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The basic reproduction number for scrapie

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The basic reproduction number R_0 provides a quantitative assessment of the ability of an infectious agent to invade a susceptible host population. A mathematical expression for R_0 is derived based on a recently developed model for the spread of scrapie through a flock of sheep. The model incorporates sheep demography, a long and variable incubation period, genetic variation in susceptibility to scrapie, and horizontal and vertical routes of transmission. The sensitivity of R_0 to a range of epidemiologically important parameters is assessed and the effects of genetic variation in susceptibility are examined. A reduction in the frequency of the susceptibility allele reduces R_0 most effectively when the allele is recessive, whereas inbreeding may increase R_0 when the allele is recessive, increasing the chance of an outbreak. Using this formulation, R_0 is calculated for an outbreak of scrapie in a flock of Cheviot sheep.

Keywords: R_0; population genetics; control; epidemiology; inbreeding; transmissible spongiform encephalopathy

1. INTRODUCTION

Of fundamental importance in understanding the dynamics of infectious-disease outbreaks is the basic reproductive number R_0, the average number of secondary infections produced by one infected individual introduced into a fully susceptible population. The parameter R_0 therefore defines threshold behaviour. When R_0 is less than unity, each infection on average fails to reproduce itself and the number of infected individuals is expected to decline towards zero. If, however, R_0 is greater than unity, each infection on average more than replaces itself and the outbreak, at least initially, will escalate (Anderson & May 1991). The concept of R_0 is therefore a valuable one in disease control: if the system can be manipulated so as to reduce R_0 below unity, major outbreaks can be prevented. Thus, this quantity can be used to both devise and assess the efficacy of disease control measures.

In this paper, we derive a mathematical expression for R_0 based on a recently developed model of the spread of scrapie through a flock of sheep (see Stringer *et al.* (1998) and Woolhouse *et al.* (1998) for a detailed discussion). We explore the sensitivity of R_0 to vertical and horizontal transmission rates and to variation in the mean sheep life span. The effect on R_0 of culling infected animals is also considered. The model incorporates genetic susceptibility to scrapie allowing investigation of the importance of the genetic composition of the flock, the role of the dominance or recessiveness of susceptibility to scrapie and the effect of inbreeding on R_0. We also calculate R_0 for a scrapie outbreak in a flock of Cheviot sheep between 1970 and 1982 (Hunter *et al.* 1996).

Scrapie is a naturally occurring disease of sheep which causes deterioration in neurological function, loss of condition and death. It is a transmissible spongiform encephalopathy (TSE), a category which includes bovine spongiform encephalopathy (BSE) in cattle and new variant Creutzfeldt–Jakob disease (nvCJD) in humans and is associated with an abnormal form of the prion protein (PrP) (Caughey & Chesebro 1997). The disease has been known to exist in the UK for over 200 years.

The epidemiology of scrapie has recently been reviewed by Hoinville (1996). Scrapie can be transmitted horizontally within a flock and vertically from ewe to lamb, although the mechanisms involved remain uncertain. A feature of this disease is its long (in the order of two years) incubation period. Experimental studies in mice (Bruce *et al.* 1991) have demonstrated that the incubation period is dose dependent and that levels of abnormal PrP in the tissues increase from the time of infection until the appearance of clinical signs. Available evidence suggests that genetic susceptibility to scrapie is governed by alleles present at the PrP locus with resistance alleles being dominant or partially dominant (Hunter *et al.* 1996; Dawson *et al.* 1998).

The relationship between host population genetics and R_0 has been of theoretical interest for some time (e.g. Roberts & Heesterbeek 1995). However, as far as we are aware, this is the first time that host population genetics have been incorporated in an expression for R_0 for any infectious disease on the basis of empirical observation. This is relevant not only to scrapie but for other infectious diseases where breeding programmes are seen as an important method of disease control.

2. THE EPIDEMIC MODEL

The model comprises a set of partial differential equations in which the population is stratified by age and, for the infected individuals, by infection load. The model assumes that genetic susceptibility to scrapie is governed by a single locus with susceptible or resistant alleles and,

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thus, three genotypes. The model incorporates horizontal and vertical routes of transmission and an initial infection load which varies according to a gamma distribution. The infectiousness of an individual is assumed to be proportional to its infection load which increases exponentially with time until it reaches a maximum level at which the individual shows clinical signs and dies. Full details of the model and its application are given elsewhere (Stringer *et al*. 1998; Woolhouse *et al*. 1998).

3. EXPRESSION FOR R_0

For simple epidemiological models with a single class of susceptibles and infecteds, the parameter R_0 is straightforward to calculate—it is the initial number of susceptibles multiplied by the per capita transmission rate multiplied by the mean lifetime of an infected individual, which, for an SIR model (a compartment model comprising susceptible, infected and resistant classes; Anderson & May 1991) is simply the initial number of susceptibles multiplied by the ratio of the per capita transmission rate and the recovery rate.

Now consider a model in which the infected class is stratified by age and infection load. The per capita transmission rate of individuals of age a and infection load θ at the time of infection is calculated at all future times and integrated over the lifetime of the infecteds. R_0 is then obtained by integrating over all initial values of age and infection load and multiplying by the number of susceptibles.

For a model with several classes of infecteds the above calculation must be performed for each class. A matrix R is obtained, of which the elements R_{ij} give the average number of secondary infections in class i produced by one infection in class j. Standard theory (Heesterbeek & Dietz 1996) tells us that the required value of R_0 is given by the leading eigenvalue of this matrix.

Since we are considering vertical and horizontal routes of transmission for a total of three genotypes, R will be a 6×6 matrix. We can regard the matrix R as being composed of four blocks, each a 3×3 matrix, which we shall denote A, B, C and D as below:

$$R=\begin{bmatrix} A & B \\ C & D \end{bmatrix}.$$

The components A_{ij} determine the level of horizontal transmission from horizontally infected animals, the components D_{ij} the level of vertical transmission from vertically infected animals, the components B_{ij} the level of horizontal transmission from vertically infected animals and the components C_{ij} the level of vertical transmission from horizontally infected animals.

We denote the density of newly horizontally infected animals of genotype j, age a and infection load θ_0 by $I_h(j,a,\theta_0)$ and the density of newly vertically infected animals by $I_v(j,\theta_0)$. We shall initially consider the case of horizontal transmission from horizontally infected animals.

(a) *Horizontal infections*

At time τ after infection, animals with age a at infection and infection load θ_0 will have age a_τ and infection load θ_τ where

$$a_\tau = a+\tau$$

and

$$\theta_\tau = \theta_0 \mathrm{e}^{c\tau}.$$

Thus, neglecting mortality, at time τ the density distribution of infecteds in terms of a_τ and θ_τ is given by

$$I_h(j,a_\tau-\tau,\theta_\tau \mathrm{e}^{-c\tau})\mathrm{e}^{-c\tau},$$

where the scaling factor $\mathrm{e}^{-c\tau}$ is required to preserve the total number of infecteds obtained by integrating the expression over a_τ and θ_τ.

Allowing for natural mortality, which is assumed to be independent of genotype, the proportion of animals alive at $t=0$ still alive at $t=\tau$ is given by

$$\frac{S(a_\tau)}{S(a_\tau-\tau)},$$

where $S(a)$ is the survivorship function.

Thus, taking into account natural mortality and noting that the model assumes that all animals die when they reach either $a_\tau = a_{\max}$ or $\theta_\tau = \theta_{\max}$, the total number of animals remaining alive at time τ is given by

$$\int_\tau^{a_{\max}}\int_0^{\theta_{\max}} I_h(j,a_\tau-\tau,\theta_\tau \mathrm{e}^{-c\tau})\mathrm{e}^{-c\tau}\frac{S(a_\tau)}{S(a_\tau-\tau)}\mathrm{d}\theta_\tau \mathrm{d}a_\tau,$$

or, equivalently,

$$\int_0^{a_{\max}-\tau}\int_0^{\theta_{\max}} I_h(j,a,\theta_\tau \mathrm{e}^{-c\tau})\mathrm{e}^{-c\tau}\frac{S(a+\tau)}{S(a)}\mathrm{d}\theta_\tau \mathrm{d}a.$$

The rate of horizontal transmission from an animal with infection load θ is given by $k_{ij}^H\theta$ where

$$k_{ij}^H = kW_{ij},$$

and W_{ij} gives the relative susceptibility of a genotype i animal to infection by a genotype j animal. In this analysis we assume no age dependency in transmission rates. In the one-locus–two-allele system W_{2j} gives the degree of dominance of the susceptibility allele; $W_{2j}=1$ represents dominant susceptibility and $W_{2j}=0$ represents recessive susceptibility.

Therefore, the rate of appearance of new horizontal infections at time $t=\tau$ per sheep horizontally infected at time $t=0$ is given by

$$N_i k_{ij}^H \int_0^{a_{\max}-\tau}\int_0^{\theta_{\max}} I_h(j,a,\theta_\tau \mathrm{e}^{-c\tau})\theta_\tau \mathrm{e}^{-c\tau}\frac{S(a+\tau)}{S(a)}\mathrm{d}\theta_\tau \mathrm{d}a,$$

where N_i is the number of susceptible animals of genotype i. The elements A_{ij} are therefore obtained by integrating this expression over the maximum length of time for which an animal may live and dividing by $\bar{I}_h(j)$, the total number of animals of genotype j infected horizontally at $t=0$, given by

$$\bar{I}_h(j)=\int_0^{a_{\max}}\int_0^{\theta_{\max}} I_h(j,a,\theta)\mathrm{d}\theta\mathrm{d}a.$$

Thus, the elements A_{ij}, which represent horizontal infections arising from horizontally infected animals, are

given by

$$A_{ij} = \mathcal{N}_i k_{ij}^H \int_0^{\tau_{\max}} \int_0^{a_{\max}-\tau} \int_0^{\theta_{\max}} \frac{I_h(j,a,\theta_\tau e^{-c\tau})\theta_\tau e^{-c\tau}}{\bar{I}_h(j)} \times \frac{S(a+\tau)}{S(a)} d\theta_\tau da d\tau,$$

where $\tau_{\max} = a_{\max}$. Similarly the elements B_{ij}, which represent horizontal infections arising from vertically infected animals, are given by

$$B_{ij} = \mathcal{N}_i k_{ij}^H \int_0^{\tau_{\max}} \int_0^{\theta_{\max}} \frac{I_v(j,\theta_\tau e^{-c\tau})\theta_\tau e^{-c\tau}}{\bar{I}_v(j)} \frac{S(\tau)}{S(0)} d\theta_\tau d\tau.$$

Note that in this case there is no integral over the age variable because, by definition, all vertically infected animals become infected at age zero.

(b) *Vertical infections*

For vertical infections, the per capita rate of infection from animals of genotype j, age a and infection load θ to offspring of genotype i is given by

$$\gamma_{ij}^V(a,\theta) G_{ij} b(a).$$

γ_{ij}^V is the fraction of births from infected animals of age a and infection load θ which result in vertical transmission and is given by $\gamma_{ij}^V = k_{ij}^V \theta$. The relative susceptibilities of different genotypes to horizontal and vertical infections are assumed to be identical. Thus k_{ij}^V can be written

$$k_{ij}^V = \gamma W_{ij},$$

where γ is a constant and W_{ij} is the susceptibility matrix as defined above. G_{ij} gives the proportion of offspring of genotype i born to genotype j mothers. The function $b(a)$ is the birth rate and set to zero for $a < 2$ since animals are assumed not to give birth before the age of two years. Thus,

$$b(a) = \begin{cases} 0 & \text{for } a < 2 \\ b & \text{for } 2 \leqslant a \leqslant a_{\max} \end{cases},$$

where b is a constant.

The elements C_{ij} and D_{ij}, corresponding to vertical transmission from horizontally and vertically infected animals, respectively, are therefore given by

$$C_{ij} = k_{ij}^V G_{ij} \int_0^{\tau_{\max}} \int_0^{a_{\max}-\tau} \int_0^{\theta_{\max}} b(a+\tau) \frac{I_h(j,a,\theta_\tau e^{-c\tau})\theta_\tau e^{-c\tau}}{\bar{I}_H(j)} \times \frac{S(a+\tau)}{S(a)} d\theta_\tau da d\tau,$$

and

$$D_{ij} = k_{ij}^V G_{ij} \int_0^{\tau_{\max}} \int_0^{\theta_{\max}} b(\tau) \frac{I_v(j,\theta_\tau e^{-c\tau})\theta_\tau e^{-c\tau}}{\bar{I}_v(j)} \frac{S(\tau)}{S(0)} d\theta_\tau d\tau.$$

4. METHODS

The reference value of R_0 is calculated for the baseline set of parameters given in Stringer *et al.* (1998). Unless otherwise specified, the population is assumed to be in Hardy–Weinberg equilibrium with a susceptibility allele frequency of 0.5 (when inbreeding is present the genotype frequencies are as given in Appendix A). The baseline level for the degree of dominance is 0.5. The demography is given by a truncated Weibull survivorship curve with maximum and mean life spans of ten and four years, respectively. The infection load has a mean initial value of 10% of the maximum and increases exponentially with time within the host. The rate of exponential increase is set to give a mean incubation period of 2.1 years. Infected animals die when they reach the maximum infection load but mortality prior to that is assumed not to be enhanced. Horizontal transmission occurs at a rate of 0.04 new infections per infected sheep per year and vertical transmission is assumed to occur at a level of 10%. The birth rate (which is not specified in the model but is calculated to maintain the population size) is taken to be the value calculated at the outset of the model run.

The components R_{ij} are calculated using numerical integration. Because one of the three genotypes is assumed to be fully resistant the system reduces to a 4×4 (rather than a 6×6) matrix, the leading eigenvalue of which is calculated using Newton iteration (Press 1996).

We explore the sensitivity of R_0 to changes in horizontal and vertical transmission rates and mean life span. In practice, vertical transmission can be reduced by culling lambs born to infected ewes and horizontal transmission reduced by changes in husbandry. We investigate the effect on R_0 of culling preclinically infected sheep, now possible due to recently developed diagnostic tests (Schreuder *et al.* 1996, 1998) and also explore the effect of inbreeding within the flock.

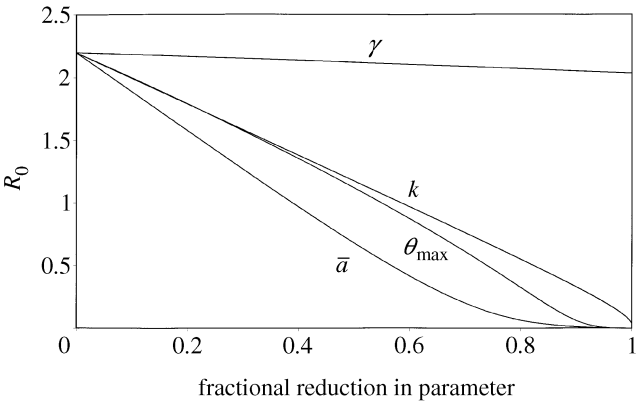

Figure 1. Sensitivity of R_0 to reduction in the horizontal transmission rate k, the vertical transmission rate γ, the mean life span $\bar{a}$ and the maximum infection load $\theta_{\max}$.

5. RESULTS

The sensitivity of R_0 to variation in horizontal and vertical transmission rates, mean life span and to removal of individuals before they reach the maximum infection load is shown in figure 1. In the absence of vertical transmission (not shown), R_0 declines linearly to zero with reduction in the horizontal transmission parameter k. The effect of including a small rate of vertical transmission is to introduce small nonlinearities into this relationship which are most noticeable at low horizontal transmission rates. The relatively small reduction in R_0 to be gained from reducing vertical transmission is clearly illustrated.

As mean life span decreases, R_0 falls at a decreasing rate (figure 1). This is a consequence of the exponential function for the rate of increase of infection load. Reducing mean life span reduces the time available to infect others and,

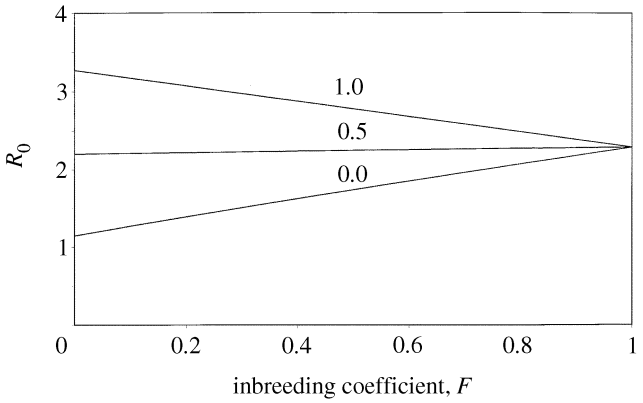

Figure 2. Sensitivity of R_0 to an increase in the level of inbreeding F for degrees of dominance of 1.0, 0.5 and 0.0.

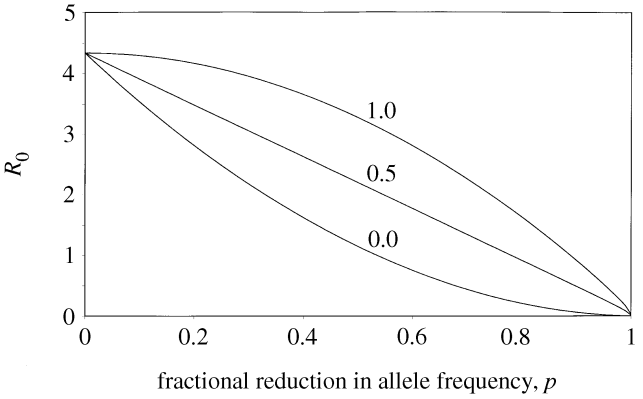

Figure 3. Sensitivity of R_0 to a reduction (from an initial value of 1.0) in the frequency of susceptibility alleles p for degrees of dominance of 1.0, 0.5 and 0.0. (The baseline value of R_0 is given by $p = 0.5$ and a degree of dominance of 0.5.)

thus, reduces mean infectiousness, but at low infection loads the relative drop in mean infectiousness, as mean life span decreases, is reduced. More important, however, is the observation that a large reduction in mean life span is required to reduce R_0 below unity.

The effect of removing infected individuals before they reach the maximum infection load is also shown in figure 1. R_0 approaches zero rapidly when the infection load at which individuals are removed falls below the mean infection load of newly infected individuals. Under these circumstances most newly infected individuals are removed instantly and, thus, prevented from causing further infections.

The effect of introducing inbreeding into the population is shown in figure 2. In the absence of vertical transmission (not shown), R_0 decreases linearly with F (the inbreeding coefficient—a full definition can be found in Appendix A) for a fully dominant susceptibility allele, increases for a fully recessive susceptibility allele and remains constant when the degree of dominance is set at 0.5. Inbreeding reduces the numbers of heterozygotes and increases the numbers of homozygotes. Thus, for degrees of dominance of zero and unity, inbreeding results in an increase and decrease, respectively, in the numbers of susceptibles available. For a degree of dominance of 0.5, inbreeding results in the replacement of partially dominant heterozygotes with half as many fully susceptible homozygotes and, thus, has a neutral effect on R_0. When vertical transmission is included (figure 2) the relationship between R_0 and F remains essentially linear: however, examination of the curve for a degree of dominance of 0.5 reveals a slight increase in R_0 as F increases. This occurs because, in a fully inbred population, all offspring of homozygote susceptibles are themselves fully susceptible, whereas, in a random mating system, a proportion of these offspring are only partially susceptible. Thus, in an inbred population the opportunity for vertical transmission is enhanced, resulting in the observed increase in R_0.

Figure 3 shows the sensitivity of R_0 to changes in the frequency of the susceptibility allele. In the absence of vertical transmission (not shown), variation in R_0 due to changes in allele frequency depends only on the numbers of susceptibles available and their relative susceptibilities to infection. Thus, when the degree of dominance is equal to 0.5, that is the heterozygotes are half as susceptible as the homozygotes, the overall susceptibility and, hence, R_0 must be proportional to the frequency of the susceptible allele. If the degree of dominance is greater than 0.5, then a greater reduction in the susceptibility allele frequency will be required to reduce R_0 to a given level and, if the degree of dominance is less than 0.5, a smaller reduction will be required. When vertical transmission (figure 3) is included a small correction is made which is most noticeable at low frequencies of the susceptibility allele.

6. R_0 FOR AN OUTBREAK OF NATURAL SCRAPIE IN A FLOCK OF CHEVIOT SHEEP

The approach described above was used to estimate R_0 for an outbreak of natural scrapie in a flock of Cheviot sheep. The flock was founded in 1960, closed in 1962 and the outbreak occurred between 1970 and 1982 (Dickinson 1974; Hunter *et al.* 1996). For a detailed account of the field data and model development see Woolhouse *et al.* (1999).

In this system, susceptibility to scrapie is assumed to be governed by a single locus with the four alleles VRQ, ARQ, AHQ and ARR giving a total of ten genotypes, all of which are represented in the flock. Natural scrapie has only been observed in two genotypes in this flock: VRQ/VRQ and VRQ/ARQ. It is assumed, therefore, that AHQ and ARR are both dominant for resistance (and so do not need to be distinguished in numerical analyses). ARQ is partially dominant for resistance. Therefore, VRQ/VRQ homozygotes are fully susceptible, VRQ/ARQ heterozygotes are partially susceptible and all other genotypes are resistant. The relative susceptibility of the VRQ/ARQ heterozygotes compared to the VRQ/VRQ homozygotes is set at 0.28.

Demography is described by a truncated Weibull distribution with maximum and mean life spans of 12 and 3.46 years, respectively. As in the previous model, infection load has a mean initial level of 10% of the maximum and increases exponentially with time. The rate of exponential increase is set to give a mean incubation period of 1.9 years. The rate of horizontal transmission is 0.09 new infections per infected sheep per year and, as above, vertical transmission is assumed to occur at a mean level of 40%. The birth rate is taken to be the value calculated at the outset of the model run.

Mating is assortative (resulting in an inbred population): 40% of matings are random among sheep without the VRQ allele (the resistant line), while 60% of matings are random among the remaining sheep (the susceptible line). It is assumed that initially 60% of the sheep, i.e. all the susceptible line, carry at least one VRQ allele. The initial frequencies of the other alleles are estimated from their relative frequencies in other UK Cheviot flocks (Hunter *et al*. 1997). The initial frequency of the VRQ allele is estimated as 0.37 and the frequencies of homozygote and heterozygote susceptibles as 0.20 and 0.15, respectively.

Applying the methods described in § 3 gives an R_0 value for this outbreak of natural scrapie of 3.9.

7. DISCUSSION

This paper provides an expression for R_0 which allows us assess its sensitivity to a range of epidemiologically important parameters. A similar study was conducted for the transmission of BSE (Ferguson *et al*. 1999), but the model in that case involved different routes of transmission and no genetic susceptibility to infection. For scrapie, the expression explicitly incorporates genetic susceptibility, allowing us to explore the effect of inbreeding within a flock and assess the impact on R_0 of reducing the frequency of susceptibility alleles. Thus, a formal expression for R_0 allows us to assess the impact of potential control measures. It should be noted, however, that when numbers of infectives or susceptibles are low stochastic effects may be important and, in particular, an outbreak for which R_0 is greater than unity may fail to take off. For R_0 less than unity, the number of infected individuals is expected to decline towards zero but extinction times may be long for R_0 close to unity.

Our results suggest that a reduction in horizontal transmission rates is an effective measure, though implementation would be difficult because the mechanisms underlying this transmission route are poorly understood (though pasture decontamination has been attempted; Sigurdarson 1991). In contrast, a reduction in vertical transmission is relatively ineffective because most cases arise through the horizontal transmission route.

Reducing mean life span, which results in the removal of the most infectious animals and limits the time available to infect others, would be very difficult to implement as demography is tightly constrained by economic factors.

The current development of diagnostic tests for scrapie (Schreuder *et al*. 1996, 1998) makes the slaughter of preclinically infected individuals a viable option and our results show this to be an effective way of reducing R_0 provided the diagnostics are sensitive enough. Recent studies (Schreuder *et al*. 1998) have detected infection in sheep as young as four months. In our model, this corresponds to detection at an infection load of or below 0.15 and a reduction in R_0, after removal of the infected individuals, of over 90%. However, this conclusion is crucially dependent on how infectiousness (particularly by horizontal transmission routes) varies during the incubation period and there is still limited data on this.

The efficacy of reducing transmission rates and the use of a diagnostic test as control measures has been explored, via simulation, in previous work (Woolhouse *et al*. 1998). Here we present an analytical tool which confirms earlier findings and, furthermore, allows a precise quantitative assessment of the effectiveness of such measures.

A novel feature of this analysis is the incorporation of the genetics of host susceptibility for a real infection in the derivation of R_0. Continuing advances in genetics make genetic improvement of the flock, achieved by selective breeding or culling of undesirable genotypes, a potentially powerful tool for controlling scrapie. Our results show that a reduction in the frequency of the susceptibility allele is most effective when the allele is recessive. However, phenotypic selection against an allele is easiest to achieve when the allele is dominant. An important result is the effect of inbreeding on R_0. If the susceptibility allele is recessive, inbreeding can increase R_0 and, hence, make an outbreak more likely. The work presented here provides, for the first time, an analytical tool for the quantitative assessment of the potential impact of genetic control measures for scrapie.

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APPENDIX A

If we assume that mating is random and let the frequencies of the susceptible and resistant alleles be denoted p and q, respectively, then the breeding matrix G_{ij}^R is given by

$$G_{ij}^R = \begin{bmatrix} p & p/2 & 0 \\ q & 1/2 & p \\ 0 & q/2 & q \end{bmatrix}.$$

In a fully inbred population the breeding matrix G_{ij}^I is given by

$$G_{ij}^I = \begin{bmatrix} 1 & 1/4 & 0 \\ 0 & 1/2 & 0 \\ 0 & 1/4 & 1 \end{bmatrix}.$$

In a partially inbred population, with inbreeding level F, the breeding matrix G_{ij}^{PI} is given by

$$G_{ij}^{PI} = (1 - S)G_{ij}^R + SG_{ij}^I,$$

where S determines the fraction of matings which are random and is related to F (Crow & Kimura 1970) by

$$F = \frac{S}{2 - S}.$$

Denoting the frequencies of the homozygote susceptibles, heterozygotes and homozygote resistants by f_{AA}, f_{Aa} and f_{aa}, respectively, the proportions are given by

$$f_{AA} = p^2(1 - F) + pF,$$

$$f_{Aa} = 2pq(1 - F),$$

$$f_{aa} = q^2(1 - F) + qF,$$

which, in the case $F = 0$, reduces to Hardy–Weinberg equilibrium.

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