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Control of scrapie in the UK sheep population

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SUMMARY

Scrapie is a fatal transmissible spongiform encephalopathy (TSE) of sheep, endemic in the UK for centuries. Interest in the disease has been heightened over the last decade by the possibility of the related BSE being transmissible to and between sheep and a range of control interventions has been proposed and implemented. In this paper, we examined the effect of these policies and their components on observed case rate, susceptible allele frequency and R_0 within the framework of a large simulation model of the British sheep population and its breeding and trading structure. We compared interventions with the natural fade-out of scrapie in the population through loss of susceptible genotypes in the absence of control. We compare the results of interventions with the natural course of the scrapie epidemic. Our model suggested that scrapie will persist in the national flock for 300–400 years with the impact on gene frequencies confined largely to high case-rate breeds, such as Shetland and Swaledale. We found the National Scrapie Plan (NSP) to be the most effective in terms of the removal of both susceptible genotypes and scrapie from the population. Complete eradication of scrapie can be achieved within 32 years (95% CI 23–43 years). The Compulsory Scrapie Flock Scheme (CSFS) is as effective as the NSP in reducing the observed case rate but has a limited impact on the frequencies of susceptible genotypes in the population overall. In combination with the NSP, eradication of scrapie is achieved >10 years faster. Of the components of the CSFS, the breeding and culling aspects are each almost as effective as the full policy, with trading restrictions contributing little. We have speculated on the impact of control measures on the possibility BSE infection within the national flock by examining their effect on flock R_0 for BSE across different breeds.

Key words: Control, modelling, sheep, TSE.

INTRODUCTION

Scrapie is a neurological disease that affects sheep and goats. It has been present in the United Kingdom for several centuries and is the only endemic transmissible spongiform encephalopathy (TSE) of livestock. Flocks infected with scrapie may experience significant production losses, but scientific study of the disease was limited until the 1990s. Interest was triggered by the BSE (a bovine TSE) epidemic in British cattle and its connection to variant Creutzfeldt–Jakob disease (vCJD) in humans. This suggested the possibility of BSE in the sheep population and vCJD in humans through consumption of lamb [1]. The mechanisms of transmission and incubation of scrapie are not yet

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well characterized, but much is known about the dependence of susceptibility on genotype for scrapie. Control policies have been developed and implemented in a number of European countries. Over the past 10–15 years in the United Kingdom, a number of policies have been designed and implemented, targeting the genetic make-up of flocks, culling of potentially infected animals and/or the movement of animals between flocks through trading. These have included voluntary, compulsory and reactive schemes and have varied in the intensity of effort put into control of movement, culling and breeding. We discuss these in the Control policies section.

Here, we employ a stochastic simulation of the national flock, based on individual flocks connected through breeding and trading [2]. Control strategies are implemented explicitly, via selective breeding, culling and trading restrictions. We look at the effect of a range of policies on the evolution of incidence, prevalence and susceptible allele frequencies in the population as a whole and also for different breeds. Policies are compared to the natural course of the epidemic without intervention. We examine the efficiency of policies in terms of observed case rates from introduction to eradication, control scheme membership and the number and infection status of culled animals, where applicable. Policies are broken down into their components of breeding, culling and trade restriction to find which aspects are most important to control. We also examine the effect of control policies on the possibility of BSE infection being supported in the national flock.

THE UK NATIONAL FLOCK

The UK national flock comprises of approximately 15 million breeding ewes in 60 000 flocks [3]. Flocks can be 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-breed.

The breeding structure of the British sheep industry is traditionally described as a stratified cross-breeding system, based largely on altitude of grazing. Pure-bred flocks are bred mainly in hill areas. 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. As a result there is a flow of animals, and hence genetic material and infection, from the pure-bred hill flocks to the lowland cross-breeding flocks.

Our simulation attempts to capture the stratified population structure and 'downhill' flow of genetic and infectious material. The model features a representative subset of UK breeds and breed groupings (details of the model can be found in the Appendix). Breeds are characterized by their genetic composition, flock sizes, flock-to-flock contact parameters and connections with other breeds. Within 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, disease and current control policy. Individual flocks implement a susceptible–infectious (SI) epidemic model stratified by age, incubation stage and genotype.

Detection probability for scrapie cases and breed and within-flock contact parameters are estimated by fitting to epidemiological data, coming from three distinct sources. An indication of the underlying prevalence of end-stage infected animals in the population can be gained from active surveillance at UK abattoirs. About 10 000 carcasses of apparently healthy sheep aged >18 months are tested for prion protein each year [4]. Data gathered from compulsory scrapie notification and anonymous postal surveys provides information on observed case rates within and among flocks and their distribution among breeds [5, 6]. Details of the model and fitting procedure can be found in our companion paper [2].

An obvious effect of scrapie within a population is that the more susceptible alleles, VRQ and to a lesser extent ARQ, are preferentially lost from the population. Over time, these alleles will reach such a low level that scrapie will be naturally extinguished from the population. In our companion paper [2], for the purposes of fitting, we rendered scrapie endemic in the population by fixing the ram allele frequencies at their current levels [5]. Since it is impossible to model selective breeding policies while also fixing ram allele frequencies, we dispense with fixed frequencies when examining control policies in this paper. We allow the rams to be chosen according to the allele frequencies of their breed and treat the natural slow decay in

prevalence and case rate and ultimate extinction as the background against which the effectiveness of policies must be viewed.

The possibility of sustained BSE infection in the national flock will depend on the frequency and distribution of BSE-susceptible genotypes in the population. Naturally occurring cases of BSE in sheep have not yet been observed. In experiments, however, animals challenged with BSE inoculum via a range of routes develop neurological disease [7]. Although a range of genotypes were successfully infected, there was considerable genetic variation in the course of the disease. ARQ homozygotes were found to have the shortest incubation period ($\sim$550 days) with VRQ and ARR homozygotes more than twice as long. ARR animals were distinguished from ARQ and VRQ by having much lower accumulations of prion protein in brain tissue on post-mortem examination. Outcomes are also strongly influenced by route of infection. The oral route generally results in longer incubation periods and lower prion accumulations. In particular, ARR homozygote animals do not appear to be susceptible to oral challenge.

Since BSE susceptibility is determined by the same alleles that govern scrapie susceptibility, the effects of scrapie in the population and of policy interventions to control it will also affect the possibility of BSE infection. Explicitly modelling co-circulation of BSE and scrapie substantially increases model complexity, so instead we examine how genotype-specific susceptibility differs for scrapie and BSE and thus how within-flock R_0 values across breeds might vary for BSE. We are thus able to evaluate the effect of proposed intervention policies on BSE as well as scrapie. Data on the variation of susceptibility with genotype for BSE are very limited, but suggest that susceptibility is associated with the alleles of the form **Q, with **Q/**Q homozygotes about 14-fold less susceptible than **R/**R homozygotes [8]. Since **R alleles have a comparable frequency to **Q in most breeds, the contribution from **R is likely to be minimal. We therefore assume that BSE susceptibility is confined to **Q homozygotes.

CONTROL POLICIES

We consider the effect of a range of different policies on the genetic make-up of the national flock and the transmission of scrapie in the United Kingdom. We look at policies which have been implemented or are currently implemented such as the National Scrapie Plan (NSP) and the Compulsory Scrapie Flock Scheme (CSFS), drawn up in response to EU decisions [9–11]. We also consider the components of these policies applied individually. This gives some insight into the role they play in controlling scrapie which can be set against the cost of implementation. We also consider possible extensions and alternatives to existing policies.

Policy details

(1) *NSP*. The national scrapie plan is a long-term breeding programme, instituted by Defra with the goal of eradicating scrapie from the UK sheep population through breeding. The scheme was started in 2001 and consists of a range of initiatives designed to genotype both ewes and rams and encourage breed practices which will increase the frequency of resistant scrapie alleles and eradicate susceptible ones. Participation has been largely voluntary, although it now contains compulsory elements, such as the CSFS described below. We model the effect of these interventions by considering a scheme to which a proportion of flocks join up to each year. The join-up rate is chosen to match the rate reported [12]. Within the group of members, a proportion implements strict breeding practices, using only ARR/ARR rams. We also examine the additional impact of ewe genotyping, allowing the choice of resistant ewes for breeding.

(2) *CSFS*. The details of the compulsory scrapie flocks scheme are laid out in a Defra booklet [13] and are a response to amendments to EU requirements concerning TSEs [11]. Joining the scheme involves the genotyping of both the rams and ewes in the flock, allowing each animal to be allocated to one of five risk categories. The most susceptible types are culled outside the human food chain. Susceptible animals cannot be bought or sold by scheme members. Membership of the scheme lasts for 3 years once a fully resistant flock has been established and conditional on no further scrapie cases appearing. Joining the scheme is compulsory for all flocks reporting a case of scrapie.

(3) We examine the individual components of the CSFS scheme:

   (*a*) *Breeding only*. Members of the scheme use only resistant rams for breeding.

   (*b*) *Trading only*. Members of the scheme are subject to CSFS-style trading restrictions.

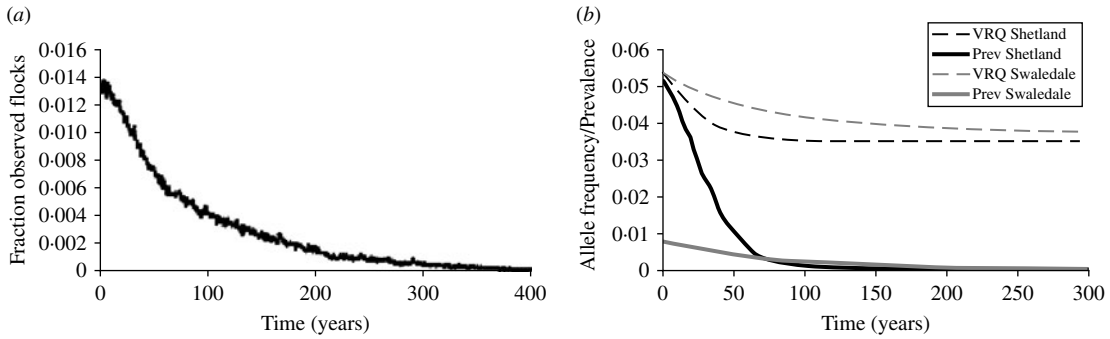

Fig. 1. (*a*) Observed annual case rate for population with genetically closed breeding strategy. (*b*) Prevalence and VRQ allele frequency in Shetland and Swaledale breeds with closed breeding strategy.

(*c*) *Culling only*. Members are subject to a flock cull when a case is reported. No trading or breeding restrictions are enforced.

(4) The EU minimum requirement is defined in a EC document [10] and is less severe than the CSFS which superseded it. The policy is aimed at flocks of high genetic merit, which we interpret as the pure hill breeds at the top of the breeding structure. The rams in participating flocks are genotyped on joining the scheme and VRQ-carrying animals cannot be used for breeding and must be destroyed within 6 months. No VRQ-carrying animal can leave the holding except for slaughter. We also examine the components of this policy individually.

RESULTS

Scrapie epidemic without intervention

Figure 1*a* shows the natural decay in the observed flock case rate due to natural loss of susceptible alleles. The observed case rate among all flocks drops by 50% over 50 years, with 95% probability of extinction within 400 years. The loss is not uniform across the population. Figure 1*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 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 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 only 1%.

NSP policies

The rate at which flocks join the NSP scheme is taken as a 6% of the flock population per year, giving an exponential take-up over time matching that observed over 2002–2006 [12]. Figure 2*a* shows the impact of the scheme on VRQ allele frequency in the population over time. With 100% compliance, VRQ alleles are removed from the population after about 60 years (reduction in ARQ frequency is effectively proportional to that of VRQ). The effect on the population participating in the NSP is more rapid, converging to that of the whole population as more flocks are recruited. Lower compliance probabilities reduce the rate of removal. However, as shown in Figure 2*b*, complete removal of VRQ alleles is not necessary for the eradication of scrapie. Flock case rates are reduced to about 10% of background levels by a halving of the VRQ allele frequency. Figure 2*b* shows that the effect on individual breeds is comparable to that of the population as a whole.

For Figure 2*d*, we supplement the NSP at 20% compliance with CSFS intervention. The CSFS causes only a small increase in the rate of removal of susceptible alleles, but has a large impact on scrapie incidence. The inclusion of CSFS reduces the time to the eradication of scrapie by a factor of 5. This is a consequence of the reactive nature of the additional intervention. Since CSFS only applies to flocks with detected symptoms, it much more effectively targets at-risk flocks, removing infected animals and preventing transmission.

CSFS

In this section, we examine the CSFS intervention in the absence of the NSP breeding programme. Figure 3*a* shows that the CSFS controls flock incidence rate more effectively than the NSP alone even with 100%

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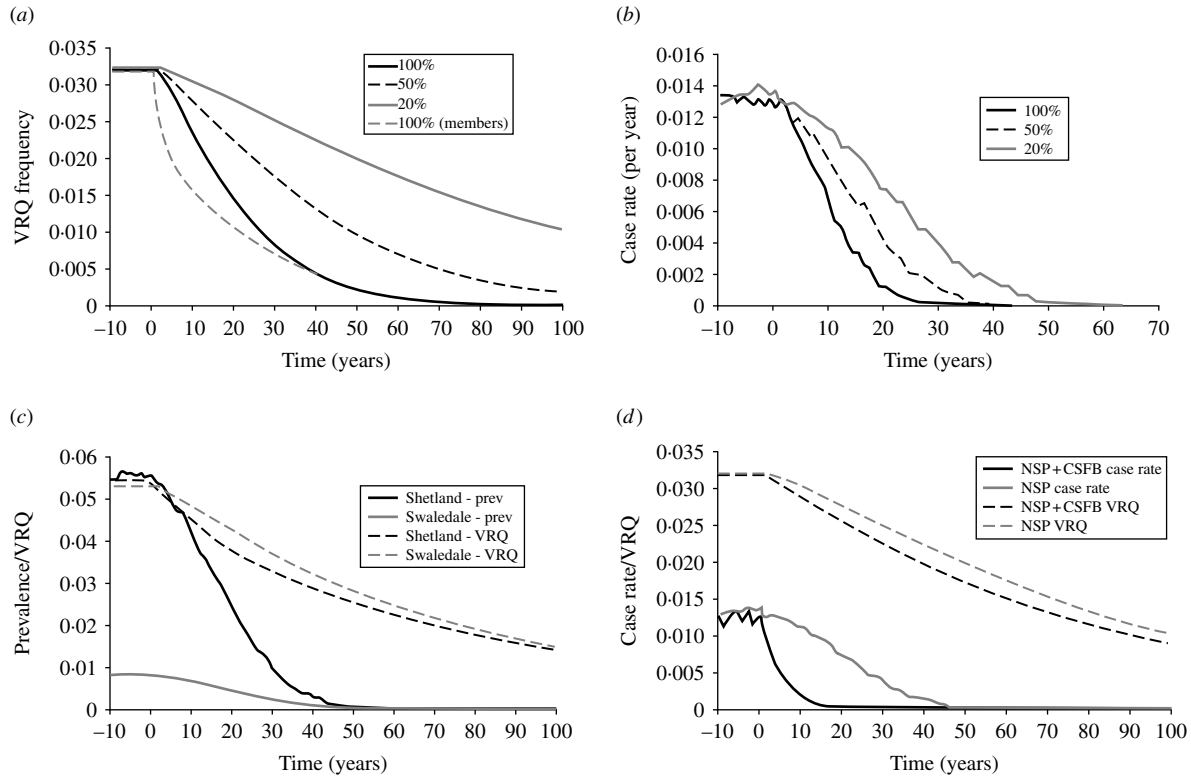

Fig. 2. National scrapie plan control policy results. (*a*) VRQ allele frequency and (*b*) observed flock case rate for various levels of compliance [also VRQ frequency for National Scrapie Plan (NSP) members]. (*c*) Prevalence and VRQ frequency in Shetland and Swaledale breeds. (*d*) NSP with 20% complaince with and without Compulsory Scrapie Flock Scheme (CSFS) included.

compliance. Only a small fraction of flocks are active members at any one time, with a maximum of around 3·5%. This figure follows directly from the incidence rate of 1% and an active membership of 3 years, given flocks maintain a disease-free and genetically resistant flock.

Figure 3*b* shows the breakdown of the CSFS into three component parts: trading restriction only, culling only and breeding with resistant rams only. Each aspect of the policy is enforced only in response to detected disease in a flock. Both culling and breeding are highly effective at reducing the observed case rate, either one being comparable to the effectiveness of the full policy. Trading restriction is markedly the least effective element of the policy, although it does lead to eradication over a timescale of several hundred years. We note that the effect of breeding restriction is almost identical to that of culling but delayed by a couple of years. This reflects impact of the two interventions: whereas culling instantaneously removes all susceptible animals from a flock, breeding takes a couple of years before both rams and ewes in a flock are both resistant and lead to only resistant progeny.

Figure 3*d* shows the prevalence of infected animals among those slaughtered across all flocks culled during the CSFS. Slaughter is restricted to ARQ- and VRQ-carrying animals. The mean percentage of animals culled that are infected is only 9%. The distribution is right-skewed with 50% having <4% infected and 90% having <25% infected. These figures will overestimate those with detectable scrapie infection as post-mortem tests can only detect scrapie in the latter period of the incubation period [14].

The EU minimum policy

Figure 4 compares the effects of the EU minimum policy with the NSP. For the purposes of comparison, we have used the same dynamics for joining the EU policy as used for the NSP: 6% probability of joining per year with 100% compliance assumed. In the case of the EU policy, membership is restricted to the high genetic-merit flocks, which we interpret as the pure-bred flocks at the top level of the stratified breeding structure. As expected, the minimal policy is slower to impact on the observed flock case rate than the

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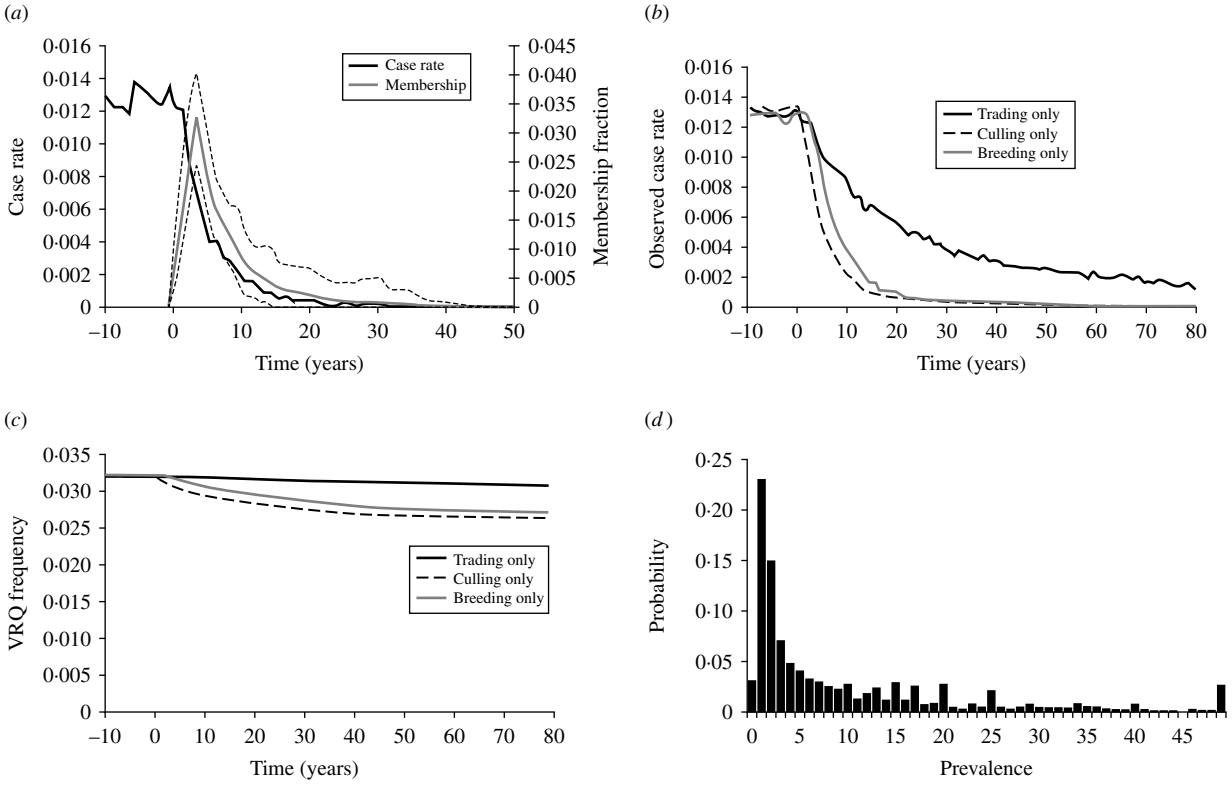

Fig. 3. Compulsory Scrapie Flock Scheme (CSFS) results. (*a*) Observed flock incidence rate under CSFS with active membership fraction. (*b*) Observed incidence rate under each component of the CSFS (trading, culling and breeding). (*c*) Evolution of VRQ frequency in population under each component. (*d*) Distribution of percentage of slaughtered animals infected with scrapie across culled flocks.

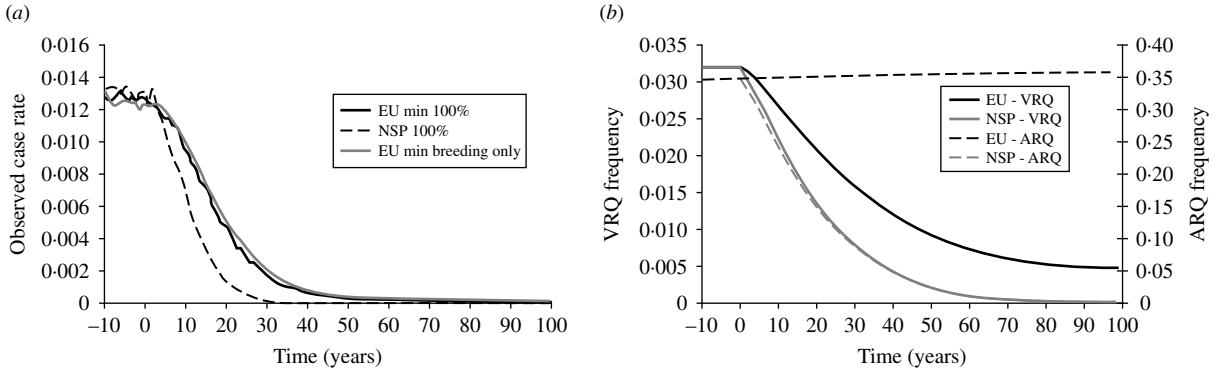

Fig. 4. Effect on (*a*) observed flock case rate and (*b*) allele frequency of the national flock under the EU minimum policy. NSP: National Scrapie Plan.

NSP. It is apparent that the effectiveness of the policy is almost entirely due to its breeding aspect with the trading component having a negligible contribution.

The difference between the minimal intervention and the NSP can be seen clearly in Figure 4*b*. The minimal policy focuses purely on the VRQ allele, resulting in a slight increase in ARQ frequency in contrast to the NSP which has an equal effect on both alleles. The smaller population covered by the minimal policy also results in a slower reduction of VRQ frequency and a non-zero final value.

Policy effects on breed R_0

Table 1 lists mean within-flock R_0 for all breeds within the model, both initially and after various interventions have eradicated scrapie from the population. The NSP focuses on both the susceptible alleles and quickly includes the whole population. As shown in

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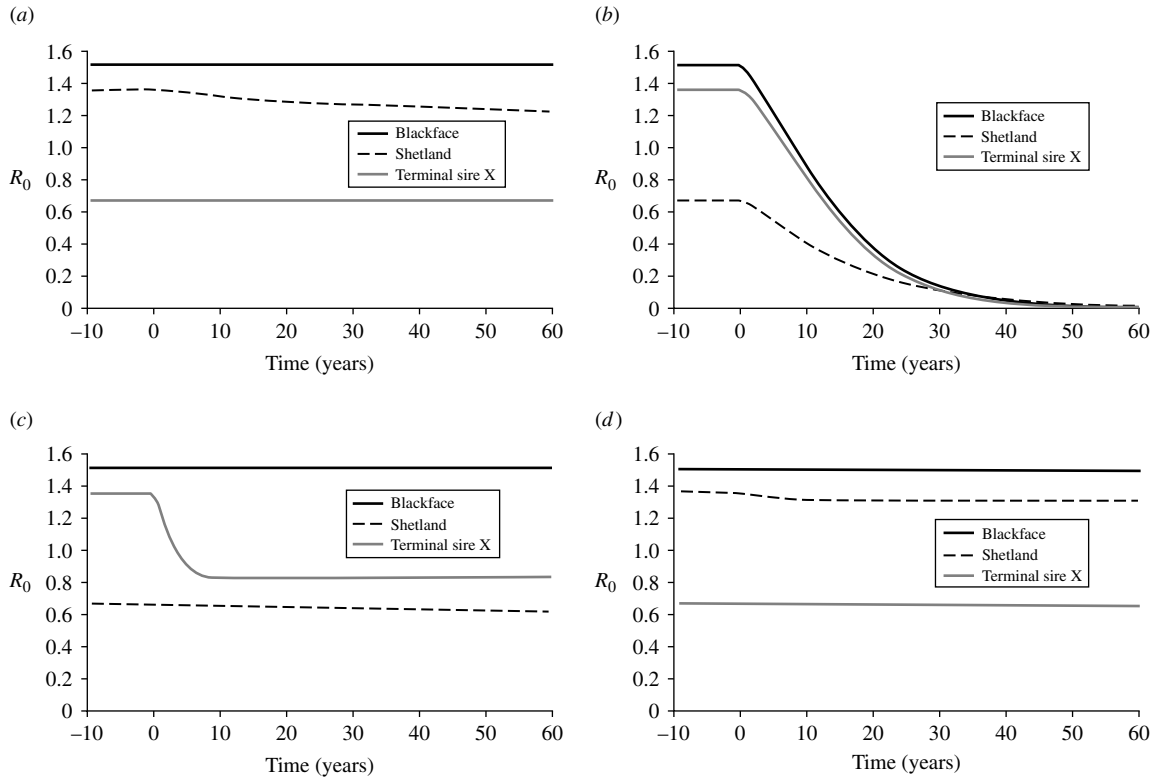

Fig. 5. Evolution of estimated flock BSE R_0 values under different interventions. (*a*) Natural decay, (*b*) National Scrapie Plan, (*c*) Compulsory Scrapie Flock Scheme, (*d*) EU minimum.

Figure 2, this leads to the eradication of both ARQ and VRQ alleles and R_0 is reduced effectively to zero. The impact of the CSFS and its components varies across the breeds. As an intervention that reacts to reported cases, it has the strongest effect on the breeds with the highest case rates; Shetland and Swaledale. Both these breeds have a fall in R_0 of about 20–25%. Other breeds, with low case rates, are subject to reductions in R_0 of about 30%, which approximately matches the decay in R_0 due to natural loss of susceptible alleles from genetic closure. As expected, different aspects of the CSFS have an almost identical effect on these breeds. For the high case-rate breeds, the impact of the various elements of the CSFS is varied. Culling and breeding restrictions, which alter genetic composition directly, have the greatest effect on R_0, while trading restrictions have a much more modest effect, although more pronounced than would be accounted for by the natural loss of susceptibles. The minimal policy targets only the VRQ allele and hence has a reduced effect on R_0 compared with the NSP. Even though the policy is not applied to cross-bred flocks, its influence on R_0 in these breed categories is clear, through the influence of allele frequency in breeding ewes.

BSE

In this section, we examine the influence of these interventions on the a possible undetected BSE epidemic. As discussed previously, we approach this problem by looking at the changes in within-flock R_0 for BSE generated by interventions. Values of R_0 were calculated from the susceptibilities calculated earlier (see UK national flock section) and arbitrarily normalized to give a R_0 of 1 for the North Country Cheviot breed. We note that the pre-intervention range of R_0 values is much narrower for BSE than for scrapie, reflecting the fairly even distribution of the ARQ allele.

Flock R_0 values for breeds before control intervention and after extinction of scrapie (100 years after intervention) are shown in Table 2. Figure 5 shows the evolution R_0 under four different interventions for a high case-rate breed (Shetland), a low case-rate breed (Scottish Blackface) and a lowland cross-breed grouping.

Natural decay of susceptible alleles due to the scrapie epidemic alone has almost no effect on BSE R_0 values. While the low incidence rate can have a large impact on the rare VRQ allele, the effect on ARQ frequency is negligible. The NSP intervention is

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Table 1. *Mean within-flock R_0 values for all breeds in the model*

	R_0						
		Intervention					
Breed	Initial	Closure	NSP (100%)	CSFS	CSFS (trading)	CSFS (culling)	EU min
Blackface	1·59	1·05	0	1·02	1·0	1·01	0·72
Welsh Mountain	1·56	0·97	0	0·96	0·97	0·96	0·26
Swaledale	1·43	0·63	0	0·32	0·72	0·31	0·3
Beulah Speckleface	1·01	0·66	0	0·69	0·69	0·68	0·34
North Country Cheviot	1·58	1·04	0	1·05	1·04	1·04	0·31
Suffolk	0·21	0·14	0	0·14	0·14	0·14	0·13
Shetland	2·43	1·2	0	0·51	1·23	0·52	0·69
Longwool cross	0·68	0·4	0	0·32	0·41	0·32	0·26
Terminal sire	0·42	0·25	0	0·21	0·24	0·22	0·19

NSP, National Scrapie Plan; CSFS, Compulsory Scrapie Flock Scheme.

Table 2. *R_0 values for breeds*

	R_0						
		Intervention					
Breed	Initial	Closure	NSP (100%)	CSFS	CSFS (trading)	CSFS (culling)	EU min
Blackface	1·52	1·52	0·00	1·51	1·52	1·51	1·52
Welsh Mountain	0·93	0·92	0·00	0·92	0·93	0·92	0·90
Swaledale	0·98	0·95	0·00	0·64	0·97	0·64	0·97
Beulah Speckleface	1·05	1·05	0·00	1·05	1·05	1·05	1·04
North Country Cheviot	1·00	1·00	0·00	0·98	1·00	1·00	0·97
Suffolk	0·60	0·60	0·00	0·59	0·59	0·60	0·60
Shetland	1·36	1·31	0·00	0·91	1·32	0·86	1·46
Longwool cross	0·79	0·78	0·00	0·70	0·78	0·69	0·78
Terminal sire	0·67	0·67	0·00	0·63	0·67	0·62	0·66

NSP, National Scrapie Plan; CSFS, Compulsory Scrapie Flock Scheme.

again effective at control since it targets ARQ and VRQ equally and throughout the entire population. The impact of CSFS on BSE R_0 is almost identical to that on scrapie R_0, reducing it by a factor of around 30% in high case-rate breeds. Since the culling and breeding aspects of the CSFS focus equally on ARQ and VRQ, this is expected. Figure 4*d* shows that the impact on the Shetland breed is pronounced and rapid, while other low case-rate breeds are barely affected. The EU minimum policy shows the greatest disparity between its effect on scrapie and on BSE. Focusing on the VRQ allele, it is a reasonably effective intervention against the scrapie epidemic, but has a negligible effect on R_0 values for BSE. There is some indication of an increase in mean R_0 for the Shetland breed, suggesting the policy might exacerbate BSE infection in this breed.

DISCUSSION

The model we present in this paper combines both breeding and transmission mechanisms on the levels of the population, flocks within breeds and at the individual level. As such, it allows us to assess the impact of complex control policies which interact with these mechanisms at various levels.

In the absence of any control intervention, preferential loss of susceptible alleles caused by scrapie gradually eradicates the disease from the population. This process occurs slowly, leading to extinction on a

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timescale of about 400 years (Fig. 1*a*). Loss of susceptible alleles is not uniform across the population, but is localized to those breeds with the highest case rates; Shetland, Swaledale and to a lesser extent, Suffolk. While Shetland and Swaledale flocks experience a reduction of 20–25% in VRQ allele frequency, other breeds are largely unaffected genetically. This raises the possibility of re-introduction of scrapie even after it has become naturally extinct.

The implementations discussed in this paper can be divided into two types. The NSP and the EU minimal policy are global, in the sense that all, or a large proportion, of the flock population are encouraged to join and comply with the relevant restrictions. The CSFS intervention is reactive, in that it is applied only when flocks have detected cases and only for a limited time.

The NSP is a highly effective policy which both eradicates susceptible alleles and scrapie from the population. Extinction of scrapie occurs when VRQ frequencies have fallen to roughly 75% of initial levels (Fig. 2). This level matches that at which prevalence in Shetland and Swaledale flocks is eradicated in the absence of control (Fig. 1). With 100% compliance, the flock case rate has dropped to negligible levels within 30 years on average. Complete eradication of scrapie from the population occurs after 32 years (95% CI 23–43 years). Even with compliance as low as 20%, eradication is achieved after 54 years (95% CI 42–69 years). The timescale of control is in rough agreement with other results on the effectiveness of breeding control policies [15].

The most effective intervention is a combination of NSP and CSFS, which corresponds to the current UK policy. This eradicates scrapie in 21 years (95% CI 15–27 years). More rapid suppression of susceptible alleles could speed up eradication. There is evidence that the NSP in the United Kingdom has reduced VRQ frequency from 3% to 1·2% among its members. This rate exceeds even 100% compliance in our model. The inclusion of choice of resistant ewes for breeding allows this eradication rate to be matched, but there is little effect on scrapie incidence. In eradicating scrapie, the CSFS intervention in isolation has a similar efficacy to the NSP with 100% compliance. However, it has little impact on the allele frequencies of the population, beyond Shetland and Swaledale breeds. As a result, even after eradication of scrapie, the possibility would remain for future outbreaks to occur. We find that not all the components of the CSFS are equally effective. Trading and culling are equally effective and either is comparable to the full policy. Trading restrictions alone have very little power to limit transmission. From this work, it seems that the CSFS is over-specified; a more efficient implementation might consist of either culling or breeding restrictions alone. As shown in Figure 3*d*, the majority of culled flocks have only a few percent of infected animals, indicating the slaughter of a large number of healthy sheep (this problem is recognized in a recent EC amendment [16]). Hence, while NSP membership levels are low, a reactive policy targeting scrapie-positive farms with resistant rams would be as effective as the full CSFS. Once breeding for resistance is established in the majority of the flock population, a reactive policy no longer has an important role to play.

Only very tentative conclusions can be drawn concerning BSE in the national flock. R_0 values are more homogeneous than for scrapie suggesting that BSE prevalence would be more homogeneously distributed across breeds than scrapie. Natural epidemic decay associated with scrapie has almost no impact on BSE R_0 values and would therefore not be expected to have an impact on levels of BSE infection. Since the ARQ allele is so abundant in all breeds, it is unlikely that preferential loss of this allele through BSE infection could have an appreciable effect on the disease unless prevalence was much higher than for scrapie.

We would expect the NSP to be as effective against BSE as scrapie as it targets ARQ alleles in addition to VRQ. While the CSFS would still be effective against BSE in the Shetland and Swaledale breeds, the more homogeneous distribution of BSE would leave it uncontrolled in the majority of the national flock. The starkest difference in potential effectiveness is seen in the EU minimal policy, while it is quite an efficient measure against scrapie, its focus on the VRQ allele means that it would have almost no effect in BSE. There is even some indication that the policy might increase BSE R_0 for the Shetland breed. However, the interactions of a low-level transmission of BSE with endemic scrapie under control interventions can only be fully assessed within a model that includes both BSE and scrapie infection and transmission processes.

APPENDIX

Model description

Population structure

The details of the construction and fitting of the model are described in a companion paper [2]. Here

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we present only its main features. The 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.

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 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 NSP [17]. Equally, 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 is matched to those found in the UK population. Flock sizes are distributed according to the means reported for each breed [3]. Table A1 shows the breeds included in the model and their flock numbers and sizes.

Within each breed, flow of genetic material is governed by the breeding structure. Ewes from pure-bred flocks are crossed with Longwool rams to produce the Longwool cross animals of the second tier of the breeding structure. Longwool cross ewes are then crossed with Suffolk rams to generate the third tier of Suffolk cross adults. The Longwool and Suffolk cross 'breeds' aim to include some of the complex web of cross-breeding characteriZing the lower two tiers of the breeding structure. The details of the interconnections are taken from a survey of the British sheep industry [3].

Genetic basis

Susceptibility to scrapie in sheep is strongly linked to genotype and is particularly associated with 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, AHQ, VRQ, ARQ and ARH. The mean genetic make-up of pure-breed flocks was taken from Eglin *et al*. [5] (see Table A2) 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 the ARH allele (~40%). Texel rams are a common choice of terminal sire and Texels and Texel crosses

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

Flock type	Breed	No. of flocks	Flock size
	Scottish Blackface	390 (232)	345
	Welsh Mountain	320 (232)	380
	Swaledale	252 (152)	333
Pure breeds	Beulah	170 (80)	234
	North Country Cheviot	320 (135)	191
	Suffolk	400 (350)	43
	Shetland	40 (24)	47
	Longwool cross adults	1280	200
Cross-breeds	Terminal sire Suffolk breeding	1280	173
	Terminal sire Suffolk adults	380	330

Flock numbers in parentheses represent flocks engaged in pure-breeding [17].

Table A2. *Mean allele frequencies by breed* [*5*] *and scrapie case rate per head per year* (*relative to Shetland breed*). *Cross-breed allele frequencies generated by breeding structure*

Breed	ARQ	VRQ	Case rate
Blackface	0·59	0·025	0·00036
Welsh Mountain	0·335	0·065	0·012
Swaledale	0·37	0·055	0·07
Beulah Speckleface	0·4	0·035	0·006
North Country Cheviot	0·365	0·065	0·008
Suffolk	0·235	0·005	0·06
Shetland	0·56	0·06	1
Longwool cross	0·32	0·03	0·0028
Terminal sire	0·28	0·017	0·0096

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Table A3. *Relative susceptibilities of genotypes represented in the model*

Genotype	Susceptibility
ARR/ARR	0
ARR/ARQ	0·0003
ARR/VRQ	0·005
ARQ/ARQ	0·025
ARQ/VRQ	0·12
VRQ/VRQ	1

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.

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. Susceptibilities of genotypes are calculated from case-rate data [17] (see Table A3). 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 [18]. For simplicity, new cohorts of lambs are generated at the same time-point 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 [19]. 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.

We found that using relative case rates calculated in Baylis *et al*. [20] leads to significantly different case 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.

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. The pattern of infectious contact between breeds is shown in Table A4. 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.

Table A4. *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

Data from the Statutory Notification Database (SND) shows considerable variation in the incidence of confirmed cases by breed [17]. This pattern of variation is markedly different from that predicted by assuming a uniform force of infection (FOI) across all flocks and calculating susceptibilities according to current estimates of breed genetic composition [5]. 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_{A}^{b} is the contact rate of breed A and C_{AB} is the probability of contact between breed 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, we

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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 [3]. 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.

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DECLARATION OF INTEREST

None.

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