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Persistence patterns of scrapie in a sheep flock

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SUMMARY

The epidemiology and transmission dynamics of sheep scrapie is as yet poorly understood. Here we present a theoretical analysis of the transmission dynamics within a sheep flock, concentrating on how persistence properties depend on transmission scenario and flock size. Patterns of disease persistence and extinction are studied analytically using branching-process approximations and numerically using stochastic model simulations. For a given basic reproduction number, disease extinction is most likely when late-stage infected animals are responsible for most of the transmission. This effect can be understood in terms of aggregation in the distribution of the number of secondary infections arising from a single primary infection. The presence of an environmental reservoir reduces the probability of extinction.

INTRODUCTION

Scrapie is a transmissible spongiform encephalopathy in sheep, endemic in many sheep producing countries. The epidemiology of scrapie is as yet poorly understood. Inconclusive evidence exists for the natural occurrence of horizontal as well as vertical transmission of scrapie [1–4]. Furthermore, evidence exists that the agent is able to persist in the environment for years [1, 5]. The susceptibility to scrapie is strongly dependent on the breed and the genotype of the animal [6, 7]. It is not known whether known 'resistant' genotypes are truly resistant against infection or in fact carriers of infection that do not develop clinical signs in their lifetime.

Following the BSE epidemic in Great Britain, and the occurrence of new-variant CJD in humans, the control of scrapie has obtained a higher priority in view of both the possibility that scrapie can overcome species barriers and the possibility that BSE has established itself in the sheep population, with a presentation similar to scrapie. The anticipated increase in the amount and quality of epidemiological data for scrapie is likely to facilitate analyses of the transmission dynamics of the disease using mathematical models. Such analyses are vital for obtaining the understanding needed for the design of successful control strategies. For a recent comparison of transmission model results with existing data on an outbreak in Cheviot sheep see [8].

Given the very incomplete understanding of the epidemiology of scrapie, and the possibility of important differences in transmission dynamics depending on breed, flock type or size, and scrapie strain, there is a large diversity in the theoretical scenarios that warrant consideration when modelling scrapie transmission. It is therefore a useful starting point to classify these various scenarios by characterizing the epidemiological patterns they might

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generate. Such a characterization was started by Woolhouse and coworkers [9, 10]. In recent work [11] we focussed on the interplay between horizontal and vertical transmission and on the characteristics of endemic states.

In these previous studies the transmission dynamics were described using deterministic models. Such models are invalid when population numbers become small enough for chance fluctuations to become important. The present study is the first to model the transmission dynamics of scrapie in an explicitly stochastic manner, i.e. treating demographic processes and disease transmission as random processes. The purpose of this work is to understand the effects of demographic stochasticity on the transmission dynamics of scrapie within a single flock. In particular, we are interested in how the distributions of epidemic size and duration depend on transmission scenario and flock size. This will serve as a starting point for the future study of scrapie persistence in a population consisting of a large number of interacting flocks.

In host populations with renewal of susceptibles, deterministic models generally predict that the introduction of a disease will lead to the formation of an ever-lasting endemic state when the basic reproduction number $R_0 > 1$. In the corresponding stochastic model the disease will always go extinct, although in many cases the expected time to extinction will be much larger than any time span of interest. Disease extinction, when it tends to occur on epidemiologically relevant time scales, is perhaps the most important feature captured by stochastic models, but not by the deterministic approximation.

For $R_0 > 1$, one may distinguish two types of disease extinction: Early extinction, corresponding to a 'minor outbreak', and extinction after a major outbreak. The latter extinction may occur from a quasi-stationary endemic equilibrium state ('endemic fadeout' [12–14]), as well as from a non-equilibrium state with a low number of susceptibles following a large outbreak [15, 16]. The occurrence of an endemic fade-out is promoted by small endemic numbers of infected animals. Small numbers of infected animals can result from a small flock size, low frequencies of susceptible genotypes, or a basic reproduction number close to 1. For later use in interpreting our results, it is helpful to define a time T_s, representing the typical time scale separating 'minor' and 'major' outbreaks. We think of major outbreaks as outbreaks that do not go extinct before the reduction, through infection, in the number of susceptible individuals starts to have a noticeable dampening effect on the rise in disease prevalence. The time scale T_s can be expressed in epidemiological characteristics using the following heuristic argument based on deterministic considerations. If we define T_0 as the time it takes for the infection prevalence to increase exponentially from $1/N$, corresponding to a single infection introduced into the population, to some fixed prevalence i_0, i.e. $i_0 = (1/N)\exp(rT_0)$, with r the initial exponential epidemic growth rate, we find

$$T_0 = \frac{\ln N}{r} + \frac{\ln(i_0)}{r} \approx \frac{\ln N}{r}. \tag{1}$$

Using an approximation discussed in [11], we can express the growth rate r in term of the basic reproduction number R_0 (defined as the expected number of secondary infections that arise due to the introduction of a single primary infection in a naive population) and the mean generation time T_g between infections (i.e. the expected time, in a naive population, between the moment a primary infection is acquired and the moment it generates a secondary infection): $r = \ln(R_0)/T_g$. This leads us to the definition

$$T_s = \frac{T_g \ln N}{\ln(R_0)}. \tag{2}$$

The mean generation time is determined by the incubation period distribution, the dependence of infectiousness on the time since infection, and the disease-free survival profile of the host population. (In the Appendix we express T_g in terms of the parameters of the transmission model discussed Section 2.)

Below, we will use branching processes to describe disease transmission in interpreting some of our results. A branching process describes 'parents begetting offspring': it is defined by specifying the probabilities q_k that a parent begets k offspring during its reproductive lifetime ($\Sigma_{k=0}^{\infty} q_k = 1$). In the context of disease transmission, we consider the population of infected individuals; q_k then represents that probability that a single primary infection generates k secondary infections during its infectious lifetime. When we describe disease transmission as a branching process, we are assuming that the transmission process is the same for each generation of infections, i.e. the probabilities q_k are fixed. This is a good approximation in the early phase of disease invasion, where we can still neglect the reduction in the number of

susceptible animals (and thus in the number of future infections) by their conversion into infected animals. The basic reproduction number R_0 is then given by $R_0 = \sum_{i=0}^{\infty} kq_k$. This branching-process approximation of the process of invasion of the host population by the disease allows us to compute the probability of the occurrence of an early extinction. As is explained in [17], the probability of an early extinction occurring is given by the smallest z $(0 \leqslant z \leqslant 1)$ that satisfies the equation

$$z = g(z), \tag{3}$$

where $g(z)$, the generating function of the branching process, is given by the infinite sum $g(z) = \sum_{k=0}^{\infty} q_k z^k$. For example, if the number of secondary infections arising from a single primary case is Poisson distributed with mean λ, the generating function takes the form

$$g(z, \lambda) = \exp[\lambda(z-1)]. \tag{4}$$

METHODS

Below we present simulation results of an age-structured susceptible-infected (SI) model; Figure 1 provides a graphical representation of its structure. We concentrate here on its main features and assumptions; an appreciation of the full mathematical details, given in the Appendix, should not be necessary to understand this paper. Our model includes: direct and indirect (via environment) horizontal transmission, vertical transmission, genotypes that differ in susceptibility to scrapie infection, age-dependent rates of slaughter, dependence of horizontal and vertical infectiousness on time since infection or time to onset, and seasonality in lambing. We assume that an environmental infectivity reservoir, if present, accumulates and loses infectivity in such small units that its infectivity level is a continuous quantity and gains and losses of infectivity can be described by a deterministic rate equation.

The deterministic analogue of our stochastic model consists of a coupled set of partial-differential-equations [11]. A similar deterministic model for scrapie transmission has been explored recently by Woolhouse and others [8–10, 18]. In the stochastic framework employed here, all possible events except changes in the infectivity level of the environmental reservoir, are treated as random processes. We simulate these random processes by drawing inter-event times from the appropriate exponential distributions [15]. The ages of all animals and the infectivity level of the environmental reservoir are updated at fixed time points with a separation of one week.

We assume that ewes mate randomly with rams (external to the flock) that have constant genotype frequencies equal to the initial genotype frequencies within the flock, that are assumed to be in Hardy–Weinberg equilibrium. We note that since the genotype frequencies of the rams are fixed in this 'open-flock' setting, allele extinctions in the ewe population as a result of genetic drift or selection for resistance to scrapie cannot occur. Disease incubation is represented by a sequence of incubation stages in each of which infected animals have an exponentially distributed residence time, preceded by a minimum incubation period of 1 year that is implemented deterministically along with the ageing process (resulting in 52 incubation stages in the first year of incubation). For definiteness we consider susceptibility to be determined by two possible alleles (one associated with susceptibility and one with resistance) at a single locus. We assume that susceptibility is independent of age and that homozygous susceptible animals and heretozygotes (when susceptible) have the same incubation period distribution and dependence of relative infectiousness on incubation stage. The survival curve is taken to be of a Weibull form as described in [9], with an average life expectancy of 4 years (in absence of disease). Lambing is modelled to occur between the 5th and the 25th week of the year, with the majority of lambs being born during April. In the numerical results presented below the mean incubation time is 2·5 years and there are three post-1-year incubation stages in each of which animals have a mean residence time of 0·5 year. The post-1-year incubation time t is then distributed according to the gamma distribution

$$\frac{2^{l+1}}{l!} t^l \exp(-2t) \tag{5}$$

with $l = 2$.

Each stochastic realization is started with the introduction of a single infection in an animal of 2 years of age, irrespective of the flock size, and the system is evolved for 30 years without further external introduction of infection. For each realization we record the total number of infections and the time to extinction (if extinction occurs within 30 years).

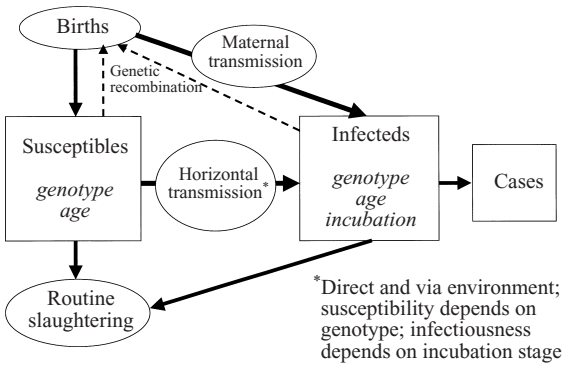

Fig. 1. Flow diagram of the model structure.

RESULTS

We are interested in patterns of disease persistence displayed by the distribution of the time to disease extinction and the distribution of the total epidemic size. In particular we discuss below how persistence patterns depend on the overall transmissibility of the disease, the genotype frequencies and their susceptibilities, the way infectiousness depends on time since infection, and the degree to which transmission is mediated by an environmental reservoir.

Disease transmissibility

When we increase the overall disease transmissibility while keeping everything else fixed, the basic reproduction number R_0 is increased without changing how the number of secondary infections arising from a single primary infection is distributed around its mean. It is well-known and perhaps intuitively obvious that this results in a reduction of the probability of early extinction. When the number of secondary cases is Poisson distributed ($\lambda = R_0$), this can be shown mathematically from Eq. (4) and Eq. (3):

$$\frac{\partial}{\partial R_0} z = \frac{\partial}{\partial R_0} g(z, R_0) = \frac{\partial}{\partial R_0} \exp(R_0(z-1)) < 0. \qquad (6)$$

Furthermore, the expected time to endemic extinction is enhanced, since the increase in R_0 will result in an increased expected number of infected individuals in the endemic state.

We illustrate the effect of R_0 on persistence in Fig. 2, in which we show the distributions of outbreak size (Fig. 2*a*, 2*d*) and of outbreak duration (Fig. 2*b*, 2*e*), obtained from 1000 realizations, for two different overall transmissibilities (corresponding to $R_0 = 1{\cdot}5$ and $R_0 = 5{\cdot}0$) and a flock size of 100 animals. For each scenario we also show the time-evolution of the number of infections for a small number of realizations, and compare these with the time-evolution of the deterministic model analogue (2*c* and 2*f*). The scenario considered in Fig. 2*a–c* will serve as a reference and assumes direct horizontal transmission only (i.e. zero maternal transmission and no environmental reservoir). It assumes $R_0 = 1{\cdot}5$, the susceptible allele frequency is 0·5, and heterozygotes are half as susceptible as homozygous susceptibles. The dependence of the relative infectiousness on incubation stage is chosen to be the same for both susceptible genotypes. It is equal to 1 in the stage just before onset, and set to 0·01 earlier in incubation. The scenario considered in Fig. 2*d–f* is identical except that the overall horizontal transmissibility is such that $R_0 = 5{\cdot}0$.

Whereas for $R_0 = 1{\cdot}5$ very few of the outbreaks persist longer than 30 years, for $R_0 = 5{\cdot}0$ this number is considerably bigger. In sharp contrast to the $R_0 = 1{\cdot}5$ scenario, the $R_0 = 5{\cdot}0$ scenario gives rise to a clear and wide gap in the duration and final-size distributions between 'minor' and 'major' outbreaks. For the $R_0 = 5{\cdot}0$ scenario the probability of endemic fade-out on a relevant time scale is small. As illustrated in Figs 2*c* and 2*f*, for both scenarios the time-evolution of major outbreaks can be much different from the deterministic model solution. We illustrate the R_0 dependence of the persistence patterns further in Fig. 3*a*, where we compare six scenarios that differ in overall transmissibility only. Here (and in Figs 3*b* and 4) we plot the fraction of outbreaks that go extinct within 30 years conditional on having at least 10 cases of infection against the fraction of realizations that have at least 10 cases of infection. The patterns shown in Figs 3 and 4 are insensitive to the choice of the threshold value of 10 infections: for threshold values of 5 and 20 the results differ quantitatively, but not qualitatively. The larger R_0, the smaller the probability of extinction, so that Fig. 3*a* displays both an increase in the fraction of realizations with at least 10 infections and a decrease in the conditional probability of extinction. We note that in Fig. 3*a* the probability of extinction within 30 years (conditional on having at least 10 cases of infection) for $R_0 \leqslant 3$ is finite but essentially independent of flock size once the flock exceeds 100 animals. This is because for those flock sizes the T_s for these transmission scenarios becomes of the order of 30 years or larger once a size of the order of 100 animals is exceeded. As a consequence, for these population sized extinctions within 30 years are 'early extinctions', i.e. they occur in the disease

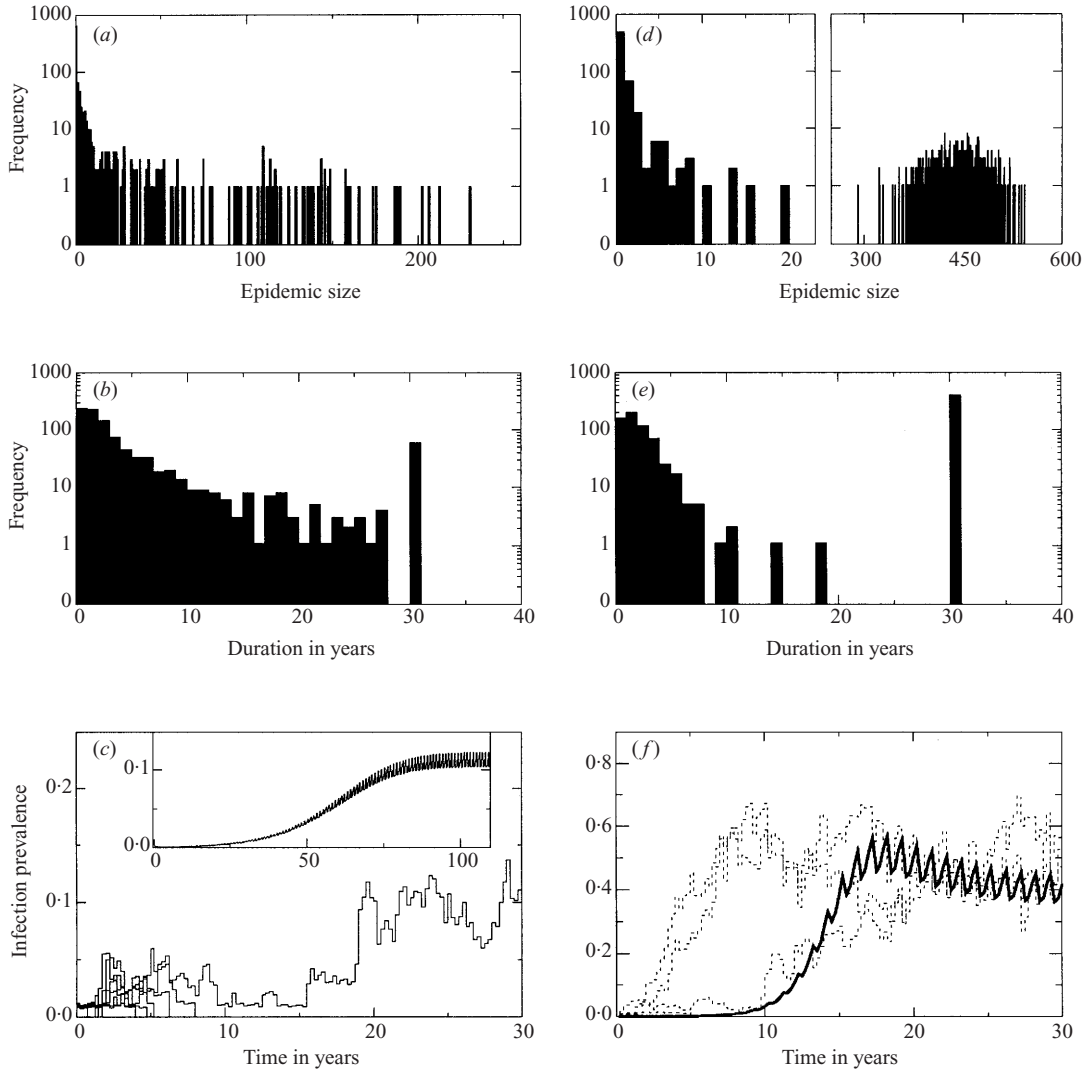

Fig. 2. Results for a flock size of 100 sheep under the reference scenario with $R_0 = 1{\cdot}5$ as described in the text (*a–c*) and under a scenario with larger overall horizontal transmission coefficient, such that $R_0 = 5{\cdot}0$ (*d–f*). Realizations are observed for 30 years. (*a*) and (*d*): Distribution of the size of outbreaks (total number of new infections occurring within the observation time of 30 years). (*b*) and (*e*): Distribution of the duration of outbreaks. Durations longer than 30 years are lumped together at the end of the histogram. (*c*) and (*f*): Infection prevalence versus time for a random selection of 10 and 6 realizations, respectively. In (*c*) there are nine extinctions and one major outbreak that persists for 30 years. Inset in (*c*): deterministic model solution. Note that in the deterministic approximation the epidemic invasion takes about 90 years, which is much slower than in typical stochastic realizations displaying major outbreaks (such as the one shown in the main figure). Yearly prevalence peaks are due to birth seasonality. In (*f*) there are three early extinctions and three major outbreaks (thin lines). The fat dashed line is the deterministic model solution.

invasion phase in which the total number of hosts is much larger than the number of infected hosts, so that the transmission process can be approximated by the same branching process irrespective of the population size.

Infectiousness as a function of time since infection

Another important factor in determining the persistence patterns is how the relative infectiousness changes with time since infection (or with incubation stage). Given a fixed value of R_0, persistence gets poorer the more the infectiousness depends on the incubation stage or on the time since infection. This is due to the large turnover of animals under usual farming practices, as embodied in the form assumed for the survival curve in our model. Since many infected animals have died or have been slaughtered before they would have become highly infectious, a large proportion of the infected animals generates

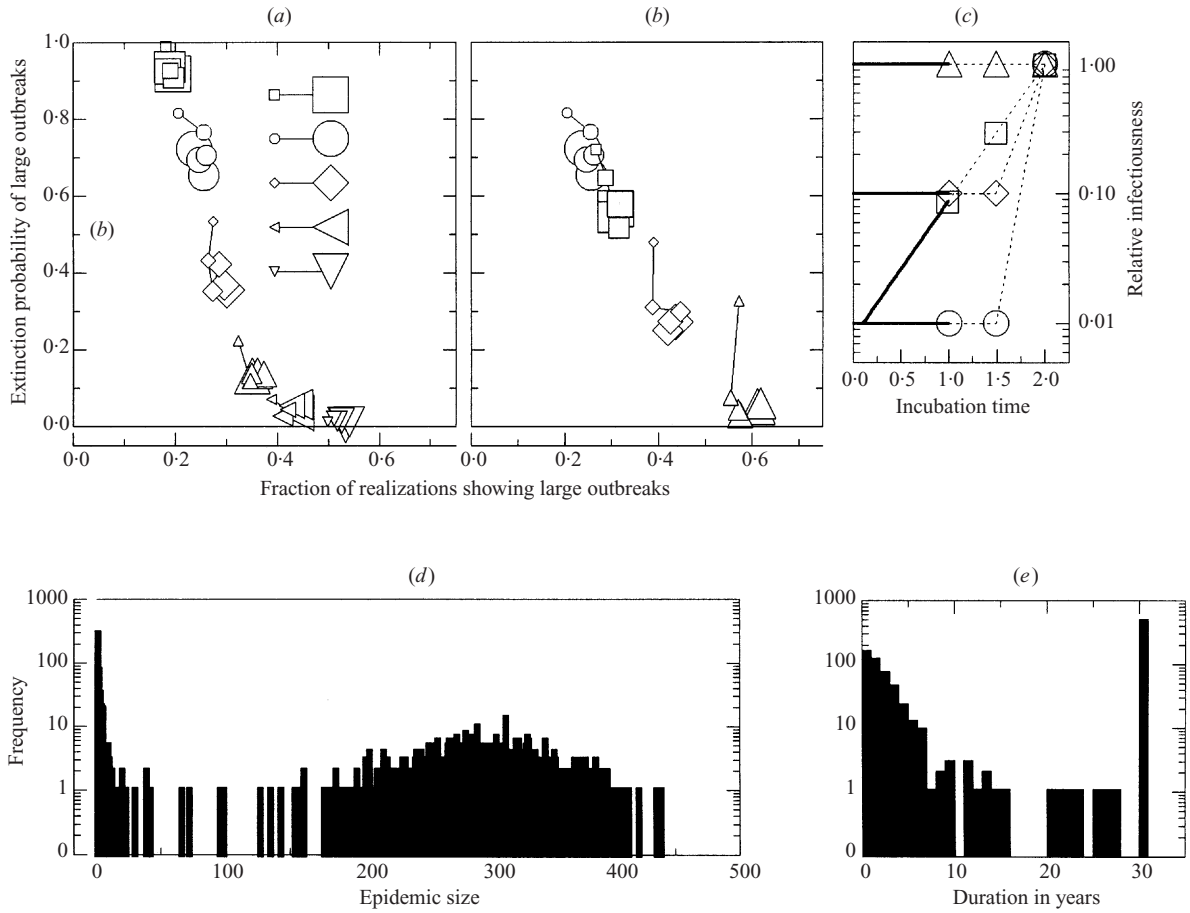

Fig. 3. Fraction of realizations that display large outbreaks against the proportion of large outbreaks that go extinct within 30 years, based on 1000 realizations. Different symbols correspond to different scenarios, and the 6 different symbol sizes correspond to flock sizes of 50 (smallest symbols), 100, 200, 400, 800, and 1600 (biggest symbols) animals. (*a*) Scenarios differ only in overall horizontal transmission coefficient. The circles correspond to the reference scenario ($R_0 = 1{\cdot}5$). (*b*) Scenarios differ in the dependence of infectiousness on the time since infection. $R_0 = 1{\cdot}5$. The chosen different dependencies of the relative infectiousness on incubation stage are represented by corresponding symbols in (*c*) Circles: reference scenario, in which the relative infectiousness equals 1 in the last stage before onset and 0·01 elsewhere. Squares: the base-line level of relative infectiousness is again 0·01, but now it starts to increase exponentially after 5% of expected time from infection to the last incubation stage has elapsed, reaching 1 again in the last stage before onset. Diamonds: relative infectiousness is 1 in the final incubation stage and 0·10 elsewhere. Triangles: relative infectiousness is equal to 1 everywhere (uniform infectiousness throughout incubation). (*c*) Dependencies of relative infectiousness on incubation stage as chosen for the scenarios considered in subfigure *b*. We represent the first year of incubation as a fat line, and the three last incubation stages, which each have a mean duration of half a year, as open symbols. (*d*) and (*e*) Size (*d*) and duration (*e*) distributions for a flock size of 100 sheep under the scenarios with uniform infectiousness (triangles in subfigure *b*).

a relatively low number of secondary infections and a small proportion of infected animals that generates a relatively high number of secondary infections: the distribution of the number of secondary infections arising from a primary infection is aggregated or overdispersed. Our numerical results show that the probability of early extinction increases with increasing aggregation in the distribution of the number of secondary infections. This effect can be understood analytically from the following branching-process argument. Assuming that the distribution of secondary infections has a negative binomial form with mean R_0 and aggregation parameter k, the equation for the probability of early extinction z reads:

$$z = g(z, k) = \frac{1}{(1+\frac{R_0}{k}(1-z))^k}. \tag{7}$$

In the limit of $k \to \infty$ we regain the Poisson result Eqn (4). It is straightforward to show that $(\partial/\partial k)g(z, k) < 0$ for $0 < z < 1$, so that the solution z to the above equation increases monotonically with increasing aggregation (decreasing k).

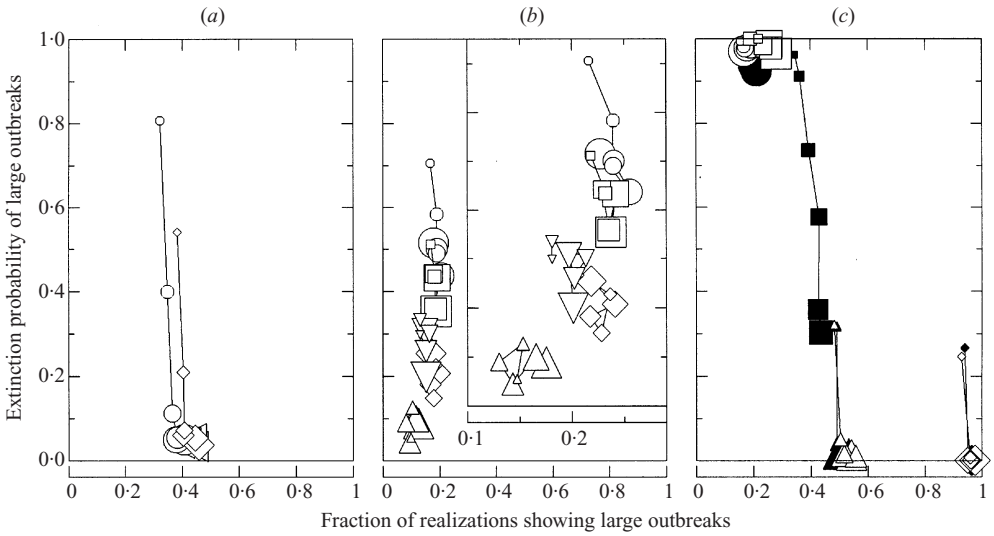

Fig. 4. Fraction of realizations that display large outbreaks against the proportion of large outbreaks that go extinct within 30 years, based on 1000 realizations. Symbol sizes as in Figure 3. (*a*) Scenarios differ in the frequency of susceptible genotypes. $R_0 = 5{\cdot}0$. Triangles: susceptible allele frequency if 0·5, as in left-pointing triangles in (*a*). Circles: susceptible allele frequency is 0·1. Diamonds: susceptible allele frequency is 0·5, heterozygotes are resistant. (*b*) Here we examine the effect of an environmental reservoir. The main figure has the same axis scales as the adjacent subfigures, facilitating direct comparisons. The inset shows the same results, but displayed using reduced axis scales for greater clarity. $R_0 = 1{\cdot}5$. Circles: reference scenario (no environmental reservoir). Squares: decay time of environmental infectivity is 50 weeks. 5/6th of transmission via environment ($\chi = 0{\cdot}1$, $\eta = 0{\cdot}02$ 1/wk). Diamonds: decay time of environmental infectivity is 200 weeks. 20/21th of transmission via environment ($\chi = 0{\cdot}1$, $\eta = 0{\cdot}005$ 1/wk). Triangles down: decay time of environmental infectivity is 500 weeks ($\chi = 0{\cdot}002$, $\eta = 0{\cdot}002$ 1/wk). 1/2 of transmission via environment. Triangles up: decay time of environmental infectivity is 500 weeks. 50/51th of transmission via environment ($\chi = 0{\cdot}1$, $\eta = 0{\cdot}002$ 1/wk). (*c*) Here we examine the effect of including maternal transmission. The results here are for resistant heterozygotes and for simplicity we assume the same dependence of infectiousness on incubation stage for maternal as for horizontal transmission. Filled symbols: no maternal transmission Open symbols: $p_{\text{mat}} = 0{\cdot}8$, where p_{mat} is the maternal transmission probability in the last incubation stage before onset. Circles: $R_0 = 1{\cdot}1$, the dependence of infectiousness on incubation stage is the same as in the reference scenario described above. Squares: $R_0 = 1{\cdot}1$, infectiousness is uniform throughout incubation. Triangles: $R_0 = 10{\cdot}0$, dependence of infectiousness on incubation stage as in reference scenario. Diamonds: $R_0 = 10{\cdot}0$, infectiousness is uniform throughout incubation.

We note that the probability of endemic extinctions also increases with increasing aggregation in the distribution of the number of secondary infections, as one can see by viewing the endemic infection process as a branching process with reproduction number equal to one. An intuitive explanation for this is that fluctuations in the number of highly infectious individuals translate into fluctuations in the number of secondary infections generated per time unit that are a factor N_{big} larger, where N_{big} is the number of secondary infections generated by a highly infectious primary infection, thus enhancing the probability that fluctuations cause infection extinction. In Figure 3*b* the effect of changing the distribution of number of secondary infections caused by a single primary infection through changing the dependence of infectiousness on incubation stage is illustrated by model simulation results. In Figure 3*d* and 3*e* we show the full size and duration distributions of the scenario with uniform infectiousness (triangles in Fig. 3*b*), which has the least aggregation in the distribution of the number of secondary infection resulting from a single primary infection. The corresponding distributions for the reference scenario, which amongst the scenarios in Figure 3*b* has the most aggregation in the distribution of the number of secondary infections, were displayed in Figures 2*a* and 2*b*.

Genotype frequencies

Extinctions become more frequent when the fraction of animals responsible for (most of) the transmission goes down, since the relative size of chance fluctuations increases for decreasing numbers of infected animals. Figure 4*a* illustrates the effect of changing the frequencies and the susceptibilities of the genotypes with respect to the choices made in the reference scenario above. Note that again we are comparing

scenarios with equal R_0 here; this calibration is achieved by adjusting the overall transmission coefficient.

Environmental reservoir

In the presence of an environmental infectivity reservoir, reaching a state with zero infected animals does not in general represent disease extinction, since the infection may be reintroduced from the reservoir. We therefore need to define what we mean by extinction in this case. The convention that we adopt here is to count as an extinction any period exceeding 5 years in which infection is not reintroduced from the environment. The effects on persistence of an environmental reservoir are illustrated in Figure 4*b*. In our model the environmental reservoir is characterized by two parameters, the decay rate of infectivity η (the inverse of the decay time), and the environmental transmission coefficient χ. The contribution of transmission via the reservoir, as measured by the fraction of R_0 due to this route, is given by $\chi/(\chi+\eta)$ in absence of maternal transmission (see Hagenaars *et al.* [11], section 3.1).

As seen from Figure 4*b*, the inclusion of an environmental infectivity reservoir leads to a reduction in the probability of extinction within 30 years of outbreaks that have at least 10 cases of infection. This enhancement of disease persistence becomes stronger both with increasing life time of reservoir infectivity and with increasing contribution to R_0 of transmission via the environment. We note that this enhancement of persistence is accompanied by a reduction in the number of outbreaks that have at least 10 infections. Examination of the full size distributions reveals that most of this reduction is accounted for by an increase in the number of realizations in which no new infections are generated within 30 years. Such an increase is expected when the generation time between infections lengthens as a result of an increase in the life time of environmental infectivity and/or an increase in the fraction of R_0 due to the environment.

Maternal transmission

We end this section by exploring the effects on persistence patterns of including maternal transmission. During disease invasion, the relative contribution to transmission of the maternal route (for a given maternal transmission probability) is highest for low R_0, where in endemicity it is highest for high R_0 [11, 19]. In Figure 4*c* we therefore show results for both low and high basic reproduction number ($R_0 =$ 1·1 and $R_0 = 10$). We consider two extreme scenarios for the dependence of infectiousness on incubation stage. For high R_0, as illustrated by the $R_0 = 10{\cdot}0$ results in Figure 4*c*, no noticeable differences are found between the duration and size distributions with and without maternal transmission. However, for low R_0 (i.e. not much bigger than unity), there are situations where we do observe noticeable effects on persistence properties of including maternal transmission. Clearly, these should be seen best when the maternal transmission probability at maximum maternal infectiousness is high, so that maternal transmission is responsible for a sizable part of R_0. If this is the case, then the effect still depends on how infectiousness changes with incubation stage for horizontal transmission. The effect is most prominent if the horizontal infectiousness is independent of incubation stage (squares in Fig. 4*c*). In this case, when comparing scenarios with equal overall R_0, the one with a sizable contribution from maternal transmission shows more frequent extinctions. This is because the distribution of the number of secondary infections arising from maternally infected primary infections takes a more aggregated form than that of the number of secondary infections arising from horizontally infected primary infections (as a direct result of the aggregation in the number of offspring per animal in the presence of a high turnover of animals), analogously to the effect of changing the dependence of infectiousness on incubation stage for horizontal transmission only discussed above. When the horizontal infectiousness is small just after infection and increasing towards onset, the ' additional' effect of the aggregation present in the distribution of maternally transmitted secondary infections becomes less important (circles in Fig. 4*c*).

Conclusions

Understanding the key determinant of observed persistence patterns of any disease is always more complex than characterizing endemic behaviour, since disease extinction is, by definition, a stochastic process. Understanding persistence properties is, however, critical to the evaluation of the potential long-term effectiveness of control policy options. In the case of scrapie, analysis of persistence behaviour is made considerably more difficult by the lack of epidemiological data, a long incubation period,

multiple transmission routes and genetically variable susceptibility to infection. This paper provides a starting point in the theoretical study of scrapie persistence, by examining the effects of various epidemiological determinants on persistence patterns in a single sheep flock.

Disease extinction is most likely when late-stage infected animals are responsible for most of the transmission, since this scenario produces the lowest prevalence of infectious animals. Conversely, the presence of a long-lived environmental infectivity reservoir generally enhances persistence, since transmission can cease through other transmission routes only to be re-introduced at some later point via the reservoir. Overall, the dependence of the relative infectiousness on incubation stage (or time since infection) represents the most critical determinant of disease persistence, allowing there to be considerable differences in the expected frequency of disease extinction under different transmission scenarios even if those scenarios do not differ in the magnitude of the basic reproduction number. As a result, the effect of a given control effort will not just depend on the corresponding reduction in the value of the basic reproduction number, but also on other characteristics of the transmission scenario.

Understanding the global persistence properties of a disease, such as the rate at which new flocks are infected or clear the disease, of course requires consideration of epidemiological coupling between isolated populations, whether through movement, occasional contact or genetic exchange – particularly if disease extinction is predicted to be frequent for an isolated small population. Work to model such metapopulation dynamics is underway. This will also allow a more realistic treatment of sheep population genetics, since the current paper has focused on the case of a genetically open flock (ie. the rams are assumed to be external, with fixed genotype frequencies). For a closed flock, an important difference is that disease extinction can occur within the deterministic model approximation when selection for resistant genotypes reduces R_0 to below 1. Furthermore, in a fully stochastic model we may see extinction of susceptibility alleles as a result of genetic drift, or as a result of the combined effect of genetic drift and selection against susceptibility.

Building on the work presented here, a more sophisticated modelling framework will allow exploration of both the local and global potential effects of a wide range of control policies, such as selective breeding or culling, quarantining, land set-aside or decontamination schemes. Furthermore, in view of the possibility that BSE has entered the UK sheep flock, design and implementation of such control programmes and greatly enhanced disease surveillance clearly remain priorities.

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APPENDIX: DETAILED MODEL DESCRIPTION

Our model of scrapie transmission is an age-structured stochastic compartmental model. We distinguish compartments of susceptible and of infective animals (SI model) as well as a continuous variable describing the environmental infectivity reservoir.

Random processes

The types of events occurring in the model are listed in Table A.1. In this Table $X^{\gamma}(a)$ ($Y_k^{\gamma}(a)$) denotes the number of susceptible (infected) sheep of age a and genotype γ (in incubation stage k). B_X^{γ} (B_Y^{γ}) denotes the birth rate of susceptible (infected animals, δ_{ij} denotes the Kronecker delta ($\delta_{ij}=1$ if $i=j$ and zero otherwise). $\lambda^{\gamma}(a)$ denotes the force of infection for the horizontal transmission routes, and $\mu(a)$ the rate of routine slaughter. Animals leaving the final incubation stage k_f reach onset of scrapie. v_k^{γ} is the transition rate from incubation stage k to $k+1$ for genotype γ. We choose these transition rates to be independent of the stage k, obtaining a gamma distribution for the incubation period, given by the probability density function.

$$\frac{(v^{\gamma})^{k_f}}{(k_f-1)!}\, t^{(k_f-1)} \exp(-(v^{\gamma})t).$$

Force of infection

The force of infection for the horizontal transmission routes is given by $\lambda^{\gamma}(t, a) = g_{\mathrm{h}}^{\gamma}(\chi I(t)+\lambda_{\mathrm{dh}}(t))$. Here I is a continuous variable that models the environmental infectivity reservoir, χ the environmental transmission coefficient, g_{h}^{γ} is the genotype-dependent (but age-independent) susceptibility, and $\lambda_{\mathrm{dh}}(t)$ is the force of infection due to direct horizontal transmission, given

Table A.1. *Events* (*random processes*) *occurring in our mathematical model of scrapie transmission and their rates*

Type of event	Symbolic representation	Rate
Birth of a susceptible animal of genotype γ'	$(X^{\gamma}(a),\ Y_k^{\gamma'}(a)) \to (X^{\gamma}(a)+\delta_{a0}\delta_{\gamma\gamma'},\ Y_k^{\gamma'}(a))$	$B_X^{\gamma'}$
Birth of an infected animal of genotype γ'	$(X^{\gamma}(a),\ Y_k^{\gamma'}(a)) \to (X^{\gamma}(a),\ Y_k^{\gamma'}(a)+\delta_{a0}\delta_{\gamma\gamma'})$	$B_Y^{\gamma'}$
Death of susceptible animal of age a' and genotype γ'	$(X^{\gamma}(a),\ Y_k^{\gamma'}(a)) \to X^{\gamma}(a)-\delta_{aa'}\delta_{\gamma\gamma'},\ Y_k^{\gamma}(a))$	$\mu(a')X^{\gamma'}(a')$ $\mu(a')X^{\gamma'}(a')$
Death of an infected animal of age a' and genotype γ' in incubation stage k'	$(X^{\gamma}(a),\ Y_k^{\gamma'}(a)) \to (X^{\gamma}(a),\ Y_k^{\gamma'}(a)-\delta_{aa'}\delta_{\gamma\gamma'}\delta_{\mathrm{kk'}})$	$\mu(a')Y_{k'}^{\gamma'}(a')$
Infection of an animal of age a' and genotype γ'	$(X^{\gamma}(a),\ Y_k^{\gamma'}(a)) \to (X^{\gamma}(a)-\delta_{aa'}\delta_{\gamma\gamma'},\ Y_k^{\gamma'}(a)+\delta_{aa'}\delta_{\gamma\gamma'}\delta_{k0})$	$\lambda^{\gamma'}(a')X^{\gamma'}(a')$
Incubation move from stage k' to $k'+1$ of an animal of age a' and genotype γ'	$(X^{\gamma}(a),\ Y_k^{\gamma'}(a)) \to (X^{\gamma}(a),\ Y_k^{\gamma'}(a)-\delta_{aa'}\delta_{\gamma\gamma'}\delta_{kk'}+\delta_{aa'}\delta_{\gamma\gamma'}\delta_{k(k'+1)})$	$\nu^{\gamma'}Y_{k'}^{\gamma'}(a')$
Removal of an infected animal of age a' and genotype γ' due to clinical onset	$(X^{\gamma}(a),\ Y_k^{\gamma'}(a)) \to (X^{\gamma}(a),\ Y_k^{\gamma'}(a)-\delta_{aa'}\delta_{\gamma\gamma'}\delta_{k_f})$	$\nu^{\gamma'}Y_{k_f}^{\gamma'}(a')$

by $\lambda_{\mathrm{dh}}(t) = \frac{1}{N(t)}\Sigma_{\gamma',k}\beta_k^{\gamma'}\int Y_k^{\gamma'}(t,a')da'$. Here β_k^{γ} denotes the infectiousness of an animals in incubation stage k of the genotype γ. The relative infectiousness $\tilde{\beta}_k$ is defined as $\tilde{\beta}_k = \beta_k^{\gamma}/\beta_{k_f}^{\gamma}$. In the single-locus, two-allele situation considered in this paper, we assume that $\beta_k^{RS}=\beta_k^{SS}$, where *RS* and *SS* denote the heterozygote and homozygote susceptible genotypes, respectively. Then $\beta_{k_f}^{RS}=\beta_{k_f}^{SS}$ serves as an overall transmission coefficient. The susceptibility is given by $g_{\mathrm{h}}^{RR}=0$, $g_{\mathrm{h}}^{SS}=1$ and $0 \leqslant g_{\mathrm{h}}^{RS} \leqslant 1$.

Environmental reservoir

The environmental infectivity reservoir I is governed by the differential equation $\frac{dI}{dt}(t) = \lambda_{\mathrm{dh}}(t)-\eta I(t)$, where η is the decay rate of environmental infectivity.

Demography and maternal transmission

The birth rates $B_X^{\gamma}(t) = B^{\gamma}(t)-B_Y^{\gamma}(t)$ and $B_Y^{\gamma}(t)$ are given by

$$B^{\gamma}(t) = s(t)B_0 b^{\gamma}(t)/\sum_{\gamma} b^{\gamma'}(t),$$

where

$$b^{\gamma}(t) = \sum_{\gamma}\int_0^{u'}\alpha(a')G^{\gamma\gamma'}(X^{\gamma}(t,a') + \sum_k Y_k^{\gamma}(t,a'))\,da'$$

and

$$B_Y^{\gamma}(t) = s(t)g_{\mathrm{V}}^{\gamma}B_0/(\sum_{\gamma} b^{\gamma''}(t)) \times \sum_{\gamma}\sum_k\int\alpha(a')G^{\gamma\gamma'}\epsilon_k^{\gamma'}Y_k^{\gamma'}(t,a')da'.$$

Here B_0 is a constant overall birth rate, $s(t)$ is a normalized birth seasonality profile, $\alpha(a)$ is an age-dependent lambing rate, $G^{\gamma\gamma''}$ is the proportion of genotype γ lambs born to genotype γ' ewes, g_{V}^{γ} the relative susceptibility to maternally transmitted infection of genotype γ (here assumed to be equal to g_{V}^{γ}), and ϵ_k^{γ} the vertical infectiousness of an animal of genotype γ in incubation stage k. In this paper we assume that $\epsilon_k^{\gamma} = p_{\mathrm{mat}}\,\tilde{\beta}_k^{\gamma}$, where p_{mat} is the maternal transmission probability from a maximally infectious ewe to a maximally susceptible lamb.

For completeness we give the expressions for of the basic reproduction number R_0 and of T_g, the mean generation time between infections, in terms of the parameters of the model described above:

$$R_0 = \frac{\chi+\eta}{\eta}\sum_{\gamma} B^{\gamma}(0) g_{\mathrm{h}}^{\gamma} \int\int \frac{S(a+\tau)}{N} \times \sum_{k} \beta_k^{\gamma} P_k^{\gamma}(\tau)\, d\tau da \quad (8)$$

$$T_g = \sum_{\gamma} B^{\gamma}(0) g_{\mathrm{h}}^{\gamma} \int\int \frac{\left(\tau + \frac{\chi}{\eta(\eta+\chi)}\right) S(a+\tau)}{N} \times \sum_{k} \beta_k^{\gamma} P_k^{\gamma}(\tau) d\tau da. \quad (9)$$

Here $P_k^{\gamma}(\tau)$ is the probability that an animal of genotype γ is in the kth incubation stage a time τ after being infected. These expressions hold in situations without maternal transmission. For the derivation of these expressions and their generalisations under transmission scenarios with maternal transmission we refer the reader to Ref. [11].

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