THE ROYAL SOCIETY

Epidemiological determinants of the pattern and magnitude of the vCJD epidemic in Great Britain

Azra C. Ghani*, Neil M. Ferguson, Christl A. Donnelly, Thomas J. Hagenaars and Roy M. Anderson

Wellcome Trust Centre for the Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK

Understanding the epidemiology and aetiology of new-variant Creutzfeldt–Jakob (vCJD) disease in humans has become increasingly important given the scientific evidence linking it to bovine spongiform encephalopathy (BSE) in cattle and hence the wide exposure of the population of Great Britain (GB) to potentially infectious tissue. The recent analysis undertaken to determine the risk to the population from dorsal route ganglia illustrated the danger in presenting point estimates rather than ranges of scenarios in the face of uncertainty. We present a mathematical template that relates the past pattern of the BSE epidemic in cattle to the future course of any vCJD epidemic in humans, and use extensive scenario analysis to explore the wide range of possible outcomes given the uncertainty in epidemiological determinants. We demonstrate that the average number of humans infected by one infectious bovine and the incubation period distribution are the two epidemiological factors that have the greatest impact on epidemic size and duration. Using the time-series of the BSE epidemic and the cases seen to date, we show that the minimum length of the incubation period is approximately nine years, and that at least 20% of the cases diagnosed to date were exposed prior to 1986. We also demonstrate that the current age distribution of vCJD cases can only arise if younger people were either exposed to a greater extent, more susceptible to infection, or have shorter incubation periods. Extensive scenario analyses show that given the information currently available, the very high degree of uncertainty in the future size of the epidemic will remain for the next 3–5 years. Furthermore, we demonstrate that this uncertainty is unlikely to be reduced by mass screening for late-stage infection.

Keywords: vCJD; BSE; prediction; epidemic size; mathematical model

1. INTRODUCTION

Scientific evidence in support of the hypothesis that the new variant of Creutzfeldt–Jakob disease (vCJD) in humans is a direct consequence of exposure to the aetiological agent of bovine spongiform encephalopathy (BSE) (Wells *et al.* 1987), has accumulated since a UK government announcement warned of this possibility in March 1996 (Will *et al.* 1996; Collinge *et al.* 1996; Hill *et al.* 1997*a*; Bruce *et al.* 1997). It is believed that the 30 vCJD cases reported up to the end of October 1998 in the UK arose via consumption of products derived from BSE-infected cattle over the period from the early to the mid-1980s, prior to the introduction of a specified bovine offal (SBO) ban in late 1989 (Satutory Instrument 1989). Recent epidemiological analyses have charted the magnitude of the exposure of the UK population to infected cattle products year by year, with some 450 000 infected cattle entering the food chain prior to the SBO ban and a further 280 000 after the SBO ban (Anderson *et al.* 1996).

*Author for correspondence (azra.ghani@zoology.ox.ac.uk).

The emergence in human communities of a new infectious disease, or a variant of a familiar pathogen, invariably creates many problems for public health authorities who are required to rapidly assess the magnitude of the threat, appropriate control measures, and the potential need for patient care facilities. The situation is most acute for a totally novel disease, where the incubation period distribution is unknown and where a diagnostic test to assess the prevalence of infection is not available. If the average incubation period is a matter of years, as opposed to days or weeks, assessing the potential magnitude of the epidemic is particularly difficult. However, if the disease has a high case morbidity and mortality rate there is much pressure on epidemiologists to provide projections of possible future scenarios to aid health care planning and to assess the potential impact of control measures. This was the case for AIDS in the mid-1980s and is now the case for vCJD in Great Britain.

Predicting the size of the vCJD epidemic is extremely difficult due to its early stage of development and to the many gaps in our understanding of prion diseases in general and vCJD in particular. The temporal pattern of human exposure depends on the time-course of the BSE

Received 11 September 1998 *Accepted* 14 October 1998

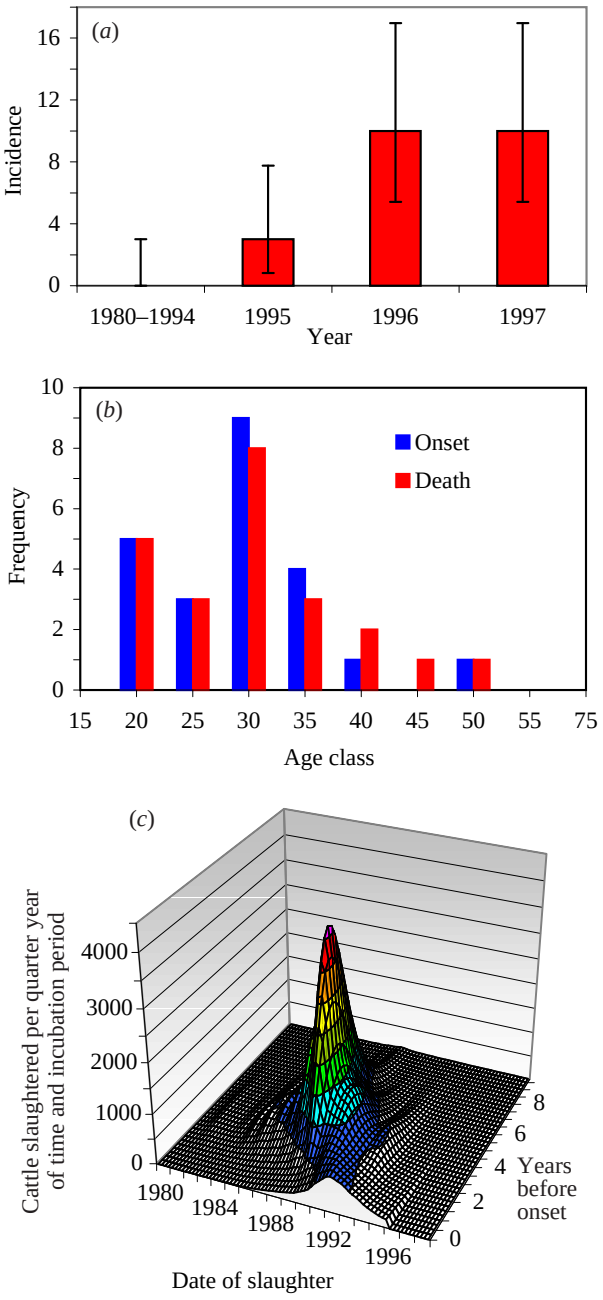

Figure 1. (*a*) Observed annual deaths of vCJD and exact 95% confidence intervals for the underlying incidence (assuming the incidence counts are Poisson distributed); (*b*) the age at onset and age at death of the 23 vCJD cases confirmed by 1 January 1998 (Robert Will, personal communication); (*c*) number of BSE-infected cattle slaughtered, stratified by quarter-year of slaughter and time to onset (i.e. time remaining from slaughter date to when an animal would have exhibited symptoms, measured in quarter-years), estimated from backcalculation models (Anderson *et al*. 1996; Ferguson *et al*. 1997). The majority of cattle were in the early stages of incubation and were slaughtered prior to the SBO ban. Late incubation stage slaughter rates were highest close to when the BSE epidemic peaked(1992–93).

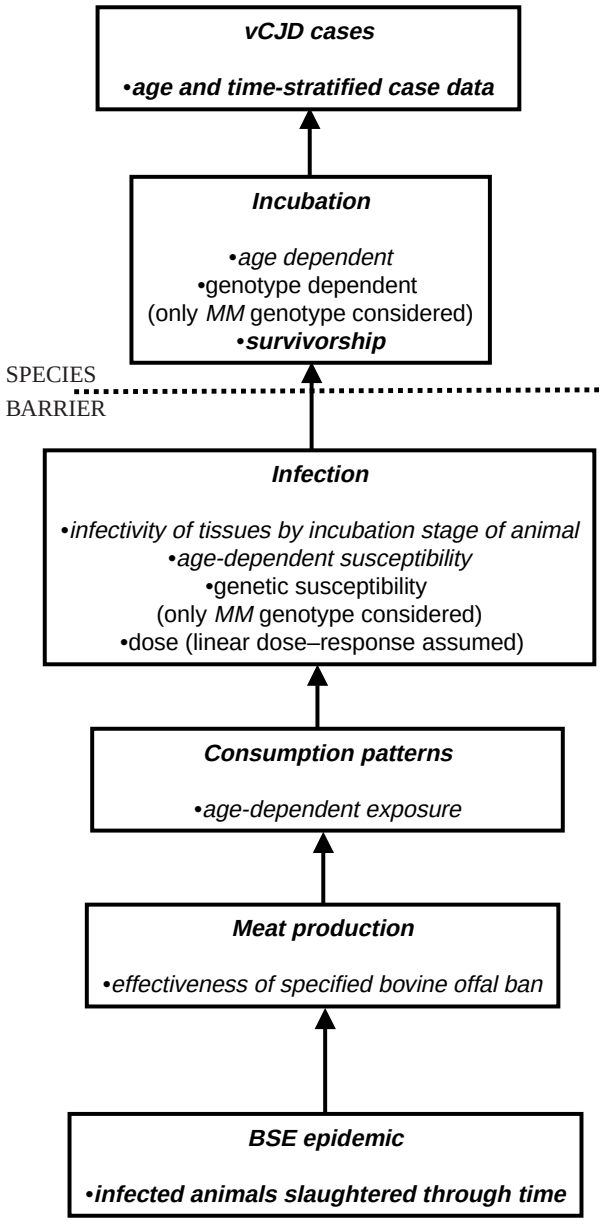

Figure 2. Methodological approach taken to generate scenarios consistent with the observed age- and time-stratified vCJD data given estimates of the numbers of infected bovines slaughtered. Data are presented in bold and the parameters varied in italics.

epidemic (both cases and infections), the effectiveness of the SBO ban, the infectiousness of various tissues derived from cattle slaughtered at different stages of the incubation period and the consumption of beef products. The greatest uncertainty lies in the infectiousness of various tissues and the consumption patterns of the UK population. In this paper, we create a general mathematical framework to relate the past pattern of the BSE epidemic to the future magnitude of the vCJD epidemic and to explore how different processes (e.g. the incubation period distribution of vCJD) influence the epidemiological pattern. The objective is to assess both the magnitude of the epidemic and the uncertainty surrounding such estimates, as information on cases of disease accumulates year by year. Analyses are rigorously constrained on the template of what is known, namely the time-series and age distribution of vCJD cases in humans, and the time-series of the number of infected cattle consumed with their distribution stratified by incubation stage.

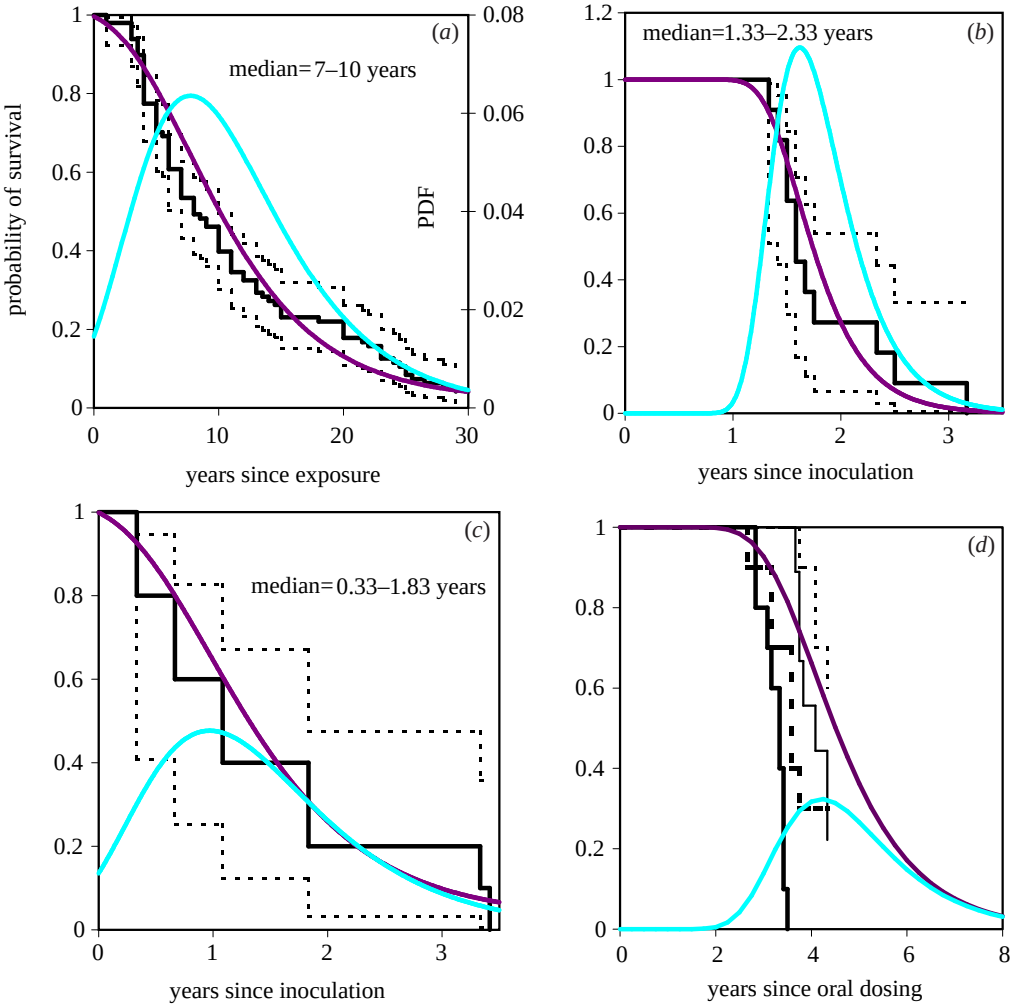

Figure 3. (*a–c*) Kaplan–Meier survival curves (solid lines with 95% confidence intervals given as dotted lines) with fitted mechanistic Weibull incubation period distributions (inverse cumulative distribution in purple and probability density function (PDF) in light blue) for kuru in (*a*) humans (Klitzman *et al*. 1984), (*b*) chimpanzees (*Pan troglodytes*) (Asher *et al*. 1973), (*c*) spider monkeys (*Ateles geoffroyi*) (Beck *et al*. 1975) inoculated intracerebrally with 0.2 ml of a 10% brain suspension from human kuru victims; (*d*) Kaplan–Meier survival curves for cattle orally dosed with 1 g (light dotted line), 10 g (light solid line), 100 g (dark dotted line) and three doses of 100 g (dark solid line) of brain from cattle affected with BSE (Anderson *et al*. 1996), with the best-fitting incubation period distribution from backcalculation analysis of the BSE case database (Ferguson *et al*. 1997) (inverse cumulative distribution in purple and probability density function (PDF) in light blue).

2. MATHEMATICAL FRAMEWORK

Our aim is to determine the ranges of key epidemiological parameters and sizes of vCJD epidemics that are consistent with the age- and time-stratified case data. By October 1998, 30 cases of vCJD had been confirmed in the UK, with ages ranging from 19–53 years. We stratify the data by date of death in yearly steps, since finer temporal stratification reveals a significant seasonal trend (more deaths in the first half of each year than the second). For this reason, we use data only up to the end of 1997 (23 cases with ages at death ranging from 19–50 years, figure 1*a*,*b*). Throughout we define the incubation period as the time between infection and death. Our approach is presented diagrammatically in figure 2.

For an infection where the incubation period is independent of host attributes and of the nature and degree of exposure at infection, the probability density function (PDF) for an individual developing clinical disease at time u and age a is

$$p(u,a) = S(u,a)\int_{u-a}^{u} f(u-t)I(t)\mathrm{e}^{-\int_0^t I(t')\mathrm{d}t'}\mathrm{d}t,$$

where $I(t)$ is the infection hazard at time t, $S(u,a)$ is the probability of surviving to time u and age a (estimated from census data (OPCS 1968–1995)) and $f(u)$ is the PDF of the incubation period. As for other transmissible spongiform encephalopathies (TSEs) (Hunter *et al*. 1989; Anderson *et al*. 1996), the incubation period of vCJD may depend on host genotype, k, age at infection, a', and infecting dose, γ. If $I_k(t,a',\gamma)$ is the infection hazard for a genotype k individual of age a' at time t consuming dose γ, then the incidence of vCJD cases at time u is given by:

$$c(u) = \sum_k \int_0^{a_{\max}} B_k(u-a)S(u,a)\int_{u-a}^{u}\int f_k(u-t,a-u+t,\gamma) \times I_k(t,a-u+t,\gamma)\mathrm{e}^{-\int_0^t\int I_k(t',a-u+t',\gamma')'\mathrm{d}\gamma'\mathrm{d}t'}\mathrm{d}\gamma\mathrm{d}t\mathrm{d}a,$$

where $B_k(t_b)$ is the birth rate of individuals of genotype k at time t_b and $f_k(u)$ is the incubation PDF for such an individual.

The key quantity determining the magnitude (though not the time-course) of the vCJD epidemic is the past risk of infection, represented by $I_k(t,a',\gamma)$. Estimation of this risk is difficult due to the complexity of the transmission process and many uncertainties in key parameters. We therefore adopt two simplifying restrictions in this analysis. First, all 23 cases to the end of 1997 have been methionine homozygous (MM) at codon 129 (R. Will, personal communication), suggesting increased susceptibility and/or reduced incubation periods for this genotype (Raymond *et al.* 1997; Goldman *et al.* 1994; Zeidler *et al.* 1997; Deslys *et al.* 1998; Cervenakova *et al.* 1998). In the absence of data on cases arising in other genotypes, our analyses are restricted to the vCJD epidemic within the MM genotype. The Caucasian population in Britain is composed of approximately 40.1% methionine homozygotes, 47.2% heterozygotes and 12.7% valine homozygotes (sample size 142 (Owen *et al.* 1990; Collinge *et al.* 1991).) If other genotypes are susceptible, then our results represent a lower bound on the maximum number of cases.

Second, we only consider infections arising through the consumption of infected cattle. Oral route transmission of vCJD, BSE and other TSEs between species has been demonstrated in a number of experiments (Barlow & Middleton 1990; Fraser *et al.* 1992; Middleton & Barlow 1993; Wells *et al.* 1994; MAFF 1996) and many TSEs, in particular BSE, appear to be able to cross host-species barriers with ease (Foster *et al.* 1996), although evidence from transgenic mouse studies suggests that the species barrier for bovine to human transmission may be significant (Collinge *et al.* 1995). Whilst strong evidence exists for vertical transmission of BSE (Wilesmith *et al.* 1997; Donnelly *et al.* 1997*a*,*b*), and weaker evidence suggests horizontal transmission of scrapie in sheep (Dickinson *et al.* 1974; Hoinville 1996), we do not consider the possibility of vCJD transmission between people here. The infection hazard is therefore determined by the pattern of human exposure to infected cattle tissue, which in turn is determined by the past pattern of the BSE epidemic and the regulations governing which bovine tissues could be used for human food (Statutory Instrument 1989). This pattern of exposure depends on the numbers of infected animals slaughtered (stratified by incubation stage), which can be estimated using back-calculation analyses (Anderson *et al.* 1996; Ferguson *et al.* 1997) (figure 1*c*).

For an MM genotype individual being exposed to dose γ at age a', the infection hazard at time t is

$$I(t,a',\gamma) = g_e(a')\nu(t)\beta(\gamma,a')\int h(\gamma|z,a')w(z,t)\mathrm{d}z,$$

where $h(\gamma|z,a')$ represents the probability density that an individual of age a' is exposed to a dose γ during consumption of tissue from an infected bovine, slaughtered at a time z prior to disease onset, and $w(z,t)$ is the proportion of cattle slaughtered at time t that are infected and at time z from disease onset. $g_e(a')$ is the mean frequency of beef consumption in people of age a', $\nu(t)$ represents the effect of control measures at time t in preventing infectious material reaching the human food supply (here assumed to equally affect the probability of exposure to any dose), and $\beta(\gamma,a')$ is the probability that a dose of size γ will infect a human of age a'.

This complex dose-dependent model can be simplified if we assume the dose distribution scales as $h(\gamma|z,a') = h(\gamma/\Gamma(z,a'))/\Gamma(z,a')$, or $h(\gamma|z,a') = h(\gamma-\Gamma(z,a))$, with Γ being a rescaling factor or offset, respectively. Epidemiologically, $\Gamma(z,a')$ represents the effect of disease pathogenesis or age-dependent meat-product consumption patterns on the dose distribution: as Γ increases, then exposure to a larger dose becomes more likely. We assume that $\Gamma(z,a')$ can be decomposed as $\Gamma(z,a') = \Omega(z)g_r(a')$, with $\Omega(z)$ being the relative infectiousness of an animal at time z prior to disease onset, and $g_r(a')$ representing the potentially increased risk that certain age groups might have of consuming high-titre meat products. Finally, for a linearly increasing risk of infection with dose (linear dose–response, as observed in Diringer *et al.* (1998)), $\beta(\gamma,a') = \beta\gamma g_s(a')$ (where $g_s(a')$ represents the relative susceptibility of an individual of age a') and a dose-independent incubation period distribution, we can integrate out γ and obtain

$$I(t,a') = \nu(t)\beta g(a')\int \Omega(z)w(z,t)\mathrm{d}z,$$

where we have combined all age dependency into a single normalized factor $g(a')$ and have redefined β as a transmission coefficient (i.e. incorporating frequency of exposure). We use this model in the scenario analyses due to its computational simplicity and the small volume of case data against which to test more complex models. However, the more complex framework may prove useful once more biological or epidemiological data are available.

Selection of potential functional forms for the incubation period distribution of vCJD was informed by the distributions observed for other TSEs (figure 3). Note that several of the distributions (including that of BSE) have relatively large minimum incubation periods, so the possibility of a substantial post-exposure delay prior to the onset of any vCJD cases must be included in potential distributions. To explore the space of incubation period distributions we used a modified form of the four-parameter generalized lambda distribution (Ramberg *et al.* 1979) (with inverse CDF $X(p) = \lambda_1 + (p^{\lambda_3} + (1-p)^{-\lambda_4} - 1)/\lambda_2$). This has the flexibility to encompass virtually all the potential shapes of other more limited forms, such as offset Weibull, gamma and log-normal distributions.

In the results presented here, bovine infectivity, $\Omega(z)$, is assumed to rise exponentially (from some baseline level) to reach a maximum at the end of the BSE incubation period—a trend consistent with currently available data on BSE and TSE pathogenesis (Fraser *et al.* 1992; Wells *et al.* 1994, 1998; MAFF 1996; Spongiform Encephalopathy Advisory Committee 1997). By varying two parameters (baseline level and exponential rate of increase), a wide variety of specific infectivity assumptions can be explored. The infection hazard is also strongly affected by the SBO ban introduced in November 1989. Our analyses assume that the ban was anywhere between 0% and 100% effective (with $\nu(t) = 1$ prior to this date). We explored two forms of age dependency; age-dependent susceptibility/

exposure and an age-dependent incubation period. For the former a variety of functional forms (normal, logistic, step) were explored. For the latter, we assumed that the f incubation period increased with age using the scaling $f(u,a) = s(a)h(u)$, where $h(u)$ is an age-independent incubation period density function and $s(a)$ is a scaling function. In the analyses presented we used a logistic function $s(a) = [\alpha_2 \exp(-\alpha_3 a) + \alpha_1]/[\exp(-\alpha_3 a) + \alpha_1]$, where α_i are parameters.

Rather than estimating parameters, we sample the space of parameter values (scenarios) consistent with the observed data. A scenario is accepted if both the age- and time-structured marginal case distributions are consistent at the 95% level with the corresponding observed marginal distributions, as judged by the distribution of Poisson likelihood deviances obtained from parametric bootstrap sampling of the observed case data. We sample over a wide range of incubation period distribution shapes, age-dependent susceptibility/exposure functions ($g(a)$), SBO ban effectiveness levels ($\nu(t)$) and patterns of infectivity of cattle at different incubation stages ($\Omega(z)$), using Latin hypercube sampling as an efficient method for exploring parameter space (Stein 1987; McKay *et al.* 1979). The scatterplots used illustrate the range of possible outcomes but do not represent likelihood densities, i.e. the density of points in a particular region of parameter space should not be interpreted as representing the likelihood that the true parameters take these values.

3. EPIDEMIOLOGICAL DETERMINANTS OF THE vCJD EPIDEMIC

Ignoring current case data, the maximum number of vCJD infections is simply determined by β, the size of the susceptible human population N, and the total number of infectious animals slaughtered during the BSE epidemic. However, for a given value of N and cattle infectivity profile, the case data act to put bounds on both the form of the incubation period distribution $f(u)$ and on the value of β. If the size of the susceptible population N is reduced, higher values of β are required to reproduce the same epidemic size. This relationship is expressed in our results using the single parameter $r = \beta N/A$, the average number of individuals that will become infected from one maximally infectious (within three months of disease onset) bovine, where A is the total rate of cattle slaughter. The value of r strongly determines the final epidemic size (figure 4*a*), encompassing the relative infectiousness of different bovine tissues (Fraser *et al.* 1992; Wells *et al.* 1994; MAFF 1996; Spongiform Encephalopathy Advisory Committee 1997), the infectivity to humans of these tissues (the species barrier), and the average number of susceptible individuals who will consume one carcass. Whilst these parameters are largely unknown, given detailed data on the production, distribution and consumption of beef products and on the relative infectivity of different tissues, an upper bound for r could potentially be estimated.

Given a value for r, the incubation period distribution influences only the time-course, and not the size, of any epidemic. Demanding consistency with the case data then restricts the possible length and shape of the incubation period distribution. Conversely, if the incubation period is known, the case data can be used to restrict the possible values of r. Thus, if r is unknown, the incubation period distribution can also be used as a predictor of epidemic size. Both the length and the shape of the left-hand side of the distribution are important determinants (figure 4*b*). Small epidemics are generated from tight distributions with short modes, with the current case data representing a large proportion of the total distribution. Conversely, large epidemics are generated by long, strongly peaked incubation period distributions, for which the cases seen to date represent a small part of the left-hand tail of the distribution.

Epidemic patterns consistent with the observed age distribution of vCJD cases could not be obtained without assuming age-dependency in either the incubation period or in susceptibility/exposure. This is because no cases of vCJD have as yet been observed in patients over 53 years old and the probability of this happening by chance, even with only 30 cases, is very small. To explain the observed age distribution, older individuals need to have a longer incubation period and/or reduced susceptibility or exposure to the BSE agent. Using a uniform age-dependent susceptibility/exposure function between ages a_l and a_u, the cases observed in older age groups demand that a_u be at least ten years. Similarly, these data restrict a significant increase in any age-dependent incubation period to those aged over approximately 25 years at their time of infection.

In the absence of significant age-dependent susceptibility/exposure, the minimum observed age of death of 19 years can only be explained by a comparable minimum incubation period for vCJD. However, even allowing for age-dependent exposure/susceptibility, figure 4*b* suggests that the case data impose a lower bound on the modal incubation period of approximately nine years. This is explained by comparing the temporal patterns of human exposure with those of vCJD cases: that no vCJD deaths prior to 1995 have been reported means that a large proportion of cases seen to date must have arisen from exposure in the first few years of the BSE epidemic. For the scenarios including age-dependent incubation periods, the fraction of cases infected prior to 1986 never fell below 0.5, whilst for age-dependent susceptibility/exposure the lower bound on this fraction is 0.2. The magnitude of these values is consistent with press reports that one vCJD case had been a vegetarian since 1986.

The existence of a lower bound on the incubation period can be demonstrated analytically by approximating the epidemiological model by tractable parametric forms. Assume that only cattle in the last six months of BSE incubation are infectious and that the SBO ban was completely ineffective. These assumptions give the lowest incubation period bounds and allow the infection hazard for vCJD to be closely approximated by back-to-back exponentials with risk beginning in 1980 and peaking in 1992. The ratio of cases from 1996–1997 to those prior to 1996 can then be approximated by

$$\frac{\int_{1980}^{1997} F(u-t)\mathrm{e}^{\alpha|1992-t|}\mathrm{d}t}{\int_{1980}^{1995} F(u-t)\mathrm{e}^{\alpha|1992-t|}\mathrm{d}t} - 1 > R_\mathrm{L},$$

where $R_\mathrm{L} = 5.04$ is the lower 95% confidence bound on the ratio obtained from the case data, $F(u)$ is the cumulative incubation period distribution function and $\alpha = 0.55$.

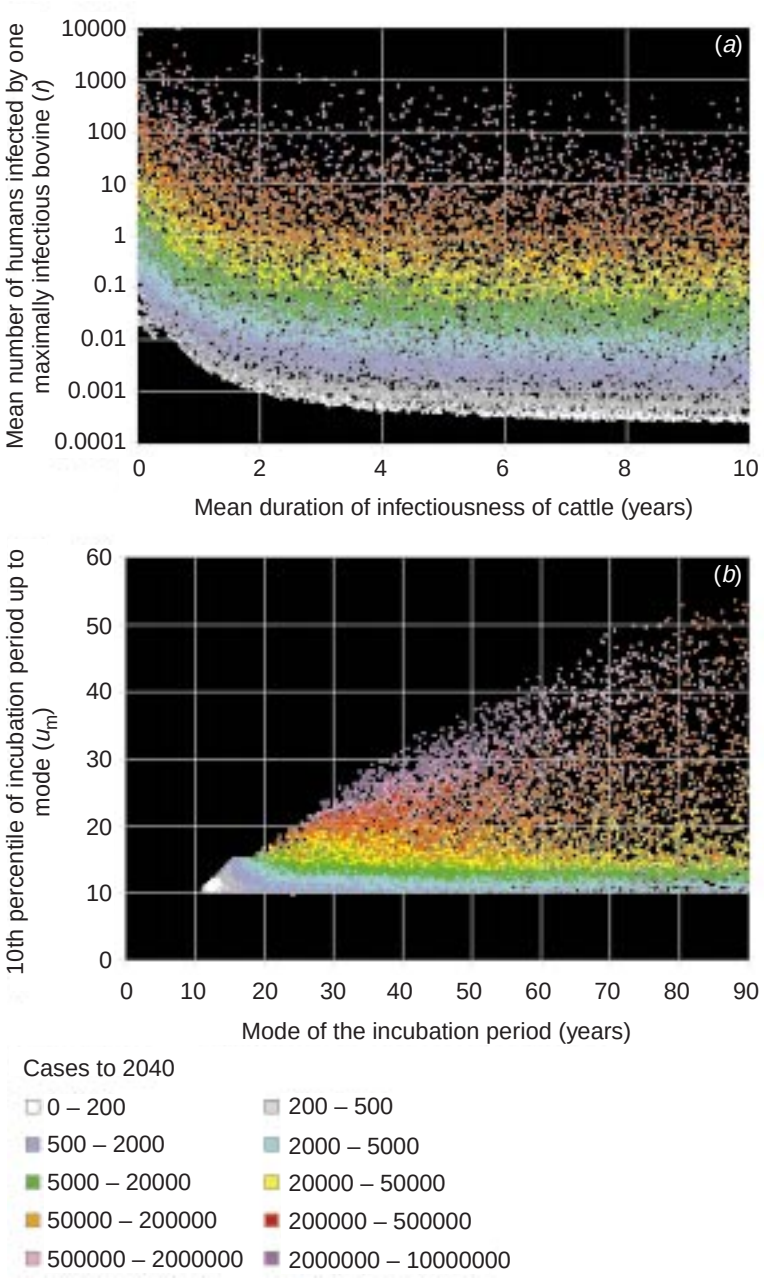

Figure 4. Scatterplot of sampled scenarios showing (*a*) the mean duration of infectiousness of cattle, d, against r, the mean number of humans infected by one maximally infectious bovine. Infectiousness is always assumed to peak at the end of the bovine incubation period ($\Omega(z) = e^{-z/d}$). Results are shown for the age-dependent susceptibility/exposure model (similar results are obtained assuming an age-dependent incubation period). Point colour represents total epidemic size. As the mean duration of infectiousness shortens, the value of r required to produce a given epidemic size increases. This effect becomes less significant for mean durations greater than about two years due to cattle survivorship patterns (most cattle are slaughtered just after two years of age) (Anderson *et al.* 1996); (*b*) incubation period distribution mode, u_m, against $u_{m_{10\%}}$ (the location of the tenth percentile of the distribution up to the mode defined by $F(u_{m_{10\%}}) = F(u_m)/10$, where $F(u)$ is the cumulative incubation period density function) for the age-dependent susceptibility/exposure model (similar patterns are observed for the age-dependent incubation period model). The latter statistic describes the relative width of the left-hand side of the incubation period distribution and has the advantage (shared with the mode) that it can be estimated as soon as the vCJD epidemic conclusively peaks. Point colour represents total epidemic size. Note that the figures do not represent likelihood densities.

For example, in the (unrealistic) case of a fixed incubation period, this equation can be solved to give a lower bound of 6.1 years.

4. EPIDEMIC PREDICTABILITY

With the constraint of 23 cases by 1 January 1998 possible epidemic sizes range from 29 to around ten million cases. This clearly indicates that the current time-series of vCJD cases contains too little information to make useful predictions. It also highlights the fact that recent speculation that a yearly time-series of reported cases running three (in 1995), ten (in 1996) and ten (in 1997) denotes a small epidemic, is totally unfounded. As figure 5 shows, a wide range of epidemic scenarios is capable of exactly reproducing this time-series.

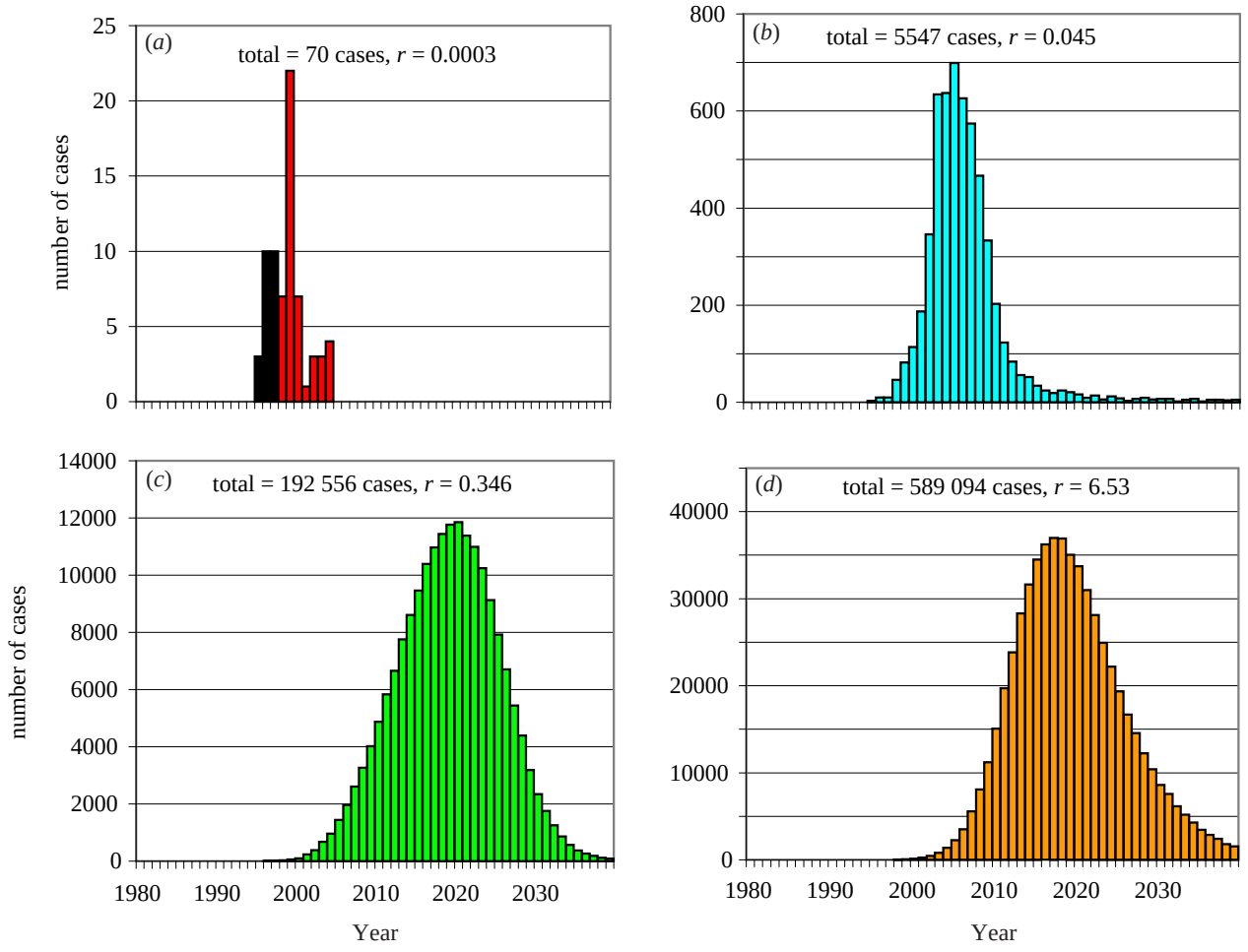

Figure 5. Time-series for four simulated epidemic scenarios. The stochastic realizations selected (30 were generated for each accepted scenario) all exactly match the case data time-series to 1997 (shown in black).

Accepting that current information is too limited to say anything sensible about future epidemic size, a key question is how the observed pattern of cases over the next few years will aid prediction. Our scenario analyses give prediction intervals of 0–104 cases in 1998, 0–172 cases in 1999 and 0–410 cases in 2000. However, the upper bound on the total epidemic size is only significantly reduced if less than around 50 deaths from vCJD are reported over this period. Above this, the range of possible epidemic sizes is large. Table 1 examines potentially smaller epidemic scenarios. How the numbers of cases over the next three years will aid prediction strongly depends on the absolute infectivity of bovine tissue to humans (the infectious dose). A maximum of 50 cases observed in 1998 constrains future epidemic size to be small (less than 10 000 cases) only if r is less than approximately 0.01. For a value of r greater than this, large epidemics are still possible even if fewer than ten cases are confirmed in 1998. By the year 2000, predictability does improve if a small number of cases are observed. A maximum of 50 cases between 1998 and 2000 constrains the epidemic to be small (less than approximately 10 000 cases) if $r < 10$. However, for a value of r between 10 and 100 much larger epidemics are still possible.

Recently, tests have been developed that are able to identify prion protein in tissues taken from vCJD patients prior to the onset of symptoms (Hill *et al.* 1997*b*; Schreuder *et al.* 1996). Such tests offer the potential of mass screening of tonsillar and appendix tissues to estimate better the infection prevalence in the population (Hilton *et al.* 1998). However, if these tests are only able to identify late-stage infection, then their potential for reducing the current uncertainty in future epidemic size is limited. For example, suppose the test is only able to identify infection in the last three years of the incubation period. Our model estimates that the prevalence of infection in the last three years of incubation in 1998 is between 0.4 and 24 infections per million people. To be 90% certain of detecting one or more infections at the highest prevalence we would need to screen approximately 96 000 individuals, while to detect the lowest prevalence would require screening a large proportion of the population. In addition, figure 6 shows that in the absence of information on r, the prevalence of late-stage infection in 1998 does not greatly improve the predictability of the epidemic. If tests are able to detect infection early in the incubation period, as suggested by experimental scrapie models (Kimberlin & Walker 1988), then predictability slightly improves if large-scale screening is undertaken (Ghani *et al.* 1998). However, whilst the duration of the incubation period during which infectivity is detectable remains unknown, the range of epidemic sizes consistent with a measured prevalence will remain large.

Table 1. *Upper and lower bounds on total vCJD epidemic size stratified by the number of cases reported in 1998, 1998–2000 and r, the mean number of people infected by one maximally infectious bovine*

(Scenarios were accepted if the deterministic mean numbers of cases were consistent with current case data. The results are based on 30 stochastic realizations of each accepted parameter point. These ranges were obtained with SBO ban effectiveness levels between 0 and 100%. If the SBO ban is assumed to have been over 90% effective, upper bounds are reduced by 5–10-fold for all but the largest band of *r* values.)

	cases 1998			cases 1998–2000		
r	0–10	10–20	20–50	0–50	50–100	100–200
0–0.01	37–8296	40–8648	53–9236	37–1851	59–8484	110–8814
0.01–0.1	29–51 468	52–85 221	53–90 114	29–7791	74–72 952	140–88 689
0.1–1.0	204–455 149	212–748 292	274–819 839	204–13 171	274–598 845	296–748 558
1–10	$1779–3.24\times10^6$	$1331–5.24\times10^6$	$1215–6.16\times10^6$	1774–11 066	$1779–3.93\times10^6$	$1215–5.24\times10^6$
10–100	$4015–5.14\times10^6$	$4032–1.10\times10^7$	$6045–1.26\times10^7$	4015–26 798	$4123–4.62\times10^6$	$6096–1.10\times10^7$
100+	—	$59\,688–1.15\times10^7$	$59\,921–1.37\times10^7$	—	$59\,472–9.58\times10^6$	$70\,112–1.30\times10^7$

5. CONCLUSIONS

The analyses are based on two key assumptions—that the incidence of vCJD is correlated with exposure to tissue from BSE-infected cattle and that the incubation period distribution of vCJD is unimodal for the PrP codon 129 methionine homozygous genotype (other genotypes are not considered but their inclusion could only increase estimates of final epidemic size). Given these assumptions, we have shown that the observed time-series of vCJD cases and their age distribution are consistent with an epidemic size ranging from that already seen to a large proportion of the susceptible population. It is therefore too early to speculate that the lack of any apparent rise in incidence over the past two years indicates that the epidemic will be small in scale.

The mathematical framework relating the BSE epidemic and the magnitude and duration of the vCJD epidemic can be extended to encompass further complications as new evidence emerges. For example, given the observed properties of prion diseases in animal models, it seems likely that host genetic background influences the incubation period, that susceptibility is age-dependent, and that the incubation period may depend both on age at exposure and dose of the agent. However, data on the precise nature of such processes are presently unavailable. We also lack data on the distribution of exposure risk in the human population (in particular the distribution of animals and animal parts in meat products), and on how risk is related to the duration, magnitude and frequency of exposure to the agent. Our analyses do not consider underreporting of vCJD cases prior to 1995. However, since a significant proportion of individuals whose death certificates recorded neurological disorders prior to 1995 were tested at autopsy for signs of vCJD, the extent of underreporting is thought to be small. Furthermore, in this analysis we did not consider potential transmission within the human population, for example, through transfusion of material from infected blood donors, contaminated surgical tools, or from mother to child. Transmission of vCJD through these routes can only increase the prevalence of infection and hence the total epidemic size.

One key objective of our analysis is the assessment of the question 'when will it be possible to narrow the range of possible outcomes?' For long incubation period infectious diseases, where the distribution of this period is unknown, epidemic size can only be estimated with a degree of precision once the peak in the epidemic curve is past. If vCJD incidence remains very low for the next few years a 'small' overall epidemic becomes more likely, since it will become increasingly probable that the epidemic peak has been reached. However, the final epidemic size is primarily determined by bovine infectiousness to humans, characterized here by *r*, the average number of humans infected by one maximally infectious bovine. For example, an incidence of fewer than 50 cases between 1998 and 2000 narrows the bounds of the total epidemic size to between 29 and 10 000 for values of *r* less than 10, and a very wide range of assumptions about the other unknown epidemiological parameters. Better estimates of the upper bound of *r* are therefore critical to improve epidemic predictability. Such estimates could be obtained by combining data on how animals are distributed in the food manufacturing process with population-based surveys of dietary habits.

The analyses extend previous studies (Cousens *et al.* 1997; Comer 1997) via the use of estimates of the number of infected cattle that entered the human food chain stratified by incubation stage, and the use of time-series and age distribution of vCJD cases to date in constraining the epidemic scenarios. The additional information provided by the age distribution of vCJD cases strongly suggests that exposure, susceptibility, and the incubation period cannot all be independent of age. More data are required to characterize the specific forms of age dependence. Together, the exposure data and time-series of cases allow a lower bound of approximately nine years to be put on the mode of the vCJD incubation period. The analyses also indicate that at least 20% of all vCJD cases reported to date were infected prior to 1986.

The scenario analyses were based on over five million simulated epidemics, all of which were consistent with the observed BSE exposure data, the time-series of vCJD cases and their age distribution. Such exhaustive sensitivity analyses of possible outcomes in the face of great uncertainty about key determinants are essential if policymakers are to understand fully the limitations in current information about risks to the human population. The

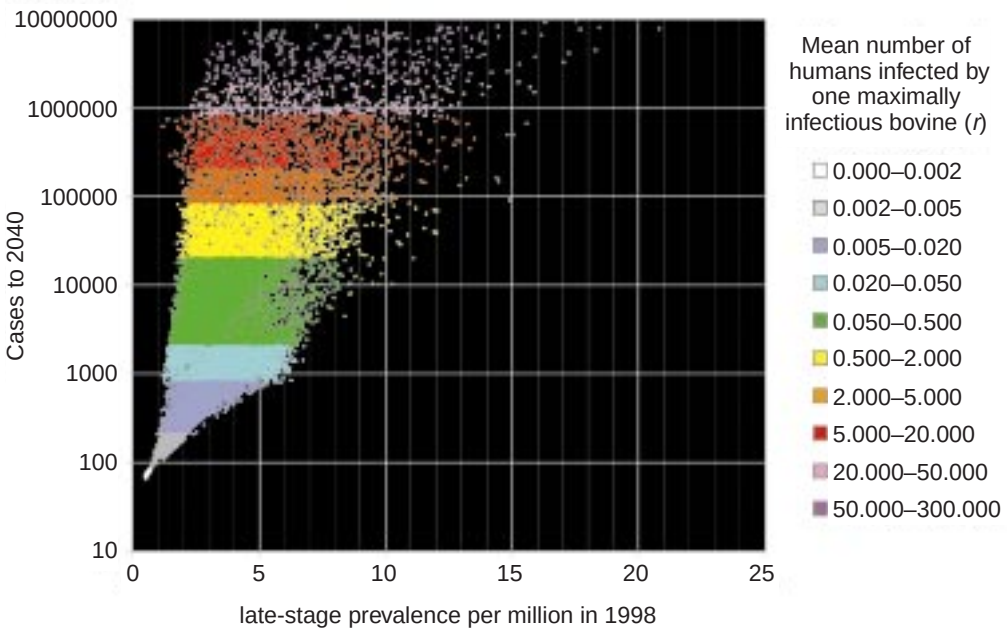

Figure 6. Scatterplot of possible scenarios showing the prevalence of late-stage infection (last three years of the incubation period) in 1998 and total epidemic size. Point colour represents *r*, the mean number of humans infected by one maximally infectious bovine. Results are shown for the age-dependent susceptibility/exposure model.

recent example of the possible risks to the population from dorsal route ganglia attached to meat cuts on the bone from BSE infected cattle (Comer 1997) well illustrated the dangers in assigning specific values to risk despite great uncertainty. Such assignments create an impression of precision in the minds of the public and policymakers, when in reality the confidence bounds on such estimates are extremely wide. Recently, tests have been developed that are able to identify infection, offering the potential for mass-screening programmes. However, caution must be exercised in interpreting results from epidemiological surveys since it is not known at what stage in the incubation period of vCJD infectivity can be detected. For example, a low prevalence will indicate a small epidemic if the test is able to detect infection throughout the incubation period, or alternatively, could indicate a larger epidemic if the test is only able to detect late-stage infection. The urgent need therefore remains the further development of diagnostic tests to identify early-stage pre-symptomatic infection, such that large-scale anonymous surveys of the UK population can begin to put a degree of precision on the relationship between exposure and the incidence of infection.

A.C.G., N.M.F., C.A.D., T.J.H. and R.M.A. gratefully acknowledge the Wellcome Trust and the UK Ministry of Agriculture, Fisheries and Food for research grant support. N.M.F. thanks the Royal Society for fellowship support. We thank David Cox, John Matthews, Bob Will, Frank Kelly, John Collinge and Michael Alpers for helpful discussions, and Edward King for assistance.

REFERENCES

Anderson, R. M. (and 14 others) 1996 Transmission dynamics and epidemiology of BSE in British cattle. *Nature* **382**, 779–788.

Asher, D. M., Gibbs, C. J., David, E., Alpers, M. P., Gajdusek, D. C. & Sadowsky, D. A. 1973 Experimental kuru in the chimpanzee: physical findings and clinical laboratory studies. In *Symp. IVth Int. Congr. Primatology* 4. *Nonhuman primates and human diseases* (ed. W. P. McNulty), pp. 43–90, Basel: Karger.

Barlow, R. M. & Middleton, D. J. 1990 Dietary transmission of bovine spongiform encephalopathy to mice. *Vet. Rec.* **126**, 111–112.

Beck, E., Bak, I. J., Christ, J. F., Gajdusek, D. C., Gibbs, C. J. & Hassler, R. 1975 Experimental kuru in the spider monkey: histopathological and ultrastructural studies of the brain during early stages of incubation. *Brain* **98**, 595–612.

Bruce, M. E. (and 12 others) 1997 Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* **389**, 498–501.

Cervenakova, L., Goldfarb, L. G., Garrute, R., Lee, H. S., Gajdusek, D. C. & Brown, P. 1998 Phenotype–genotype studies in Kuru: implications for new variant Creutzfeldt–Jakob disease. *Proc. Natn. Acad. Sci. USA* **95**, 13 329–13 241.

Collinge, J., Palmer, M. S. & Dryden, A. J. 1991 Genetic predisposition to iatrogenic Creutzfeldt–Jakob disease. *Lancet* **337**, 1441–1442.

Collinge, J., Palmer, M. S., Sidle, K. C. L., Hill, A. F., Gowland, I., Meads, J., Asante, E., Bradley, R., Doey, L. J. & Lantos, P. J. 1997 Unaltered susceptibility to BSE in transgenic mice expressing human prion protein. *Nature* **378**, 779–783.

Collinge, J., Sidle, K. C. L., Meads, J., Ironside, J. & Hill, A. F. 1996 Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD. *Nature* **383**, 685–690.

Comer, P. J. 1997 *Assessment of risk from possible BSE infectivity in dorsal root ganglia*. Det Norske Veritas (see http://www.dnv.com).

Cousens, S. N., Vynnycky, E., Zeidler, M., Will, R. G. & Smith, P. G. 1997 Predicting the CJD epidemic in humans. *Nature* **385**, 197–198.

Deslys, J.-P., Jaegly, A., d'Aignaux, J. H., Mouthon, F., de Villemur, T. B. & Dormont, D. 1998 Genotype at codon 129 and susceptibility to Creutzfeldt–Jakob disease. *Lancet* **351**, 1251.

Dickinson, A. G., Stamp, J. T. & Renwick, C. C. 1974 Maternal and lateral transmission of scrapie in sheep. *J. Comp. Pathol.* **84**, 19–25.

Diringer, H., Roehmel, J. & Beekes, M. 1998 Effect of repeated oral infection of hamsters with scrapie. *J. Gen. Virol.* **79**, 609–612.

Donnelly, C. A., Ferguson, N. M., Ghani, A. C., Wilesmith, J. W. & Anderson, R. M. 1997*a* Analysis of dam–calf pairs of BSE cases: confirmation of a maternal risk enhancement. *Proc. R. Soc. Lond.* B **264**, 1647–1656.

Donnelly, C. A., Ghani, A. C., Ferguson, N. M., Wilesmith, J. W. & Anderson, R. M. 1997*b* Analysis of bovine spongiform encephalopathy maternal cohort study: evidence for direct maternal transmission. *Appl. Statist.* **46**, 321–344.

Ferguson, N. M., Donnelly, C. A., Woolhouse, M. E. J. & Anderson, R. M. 1997 The epidemiology of BSE in GB cattle herds. II. Model construction and analysis of transmission dynamics. *Phil. Trans. R. Soc. Lond.* B **352**, 803–838.

Foster, J. D., Bruce, M., McConnell, I., Chree, A. & Fraser, H. 1996 Detection of BSE infectivity in brain and spleen of experimentally infected sheep. *Vet. Rec.* **138**, 546–548.

Fraser, H., Bruce, M. E., Chree, A., McConnell, I. & Wells, G. A. H. 1992 Transmission of bovine spongiform encephalopathy and scrapie to mice. *J. Gen. Virol.* **73**, 1891–1897.

Ghani, A. C., Ferguson, N. M., Donnelly, C. A., Hagenaars, T. J. & Anderson, R. M. 1998 Estimation of the number of people incubating variant CJD. *Lancet* **352**, 1353–1354.

Goldmann, W., Hunter, N., Smith, G., Foster, J. & Hope, J. 1994 PrP genotype and agent effects in scrapie: change in allelic interaction with different isolates of agent in sheep, a natural host of scrapie. *J. Gen. Virol.* **75**, 989–995.

Hill, A. F., Desbruslais, M., Joiner, S., Sidle, K. C. L., Gowland, I., Collinge, J., Doey, L. J. & Lantos, P. 1997*a* The same prion strain causes vCJD and BSE. *Nature* **389**, 448–450.

Hill, A. F., Zeidler, M., Ironside, J. & Collinge, J. 1997*b* Diagnosis of a new variant Creutzfeldt–Jakob disease by tonsil biopsy. *Lancet* **349**, 99–100.

Hilton, D. A., Fathers, E., Edwards, P., Ironside, J. W. & Zajick, J. 1998 Prion immunoreactivity in appendix before clinical onset of variant Creutzfeldt–Jakob disease. *Lancet* **352**, 703–704.

Hoinville, L. J. 1996 A review of the epidemiology of scrapie in sheep. *Rev. Sci. Tech. Off. Int. Epiz.* **15**, 827–852.

Hunter, N., Foster, J. D., Dickinson, A. G. & Hope, J. 1989 Linkage of the gene for the scrapie-associated fibril protein (PrP) to the *Sip* gene in Cheviot sheep. *Vet. Rec.* **124**, 364–366.

Kimberlin, R. H. & Walker, C. A. 1988 Pathogenesis of experimental scrapie. *Ciba Foundation Symp.* **135**, 37–62.

Klitzman, R. L., Alpers, M. P. & Gajdusek, D. C. 1984 The natural incubation period of kuru and the episodes of transmission in three clusters of patients. *Neuroepidemiology* **3**, 3–20.

McKay, M. D., Beckman, R. J. & Conover, W. J. 1979 A comparison of three methods for selecting values on input variables in the analysis of output from a computer code. *Technometrics*, **21**, 239–245.

Middleton, D. J. & Barlow, R. M. 1993 Failure to transmit bovine spongiform encephalopathy to mice by feeding them with the extraneural tissue of affected cattle. *Vet. Rec.* **132**, 545–547.

Ministry of Agriculture, Fisheries and Food 1996 *Programme to eradicate BSE in the United Kingdom*. London: HMSO.

Office of Population Censuses and Surveys 1968–1995 *OPCS monitor*. London: HMSO.

Owen, F., Poulter, M., Collinge, J. & Crow, T. J. 1990 Codon 127 changes in the prion protein gene in Caucasians. *Am. J. Hum. Genet.* **46**, 1215–1216.

Ramberg, J. S., Tadikamalia, P. R., Dudewicz, E. J. & Mykytka, E. F. 1979 A probability distribution and its uses in fitting data. *Technometrics* **21**, 201–209.

Raymond, G. M. (and 14 others) 1997 Molecular assessment of the potential transmissibilities of BSE and scrapie to humans. *Nature* **388**, 285–288.

Schreuder, B. E. C., van Keulen, L. J. M., Vromans, M. E. W., Langeveld, J. P. M. & Smits, M. A. 1996 Preclinical test for prion disease. *Nature* **381**, 563.

Spongiform Encephalopathy Advisory Committee 1997 *Advice to Ministers on dorsal root ganglia*. 3 December 1997.

Statutory Instrument 1989 *The Bovine Offal (Prohibition) Regulations 1989*. Statutory Instrument 1989, no. 2061. London: HMSO.

Stein, M. 1987 Large sample properties of simulations using Latin hypercube sampling. *Technometrics* **29**, 143–151.

Wells, G. A. H., Scott, A. C., Johnson, C. T., Gunning, R. F., Hancock, R. D., Jeffrey, M., Dawson, M. & Bradley, R. 1987 A novel progressive spongiform encephalopathy in cattle. *Vet. Rec.* **121**, 419–420.

Wells, G. A. H., Dawson, M., Hawkins, S. A. C., Green, R. B., Dexter, I., Francis, M. E., Simmons, M. M., Austin, A. R. & Horigan, M. W. 1994 Infectivity in the ileum of cattle challenged orally with bovine spongiform encephalopathy. *Vet. Rec.* **135**, 40–41.

Wells, G. A. H., Hawkins, S. A. C., Green, R. B., Austin, A. R., Dexter, I., Spencer, Y. I., Chaplin, M. J., Stack, M. J. & Dawson, M. 1998 Preliminary observations on the pathogenesis of experimental bovine spongiform encephalopathy (BSE): an update. *Vet. Rec.* **142**, 103–106.

Wilesmith, J. W., Wells, G. A. H., Ryan, J. B. M., Gavier-Widen, D. & Simmons, M. M. 1997 A cohort study to examine maternally associated risk factors for bovine spongiform encephalopathy. *Vet. Rec.* **141**, 239–243.

Will, R. G., Ironside, J. W., Zeidler, M., Cousens, S. N., Estibeiro, K., Alperovitch, A., Poser, S., Pocchiari, M., Hofman, A. & Smith, P. G. 1996 A new variant of Creutzfeldt–Jakob disease in the UK. *Lancet* **347**, 921–925.

Zeidler, M., Stewart, G., Cousens, S. N., Estibeiro, K. & Will, R. G. 1997 Codon 129 genotype and new variant CJD. *Lancet* **350**, 668.

As this paper exceeds the maximum length normally permitted, the authors have agreed to contribute to production costs.