

Assessment of the risk posed by bovine spongiform encephalopathy in cattle in Great Britain and the impact of potential changes to current control measures

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We extended an existing back-calculation model to analyse data on reported clinical cases of bovine spongiform encephalopathy (BSE), data from random testing of healthy animals slaughtered in abattoirs and testing data from animals reported as sick or dying on the farm. Extensive analysis of demographic data was also undertaken. We estimated past and current BSE infection prevalences in the cattle population and the degree of case under-ascertainment resulting from excess mortality in cattle near to disease onset. Ongoing levels of human exposure to BSE infectivity were also estimated, together with the effect on these of a range of possible exposure–reduction strategies that might replace the current rule banning tissue from cattle over 30 months (OTM) of age from the human food supply. While any policy change that allows a wider age range of animals into the human food supply will increase levels of human exposure to infectivity, the risk posed by such increases is small by comparison with historical exposure levels. Making the pessimistic assumption that there will be 5000 deaths during the variant Creutzfeldt–Jakob disease (vCJD) epidemic in total, our analysis indicates that replacement of the OTM rule with testing would result in 0.04 additional vCJD deaths over the next 60 years. However, there is substantial (more than 40-fold) uncertainty surrounding this estimate, the sources of which are discussed.

Keywords: bovine spongiform encephalopathy; variant Creutzfeldt–Jakob disease; risk assessment; epidemiology; back-calculation

1. INTRODUCTION

Since bovine spongiform encephalopathy (BSE) was first diagnosed in late 1986 (Wells *et al.* 1987), more than 179 000 confirmed clinical cases have been identified in Great Britain (GB). In addition to these passive surveillance data, the recent development of rapid screening tests (Moynagh *et al.* 1999) has enabled active surveillance of BSE across the European Union (EU) via testing of slaughtered cattle (see European Commission 2002). However, the estimation of the prevalence of infection in slaughtered cattle depends not only on the number of test positives and the number tested, but also upon the sensitivity of the diagnostic tests. Unfortunately, the sensitivity profiles of current tests remain poorly characterized, and, while test sensitivity and specificity are high for samples taken from animals with clinical disease, sensitivity may be very low early in the long incubation period of BSE. Interpretation of data from screening programmes must take account of these uncertainties, with the most information being gained from analysing both screening and clinical-case data.

The over 30 month (OTM) rule banning OTM cattle from the human food supply was introduced in GB in April 1996 following the identification of variant Creutzfeldt–Jakob disease (vCJD) and its link to BSE. The current study aims to provide a rigorous quantitative basis for

the assessment of the past, current and future impact of this risk-reduction measure. We estimate the impact on human exposure of replacing the OTM rule with alternative screening-based risk-reduction measures, and place ongoing risk levels in the context of the overall human exposure throughout the BSE epidemic. The analyses presented extend earlier work (Donnelly & Ferguson 2000) by incorporating screening data from ‘high-risk’ cattle into the back-calculation (Anderson *et al.* 1996; Ferguson *et al.* 1997) model used. Back-calculation methods (Anderson *et al.* 1996; Ferguson *et al.* 1997; Donnelly & Ferguson 2000) allow estimation of past infection incidence from clinical-case data, given knowledge of the incubation-period distribution of the disease and the survivorship of the host (Brookmeyer & Gail 1986, 1988; Isham 1989). Earlier work (Donnelly *et al.* 2002) extended back-calculation models to allow the integrated fitting of clinical-incidence data and screening data from apparently healthy cattle. We also analyse detailed demographic data to look for changes in the British cattle population that would affect the interpretation of the data on both clinical cases and the detectable infection prevalence in screened cattle.

2. METHODS

(a) Data used

Several data sources (discussed more fully in electronic Appendix A available on The Royal Society’s Publications Web site) were analysed for this study.

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- (i) BSE clinical-case data. The database of all confirmed cases of BSE arising in GB is maintained by the Veterinary Laboratories Agency (see Donnelly *et al.* (1997) and Donnelly & Ferguson (2000) for additional details). Figure 1*a* presents BSE case incidence stratified by year of clinical onset and birth cohort, where a birth cohort is defined as animals born from July of the preceding year to June of the year being considered. Note that 2001 case numbers are higher than expected (see electronic Appendix A), perhaps as a result of the 2001 foot and mouth disease epidemic. The causes of this perturbation in case numbers (which complicates prediction of future clinical-case trends) are the topic of ongoing research.
- (ii) BSE screening data. The first two surveys of apparently healthy cattle in GB mainly targeted animals over 5 years of age (Donnelly *et al.* 2002). The current analysis incorporates additional screening data collected in 2001 and 2002 on 70 739 apparently healthy cattle (7 positives detected), 108 533 casualty cattle (488 positives detected) and 67 889 fallen stock cattle (165 positives detected) (figure 1*b–d*). The differences in detected infection levels between age groups are the result of a combination of time-varying infection incidence and incubation-stage-dependent test sensitivity. The detected prevalence was greatest in casualty animals and lowest in apparently healthy animals.
- (iii) Cattle tracing scheme (CTS) database. Individual animal data were obtained from the CTS database on 21.7 million cattle out of which 12.0 million were recorded as having died (by 9 July 2002). These data were used to update estimates of the number of calves born into each annual birth cohort and the survival of cattle, both required by the back-calculation model. The CTS database was also used to estimate the proportion of cattle mortality resulting from fallen stock or the on-farm slaughter of casualty animals. Although the CTS does not record which cattle deaths are fallen stock or casualties, deaths on the farm were seen to account for a remarkably consistent 24% of mortality in animals over 3 years of age.

These databases were cross-linked to evaluate how representative the cattle screened for BSE infection were of the cattle population as a whole, and no systematic bias in the apparently healthy OTM animals screened for infection was detected (see electronic Appendix A for details). Data from apparently healthy animals screened in other EU countries in 2001 and 2002 were analysed to obtain independent estimates of the lower limit on the specificity of the diagnostic tests used for rapid screening. The results (see electronic Appendix A) demonstrate that the specificity of the screening tests, though possibly less than 100%, is unlikely to be less than 99.9984%. Thus, very few, if any, of the animals testing positive in the screening programmes are likely to have been false positives.

(b) Modelling approach

Two different possible mechanisms underlie the apparent underascertainment of cases indicated by the British screening data: excess mortality of BSE-infected and non-infected animals and underreporting of clinical cases. However, since past work (Donnelly *et al.* 2002) found that excess mortality fitted the clinical-case incidence and screening data substantially better than did underreporting, here we focus on examining differential-mortality scenarios.

For this study, we extended past work (Donnelly *et al.* 2002) to model infection risk in animals that die on the farm (casualty or fallen stock) separately from those that die at abattoirs, with the age-specific proportion of mortality occurring in each category being estimated from CTS data (see electronic Appendix B). This enabled screening data from casualty or fallen stock to be fitted separately from screening data from apparently healthy animals slaughtered at abattoirs. In addition, the model allows the excess ('differential') mortality of infected animals prior to clinical onset to be disproportionately biased towards on-farm death, so that infected animals have a greater chance of ending their lives as casualties or fallen stock. Test sensitivity was also modelled as a continuous function of the stage of incubation, with three different scenarios being explored (figure 2*a*). The fit of the model to the data used is discussed in the electronic Appendix D.

The back-calculation model produces estimates of the numbers of infected animals entering the human food supply over time, stratified by animal birth date and incubation stage. We used results from an independent study (DNV Ltd 2003) to translate these exposure estimates into estimates of risk, by weighting model estimates of the number of infected animals entering the human food supply by the estimated infectivity (in bovine infectious dose, ID₅₀ units) of each such animal. Figure 2*b* shows the estimates used of infectivity entering the human food supply per animal slaughtered at the point of clinical onset. These estimates have very high levels of uncertainty associated with them. However, much of this uncertainty (i.e. that associated with poor knowledge of the bovine or human infectious dose) is removed if risk estimates are presented in terms of relative changes in exposure over time, rather than absolute estimates of infectivity entering the food supply.

The infectivity associated with animals at earlier stages of incubation is even more problematic to estimate, owing to the paucity of quantitative tissue-specific pathogenesis data. The best current estimate is that infectivity grows approximately exponentially, with variable initial doses but fairly constant final levels of infectivity by clinical onset. The doubling time is assumed to be 2 months in this study, but given the uncertainty we also examined the effect of changing this to 4 months.

3. RESULTS

To inform policy discussions, we estimated the effectiveness of the current OTM rule as well as those of two possible alternative policy options (assumed to be introduced at the start of 2004): (i) increasing the current 30 month age cut-off (over which animals are not allowed to enter the human food supply), and (ii) moving to a birth-date-based cut-off (for instance permitting all animals born after 1 July 1996 to enter the food supply). Both of these options are assumed to be coupled with testing all of OTM cattle entering the food supply.

We first explore in detail the baseline (and arguably most likely) scenario of an infectivity doubling time during BSE incubation in cattle of 2 months, differential mortality occurring solely in the last 3 months of the incubation period, and the most pessimistic test-sensitivity profile of the three we examined (figure 2*a*), namely 100% test sensitivity only in approximately the last 3 months of the incubation period. We assumed that BSE infection incidence in cattle remained constant after the last date for which it could be estimated (i.e. 1999, on the basis of current data). This is also arguably a pessimistic assumption.

Table 1. Estimated cumulative exposure of the human population to BSE infectivity during 2004–2009 for 12 differing scenarios regarding test sensitivity and the portion of the bovine incubation period over which differential mortality is distributed (see § 3). (Results for three policy options are shown: continuation of the OTM rule (‘OTM’); introduction of a July 1996 birth-date cut-off (‘July 1996’); and allowing all animals into the food supply (‘all’). Values shown for the last two policies are the excess risks over the OTM rule caused by those policies. Three measures of risk over the period 2004–2009 are presented: numbers of animals entering the human food supply in the last 12 months of incubation; bovine ID₅₀ units entering the human food supply; and number of vCJD deaths over the next 60 years resulting from exposure during 2004–2009 (assuming that a total of 5000 deaths arise during the entire course of the vCJD epidemic). For the last risk measure, the upper 95% confidence bound is also given (see § 3). The first row corresponds to the baseline scenario, while the fourth row gives the worst-case scenario. All figures assume that OTM casualties are banned from the food supply; including casualties increases the risk by up to 80% (in the worst-case scenario).)

scenario		risk over the period 2004–2009											
		animals in last year of incubation entering food supply			bovine ID ₅₀ s entering food supply			vCJD deaths (over next 60 years), assuming 5000 in total			upper 95% bound on vCJD deaths, assuming 5000 in total		
sensitivity profile (see figure 2a)	months of differential mortality	OTM	July 1996	all	OTM	July 1996	all	OTM	July 1996	all	OTM	July 1996	all
1	3	0.9	60	89	6.8	270	410	6 × 10 ⁻⁴	0.024	0.037	6 × 10 ⁻³	0.24	0.37
1	6	1.3	150	230	9.8	980	1500	7 × 10 ⁻⁴	0.070	0.11	8 × 10 ⁻³	0.83	1.3
1	9	2.0	240	350	14.0	1200	1800	1 × 10 ⁻³	0.091	0.13	0.012	1.0	1.6
1	12	3.2	270	400	16.0	1100	1700	1 × 10 ⁻³	0.090	0.14	0.016	1.0	1.6
2	3	0.9	39	56	6.5	110	160	7 × 10 ⁻⁴	0.012	0.017	7 × 10 ⁻³	0.11	0.17
2	6	0.8	41	61	6.2	140	210	8 × 10 ⁻⁴	0.018	0.027	8 × 10 ⁻³	0.18	0.27
2	9	1.1	76	110	7.4	240	370	9 × 10 ⁻⁴	0.030	0.045	0.010	0.32	0.49
2	12	1.7	110	160	8.8	270	410	1 × 10 ⁻³	0.033	0.050	0.012	0.38	0.58
3	3	0.8	23	33	6.1	52	73	7 × 10 ⁻⁴	0.006	0.009	7 × 10 ⁻³	0.06	0.09
3	6	0.8	21	31	5.7	49	73	8 × 10 ⁻⁴	0.007	0.011	8 × 10 ⁻³	0.07	0.11
3	9	0.8	29	44	5.7	73	110	9 × 10 ⁻⁴	0.012	0.018	9 × 10 ⁻³	0.12	0.18
3	12	1.2	47	72	6.3	90	140	1 × 10 ⁻³	0.015	0.023	0.011	0.16	0.25

tion given the substantial drops in BSE infection incidence since 1988. Results presented in electronic Appendix C show the effect of assuming a decline in BSE incidence levels after 2001.

For the baseline scenario, we estimate that 71% of infected animals reaching the last 3 months of incubation suffered differential mortality (i.e. were slaughtered early but without recognition of clinical signs of BSE). An estimated four million cattle were infected with BSE during the epidemic, out of which *ca.* 180 000 were reported as clinical cases, 3.3 million entered the human food supply and 510 000 died on the farm as casualty animals or fallen stock. Out of the 3.8 million undiagnosed infected animals slaughtered during the epidemic, 430 000 suffered differential mortality in the last 3 months of incubation, and these had a 2.6-fold higher risk of dying on the farm than did uninfected cattle (meaning 260 000 such animals died on the farm). Table 4 in the electronic Appendix D lists confidence bounds on the parameters underlying these estimates.

Combining model output of the number of infected animals entering the human food supply over time (see electronic Appendix C) with the per-animal estimates of infectivity (figure 2b), figure 3 presents estimated numbers of bovine ID₅₀ units entering the food supply for various possible policies under the baseline scenario, and the excess risk that might be posed by allowing OTM casualties into the food supply. While the exposure estimates may appear considerable, they can be placed in perspective by comparing them with historical exposure levels in

GB. Figure 4a illustrates that current exposure is over 10 000-fold less than that seen at the peak of the epidemic. Therefore, a useful way of presenting the risks associated with different policies is to express the exposure estimates presented in figure 3 as proportions of the total exposure throughout the epidemic. Assuming that the incidence of vCJD infection is proportional to human exposure to infectivity, this risk measure also corresponds to the proportion of all future vCJD deaths (figure 4b,c) that will arise from the increase in human exposure under each policy option. A further advantage of presenting risk estimates in this manner is that they do not depend on (highly uncertain) estimates of infectious doses for bovines or humans, and are therefore subject to much less uncertainty than any absolute infectivity-based measure of risk.

For rigorous risk assessment, it is necessary to consider not only central estimates of future risk, but also the uncertainty associated with these estimates. Sensitivity analysis was therefore undertaken for key model parameters. We examined the three different profiles for test sensitivity already presented (figure 2a) and four different differential (or excess) mortality scenarios, corresponding to the excess mortality of infected animals being evenly distributed over the last 3, 6, 9 or 12 months of the incubation period. For each of these 12 scenarios the key additional factor giving rise to uncertainty in the risk estimates is the infection incidence in cattle assumed from 1999 onwards. We therefore calculated the 95% confidence range of risk estimates generated by varying this parameter.

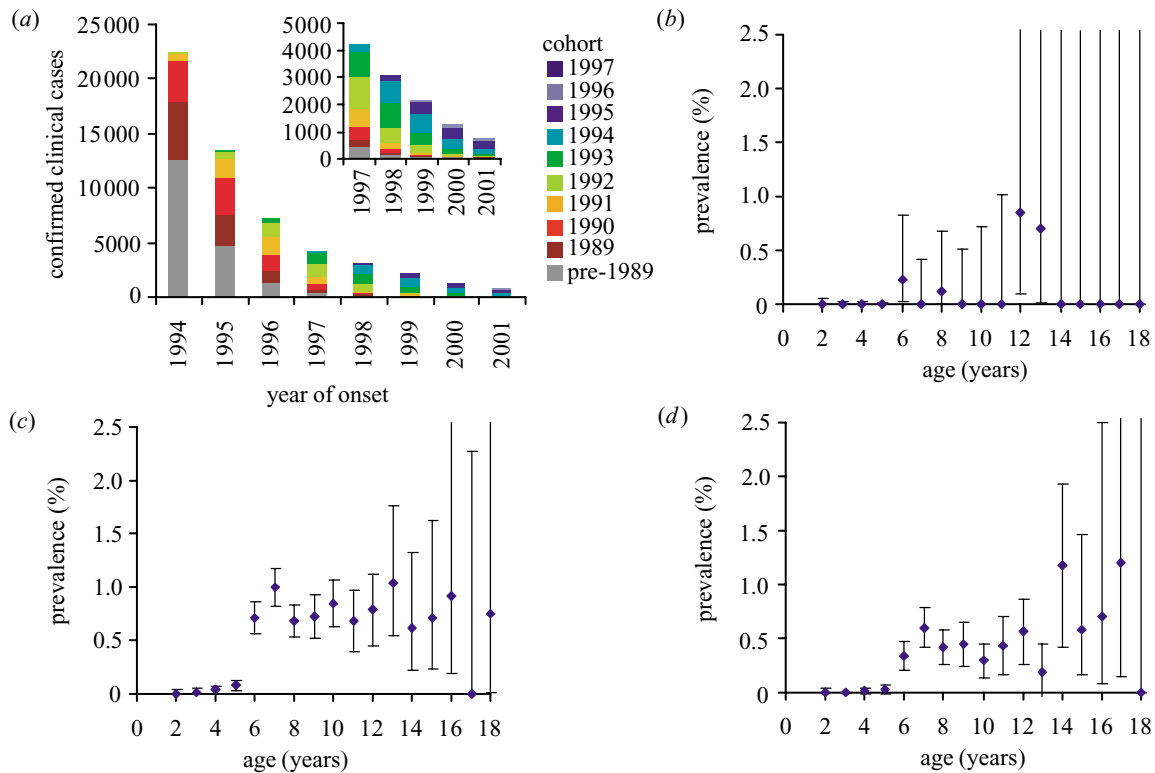


Figure 1. (a) Reported confirmed clinical cases of BSE as at 10 October 2002 by year of clinical onset (from 1994 to 2001) and birth cohort. Inset shows the period 1997–2001 in more detail. (b) Detectable prevalences in apparently healthy animals slaughtered at the abattoir. (c) As (b) but for casualty animals. (d) As (b) but for fallen stock. Results shown are for testing performed in 2001 and 2002 (see electronic Appendix A for data in tabular form). Exact binomial 95% confidence intervals are also plotted. Currently all casualties over 24 months of age and all fallen stock but only a sample of apparently healthy animals are screened.

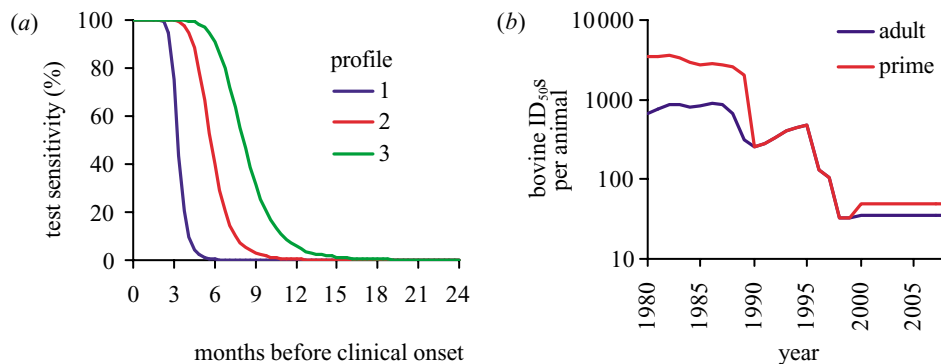


Figure 2. (a) Assumed test-sensitivity profiles as a function of the incubation stage of each tested animal. Profiles 1, 2 and 3 correspond to high sensitivity to detect infection only in approximately the last 3, 6 and 9 months of the incubation period, respectively. (b) Average bovine ID₅₀ units of infectivity entering the food supply per infected animal slaughtered for food at the point of clinical disease onset, as a function of the year of slaughter and the age of the animal ('adult' approximately equates to animals OTM, and 'prime' to younger animals). The values shown were estimated by DNV Ltd (2003) in a separate study. Historically, brain entering the food supply was predominantly from young animals, hence the difference between adult and prime values up to 1989. Differences after 2000 are caused by the removal of the entire vertebral column for OTM (but not for younger) animals. The observed changes through time were caused by the varying impact of specified-risk-material controls designed to protect human health.

Table 1 gives summary risk estimates and upper 95% confidence bounds for these 12 scenarios and two possible alternatives to the OTM rule (see electronic Appendix D for estimates of underascertainment parameters and predictions of future active surveillance trends for these scenarios). In general, increasing the period of differential

mortality increases risk estimates, while assuming greater test sensitivity reduces risk estimates. The doubling time of infectivity during cattle incubation is a further uncertain parameter, which affects risk estimates even when expressed as a proportion of the total historical exposure. Assuming this parameter to be 4 months rather than 2

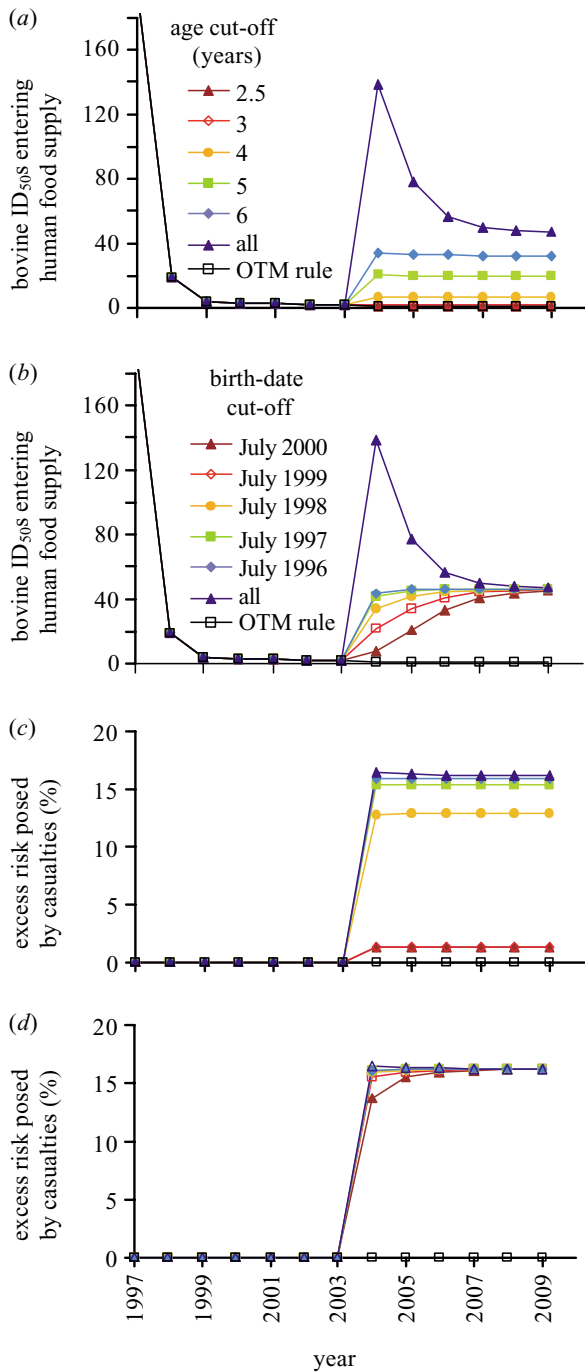


Figure 3. Exposure estimates (in units of bovine ID_{50s}) for various risk-reduction policies (OTM rule or age-based or birth-date-based alternatives) assuming that all differential mortality occurs in the last 3 months of the incubation period and 100% test sensitivity in the last 3 months of incubation (i.e. profile 1). (a) Exposure from infected non-casualty animals for age-based policies. (b) As (a) but for birth-date-based policies. (c) Increase in exposure shown in (a) that would occur if casualty animals were allowed to enter the food supply. (d) As (c) but for birth-date-based policies.

months increases the excess vCJD mortality estimates in table 1 by *ca.* 40%. The last key uncertainty that affects risk estimates is the historical effect of specified-risk-material controls in reducing per-animal infectivity entering the food supply. The estimates presented in figure 2*b* correspond to more than a 20-fold drop in per-

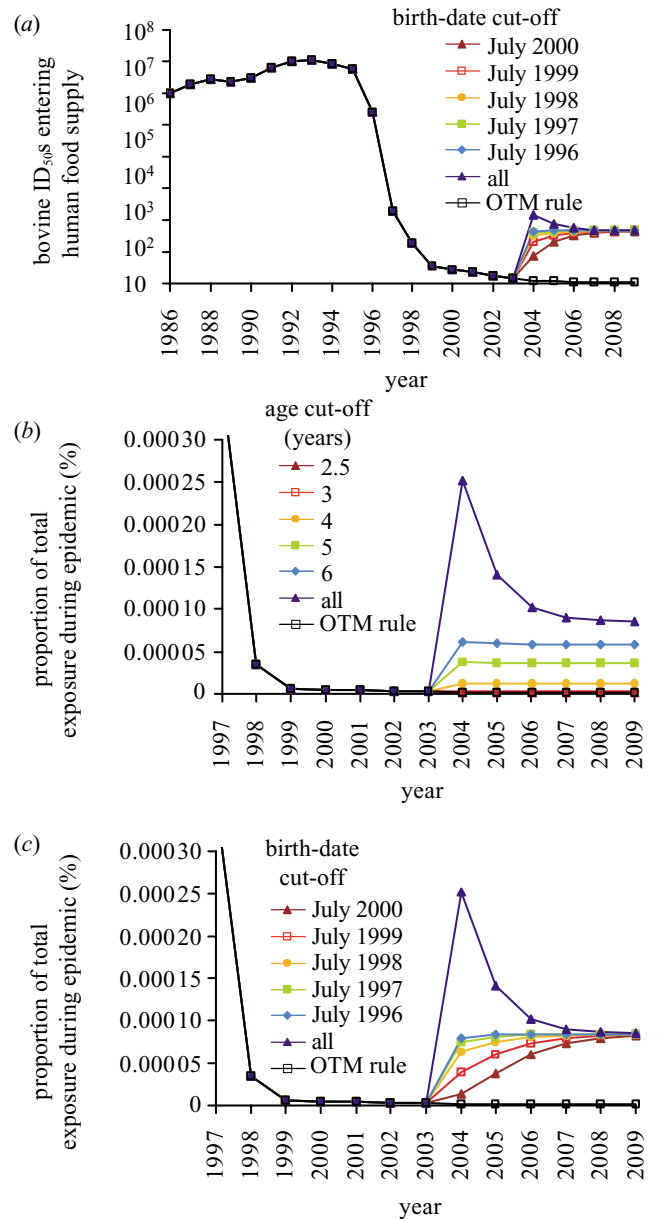


Figure 4. Risk estimates for various risk-reduction policies for baseline scenario. (a) Exposure in bovine ID₅₀ units over the entire course of the BSE epidemic, plotted with a logarithmic scale to show the details of recent trends (birth-date-based policies shown). (b) Exposure over the period 1997–2009 for age-based policy options shown as a proportion of the total exposure of the human population throughout the BSE epidemic. (c) As (b) but for birth-date-based policy options.

animal risk between 1988 and 2000. Smaller reductions in per-animal infectivity would increase the risk estimates in table 1.

All these exposure and risk estimates allow for the effect of testing of all animals OTM of age destined for human consumption; i.e. the estimates represent exposure only from animals that would be expected to have negative test results under any post-OTM-rule testing regime. For the baseline scenario, we estimate that testing would eliminate 95% of human exposure to infectivity, falling to 60% for the worst-case scenario given in table 1.

4. CONCLUSIONS

Under all scenarios examined, adoption of a less restrictive age-based or birth-date-based cut-off would inevitably increase human exposure to potentially infectious material, with the smallest changes to the OTM rule (e.g. an increase from 30 to 36 or 42 months of age) increasing exposure by the smallest amounts. However, estimates of exposure to infectivity alone can inform policy making to only a limited extent; optimally some assessment of the absolute risk to human health posed by such exposure needs to be made. Careful choice of risk measures is therefore key, particularly in the area of BSE where much uncertainty remains. Here, we quantify exposure by the estimated number of bovine ID₅₀ infectious units entering the food supply each year. Given the lack of knowledge of the species barrier between bovines and humans, this measure of exposure says little about risk unless it is compared with estimates of the overall exposure of the human population throughout the BSE epidemic. In this context, it is important to note that, while a substantial (more than 100%) increase in human exposure is likely with any modification of the OTM rule, the resulting risk levels are still much lower than that experienced by the consumer population before 1998 and correspond to very low absolute risk levels, as quantified by the expected number of vCJD deaths under a very pessimistic scenario of future vCJD incidence.

Assuming that there will be 5000 vCJD deaths over the next 60 years, the risk associated with moving from the OTM rule to allowing all animals born after July 1996 into the food supply (coupled with the testing of OTM animals entering the food supply) equates to an additional 0.024 extra vCJD deaths for the baseline scenario. Complete removal of the OTM rule and replacement with an OTM testing regime would increase this figure to 0.037. These figures increase *ca.* 40-fold if one examines the upper 95% confidence bound on the worst-case parameter scenario (see table 1), to 1.0 and 1.6 additional vCJD deaths, respectively. These estimates assume that all OTM casualties are banned from the food supply following any change to the OTM rule. Allowing casualties into the food supply would increase risk by between 15% and 80%, depending on the scenario. It should also be emphasized that the assumption of 5000 vCJD deaths currently appears very pessimistic, with the best epidemiological estimates of the total vCJD epidemic size (Huillard d'Aignaux *et al.* 2001; Ghani *et al.* 2003) now lying in the range 200–500. Assuming 500 vCJD deaths in total reduces the risk estimates above by 10-fold.

It will be important to update these analyses as more data accumulate from both clinical-case incidence and screening programmes. This will allow the incidence of BSE in cattle to be estimated beyond 1999, thereby addressing one of the key uncertainties in the present analysis. If incidence is found to have fallen substantially after 1999, this will similarly reduce the estimated risk associated with any policy change.

We thank the following for data provision: John Wilesmith, Judi Ryan and other VLA staff; Phill Morris and Matthew Peach (CTS); John Bleasdale (Agricultural Statistics, Welsh

Assembly Government); Helen Buchanan (DEFRA Farming Statistics); Natalie Hatfield (DEFRA York); and Tom Sharp (Census Branch, SEERAD). We also thank: Philip Comer and other staff at DNV Ltd for providing estimates of the infectivity entering the human food supply over time per infected bovine; members of the Food Standards Agency (FSA) Risk Assessment Group for useful discussions; the FSA for research funding, and its staff (Irene Hill particularly) for facilitating data acquisition.

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