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Transmission dynamics and mechanisms of endemicity of scrapie in the UK sheep population

J. E. TRUSCOTT* AND N. M. FERGUSON

Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, London, UK

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SUMMARY

Scrapie is a fatal neurological disease of sheep which is endemic in the United Kingdom. It is one of the family of transmissible spongiform encephalopathies (TSEs) that includes BSE. In this paper, we developed a micro-simulation model for scrapie in the UK sheep population, incorporating the genetic and structural diversity of the population and infectious contact between flocks through trading. The simulation was fitted to epidemiological data from a range of sources. We found a detection/reporting probability of 16% (95% CI 12–17) for animals dying of scrapie. Prevalence of infected animals in the population was about 0·15%. Infected individuals were found in 9% of flocks overall, rising to 60% in Shetland and 75% in Swaledale flocks. Mean values of R_0 for flocks varied with breed from 2·43 (Shetland) to 0·21 (Suffolk). We also examined the possible long-term persistence of scrapie in the UK flock in the absence of any intervention.

Key words: Modelling, sheep, TSE, United Kingdom.

INTRODUCTION

Scrapie is a fatal neurological disease of sheep which has been present in the United Kingdom for several hundred years. It is the oldest recognized transmissible spongiform encephalopathy (TSE) and the only one naturally endemic in the United Kingdom. It has always represented an economic problem for farmers and breeders, but has not been connected previously with any human diseases. As a result, it attracted limited scientific attention in the past. However, the BSE epidemic of the early 1990s and the connection between BSE and variant Creutzfeldt–Jakob disease (vCJD) in humans brought TSEs in general back into focus. In particular, experiments showing oral transmission of BSE to sheep, giving rise to scrapie-like symptoms, raised the possibility that BSE might be present in the UK flock and posing a risk to human health [1]. Scrapie in sheep and goats has been a notifiable disease since 1993. The mechanisms of transmission and incubation of scrapie are not yet well characterized, but much is known about the dependence of susceptibility on genotype for scrapie. As a result, national control policies have been developed in a number of European countries. Over the past decade, a variety of voluntary [2] and, latterly, compulsory schemes [3] have been in place in the United Kingdom to control the spread of scrapie through increasing the overall resistance of the national flock with selective breeding and also through control of the movement of susceptible animals. These schemes have been developed in response to a number of EC regulations [4–6].

In the present work, we build on the models of flock-leveldisease transmission developed previously

* Author for correspondence: Dr J. E. Truscott, Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK.
(Email: j.truscott@imperial.ac.uk)

[7, 8], making a number of extensions and refinements. A population of individual flocks is simulated, connected through a simple trading/breeding structure model. Breeding structure and demography of the population was based on the British Sheep Breed survey [9] with breed genetic composition taken from data gathered under the operation of the National Scrapie Plan [10].

We fit our model to a combination of epidemiological data from abattoir testing, compulsory case notification and anonymous postal survey data. We examine the implications for a range of aspects of the disease; flock R_0, disease reporting rates, distribution of infected animals in the population and flock trading practice.

THE UK NATIONAL FLOCK

The UK national flock comprises of about 15 million breeding ewes in 60 000 flocks [9]. Flocks can be well classified by breed and also by the role they play within the industry. About half the population is made up of flocks of pure-bred animals and half of cross-breeds. There are at least 90 breeds recognized, of which the five most common constitute about 60% of the pure-bred population. Given the large number of pure-breeds, there is a correspondingly huge range of possible cross-breeds.

The breeding structure of the British sheep industry is traditionally described as a stratified cross-breeding system. In the top stratum are found the pure-bred flocks, in which ewes are bred with rams of their own breed. After three or four crops of lambs, ewes from these flocks are drafted into upland flocks where they are crossed with Longwool and Down rams. Cross-bred ewes from upland flocks are then sold on to lowland farms, where they are bred with terminal sire rams to generate lambs for the meat market.

Model

Our model of the national sheep flock is based on a large-scale stochastic simulation of individual animals, grouped into flocks and clustered into breeds. Each flock incorporates the demographic dynamics of the livestock, including the effect of animal trading, the progress of disease (when present) through the population and the evolution of gene frequencies, under the influence of breeding and disease. Individual flocks implement a susceptible–infectious (SI) epidemic model stratified by age, incubation stage and genotype.

Movement of animals between breeds and cross-breeds determines the evolution of allele frequencies and the transmission of scrapie. Pure breeds are largely independent of each other genetically, but provide ewes for the cross-breeding flocks. The movement of ewes influences the genetic composition of the cross-breeding flocks as well as being a source of infection. Cross-breeding flocks in turn provide ewes to cross-breeding flocks of the lowest stratum of the breeding structure, in which lambs are produced mainly for slaughter. This set of flocks implicitly contains most of the breeding complexity of the industry. The model and the data used to construct this are described in detail in the Appendix.

Data

Epidemiological data on scrapie in the national flock arises from two surveillance mechanisms. The Department for Environment, Food and Rural Affairs (Defra) has pursued an active surveillance policy within abattoirs since 2002, sampling animals slaughtered for human consumption. Between 10 000 and 60 000 carcasses of animals over 18 months are tested for scrapie every year. These data provide a measure of the prevalence of scrapie within the population as a whole [11]. In the model, we assume that scrapie is detectable via testing in the final incubation stage of the disease before clinical symptoms, corresponding to the last $\sim$6 months of the latent period. This figure is certainly towards the pessimistic end of possible detection windows [12, 13].

Data from passive surveillance comes from two sources. Scrapie is a notifiable disease and all confirmed cases are registered with the Veterinary Laboratories Agency (VLA). Since 1998, epidemiological investigations have been initiated on all premises with suspected cases and the resulting data have been recorded in the Statutory Notification Database (SND). An analysis of these data up to 2002 is found in Del Rio Vilas *et al.* [14] and provides information on the distribution of confirmed cases across different breeds.

In addition, large-scale anonymous postal surveys were also carried out in 1998 and 2002, with the aim of compensating for shortcomings in voluntary notification [15, 16]. On both occasions, over 10 000 questionnaires were sent out to randomly selected sheep farms with the aim of quantifying the proportion of flocks affected by scrapie and the attendant risk factors. Comparison of the results of the postal surveys with official notification data shows some

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discrepancies due to under-reporting and bias. In particular, the observed flock case and within-flock case rate figures from the SND are likely to be less accurate than those calculated from the survey [16]. Since these are two of the quantities to which we fit our model, we take these data from postal survey sources.

Fitting

The endemic state

As discussed in the Introduction, there is very little quantitative information on scrapie in the United Kingdom outside the last 20 years. Clearly, the more susceptible alleles, VRQ and ARQ, are preferentially lost from the population as animals carrying them have a higher risk of infection and hence earlier death. Therefore the prevalence of susceptible alleles and susceptible animals gradually dies away, but this process is quite gradual (see below). Our simulation is complex and takes many simulated years to approach equilibrium, during which time the genetic composition of the flock will be substantially changed. For the purposes of fitting, we therefore balance the natural loss of susceptible genes in the population to allow a stable endemic situation to arise which can be fitted to the known incidence levels in the country. We achieve a balance by maintaining ram gene frequencies at a constant initial level for each breed. In practice, this would be equivalent to breeders within each breed choosing rams for some phenotypic quality (such as hardiness or meat quality) linked to the susceptible allele. In the Results section, we examine the effect of reverting to an unbiased choice for rams, in which animals are chosen to match the allele frequency of their breed at the time.

Fitting to data

We fit our endemic scenario to four types of epidemic data. We take the fraction of flocks reporting scrapie in the last 12 months from Sivam *et al.* [16] at a rate of 1%. From that survey we also take the mean within-flock incidence from flocks that had had a case of scrapie during the last 12 months. Although the sample is small, it is directly dependent on the within-flock contact rate, β_0. We fit to the mean value of 1·0 reported cases per year/100 ewes [16]. The distribution generated by the simulation is compared to the data in Figure 1*d*. From active abattoir surveillance data, we take the fraction of positive scrapie detections in apparently healthy carcasses aged >18 months. Over the five years to 2006, an average of nine infected carcasses per 10 000 were detected [11]. Finally, from the SND, we use the distribution of cases *per capita* by breed, for each breed in the model [10]. These data are used to fit the within-breed contact rates between flocks (see Table 1).

Since our model applies to a subset of the full population, it is necessary to adjust quantities related to population size. In general, the adjustment is small, indicating that our subset is representative. The simulated population represents just over 52% of the full population [9]. This proportion of the population generates 67% of the cases [14]. Hence our modelled sub-population produces about 1·3 times more cases per head than the entire population. We use this adjusting factor to correct the abattoir active surveillance proportion and the proportion of flocks experiencing a case within the last 12 months. We assume that the infected flock case rate, as a flock-level phenomenon, will be unchanged.

The parameter fitted to this data are the within-flock contact rate, β_0, the probability of detection, p_d, and the breed-specific mixing rates, β_f. Probability of detection is defined as the probability that an animal dying of end-stage scrapie will be reported. Since our observed flock case rate is taken from postal survey data, reporting means notification in the same context. Our fitting procedure has two stages. In the initial phase, we use an iterative algorithm to converge to and identify the neighbourhoods of the correct parameter values. We then use a Latin hypercube sampling method to explore parameter space in the region of interest and calculate a likelihood for the data given our parameter values, constructed from 200 iterations of the simulation from which confidence regions can be constructed. For all runs of the simulation we allow the endemic disease prevalence and genetic composition of the population to equilibrate for 300 years.

RESULTS

Fitting

Figure 1(*a*, *b*) shows the graphs of the best fit of mean model output to the fraction of observed farms, abattoir survey results and relative case rate by breed as a function of the within-flock contact rate, β_0. The behaviour of the simulation proved highly sensitive to the within-flock contact rate: increasing β_0 raises

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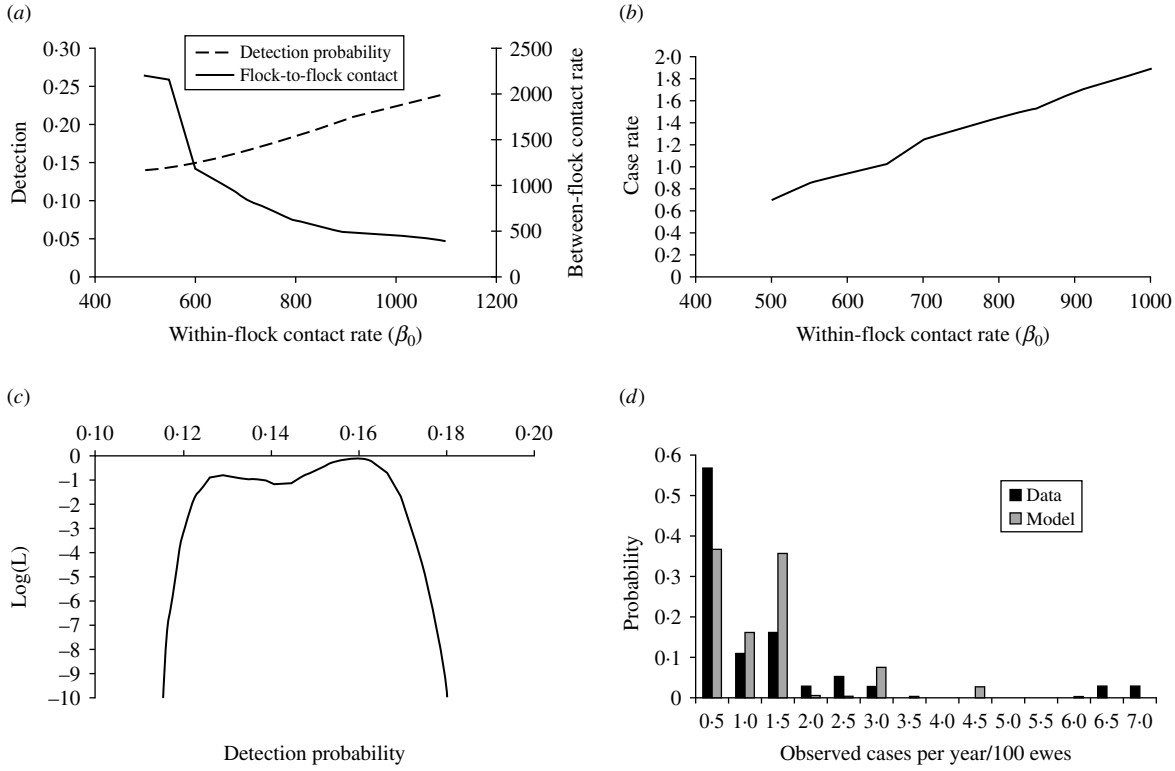

Fig. 1. Model fitting results. (*a*) Best fit for detection probability and flock-to-flock contact rate as a function of the assumed within-flock contact rate, β_0. (*b*) Best fit for case rate in recently detected flocks as a function of within flock contact rate, β_0. (*c*) Approximate profile likelihood for case detection probability. (*d*) Distribution of observed cases from recently detected flocks.

R_0 on individual farms, increasing the proportion of farms that can support an epidemic and also the prevalence on those that do. At the same time, increased prevalence increases the probability of transmission between farms, raising the force of infection (FOI) for farms. Accordingly, Figure 1*a* shows a strong negative correlation of β_0 with the strength of flock-to-flock transmission. This relationship breaks down at around $\beta_0 \approx 550$, at which point within-flock contact is too weak to support epidemics in infected flocks. Figure 1*b* shows an effectively linear relationship between observed prevalence in detected flocks and β_0, as expected. Figure 1*d* shows the distribution of the cases per year/100 ewes in flocks reporting a case in the last year, comparing the model output to data from the postal survey [16]. Although data are available from only a small number of flocks, it is the data most closely related to prevalence of infection in infected flocks and hence to the within-flock contact parameter. The mean of the distribution is fitted to that of the data, but we also recover a comparable distribution.

Of the fitted parameters, probability of detection is the most model-independent and directly informative. Scanning parameter space using Latin hypercube sampling indicates that 0·16 is the maximum likelihood estimator for detection. We have constructed an approximate likelihood profile for the detection probability estimate of the range of acceptable values independent of correlations with other parameters. Assuming a simple multivariate-normal distribution for the likelihood surface locally, the maximum likelihood profile will lie along the eigenvector of the correlation matrix with the largest eigenvalue. Using this approximation, we generate the likelihood profile shown in Figure 1*c*, which indicates a range from about 0·12 to 0·17. The extremes of the curve correspond with values of β_0 that no longer support epidemics within flocks and values of flock-to-flock transmission that no longer support epidemics among flocks respectively, although the slightly bimodal shape indicates a more complex surface than our assumption allows.

Breed-specific risk

Relative *per capita* case rates by breed are calculated from the cases confirmed in the SND as a proportion

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Table 1. *Relative case rate* per capita *from data, susceptibility-based risk, relative case rate* per capita *based on breed-independent contact rate and fitted contact parameters by breed*

Breed	Relative case rate (data)	Susceptibility risk	Uniform mixing	Optimal β_f
Scottish Blackface	0·0004	0·57	0·05	$1{\cdot}7 \times 10^{-6}$
Welsh Mountain	0·012	0·61	0·0013	6·76
Swaledale	0·07	0·59	0·018	33·5
Beulah	0·006	0·41	0·008	0·05
North Country Cheviot	0·008	0·65	0·0026	3·5
Suffolk	0·065	0·06	0·0011	12·4
Shetland	1	1	1	1
Longwool cross	0·003	0·25	0·0004	10·6
Suffolk cross	0·0096	0·18	0·00055	17·65

of the breed populations described in Pollott & Stone [9] and which form the basis of our model population structure. The case rates relative to the Shetland breed are given in Table 1. The mean relative susceptibility of a breed can be calculated from the susceptibility of the individual genotypes and the frequency of genotypes in each breed. Given that FOI is uniform across different breeds, relative breed susceptibility should be a good proxy for *per capita* case rates. Table 1 shows this is not the case. The *per capita* case rate for most breeds is at least an order of magnitude below that of the Shetland breed while the susceptibilities are in general only around half as much. Only Shetland and Suffolk case rates approximately reflect the ratio of susceptibilities. This suggests that the FOI varies considerably among different breeds.

With breed-independent contact rate (β_f equal for all breeds), we find that the high case rate for the Shetland breed arises naturally. Allowing all flocks to have the same contact rate, the much smaller Shetland flock population leads to a higher rate of contact between any given susceptible flock and the infectious sub-population. The resulting high FOI combined with a high genetic susceptibility leads to a case rate about 2 orders of magnitude greater than other breeds. To account for the remaining heterogeneity among flock susceptibilities, we allow the breed-specific contact rates to vary. The best-fit values are found in the last column of Table 1.

Breed R_0 values

Mean R_0 values for breeds included in the simulation range from a maximum of 2·43 for Shetland to 0·21 for Suffolk terminal sire adults (Table 2). Variation around mean values is generated by random variation in genetic composition around mean allele frequencies of each breed and the effect of preferential loss of susceptible sheep in infected flocks. In general, cross-bred lowland flocks have much lower values than the pure-bred hill breeds as a consequence of low frequencies of VRQ and ARQ alleles in the ram populations used to generate them. The lowland cross-breed categories we have used are an agglomeration of a large range of possible cross-breeding strategies, so it is very likely that the real variation of reproduction number within these groups is much higher than indicated by the model population.

Table 2. *Mean and standard deviation of R_0 for flock of each breed within the simulation*

	R_0 value	
Breed	Mean	S.D.
Blackface	1·59	0·27
Welsh Mountain	1·56	0·48
Swaledale	1·43	0·4
Beulah Speckleface	1·01	0·33
North Country Cheviot	1·58	0·64
Suffolk	0·21	0·15
Shetland	2·43	1·03
Longwool cross	0·68	0·31
Terminal sire	0·42	0·24

Prevalence

Prevalence of scrapie-infected animals per head overall in the modelled population is about 0·1% at equilibrium. However, there is enormous variation among breeds. Figure 3 shows three aspects of scrapie

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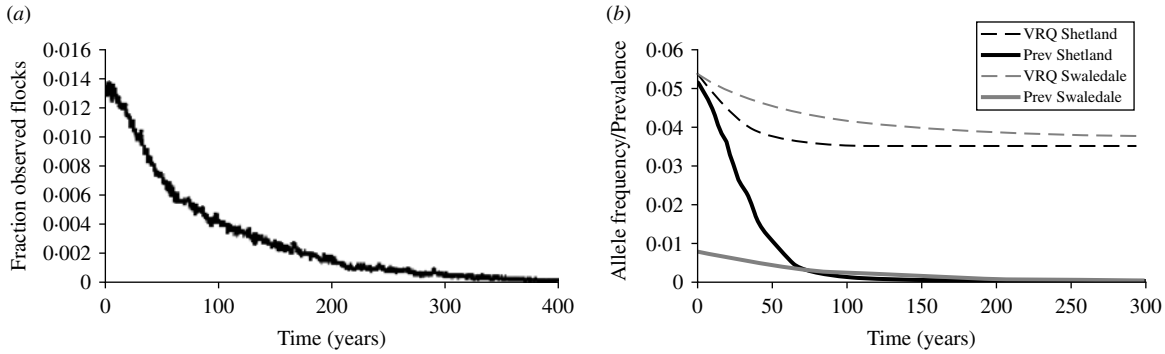

Fig. 2. (*a*) Observed case rate for population with genetically closed breeding strategy. (*b*) Prevalence and VRQ allele frequency in Shetland and Swaledale breeds with closed breeding strategy.

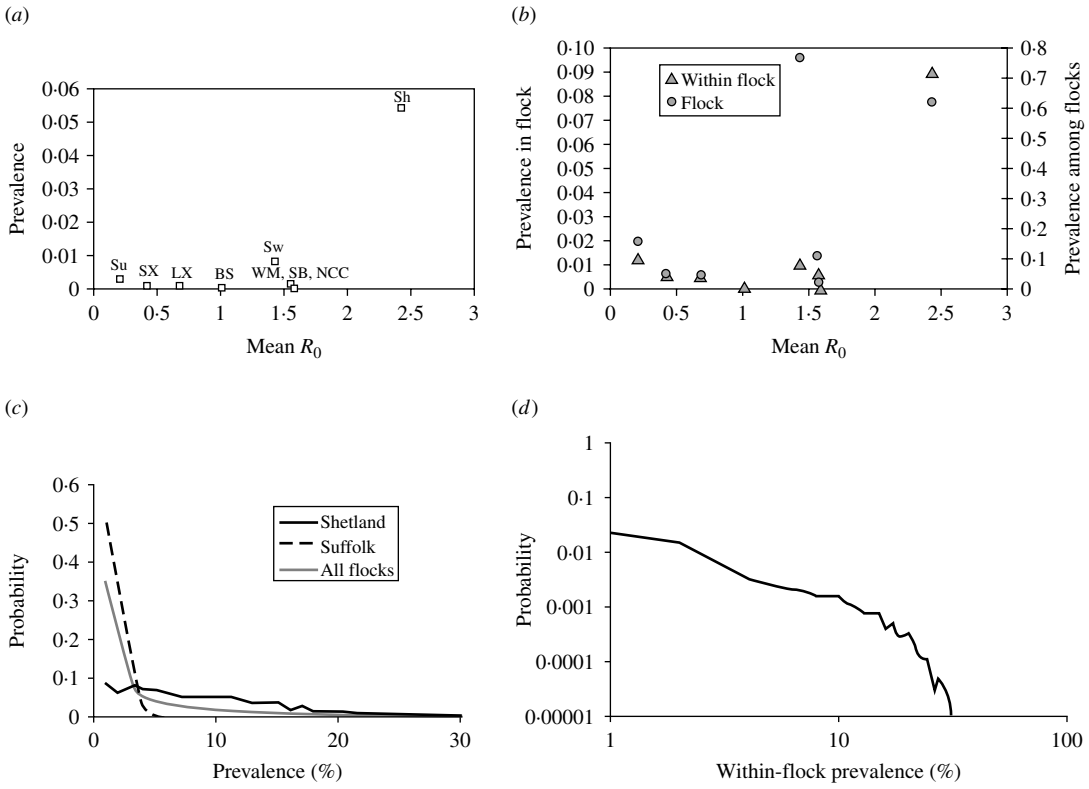

Fig. 3. (*a*) Infection prevalence *per capita*. (*b*) Prevalence among flocks (proportion of flocks carrying disease) by breed. (*c*) Distribution of within-flock infection prevalence (%) across all flocks in population and within the Suffolk and Shetland breeds. (*d*) Within-flock prevalence across whole population (log-scale).

prevalence by breed against R_0: prevalence of infected animals per head, fraction of infected flocks and prevalence of infected animals within infected flocks.

In general, R_0 is a good indicator of prevalence in breeds. Flocks with $R_0 < 1$ have very low prevalences, supported by inter-breed transmission which re-introduces infection from other more susceptible breeds. Support for within-breed endemic scrapie requires not only a relatively high flock R_0 (>1·5) but also a high flock-to-flock transmission rate. While the Swaledale, Welsh Mountain, North Country Cheviot and Scottish Blackface breeds all have R_0 values around 1·5, only the Swaledale breed, with a large fitted β_f, has a high case rate.

Prevalence within infected flocks shows a wide distribution which is strongly dependent on breed. Figure 3*c* shows the distribution of prevalences per head across all flocks and within the Shetland and Suffolk breeds. Across the whole population, the distribution among infected flocks is heavily

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right-skewed, with a mean of 4·2% but with 5% having prevalences of ⩾15%. A log-log graph of the distribution of number of infected animals per flock across the population shows an approximate power-law distribution for within-flock prevalence, but tailing-off for high prevalences (Fig. 3*d*). Distributions within specific breeds can be significantly different. Within Suffolk flocks, the mean prevalence is much lower at 1·7% with 95% below 2·5%. The low R_0 for this breed means that most infected individuals are the result of background infection and not within-flock transmission, making large outbreaks very rare. In contrast, Shetland flocks have a high R_0 and can support large outbreaks. At any time, 5% of flocks support a prevalence of over 20%.

Endemicity

For the fitting described earlier (see Fitting section), ram allele frequencies are held constant. If scrapie is assumed to be endemic or close to endemic, such a mechanism is required to balance the loss of susceptible alleles through reduced fitness. In this section, we examine the progress of the disease if this constraint is removed and rams are chosen according to the allele frequency of their breeds. Figure 2*a* shows the impact on the fraction of flocks with observed cases within the last year. The observed case rate among all flocks drops by 50% over 50 years, with 95% probability of extinction within 400 years. The reduced case rate is the result of loss of susceptible alleles, but the loss is not uniform across the population. Figure 2*b* shows VRQ allele frequency and *per capita* prevalence for the Swaledale and Shetland breeds. These two breeds account for the majority of cases. Reduced VRQ frequency is matched by falling prevalence in both breeds. Shetland flocks, with a higher R_0, support higher within-flock prevalences (see Fig. 3) and hence exhaust VRQ alleles quicker than Swaledales. As a result, the long tail of the epidemic is made up mostly of cases from the Swaledale breed. Mean R_0 values for Shetland and Swaledale breeds drop to 0·95 and 1·61 respectively by the time scrapie has become extinct. Across the whole population, however, effects on allele frequencies are slight, with VRQ falling by 12% and ARQ by only 1%.

DISCUSSION

This model attempts to combine essential features of the breeding and genetic structure of the UK sheep population without including the undoubted complexity of either. By treating flocks as collections of individual animals, we can make direct use of individual-level data, such as active surveillance data from abattoirs and case rates in infected flocks, and also address issues of prevalence at a within-flock and within-breed level. As such, our model complements the only other large-scale simulation of scrapie in the UK we know of, which concentrates on details of breeding and trading structure but has the flock as its basic unit [17].

Fitting of the model to epidemiological data gives a range of about 12–17% for the probability of individual cases being reported. The uncertainty in this estimate is largely due to insensitivity of the number of cases per year in infected flocks to the within-flock contact parameter. The within-flock and between-flock parameters are strongly correlated, as the effect of reduced flock-to-flock contact can be compensated by increased numbers of infected individuals in the infecting flock. Simply put, the high estimate for detection corresponds to the limit in which insufficient within-flock transmission is occurring to support the disease, while the low estimate corresponds to a scenario where insufficient flock-to-flock transmission is occurring to propagate the disease to new flocks. Our estimate falls roughly in the middle of previous estimates, such as 12% from the 1998 postal survey and 38% from 2002 [15, 16].

In order to fit the model to data, we have effectively biased the breeding process to maintain levels of susceptible alleles in the population. Such a mechanism would be equivalent to farmers choosing breeding rams consistently with respect to genetic composition, independent of any genetic changes in the population as a whole. There is no direct evidence that this practice occurs. When we allow rams to be picked with allele frequencies reflecting their breeds, we find a slow decline in the observed case rate among flocks, leading to almost certain extinction within 400 years. The loss of susceptible alleles is most pronounced in the Shetland and Swaledale breeds which have the highest case rates. Overall impact of the epidemic on allele frequency is quite small. Mean R_0 remains around 1·5 in Scottish Blackface, Welsh Mountain, North Country Cheviot and Shetland breeds. An increase in contact rates between flocks in these breeds would allow a new epidemic to establish itself.

Across the entire population, we find a *per capita* prevalence of 0·1%, distributed among 9% of the flocks. This is lower than some other model estimates

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(0·3% [18], 0·8–1·2% [17]). This can be explained by the highly heterogeneous distribution of infected animals. Around 75% of Swaledale flocks are infected with a mean prevalence of 1% at the flock level. This rises to almost 95% for Shetland flocks with 8% prevalence. Overall, most infected flocks contain only one or two infected animals (See Fig. 3*d*). When considering genotype-specific susceptibility, we find that the relative risk of incidence for individual animals is a very good proxy. Analysis of risk within individual breeds and in the population as a whole from the data in Eglin *et al.* [10] gave very similar values for genotype-specific incidence rates. When these values were used as a proxy for relative susceptibility, our model returned very similar relative incidence rates. However, mean allele frequencies and genotype-specific susceptibilities prove to be a poor indicator of relative case rates within a breed, as shown in Table 1.

Case rates in breeds are a product of both flock-level R_0 and flock-to-flock contact rate. A high flock R_0 leads both to longer and larger within-flock epidemics and results in a high prevalence among and within flocks respectively. Both these features make transmission of infected animals within a breed more efficient. Hence, the Shetland breed supports a high case rate with a much lower contact rate than Swaledale, which has a lower R_0. For Swaledale flocks, the high contact rate generates a high proportion of flocks containing infected animals (75%), but the prevalence of infection within these flocks is low ($\approx$1%). The Swaledale breed can be compared to the Welsh Mountain, North Country Cheviot and Scottish Blackface breeds, which are all pure-breds and have similar R_0 values. All these breeds show much lower case rates and flock prevalences ($<$10%) and have contact rates at least fourfold lower. The Swaledale breed is one of the most numerous among pure-breeds and as such contains the majority of infected animals. Our results suggest that reduction in contact among Swaledale flocks could dramatically reduce the prevalence of infection in the breed and hence in the population as a whole. Anomalous behaviour is seen most clearly in the Suffolk breeds. The Suffolks have a very low R_0, due to low frequencies of both VRQ and ARQ alleles, but a relatively high incidence rate. This may be due to the breed's extensive involvement in cross-breeding bringing them into much closer contact with other breeds and sources of infection. Within the model, the high case rate is generated by a large mixing parameter.

The large range in values for the fitted parameter β_f suggests that genetic variation and mixing within and between breeds may not account for all the variation in observed cases. In particular, the model struggles to account for the high incidence in the Suffolk breed (with a very low prevalence of VRQ) and the low incidence in Scottish Blackface (where VRQ is relatively common). In Suffolks, the high incidence is in part due to the presence of a scrapie strain targeting ARQ-bearing animals. However, this strain does not appear to have made significant inroads into other breeds. Together with the apparent resistance of the Scottish Blackface breed, this suggests that other important breed-specific effects must be present to account for the case distribution observed.

A number of improvements of this simulation are possible. At present, the ARH allele has been excluded, which in turn requires the exclusion of Texel and Texel cross-breeds. Pure-bred Texel ewes make up only about 2% of the national flock but have a significant role as terminal sires. Introduction of an extra allele would be a fairly simple addition, but would computationally be costly. Last, the modelling of inter-flock contact patterns might be improved by replacing the current meta-population structure with a directed network derived from sheep movement data as suggested by Kiss *et al.* [19]. However, such a simulation would represent a considerable increase in complexity over the current model.

APPENDIX

The model

Our model is a stochastic micro-simulation of a representative portion of the UK national sheep flock. We simulate a population of flocks, with distributions of flock sizes, breed and allele frequencies matched to the UK population. Transmission of scrapie is through contact between animals within individual flocks and via the movement of infected animals between flocks.

Model population

The breeding structure of the sheep population is central to the behaviour of the model as it governs both the evolution of the genetic make-up of the population and also the transmission of infection between animals. In our model population, we include the main features of the three-tier stratified

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Table A1. *Demography of model population and relative case rates within the model population by breed*

Flock type	Breed	No. of flocks	Flock size	Recorded cases
	Scottish Blackface	390 (232)	345	0·00031
	Welsh Mountain	320 (232)	380	0·01
	Swaledale	252 (152)	333	0·06
Pure breeds	Beulah	170 (80)	234	0·0051
	North Country Cheviot	320 (135)	191	0·0068
	Suffolk	400 (350)	43	0·056
	Shetland	40 (24)	47	0·85
	Longwool cross adults	1280	200	0·0024
Cross-breeds	Terminal sire Suffolk breeding	1280	173	—
	Terminal sire Suffolk adults	380	330	0·0081

Flock numbers in parentheses represent flocks engaged in pure breeding [14].

cross-breeding system and include the important breeds, both in terms of their contribution to the population as a whole and to the confirmed cases of scrapie as identified in the SND [14]. However, we wish to avoid the excessive complication of including all identified breeds and their combination into possible cross-breeds.

The model population comprises seven pure breeds and two categories of aggregated cross-breeds. The proportions of flocks of each breed are matched to those found in the UK population. Flock sizes are distributed according to the means reported for each breed [9]. Table A1 shows the breeds included in the model and their flock numbers and sizes. Flocks have contact with other flocks of their own breed and also with selected other breeds, as determined by patterns of cross-breeding.

Pure-bred flocks have contact with others of their own breed and also with flocks using pure-bred ewes for breeding (disease transmission follows the movement of animals). Cross-bred ewes are separated into two types of flocks. Initially, they are generated in cross-breeding flocks, in which pure-bred ewes are put to rams of a different breed. In the case of Longwool crosses, the ewes are a mixture of upland pure-breds and the rams are a mixture of blue-faced and border Leicester. For terminal sire Suffolk crosses, ewes are taken from the Longwool cross population and put to Suffolk rams. The adult ewes from cross-breeding flocks are transferred to the adult cross-breed flocks. In this way, we capture essential genetic relationships between the first three layers of the stratified breeding structure. The allele frequencies of the pure-bred flocks directly influence those of the Longwool cross sheep and these in turn govern the genetic make-up of the lowland terminal sire crosses. The Longwool cross and Suffolk terminal sire 'breeds' conflate a variety of different cross-breed flocks. The complex cross-breeding structure of lowland flocks is subsumed into the flock-to-flock contact parameters for these aggregated breed classes. The contribution of the various pure-breeds to the Longwool class is taken from Pollott & Stone [9] and is determined by the fraction flock not involved in pure-breeding (see Table A1). These weightings also determine the strength of infectious contact between the pure-breeds and the Longwool class (Table A2).

Table A2. *Contact probabilities for breeds most involved with the stratified cross-breeding programme*

	Contact	
Breed	Self	Longwool breeding flocks
Scottish Blackface	0·75	0·25
Welsh Mountain	0·87	0·13
Swaledale	0·56	0·44
Beulah	0·56	0·44
North Country Cheviot	0·9	0·1
	Self	Terminal sire breeding flocks
Longwool cross	0·5	0·5

Susceptibility to scrapie in sheep is strongly linked to genotype and is particularly associated with

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polymorphisms at codons 136, 154 and 171 on the ovine prion protein gene. Alleles associated with scrapie resistance or susceptibility are typically characterized by the amino acids coded at these three positions, the commonest being ARR, VRQ, ARQ, AHQ and ARH. The mean genetic make-up of pure-breed flocks was taken from Eglin *et al*. [10] and flocks were constructed according multinomial realizations from the breed mean. The allelic composition of cross-breed flocks arise naturally from the rams and pure-bred ewes through the Hardy–Weinberg breeding model. Our model is based around the first three of these, giving six possible combinations. We subsume the AHQ allele into ARR since both are associated with high resistance. The ARH allele is associated with susceptibility chiefly through the ARH/VRQ genotype, which accounts for about 4·5% of cases. Relative case rates indicate a susceptibility close to that of the ARQ/VRQ genotype. Amongst common breeds, only the Texel has a significant frequency of ARH allele (~40%). Texel rams are a common choice of terminal sire and Texels and Texel crosses are well represented in the national flock and also among contributors to the scrapie cases. However, the inclusion of the ARH allele would considerably complicate our model. We have adjusted the epidemiological data to reflect this (see UK national flock section).

The within-flock model

Demography and genetics

Each flock is stratified into six genotypes, corresponding to the possible combinations of the alleles ARR, ARQ and VRQ. Genotype sub-populations are structured by yearly cohort and also by disease status; susceptible, infected (five incubation stages) and symptomatic. Symptomatic animals are assumed to be removed from the flock. Sheep demography is constant across genotypes and is based on an estimated pattern of sheep survival [20]. For simplicity, new cohorts of lambs are generated at the same time-point in each year. The birth rate per ewe is assumed age-independent (>1 year old) and is kept fixed and calibrated to maintain a steady average population size for a flock. Flock sizes are drawn from a log-normal distribution, based on postal survey data [21]. The genotype distribution of new lambs is generated from a stochastic Fischer–Wright breeding model, given the gene frequencies of ewes and breeding rams for each flock.

Incubation and infectiousness

Incubation in infected individuals is modelled with five pre-symptomatic incubation stages followed by a symptomatic 'clinical' stage which is assumed to be removed from the flock and no longer infectious. Transition from stage to stage is at constant rate, ν, and hence the incubation period probability distribution is described by a gamma function

$$\frac{\nu^k t^{k-1}}{(k-1)!}\exp(-\nu t),$$

where $k=5$. The mean incubation period is matched to the measured period through the parameter ν. Each incubation stage is assigned an infectiousness, β_i, and these are adjusted to match the infectivity profile for BSE in sheep developed by Ferguson *et al*. [20].

Infection and susceptibility

Within flocks, we consider only horizontal disease transmission. Infection within a flock is modelled as a mass-action process. FOI is given by

$$\lambda=\beta_0\sum_k \beta_k \sum Y_{a,k},$$

where β_0 is the 'basic' contact rate, β_k is the incubation stage-dependent component and $Y_{a,k}$ are animals of age a and incubation stage k. The rate of infection experienced by susceptible individuals of age a and genotype γ, X_a^γ, is

$$\frac{X_a^\gamma g_a^\gamma}{N}\lambda,$$

where g_a^γ is the susceptibility of an individual of age a and genotype γ. Susceptibility is further resolved into the product of age- and genotype-dependent factors, $g_a^\gamma=h^\gamma l_a$. Susceptibility is taken to be strongly dependent on age with a maximum relative susceptibility of 1 during the first year, 0·3 in the second year and zero for $\geqslant 2$ years [22]. The relative susceptibility by genotype, h^γ, was calculated from the case rate *per capita* by genotype. We analysed the relative cases rate from SND data as presented in Del Rio Vilas *et al*. [14]. The frequency of genotypes within each breed was calculated from breed allele frequencies [10]. For given genotype-specific susceptibilities, the expected distribution of cases by genotype could be calculated for each breed. Comparing these case numbers to those reported by genotype, we were able to fit the susceptibilities (see Table A3).

We found that using relative case rates, calculated in Baylis *et al*. [23], leads to significantly different case

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Table A3. *Default parameter values*

Parameter	Symbol	Value	Source
Flock life, mean (S.D.)		40 (5) years	[25]
Number of inc. stages	k	5	[20]
Mean period in each stage	$1/\nu$	0·5 year	[20]
Infectivity by inc. stage	β_k	0, 0, 0·55, 0·78, 1·0	[20]
Susceptibility by age group	l_a	1, 0·3, 0, 0, …	[22]
	h_{1-3}	0, 0·004, 0·0003	
Susceptibility by genotype	h_{4-6}	0·025, 0·12, 1	Fitted

Order of genotypes: ARR/ARR, ARR/VRQ, ARR/ARQ, ARQ/ARQ, ARQ/VRQ, VRQ/VRQ.

rates from our model results. We speculate that this anomaly arises from a bias in the background populations used in the case-rate calculation in this paper.

Flock R_0

The basic reproductive number, R_0, is the largest eigenvalue of the next-generation matrix [24]. As the next-generation matrix is separable in this case, R_0 is given by

$$\beta_0 \sum_a \sum_\gamma \frac{X_a^\gamma g_a^\gamma}{N} \int_t \beta^\gamma(t) \frac{S(a+t)}{S(a)} \mathrm{d}t,$$

where X_a^γ is the stable demographic profile of genotype γ in an uninfected flock, $S(t)$ is the survival probability to age t and $\beta(t)$ is the infectiousness a time t after infection.

Flock disbanding

The number of flocks within the model is constant through a simulation, but no individual flock will persist over centuries. Flocks have a natural lifespan, after which they are disbanded [25]. In our model, animals from a disbanded flock are dispersed among other flocks unless a case has been observed within the last year, in which case the animals are culled. Hence animals from infected but not symptomatic flocks can start epidemics in other flocks. A new flock of the same type is initiated in place of the disbanded one to maintain the overall numbers. This allows flocks to effectively replenish their genetic stock from the background allelic frequency of their breed.

The between-flock model

Trading and transmission model

Transmission between flocks in the simulated population is both within and between breeds. For the pure-breeds, the probability that a given potentially infectious contact event is either within the breed or to an appropriate cross-breeding flock is taken as proportional to the number of breeding ewes employed for pure-breeding and cross-breeding respectively (see Table A1). Infected offspring from the cross-breeding flocks are distributed directly to the adult cross-breed flocks. We assume adult cross-bred flocks have contact only with other flocks of the same kind.

Data from the SND shows considerable variation in the incidence of confirmed cases by breed [14]. This pattern of variation is markedly different from that predicted by assuming a uniform FOI across all flocks and calculating susceptibilities according to current estimates of breed genetic composition [10]. To allow for the variation of FOI within different breeds, we assign mixing rates to each breed which can be fitted to the known relative incidence rates. The infectious contact rate from a flock of breed A to one of breed B is given by

$$\beta_{\mathrm{A}ij\mathrm{B}} = \beta_f^{\mathrm{A}} C_{\mathrm{AB}},$$

where β_f^{A} is the contact rate of breed A and C_{AB} is the probability of contact between breeds A and B.

The infectiousness of a flock is a function of the prevalence of infected animals within it. It is assumed that potentially infectious contact involves the movement of a single 'lot' of animals which are chosen randomly with respect to the genotype and incubation stages of animals in the donor flock. The number of infected animals transmitted is drawn multinomially from the distribution of infected animals in the donor flock stratified by genotype and incubation stage. We do not follow the movement of healthy animals during contact events as this would increase the computational effort considerably without significantly changing the dynamics of infection. In practice,

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we find that any sensitivity to lot size in the simulation is absorbed by the transmission rates, β_f.

Trading contact between breeds

Infectious contact between pure-breeds and Longwool crosses is assumed to be due to the acquiring of mainly mature pure-bred ewes by cross-breeding flocks. As an approximation to this movement, we divide flock-to-flock contact of pure-bred flocks between other pure-breds and cross-breeding according to the fraction of ewes used for pure-breeding and cross-breeding respectively [9]. The same is done for adult Longwool crosses and their contact with terminal sire crossing flocks. Infection is transferred from cross-breeding flocks to adult cross-bred flocks by direct movement of the infected animals within the simulation. All other breeds are assumed to have contacts only with other flocks of the same breed.

Background infection process In addition, flocks are subject to low-level FOI generated by all infected flocks. This mechanism represents other infection-transmitting movements not explicitly modeled. We have included this process to avoid stochastic extinction events in our model flock population, particularly among pure breeds at the 'top' of the breeding structure. However, the strength of this interaction is set at such a low level that other mixing parameter values are not sensitive to it. We do not investigate the effect of this mechanism further in this paper.

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DECLARATION OF INTEREST

None.

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