24. At the coding regions, *Sinv.b'* differs from the other *b*-like alleles of *S. invicta* at four nucleotide positions, resulting in three amino acid differences (Fig. 2). Three of these four divergent *Sinv.b'* nucleotides are identical to the corresponding nucleotides in all *B* alleles, with the result that only six amino acids differ between *Sinv.b'* and the *B* alleles. None of these six amino acid differences is expected to produce a net charge difference (*Sinv.b'* and the *B* alleles share a glutamic acid at position 151), explaining why the protein product of *Sinv.b'* is electrophoretically indistinguishable from that of the *B* alleles. All noncoding regions of *Sinv.b'* are identical to *Sinv.b1*.
25. Differences in nucleotide sequence between the *B* and *b*-like alleles of *Gp-9* were used to design a diagnostic PCR/RFLP assay (*27*). Genomic DNA was amplified with gene-specific primers, and the resulting 828-bp product was purified and digested with Bsa AI. The allele-specific fragments produced were separated in a 1% agarose gel containing ethidium bromide and then visualized under ultraviolet light.
26. Single specimens for sequencing were obtained for the fire ant species *Solenopsis amblychila*, *S. aurea*, and *S. geminata* from the United States, the fire ant species *S. interrupta*, *S. macdonaghi*, *S. quinquecuspis*, *S. richteri*, and *S. saevissima* from Argentina and Brazil, the thief ant species *S. globularia littoralis* from the United States, and an unidentified species of the solenopsidine genus *Monomorium* from the United States. The specimens of *S. macdonaghi*, *S. quinquecuspis*, and *S. richteri* were obtained from known polygyne nests (*19*); all other fire ant specimens were from known or presumed monogyne nests. *Gp-9* sequences are deposited in GenBank under the accession numbers AF427889 through AF427906 and AF459414; the aligned sequences are presented in Web fig. 1 (*27*).
27. Supplementary material, including details of methods and complete aligned sequences, is available on *Science* Online at www.sciencemag.org/cgi/content/full/1065247/.
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31. Selection is implicated when the rate of nonsynonymous substitutions, which lead to amino acid changes, significantly exceeds (positive selection) or falls short of (negative selection) the rate of synonymous substitutions, which do not lead to such changes (*32*, *33*). Fisher's exact test of homogeneity was used to test $n/N = s/S$ along each branch under the null hypothesis of neutral evolution, where $n$ and $s$ are the numbers of nonsynonymous and synonymous substitutions per *Gp-9* sequence, respectively, and $N$ and $S$ are the numbers of potential nonsynonymous and synonymous sites (*32*). We pooled coding region synonymous sites with intron sites for these tests (*33*) after determining that there are no differences in substitution rates between them (Fisher's exact test, all $P > 0.09$). No episodes of negative selection were detected in this study.
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38. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
39. The tree was generated with the neighbor-joining algorithm (*36*) on the uncorrected pairwise sequence divergences over 2200 bp that include the *Gp-9* exons and introns, the 3′ untranslated region (UTR), and the 3′ flanking region (*27*, *37*). The strict consensus of five maximum parsimony trees obtained with the branch-and-bound method has a topology identical in its essential features to the neighbor-joining tree (*27*).

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# The Potential Size and Duration of an Epidemic of Bovine Spongiform Encephalopathy in British Sheep

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**Because there is a theoretical possibility that the British national sheep flock is infected with bovine spongiform encephalopathy (BSE), we examined the extent of a putative epidemic. An age cohort analysis based on numbers of infected cattle, dose responses of cattle and sheep to BSE, levels of exposure to infected feed, and number of BSE-susceptible sheep in the United Kingdom showed that at the putative epidemic peak in 1990, the number of cases of BSE-infected sheep would have ranged from fewer than 10 to about 1500. The model predicts that fewer than 20 clinical cases of BSE in sheep would be expected in 2001 if maternal transmission occurred at a rate of 10%. Although there are large uncertainties in the parameter estimates, all indications are that current prevalence is low; however, a simple model of flock-to-flock BSE transmission shows that horizontal transmission, if it has occurred, could eventually cause a large epidemic.**

BSE in the United Kingdom was spread through feed containing meat and bone meal (mbm) contaminated with BSE-infected animal material (*1*). Sheep in the United Kingdom were also fed mbm, and it is known that sheep can be infected with BSE by the oral route (*2*). No field cases of sheep BSE have been observed, but it has been a concern for a number of years (*3*), and the Food Standards Agency of the UK government has recently demanded a comprehensive search for it (*4*), in part because sheep are the natural hosts of scrapie, a transmissible spongiform encephalopathy (TSE) that has clinical signs indistinguishable from BSE. If BSE is masquerading as scrapie in the national flock, two independent estimates show that the current number of BSE cases (i.e., sheep that live long enough to show signs of infection) in sheep is likely to be few. First, an extensive survey of UK flocks found no indication of an increase in scrapie incidence during the height of the cattle BSE epidemic (*5*, *6*). The sensitivity of this study implies that fewer than 200 flocks could have been acquiring a case of BSE per year at the peak. Second, in the late 1990s, of 156 brains taken from sheep purported to be infected with scrapie, none contained BSE, indicating that between 0 and 100 or at most 2% of yearly scrapie cases were actually BSE at that time (*4*).

Using a simple age cohort analysis, we examined the extent of a putative epidemic of BSE in British sheep and compared our results with these estimates. Our calculations are based on the cattle infection rate, the dose responses of cattle and sheep, their relative yearly consumption of mbm, and estimates of the number of BSE-susceptible sheep obtained from a survey of sheep PrP genotypes (*7*, *8*). In the year of the epidemic peak, the number of cases of BSE-infected sheep calculated is consistent with both of the existing estimates. Should there be horizontal transmission of BSE from sheep to sheep, a model of flock-to-flock BSE transmission shows that even if current cases are few, such an epidemic could be in its very early stages and a substantial epidemic in the future cannot be ruled out.

The susceptibility of sheep to BSE is strongly associated with the encoding of glutamine

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(Q) at codon 171 in the PrP gene (*9*); sheep that are $QQ^{171}$ homozygous for this allele are characterized by shorter incubation periods than $QR^{171}$ heterozygotes (*10*). Sheep that do not encode Q at position 171 appear to be resistant to BSE. The number of susceptible sheep in the United Kingdom was calculated from a study of UK sheep farms in which over 10,000 sheep in 36 flocks from 27 breeds have been PrP genotyped (*11*). We restricted our analysis to 4580 sheep born before 1997, because the introduction of genotyping at this time began to substantially increase the numbers of TSE-resistant sheep in our study. These data were combined with the breed distribution of British sheep revealed by a recent postal survey (*12*) to obtain an estimate of the total genetic contribution of the various breeds. All flocks were categorized as either "Hill and Upland" or "Lowland," and the genotype profiles for these two sectors were calculated from the breed proportions. These sectors were considered separately because of their different breeding structure and different per capita consumption of feed concentrate that was potentially BSE contaminated (*13*). Average genotype proportions were assumed for breeds for which there were insufficient data, and genotypes of crossbreeds were inferred from the genotype profile of the sire and dam breed types. Of about 8.0 million breeding ewes in the Hill and Upland sectors in 1987, we calculated that 35% were $QQ^{171}$ homozygous, 49% were $Q(R/H)^{171}$ heterozygous, and 16% did not encode Q at position 171. Of 8.6 million breeding ewes in the Lowland sector, the percentages are 31, 52, and 17%, respectively. We assume equal susceptibility for all $Q^{171}$ carriers but (based on experimental sheep infections) different incubation periods. Oral exposure of $QQ^{171}$ sheep to high doses of BSE resulted in 30% with clinical signs after 2 years post infection (ypi) and another 20% by 4 ypi (*14*). The experiment is ongoing, and we assumed that the remainder would develop clinical signs by the end of their next ypi, i.e., another 20% at 5 ypi and the last 30% at 6 ypi. Only one incubation period is known for $QR^{171}$ heterozygotes; at about 5 ypi, it is consistent with incubation periods for heterozygotes in intracerebral inoculation experiments (*14*). We assumed an incubation period for $Q(R/H)^{171}$ heterozygotes that took the same shape as for the homozygotes but shifted to be 3 years longer.

We calculated the dose response for sheep using a logistic curve, with a slope estimated from titrations of scrapie in mice (*15*). The intercept is obtained by noting that 2 of 10 [95% confidence interval (CI): 4 to 56%] susceptible sheep developed BSE after consuming 0.5 g of infected cattle brain (i.e., 20% of sheep developed BSE after being fed an infectious dose of 0.5 g, or $ID_{20}$ = 0.5 g) (*10*). These parameters are consistent with the prevalence in two ongoing experiments of BSE infection observed in $QQ^{171}$ sheep fed 5 g of brain (*14*, *16*). For cattle, we assumed the same slope and noted that 70% (95% CI: 35 to 92%) of cattle exposed to 1 g of brain became infected ($ID_{70}$ = 1 g) (*17*). The difference between the two curves (Fig. 1A) represents the species barrier (*17*). As the confidence intervals overlap, we considered that, at worst, contaminated mbm is equally infectious to sheep and cattle.

We considered four factors when determining the exposure of sheep to contaminated mbm: consumption of contaminated mbm by cattle, distribution of contaminated material in mbm, relative consumption of feed concentrate by sheep compared with cattle, and relative proportion of mbm in sheep and cattle feed concentrate. We did not consider the possible, but unquantifiable effects of scrapie infectivity also being in mbm, as any effect of competition between scrapie and BSE strains (*18*) would only be to lower the limit on the number of BSE infections initiated in sheep.

The first cases of BSE in cattle may have occurred as early as the 1970s. Because of recycling of infectivity in feed, the force of infection of BSE on cattle increased every year, with cattle born in 1988 at greatest risk of BSE infection. In that year, the ruminant feed ban greatly reduced the force of infection, and the comprehensive ban of mammalian mbm in all animal feed in 1996 is likely to have virtually eliminated it (*1*). It was estimated that 17% of cattle born in 1988 were infected with BSE and would have shown clinical signs had they lived to 10 years of age (*19*). Dairy cattle were at the greatest risk, accounting for almost 90% of cases (*19*), implying that 28% of dairy cattle would have been infected. Although there are indications that exposure was likely to have been broad and at low dose (*20*), we used two scenarios to calculate the exposure limits. In the first scenario, we assumed that cumulative $ID_{28}$'s were fed to 100% of cattle in dairy herds. In the second scenario, we considered highly aggregated doses, where 24% of all cattle (or 37% of dairy) are assumed to have received $ID_{75}$ doses. As an additional scenario to illustrate the range of possible results, we also calculated the epidemic size for the situation where 56% of dairy cattle received $ID_{50}$ doses. We assumed that aggregation of infectivity in cattle and sheep feed is proportionate (for example, if all cattle were exposed, this implies that all sheep were exposed), and this resulted in more infected sheep in the second scenario than in the first,

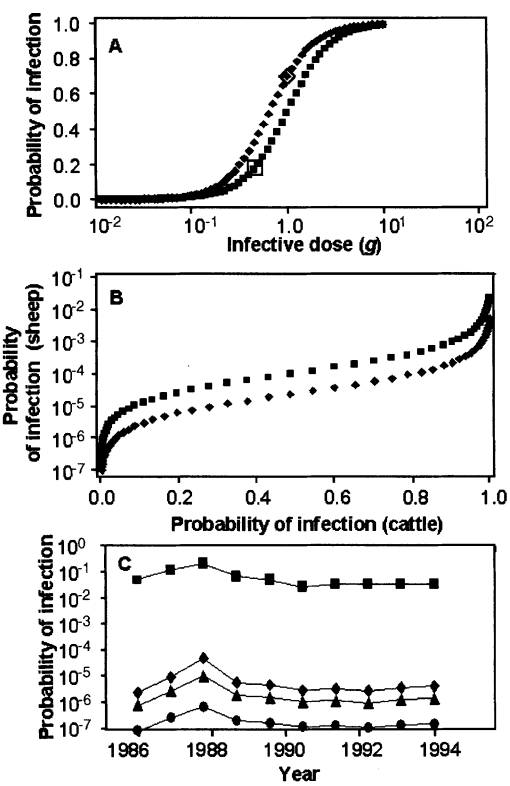


**Fig. 1.** Calculation of the force of infection due to consumption of infected mbm. (**A**) The probability of infection is given by the logistic regression equation $\ln[p/(1-p)] = \beta_0 = \beta_0 \log(x)$, where $x$ is the dose in grams, $p$ is the probability of infection, and $\beta_0$ is the intercept (about equal to −0.032 for sheep and 0.85 for cattle) and the slope $\beta_0$ is fixed to be 4.5 for both. For a given probability of infection for cattle, we can calculate the infective dose. This dose is multiplied by the relative amount of feed concentrate given to sheep compared with cattle and the relative proportion of mbm in feed, giving the corresponding dose to sheep and thus the probability of infection. For a given infectious dose to cattle, these figures imply that a 1.6-fold dose increase would have the same probability of infection in sheep. The open symbols represent the known data (■, 2 of 10 sheep infected at 0.5 g; ◆, 7 of 10 cattle infected at 1 g). (**B**) The relative probability of infection for cattle and sheep given by the solution for $p^s$ of the equation $\ln[p^s/(1-p^s)] = \beta_0^s + \beta_0^s(\log(y) + (\{\ln[p^c/(1-p^c)]\} - \beta_0^c)/\beta_0^c)$, where the superscripts represent the respective quantities for sheep and cattle in the logistic regression equation and $y$ is the relative amount of mbm fed to sheep compared with cattle. In this figure, 50% of dairy cattle are assumed to have been exposed to $ID_{56}$'s, and sheep concentrate is assumed to contain 50% as much mbm as cattle concentrate. (**C**) Probability of infection for sheep and cattle between 1986 and 1995. As the probability of infection for cattle is known from 1986 to 1995 (*19*), we can generate the equivalent probability of infection for sheep. The three lower curves represent low infectivity (◆, 100% of dairy cattle are exposed to $ID_{28}$'s, 10% as much mbm in sheep feed as in cattle feed), intermediate infectivity (▲, 50% exposed to $ID_{56}$'s, 30% as much mbm in sheep feed), and high infectivity (●, 37% exposed to $ID_{75}$'s, 50% as much mbm in sheep feed).

with intermediate values in the third scenario.

The yearly production of feed concentrate for sheep and cattle in the United Kingdom is known (*21*) as well as the number of breeding ewes and cattle that consumed it. Lowland sheep consumed the most feed concentrate, and all lambs consume little. Here we assume that their consumption is negligible (*13*). The sheep per capita consumption of concentrate rose slowly in the years of interest. Compared with cattle, sheep were fed about 100-fold less concentrate in 1986 and 50-fold less in 1995. Throughout the time frame considered here, the proportion of mbm in sheep feed concentrate would have varied but would have been at most equal to the proportion in cattle feed concentrate and probably much less (*13*, *21*, *22*). In this analysis, we investigated a range of between 10 and 75% inclusion of mbm in sheep feed compared with cattle feed. Using these scenarios, we calculated that, at the peak of exposure in 1988, between 0.0016 and 0.0046% of susceptible Hill and Upland sheep and between 0.0067 and 0.19% of Lowland sheep became infected. Exposures were calculated in a similar fashion for all years between 1986 and 1995 (Fig. 1C). Exposure through mbm in other years was assumed to be negligible.

There is evidence for the maternal transmission of natural scrapie in sheep (*23*), and it must therefore be considered a possibility for BSE in sheep. Scrapie infectivity has been found in the placenta of infected ewes as early as 477 days before their developing clinical signs (*24*). In our analysis, we considered maternal transmission rates of 0, 10, and 30% occurring over the entire course of the infection.

We calculated the time course of the feed-borne epidemic using an iterative model, updated in yearly time steps. Variables included infection status, age cohort, genotype, and flock type (*25*). For 50% mbm inclusion in sheep feed compared with cattle, at the epidemic peak in 1990, there were about 210, 110, and under 80 clinical cases, for the scenarios where 37% of cattle received $ID_{75}$'s, 58% received $ID_{50}$'s, and all received $ID_{28}$'s respectively. For 30, 10, and 0% maternal transmission, the number of cases of BSE in 2001 was calculated to be 19, 4, and 0 for the upper limits of infected feed exposure, 16, 4, and 0 for the intermediate values, and 14, 4, and 0 for the lower limits. Example epidemics are shown in Fig. 2. The "worst" of these scenarios presents a sensible outer limit for parameters values. However, data on key parameters are scarce, and so in Fig. 3, we present the impact of extreme parameter values, while stressing that they lie at the limits of consistency with the best information currently available. Even for these extreme scenarios, the predicted number of current cases of BSE in sheep is few.

If BSE in sheep behaves like scrapie, it may be horizontally transmissible. Furthermore, because of the high prevalence of the $Q^{171}$ codon, virtually all sheep flocks would have some susceptible animals and be considered to be at risk. This is very different from scrapie, for which the epidemic peaked several hundred years ago, possibly because of selection against susceptible genotypes (*26*), and thus, a BSE epidemic is potentially much larger than one might infer from the current low prevalence of scrapie. TSEs have very long incubation periods, and so the impact of horizontal transmission may not yet be felt. A hypothetical scenario based on a flock-to-flock model of scrapie in sheep (*27*, *28*), which is consistent with existing within-flock scrapie transmission models (*29*, *30*) and known large scrapie outbreaks (*26*), shows that an epidemic based on horizontal transmission may yet be in its early stages and below the detection level of prior analyses (Fig. 4).

The uncertainties in some parameters leave wide margins on our estimate of how many sheep may currently be infected with BSE, but these analyses provide reassurance that, so long as BSE is not horizontally transmitted and is vertically transmitted at rates comparable with other TSEs, the current population of UK sheep contains none or at most only tens of individuals that are infected with BSE. These are most likely in the lowland flocks that consume the majority of feed concentrate. Should horizontal transmission be occurring at a significant level, current numbers are still likely to be low, but they may be rising, emphasizing the importance

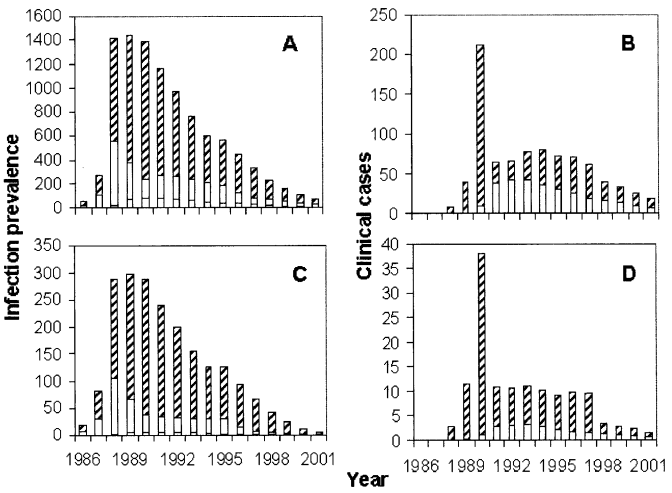


**Fig. 2.** The number of BSE-infected sheep and number of clinical cases from 1985 and 2001. (**A**) Prevalence of sheep infected with BSE for upper (37% $ID_{75}$'s, 30%, 50%) values of the epidemic parameters. (**B**) Yearly incidence of clinical cases of BSE in sheep for the same parameter values as above. The white area represents those age 0 to 3, and the diagonally dashed are those aged 3 and above. The proportion of the white area below the solid lines is the number of maternally transmitted infections. (**C**) Prevalence of sheep infected with BSE for intermediate (56% of dairy cattle receiving $ID_{50}$'s, 10% maternal transmission and mbm in sheep feed, 30% compared with cattle feed) values of the epidemic parameters. (**D**) As for (B), referring to parameters in (C). For lower values of parameters (100% $ID_{28}$'s, 0%, 10%), the number of cases is near zero (maximum of 20 infected sheep in 1990, none in 2001). The white area represents those age 0 to 3 and the diagonally dashed are those aged 3 and above. The proportion of the white area below the solid lines is the number of maternally transmitted infections.

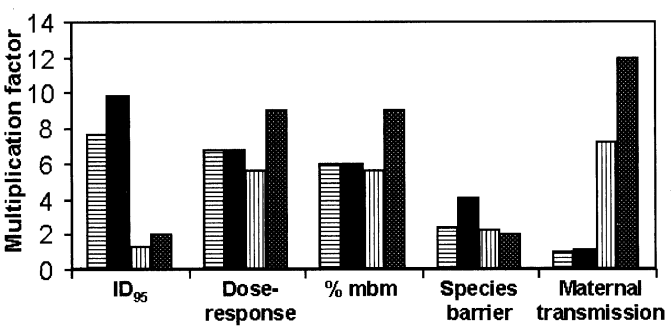


**Fig. 3.** Sensitivity analysis. Comparison of model output for changes in various parameters with an assumed baseline of 58% of dairy cattle receiving $ID_{50}$ doses, slope of the dose response curve of $\beta_1$ = 4.5, 30% mbm fed to sheep as compared with cattle, $ID_{50}$ dose for sheep 1.6 times the $ID_{50}$ dose for cattle (species barrier effect), and 10% maternal transmission. Represented on the figure are changes in (i) the number of infected sheep in 1988 (solid bars, baseline value 295 infected), (ii) number of clinical cases in 1990 (horizontal stripes, 38 cases), (iii) number of infected in 2001 (dot pattern, eight infected), and (iv) number of clinical cases in 2001 (vertical stripes, one case). Along the *x* axis, each group of bars represents, from left to right, 28% of dairy cattle receive $ID_{95}$'s, $\beta_1$ = 3.5, 75% mbm, no species barrier, and 50% maternal transmission. Changing the distribution of infected mbm so that relatively few sheep ate large lumps of potentially infectious mbm had the greatest effect on the early epidemic. Of most current concern is maternal transmission, which is the most important parameter for prolonging the epidemic and increases the current number of clinical by more than an order of magnitude.

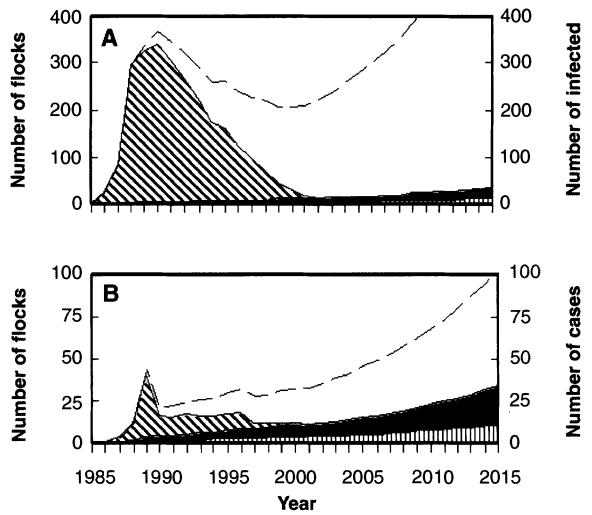


**Fig. 4.** Flock-to-flock BSE transmission. The model was modified from a flock-to-flock model of scrapie dynamics, where trading of infected sheep was assumed to be the predominant mode of transmission (*27*). Sheep flocks were described as susceptible, exposed (an infected sheep has been brought in, and within-flock transmission occurs at most at low levels), and afflicted (the flock harbors a major within-flock epidemic). Sheep infected through the feed route were assumed to be potentially infectious up to 1 year before developing clinical signs. Sheep infected through the feed route might have a different probability of infecting others than sheep infected by horizontal transmission, and so here we seeded the epidemic with 10% of all sheep infected through feed in their last year before developing clinical signs. For the parameters used here (the baseline parameters from Fig. 3), the number of sheep infected by maternal transmission was small, and so these sheep were not treated differently from sheep infected through feed. Within-flock epidemics were characterized to be consistent with documented scrapie epidemics and existing within-flock models. The relevant model parameters were as follows: the within-flock basic reproduction ratio, $R_0^w = 3.0$ (the average number of secondary infections resulting from introducing a single infected animal into an otherwise susceptible flock, which must be greater than 1 for an epidemic to occur), the rate of recovery of exposed flocks (0.5 year$^{-1}$), the rate of development of major epidemics (0.1 year$^{-1}$), the rate of recovery from major epidemics (0.1 year$^{-1}$), and the average disease prevalence in exposed flocks (two per flock) and afflicted flocks (55 per flock). (**A**) The number of flocks with infected sheep (of 50,000 flocks in the national flock) and the number of infected sheep. (**B**) The number of flocks that experience clinical cases per year and the incidence of clinical cases. Curves are stacked to show the sum of afflicted flocks (vertical lines), exposed flocks (solid region), and flocks containing sheep infected through the feed route (diagonal stripes). The dashed line (not stacked with others) represents the prevalence of infected sheep in the national flock (A) or the annual incidence of clinical cases (B). This is a hypothetical epidemic to show that horizontal transmission is consistent with the estimates of low current incidence; however, there are many scenarios for which this is true. In particular, if the between-flock $R_0$ is less than 1, the epidemic dies out even if $R_0^w$ is greater than 1 (although any horizontal transmission will increase the duration of the epidemic). Unless the peak of the feed-borne epidemic is sufficiently large, stochastic effects may also drive the horizontally transmitted epidemic to extinction before it can take off; however, our purpose is to describe the long-term behavior of an epidemic consistent with low current prevalence rather than make an exact prediction.

of the rapid implementation of the National Scrapie Plan to create a TSE-resistant national flock (*31*).

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25. Age cohort equations for Hill and Upland flocks:

$$V_{QQ}(t) = \sum_{\tau=1}^{\tau_f} \sum_{a=t0}^{t} \left\{ I_{QQ}(t,\tau,a)b(\tau)v\left(f_{QQ} + \frac{1}{2}f_{QR}\right) + I_{QR}(t,\tau,a)b(\tau)v\left(\frac{1}{2}f_{QQ} + \frac{1}{4}f_{QR}\right) \right\}$$

$$I_{QQ}(t,1,t) = V_{QQ}(t)$$

$$I_{QQ}(t,\tau,a) = I_{QQ}(t-1,\tau-1,a)d(\tau)\mu_{QQ}(t-a) + S_{QQ}(t-1,\tau-1)F(t)d(\tau) \quad \text{for } \tau > 1$$

$$V_{QR}(t) = \sum_{\tau=1}^{\tau_f} \sum_{a=t0}^{t} \left\{ I_{QQ}(t,\tau,a)b(\tau)v\left(f_{RR} + \frac{1}{2}f_{QR}\right) + I_{QR}(t,\tau,a)b(\tau)v\left(\frac{1}{2}f_{QR} + \frac{1}{4}f_{RR}\right) \right\}$$

$$I_{QR}(t,1,t) = V_{QR}(t)$$

$$I_{QR}(t,\tau,a) = I_{QR}(t-1,\tau-1,a)d(\tau)\mu_{QR}(t-a) + S_{QR}(t-1,\tau-1)F(t)d(\tau) \quad \text{for } \tau > 1$$

The first and fourth equations refer to maternal transmission, the second and fifth equations refer to the first age cohort (0 to 1), and the last two to all other age cohorts. For the two genotypes labeled *QQ* and *QR* (note that "*R* includes all resistant alleles), $I_{QQ}(t,\tau,a)$ and $I_{QR}(t,\tau,a)$ are the number of animals infected for a given age cohort $\tau$, infected at time $a$, that survive to time $t$. The remaining parameters are the frequency of the two genotypes $f_{QQ}$ and $f_{QR}$, the first year of the calculation $t_0$ (1986) and the oldest age cohort considered, $\tau_f$ (9 years). The variables $S_{QQ}(t,\tau)$ and $S_{QR}(t,\tau)$ are the numbers of highly and partially susceptible sheep of age cohort $\tau$ that survive to time $t$, the incidence of disease is recorded for the time $t$ and the infected population $I$ is determined through a combination of infection through consumption of infected feed with force of infection $F(t)$ and vertical transmission with probability $v$. The natural survival proportion is $d(\tau)$, and the proportion that survives disease for a time $t - a$ since infection is $\mu(t - a)$. The annual contribution of each age cohort to the breeding population is given by $b(\tau)$ in general, but for these calculations, it is assumed to be fixed. The extension of these equations to include Lowland flocks is straightforward, and the equations are not presented for brevity. Although some Hill and Upland ewes will be "drafted" into lowland flocks and this is included in the genotype proportion calculations, we do not consider the drafting of infected sheep, as the differences in the infection totals would be negligible, although it is important when considering horizontal transmission and is included there (*28*).

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