off in the total number of infected animals. Due to the long incubation period, there is a considerable lag between the peaks in new infections (1988) and observed BSE cases (1993). The model confirms that **the number of diagnosed BSE cases was just the tip of the iceberg** - only around one third of animals having developed BSE signs appear to have been reported up to 1988, and many more animals were infected but slaughtered before the disease had time to develop fully. Overall, best estimates suggest that around 900,000 animals had been infected by 1995. Of these, only around 160,000 (~18%) had actually developed BSE signs, with **the vast majority of the rest (729,000 or ~81%) entering the human food chain after being slaughtered,** both before and after the ban on the use of offals for human consumption in 1989 (see later).

Figure 2 CHANGES IN THE INCIDENCE OF BSE INFECTIONS ESTIMATED IN THE OXFORD MODEL

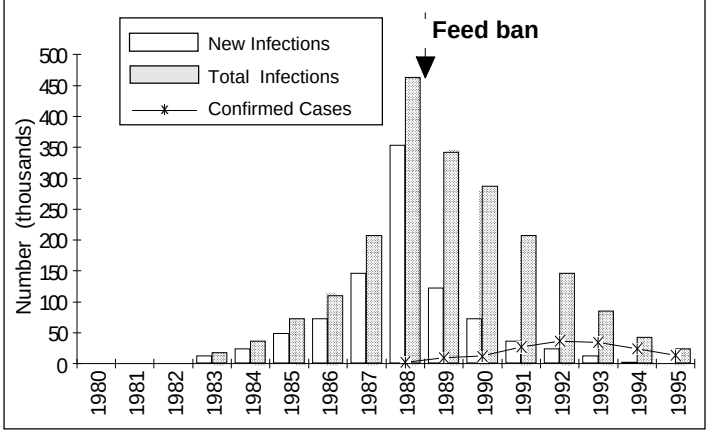
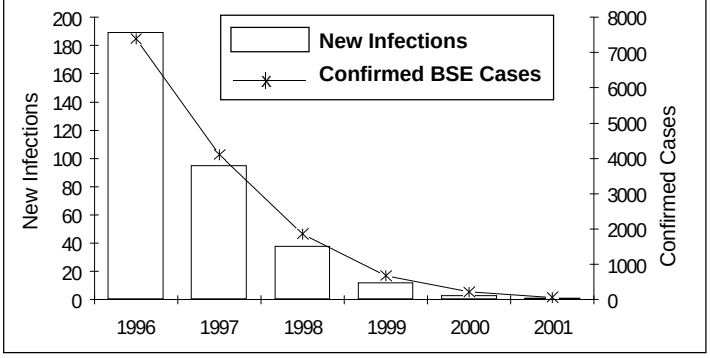


Figure 3 PREDICTED LIKELY FUTURE TRENDS IN THE INCIDENCE OF INFECTIONS AND CONFIRMED CASES



If a maternal transmission route is established as the source of new infections, the model suggests this is sufficient to account for recent new infections. Contaminated feed may have thus ceased to be a significant source of new infections after 1994. Since the maternal transmission indicated in the CVL study is too low to sustain the epidemic, as shown in **Figure 3**, the model predicts that **new** infections will fall from ~189 in 1996 to just 1 by the year 2001. Because the key factors are not known precisely, different values and functional forms were used in the model runs. These gave a range of predictions, 95% of which fell between 155 and 11,300 new infections for 1996, and between 0 and 33 for 2001. Trends in the number of confirmed BSE cases will, of course, lag behind the fall in infections, and are predicted to drop from ~7,400 (95% prediction limits 6,500-8,900) in 1996 to ~70 (45-1600) by 2001 (also in Figure 3).

ASSESSING CULLING OPTIONS

Once established, the model can be run under different culling policies, to see what effect they have on the future shape of the epidemic. Many options have been analysed by the Oxford Group, from a total cull of all

4. Most cattle are slaughtered at age 2-3 years, so the majority of infected cases would not have had time to develop clinical signs of BSE.

British cattle to strategies targeted at specific age groups, herds, individuals born to infected dams or various combinations of these, as detailed in **Box 2**. Fourteen of these have been published[5], and others presented to MAFF. The effects of some on the likely future shape of the epidemic are shown in **Figure 4**.

If no culling took place at all, the model predicts that there will be 6,950 cases (95% prediction limits 4,720 to 25,850) of BSE from 1997 to the year 2001. After this, the source of the epidemic would effectively have dried up as new infections ceased, although further cases of BSE (in tens rather than hundreds) would still occur, possibly for some years in animals already infected. All culling policies are thus relative to this 'do-nothing more' scenario. A total cull of all British cattle (option 1 in Box 2) would obviously prevent all 6,950 projected future BSE cases. This would however involve the slaughter of 9.36 million animals in 111,000 herds - a kill of 1300 animals for every one future case of BSE 'saved'.

In between these two extremes lie policies targeting the cull at specific groups of relatively 'high risk' cattle. Here the difficulty is how to identify cattle at risk, since there is no single criterion which determines that an animal is highly likely to develop BSE and, as already mentioned, no test to screen for infected animals.

In practice, the bases for screening are on:

- **Exposure to infection through feed.** Here the main criteria are **age and herd** - for each BSE case identified, cattle born in the same herd and / or in the same age group (cohort) may share a higher risk of having been exposed to contaminated feed;
- **Parentage**. Here calves born to infected dams have an increased risk of contracting BSE.

The scenarios in Box 2 explore different cull policies targeted at one or more of these risk categories. These vary in terms of their **'efficiency'** (i.e. number of cattle culled per case saved), and **'effectiveness'** (i.e. the resulting reduction in BSE cases in the years ahead). Thus, a simple age-targeted policy (e.g. option 3 in Box 2) would have a substantial impact on the epidemic, saving around half (3,600) of the estimated future cases of BSE, but the **'cost'** would be high - around 2 million cattle (564 per case prevented) would have to be culled, and virtually all British herds would be affected.

Targeting the cull at all the herds from which BSE cases have originated (e.g. option 4 in Box 2) would reduce the number of BSE cases expected by 90%, so that by 1999, less than 70 cases of BSE would be predicted (Figure 4). However, the 'cost' would again be high (Box 2) - almost one third (2.87 million) of the cattle population would have to be slaughtered (455 animals culled per case saved), and around 1 in 4 British herds would be affected. Modifying this herd-targeted policy by only culling cattle born at the same time as the confirmed cases (e.g. option 6 in Box 2) would have a smaller impact (Figure 4), reducing the number of BSE cases expected by 23%, at a 'cost' of 127,000 animals (80 culled for each BSE case saved) in 6,240 herds.

A further modification of herd-targeted policies involves only culling animals in those herds where the incidence of BSE exceeds a certain threshold. In general, this approach is more 'efficient' than the simple herd-targeted options. For instance, restricting the cull to those herds with a threshold incidence of 1 case in 50 (option 8, Box 2) would have a similar impact on the future BSE epidemic (Figure 4) to option 6, but would require fewer cattle to be slaughtered (71,900) and thus the cattle culled per case saved figure falls to 51.

Although maternally-targeted culling policies alone would have only a limited impact in preventing future BSE cases (see Box 2), combining them with herd-targeted approaches produces **some of the most effective and efficient options**. For instance, taking option 8 (which saves ~20% of BSE cases at a cost of 51 cattle per case saved) and combining it with the maternally-targeted option 9, yields option 12 which saves more BSE cases (29%) at a lower cost (47 cattle per case saved). Similarly, option 6 (23% of cases saved at 80 per case) becomes both more efficient and effective when combined with option 9 (option 14, 31% of BSE cases saved at a cost of 69 cattle per case).

ISSUES

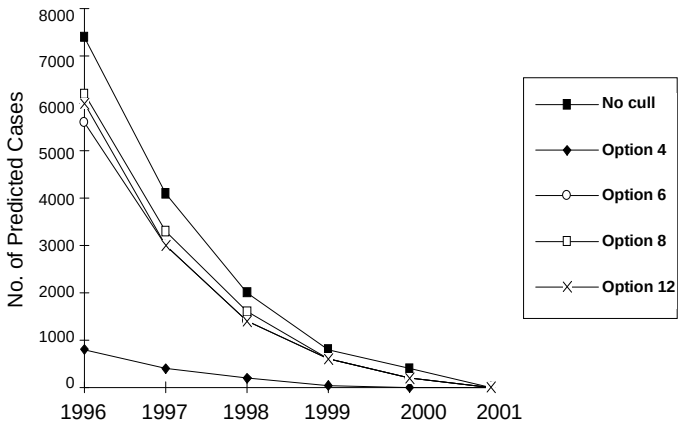
Implications for Culling Policy

This model offers a powerful tool to policymakers by enabling them to predict the effect of different possible culling strategies and to **translate clear policy objectives into a cull strategy likely to achieve them**. Indeed, the results of the Oxford model have already had an impact on UK policy, and the proposals emanating from the Florence Summit have been suspended pending further discussion both nationally and within the EU (the Florence agreement makes provision for reviewing cull policy in the light of the latest scientific evidence). In view of the use being made of these results, **policymakers need to understand that the science is continually evolving and that new insights into the disease and its transmission, as well as improvements to the model itself, will undoubtedly cause future modifications to current predictions**.

At present, the model has both strengths and weaknesses. Strengths lie in its being a detailed and sophisticated representation of the disease, bringing in key experience from human disease epidemiology. In this

5. Anderson, RM *et al*, 1996. 'Transmission Dynamics and Epidemiology of BSE in British Cattle', Nature, 382, 779-788.

Figure 4 FUTURE CASES OF BSE UNDER DIFFERENT CULLING SCENARIOS



respect it is a significant advance on the much simpler animal model previously used by MAFF. On the other hand, its complexity, combined with the still evolving understanding of some aspects (e.g. maternal transmission) and the impossibility of quantifying others (e.g. extent of BSE case under-reportings in early years) means that the model has to rely on a number of assumptions. However reasonable these may be, they do introduce uncertainties which are reflected in the range of figures produced. Thus, as described above, while the central prediction for the number of BSE cases from 1997 to 2001 is 6,950, the model also shows that there is a good chance that the outcome will be significantly different - with 95% of the predictions based on different values lying between 4,720 and 25,850.

The model results are sensitive to:

- the risk of infection from feed (especially after 1993);
- the variation of susceptibility to infection with age;
- and, to a lesser extent, more detail on maternal transmission rates, the shape of the incubation period and extent of under-reporting in the early stages of the epidemic.

As new data emerge which change the figures used, this will affect the overall outcome.

Despite these qualifications, the model is widely seen as a vast improvement on previous methods, and is generally regarded as being sufficiently robust to be used to inform policy in this area[6]. Overall, the analysis confirms that **there are no easy answers, and no single obvious course of action** - rather, the policy chosen will depend on the relative weight given to political, economic, logistical and ethical (animal welfare) considerations as well as to any change in the assessment of current risk to humans. For instance, if the prevention of **any** future cases of BSE is the overriding consideration, then this can only be achieved by a cull of all cattle. If a 90% reduction in BSE cases were the policy objec-

6. Latest model runs show that the set of values (forall factors except feed risk) which gave the best fit for MAFF data also explained best the development of the disease in Northern Ireland.

Box 2 ANALYSIS OF DIFFERENT CULLING POLICIES

The likely impact of a range of different culling policies have been analysed using the model. These fall into six basic categories:-

- **Non-targeted** - a total cull of the British cattle population (**option 1**, see Table).
- **Age-targeted** - culling in specific age groups. Two particular groups are suggested, cattle over 8 years old (born before July 1988, **option 2**), and those in the age range 3-6 years (born between October 1990 and June 1993, **option 3**).
- **Herd-targeted (by case)** - a cull of cattle from all herds from which a BSE case originated between 1991 and 1995. Three main options have been suggested here. First, a cull of all cattle in these herds (**option 4**). Second, culling only those animals in the same birth cohort (of the three cohorts between October 1990 and June 1993) as the confirmed case(s) of BSE (**option 5**). Third, as for the previous option, but extending the cull to include the four birth cohorts between July 1989 and June 1993 (**option 6**).
- **Herd-targeted (by incidence)** - a cull of cattle from all herds where the incidence of confirmed BSE cases exceeded a certain threshold between 1991 and 1995. Two proposals have been analysed. First (**option 7**), culling all animals in a particular birth cohort (including the three cohorts between July 1989 and June 1992) in herds where the incidence of confirmed cases exceeds 1 in 27. Second, as for the previous option but using an incidence threshold of 1 in 50 (**option 8**).
- **Maternally targeted** - culling calves born (after Oct 1990) to dams that have since developed BSE. **Option 9**, restricted culling to animals born in the 6 months prior to their dam developing BSE. **Option 10** assumed that 10% transmission rate applied for the last 12 months of the maternal incubation period, so calves born in this period were culled.
- **Combined herd- and maternally-targeted** - various combinations of the above-described policies. **Option 11** is a combination of options 7 and 9, **option 12** of 8 and 9, **option 13** of 5 and 9, and **option** 14 of 6 and 9.

The model assumes a 10% maternal transmission rate in the 6 months prior to a dam developing BSE (except for option 10, see above), and provides estimates of the total number of cattle that have to be culled, the number of BSE cases prevented and the number of holdings affected (see Table) between 1997 and 2001. Maternally-targeted policies (options 9 and 10) are modelled as 'running' culls (i.e. the appropriate animals are culled as and when their dams develop BSE up to the year 2001), whereas the other options assume a 'one-off' cull in 1996.

Table COMPARISON OF VARIOUS CULLING OPTIONS

Option Number	No. of cattle culled (%)	No. of BSE cases saved (%)	No.culled per case saved	No. of holdings affected
1	9,360,000 (100%)	6,950 (100%)	1,300	110,00
2	352,000 (3.8%)	250 (4%)	1,400	<110,00
3	2,030,000 (22%)	3,600 (51%)	564	<110,000
4	2,870,000 (31%)	6,300 (90%)	455	28.500
5	30,100 (0.32%)	650 (9%)	46	1,460
6	127,000 (1.4%)	1,580 (23%)	80	6,240
7	21,300 (0.23%)	691 (10%)	31	638
8	71,900 (0.77%)	1,420 (20%)	51	2,000
9	<22,000 (0.24%)	584 (8%)	<38	<22,000
10	<44,000 (0.47%)	1,100 (22%)	40	<35,000
11	<44,000 (0.47%)	1,277 (18%)	34	<25,500
12	<94,000 (1%)	2,007 (29%)	47	<26,800
13	<53,000 (0.57%)	1,237 (18%)	43	26,300
14	<150,000 (1.6%)	2,167 (31%)	69	<31,000

tive, then the model shows that this could be achieved by culling around 1 in 3 animals. Similarly, a 50% reduction in cases would require around 1 in 5 cattle to be culled. However, it is worth recalling that **in predicting the end of new infections of BSE in 2001, the model does not predict the end of BSE cases by that date** - these would continue in declining numbers for some years more. **If a policy goal were to have no cases of BSE in the UK, this remains a distant prospect without removal of most or all of the national herd.**

The evolution of Government policy on culling is outlined in **Box 3**, and was formulated mostly before the Oxford group's results. MAFF considered a range of different policies[7] before deciding that the preferred approach was to trace back from confirmed cases, slaughtering all the animals born in the same herd and at around the same time as these cases. The likely impact of these different options was evaluated, but predictions beyond 1996 could not be made with any degree of accuracy. For instance, MAFF's estimate for the policy chosen was that it would involve culling ~41,900 cattle to save some 1,200 cases in 1996 alone, whereas the Oxford model suggests that this policy (option 5 in Box 2) would save around 650 cases of BSE by culling ~31,000 animals over the period 1997-2001.

As noted in Box 3, this culling policy was subsequently modified at the EU Florence Summit. Analysis of the new policy (Option 6 in Box 2 and Figure 4) suggests that it would result in an overall saving of 23% of future BSE cases between 1997 and 2001, but involve the slaughter of some 127,000 animals (an efficiency of 80 killed for each case saved). If this is taken as a policy 'baseline', the Oxford model suggests that, if maternal transmission occurs, there are other considerably more efficient options. For instance, option 12 is projected to save more cases of BSE (29% of cases saved) by slaughtering fewer cattle (94,000) than the Florence policy, and has almost double the efficiency (requiring 47 animals to be killed for each case saved). Option 14 could also be seen as a more efficient alternative since, while it involves killing more cattle (~150,000 compared to 127,000), it is projected to prevent more cases of BSE (31% vs 23%).

As already mentioned, the baseline case in Figure 4 assumed no cull. However, since April 1996, there has been an 'over thirty month' (OTM) policy whereby all animals bred for human consumption should be slaughtered before 30 months, with farmers receiving compensation to keep animals slaughtered after this time out of the food chain. It is not clear whether this policy has merely formalised pre-existing farming practice, or has led to more animals being culled or a change in the age distribution of those slaughtered. The age of animals culled under this policy is not available in a database, so the **effects of the OTM policy on the future course of the BSE epidemic cannot be predicted**. It is possible that by targeting specific cohorts (e.g. those born between 1988 and 1991) first, the OTM policy may be 'fine-tuned' to maximise the subsequent fall in BSE cases, and this is under investigation.

Box 3 POLICY ON SELECTIVE CULLING

Policy on selective culling has evolved rapidly in recent months. Key 'milestones' are described below.

- **29 April 1996** - MAFF consultation document circulated detailing proposals for selective culling.
- **29 / 30 April 1996** - proposals discussed at the Council of Agricultural Ministers.
- **31 May 1996** - policy proposals formulated and published as part of MAFF's Eradication Plan. The proposed policy was to identify all cases of BSE in cattle born in the three birth cohorts between October 1990 and June 1993, and to slaughter all other cattle born on the same farms at about the same time as these cases. MAFF predicted that such an approach would require the culling of 41,900 cattle and prevent 1,200 cases of BSE in 1996. Predictions for 1997 and subsequent years were not possible using the MAFF model. This equates to option 5 in the Oxford group model.
- **21 June 1996** - proposals discussed by the EC Heads of Government summit in Florence. In return for a *"phased lifting of the export ban"* on live cattle and cattle products, the UK agreed (*inter alia*) to introduce selective culling of animals thought to be at highest risk of developing BSE. The policy outlined above was agreed on a compulsory slaughter basis - in addition it was agreed that appropriate cows born in the preceding birth cohort (July 1989 to October 90) would be included, but only slaughtered on a voluntary basis (i.e. if the farmer agreed). This equates to Option 6 in the Oxford model.
- **3 July 1996** - modified proposals circulated to interested parties in MAFF consultation document, with a view to making the necessary legislation before Parliament rose for the Summer recess.
- **19 September 1996** - statement issued by the Government suspending the cull ("*for the present, the Government is not proceeding with the selective cull but will return to cull options in the light of the developing science*").

Detecting the TSE infections

The absence of a test for infection ahead of clinical signs of disease hampers control of the Transmissible Spongiform Encephalopathies (TSEs), since we must rely on slow animal bioassays of uncertain sensitivity to tell whether a tissue carries the infective prion agent or not (see earlier POST report). For this reason, MAFF and others have supported research towards diagnostic tests, and interest has recently been aroused in a new test developed in the USA and Germany. This measures a protein (Harrington's protein) in spinal fluid

7. Options rejected by MAFF on the basis of poor cost/benefit ratio include the slaughter of all dairy cows born before July 1988, all herds from which a confirmed case of BSE originated, herds from which a confirmed case of BSE originated after July 1988, and herds with a high incidence of confirmed BSE cases.

which may be a by-product of brain degeneration due to spongiform encephalopathy (SE). The test has been validated on patients with early symptoms of dementia and can allow an accurate diagnosis of Creutzfeldt-Jakob disease (CJD) up to 15 months before death.

In the current climate of uncertainty about the likely extent of any 'new variant' (nv)-CJD epidemic in the UK, each confirmed case in people under 45 takes on a huge significance. The UK CJD Surveillance Unit (CJDSU) has collaborated with US researchers and confirmed diagnoses of nv-CJD in the final stages of the disease in two patients, and the question clearly arises how this test should be incorporated (if at all) into the current strict diagnostic protocol for nv-CJD. **There could be several stages here**. Firstly, to deploy a national capability to carry out the test; secondly to design experiments to evaluate the test's efficacy (e.g. how far back into the incubation period the test can be successfully deployed and the extent of false positive results in younger patients); thirdly, whether the test could replace brain histology as the ultimate diagnostic criterion, or even be considered as an initial screening procedure soon after referral from neurology depts.

It is not yet known how early a warning would be provided of BSE in cows, but the test's dependence on the side effects of brain neuron damage leads scientists to doubt whether it can detect the earlier stages of infection. **These developments do not therefore reduce the need for a test to detect the prion protein itself in brain, nervous or other tissues.** In this respect, the recent discovery of 'markers' for BSE and nv-CJD prion (see later) may be important, if the advances in the last decade in the technology of diagnostics, can be successfully applied to yield a test for prion infection in tissues other than brain. Much of the leading expertise lies in pharmaceutical diagnostic companies and has not been engaged because the 'market' (in CJD cases etc.) is too small to justify the required research. **Engaging this would require Government encouragement.**

Implications for Human Health

Since SEAC announced the first ten cases of 'new variant CJD' (see earlier POST report) in March 1996, there have been a further four cases confirmed by the CJDSU (as well as one reported from France). A case of nv-CJD is only confirmed following a strict and thorough protocol involving brain histology, and thus may take some weeks after the death of the patient to complete. No information (e.g. on the number of referrals of possible CJD cases under age 45) is currently released before final confirmation, and the main official channel of publication is the Chief Medical Officer's (CMO) Quarterly report on CJD. Even though there is no scientific proof (or disproof) of a causal link between eating BSE-infected food and these cases of nv-CJD, for public health purposes, policy has to be set on the basis that it is possible that BSE may be transmitted to humans. In this respect, a succession of measures have been applied to reduce or eliminate the risk of people eating BSE-infected food, starting with the destruction of BSE-diagnosed animals in August 1988, the introduction of the ban on offals for human consumption from all animals in July 1989 (and its subsequent tightening to cover additional organs), and the OTM policy introduced in April 1996.

As discussed in the previous POST report, evaluating the risk posed by BSE to human health depends on a range of different factors, including:

- the number of infected cattle entering the food chain at any given time;
- the infectiousness of this material - some types of tissue are more infectious than others, and animals near the end of their incubation period are likely to present a bigger risk. Although none of the tissues **currently** allowed into the human or animal food chains have any detectable infectivity, assessing the risk posed in earlier years is important;
- susceptibility - some individuals may be more inherently (i.e. genetically)[8] at risk than others, and the risk of infection is likely to depend on dose.

As far as the first of these is concerned, the Oxford model provides us with a profile of the number and age of infected animals entering the food chain throughout the epidemic, so that better estimates can be made of the extent of human consumption of products derived from BSE-infected cattle. For instance, before the 1989 offal ban, **over 3,000 cattle with BSE and 446,000 infected (but with no clinical signs) cattle are estimated to have reached slaughterhouses. While most of the latter will have been in the early stages of incubation, there were at that time no restrictions on tissues for human consumption.** After the offal ban, some 283,000 infected cattle may have reached the slaughterhouse from whence the meat and other non-prohibited tissues (of no detectable infectivity) will have entered foods.

Since the ages of these cattle are known, this information allows the age-related aspect of infectiousness to be taken into account. Other aspects of infectiousness require detailed information on what type of tissue was processed into which kind of food at different stages of the epidemic. This involves a detailed audit of food processing (MAFF have only recently commissioned this work but results are expected in the next few months), as well as consideration of the effectiveness of the various measures taken to eliminate specified bovine offal from the human food chain throughout the

8. In this respect, all nv-CJD cases to date involve patients with the same genetic variant in the gene responsible for the brain protein whose deformation causes CJD. As described in the earlier POST report, the variant involved has two methionine groups at position 129, a characteristic shared by 38% of the population.

epidemic. Taking all these factors into account would allow modellers to build up a profile of the **exposure risk** to humans at each stage of the epidemic.

Recent work at St Mary's Hospital shows common 'markers' in the BSE and nv-CJD prions which are not shared by 'normal' CJD - consistent with the hypothesis of a link between nv-CJD and BSE. This suggests that epidemiologists should start modelling the development of nv-CJD cases, just as they have with BSE in cattle, and use it to explore hypothetical scenarios in the event of a link being shown to exist[9]. For instance, what might happen with mean incubation periods of 5, 10, 15, 20 years with individual variations between 4 and 40 years? At present, the number of cases is too few to enable useful predictions to be made of the possible future course of nv-CJD. However, some epidemiologists are arguing for changes in the way reports are made to allow such models to be deployed as soon as possible. One suggestion is that the CMO's quarterly report on nv-CJD should, in addition to confirmed cases, **include all suspected cases under age 45 which have been referred to the CJDSU**. If a pattern emerges (e.g. that a certain proportion of referrals generally end up being confirmed cases), this could provide an extra 6-12 months notice of changes in nv-CJD incidence.

A related issue concerns the collection of data on **individuals who may be most at risk** if a significant nv-CJD epidemic does emerge. They might include abbatoir workers, children born to CJD patients, etc., and some epidemiologists suggest that a database on such groups should be set up now, as a precautionary measure. Recent data on maternal transmission of BSE also raise questions since we do not yet know whether this is genetic or happens before (e.g. via the placenta), during (e.g. via blood or other body fluids) or after (e.g. via milk) birth. All tests to date have failed to demonstrate any infectivity in blood or milk, so further research on the exact mechanism involved is seen as a priority.

Research Priorities

In March 1996, the Secretary of State for Health instructed the Department's Director of Research and Development to prepare a directed programme of research, involving all the main funding bodies. Following this, the Director appointed two advisory groups:

- the TSE R&D Funders Coordination Group, brings together MAFF (up to £10M spend on BSE R&D in 1996/7), BBSRC, MRC (£3M p.a. each over the next 5 years), DH (£3.5M for 1996/7) and the Wellcome Trust, to "*ensure that ..... R&D funded in this field addresses priority issues of national interest and constitutes a coherent strategy .....*";
- joint DH/MRC TSE Research Advisory Group to "*advise ..... on a scientific strategy and priorities for basic and applied research on the human aspects of SEs .....*".

A national strategy has been produced with input from the main funding bodies identifying specific areas of research as requiring urgent R&D. These include:

- the nature of the relationship of nv-CJD and BSE, including current epidemiology and surveillance;
- transmissibility of BSE including aspects quantifying potential direct and indirect risk to man;
- development of new diagnostic methods;
- nature of the agents and pathogenesis;
- developing/assessing potential therapeutic agents.

Implementation of this R&D strategy is already underway, following the publication of a joint MRC/DH call for research proposals in the academic press. Outline proposals have been short-listed by the Research Advisory Group and successful applicants will be asked to submit full proposals for funding consideration by the MRC or DH. While the academic world in general has welcomed these moves, some scientists suggest that the funding procedure **is still too long-winded, with almost a year expected to elapse between the first 'calls for proposals' and the first decisions on funding.** They argue that the whole research area is so fast-moving, and of such potential importance to public health, that ways should be found of further streamlining the assessment procedures.

Finally, recent results have been portrayed by some as revealing missed opportunities. Thus the 'tell-tale' protein linked to CJD was discovered in 1986 and led to work to develop a test in the USA and Germany, but not in the UK with its greater need for one. The Oxford model could have been developed and applied 4-5 years ago, and even this year required an external initiative funded by the Wellcome Trust. Such experiences demonstrates the **importance of mobilising expertise and resources outside Departments to provide the best possible scientific basis to policy and a broader perspective transcending departmental boundaries**.

Expert committees (e.g. the Tyrrell committee) have advised on BSE research needs in the past, and SEAC advises on this now, but some argue that MAFF's detailed research planning might have benefited from more expert involvement and peer review to ensure that appropriate disciplines (outside those of MAFF's mainstream sciences such as veterinary science) were involved (e.g. along the lines of the DH/MRC Research Advisory Group mentioned above). Others see a broader role for the Office of Science and Technology (via an appropriate expert committee) to focus on critical scientific issues and assess the adequacy of departmental responses, enabling outside expertise to be mobilised swiftly where necessary.

9. Experiments are underway to shed more light on this, by testing tissue from nv-CJD patients in a panel of experimental mice, which have been shown to give a characteristic pattern of disease response to BSE in earlier experiments - see earlier POST report No 78.