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Estimation of the basic reproduction number of BSE: the intensity of transmission in British cattle

N. M. Ferguson[1*], C. A. Donnelly[1], M. E. J. Woolhouse[2] and R. M. Anderson[1]

[1] *Wellcome Trust Centre for the Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK* (*neil.ferguson@zoo.ox.ac.uk*)

[2] *Centre for Tropical Veterinary Medicine, University of Edinburgh, Easter Bush, Roslin, Midlothian EH25 9RG, UK*

The basic reproduction number, R_0, of an infectious agent is a key factor determining the rate of spread and the proportion of the host population affected. We formulate a general mathematical framework to describe the transmission dynamics of long incubation period diseases with complex pathogenesis. This is used to derive expressions for R_0 of bovine spongiform encephalopathy (BSE) in British cattle, and back-calculation methods are used to estimate R_0 throughout the time-course of the BSE epidemic. We show that the 1988 meat and bonemeal ban was effective in rapidly reducing R_0 below 1, and demonstrate that this indicates that BSE will be unable to become endemic in the UK cattle population even when case clustering is taken into account. The analysis provides some insight into absolute infectiousness for bovine-to-bovine transmission, indicating maximally infectious animals may have infected up to 400 animals each. The relationship between R_0 and the early stages of the BSE epidemic and the requirements for additional research are also discussed.

Keywords: BSE; reproduction number; epidemiology; epidemic model

1. INTRODUCTION

Over 172 000 confirmed cases of BSE had been reported in British cattle by January 1998. Whilst the effect of the epidemic on animal health and European agriculture has been severe, greatest concern now centres around the potential implications for human health, given evidence supporting a link between BSE and a new variant of Creutzfeldt–Jakob Disease (vCJD) in humans (Collinge *et al.* 1996; Bruce *et al.* 1997; Hill *et al.* 1997).

It is particularly important to public health and agricultural policy makers to establish that BSE in Great Britain (GB) is in permanent decline, and that no potential exists for the disease to persist endemically via direct horizontal and vertical transmission within the GB cattle herd. Such epidemiological considerations will directly affect decisions on the relaxation of the export ban on GB cattle and measures to limit human exposure to potentially infected animals (including the ban on the consumption of beef from older animals and the ban on beef on the bone). The fundamental epidemiological quantity determining whether an infectious disease will persist in a host population is the basic reproduction number, R_0 (Anderson & May 1991). This is defined as the expected number of secondary infections caused in an entirely susceptible population by a typical infected host. R_0 is a key factor in determining how fast an infection will spread in a population previously unexposed to that pathogen, and the total proportion of the population which will be infected once the infection becomes endemic. If $R_0 > 1$, the infectious agent has the potential to persist indefinitely, whilst if $R_0 < 1$, the incidence of infection will decay to zero. The reason is clear: if any one primary infection is unable to generate at least one replacement secondary infection, the numbers of infected hosts in the population will inevitably decline through time.

This paper represents the most comprehensive analysis to date estimating R_0 for BSE from the case data (but see Woolhouse & Anderson 1997). For many models of human diseases, R_0 is often assumed to be unchanging through time, though long-term changes in human demography mobility and behaviour (Anderson & May 1991; Noin & Woods 1993) make this approximation invalid over time-scales of more than a few decades. R_0 for BSE is likely to have changed dramatically in value throughout the course of the epidemic, however, due to various interventions designed to halt transmission. The route of transmission was also unusual, namely through the recycling of infectious bovine tissues back into bovine feed via the rendering and feed manufacturing industries. Changes in the feed industry (Wilesmith *et al.* 1991) are therefore also likely to have had considerable and rapid effects on the efficiency of transmission and hence R_0.

Much research effort is being directed towards estimating the potential magnitude of the past exposure of the human population to infectious material. However, the uncertainties in key epidemiological parameters are currently too large to allow precise risk assessment. In particular, very little information is available on the

*Author for correspondence.

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infectiousness of infected bovine tissues to humans and the incubation period of vCJD. Much of the limited information currently available is derived from studies using bovine, mouse or primate animal models (Fraser *et al.* 1992; Lasmezas *et al.* 1996; Wells *et al.* 1998). This paper sheds further light on the efficiency of the bovine-to-bovine infection process (and thereby within-species infectiousness), by calculating the expected number of infections, caused by an infected animal at a particular point in its incubation period, needed to produce a BSE epidemic consistent with the reported case data. We show that such estimates (together with estimates of R_0 itself) are highly dependent on assumptions made about how the infectivity of affected tissues increases as the disease progresses. In particular, if infectivity is mainly confined to the end of the incubation period (as is suggested, though not proven, by interim results from a study of BSE pathogenesis in cattle (Dawson *et al.* 1990; Wells *et al.* 1994, 1998)), the absolute infectiousness of such animals is shown to have been very high to generate the observed epidemic. This reinforces the results from the continuing oral dosing studies of cattle (Anderson *et al.* 1996) which suggest that an LD_{50} dose of less than 1 g of brain homogenate is needed for bovine-to-bovine transmission via oral exposure.

Even allowing for a substantial species barrier reducing the efficiency of transmission from bovines to humans, this analysis has implications for vCJD risk assessment: if all BSE-infected animals were equally infectious, the temporal pattern of human exposure would have closely tracked the epidemic of new infections in cattle (Anderson *et al.* 1996), with exposure peaking in 1989–90—largely prior to the introduction of the 'specified bovine offal' (SBO) ban introduced to protect human health (Bovine Offal Regulations 1989). If, however, significant infectivity were only found in late-incubation-stage animals, human exposure would have tracked BSE case incidence, peaking in 1992–93—after the SBO ban.

The origins of the BSE epidemic in GB are the subject of much speculation at the moment (BSE Inquiry 1998; Dickson 1998). The analyses presented here shed some additional light on this topic, by addressing the question of the type and timing of infection source which would have been required to start the epidemic in a manner consistent with a relatively constant value of R_0 in the earliest stage of the epidemic. We discuss when a single 'cross-over' event (from sheep scrapie, for instance) might have occurred, together with the hypothesis that some low-level external source of infection (from a sporadic bovine spongiform encephalopathy) acted over several years to generate the epidemic. The uncertainties surrounding the origin of BSE and the need for additional research are highlighted.

2. METHODS

We use the backcalculation model described in earlier papers (Anderson *et al.* 1996; Ferguson *et al.* 1997) to estimate the infection hazard (or 'force of infection') for BSE experienced by GB cattle between 1980 and 1996. This, together with a model for the infectivity of cattle as a function of incubation stage, is then used to estimate the transmission coefficient of BSE through the feed-borne route, β_F, and so the basic reproduction number via that route, R_0^{FF}. We follow the notation used in Ferguson *et al.* (1997).

Unlike our earlier backcalculation studies, estimation of R_0 requires explicit consideration of the infectivity recycling ('feedback') process that gave rise to the BSE epidemic, not just estimation of a past temporal trend of infection hazard (feed risk). More precisely, we explore epidemic models which are capable of reproducing the force of infection estimates generated by the backcalculation model. One aim of this work is to introduce to a wider community than hitherto the methodology required for modelling long (non-exponentially distributed) incubation period diseases with potentially complex relationships between incubation stage and infectiousness (sheep scrapie (Woolhouse *et al.* 1998) is another example). The analysis presented below is therefore made as general (and thus widely applicable to other disease systems) as possible; a more mathematically rigorous discussion of the derivation of R_0 for structured populations can be found in a variety of other papers (Diekmann *et al.* 1990; Heesterbeek & Dietz 1996).

(a) *The epidemic model*

Let $Q(t,a)$ be the total infection hazard experienced at time t by susceptible hosts of age a, and $p_I(t_0,a)$ be the probability that an animal born at time t_0 is infected by age a, in the absence of mortality. Then

$$\frac{\partial p_I(t_0,a)}{\partial a} = Q(t_0+a,a)(1-p_I(t_0,a)). \tag{1}$$

Note that this equation has the solution

$$p_I(t_0,a) = \int_0^a Q(t_0+a',a')\mathrm{e}^{-\int_0^{a'} Q(t_0+a'',a'')\mathrm{d}a''}\mathrm{d}a'. \tag{2}$$

In general, $Q(t,a)$ is made up of contributions from multiple transmission routes—feed-borne (F), maternal (M) and direct horizontal (H): i.e. $Q(t,a) = \sum_{i=F,M,H} Q_i(t,a)$. Let us now consider the form of the hazard function for the direct horizontal transmission route, postponing consideration of age-dependent susceptibility. The hazard at any time t is proportional to the fraction of animals alive at that time which are infected, weighted by the relative infectivity of those animals and the transmission coefficient through the horizontal route:

$$Q_H(t,a) = \beta_H(t)\int_0^t\int_0^{a'} \frac{n(t,a')}{N(t)}\psi_H(\tau)p_I'(t-a',a'-\tau)\mathrm{d}\tau\mathrm{d}a'. \tag{3}$$

Here, $n(t,a')$ is the density of hosts of age a' in the population at time t, such that $N(t) = \int_0^\infty n(t,a')\mathrm{d}a'$ is the total population size at time t, $\beta_H(t)$ is the transmission coefficient for horizontal transmission from a maximally infectious host at time t, $\psi_H(\tau)$ is the relative infectivity (here standardized to have a maximum value of 1) of a host at time τ after infection, and $p_I' = \partial p_I(t_0,a)/\partial a$, the probability density function (PDF) for infection at age a, for an animal born at time t_0. p_I' can also be thought of as the age-specific per-capita incidence of infection for hosts born at time t_0.

This form of infection hazard assumes 'mass-action' mixing (De Jong *et al.* 1995), namely that the infection hazard experienced by any host is proportional to the proportion of all contacts that are with infectious animals, and that animals of all ages mix homogeneously. The latter assumption means that the infection hazard experienced by any individual is proportional to the fraction of the population which is infectious. This

explains the origin of the $\mathcal{N}(t)$ denominator in equation (3). Mass-action implies global mixing of all cattle feed, with infectivity being evenly distributed within the feed. § 3 discusses the effect of relaxing this assumption (see also Hagenaars *et al.* 1999).

Note that $n(t,a')$ is given by

$$n(a',t) = B(t-a')S(t-a',a'), \tag{4}$$

where $B(t_0)$ is the birth rate of cattle at time t_0, and $S(a',t_0)$ is the probability that a bovine born at time t_0 survives to age a'. For later ease of notation we define the PDF for the age, a', of animals alive at time t to be

$$\sigma_H(t,a') = n(t,a')/\mathcal{N}(t). \tag{5}$$

We can now express $p'_I(t)$ in terms of the infection hazard experience prior to time t. From equation (2),

$$p'_I(t_0,a') = Q(t_0+a,a)\mathrm{e}^{-\int_0^a Q(t_0+a',a')\mathrm{d}a}. \tag{6}$$

In the absence of transmission routes other than horizontal, putting equations (3) and (6) together gives an integral equation for the time evolution of the infection hazard:

$$\begin{aligned} Q_H(t,a) = \beta_H(t) \int_0^t \int_0^{a'} \sigma_H(t,a')\psi_H(\tau)Q_H(t-\tau,a'-\tau) \\ \times \exp\left[-\int_0^{a'-\tau} Q_H(t-a'+a'',a'')\mathrm{d}\tau\mathrm{d}a'\right]. \end{aligned} \tag{7}$$

Whilst this equation can be rewritten as a set of time-delayed partial differential equations, we prefer the above form due to its simple interpretation in terms of 'generations' of infections and its easy application to backcalculation analysis.

In the simple case of $\psi_H(\tau) = \mathrm{e}^{-\tau/T}$, an exponentially distributed infectious period, this equation can be reduced to the simple Kermack & McKendrick SI (susceptible–infected) model (Kermack & McKendrick 1927; Anderson & May 1991). However, for BSE, the relationship between the infection hazard, Q, and the profile of infection prevalence in the host population, p_I, is considerably more complex than for the simple SI model. We need to allow for age-dependent susceptibility to infection, which gives

$$Q_H(t,a) = g_H(a)\beta_H(t) \int_0^t \int_0^{a'} \sigma_H(t,a')\psi_H(\tau)p'_I(t-a',a'-\tau)\mathrm{d}\tau\mathrm{d}a', \tag{8}$$

where $g_H(a)$ is the relative susceptibility of an animal of age a. We can write this as

$$Q_H(t,a) = g_H(a)r_H(t). \tag{9}$$

Note that our ability to separate the age- and time-varying components of the infection hazard in equation (9) considerably simplifies the following analysis.

A very similar expression to equation (8) is obtained for the feed-based and maternal transmission route hazards, Q_F and Q_M. For $i = F,M$,

$$Q_i(t,a) = g_i(a)r_i(t). \tag{10}$$

Here, $r_i(t)$ is given by

$$r_i(t) = \beta_i(t) \int_0^t \int_0^{a'} \sigma_i(t,a')\psi_i(\tau)p'_I(t-a',a'-\tau)\mathrm{d}\tau\mathrm{d}a', \tag{11}$$

where we have used the i subscript to signify potentially route-dependent parameters. $\sigma_F(t,a)$ is the PDF of the age at slaughter for animals slaughtered at time t,

$$\sigma_F(t,a) = \frac{B(t-a')\dfrac{\mathrm{d}S}{\mathrm{d}a}(a,t-a)}{\int_0^\infty B(t-a')\dfrac{\mathrm{d}S}{\mathrm{d}a}(a',t-a')\mathrm{d}a'}, \tag{12}$$

whilst $\sigma_M(t,a)$ is the PDF of the age at calving of dams giving birth at time t,

$$\sigma_M(t,a) = \begin{cases} 0, & a \leqslant 2 \\ \dfrac{B(t-a)S(a,t-a)}{\int_0^\infty B(t-a')S(a',t-a')\mathrm{d}a'}, & a > 2 \end{cases}. \tag{13}$$

This latter equation assumes only animals over two years of age produce offspring, and that the great majority of animals over two years of age are female.

It should be noted that all the above expressions for infection hazards via different transmission routes assume animals are only infectious prior to disease onset. For feed-based transmission this is an approximation, especially in the early years of the epidemic, since it is likely that many of the carcasses of undiagnosed/unreported cases may have been recycled for animal feed, even if not passed fit for human consumption. We do not present here the more complicated expressions for the feed-based hazard, including recycling of non-reported cases, but the effect of including such a term is discussed in more detail at the end of § 3c.

Note that, given estimates of $r_F(t)$ (termed the 'feed risk profile' in Anderson *et al.* (1996) and Ferguson *et al.* (1997)) and $\psi_F(\tau)$, equations (11) and (6) allow $\beta_F(t)$ to be estimated:

$$\begin{aligned} \beta_F(t) = r_F(t) \Big/ \Bigg[\int_0^t \int_0^{a'} \sigma_F(t,a')\psi_F(\tau)Q(t-\tau,a'-\tau) \\ \times \exp\left[-\int_0^{a'-\tau} Q_H(t-a'+a'',a'')\mathrm{d}\tau\mathrm{d}a'\right]\Bigg]. \end{aligned} \tag{14}$$

However, if one assumes that infectivity peaks at the onset of clinical symptoms, it is useful to specify infectivity in terms of the time remaining until clinical onset of BSE, rather than in terms of the time since infection. Defining $\Omega_i(\nu)$ to be the infectivity at time ν prior to disease onset, $\psi_i(\tau)$ is obtained by convoluting $\Omega(\nu)$ with the incubation period distribution PDF, $f_i(u)$:

$$\psi_i(\tau) = \int_0^\infty f_i(\nu+\tau)\Omega_i(\nu)\mathrm{d}\nu. \tag{15}$$

(b) *Derivation of R_0*

For the simple Kermack & McKendrick SI model with exponentially distributed infectious period and time-invariant transmission coefficient, $R_0 = \beta T$, where T is the mean infectious period. Variants of this form of R_0 are applicable for the vast majority of epidemic models in use today (Anderson & May 1991). However, the time-varying nature of the transmission coefficient, the complex (non-exponential) infectious and incubation period distributions, and age-dependency in susceptibility to infection make derivation of R_0 more complex for BSE. The key to the analysis is the procedure used to average over all possible primary and secondary infection types. By infection 'type', we mean the age of the animal at infection, the time of infection and the route through which infection occurred.

It is also important to define what is meant by the time, t, at which an estimate $R_0(t)$ is made. In the mathematical derivation which follows we use the most straightforward and commonly

used definition, where t is the time of infection of the primary host. However, since the majority of animals in the BSE epidemic were infected via consumption of dead animal tissue, this definition can give somewhat non-intuitive results, since the value of R_0 at time t then corresponds to infections occurring at time $t+2$ years or later (given that most animals are infected in the first year of life, and are slaughtered at two years of age or later). We therefore extend our derivation to define $R_0(t_s)$, where t_s represents the date of slaughter of the primary infection, as t_s is more temporally correlated with the generation of secondary infections. We then use this form when presenting the results of our analyses.

Note also that in this paper we are defining R_0 in terms of the numbers of secondary infections caused by a primary infection, rather than the cases per case definition used for direct horizontal transmission in Ferguson *et al.* (1997). Both definitions give the same values of R_0 in the case of non-varying transmission coefficients and for the maternal or direct horizontal transmission routes, but the case-per-case definition is rather counter-intuitive for the feed-borne route, since only animals slaughtered prior to identification as a BSE suspect were able to infect other animals through that route.

In determining the age distribution of primary infections through transmission route i (where $i=F,M,H$), we assume that the entire population alive at time t is subject to an infinitesimal infection hazard. In the absence of mortality, the age distribution of primary infections will just be given by the relative susceptibility–exposure of an animal of age a, $g(a)$ (normalized to be a PDF over the lifespan of the host). Allowing for mortality, the age distribution at time t is given by

$$q_i(t,a)=\frac{g_i(a)\sigma_H(t,a)}{\int g_i(a')\sigma_H(t,a')\mathrm{d}a'}=\frac{g_i(a)n(t,a)}{\int g_i(a')n(t,a')\mathrm{d}a'}. \tag{16}$$

We then consider one host drawn from this distribution infecting another host at time $t+\tau$ through transmission route j. The probability that this event occurs is the product of various elements: the probability that the primary infection will survive to age $a+\tau$ (for horizontal or maternal transmission routes) or be slaughtered at age $a+\tau$ (for the feed-based transmission route), given that the animal survived to age a; the proportion of alive, or dead (depending on transmission route), hosts at time $t+\tau$ represented by this one infected animal (this is required because, under the mass-action formulation, infection hazard is proportional to the fraction of hosts infected); the transmission coefficient via route j; the relative infectiousness via route j of an animal at time τ after infection (assumed here to be independent of the route by which the primary case was infected); the susceptibility of secondary hosts of age a'; the number of hosts of age a' at time $t+\tau$. Symbolically, for the direct horizontal transmission route ($j=H$) this is expressed as

$$\begin{aligned}R_0^{iH}(t)=&\int_0^\infty\int_0^\infty\int_0^\infty q_i(t,a)\frac{S(a+\tau,t-a)}{S(a,t-a)}\frac{1}{\mathcal{N}(t+\tau)}\\&\times\beta_H(t+\tau)\psi_H(\tau)g_H(a')n(t+\tau,a')\mathrm{d}a'\mathrm{d}\tau\mathrm{d}a.\end{aligned} \tag{17}$$

Using equations (5) and (16), this can be rewritten in the form

$$\begin{aligned}R_0^{iH}(t)=&\int_0^\infty\int_0^\infty\frac{W_H(t+\tau)}{W_i(t)}g_i(a)\sigma_H(t+\tau,a+\tau)\\&\times\beta_H(t+\tau)\psi_H(\tau)\mathrm{d}\tau\mathrm{d}a,\end{aligned} \tag{18}$$

where $W_i(t)$ is defined as

$$W_i(t)=\int_0^\infty g_i(a')B(t-a')S(a',t-a')\mathrm{d}a'. \tag{19}$$

More generally, for primary infections via transmission route i, and secondary infections through route j, R_0^{ij} can be shown to be given by

$$R_0^{ij}(t)=\int_0^\infty\int_0^\infty\frac{W_j(t+\tau)}{W_i(t)}g_i(a)\sigma_j(t+\tau,a+\tau)\beta_j(t+\tau)\psi_j(\tau)\mathrm{d}\tau\mathrm{d}a. \tag{20}$$

Note that, if the birth rate, $B(t)$, and survivorship, $S(a,t_0)$, are independent of time, the expression for R_0^{ii} simplifies to the type of expression given in Heesterbeek & Dietz (1996):

$$R_0^{ii}=\int_0^\infty\int_0^\infty g_i(a)\sigma_i(t,a)\beta_j(t+\tau)\psi_i(\tau)\mathrm{d}\tau\mathrm{d}a. \tag{21}$$

Given the three potential transmission routes of BSE, we have been left with a 3×3 matrix of R_0^{ij} values. In this situation, the global R_0 value obtained by 'averaging' over transmission routes is given by the dominant eigenvalue of the R_0^{ij} matrix (Heesterbeek & Dietz 1996). This is the same procedure as is used when calculating R_0 for any system with discrete heterogeneity and between-class mixing (e.g. discrete age-structure in childhood disease models or sexual activity classes in sexually transmitted disease models (Anderson & May 1991)). In essence, the dominant eigenvalue corresponds to the multiplication factor seen between adjacent generations of infection for the (quasi-stationary) growth of an epidemic in an infinite host population.

It is also worth noting that we have adopted the simplifying assumption above that the infectiousness through route j at time τ after infection, $\psi_j(\tau)$, is independent of the route by which that animal was itself infected. Given equation (15), this implicitly assumes that the incubation period of BSE does not depend on the route of infection. Comparing the limited data from the MAFF maternal cohort study (Wilesmith *et al.* 1997; Donnelly *et al.* 1997*c*; Curnow *et al.* 1997; Gore *et al.* 1997) with data from the BSE case database, there is no evidence of a significant difference in incubation periods by likely infection route, but the limited sample size and confounding factors mean this possibility cannot be excluded. However, given the low estimated probability of maternal transmission, any such effect will, in any case, have a neglible impact on the transmission dynamics of the pathogen.

Up until now, our derivations of $R_0^{ij}(t)$ have defined t to be the time at which the primary case was infected. Defining an $R_0^{ij}(t_s)$ where t_s is the time of slaughter of the primary infection is straightforward in the case $j=F$, since secondary infection can only occur on the death of the primary infected animal:

$$R_0^{iF}(t_s)=\beta_F(t_s)\int_0^\infty\int_0^\infty\frac{W_F(t_s)}{W_i(t_s-\tau)}g_i(a)\sigma_F(t_s,a+\tau)\psi_F(\tau)\mathrm{d}\tau\mathrm{d}a. \tag{22}$$

It is more complex to change time coordinates in the case of maternal or direct horizontal secondary infections, however, and so we omit the details here.

Lastly, it will prove informative to examine the average number of secondary infections caused (in an entirely susceptible population) by one maximally infectious (i.e. $\psi_F(\tau)=1$) animal which is slaughtered prior to disease onset, $I^{iF}(t_s)$:

$$I^{iF}(t_s)=\beta_F(t_s)\int_0^\infty\int_0^\infty\frac{W_F(t_s)}{W_i(t_s-\tau)}g_i(a)\sigma_F(t_s,a+\tau)\mathrm{d}\tau\mathrm{d}a. \tag{23}$$

3. RESULTS

We focus on the feed-borne transmission route alone in presenting these results: analyses of the MAFF maternal cohort study (Wilesmith *et al.* 1997; Donnelly *et al.* 1997*c*; Curnow *et al.* 1997; Gore *et al.* 1997), and of dam–calf pairs in the BSE database (Donnelly *et al.* 1997*a*), indicate maternal transmission occurs at a rate that will contribute negligibly (<0.01) to the total R_0 value for BSE. The potential for direct horizontal transmission (for which no evidence exists) to enable persistence of BSE has already been discussed in Ferguson *et al.* (1997), where an upper bound of $R_0^{HH} = 0.15$ was estimated.

We use a refined version of the backcalculation model of Ferguson *et al.* (1997) (assuming $r_F(t) = 0$, for $t < 1980$), to obtain estimates of $r_F(t)$ whilst exploring a variety of infectivity assumptions (which determine the form of $\psi_F(\tau)$). The baseline estimates are shown in figure 1. The parametric and functional assumptions used in deriving these estimates are described in detail in Ferguson *et al.* (1997), but it is relevant to repeat here that we only allow for underreporting prior to mid-1988, the time when BSE became a notifiable disease.

Our principal aim here is to demonstrate how different assumptions about the relative infectivity of cattle at different incubation stages affect our estimates of R_0 and related quantities, and the implications of these results. We present results from two infectivity models. The first assumes infectivity rises exponentially throughout the incubation period, with a growth coefficient of two per year (i.e. $\Omega_F(\nu) = \mathrm{e}^{-2\nu}$). Given the equivalent interpretation of $1 - \Omega_F(\nu)$ as the cumulative distribution function for the duration of infectiousness, this model corresponds to a mean duration of infectiousness of six months at the end of the incubation period. The second model assumes animals are equally infectious throughout their incubation period ($\Omega(\nu) = 1$, for $0 \leqslant \nu \leqslant a_{\max}$, and $\Omega(\nu) = 0$, for $\nu > a_{\max}$, where $a_{\max}$ is the maximum lifespan of an animal).

These models are chosen as representing epidemiological extremes, in the sense that intermediate models (e.g. exponential growth of infectivity, with a growth rate of 0.5 per year) give epidemiological estimates (e.g. of R_0) that lie between those obtained from these scenarios. Similarly, if one scales the mean duration of infectiousness below six months, R_0 estimates are correspondingly increased. It should also be noted that whilst an exponential is used here, the results are relatively insensitive to the function form of $\Omega(\nu)$: assuming a step function (zero infectivity until the last six months of incubation, and constant infectivity thereafter) gives very similar results. A six-month mean infectious period was chosen for the first model as being most consistent with current experimental data on BSE pathogenesis (Wells *et al.* 1998), results from the BSE maternal cohort study (Wilesmith *et al.* 1997; Donnelly *et al.* 1997*c*; Curnow *et al.* 1997; Gore *et al.* 1997), and analysis of dam–calf pairs in the BSE case database (Donnelly *et al.* 1997*a*). The pathogenesis data suggest that infectivity titres in central nervous system tissues grow rapidly in the last few months of incubation, whilst the latter analysis indicates that the enhanced risk of BSE experienced by the offspring of BSE affected dams also increases dramatically in the last stages of the maternal incubation period—suggesting a corresponding increase in infectious titres in that period.

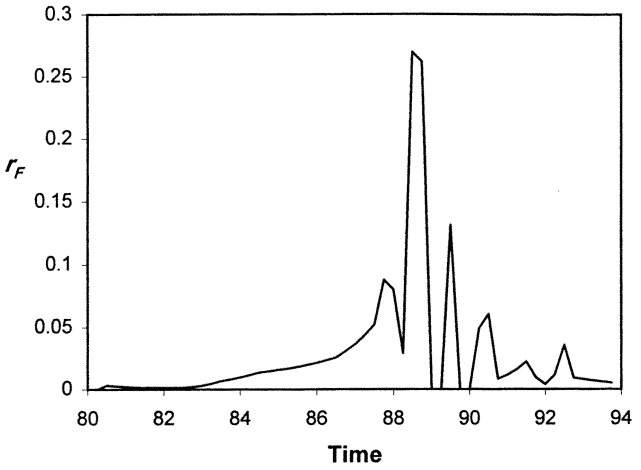

Figure 1. Backcalculation model estimates of feed–risk profile, $r_F(t)$ from 1980–1993, calculated from a model with no horizontal or maternal transmission, or 'external' infection hazard. Estimates of $r_F(t)$ prior to 1980 are not significantly different from zero.

(a) *Transmission dynamics and persistence of BSE*

Figure 2 shows estimated annual average $R_0^{FF}(t_s)$ values from 1983–1993 under the assumption of entirely feed-borne transmission. Annual averages are used because of the considerable seasonality seen when finer time stratifications are used. Values after 1993 cannot reliably be estimated due to the limited number of BSE cases that have yet been diagnosed from post-1993 birth cohorts. The extrapolation techniques used in Anderson *et al.* (1996) and Ferguson *et al.* (1997) inevitably send $R_0 \to 0$ in August 1996, by assuming enhanced implementation of control measures would have meant $r_F(t)$ was zero after that time. Prior to 1989, the higher values of R_0 seen under the first infectivity scenario (figure 2*a*) are due to the increased 'generation time' between infections under that model: when infectivity is restricted to the end of the incubation period, the average time between an animal being infected and when it infects other animals is in the order of five years (the mean incubation period of BSE), whilst if animals are equally infectious throughout the incubation period, this time is around one to two years (most animals are slaughtered at around two years of age).

Figure 2*c*,*d* shows the effect of relaxing our previous assumption that infected animals were only recycled into ruminant-based meat and bonemeal (MBM) if they were slaughtered prior to the onset of symptoms. By definition, the heads (and, after mid-1988, the whole carcasses) of diagnosed BSE cases were never recycled, since the basis of diagnosis was always neuropathological examination at the UK Central Veterinary Laboratory. However, it is unclear what proportion of carcasses from non-reported BSE cases were processed in the usual way by feed mills or abbatoirs. For that reason, the estimates shown in figure 2*c*,*d* were derived using models that assumed all non-reported BSE cases were processed for MBM, and that such animals were maximally infectious. It can be seen that R_0 estimates are fairly insensitive to this assumption, for the reasons discussed in § 3b.

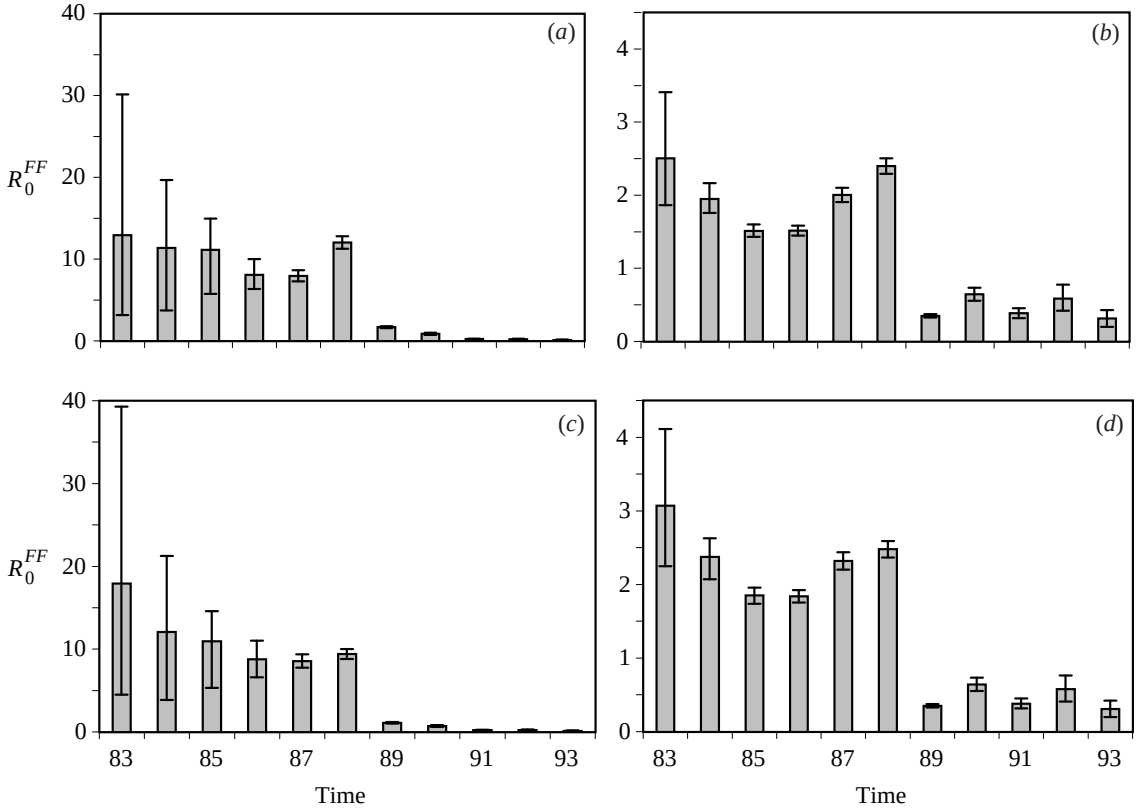

Figure 2. Estimated annual averages of R_0^{FF}, as a function of t_s, the time of slaughter of the primary infection, for 1983–1993. (*a*) Exponentially rising infectivity model; (*b*) constant infectivity model. Error bars were calculated from the backcalculation model using the techniques described in Ferguson *et al.* (1997). (*c*, *d*) (as (*a*) and (*b*)), but using a model which assumes all non-reported case carcasses are recycled for cattle feed. The difference in vertical scale between (*a*, *c*) and (*b*, *d*) should be noted.

The temporal trends in R_0 revealed by figure 2 are broadly consistent with a relatively unchanging epidemic process (roughly constant R_0) prior to the introduction of the ban on the use of MBM in feed (BSE Order 1988)—at least for the exponentially increasing infectivity model—then with a dramatic fall in the efficiency of feed-borne transmission. That stated, the fluctuations seen in R_0 prior to 1988 are significant, even allowing that the confidence limits shown are narrower than those which would be obtained from a (computationally infeasible) calculation of the full multivariate confidence region around the best-fit point of the backcalculation model (see Ferguson *et al.* (1997) for details of how confidence limits are calculated). In particular, the dip in R_0 seen in 1985–1986 requires explanation, especially for the model assuming constant infectivity throughout the incubation period. This will probably only be found from analyses of BSE transmission dynamics which examine transmission heterogeneity—in particular, case clustering at the herd level (Donnelly *et al.* 1997*b*, 1999) and potential spatial processes underlying epidemic spread.

Under both infectivity models, R_0 falls dramatically following the introduction of the ruminant feed ban in 1988 (BSE Order 1988), dropping to below 1 by 1990, and below 0.5 by 1993. Indeed, for the more realistic infectivity model (figure 2*a*), $R_0 < 0.15$ in 1993. This is the same bound as was found in the analysis of potential direct horizontal transmission in Ferguson *et al.* (1997). In that analysis, when $R_0^{HH} \simeq 0.15$, virtually all transmission in 1993 was estimated to have been through that route—i.e. even when multiple transmission routes are allowed for, the maximum bound on the total R_0 value was approximately 0.15 in 1993.

These estimates of R_0 suggest that BSE will not become endemic in the UK. Again, however, it should be remembered that the models used assume homogeneous mixing of cattle and cattle feed in the UK. To what extent might heterogeneity in transmission provide a mechanism allowing pockets of $R_0 > 1$ transmission to remain? Under the hypothesis that only a closed subpopulation of the UK cattle herd was ever exposed to infected MBM (and thereby reducing the effective population size within which the epidemic occurred), estimated R_0 values change little. Similarly, if one makes the reasonable assumption that the effect of the MBM was not to lower infectivity in that MBM which was still being produced, but to reduce the proportion of the cattle population exposed, the only way in which R_0 might remain above 1 in that exposed subpopulation would be if the recycling process was entirely local: e.g. if the MBM consumed by cattle in one holding was manufactured from cattle in that holding. Under this, or most other scenarios in which a subpopulation is suffering BSE transmission with $R_0 > 1$, one would have expected to see an increase in the degree of case clustering (Donnelly *et al.* 1997*b*, 1999) following the MBM ban. However, statistical analysis of clustering at the herd level has so far failed to reveal any significant difference between the degree of clustering seen before and after the MBM ban (Donnelly *et al.* 1997*b*).

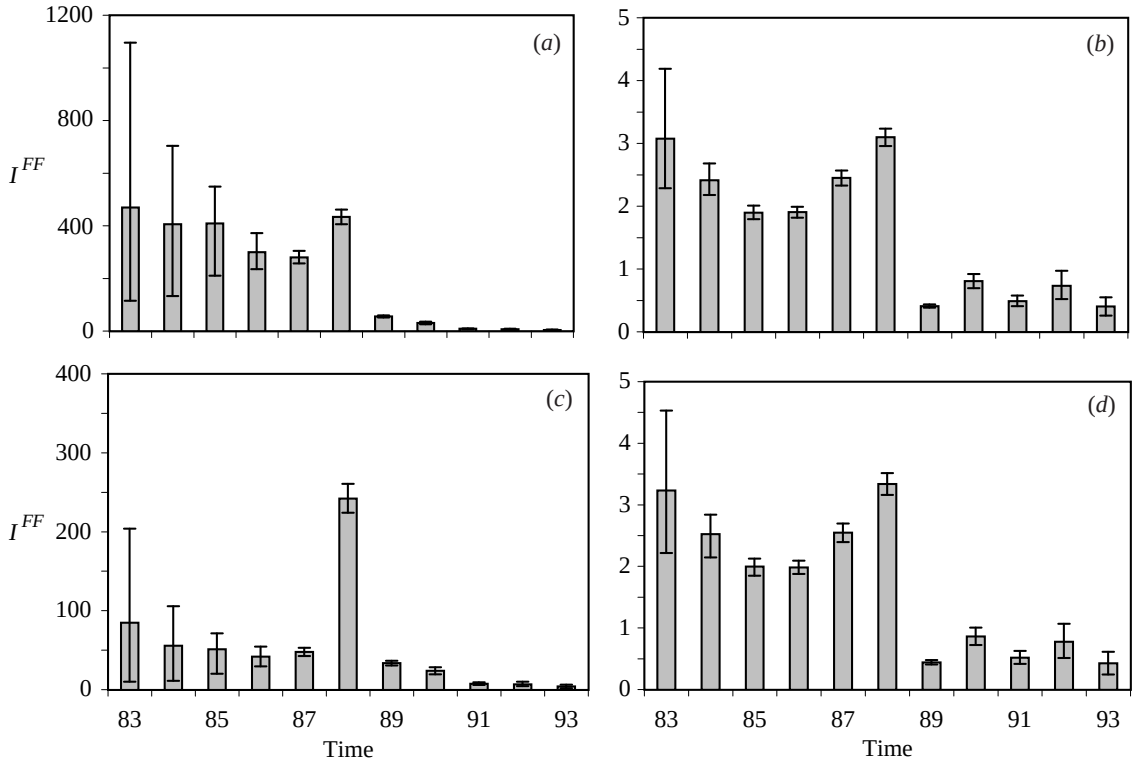

Figure 3. Estimated annual averages of I^{FF}, the average number of animals infected by a maximally infectious bovine in an entirely susceptible population, as a function of time of slaughter of the infectious bovine. (*a*) Exponentially rising infectivity model; (*b*) constant infectivity model. (*c*, *d*) (as (*a*) and (*b*)), but using a model which assumes all non-reported case carcasses are recycled for cattle feed.

(b) *Infectiousness of cattle through the feed-borne transmission route*

Figure 3*a*,*b* shows estimated annual averages of I^{FF}, the expected number of infections per maximally infectious primary infection slaughtered in an entirely susceptible population. As expected, for the model in which infectivity is assumed to be constant throughout the incubation period (figure 3*b*), I^{FF} is very similar in value to R_0, the slight difference being because the calculation of R_0 allows for the proportion (around 20%) of animals which develop BSE symptoms prior to slaughter not being recycled as MBM. However, under the assumption that infectivity is greatest at the end of the incubation period, I^{FF} is much larger than R_0. This is because under this infectivity scenario, the 'typical primary infection' (i.e. an animal slaughtered several years prior to disease onset) has a very low probability of infecting other animals, meaning that the small proportion of cattle which survive to be slaughtered just prior to the onset of symptoms need to generate very large numbers of infections per capita in order to reproduce the growth rate seen in the BSE epidemic. Indeed, the numbers are sufficiently large to imply that feed-based transmission was a highly efficient transmission route, assuming (from ongoing experimental studies of the oral susceptibility of cattle (Anderson *et al.* 1996)) that the oral LD_{50} of brain homogenate for cattle is, say, *ca.* 0.1 g, and given the inevitable dilution of brain material that must have occurred in the feed manufacturing process.

The differences in I^{FF} under these two pathogenesis scenarios reflect the fact that a fixed amount of infectivity (in terms of LD_{50} doses) had to have been consumed by cattle during the BSE epidemic to generate the particular number of cases seen, regardless of how this infectivity was distributed as a function of incubation stage. This effect should be allowed for in vCJD risk assessments when exploring the effect of different bovine tissue infectivity assumptions on past levels of human exposure to infectious material.

Figure 3*c*,*d* shows the same estimates as figure 3*a*,*b*, but calculated under the assumption that all non-reported case carcasses are recyled for MBM. Unlike R_0 estimates, these estimates are very sensitive to this assumption in the case of the six-month infectivity scenario. The reason for this difference in sensitivity is that, for the six-month infectivity scenario, the total number of infectious animals being recycled increases over threefold early in the epidemic, if unreported cases are assumed to be recycled. This lowers the estimate of the transmission coefficient, β_F, and hence the infectivity, since there are now more infectious carcasses available to produce the observed epidemic. Conversely, however, the generation time of the epidemic is relatively unaffected by the additional infectious carcasses, and since the real-time growth rate of epidemic is also fixed (being given by the case data), estimates of R_0 must remain relatively unchanged. This is because the R_0 is essentially given by the product of the real-time growth rate and the generation time.

Figure 3*c* does show somewhat counter-intuitive behaviour, in that I^{FF} rises from *ca.* 60 to 250 in 1988 (when underreporting is assumed to fall to zero after BSE was made notifiable). This tends to suggest that either the underreporting levels estimated by the backcalculation model are unrealistically high (see § 3c), or that only a

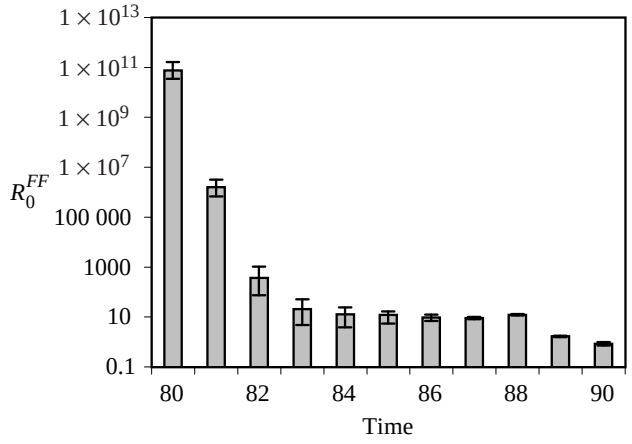

Figure 4. Estimated annual averages of R_0^{FF}, for early stages of the epidemic, showing divergence of estimates prior to 1984 seen for the exponentially rising infectivity model.

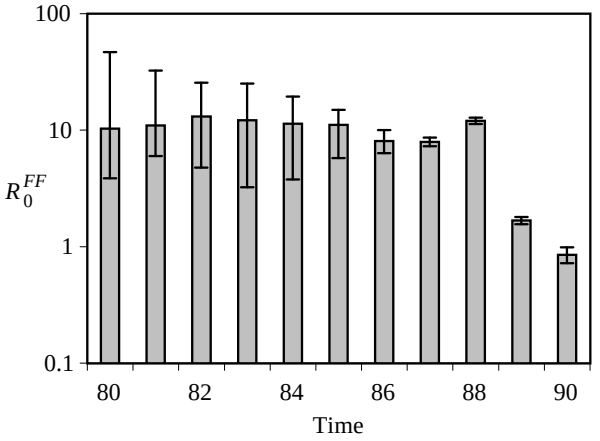

Figure 5. Estimated annual averages of R_0^{FF}, for early stages of the epidemic, obtained using a single origin infection event generating 1500 infections in spring 1977, for the exponentially rising infectivity model. A wide range of timings of initial infection pulses between 1974 and 1979–1980 are capable of generating similar patterns (see text).

minority of non-reported case carcasses were in fact recycled. It is for this reason that we have concentrated on presenting results from models which assume no cases are recycled for MBM.

(c) *Origins and underreporting*

The BSE case database on which the preceding analysis is based reveals a case epidemic appearing 'from nowhere' in 1986. It is inevitable, therefore, that models which do not explicitly include an origin term, yet describe the recycling process, will inevitably break down in trying to explain the origin of the epidemic (even if the significant levels of underreporting which probably occurred in the early 1980s are allowed for). This is reflected by the observation that our estimates of R_0 diverge to increasingly large values for times prior to 1985 when infectivity is largely restricted to the end of the incubation period (figure 4). For the constant infectivity scenario a lack of clear pattern (not shown) reflects the much shorter 'generation time' (period between the infection of one animal and that animal infecting another) of around one year seen under this scenario. A short generation time means that the few cases arising from the 1982 cohort, can, say, be explained as having been generated by infections in the 1981 cohort with R_0 values similar to that seen later in the epidemic. R_0 is automatically zero prior to 1980 due to the assumption used here that r_F is zero prior to that time. For the longer (three- to four-year) generation time of the exponential infectivity model, 1982 cohort infections have to have been largely generated by the very small number of predicted infections in the 1978–1979 cohorts. This results in very large R_0 estimates for the 1980–1982 cohorts. Put another way, the backcalculation model estimates that there were so few infections in the very early cohorts that R_0 would have had to have been very high to allow animals from those cohorts to generate the many more infections seen in later cohorts.

This effect enables us to explore the extent to which differing source terms for BSE might generate values of R_0 that remain relatively constant up to the introduction of the MBM ban. We model possible origins of BSE by considering one additional transmission hazard, $Q_E(t,a)$, representing a feed-based risk of infection from an 'external' source—e.g. sheep scrapie or a sporadic spongiform encephalopathy of cattle. Different forms of such a hazard can represent different types of origin scenario: a single pulse of infection might represent a single, rare 'cross-over' event from sheep scrapie or a non-bovine transmissible spongiform encephalopathy (TSE), whilst a constant low-level background risk might represent the effect of some low frequency sporadic TSE of cattle, or some low prevalence strain of scrapie capable of infecting cattle. The model used here is not capable of distinguishing these scenarios, in that a wide range of different durations of external hazard are capable of generating constant R_0 values early in the epidemic—ranging from a single pulse some time between 1974 and 1978 to a continuous background risk from 1974 to the introduction of the MBM ban. Figure 5 shows an example of such a scenario, for a single pulse of infection in 1977. It should be noted that pulses starting post-1980 are unable to generate constant R_0 estimates from 1981–1982 onwards due to the three- to four-year generation time of the epidemic under the exponentially increasing infectivity scenario.

For the >200 origin scenarios (which sampled a variety of magnitudes, start and stop dates for the external hazard) explored for each infectivity scenario, at least 1500 BSE infections (either caused by the external hazard, or by recycling within the bovine population) were required to have occurred prior to 1980 to produce a constant R_0 profile in the early 1980s. The backcalculation model is therefore only able to maintain its quality of fit to the BSE case data by estimating very high levels of underreporting prior to 1986 (before which date no BSE cases were reported). It is open to question as to how reasonable it is to assume that a novel disease would only have been identified after over 300 cases had occurred (the absolute minimum number obtained in the model runs performed: most runs estimated 1000+ unreported cases prior to 1986), even allowing for the somewhat speculative nature of this analysis (note the very large error bars around the estimates of R_0 in the early phase of

the epidemic). That said, it should be noted that only around 70% of BSE cases currently being diagnosed are being confirmed through neuropathological examination as BSE. This demonstrates the difficulties inherent in making a clear diagnosis, and the potential for confusing symptoms with those caused by other (e.g. metabolic) diseases.

Of course, it is clearly possible that changes in the rendering industry or in the spatial distribution of feed in the 1980s did lead to changes in R_0 during the BSE epidemic (as suggested by the as yet unexplained dip in R_0 estimates in 1985–1986). Indeed, it is widely supposed that the changes in rendering practices in the late 1970s (Wilesmith *et al.* 1991) increased the likelihood that an infectious agent could resist the rendering process. However, such a change would cause R_0 to increase early in the epidemic, and therefore could not produce the rapid drop seen in figure 4*a*. Moreover, even in the absence of source terms (and irrespective of which infectivity scenario is adopted), previous work (Ferguson *et al.* 1997) has shown that very high levels of underreporting are required to explain the apparently changing age structure of cases in the first few years of the epidemic. In essence, the average age of onset dropped from around ten years to about six years from the 1980 to the 1984 cohorts, which in the absence of a changing incubation period (and given a narrow age window of high susceptibility–exposure) can only be explained by high levels of underreporting prior to mid-1988.

Given this overall uncertainty, additional research is certainly warranted on how potential changes in the pathogen during the early epidemic might provide an alternative explanation of the observed changing age structure of early cases. In particular, if the BSE epidemic originated from a TSE strain in different species, we might expect 'adaptation' of the pathogen to cattle and a consequent shortening of the incubation period during the first few generations of infection. Examining changing incubation period hypotheses with backcalculation models poses methodological difficulties at present, however. The potential for spatially heterogeneous transmission processes (which gave rise to the observed clustering of BSE cases) to influence the pattern of the early epidemic also requires exploration. As well as explaining shifting age structure, such mechanisms might then also enable the origin date of the BSE epidemic to be brought forward to as late as 1981–1982, and therefore not require such high levels of underreporting to explain the lack of identified cases prior to 1986.

4. CONCLUSIONS

This paper represents the analysis of how the process of recycling bovine tissues in cattle feed gave rise to the BSE epidemic in GB. We have characterized the epidemic process by estimating the basic reproduction number of BSE, R_0. The usefulness of R_0 as a summary statistic for the transmission dynamics of an infectious agent is well known (Anderson & May 1991): it characterizes the rate of growth of an epidemic, gives insight into the proportion of the population which will be affected once the disease becomes endemic, and determines the criteria for disease elimination.

We have demonstrated that BSE was a highly infectious agent through the feed-based route of transmission; under the more realistic of the infectivity models explored (infectivity peaking at the end of the incubation period), $R_0 \simeq 10$–12 prior to the introduction of the first control measures (the MBM ban) in 1988. This result is within the range estimated by earlier work (Woolhouse & Anderson 1997), and suggests that BSE had the potential to infect over 90% of GB cattle exposed to MBM in feed, had control measures not been introduced. Moreover, our analysis gives insight into the absolute infectiousness of late incubation stage animals, indicating that each such animal must have infected up to 400 other animals in order to produce the epidemic seen. From this perspective, the ruminant feed ban introduced in 1988 (BSE Order 1988) appears to have been relatively successful in rapidly reducing transmission to the point where BSE will inevitably be driven to extinction ($R_0 < 1$).

Explicit modelling of the recycling process also allows investigation of possible origins of the BSE epidemic. Our results indicate that the observed case data can be explained by either some constant low-level 'external' source of infection over a period of years, or by a single origin event, but that under either scenario over 1500 animals had to have been infected by 1980. Thus, whether this scenario fits the case data is highly dependent on assuming that underreporting of cases was very high early in the epidemic (Ferguson *et al.* 1997). This result may therefore offer circumstantial evidence that changes in the pathogen early in the epidemic may have played a key role in the transmission dynamics of BSE early on.

The one caveat that must be placed on these conclusions is that the models used assume homogeneous mixing and exposure of the GB cattle population. In fact, significant clustering of BSE cases was seen. However, clustering by itself is insufficient to invalidate our conclusion that BSE will not become endemic (even at a low level) in British cattle—especially given the very low value of $R_0 \simeq 0.15$ estimated for 1993. Clustering can arise due to heterogeneities in exposure alone (but with quasi-global mixing of MBM), or heterogeneities in both exposure and transmission. The latter is required before persistence of BSE in some 'core' subset of cattle is possible. More specifically, the population dynamics of BSE would have to exhibit a rather extreme metapopulation structure: i.e. subsets of cattle (perhaps characterized by spatial regions) would have to be experiencing largely self-contained epidemics, with only weak interactions between these subsets. Had this been the case, and if the effect of the MBM ban had been to merely reduce the proportion of subsets within which BSE transmission continued, one would expect to have seen an increase in case clustering following the MBM ban. The fact that this cannot detected in the case data (Donnelly *et al.* 1999) therefore increases the confidence that can be held in conclusions derived from global models. The extent to which analyses of spatial clustering and transmission processes might shed light on the origin of the epidemic remains to be seen, however.

In conclusion, whilst more detailed research into BSE transmission dynamics—in particular into case clustering patterns and possible changes in the pathogen early in the epidemic—remains of scientific interest, this paper,

together with earlier work (Anderson *et al*. 1996; Donnelly *et al*. 1997*a*,*b*; Ferguson *et al*. 1997) completes a comprehensive analysis of the epidemiology of BSE in GB at the population level. The application of this work to the analysis of vCJD transmission dynamics has been undertaken (Ghani *et al*. 1998*a*,*b*).

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