Scientific Report of the European Food Safety Authority on the BSE surveillance model (BSurvE) established by the Community Reference Laboratory for TSE

(Request N° EFSA-Q-2004-083)

(Adopted on October 2004)

SUMMARY

In 2003, the European Commission (EC) requested the Community Reference Laboratory (CRL) to develop, on the basis of the analysis of the results of the Community BSE monitoring programmes, an epidemiologically valid integrated approach to evaluate the BSE status of individual countries. The statistical model (BSurvE) uses demographic information about the national cattle population of a country and BSE surveillance data for that country, to estimate the true BSE prevalence (with confidence limits) in the standing population. In addition, BSurvE offers procedures to evaluate surveillance activities and optimise resource allocations for those activities.

The European Food Safety Authority (EFSA) was invited by the EC to provide advice on the general approach used within the BSE surveillance model (BSurvE).

From the analysis of the report and spreadsheet provided by the CRL, EFSA and its Scientific Expert Working Group conclude that the model is an excellent development and potentially represents a major step forward in the development of appropriate national surveillance programmes for BSE. It is a very powerful tool and has been technically well designed. It is relatively user-friendly, very accessible and has a high level of transparency. It was further also concluded that the model structure is likely to be sound but should be further analyzed. The model is based on different assumptions and on various data and parameter values that might not be available in a number of situations and countries.

In order to check the robustness of the model in the case of nationally-inaccurate data or nationally-inappropriate assumptions, EFSA and its Scientific Expert Working Group recommend that the developers of the model perform a series of relevant sensitivity analyses using data from different countries in addition to presenting national results for the baseline setting of late-stage BSE being detectable only in the last three months prior to clinical onset. In addition, it is recommended that the results provided by the model be compared with the results of back-calculation models using the same hypotheses and the same sets of data. Complementary analyses based on simulation should also be undertaken to check the model integrity. The efficiency of the model in addressing a given question cannot be assessed more precisely without the results of these complementary analyses being considered in the first instance. Finally, member states may wish to use the model to predict expected BSE positives in a forthcoming year. A projection module could therefore be a useful addition to the current program.

KEY WORDS

BSE, prion, cattle, statistical model, surveillance, epidemiology.
BACKGROUND

In 2003, the European Commission (EC) requested the Community Reference Laboratory (CRL) for Transmissible Spongiform Encephalopathies (TSEs) to add to its annual work programme 1) the analysis of the results of the Community Bovine Spongiform Encephalopathy (BSE) monitoring programme and 2) the development, on the basis of such analysis, of an epidemiologically valid model to initiate and continue the evaluation of country-specific BSE status.

The model was developed by the Community Reference Laboratory in cooperation with Professor Roger Morris and his colleagues at the EpiCentre, Massey University, New Zealand. The project leader, Professor John Wilesmith, presented details of the model at three expert meetings with the Member States. The model was further developed as a result of feedback received at these meetings.

In March 2004, the CRL study (hereafter: BSurvE) was concluded. The Member States agreed to submit the model to the World Organisation for Animal Health (OIE) for consideration when revising the current Appendix on surveillance and monitoring of the Terrestrial Animal Health Code. On 5-6 May 2004 during the OIE mediated discussion between USA and European Union (EU) on the interpretation of the BSE chapter, OIE surveillance experts evaluated the model and unanimously supported the scientific basis of the approach taken in the model.

TERMS OF REFERENCE

The European Food Safety Authority (EFSA) was invited to provide scientific advice on the general approach used within the BSurvE model.

As mentioned by the EC during the Working Group meeting on September 9, 2004, no precise question has been defined currently for the model to answer, which explains why only an advice on the general approach was requested.

ASSESSMENT

The model BSurvE uses demographic information about the national cattle population of a country and BSE surveillance data for that country to:

- Convert test results from the four surveillance streams into an estimate of the proportion of animals that were infected and an estimate of the prevalence of BSE in the national standing cattle population, with confidence limits on that estimate;
- Provide an assessment of the historical pattern of BSE exposure which underlies the surveillance data;
- Offer a procedure for evaluating the adequacy of the nature and scale of the surveillance activities being reported by an individual country;
- Determine surveillance requirements for a country which has detected either no cases of BSE or a very small number of cases and;
- Guide countries in optimally allocating resources to each of the four components of the surveillance strategy (for both infected and disease-free countries) in terms of case detection success and cost effectiveness.

From the analysis of the report and spreadsheet provided by the EC, the members of the EFSA Scientific Expert Working Group reached the following conclusions:

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1 This opinion was also presented and commented on during the EFSA BSE/TSE Working Group meeting on 19 October 2004 and the Plenary meeting of the EFSA Scientific Panel on Biological hazard, 20-21 October 2004.
General statements

The Working Group agreed that the epidemiological basis for the BSurvE model appears to be sound and that the model is an excellent development. The model is a very powerful tool and has been technically well designed. It gives useful results provided that the data given by the country are accurate and that the underlying hypotheses are true. It is relatively user-friendly, very accessible and with a high level of transparency for both the estimation of BSE prevalence and the evaluation of surveillance programmes. The points system used is a novel way of indicating the most cost effective surveillance strategy having regard to the particular conditions in individual countries.

It is primarily a tool for use by veterinary epidemiologists who bring their own specialist expertise to its interpretation. The best use of the BSurveE would be when the results of the model are linked to the assessment of the exposure history of the cattle population in the country, which gives a complementary view of the epidemiological situation. Moreover, this linkage would enable epidemiological inferences on the true BSE status of a country including freedom from BSE. In the later case, a precondition is no exposure of the BSE agent of the cattle cohorts too young to be tested.

The authors should be invited to consider publishing the model in scientific peer reviewed journals as soon as possible.

Structure of the model

The model appears to have a sound epidemiological structure.

However, in order to analyse the model further and test its integrity, two different actions might be feasible:

- The first one would be to compare the results provided by the model with the results of other back-calculation models with the same hypotheses and the same set of data. This has been done already for the Danish data. The results were said to be roughly the same after some modifications were made in BSurvE model to population structure and exit probabilities to better reflect the Danish situation. However, the Danish results were not available to the Working Group.

Before validation of the model structure, it is important to see the results of a simulation-based investigation of the properties of the model's prevalence estimators (equations A10-12) \(^2\) and confidence interval calculators (equations A13). Computer simulation of “surveillance sampling” from the exit streams under a known prevalence would allow estimation of the degree of potential bias in the prevalence estimates and whether the confidence intervals are indeed close to the nominal 95% level. The simulation results of the system under conditions of low prevalence will be of particular interest. It might consist in creating an artificial data set corresponding to e.g. a hypothetical country with a low BSE prevalence, to randomly sample animals from the different exit streams as if they were surveillance data, to compare those simulated data with the results of the model and to check if the simulated prevalence falls within the confidence interval of the prevalence estimated from the model. Coverage probabilities and estimation bias could also be assessed when input data/parameters for running BSurvE deviated from true (i.e. from those used to generate the simulated data sets) to assess to which deviations BSurvE's outputs were most sensitive.

- The input data required for the model are extensive and might not be readily available in various situations and countries. In some cases, they may have to be estimated using expert opinion. Because of this need, the successful use of the model will, in many cases, require the input of epidemiologists with direct knowledge of the country for which the model is being run. These input data include the

\(^2\) These equations are in a supporting document provided to EFSA by the Central Reference Laboratory document entitled “Development of a Method for Evaluation of National Surveillance Data and Optimization of National Surveillance Strategies for Bovine Spongiform Encephalopathy - A Project Conducted by the European Union TSE Community Reference Laboratory, Veterinary Laboratories Agency Weybridge, United Kingdom”
age distribution of the standing population, stratified by beef and dairy, the age distribution of non-infected cattle at the time of exit and the age distribution of infected cattle that are showing clinical signs at the time of exit in each stream, i.e. normal slaughter, fallen stock, casualty slaughter or clinical suspect. Particularly important is the assessment of exit probabilities. For example, veterinary epidemiologists may assess that 2% of deceased adult cattle exit as casualty stock. If casualty stock represents only 1% of the deceased adult stock subject to BSE surveillance, then experts might conclude that surveillance of casualty stock was only 50% effective in the country. For the exit probabilities for cattle with clinical symptoms, one must take account of the slow development in symptoms from minor and non-specific to very severe and specific. During this development, the effect of local conditions on exit route probabilities is very large but very hard to assess without data. Therefore, any good judgement on this would tend to be based on the available case data leading to a somewhat circular method for assessing these data. In order to check the robustness of the model when a number of inputs have to be based on expert opinion and which might not be accurate, it seems appropriate / necessary to carry out a sensitivity analysis.

In the same way, the manner and extent to which the model is sensitive to the main assumptions needs to be assessed using sensitivity analyses. The main assumptions are:
- The size and age structure of the national herd does not vary over years;
- The age at clinical onset follows a lognormal distribution with mean being five years of age;
- The distribution of exiting infected animals showing clinical signs apportioned between surveillance streams will not change over time;
- Only cattle less than one year of age are susceptible to the infection;
- The test is 100% sensitive during the period 0-3 months prior to the onset of clinical signs (In the updated version);
- There is no spontaneous case of BSE.

Uses of the model

There are two main uses of the model:
1. As a retrospective analysis tool in order to analyse the surveillance data and provide estimates of the BSE prevalence, with confidence intervals. It includes a module to assess the quality of the surveillance based on the surveillance counts in the different exit streams. The calculation of the prevalence is based on the number of cattle over 24 months of age.
2. As a prospective design tool in order to design a surveillance system, to provide a given objective for the precision of the prevalence estimate or to modify an existing monitoring system by optimizing the cost of such a programme.

The working group would like to emphasise the following points in relation to the uses of the model:
- Because there is only a limited chance of detecting BSE during the usually long incubation period of BSE (BSE is not detectable long before the clinical onset), models cannot give precise estimates for younger cohorts. The model cannot therefore provide an indication of recent changes in the trend of an epidemic. For example, in a country with an increasing risk in the last four years, the model will minimize the real prevalence level in the overall population. In other words, the model cannot give estimates for younger cohorts (less than 3 years of age) and will give biased results for the overall prevalence if the exposure has changed during the last 3-5 years.

- Caution is needed in relation to the use of the BSE Surveillance Assessment component of the model. It can highlight shortfalls in surveillance intensity in a particular stream given a known true prevalence in the standing population; however the prevalence is itself estimated with the model.

- The optimisation tool for surveillance resource allocation needs to be used prudently, in the sense that the model does not take account of the fact that decreased testing in one stream might have a perverse...
effect in redirecting affected animals from one stream with testing to another one with no/less testing. Hence, this reflects the need to use to the model within a proper epidemiological context.

-It would be helpful if BSurvE could provide the same measure of national prevalence (and uncertainty) as is used by OIE and the EC, i.e. the number of BSE cases per million of cattle population over 24 months of age in the country calculated over the past 12 months

-Individual countries may wish to use the model to predict expected BSE positives in a forthcoming year. A projection module could therefore be a useful addition to the current program, but would require additionally funded research work for its incorporation. As such projections can be corroborated/falsified by data, this module could also be of assistance in refining the model in the light of experience into its projection capability.

CONCLUSIONS

The EFSA and its Scientific Expert Working Group conclude that the BSurvE model represents a major step forward in the analysis of BSE prevalence having regard to age distributions and surveillance streams and statistical uncertainty (confidence intervals) when compared to the use of current OIE thresholds for BSE prevalence that are crude prevalences.

The model structure appears to be sound. The model is based on different assumptions and on various data that might not be available in a number of situations and countries. In order to assess the robustness of the model in the case of inaccurate data or assumptions, a series of sensitivity analyses would be required. The efficiency of the model in addressing a given question cannot be assessed more precisely without the results of these complementary analyses being addressed in the first instance, in particular via simulation studies.

RECOMMENDATIONS

-To report as a default setting the detectability in three months prior to BSE onset;
-To carry out a series of sensitivity analyses regarding the assumptions made in the model and the parameters estimated from the field data;
-To compare the results provided by the model with the results of other back-calculation models;
-To carry out a complementary analysis to check the model integrity based on simulation (see above);
-To clarify that the methodology used in the “BSE Surveillance Assessment” component of the model is valid;
-To add a module that would allow the number of BSE cases in future years to be predicted;
-To publish details of the model in a peer reviewed scientific journal.

DOCUMENTATION PROVIDED TO EFSA

-Letter from the EC (D(2004)/KVD/ip/420621) inviting EFSA to provide scientific advice on the general approach used within the BSurvE model.
-Excel sheet of the model.
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