A Bayesian framework to assess the potential for controlling classical scrapie in sheep flocks using a live diagnostic test

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ABSTRACT

Current strategies to control classical scrapie remove animals at risk of scrapie rather than those known to be infected with the scrapie agent. Advances in diagnostic tests, however, suggest that a more targeted approach involving the application of a rapid live test may be feasible in future. Here we consider the use of two diagnostic tests: recto-anal mucosa-associated lymphatic tissue (RAMALT) biopsies; and a blood-based assay. To assess their impact we developed a stochastic age- and prion protein (PrP) genotype-structured model for the dynamics of scrapie within a sheep flock. Parameters were estimated in a Bayesian framework to facilitate integration of a number of disparate datasets and to allow parameter uncertainty to be incorporated in model predictions. In small flocks a control strategy based on removal of clinical cases was sufficient to control disease and more stringent measures (including the use of a live diagnostic test) did not significantly reduce outbreak size or duration. In medium or large flocks strategies in which a large proportion of animals are tested with either live diagnostic test significantly reduced outbreak size, but not always duration, compared with removal of clinical cases. However, the current Compulsory Scrapie Flocks Scheme (CSFS) significantly reduced outbreak size and duration compared with both removal of clinical cases and all strategies using a live diagnostic test. Accordingly, under the assumptions made in the present study there is little benefit from implementing a control strategy which makes use of a live diagnostic test.

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Introduction

Classical scrapie is a transmissible spongiform encephalopathy (TSE) that occurs in sheep and goats, which has been present in European sheep flocks for more than 250 years and has been reported in many other parts of the world (Detwiler and Baylis, 2003). The link between bovine spongiform encephalopathy (BSE) and variant Creutzfeld–Jakob disease (vCJD) raised fears that scrapie could be masking an epidemic of BSE in sheep, prompting the establishment of scrapie control programmes throughout the European Union (Dawson et al., 2008).

Current measures for action in scrapie-affected flocks aim to control scrapie by removing animals at risk of scrapie rather than those known to be infected with the scrapie agent. Advances in ante mortem diagnostic tests for classical scrapie, however, suggest that a more targeted approach involving the application of a rapid live test may be feasible in future (Schreuder et al., 1997, 1998; O’Rourke et al., 2000, 2002; Gonzalez et al., 2006, 2008). In particular, Gonzalez et al. (2008) have developed a recto-anal mucosa-associated lymphatic tissue (RAMALT) biopsy procedure which could be suitable for large scale screening (see, for example, Gonzalez et al., 2009). More recently, blood-based assays have been developed for a number of TSEs (Terry et al., 2009; Edgeworth et al., 2011), and these could also potentially be used for large-scale screening in future.

Before implementing a control strategy using a live diagnostic test, it is essential to assess whether or not it is likely to be effective and how its efficacy compares with current requirements. This paper investigates whether or not a control strategy using either RAMALT biopsies or a blood-based assay are likely to be effective and, if they are, the best approach to take. To address these questions, we developed a stochastic model for the transmission of classical scrapie within a sheep flock, which was implemented in a Bayesian framework. This facilitated the integration of datasets from routine surveillance, disease outbreaks, pathogenesis studies and diagnostic test development into the analysis. It also allowed parameter uncertainty to be incorporated in model predictions for the impact of the control strategies.
Table 1
Summary of the control strategies for classical scrapie considered in the study.

| Identifier | Description                                                                 |
|------------|-----------------------------------------------------------------------------|
| 1          | Removal of clinical cases of scrapie                                          |
| 2          | Whole-flock genotyping, followed by culling of at-risk genotypes*            |
| 3          | Whole-flock genotyping; testing of at-risk genotypes*; and culling positives |
| 4          | Sampling a proportion of ewes over one year old; genotyping them; testing at-risk genotypes*; and culling positives |
| 5          | Sampling a proportion of ewes between two and four years of age; genotyping them; testing at-risk genotypes*; and culling positives |
| 6          | Sampling a proportion of ewes over one year old; testing them; and culling positives |
| 7          | Sampling a proportion of ewes between two and four years of age; testing them; and culling positives |

* At-risk genotypes are defined to be all those which do not include the ARR allele and Arr/VRQ.

Materials and methods
Strategies for the control of classical scrapie

In the 1990s an association between prion protein (PrP) genotype and the risk of classical scrapie was identified (Goldmann et al., 1994; Belt et al., 1995) and this association has been central to most control strategies developed subsequently (Dawson et al., 2008). Five alleles of the PrP gene (defined by the amino acids at codons 136, 154 and 171) are commonly found in sheep, which, in order of increasing risk of clinical disease and decreasing age-at-onset, are ARR, AHQ, ARH, ARQ and VRQ (Baylis et al., 2004; Tongue et al., 2006; Gubbins, 2008).

We considered the impact of control strategies which differ according to how RAMALT biopsies or the blood-based assay are used and, in particular, whether or not animals of particular age groups or PrP genotypes are targeted for testing. In addition, we consider two baseline strategies: the current Compulsory Scrapie Flocks Scheme (CSFS) in the UK; and only removing clinical cases of scrapie. The strategies are summarised in Table 1, but the details for each strategy are:

1. No action, other than removing clinical cases of scrapie.
2. Current CSFS: when there is a confirmed case of scrapie in the flock, the whole flock is genotyped and sheep of at-risk genotypes are culled.
3. Whole-flock genotyping; annual testing of at-risk genotypes; and culling positives.
4. Annual sampling of a proportion of ewes over one year old; genotyping them; testing at-risk genotypes; and culling positives.
5. Annual sampling of a proportion of ewes between two and four years of age; genotyping them; testing at-risk genotypes; and culling positives.
6. Annual sampling of a proportion of ewes over one year old; testing them; and culling positives.
7. Annual sampling of a proportion of ewes between two and four years of age; testing them; and culling positives.

At-risk genotypes are defined to be all those which do not include the ARR allele and ARR/VRQ. Where a proportion of ewes was sampled (i.e. strategies 4–7), we considered the impact of sampling either 50% or 100% of ewes in the appropriate age group. Consequently, the potential impact of a total of 20 strategies was assessed. We assumed that control measures would be implemented once the first case of scrapie occurred in the flock.

Table 2
Steps and probabilities for the stochastic model for classical scrapie.

| Step | Probability distribution | Equations |
|------|--------------------------|-----------|
| No. of replacement lambs | \( L_r \sim \text{Multinomial}(N_r, f_r) \) | (6) |
| No. of lambs infection | \( S_{i,t} = L_r - I_{a,t} \) | (1) and (2) |
| No. of clinical cases | \( C_{a,t} \sim \text{Binomial}(I_{a,t}, \phi_a) \) | (3) |
| No. of infected sheep detected | \( D_{a,t} \sim \text{Binomial}(I_{a,t} - C_{a,t}, d_{a,t}) \) | (4) |
| No. of sheep removed | \( S_j = r_1 - I_{a,t} - \text{Binomial}(S_j, 1 - k_a) \) | (5) |

Modelling framework

To assess the potential impact of the control strategies we used an epidemiological model for scrapie implemented in a Bayesian framework, the structure of which is shown in Fig. 1. This facilitated integration of surveillance data (Gubbins, 2008; Gubbins and Mclntyre, 2009) and pathogenesis data (van Keulen et al., 2008; Houston et al., 2008) through the use of informative priors. Joint posterior distributions for the epidemiological parameters were inferred using outbreak data from 23 flocks in the UK (Mclntyre et al., 2008). In a separate analysis, a joint posterior distribution for the diagnostic test parameters was inferred using sequential test data (Gonzalez et al., 2008; Terry et al., 2009). These joint posterior distributions were subsequently used to incorporate parameter uncertainty in model predictions for the impact of control.

Within-flock dynamics of scrapie

We developed a stochastic model with an annual time-step to describe the transmission of scrapie within a sheep flock. In the model we only describe the ewe population in any detail; the ram population is considered only with respect to PrP genotype frequencies in each lamb crop. The ewe population is divided into two classes (susceptible and infected) and within each class animals are categorised by age, PrP genotype and time since infection (if infected). More specifically, \( S_{jat} \) is the number of susceptible animals of genotype \( j \) in age class \( a \) (comprising animals between \( a - 1 \) and \( a \) years of age) in year \( t \) and \( I_{jat} \) is the corresponding number of infected animals. Because animals are assumed to become infected at or close to birth (see below), age is equivalent to time since infection for the infected animals. Steps for updating the populations in the model (infection, onset of clinical disease and removal from the flock) are stochastic processes with probabilities and distributions defined in Table 2.

Because of evidence for an increased risk of transmission during the perinatal period (Foster and Dickinson, 1989; Hunter and Cairns, 1998; Touzeau et al., 2006) and of a decrease in the risk of infection with age (Matthews et al., 2001; St Rose et al., 2006; Nodelijk et al., 2011), animals were assumed to become infected at or close to birth. The probability that a lamb (i.e. an animal in age class 1) of genotype \( j \) becomes infected in year \( t \) is given by

\[
\phi_{jt} = r_j \left( 1 - \exp \left( -\beta \sum_k \omega_{ka} k_a \right) \right),
\]

where \( \beta \) is the transmission parameter, \( r_j \) is the relative risk of infection for genotype \( j \) and \( \omega_{ka} \) is the relative infectiousness of an infected animal of genotype \( k \) in age class \( a \). An infected animal was assumed to become infectious in the final proportion of its incubation period, so that the relative infectiousness is given by,

\[
\omega_{ka} = \int_0^{a-1} f_k(v) dv - \int_0^a f_k(v) dv.
\]
where \( f_k \) is the probability density function (PDF) for the log-normal incubation period (with genotype-specific parameters \( \mu_k \) and \( \sigma_k \); see Supplementary Material) and \( \varepsilon \) is the proportion of the incubation period for which an infected animal is infectious. This expression is assumed to incorporate all modes of transmission, including horizontal, vertical and environmental routes.

The probability that an infected animal of genotype \( j \) develops clinical disease in age class \( a \) is given by,

\[
c_a = \frac{\int_{a-1}^{a} f_j(v) \, dv}{1 - \int_{0}^{a-1} f_j(v) \, dv},
\]

where \( f_j \) is the PDF for the log-normal incubation period (see above).

An infected animal was assumed to be detected by the diagnostic test provided it was the final proportion of its incubation period (Gubbins, 2008). In this case, the probability that an infected animal of genotype \( j \) is detected when in age class \( a \) is given by,

\[
d_j = d_j^{\text{max}} \frac{\int_{a}^{\infty} 1 - \frac{1}{\epsilon} f_j(v) \, dv}{1 - \int_{0}^{a-1} f_j(v) \, dv},
\]

where \( f_j \) is the PDF for the log-normal incubation period (see above), \( \epsilon \) is the proportion of the incubation period for which an infected animal is detectable (cf. relative infectiousness) and \( d_j^{\text{max}} \) is the sensitivity of the diagnostic test in animals of genotype \( j \) at clinical onset.

The probability of an animal being removed from the flock in age class \( a \) is given by,

\[
k_a = 1 - \frac{s_{a+1}}{s_a},
\]

where \( s_a \) is the probability of survival to age class \( a \) at birth. This is assumed to be independent of PrP genotype and scrapie status.

For simplicity, we assumed random mating and a sex ratio for lambs of 1:1. In this case, the frequency of ewe lambs of each genotype (comprising alleles \( j \) and \( k \)) in year \( t \) is given by,

\[
f_{(jk)}^{(t)} = \frac{1}{2} \frac{g_{jk}^{(E)}}{\sum_{j} g_{jk}^{(E)} g_{jk}^{(R)}},
\]

where

\[
g_{jk}^{(E)} = f_{j(k)}^{(E)} + \frac{1}{2} \sum_{k} f_{j(k)}^{(R)}
\]

is the frequency of allele \( j \) in the ewe (\( E \)) and ram (\( R \)) populations and \( f_{j(k)}^{(R)} \) is the frequency of genotype \( jk \). The number of replacement ewe lambs \( N_t \) was assumed to be equal to the number of ewes removed from the flock (due to clinical disease, detection or removal).

Each outbreak was assumed to be initiated by the purchase of an infected animal (McLean et al., 1999; Hopp et al., 2001; Healy et al., 2004; McIntyre et al., 2006, 2008), which was represented in the model by introducing a single two-year old infected ewe of the VRQ/VRQ genotype into the flock. Control measures were assumed to be implemented once the first case occurred in the flock.

**Parameter estimation**

Epidemiological parameters (transmission parameter, stage of incubation at which an animal becomes infectious, relative risk of infection and incubation period parameters for each PrP genotype) were estimated in a Bayesian framework using a combination of surveillance and outbreak data (see Appendix S1 for details). Joint posterior distributions for the epidemiological parameters were generated for outbreaks in 23 scrapie-affected flocks in the UK, where the number of cases ranged from 1 to 131.

Parameters on test performance (preclinical detection period and sensitivity in clinical cases) were also estimated in a Bayesian

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**Fig. 1.** Bayesian framework for predicting the impact of control strategies for classical scrapie which make use of a live diagnostic test. Models (likelihoods) are shown in white, prior and posterior distributions in light grey and data-sets in dark grey. Genotype-specific parameters are relative risk of infection and incubation period parameters.
framework using data on sequential testing of infected animals (see Appendix S2 for details); the test was assumed to be 100% specific.

**Flock demography**

Survival probabilities \( s_a \) were assumed to be the same for all flocks: those for ewes were taken from the results of an anonymous postal survey conducted in 2002 (Sivam et al., 2003; see also Gubbins, 2008); those for rams were taken from Roden et al. (2006). It was assumed there was one ram for every 40 ewes and each ewe produced on average 1.3 lambs (McLean et al., 1999; Pollott and Stone, 2006).

**Sensitivity analysis**

To assess the sensitivity of the model predictions for the impact of control nine outbreak scenarios were considered in which the following were varied:

(a) **Flock size**: small (61 ewes); medium (267 ewes); or large (817 ewes). These are the minimum, median and maximum flock sizes in the outbreaks used to parameterise the model (see appendix S1).

(b) **Risk profile**: all flocks; low-risk flocks only (flocks 2, 8 and 13 using the identifiers in McIntyre et al., 2008); or high-risk flocks only (flocks 21, 22, 24 and 30). Low-risk flocks were assumed to be those with >60% of sheep carrying the ARR, but no VRQ allele and <10% sheep carrying the VRQ, but no ARR allele. High-risk flocks were those which reported >20 cases and had >10% of sheep carrying the VRQ, but no ARR allele.

For each of the 9 outbreak scenarios and 20 control strategies (i.e. 180 combinations) 1000 replicates of the model were simulated for 50 years. In each replicate the ewes and rams were assigned PrP genotypes by selecting a flock at random from the list of flocks included in the outbreak scenario, then sampling genotypes based on the initial frequencies in that flock (Fig. 2a). Epidemiological parameters were generated by drawing a parameter set from the joint posterior distribution for the flock used to generate the initial PrP genotypes. Test parameters were drawn from the joint posterior distribution for the sensitivity in clinical cases and the preclinical detection proportion for the test.

Within an outbreak scenario the results for each control strategy were assessed by comparing the posterior predictive distributions (generated as described above) for outbreak size (cumulative number of clinical cases) and outbreak duration (number of years for which infection is present in the flock). In particular, posterior predictive P-values were calculated by bootstrap sampling from the posterior predictive distributions for pairs of strategies. The number of animals tested, the number of infected animals detected and the number of animals culled was also recorded.

**Results**

**Parameter estimation**

Joint posterior distributions for the transmission parameter, stage of incubation at which animals become infectious and the relative risk of infection and incubation period parameters for each PrP genotype were obtained for outbreaks in 23 sheep flocks (see appendix S1 for details). Comparing the observed and expected frequencies of cases indicated that the model provides an acceptable fit to the data and, hence, is a reasonable basis for assessing the impact of control measures on the occurrence of scrapie within
Fig. 3. Boxplots of the predicted impact of 20 control strategies on the cumulative number of clinical cases in outbreaks of classical scrapie under nine scenarios which differ in flock size, epidemiological parameters and initial PrP genotype frequencies. Each panel shows the median (target), interquartile range (box), 1.5 times the interquartile range (whiskers) and any outliers (points) for the number of cases (note the logarithmic scale on the y-axis), while the symbol colour indicates the diagnostic test used: none (light grey); RAMALT (medium grey); or blood (dark grey). The identifiers for each control strategy are as given in Table 1, with the letter indicating the test used (R: RAMALT biopsy and B: blood-based assay) and the percentage indicating the proportion of the relevant age classes sampled.

a sheep flock. Similarly, joint posterior distributions for the test parameters were computed for the RAMALT biopsy and blood-based assay (Table 3; see Appendix S2 for details).

To summarise the epidemiological parameters, we computed the basic reproduction number for each outbreak (Fig. 2b). Posterior medians for the basic reproduction number ($R_0$) ranged from 2.1 to 68.1 (median 7.5). For most (19 out of 23) outbreaks $R_0$ was significantly above one; those for which $R_0$ was not significantly greater than one include both flocks which had only a single case (flocks 8 and 25).

**Table 3**
Summary statistics for the marginal posterior densities for the test parameters for the RAMALT biopsy and blood-based assay.

| Test parameter                           | Mean | Median | 95% credible limits |
|------------------------------------------|------|--------|---------------------|
| **RAMALT biopsy**                        |      |        |                     |
| Preclinical detection proportion ($\delta$) | 0.520 | 0.520  | 0.360 0.672         |
| Sensitivity in clinical cases $g_i^{\text{max}}$ |      |        |                     |
| Non-ARR-bearing genotypes                | 0.986 | 0.990  | 0.950 1.000         |
| ARR-bearing genotypes                    | 0.667 | 0.676  | 0.390 0.891         |
| **Blood-based assay**                    |      |        |                     |
| Preclinical detection proportion ($\delta$) | 0.663 | 0.663  | 0.564 0.759         |
| Sensitivity in clinical cases $g_i^{\text{max}}$ | 0.614 | 0.615  | 0.522 0.702         |

**Predicted impact of control strategies**

In small flocks there were no significant differences between any of the control strategies in terms of outbreak size or duration in the ‘all flocks’ or ‘low-risk flocks only’ scenarios (Figs. 3 and 4). This is largely a result of the fact that even with minimal control measures (i.e., removal of clinical cases) most outbreaks are small (<20% of outbreaks have more than a single case). In the ‘high-risk flocks only’ scenario the only difference amongst the strategies was that the current CSFS (i.e., strategy 2) resulted in shorter outbreaks compared with all other strategies (which did not differ significantly from one another) (Fig. 4).

In medium flocks those strategies in which all ewes over one year are genotyped and/or tested (i.e., strategies 3 and 4 or 6 where 100% of animals are sampled) using either live diagnostic test (i.e., RAMALT biopsy or blood-based assay) resulted in significantly smaller and shorter outbreaks compared with removal of clinical cases, as did the current CSFS (strategy 2) (Figs. 3 and 4). Moreover, in the ‘high-risk flocks only’ scenario the current CSFS (strategy 2) also resulted in significantly smaller outbreaks than any of the strategies which make use of a live diagnostic test, while in all scenarios for ‘risk profile’ it (strategy 2) resulted in significantly shorter outbreaks compared with all those strategies using a live diagnostic test.

Finally, for large flocks all strategies using either live diagnostic test, except those in which only 50% of animals between two and four years of age are sampled or tested (i.e., strategies 5 and 7),
produced significantly smaller outbreaks compared with removal of clinical cases (Fig. 3). In addition, those strategies in which all ewes over one year are genotyped and/or tested (i.e. strategies 3 and 4 or 6 where 100% of animals are sampled) using either live diagnostic test (i.e. RAMALT biopsy or blood-based assay) resulted in significantly shorter outbreaks compared removal of clinical cases, though the differences were small (Fig. 4). However, the current CSFS (strategy 2) resulted in significantly smaller and shorter outbreaks than any of the other strategies considered (Figs. 3 and 4).

The number of tests carried out under each strategy (Fig. S9) reflects the level of testing required and whether or not testing is targeted at specific age classes or PrP genotypes. Essentially, strategies which target PrP genotypes (strategies 3–5) require fewer tests than the corresponding untargeted strategies (6 and 7), and those which target specific age classes also require fewer tests. The number of infected animals detected broadly reflects testing effort, though this is less marked for small flocks (Fig. S10). Finally, the number of animals culled (excluding clinical cases) reflects the requirements of the strategy, with most animals culled under the current CSFS, while the number culled under a strategy using a live diagnostic test equal to the numbers detected (Fig. S11; cf. Fig. S10).

**Discussion**

Integration of surveillance and outbreak data is essential when estimating epidemiological parameters for scrapie, largely because of the influence of PrP genotype. In particular, there are often too few cases in a single outbreak to allow robust estimation of genotype-specific parameters, especially for those genotypes in which disease occurs infrequently (cf. Figs. S3–S5). Despite this, most previous analyses have relied on data for a single outbreak (see Gubbins et al., 2010 for a review) and the present study represents the first attempt to link surveillance data and outbreak data in a rigorous manner. In addition, the present study analysed data for a large number of outbreaks, which allowed us to incorporate flock-to-flock variation in epidemiological parameters when assessing the impact of control measures.

Comparison of epidemiological parameters from different models (e.g. transmission parameters) is problematic because of differences in model formulations. However, the basic reproduction number ($R_0$) is straight-forward to compare across modelling approaches. In this case, the range of values for $R_0$ (2.1–68.1; median 7.5) obtained for the 23 outbreaks included in the present study (Fig. 2b) are broadly comparable with those reported previously: 3.9 (one flock; Matthews et al., 1999); 2.5–14.0 (one flock; Hagenaars et al., 2003); and 0.8–8.0 (four flocks; Nodelijk et al., 2011).

For small flocks or flocks with a low-risk PrP genotype profile, outbreaks often resulted in only a small number of cases (Fig. 3). This is consistent with data from flocks culled as part of the CSFS, where no additional cases were detected in 68.5% of flocks tested (Ortiz-Pelaez and del Rio Vilas, 2009). Longer and larger outbreaks...
were predicted to occur primarily in medium or large flocks with high-risk PrP genotype frequencies (Figs. 3 and 4). Whether or not a flock is of this type could be ascertained once clinical disease has been reported. The PrP genotypes in the flock at the time of reporting may not, however, be the same as at the time of introduction, especially if there is a long delay before reporting (Baylis et al., 2000; McIntyre et al., 2008).

For small flocks there was little difference between any of the control strategies considered in the present study (Table 1) in terms of their impact on outbreak size and duration. This suggests that the more stringent control measures required by the CSFS or a strategy making use of a live diagnostic test may be unnecessary and that removal of clinical cases will be sufficient to control disease in these flocks. By contrast, stringent measures are essential to control disease in medium or large flocks, especially those with a high-risk PrP genotype profile. In this case, the CSFS was the best performing strategy and was the only strategy able to consistently reduce outbreak size and duration.

Even when the CSFS was implemented, however, there were still occasionally large outbreaks (Figs. 3 and 4), which is a consequence of the uncertainty in the epidemiological parameters. The sampled risk of infection in PrP genotypes allowed under the strategy (i.e. sheep carrying at least one ARR allele and no VRQ allele) was sufficiently high to allow an outbreak of scrapie to sustain itself. Such a scenario could occur with the emergence of a novel strain of scrapie (cf. atypical scrapie which attacks different PrP genotypes compared with classical scrapie; Fedaevsky et al., 2008), in which case any control strategy would need to be reconsidered. A similar situation could arise if a strain of scrapie were to arise that is able to exploit polymorphisms in the PrP gene (Goldmann, 2008), which have not been accounted for in the present study.

Furthermore, the number of animals culled under the current CSFS was typically much higher than under any of the strategies using a live diagnostic test (Fig. S11). Any benefits of reduced levels of culling under these strategies, however, would need to be weighed against the longer duration of outbreaks under these strategies. In particular, longer outbreaks could result in substantial economic costs to the farmer (for example, through loss of sales), depending on what additional restrictions are placed on an affected farm.

Another recent modelling study has also considered the use of RAMALT biopsies in the control of classical scrapie (Boden et al., 2010). As with the present study their results indicated that for some flocks a control strategy less stringent than the CSFS could be put in place, potentially one which makes use of a live diagnostic test. For high-risk flocks (defined by the authors as large flocks which breed a high proportion of their own replacement animals), however, they also argued that the CSFS may be the most appropriate strategy, especially if there is a delay in detecting disease within the flock. In a subsequent study, Boden et al. (2012) undertook a cost-benefit analysis of different control strategies. They concluded that the CSFS was more cost-effective than a multiple testing strategy using RAMALT biopsies, unless the cost of the diagnostic test was sufficiently low.

As well as RAMALT biopsies, which have been used in an outbreak investigation (Gonzalez et al., 2009), we have also considered the use of a blood-based assay, which has not. There were no differences between the performance of strategies using either diagnostic test, despite differences in test performance (Table 3). In effect, the higher sensitivity in clinical cases for RAMALT biopsies (98.6%) compared with a blood-based assay (61.4%) is offset against the ability of the blood-based assay to detect infection earlier in the incubation period (preclinical detection proportion: 0.66 (blood) versus 0.52 (RAMALT)).

In this study, we have used a Bayesian framework to assess the impact of control strategies for classical scrapie in a sheep flock. Importantly, this allowed us to integrate data from the wide range of sources necessary to assess control in a robust manner and to incorporate parameter uncertainty in model predictions. Although applied to a specific disease, the general conceptual framework can be applied to the control of other infections, such as foot-and-mouth disease (Jewell et al., 2009a; Chis-Ster et al., 2012), influenza (Cauchemez et al., 2008; Jewell et al., 2009b) or bovine tuberculosis (Conlan et al., 2012).

Conclusions

Under the assumptions made in the present study about scrapie epidemiology and test performance, there is little benefit from implementing a control strategy which makes use of a live diagnostic test.

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Conflict of interest

None.

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Author contributions

Conceived the study: S.G. Developed the model: A.G. Estimated parameters: S.G. Analysed the control strategies: A.G., S.G. Wrote the paper: A.G., S.G. Both authors approved the final article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.epidem.2013.05.001.

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