The flock-to-flock force of infection for scrapie in Britain

Mike B. Gravenor^{1*}, D. R. Cox², Linda J. Hoinville³, Alies Hoek³
and Angela R. McLean^{1†}

¹*Institute for Animal Health, Compton, Berkshire RG20 7NN, UK*

²*Department of Statistics, University of Oxford, Oxford OX1 3TG, UK*

³*Department of Epidemiology, Veterinary Laboratories Agency, New Haw, Addlestone, Surrey KT15 3NB, UK*

A postal survey of British sheep farmers provided information on the proportion of farms that experienced their first case of scrapie in each year between 1962 and 1998. We found no evidence of a large increase in the proportion of scrapie-affected farms prior to, during or following the epidemic of BSE in British cattle. After correcting for between-farm heterogeneity in the probability of acquiring scrapie, we estimated the yearly between-flock force of infection since 1962. The current force of infection is estimated at approximately 0.0045 per farm per year and combined with a simple model of scrapie spread provides an estimate of the average duration of a scrapie outbreak on an individual farm. Considering all farms, the average outbreak lasts for five years, but if only those farms that have cases in animals born on the farm are considered, it lasts 15 years. We use these parameter estimates to compare the proportion of farms with scrapie in time periods of different lengths. In the survey, 2.7% of farms had a case in 1998. The 5.3% of farms reporting having a case between 1993 and 1997 is consistent with the hypothesis that the scrapie force of infection remained constant over this period.

Keywords: scrapie; epidemiology; force of infection; bovine spongiform encephalopathy; mathematical model

1. INTRODUCTION

Scrapie is a fatal disease of sheep that has been endemic in Britain for over 200 years (Stamp 1962). It is a member of the transmissible spongiform encephalopathy (TSE) group of diseases which includes bovine spongiform encephalopathy (BSE or mad cow disease) and the human Creutzfeldt–Jakob disease (CJD). The UK epidemic of BSE (Donnelly & Ferguson 1999), and the link between BSE and variant CJD in humans (Collinge *et al.* 1996; Bruce *et al.* 1997) has sparked interest in the epidemiology of scrapie and there are incentives for producers and, if possible, countries to become scrapie-free.

Control of scrapie has proved notoriously difficult (Detwiler 1992) and eradication programmes require a thorough understanding of the factors that determine the rate of spread between farms. At present these factors are poorly understood. Although scrapie became notifiable in 1993, accurate incidence estimates remained unavailable and it was not even possible to describe how scrapie incidence has changed over the past 20 years (Butler 1998). A recent large-scale anonymous survey of sheep farmers has provided information that can be used to address these deficiencies.

The postal survey was designed primarily to determine the current prevalence of scrapie, investigate risk factors associated with acquiring scrapie and provide background demographic information on the British sheep industry (Hoinville *et al.* 1999, 2000; McLean *et al.* 1999). Here we use the data collected in the survey

to estimate the between-farm scrapie force of infection (FI) and describe how it has changed over time. Temporal trends in the rate farms acquired scrapie during the 1980s and 1990s are used to look for any evidence of increased scrapie risk that coincide with the BSE epidemic in cattle. Estimates of the current FI are incorporated into a simple epidemic model to generate an estimate of the average duration of a scrapie outbreak on an affected farm. The rate farms acquire and eliminate scrapie is used to compare the proportion of flocks that have a case of scrapie in time periods of differing length. The contributions of the postal survey to estimates of the epidemiological parameters of scrapie in Britain are summarized.

2. MATERIAL AND METHODS

(a) *Postal survey data: first-case force of infection (FI₁)*

Over 11 000 questionnaires were sent out to randomly selected farms having more than 30 breeding ewes. From an overall response rate of 61%, 838 farmers reported ever having had a case of scrapie (this represents 13% of the relevant responders, Hoinville *et al.* 1999). The following questions were included to investigate the rate that farms acquire a case. In which year did scrapie first appear in your flock? Did any cases of scrapie occur in the last 12 months? Did any cases of scrapie occur in the previous five years? The year that the farmer became involved in farming sheep was also recorded, allowing a calculation of the proportion of farms experiencing a first case to be calculated each year. If the denominator is corrected to include only those farms that have not yet had a case in each year, we define this proportion as the first-case yearly flock-to-flock force of infection (FI₁).

* Author for correspondence (michael.gravenor@bbsrc.ac.uk).

† Present address: Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK.

(b) Estimation of force of infection from FI_1

If all farms have an equal chance of acquiring scrapie, the actual force of infection for all farms (FI) is equal to FI_1 . However, if some farms are more likely to be affected then FI_1 will be a biased estimator of FI . For example, farms that have had cases in the past and since eradicated the disease may be more likely to be reinfected in the future. In this scenario, data on the acquisition of first cases will lead to an underestimate of FI as time goes by. A number of factors can cause heterogeneity in the probability of acquiring scrapie (McLean *et al.* 1999), the most obvious being variability in flock size.

Here we derive an estimate of the mean FI (and variability) from the observed rate that farms acquire their first cases. Let the probability of a case in any year n be θ_n . The rate θ per year is FI , and initially assumed independent of time. Let A denote the occurrence of a case in year n . Let B denote no occurrences in the years $1, \dots, n-1$. Using a Poisson approximation, $P(A) = 1 - e^{-\theta}$, and $P(B) = e^{-(n-1)\theta}$. If $p(\theta)$ denotes the probability density function of θ across farms, then the probability of a case in year n given no occurrences beforehand (i.e. FI_1) is $P(A|B) = \phi_n$. The aim is to express ϕ in terms of θ . We have

$$\phi_n = \frac{\int_0^\infty (1 - e^{-\theta}) e^{-(n-1)\theta} p(\theta) d\theta}{\int_0^\infty e^{-(n-1)\theta} p(\theta) d\theta} = 1 - \frac{p^*(n)}{p^*(n-1)},$$

where

$$p^*(n) = \int_0^\infty e^{-n\theta} p(\theta) d\theta$$

is equivalent to the moment generating function of the density $p(\theta)$. We assume that the probability density function of θ is an I' distribution of mean m and coefficient of variation (standard deviation/mean) squared $(CV^2) = c^{-1}$, then

$$p^*(n) = \left(1 + \frac{mn}{c}\right)^{-c}$$

and

$$\phi_n = 1 - \left(\frac{c + mn}{c + m(n-1)}\right)^{-c}. \quad (1)$$

One of the primary indicators of the risk of having had scrapie is flock size (McLean *et al.* 1999), hence an initial estimate of c can be made from the observed variation in the number of sheep per farm recorded in the survey. The sensitivity of this assumption can be explored by varying c about this value. For given values of c , the mean FI can be estimated by fitting the expression for ϕ to the observed FI_1 , and estimating m .

The method can be extended to include time trends in FI . If FI is a function of time, for example $\theta_n = \theta(1 + \alpha n + \beta n^2)$ where α and β are constants and θ is a random variable, we can proceed as above to obtain the following expression for ϕ_n in terms of n, m, c, α and β (described fully in Appendix A).

$$\phi_n = 1 - \left(\frac{c + m \left(n + \frac{\alpha n(n+1)}{2} + \frac{\beta n(n+1)(2n+1)}{6} \right)}{c + m \left((n-1) + \frac{\alpha n(n-1)}{2} + \frac{\beta n(n-1)(2n-1)}{6} \right)} \right)^{-c}. \quad (2)$$

We then test the significance of the linear (α) and nonlinear (β) components of the model to characterize the time trends in FI .

In §3, we use only the most recent and reliable (least affected by recall bias) data, since 1990, to estimate the current FI . Over this period we found that equation (1) provided a sufficient fit to the data since time trends were very small ($\alpha = \beta = 0$). The more complex model (equation (2)) was used in an attempt to identify longer-term trends in the full data set (1962–1998).

(c) Basic model of scrapie spread

This model describes a homogenous population of farms. For a constant total number of farms, s and i are the proportion unaffected and affected respectively. Unaffected farms become affected (here defined as having detected a case) at the rate $\lambda \text{ yr}^{-1}$ (FI). Following an initial case, the farm remains affected for a period during which transmission potentially occurs within the flock. Farms eradicate scrapie (through cull of infected animals and their relatives, or failure of a primary case to establish infection in the rest of the flock) at the rate $\gamma \text{ yr}^{-1}$ and return to the unaffected category. The time period for which a farm remains affected is on average γ^{-1} . Then in a simple deterministic model for a closed population, the number of susceptible and affected farms satisfy $ds/dt = \lambda s + \gamma i$ and $di/dt = \lambda s - \gamma i$. Although within-flock transmission is not explicitly included, for interpretation of the data we assume that while in the affected class, at least one secondary case occurs each year (the median within-flock yearly incidence is estimated as 0.4 per 100 ewes; Hoinville *et al.* 2000). Cases occurring in consecutive years are assumed to be due to within-flock transmission or the same source of infection and not due to newly introduced cases, i.e. the time to acquire infection is much greater than the period during which cases occur on a farm ($\lambda \ll \gamma$). At an endemic equilibrium, where $di/dt = 0$, the proportions of farms susceptible and affected are $s^* = \gamma/(\lambda + \gamma)$ and $i^* = \lambda/(\lambda + \gamma)$.

The proportion of farms experiencing a case over a 12-month period (I_{12}) can be expressed as those affected at the start plus those that become affected at some point over the next 12 months: $I_{12} = i^* + s^*(1 - e^{-\lambda})$. Thus γ (and the duration of an outbreak) can be estimated using

$$\gamma = \frac{\lambda(I_{12} - 1)}{(1 - I_{12} - e^{-\lambda})}. \quad (3)$$

Similarly, the predicted proportion of farms having had cases over five years, under the hypothesis that λ remained constant, is $I_{60} = i^* + s^*(1 - e^{-5\lambda})$. The five-yearly value is therefore unlikely to be five times larger than the 12-month value. If the eradication rate is low, the two proportions will be similar.

Since an affected farm is defined by the detection of a case, the above model does not describe farms with infected but undetected animals. The equations provide a good approximation to an extended model that includes this further category of farm assuming (i) the time for a farm to acquire an infected animal is much longer than the time for an infected animal to be detected having arrived on the farm; and (ii) the number of farms on which scrapie is never detected is small compared with the total number of farms.

3. RESULTS**(a) First-case force of infection**

Figure 1 shows FI_1 from 1962 to 1998 (from 1962 onwards at least one first case is reported each year; prior

Figure 1. FI_1 , observed first-case scrapie force of infection (proportion of farms that have never yet had scrapie experiencing a first case per year). Trend line fitted by logistic regression: $y = -16.8 + 0.26x - 0.0015x^2$ (x denoted year, a two-digit number). The majority of BSE cases in cattle occurred between 1990 and 1995. In 1992, *ca.* 9% of herds acquired a first case of BSE.

to this the data are sparse). On first inspection, despite a degree of year-to-year variation, the proportion of new infections gradually increased from the 1960s to the 1980s and possibly declined slightly since. Notable are ten-year peaks coinciding with the beginning of each decade that are very likely to be bias introduced by digit preference. A trend line fitted by logistic regression has a significant linear coefficient ($p=0.001$) and significant negative quadratic coefficient ($p=0.001$). Sensitivity of the regression to the high reports of first cases at the beginning of each decade was explored by either omitting the reports from 1970, 1980 and 1990 or smoothing the data with moving averages. This led to an improvement in the fit of the model, but the coefficients and subsequent conclusions were largely unaltered.

The majority of the BSE epidemic in cattle occurred between 1990 and 1995 when over 5000 cases were reported every six months (Anderson *et al.* 1996). The percentage of herds having a first case of BSE increased from 0 in 1984 to a peak of 9% in 1992, declining to 0.6% in 1998. If this epidemic was linked to a TSE increase in sheep, we might expect a substantial increase in new scrapie-affected farms around this time (determined specifically by the unknown incubation period of 'natural' BSE in sheep, experiments indicate a shorter incubation in sheep than cattle; Foster *et al.* 1993). Instead the trend shows a steady increase in FI_1 , from an estimated mean of 0.2% of farms having a first case in 1970 to 0.4% in 1990. Despite the significant nonlinear component to the curve, there was no peak of new cases during the 1980s or early 1990s. First, the curvature is gentle and there is no obvious peak to the raw data. Second, although the maximum of the regression curve occurs in 1988, the formal 95% confidence interval (CI) for the maximum is wide, spanning the range 1962 to 2114. Hence, although the proportion of farms having a first case of scrapie apparently has gradually increased, there

Figure 2. FI, estimated force of infection for all farms over period 1962 to 1998. Solid line, FI. Parameter estimates (95% CI): $m = 0.0031$ (0.0022, 0.0039), $\alpha = 0.039$ (0.015, 0.062), $\beta = 6.6 \times 10^{-5}$ (-0.0018, 0.0019), i.e. no significant departure from linearity. FI estimated using current coefficient of variation for flock size (1.3) as an approximation of the between-farm heterogeneity in the probability of acquiring a case. Dotted lines show estimated FI if the heterogeneity is +50% or -50% that of the variation in flock size. Trend in rate farms are first affected (FI_1 , triangles) is shown for comparison.

is little evidence for a significant peak in the 1980s or a significant decrease over the 1990s.

(b) Force of infection

An estimate of the recent FI, using the current coefficient of variation for flock size (1.3), was obtained by applying equation (1) to the data from 1990 to 1998 only. The mean FI was estimated at 0.0045 ± 0.0005 . The average observed FI_1 over this period is 0.004, suggesting an underestimate of the underlying FI in the order of 10%.

Long-term trends in FI (rather than FI_1), were obtained by applying equation (2) to the full data set (1962–1998). The model indicates an underlying trend in FI that increased linearly over time, with no significant non-linear component (figure 2). It is interesting to note that between-farm heterogeneities can introduce a quadratic shape to FI_1 , even if the underlying FI is linear. Figure 2 shows that if there is little variation in the risk of acquiring scrapie (specifically that the coefficient of variation is less than 50% of that for flock size), the two measures of scrapie spread are similar until very recently. If the variation in risk is much larger than the variation in flock size, FI_1 provides a considerable underestimate of FI, particularly in the later years.

(c) Duration of a typical outbreak

In combination with the basic model of disease spread, the current FI and the proportion of farms affected in 1998 were used to estimate the average duration of a scrapie outbreak on a farm (using equation (3)). We found that 2.7% of farms had a case in the 12 months prior to the survey (I_{12} , 95% CI = 2.3–3.2%), suggesting average outbreaks of approximately five years. This represents an average over all farms, some of which will have a

Table 1. *Epidemiological parameters for scrapie estimated from postal survey*

parameter	estimate/reference
average flock-to-flock force of infection (FI)	0.0045 yr ⁻¹
FI: flock has scrapie in animals born on the farm	0.0011 yr ⁻¹
FI: flock has scrapie in bought-in animals only	0.0029 yr ⁻¹
average duration of scrapie outbreak	5 years
outbreak duration: farms with scrapie in animals born on the farm	15 years (see also Woolhouse <i>et al.</i> 1999)
outbreak duration: bought-in scrapie only	2 years
proportion of farms affected 1998	2.7% (Hoinville <i>et al.</i> 1999, 2000)
within-flock scrapie incidence	0.4 yr ⁻¹ per 100 ewes (Hoinville <i>et al.</i> 2000)
farm risk factors for acquiring scrapie	McLean <i>et al.</i> (1999), Hoinville <i>et al.</i> (2000)
proportion of flock home-bred	0.6 (McLean <i>et al.</i> 1999)
proportion of flock traded each year	0.075 (Kao & McLean 2001)
probability of acquiring a case when trading with affected flock	Kao <i>et al.</i> (2001)

considerably longer duration of infection and others a much shorter one. The analysis was repeated for two subgroups of affected farms (McLean *et al.* 1999): (i) 'scrapie-challenged', farms where scrapie occurred but none in sheep born on the farm, and (ii) 'scrapie-born', farms where at least one case occurred in a home-bred animal. The estimated FIs in each group were 0.003 and 0.001 yr⁻¹, respectively. In combination with the observed percentage of farms in these groups reporting having had cases in the last 12 months (0.9% and 1.7%), estimated outbreak periods were 2 and 15 years.

(d) *Interpreting the reported proportion of affected farms 1993–1998*

In addition to 2.7% of farms reporting having had a case in the 12 months prior to the survey, 5.3% had a case in the previous five years (I_{60}). What do these observations tell us about any changes in the rate of scrapie spread? Based on the rates that farms acquire and lose scrapie, if 2.7% of farms have scrapie in one year, assuming no change in FI, the expected I_{60} is between 4.0 and 5.0% (mean 4.4). This range overlaps with the observed CI for I_{60} (4.8–5.9), and suggests the numbers of farms affected in the 12 months prior to the survey and the preceding five years are consistent with little change to the scrapie force of infection. Repeating this analysis for the two subgroups of scrapie-affected farms led to the same conclusion. For farms with cases in bought-in animals only, the expected I_{60} was 2.1% compared with an observed 2.3% (2.0–2.7). For farms with home-bred cases the expected I_{60} , under the hypothesis of constant FI, was 2.1% compared with an observed 2.6% (2.1–3.0).

Note that this analysis is independent (derived from different survey questions) of the data in figure 1. Although a linear increase in FI is estimated in figure 2, the conclusions here are not contradictory. The increase is only identifiable over the long time period and as discussed below it may have several underlying causes. Between 1993 and 1998 the increase in FI is small and associated with a relatively wide confidence interval.

For these estimates it was assumed that c in equation (1) could be approximated by the (inverse of the squared) current CV in flock size. If the between-farm variation in risk of acquiring scrapie is less, the above estimates are very similar. If the variation is twofold larger, the

average duration of outbreak estimate is reduced to 3.7 years. However, conclusions on the comparison of incidence between 1993 and 1998 remain the same.

4. DISCUSSION

The temporal trend in force of infection calculated from the postal survey gives the only available indication of past levels of scrapie infection in Britain (Gravenor *et al.* 2000). In the early 1980s, the BSE epidemic in cattle was caused by widespread exposure to infected protein supplements in animal feed (Wilesmith *et al.* 1988). Sheep can be experimentally infected with BSE via the oral route, leading to a disease with clinical signs very similar to those of scrapie (Foster *et al.* 1993). Since British sheep were exposed to BSE-contaminated feed until a ban was introduced in 1988 (and reinforced during the 1990s), concerns have been raised as to whether BSE affected large numbers of sheep but went unnoticed due to misdiagnosis. The data here are the only quantitative evidence that suggests a large epidemic of this type did not occur.

A retrospective analysis such as this has limitations and cannot exclude smaller-scale outbreaks of BSE. However, at present no studies are underway to test sheep on a large scale for BSE. Due to clinical similarities between scrapie and experimentally induced BSE (Foster *et al.* 1993), the only way the two diseases can be reliably distinguished is by inoculating mice and analysing incubation periods and lesion profiles, a lengthy process (Bruce *et al.* 1997). So far only a handful of sheep have been tested, all being negative. Further experiments are planned and other diagnostics offer the possibility of widespread initial screening (Hill *et al.* 1998), but few are currently underway.

There are a number of possible explanations for the estimated linear increase in scrapie force of infection. When analysed as a risk factor for having had a case of scrapie in the past 12 months, a threefold increase in farm size is associated with a doubling in the odds ratio for ever having had scrapie (McLean *et al.* 1999). The roughly 1.5-fold increase in flock size since 1970 (MAFF census statistics, <http://www.maff.gov.uk>) is therefore likely to have contributed to the increased FI. It is also possible that biases will be introduced into such historical data by

variation in recall of past events. If those farmers who have had a recent first attack of scrapie are more likely to answer the question, this may contribute to an increasing proportion of new cases over time. One hundred and seventy-four farmers who reported ever having had a case did not indicate the year in which the first case occurred. There was no evidence that these 174 represented an older set of farmers, and it was found that they had, on average, been farming sheep for the same length of time as those who had answered the question in full. An important determinant of susceptibility to scrapie is the sheep genotype (Hunter 1997). Considerable information on the genetic susceptibility of the national flock is currently being collected, but the trends over time are unknown.

Public consultation for a National Scrapie Plan for the control and eradication of the disease in Great Britain was announced in July 2000 (<http://www.maff.gov.uk>). Such efforts are also likely to be echoed in other countries. An accurate mathematical model of the flock-to-flock transmission of scrapie would provide a useful framework for developing such a programme. Such a model must be based on a thorough understanding of the between-flock dynamics of scrapie transmission. McLean *et al.* (1999) identified the most relevant groups of farms to include, and described their distribution among the national flock and other basic demographic characteristics of the complex British sheep industry. Here we provide initial estimates of important parameters of the rate of scrapie spread.

The current flock-to-flock FI for scrapie is *ca.* 0.0045 yr^{-1} , implying an average waiting time before a farm acquires a case of over 200 years. When affected farms were grouped according to whether or not animals born on the farm had been affected, the rate was three times higher for those farms that had scrapie only in bought-in animals than for those with home-bred cases. In apparent contradiction, twice as many farms affected during 1998 were in the scrapie-born group. This is likely to reflect the relative duration of a scrapie outbreak on the two farm categories, and highlights the importance of considering the rate farms acquire and eliminate the disease. Using a basic epidemiological model, scrapie-challenged farms were estimated to remain affected for two years, and scrapie-born farms for 15 years. The latter estimate is similar to that obtained by detailed modelling of scrapie within a single high-incidence flock (Woolhouse *et al.* 1999).

The rate parameters were used in conjunction with the basic model to interpret potentially confusing statistics obtained in the postal survey: the reported proportion of farms having had cases in different time periods. This exercise provided further evidence that scrapie FI has been relatively constant in recent years.

The epidemiological parameters of scrapie obtained in the postal survey are summarized in table 1. These estimates now allow relatively detailed models of scrapie control to be constructed. Kao *et al.* (2001) suggest that an unknown but crucial parameter is the rate at which a farm develops scrapie in home-bred animals, after a scrapie case has been brought in to the flock. This, in addition to information on the genetic susceptibility of the national flock, is an essential component of the epidemiology of scrapie that remains to be characterized.

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APPENDIX A: DERIVATION OF TIME-DEPENDENT FORCE OF INFECTION FROM FI

If $\theta_n = \theta(1 + \alpha n + \beta n^2)$, let A denote an occurrence in year n . Let B denote no occurrences in the years $1, \dots, n-1$. Using a Poisson approximation:

$$P(A) = 1 - e^{-\theta_n} = 1 - e^{-\theta(1 + \alpha n + \beta n^2)},$$

and

$$P(B) = \exp\left(-\theta\left[(n-1) + \frac{\alpha n(n-1)}{2} + \frac{\beta(n-1)n(2n-1)}{6}\right]\right).$$

Therefore,

$$\phi_n = 1 - \frac{p^*(C_n)}{p^*(C_{n-1})},$$

where

$$C_n = n + \frac{\alpha n(n+1)}{2} + \frac{\beta n(n+1)(2n+1)}{6}.$$

Assuming the probability density function of θ is an I' distribution of mean m and $\text{CV}^2 = c^{-1}$ then $p^*(C_n) = (1 + mC_n/c)^{-c}$, and ϕ_n can be expressed in terms of m, c, n, α and β .

$$\phi_n = 1 - \left(\frac{c + m\left(n + \frac{\alpha n(n+1)}{2} + \frac{\beta n(n+1)(2n+1)}{6}\right)}{c + m\left((n-1) + \frac{\alpha n(n-1)}{2} + \frac{\beta n(n-1)(2n-1)}{6}\right)} \right)^{-c}.$$

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