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Prevalence of scrapie infection in Great Britain: interpreting the results of the 1997–1998 abattoir survey

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An accurate estimate of the prevalence of scrapie infection in the Great Britain (GB) sheep flock is essential when assessing any potential risk to human health through exposure to sheep transmissible spongiform encephalopathies (TSEs). One method for assessing the prevalence is to sample sheep intended for human consumption using a diagnostic test capable of detecting infected animals prior to the onset of clinical signs. An abattoir survey conducted in Great Britain in 1997–1998 tested brain samples from 2809 apparently healthy sheep of which none was found to be positive for scrapie by histopathology or immunohistochemistry (IHC) although 10 were positive for scrapie-associated fibrils (SAF). Subsequently, the tonsils from a subset of the animals sampled were examined using IHC, one of which tested positive. To interpret these results we use a likelihood-based approach, which accounts for the variation in the prevalence of infection with age and test sensitivity and specificity with stage of infection. Combining the results for all of the diagnostic tests yields an estimate of the prevalence of scrapie infection in the GB sheep flock of 0.22% (95% confidence interval: 0.01–0.97%). Moreover, our analysis suggests that all of the diagnostic tests used are very specific (greater than 99%). Indeed, only SAF detection yields a specificity estimate of less than 100%, which helps to account for the high number of samples found to be positive for SAF.

Keywords: transmissible spongiform encephalopathy; model; likelihood; diagnostic test; sensitivity; specificity

1. INTRODUCTION

The experimental transmission of bovine spongiform encephalopathy (BSE) to sheep (Foster *et al.* 1993, 2001) raised the possibility that sheep in Great Britain may have been infected following exposure to contaminated feed during the 1980s (Ferguson *et al.* 2002; Kao *et al.* 2002) and, consequently, could act as a source of infection for the human population (Butler 1998; Ferguson *et al.* 2002). To assess the potential risk to human health it is necessary to have an estimate of the possible prevalence of BSE in sheep, though this is difficult to obtain directly because of the large number of animals that it would be necessary to screen. However, it is possible to estimate the proportion of scrapie cases that may, in fact, be BSE (Gravenor *et al.* 2003) which, combined with an estimate for the prevalence of scrapie infection in the national flock, would yield an estimate for the prevalence of BSE in sheep.

Several methods can be used to estimate the prevalence of scrapie, all of which have drawbacks. Statutory notification data provide one source for estimating the incidence of clinical cases, but suffer from under-reporting (Hoinville *et al.* 2000). An anonymous postal survey conducted in 1998 helped to overcome the reluctance of farmers to report suspect cases, but the accuracy of the results depends on farmers' ability correctly to diagnose scrapie in their animals (McLean *et al.* 1999; Hoinville *et al.* 2000). Alternatively, an abattoir survey can be used to estimate the prevalence of scrapie infection, but this relies on the detection of infected animals prior to the onset of clinical signs.

A survey conducted in Great Britain in 1997–1998 tested brain samples from 2809 apparently healthy sheep, of which none was unequivocally positive for scrapie (Simmons *et al.* 2000). Analysis of these results suggested that the absence of any positive results was consistent with a prevalence of infection in the national flock of up to 12% (Webb *et al.* 2001). We extend these earlier analyses using a likelihood-based approach to provide point estimates for the prevalence of infection based on the results of the 1997–1998 abattoir survey, but also including some newly available data. Two features are of particular importance when assessing the prevalence of scrapie: (i) the variation in the distribution of infection within a population with age; and (ii) the effects of diagnostic test sensitivity and specificity on the number of positive results. Consequently, we develop a model that incorporates these factors and, moreover, which provides a method to relate the prevalence of infection in the abattoir population to that in the population as a whole.

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Table 1. Results for the 1997–98 abattoir survey.
(Diagnostic tests used are: histopathology (*H*); SAF detection (*S*); brain IHC (*B*); and tonsil IHC (*T*).)

		sample group							
		1 (tests used: *H*, *S*, *B*, *T*)		2 (tests used: *H*, *S*, *B*)		3 (tests used: *H*, *S*, *T*)		4 (tests used: *H*, *S*)	
age class	age range (months)	positive	sampled	positive	sampled	positive	sampled	positive	sampled
1	0–15	*H*, *B*, *T*: 0; *S*: 4	224	0	5	*H*: 0; *S*: 3; *T*: 1	459	0	778
2	15–21	0	1	—	0	0	10	0	46
3	21–27	—	0	—	0	0	3	0	58
4	27–32	—	0	—	0	0	1	0	99
5	32–36	0	1	—	0	0	7	0	293
6	36–132	*H*, *B*, *T*: 0; *S*: 2	224	0	31	*H*, *T*: 0; *S*: 1	9	0	450

2. SURVEY DESIGN AND RESULTS

A full description of the survey is presented elsewhere (Simmons *et al.* 2000; see also Webb *et al.* 2001) and here we provide only a summary of the design and results. Between August 1997 and August 1998 brain samples from 2809 apparently healthy sheep were collected from 125 abattoirs throughout Great Britain. No more than five samples were taken from each abattoir on the same day to prevent any bias from clustering as a result of sampling animals from the same flock. Suitable samples were examined for histopathological changes and for scrapie-associated fibrils (SAF). Several samples taken early in the study or that were inconclusive by histopathology were also examined using immunohistochemistry (IHC). No samples were positive by histopathology or IHC (table 1). Twenty-five samples were inconclusive by histopathology, but these were all negative by brain IHC and SAF detection. Ten samples were positive by SAF detection (table 1). There is no inconclusive category for SAF detection.

In a continuation of this survey, tonsils from two groups of animals were examined using IHC: (i) animals that were positive or inconclusive by histopathology or SAF detection and for a selection of those animals for which brain samples were examined by IHC; and (ii) 500 randomly selected animals under 15 months of age (table 1). One of those tonsils tested was positive by IHC (table 1), though this was not taken from an animal that tested positive for SAF detection.

The age of each sheep (table 1) was estimated from dentition records and whether or not the animal was broken-mouthed (Webb *et al.* 2001). These data were missing for 72 animals (so it was not possible to estimate age), so their results, which were all negative, are excluded from the analyses.

3. ESTIMATING THE PREVALENCE OF INFECTION

To estimate the prevalence of scrapie infection in the GB sheep population we use simple models to describe changes in the prevalence of infection with age and the sensitivity and specificity of the diagnostic tests and their dependence on the stage of infection. These models are combined to produce a likelihood function that, essentially, describes the probability that the abattoir survey results arise for given values of the prevalence of infection and the sensitivity and specificity of the diagnostic test.

(a) *Prevalence of infection*

Given that the risk of infection is greatest during the perinatal period (Foster & Dickinson 1989; Hunter & Cairns 1998) and there is evidence for age dependence in susceptibility (Matthews *et al.* 2001), we assume that all animals are infected at or close to birth. Moreover, we assume that animals infected with scrapie are not preferentially selected for slaughter prior to the onset of clinical signs. Consequently, the change in the prevalence of infection with age a reflects the rate at which infected animals develop clinical disease and is described by the following differential equation

$$\frac{\mathrm{d}p}{\mathrm{d}a} = -h(a)\,p(1-p), \tag{3.1}$$

where

$$h(a) = \frac{f(a)}{1 - \int_0^a f(\theta)\mathrm{d}\theta}$$

is the hazard function and $f(a)$ is the probability density function for the log-normal incubation period with parameters μ and σ (table 2; figure 1*a*). The incubation period parameters are estimated from data on the age at death, from scrapie for 396 animals from 14 scrapie-affected flocks (Hoek *et al.* 2003) using maximum-likelihood methods.

The prevalence of infection in the national flock, p_{POP}, is given by

$$p_{\mathrm{POP}} = \sum_j f_j P_j, \tag{3.2}$$

where f_j is the proportion of the national flock between j and $j+1$ years of age (table 2; taken from Webb *et al.* 2001; cf. Ferguson *et al.* 2002). The prevalence of infection in each age class, P_j, is calculated as

$$P_j = \frac{1}{a_{\max} - a_{\min}} \int_{a_{\min}}^{a_{\max}} p(a)\mathrm{d}a, \tag{3.3}$$

where $a_{\min}$ and $a_{\max}$ are the minimum and maximum ages in the class, respectively. The prevalence of infection in

Table 2. Model parameters.
(Abbreviation: CI, confidence interval.)

parameter	description		value	
			estimate	95% CI
μ	incubation period parameter		1.052	(1.015, 1.090)
σ	incubation period parameter		0.365	(0.339, 0.391)
β	parameter for the sensitivity of tonsil IHC		6.710 yr^{-1}	(2.940, 12.690)
δ	parameter for the sensitivity of tonsil IHC		0.856 years	(0.670, 1.051)
T_p	preclinical detection period	histopathology	0.083 years	—
		SAF detection	0.5 years	—
		brain IHC	0.25 years	—

f_j	age structure of the national flock										
age class j	1	2	3	4	5	6	7	8	9	10	11
age (years)	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	> 10
percentage	56.5	11.1	9.6	7.2	5.5	4.5	3.6	1.2	0.5	0.2	0.1

each survey age class (table 1) is also computed using equation (3.3), which assumes that the ages of the animals sampled are uniformly distributed within the age class. This is reasonable because animals were sampled throughout the year (Simmons *et al.* 2000; cf. Webb *et al.* 2001). Different values for the population prevalence (equation (3.2)) are obtained by varying the prevalence of infection at birth, $p(0) = p_B$.

(b) *Sensitivity and specificity of diagnostic tests*

Data on sensitivity for tests involving central nervous system (CNS) tissues (histopathology, SAF detection and brain IHC) are reported in terms of the stage of incubation at which preclinically infected animals are detected by the test (Webb *et al.* 2001). Consequently, the probability of detecting an infected animal of age a is given by the probability that the animal is in the appropriate stage of incubation,

$$\phi(a) = \frac{F(a + T_p) - F(a)}{1 - F(a)}, \tag{3.4}$$

where $F(a)$ is the cumulative distribution function for the log-normal incubation period with parameters μ and σ (table 2) and T_p is the preclinical detection period. The preclinical detection period for histopathological examination is estimated to be approximately one month, for SAF detection it is approximately six months and for brain IHC it is approximately three months (table 2; obtained from expert opinion by Webb *et al.* 2001).

Sensitivity data for the examination of tonsils by IHC are reported as the proportion of animals for which tonsil samples were positive for disease-associated prion protein (PrP^{Sc}) at a given age and show a sigmoidal rise to an asymptote at 100% sensitivity (Jeffrey *et al.* 2001; figure 1*b*). Hence, the probability of detecting an infected animal of age a is described by the function

$$\phi(a) = \frac{1}{1 + \exp(-\beta(a - \delta))}. \tag{3.5}$$

The parameters β and δ are estimated by fitting equation (3.5) to the data for test sensitivity (Jeffrey *et al.* 2001) using maximum-likelihood estimation assuming binomial errors (table 2; figure 1*b*).

The probability that an infected animal in age class j is detected is given by

$$\Phi_j = \frac{1}{a_{max} - a_{min}} \int_{a_{min}}^{a_{max}} \phi(a) \mathrm{d}a, \tag{3.6}$$

where $\phi(a)$ is given by equation (3.4) or (3.5) and a_{min} and a_{max} are the minimum and maximum ages in the class (table 1; cf. equation (3.3)).

Little information is available on the specificity of each diagnostic test and its dependence on the age of the animal sampled. Consequently, we assume there is a constant probability, ζ, that a sample from an uninfected animal in any age class does not generate a positive result (i.e. ζ is the specificity of the diagnostic test).

(c) *Maximum-likelihood methods*

Animals sampled as part of the abattoir survey are divided into groups according to which combination of tests was used on them and, within each group, according to the age of the animals (table 1). Results for the survey are given as the number of positive results, $D_{jk}^{(\tau)}$, from a sample of N_{jk} animals in age class j and sample group k for each diagnostic test τ used in the sample group (table 1). The probability of obtaining these results given that there are i infected animals in the sample is

$$\xi_\tau(D_{jk}^{(\tau)}, N_{jk} | i) = \sum_{d=0}^{D_{jk}^{(\tau)}} \left[\binom{i}{d} \Phi_j^{(\tau)d} (1 - \Phi_j^{(\tau)})^{i-d} \times \binom{N_{jk} - i}{D_{jk}^{(\tau)} - d} \zeta_\tau^{(N_{jk}-i)-(D_{jk}^{(\tau)}-d)} (1 - \zeta_\tau)^{D_{jk}^{(\tau)}-d} \right], \tag{3.7}$$

where d is the number of true positive results in the sample, $\Phi_j^{(\tau)}$ is the probability of detecting an infected animal in age class j with diagnostic test τ (defined by equation (3.6)) and ζ_τ is the specificity of diagnostic test τ. Consequently, the probability of observing the results for age class j and sample group k is given by

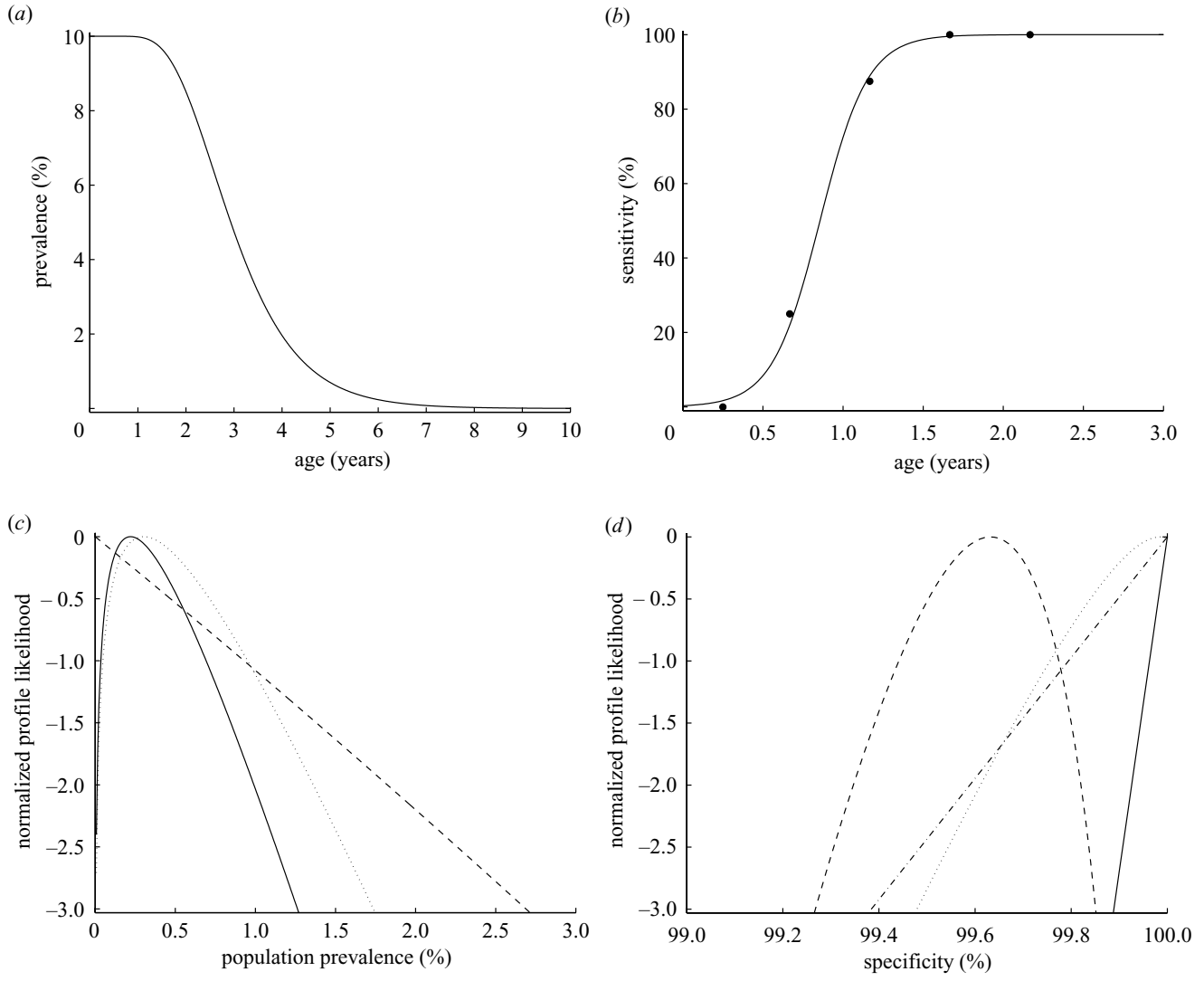

Figure 1. (*a*) The prevalence of infection as a function of age given by equation (3.1). The prevalence of infection at birth is 10% and the remaining parameters are given in table 2. (*b*) The probability of detecting an infected animal and its dependence on age when testing tonsils using IHC. The circles show the proportion of animals (out of eight that subsequently developed clinical disease) for which PrP^{Sc} was detected by tonsil biopsy (Jeffrey *et al.* 2001). The curve is given by equation (3.5), with parameters estimated using maximum-likelihood methods assuming binomial errors (table 2). (*c*,*d*) Profile likelihood for: (*c*) the prevalence of infection (%) in the GB sheep population based on the combined results for all diagnostic tests (solid line), SAF detection results only (dashed line) and tonsil IHC results only (dotted line); and (*d*) diagnostic test specificity (%) for histopathology (solid line), SAF detection (dashed line), brain IHC (dot-dash line) and tonsil IHC (dotted line). In each figure, the profile likelihood has been normalized so that the maximum value is zero. Parameters are given in table 2.

$$\Psi_{jk} = \sum_{i=0}^{N_{jk}} \left\{ \left[\prod_{\tau \in T_k} \xi_\tau(D_{jk}^{(\tau)}, N_{jk} | i) \right] \times \binom{N_{jk}}{i} P_j^i (1 - P_j)^{N_{jk} - i} \right\}, \tag{3.8}$$

where ξ_τ is defined in equation (3.7), T_k is the set of diagnostic tests used on sample group k (see table 1) and P_j is the prevalence of infection in the age class (defined by equation (3.3)). The likelihood is the product of the probabilities (equation (3.8)), for all sample groups and age classes. However, it is more convenient to work with the logarithm of the likelihood (the log-likelihood or support), which is given by

$$L(p_{\mathrm{POP}}, \zeta) = \sum_{j=1}^{6} \sum_{k=1}^{4} \ln(\Psi_{jk}), \tag{3.9}$$

where p_{POP} is the prevalence of infection in the population (defined in equation (3.2)) and $\zeta = \{\zeta_H, \zeta_S, \zeta_B, \zeta_T\}$ are the specificities for each diagnostic test considered.

For comparison with the combined results, we also consider the results for each diagnostic test individually. When doing this, the number of animals sampled and number of positive samples are obtained by aggregating the appropriate data from table 1 across sample groups. In the analysis, we use the likelihood defined by equations (3.7)–(3.9) with a single test group and diagnostic test within the group.

Estimates for the prevalence of infection in the population and the test specificities are obtained by determining the values that maximize the likelihood. However, it is often more convenient to consider the prevalence or test specificities individually, which can be done using the profile likelihood (Pawitan 2001). For the prevalence of infection in the population, p_{POP}, this is given by

Table 3. Maximum-likelihood estimates (MLE) and approximate 95% confidence intervals (CI) for the prevalence of scrapie infection in the GB sheep population and for the specificity of diagnostic tests used.

	prevalence (%)		specificity (%)	
results used	MLE	95% CI	MLE	95% CI
all diagnostic tests	0.22	(0.01, 0.97)	—	—
histopathology only	0.0	(0.0, 6.90)	100.0	(99.93, 100.0)
SAF detection only	0.0	(0.0, 1.75)	99.63	(99.35, 99.81)
brain IHC only	0.0	(0.0, 25.70)	100.0	(99.61, 100.0)
tonsil IHC only	0.30	(0.02, 1.33)	100.0	(99.66, 100.0)

$$L_p(p_{\mathrm{POP}}) = L(p_{\mathrm{POP}}, \hat{\zeta}),$$

where L is the likelihood (equation (3.9)), and $\hat{\zeta}$ is the vector containing the maximum-likelihood estimates for the test specificities. An approximate confidence interval can be computed from the profile likelihood using the result that, asymptotically,

$$2(L_p(\hat{p}_{\mathrm{POP}}) - L_p(p^*_{\mathrm{POP}})) \sim \chi^2_1,$$

where $\hat{p}_{\mathrm{POP}}$ and p^*_{POP} are the maximum-likelihood estimate and the 'true' prevalence, respectively (Pawitan 2001). Corresponding definitions can be given for the profile likelihood for each test specificity.

4. RESULTS

Analysis of the combined results for all diagnostic tests used in the 1997–1998 abattoir survey (table 1) produces a prevalence estimate of 0.22% (95% confidence interval: (0.01, 0.97); table 3; figure 1*c*). Estimates and confidence intervals for the specificities indicate that all tests used are highly specific and only that for SAF detection was less than 100% (table 3; figure 1*d*).

Considering each test individually yields estimates and confidence intervals for test specificity that are the same as those for the combined results (table 3). However, the prevalence estimates do differ (table 3; figure 1*c*). Analyses of the results for histopathology, SAF detection and brain IHC yield prevalence estimates of zero (table 3), although confidence intervals suggest the results are consistent with a prevalence of up to 6.9%, 1.75% or 25.7%, respectively (table 3). By contrast, analysis of the results for tonsil IHC provides a prevalence estimate of 0.3%, comparable with that for the combined results (table 3; figure 1*c*) although the confidence interval is somewhat larger (table 3; figure 1*c*).

5. DISCUSSION

Although an abattoir survey is a natural method to assess the prevalence of infection in animals slaughtered for human consumption, we have demonstrated that it is also possible to extrapolate from such a survey and estimate the prevalence of infection in the national flock. This paper has focused on the analysis of a historical survey conducted in 1997–98. However, the methodology used is appropriate for interpreting the results of other scrapie abattoir surveys, for example, the statutory survey required by the European Union (Anonymous 2002). Moreover, our approach is similar to those used to analyse surveillance data for BSE in cattle (Donnelly *et al.* 2002) and vCJD in humans (Ghani *et al.* 2000).

The results for the 1997–98 abattoir survey yield an estimate for the prevalence of infection in the GB sheep flock of 0.22% (table 3; figure 1*c*). Comparing this result with those obtained for the individual tests highlights the impact of test sensitivity and specificity and sample size on the prevalence estimates obtained from a survey. The estimates and confidence intervals obtained for histopathology, SAF detection and brain IHC (table 3) reflect the relative insensitivity of the test (histopathology and brain IHC), the small sample size (brain IHC) and the specificity of the test (SAF detection). Similarly, the somewhat larger confidence interval obtained using the results for tonsil IHC reflects the smaller sample size used (table 3; figure 1*c*; cf. table 1).

Previous analysis of results of the 1997–1998 abattoir survey suggested that they were consistent with a prevalence of infection in the national flock of up to 12% (Webb *et al.* 2001; cf. table 3). Although this does not contradict the results presented here, we have been able to determine point estimates for the prevalence with narrower confidence intervals. This has been achieved by using a likelihood-based approach, by combining the results for all the diagnostic tests used (i.e. making maximum use of the information provided by the survey) and, in particular, by including the newly available results for tonsil IHC.

An anonymous postal survey conducted in 1998 provides an alternative source of data with which to estimate the prevalence of infection (Hoinville *et al.* 2000). Assuming a prevalence of affected flocks of 6.1% (percentage of respondents reporting clinical cases in the past 5 years), a within-flock incidence of 0.5% (modal incidence of clinical cases within flocks) and, based on modelling analysis of within-flock scrapie epidemics, that there are three infected animals per clinical case (Woolhouse *et al.* 1998; Matthews *et al.* 2001), this yields an estimate for the prevalence of 0.09%. This is lower than the point estimate obtained from the abattoir survey results but does lie within the confidence intervals obtained (table 3) and, hence, is consistent.

Incorporating the effect of test specificity into the model produces consistent prevalence estimates across all diagnostic tests, something that is not achieved if it is neglected (cf. Webb *et al.* 2001). Our analysis indicates that all of the diagnostic tests used are very specific ($\zeta > 99\%$) and, indeed, only SAF detection yielded a specificity estimate of less than 100% (table 3). This result suggests that SAF detection does produce false positives (probably as a

result of operator error; see Simmons *et al.* 2000), which helps to account for the unexpectedly high number of positive results obtained in animals under 15 months of age (table 1; Simmons *et al.* 2000; Webb *et al.* 2001). A fuller discussion of the possible methodologically based reasons for the variation in the results among the tests is given in Simmons *et al.* (2000).

We have focused on obtaining an estimate of the prevalence of scrapie infection in the GB sheep population at a particular point in time. However, to investigate changes in the prevalence of infection over time (for example, to ascertain the effects of the National Scrapie Plan, which aims to eradicate scrapie by breeding a resistant national flock), surveillance must be undertaken with sufficient care to ensure that any differences observed between years can be ascribed to changes in prevalence rather than variability in the results of the survey. Consequently, any future survey must be designed carefully to ensure that it provides reliable results.

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REFERENCES

Anonymous 2002 Commission Regulation (EC) No. 270/2002. *Off. J. Eur. Communities* **L45**, 4–15.

Butler, D. 1998 Doubts over ability to monitor risk of BSE spread to sheep. *Nature* **395**, 6–7.

Donnelly, C. A., Ferguson, N. M., Ghani, A. C. & Anderson, R. M. 2002 Implications of BSE infection screening data for the scale of the British BSE epidemic and current European infection levels. *Proc. R. Soc. Lond.* B **269**, 2179–2190. (DOI 10.1098/rspb.2002.2156.)

Ferguson, N. M., Ghani, A. C., Donnelly, C. A., Hagenaars, T. J. & Anderson, R. M. 2002 Estimating the human health risk from possible BSE infection of the British sheep flock. *Nature* **415**, 420–424.

Foster, J. D. & Dickinson, A. G. 1989 Age at death from natural scrapie in a flock of Suffolk sheep. *Vet. Rec.* **125**, 415–417.

Foster, J. D., Hope, J. & Fraser, H. 1993 Transmission of bovine spongiform encephalopathy to sheep and goats. *Vet. Rec.* **133**, 339–341.

Foster, J. D., Parnham, D., Chong, A., Goldmann, W. & Hunter, N. 2001 Clinical signs, histopathology and genetics of experimental transmission of BSE and natural scrapie to sheep and goats. *Vet. Rec.* **148**, 165–171.

Ghani, A. C., Donnelly, C. A., Ferguson, N. M. & Anderson, R. M. 2000 Assessment of the prevalence of vCJD through testing tonsils and appendices for abnormal prion protein. *Proc. R. Soc. Lond.* B **267**, 23–29. (DOI 10.1098/rspb.2000.0961.)

Gravenor, M. B., Ryder, S. J., Gubbins, S., Hunter, N., Baylis, M. & Kao, R. R. 2003 Searching for BSE in sheep: interpreting the results so far. *Vet. Rec.* **152**, 298–299.

Hoek, A., Zekveld, C., Murray, A. H., Martin, T., Keyes, P. & Hoinville, L. J. 2003 PrP genotype and susceptibility to scrapie on 14 affected farms. *Prevent. Vet. Med.* (In the press.)

Hoinville, L. J., Hoek, A., Gravenor, M. B. & McLean, A. R. 2000 Descriptive epidemiology of scrapie in Great Britain: results of a postal survey. *Vet. Rec.* **146**, 455–461.

Hunter, N. & Cairns, D. 1998 Scrapie-free Merino and Poll Dorset sheep from Australia and New Zealand have normal frequencies of scrapie-susceptible PrP genotypes. *J. Gen. Virol.* **79**, 2079–2082.

Jeffrey, M., Martin, S., Thomson, J. R., Dingwall, W. S., Begara-McGorum, I. & Gonzalez, L. 2001 Onset and distribution of tissue PrP accumulation in scrapie-affected Suffolk sheep as demonstrated by sequential necropsies and tonsillar biopsies. *J. Comp. Pathol.* **125**, 48–57.

Kao, R. R., Gravenor, M. B., Baylis, M., Bostock, C. J., Chihota, C. M., Evans, J. C., Goldmann, W., Smith, A. J. A. & McLean, A. R. 2002 The potential size and duration of an epidemic of bovine spongiform encephalopathy in British sheep. *Science* **295**, 332–335.

McLean, A. R., Hoek, A., Hoinville, L. J. & Gravenor, M. B. 1999 Scrapie transmission in Britain: a recipe for a mathematical model. *Proc. R. Soc. Lond.* B **266**, 2531–2538. (DOI 10.1098/rspb.1999.0956.)

Matthews, L., Coen, P. G., Foster, J. D., Hunter, N. & Woolhouse, M. E. J. 2001 Population dynamics of a scrapie outbreak. *Arch. Virol.* **146**, 1173–1186.

Pawitan, Y. 2001 *In all likelihood: statistical modelling and inference using likelihood*. Oxford University Press.

Simmons, M. M., Ryder, S. J., Chaplin, M. C., Spencer, Y. I., Webb, C. R., Hoinville, L. J., Ryan, J., Stack, M. J., Wells, G. A. H. & Wilesmith, J. W. 2000 Scrapie surveillance in Great Britain: results of an abattoir survey, 1997/98. *Vet. Rec.* **146**, 391–395.

Webb, C. R., Wilesmith, J. W., Simmons, M. M. & Hoinville, L. J. 2001 A stochastic model to estimate the prevalence of scrapie in Great Britain using the results of an abattoir-based survey. *Prevent. Vet. Med.* **51**, 269–287.

Woolhouse, M. E. J., Stringer, S. M., Matthews, L., Hunter, N. & Anderson, R. M. 1998 Epidemiology and control of scrapie within a sheep flock. *Proc. R. Soc. Lond.* B **265**, 1205–1210. (DOI 10.1098/rspb.1998.0421.)