



BSE IN SHEEP CONTINGENCY PLANNING

ISSUE

1. The Food Standards Agency (FSA) is currently reviewing its advice to UK Government on the measures needed to manage the risk to consumers if BSE were found in UK sheep, to take into account the latest assessments of the possible prevalence of BSE in UK sheep.
2. The FSA has asked Dr Rowland Kao to advise, from an epidemiological standpoint, on the current likelihood of finding BSE in UK sheep and on what findings of BSE in UK sheep, in terms of numbers of both cases and affected flocks, could lead to a view that the possible prevalence of BSE in sheep might be higher than is currently estimated.
3. SEAC is requested to consider the attached paper prepared by Dr Kao, with input from Professor John Wilesmith and Dr Simon Gubbins.

BACKGROUND

4. Defra have published a contingency plan setting out the Government's strategy for responding to a finding of BSE in sheep. The plan is based on the FSA's probable advice on the actions needed to protect public health were such a finding to be made. Until April 2006, the FSA's policy in the event of finding BSE in UK sheep was that only sheep that were either genetically resistant to BSE, or semi-resistant and aged under 12 months, would be allowed to enter the food supply.
5. As a result of statistical analysis of the results of discriminatory testing of scrapie positive cases, SEAC has now concluded that the most likely prevalence of BSE in UK sheep is zero or at most extremely low.
6. At its April 2006 meeting, the FSA Board agreed that, if only a single UK sheep with BSE were found, the above genotype-based restrictions would not apply. The Board however agreed that, in that case, intensive and targeted surveillance should be carried out to (i)

determine whether the case was an isolated one and (ii) estimate what the prevalence of BSE might be in the UK sheep flock.

7. The FSA Board held a further discussion on this issue at its meeting in June 2006. At that meeting the Board agreed that measures to protect consumers, should BSE be found in the UK flock, should be graduated according to the level of BSE found. The Board also agreed that a number of key uncertainties had been highlighted. These uncertainties included the point at which the contingency plan should be initiated; the nature of the epidemiological surveillance that would be required to determine prevalence should BSE be found in sheep; what constitutes an 'unrelated flock'; and related questions on geography and timing. The Board remitted these questions to the Agency's TSE division and SEAC.
8. To help prepare the ground for further consideration of these issues, the FSA asked Dr Rowland Kao, Professor John Wilesmith and Dr Simon Gubbins for their advice on a number of relevant questions. That advice is set out in the attached paper prepared by Dr Kao, with input from Professor Wilesmith and Dr Gubbins (Annex 1).

ADVICE SOUGHT FROM THE COMMITTEE

9. The advice of the Committee is requested on the following questions:
 - does the Committee agree with the principles laid out in the attached paper?
 - given the surveillance results in UK and Europe, is it now unlikely that horizontal transmission of BSE between sheep has been occurring?
 - with respect to a finding of BSE in one or more sheep, if epidemiological investigation had established that the animal/s had been imported or there was a likely feed-borne source of infection, and all those sheep identified as being at risk of infection have been culled, what would that finding indicate about risk to human health?
 - with respect to multiple cases of BSE in sheep in single or multiple flocks and in the absence of any obvious source of infection, would that indicate that horizontal transmission is likely to have occurred and would the rate at which BSE could be spreading between sheep be unknown?
 - with respect to the question of whether BSE-affected flocks are 'related' or 'unrelated' (i.e. whether or not an epidemiological

link between them can be established), would multiple cases of BSE in sheep be likely to be related?

- if a finding of one or multiple BSE cases in sheep led to a view that horizontal transmission of BSE between sheep were likely, would it be possible at that point (i.e. before any further surveillance or work to determine the possible rate of transmission had been carried out) to provide any estimate of risk from BSE in sheep?
- with respect to improving estimates of prevalence of BSE in sheep entering the food supply if BSE were found in sheep, would surveillance of fallen stock be the most effective approach?
- does the Committee have any other comments?



COMMENTARY ON ISSUES RAISED BY THE FSA BOARD

1. On the basis of epidemiology (vs statistics), why would a finding of BSE in UK sheep now be unexpected, and what can be learned from French/aggregated European data in relation to likelihood that BSE might be present in UK sheep.

A putative feedborne epidemic of BSE in sheep would be expected to have peaked around 1990 as it would have mirrored the BSE epidemic in cattle. Thus, in the absence of horizontal transmission of BSE in sheep, numbers of BSE-infected sheep would be expected to be declining, rapidly now as we are well past the point when the average feed-infected sheep would have been expected to have been slaughtered. We note that true maternal (i.e. in utero) transmission alone cannot maintain an epidemic, only slow its decline but that this might mean that there are some relatively young sheep currently infected with BSE. Given that BSE has not yet been found in sheep, and assuming that there is no horizontal transmission then the likelihood of finding even one case, and certainly more than one should be exceptionally small, at least in the absence of increased surveillance and/or improved sensitivity of detection.

The absence of additional cases from the broader sampling across Europe provides increased confidence that horizontal transmission of BSE in sheep has not occurred in the field. Because "proof of principle" has not been established for horizontal transmission in the field, any evidence that horizontal transmission has occurred could be important in determining our point-of-view, even if these cases occur elsewhere and have no epidemiological links to the UK. For example, if the numbers of BSE infected sheep were increasing at an unknown rate, this would mean that it would be very difficult to use surveillance in prior years as a way of improving our estimate of the current number of BSE-infected sheep.

2. What findings might lead to a conclusion that horizontal transmission between sheep has occurred?

Even a single infected sheep may raise suspicions of horizontal transmission, especially if that sheep is not an import, and if born after the majority of feed-borne risk is deemed to have past, as the only other likely cause of infection is in utero transmission. Occurrence of multiple cases in sheep would raise concerns that horizontal transmission has occurred, if no obvious source for these cases is determined (e.g. definite evidence of potentially contaminated feed in all cases or if maternal relationships can be shown), as feed borne sources of infection would be expected to be declining. Thus finding two BSE-infected sheep in the absence of horizontal transmission is extremely improbable, barring a dramatic increase of surveillance (see below on sample sizes) and/or detection sensitivity.

Because we have gone so long without finding BSE in sheep, as long as only one or a few cases of BSE in sheep are found, the default hypothesis is that, if BSE is spreading from sheep-to-sheep, it is only doing so slowly. As an example (using hypothetical figures), given that the peak in any feedborne epidemic would have occurred around 1990, this would imply that, roughly speaking, if the basic reproduction number or R_0 of the disease was 1.1 ($R_0 \geq 1$ is the threshold for having a sustainable epidemic) and the generation time of the disease four years, then in 2006 we would have had approximately four generations of infected sheep and about 50% more sheep infected in 2006 than in 1990. Unless the nature of the epidemic were to change either through adaptation of agent or through changing characteristics of the sheep population, in either case so as to dramatically increase the basic reproduction rate or reducing the generation time of the disease, it would be another 16 years before the number of infected sheep per generation were to increase by 50% again. On the other hand, if R_0 was significantly higher (for example, 1.5), this would imply an increase over four generations of 500% compared to 1990, and thus we would have been much more likely have already detected BSE. As the current prevalence of BSE in the sheep flock is likely to be zero and estimated to be no more than 0.002%, it is unlikely that that the relative risk to human health will increase rapidly in the next few years, however the absolute risk to human health is dependent on the number of humans expected to be infected by a single infected sheep, and is outside the scope of this document.

Should there be evidence for horizontal transmission and in particular if multiple cases are found, it is important to act decisively to eradicate the disease; the widespread movement of sheep in the UK means that, over the timescale of a BSE infection, and should there be reason to suspect self-sustaining levels of horizontal transmission, one could treat much of the national flock as a single large entity and BSE-infected sheep could therefore very quickly be found in every part of the UK.

3. What findings might lead to a view that there might be more BSE in sheep than is currently thought (as at point 1)?

Because the British national sheep flock is so diverse, it is difficult to make definite conclusions based on broad characteristics from relatively few experiments involving small numbers of animals from a few breeds. Thus it is possible (though there is as yet no evidence for this) that differences in sheep breeds may lead to different epidemiological characteristics of BSE in sheep depending on the breed in which it was found. Should there be evidence that shows BSE in sheep is unlikely to be detected by current surveillance (e.g. if it is more likely to be found in tissues not sampled by current surveillance) this would also increase the possible prevalence.

If horizontal transmission between sheep is likely, the issue would then be how much may be occurring and whether a sustained epidemic is likely. A singleton case may be evidence of horizontal transmission if it is clearly home bred with no evidence of exposure to feed and with a home bred dam with no evidence of exposure to feed (making in utero transmission unlikely, unless the dam was exposed via horizontal or in utero transmission itself). If there are more than one case, and no strong evidence of an epidemiological link due to feed or in utero transmission, this should be viewed as highly suspicious wherever the infected sheep are found (i.e. a single or multiple flocks). Given that the most likely scenario is no BSE-infected sheep, it is unlikely at this time to find more than one. Initially it is likely that there will be insufficient epidemiological evidence to determine if there is a sustainable epidemic. We shall only know this if there are sufficient cases to provide robust parameter estimates and this may require several generations of infection (i.e. several years). As an example, supposing that R_0 is exactly one, and that the distribution of the number of next generation cases is Poisson, then no transmission events will occur roughly 37% of the time,

and two or more secondary cases will occur 26% of the time. A value of R_0 of one or less can only be excluded with 95% confidence if there are four or more secondary cases. This of course does not even consider our probability of finding these cases, which depends on the sampling regime (see below). Note also that long chains of transmission events may still occur even if $R_0 < 1$, purely due to stochastic effects, and the distribution of infection chain lengths in this case is highly overdispersed (i.e. long chains occur surprisingly often).

If current estimates of BSE prevalence (less than 0.002% of the national flock) can be used as a guideline, then a sample of 150000 is required to detect at least one BSE case (assuming a test of 100% specificity and sensitivity) with 95% confidence. For a sample of that size, the probability of finding exactly one case is roughly 15%, while two or three cases (assuming that cases are random) will be found 45% of the time. Thus anything more than three is likely to be a result of an epidemiological link amongst at least some of the cases, and this includes the possibility of horizontal transmission. Note that should the sample size drop to 35000, there is only a 50% chance of finding at least one BSE case, and finding more than two would occur only 15% of the time. Thus as a rule of thumb, assuming a sufficiently large sample, if we were to find a singleton case, especially if it were imported or could be attributed to feed-borne infection, this would be of less concern (no evidence of significant horizontal transmission). If we were to find a reasonable number of cases (say four or more), this would most likely be due to horizontal transmission. If we found two or three cases we would be in a grey area where it could be feed-borne or horizontal transmission.

4. Would a finding of BSE in more than one flock increase risk?

It is difficult to hypothesize on this in general, as the movements of sheep in the UK are so extensive, and so how this should be viewed would be very case dependent. However, BSE in multiple flocks should as a default be considered as possibly the result of horizontal transmission just as would multiple cases in a single flock.

5. Which of the above scenarios would lead to increased uncertainty about the prevalence of BSE in sheep and what additional

surveillance would be likely to be most effective in reducing that uncertainty?

Because we are in an extremely low prevalence situation, random sampling (such as with an abattoir survey) is unlikely to find anything before BSE would have spread widely throughout the national sheep flock. Abattoir surveillance will not be cost-effective for estimating the prevalence of BSE in sheep. From current surveillance, the prevalence of sheep TSEs is around 0.1%, of which at most 2% could be BSE (based on annual testing data). Thus, the prevalence of BSE in sheep is likely to be less than 0.002%. To detect at least one BSE-positive animal with 95% confidence at this prevalence would require a sample size of 150000 assuming a test with 100% specificity and sensitivity. This is the same as the total number of animals sampled since 2002.

Fallen stock has the advantage that animals are already collected through the National Fallen Stock scheme, they can be traced to holdings and should provide a reasonable number of animals to test. The principal additional cost would be the TSE testing. Further, as it is likely that there will be an increased incidence of mortality amongst sheep infected with BSE, fallen stock as a group are likely to contain a higher than average prevalence of BSE, and thus more likely to identify cases of BSE than an abattoir survey of the same size. It is difficult to compare directly the likelihood that a fallen stock survey will attain a positive result as we would need to know the relationship between increased mortality due to BSE compared to the average sheep. However a crude estimate can be made by considering that, for 2004, 12 of 4372 fallen stock samples were positive for classical scrapie, compared to 9 of 10589 abattoir survey samples (plus 17 samples positive for atypical scrapie), i.e. fallen stock were just over three times as likely to be found to be positive for classical scrapie as via abattoir surveillance. Keeping in mind that results of fallen stock surveys are more dependent on farmer behaviour than an abattoir survey, if these relative proportions were to hold for BSE in sheep, this would imply that roughly 46000 fallen stock samples would be required to detect at least one BSE-positive animal with 95% confidence. The disadvantage of a fallen stock survey is that more complicated calculations must be made to determine the impact on the amount of BSE entering the human food chain. However, a crude estimates could be made as above, by assuming that the relative proportion of BSE at the abattoir compared to fallen stock would be similar to the relative proportion for classical scrapie (i.e. 3.2 times lower, if 2004 survey results are applicable). It should also be borne in mind that

the population being sampled at the abattoir is also skewed and not directly representative of human consumption.