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Review article

The role of mathematical modelling in understanding the epidemiology and control of sheep transmissible spongiform encephalopathies: a review

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Abstract – To deal with the incompleteness of observations and disentangle the complexities of transmission much use has been made of mathematical modelling when investigating the epidemiology of sheep transmissible spongiform encephalopathies (TSE) and, in particular, scrapie. Importantly, these modelling approaches allow the incidence of clinical disease to be related to the underlying prevalence of infection, thereby overcoming one of the major difficulties when studying these diseases. Models have been used to investigate the epidemiology of scrapie within individual flocks and at a regional level; to assess the efficacy of different control strategies, especially selective breeding programmes based on prion protein (PrP) genotype; to interpret the results of scrapie surveillance; and to inform the design of surveillance programmes. Furthermore, mathematical modelling has played an important role when assessing the risk to human health posed by the possible presence of bovine spongiform encephalopathy in sheep. Here, we review the various approaches that have been taken when developing and analysing mathematical models for the epidemiology and control of sheep TSE and assess their impact on our understanding of these diseases. We also identify areas that require further work, discuss future challenges and identify data gaps.

epidemiology / transmissible spongiform encephalopathy / scrapie / mathematical modelling / sheep

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1. INTRODUCTION

Transmissible spongiform encephalopathies (TSE) are a family of neurodegenerative diseases which afflict a range of animal species, and include bovine spongiform encephalopathy (BSE) in cattle, variant Creutzfeldt-Jakob disease (vCJD) in humans, chronic wasting disease (CWD) in deer and classical and atypical scrapie in sheep and goats. Many of these disorders have been identified only recently, but classical scrapie has been present in sheep and goats for several centuries [70]. Despite this, the epidemiology of classical scrapie remained relatively poorly understood [10, 11, 42]. The experimental transmission of BSE to sheep [23, 24] raised the possibility that sheep in Great Britain (GB) may have been infected following exposure to contaminated feed during the 1980s [20, 51] and may pose a risk to human health [6, 20]. As a consequence of this risk a number of regulations have been adopted throughout the European Union (EU) since 2001 aimed at the control of sheep TSE, requiring (amongst other things) intensive surveillance of animals slaughtered for human consumption or found dead on farm, selective breeding programmes for TSE resistance and implementation of control measures in affected flocks.

Several features of the epidemiology of scrapie make it particularly difficult to study. First, the incubation period for the disease is typically of the order of several years [9, 42], which is comparable to the commercial life-span of a sheep. Second, until recently there has been no live diagnostic test suitable for large scale use in the field. These two features mean that only clinical cases, not infected animals, are observed in most outbreaks. Consequently, a large proportion of infected animals go undetected, because only a small proportion of infected animals survive to disease onset. Moreover, the clinical signs of scrapie can be difficult to discern [11] and, hence, not all clinical cases may be identified. Third, scrapie has a strong host genetic component associated with the prion protein (PrP) gene which influences both the risk of infection and the incubation period. Five alleles of the PrP gene (defined by amino acids at codons 136, 154 and 171) are commonly found in sheep, which in order of increasing risk of clinical disease and decreasing age-at-onset are: ARR, AHQ, ARH, ARQ and VRQ [3, 11, 35, 73]. Finally, the routes of transmission have yet to be elucidated [10, 11, 42], and, indeed, the infectious agent has yet to be fully characterised [7, 11].

To deal with the incompleteness of observations and disentangle the complexities of transmission much use has been made of mathematical modelling when investigating the epidemiology of sheep TSE and, in particular, scrapie. Importantly, these modelling approaches allow the incidence of clinical disease to be related to the underlying prevalence of infection, thereby overcoming one of the major difficulties when studying these diseases. Models have been used to investigate the epidemiology of scrapie within individual flocks (Tab. I) and at a regional level (Tab. II); to assess the efficacy of different control strategies (Tabs. I and II), especially selective breeding programmes based on PrP genotype; to interpret the results of scrapie surveillance (Tab. III); and to inform the design of surveillance programmes (Tab. III). One further area where mathematical modelling has played an important role is when assessing the risk to human health posed by the possible presence of BSE in sheep (Tab. IV).

In this paper, we review the various approaches that have been taken when developing and analysing mathematical models for the epidemiology and control of sheep TSE and assess their impact on our understanding of these diseases. We also identify areas that require further work, discuss future challenges and identify data gaps.

2. TRANSMISSION OF SCRAPIE WITHIN FLOCKS

Analyzing field data on scrapie outbreaks is a natural starting point for studying the transmission dynamics and control of scrapie within farms (Tab. I). Mathematical modelling of the transmission process is necessary to interpret the observed development of an outbreak

Table I. Summary of models used to describe the transmission of scrapie within a sheep flock.

Author(s)	Aims	Modelling approach	Conclusions
Hagenaars et al. [37][a]	Obtain general insights into the population-dynamical properties of possible scenarios of scrapie transmission in a sheep flock	• Deterministic model framework comprising most of the aspects that are of relevance (potentially or in reality) to the transmission dynamics of scrapie • General insights from analytical considerations and approximations	• Dependence of basic reproduction number (R_0) and generation time on other parameters gives insight into the effects of these parameters • Simplified model yields insights into interplay of horizontal and vertical transmission, and the characteristics of endemic scrapie
Hagenaars et al. [38][a]	Understand how persistence of scrapie in a flock depends on transmission and flock size	• Stochastic model of within-flock transmission • Analytical calculations using branching-process approximations and • Numerical calculation using stochastic model simulations	• Disease extinction is most likely when late-stage infected animals are responsible for most of the transmission • Presence of an environmental reservoir reduces the probability of extinction
Hagenaars et al. [39][a]	Estimate transmission parameters from a scrapie outbreak	Fitting stochastic transmission models to the outbreak data	• Mean incubation period for the outbreak is less than 1.5 years • Infectiousness of infected animals becomes appreciable at early stage of incubation • Difficult to quantify R_0: the data are consistent with a broad range of values
Matthews et al. [57][b]	Examine the role of a range of epidemiologically important parameters and the effects of genetic variation in susceptibility	• Mathematical expression for R_0 is derived based on a transmission model • Sensitivity of R_0 to various parameters and genetic variation is studied	• Reduction in the frequency of the susceptible allele reduces R_0 most effectively when the allele is recessive • Inbreeding may increase R_0 when the susceptible allele is recessive, increasing the chance of an outbreak • Point estimate of R_0 for an outbreak in Cheviot sheep is given ($R_0 = 3.9$)
Matthews et al. [58][b]	Analysis of a scrapie outbreak in a flock of Cheviot sheep	Fitting a deterministic model to outbreak data	• Model reproduces observed allele frequencies and total numbers of susceptible animals remaining at the end of the outbreak • Indication that older animals have reduced susceptibility to scrapie

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Table I. Continued.

Author(s)	Aims	Modelling approach	Conclusions
Sabatier et al. [66]	Explore the impact of genetic resistance and flock management practices on scrapie outbreaks	Discrete-time deterministic mathematical model of the within-herd transmission dynamics of scrapie	• Three main observed patterns of outbreaks: sporadic, endemic and epidemic can be reproduced depending on parameter settings • Model results suggest that overall size of the outbreak is determined primarily by the initial genetic composition of the flock • Outbreak type is determined mainly by the herd management practices
Stringer et al. [71][b]	• Develop within-flock scrapie transmission model for assisting the interpretation of field data • Use model to explore properties of scrapie transmission dynamics	Deterministic model defined using partial differential equations with respect to time, age and infection load	• Scrapie outbreak is likely to be of long duration • Will lead to a reduction of scrapie susceptible allele frequency (but not to zero)
Touzeau et al. [74][b]	Explore hypothesis of increased scrapie transmission during lambing season	• Partial-differential equation model of scrapie within-flock transmission dynamics • Applied to a natural outbreak in Romanov sheep	• The observed patterns of seasonality in incidence cannot be accounted for by seasonality in demography alone • Provides support for the hypothesis of increased transmission during lambing

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Table I. Continued.

Author(s)	Aims	Modelling approach	Conclusions
Woolhouse et al. [79][b]	Explore the course of an outbreak in a sheep flock, and the potential impact of different control measures	• Partial-differential equation model of scrapie within-flock transmission dynamics • Parameter values consistent with available data	• In a closed flock, scrapie outbreaks may have a duration of several decades, reduce the frequency of susceptible genotypes, and may become endemic if carrier genotypes are present • In an open flock, endemic scrapie is possible even in the absence of carriers • Control measures currently or likely to become available may reduce the incidence of cases but may be fully effective only over a period of several years
Woolhouse et al. [80][b]	Analysis of an outbreak of natural scrapie in a flock of Cheviot sheep	• Partial-differential equation model of scrapie within-flock transmission dynamics	• Model is able to reproduce key features of the outbreak, including its long duration and the ages of cases • Many infected sheep do not survive to show clinical signs • Most cases arise through horizontal transmission • Strong selection against susceptible genotypes

References with a common superscript use the same basic modelling approach: [a] Hagenaars et al. [37]; or [b] Stringer et al. [71].

Table II. Summary of models used to describe the transmission of scrapie between sheep flocks.

Author(s)	Aims	Modelling approach	Conclusions
Durand et al. [15]	Develop a regional model for spread between flocks	• One-dimensional arrangement of flocks • Winter transmission only between neighbouring flocks • Summer transmission also between flocks which share grazing • Gene-flow between flocks • Selective breeding programmes	Model developed, which can in future be used to assess control strategies
Gravenor et al. [27]	Estimate the flock-to-flock force of infection for scrapie in Great Britain	Simple *SI* model for flocks	• Force of infection: 0.0045 per farm per year • Mean outbreak duration: 5 years • No evidence for an increase in the force of infection before, during or after the BSE epidemic in British cattle
Gravenor et al. [28]	• Estimate transmission parameters for scrapie in Cyprus • Investigate the impact of control measures	Simple *SEI* model for flocks, including effect of culling and quarantine	• R_0 = 1.4–1.8 • Early identification and quarantine of affected flocks most effective for control of disease
Gubbins [31]	Develop modelling approach to describe the spread of scrapie between sheep flocks in Great Britain	• Stochastic, spatial flock-level model • Acquisition of infection depends on trade • Probability and duration of a within-flock outbreak depends on flocks size and PrP genotype profile	• Model is able to capture the spatial dynamics of scrapie • There is considerable uncertainty when predicting long-term trends for disease
Gubbins and Webb [32]	Assess the efficacy of control strategies to eradicate scrapie from Great Britain		• Feasible to eradicate scrapie, but it will take decades to do so • The most-effective strategy is whole-flock culling, though whole-flock genotyping and selective culling is also effective
Gubbins and Roden [33]	Assess the impact of selective breeding programs on prevalence and incidence of scrapie	• Simple age- and genotype-structured *SI* model • Flock structure ignored (same force of infection for all sheep)	• Selective breeding strategies will reduce the prevalence and incidence • Targeting only the VRQ allele is sufficient to have a large impact on disease occurrence

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Table II. Continued.

Author(s)	Aims	Modelling approach	Conclusions
Gubbins et al. [34]	Estimate basic reproduction number (R_0) and mean outbreak duration (D) for spread between flocks in the Shetland Isles	Simple *SIR* model for flocks	• R_0 = 1.47 (95% CI: 1.45–1.50) • D = 2.11 years (95% CI: 2.01–2.23)
Hagenaars et al. [40]	Use surveillance data to estimate key epidemiological parameters	Simple *SI* model for flocks	• Large proportion of cases (80%) go undetected • Occurrence of scrapie may provoke changes in flock management which reduces outbreak duration • Within-flock R_0 = 1.5–6.0
Kao et al. [50]	• Formulate a flock-to-flock model of scrapie spread • Assess potential control programmes	• *SEI* epidemic model with affected flocks of "low'' and "high" risk (depending on genetic structure) which determines whether they experience outbreaks following exposure • Acquisition of infection depends on trade	• R_0 = 1.1–1.2 • High risk flocks predicted to comprise 3–20% of the national population • Targeted programmes predicted to eradicate scrapie more quickly than those aimed at the general population
Truscott and Ferguson [75]	• Develop a model for spread of scrapie in UK sheep population • Use the model to estimate infection prevalence (overall and by breed), and to evaluate possible long-term persistence of scrapie	• Metapopulation model based on the coupling of fairly detailed within-flock *SI* epidemic models (genotype, age, and infection stage structure) • Flock-level acquisition of infection occurs by breeding, trading, or through homogeneous low-level contamination generated by all flocks	• Detection/reporting probability of 16% (12–17) • Prevalence of infected animals in the population estimated to be 0.15% • 9% of flocks estimated to be infected overall, rising to 60% in Shetland and 75% in Swaledale flocks
Truscott and Ferguson [76]	• Assess impact of different strategies for control of scrapie in UK sheep	• Flocks differ in breed, size, and PrP allelic composition	• UK National Scrapie Plan (NSP) is the most effective scheme • NSP and UK Compulsory Scrapie Flock Scheme (CSFS) both reduce the case incidence, but CSFS is less effective in decreasing the susceptible allele frequency • Trading restrictions have a limited impact compared to selective breeding and culling

Table III. Summary of the models used to inform scrapie surveillance.

Author(s)	Aims	Modelling approach	Conclusions
Gubbins et al. [30]	Estimate prevalence of scrapie infection in GB based on an abattoir survey in 1997/1998	• Simple age-structured prevalence model • Probability of detection dependent on stage of incubation • Diagnostic tests less than 100% specific	• Prevalence of scrapie 0.22% (95% CI: 0.01–0.97%) • All tests used very specific (> 99%), with only one less than 100%
Gubbins [35]	Estimate prevalence of classical scrapie in GB by integrating data on reported cases and the results of abattoir and fallen stock surveys for 2002	• Back calculation approach • Probability of detection dependent on stage of incubation and PrP genotype	• Prevalence ranges from 0.33% to 2.06% depending on stage of incubation at which diagnostic test able to detect infected animals • Risk of infection much higher than the risk of clinical disease • Analysis of surveillance data needs to account for PrP genotype
Gubbins and McIntyre [36]	Estimate prevalence of classical scrapie in GB for 1993–2007 by integrating data on reported cases (1993–2007) and the results of abattoir and fallen stock surveys (2002–2007)	• Back calculation approach • Probability of detection dependent on stage of incubation and PrP genotype • Baseline risk of infection changes over time • Frequency of PrP genotypes in a birth cohort changes over time • Proportion of cases reported changes over time	• Prevalence was approximately constant for 1993–2003 and was estimated to be 0.3% to 0.7% depending on stage of incubation at which diagnostic test able to detect infected animals • Prevalence declined by around 40% between 2003 and 2007
Hopp et al. [44]	Assess the efficacy of different strategies for identifying scrapie-affected flocks in Norway	• Stochastic simulation of strategy based on the probability of detecting an infected animal through each surveillance stream • Includes effect of PrP genotype on risk of scrapie, incubation period and probability of detection	• Less than 9% of affected flocks are identified by either abattoir or fallen-stock surveillance • Samples sizes much lower for fallen stock than abattoir surveys • Abattoir surveillance most affected by an increase in test sensitivity
Webb et al. [78]	• Estimate prevalence of scrapie infection in GB based on abattoir survey data • Assess design of an abattoir survey	• Simple age-structured prevalence model • Probability of detection dependent on stage of incubation • Stochastic simulation of survey	• Survey results consistent with a prevalence in the slaughter population of up to 11% • Sample sizes need to be larger • Diagnostic tests need to be assessed in relation to genotype and stage of infection

Table IV. Summary of the models for the possible consequences of BSE in sheep.

Author(s)	Aims	Modelling approach	Conclusions
Ferguson et al. [20]	Estimate the human health risk from possible BSE infection in the GB sheep flock	• Deterministic age-structured *SI* model for within-flock spread • Deterministic *SIRS* model for spread between flocks • Deterministic model for transmission to human population	• Public health risk from ovine BSE is likely to be greater than from cattle • Risk could be reduced through additional restrictions on sheep products entering the food chain • Upper bound for vCJD cases increases to 150 000 when worst-case ovine BSE scenario included in predictions
Fryer et al. [25]	Assess the impact of different control strategies to protect public health from exposure to BSE in sheep	• Age- and genotype-structured within-farm model used to estimate the exposure of humans to infectivity from BSE-infected sheep entering the food chain • Assumes constant number (4) of BSE-affected flocks in GB	• If BSE were present in the GB national flock, the exposure to consumers from a single infected sheep would be high • Annual exposure from four BSE-affected flocks could be considerable • Small reductions in exposure can be achieved by strategies based on tissue testing, a 12-month age restriction or expanded definitions of high-risk tissues • A 6-month age restriction is more effective • Genotype-based restrictions are most effective
Kao et al. [51]	Estimate the possible size of a BSE epidemic in British sheep	• Age- and genotype-structured model to predict size of feed-borne epidemic • Flock-level model to predict impact of horizontal transmission on epidemic • See also [51] (Tab. II)	• Feed-borne epidemic peaked in 1990 with between 10 and 1 500 infected sheep • In 2001, at most 20 clinical cases of BSE would be expected • If horizontal transmission occurs, it could cause a large epidemic
Kao et al. [52]	Assess the impact of ARR/ARR sheep being susceptible to BSE	• Age- and genotype-structured model for feed-borne epidemic • Deterministic model for flock-to-flock transmission • See also [51, 54]	• Predictions for size of feed-borne epidemic not affected if ARR/ARR animals can become infected • Selective breeding for ARR/ARR should control a BSE epidemic, but there are scenarios consistent with the data in which control fails

through time, by characterizing the properties of different transmission scenarios and by testing if these are consistent with the data. Once such scenarios have been identified, the model can be used to explore, for example, the impact of selective breeding strategies designed to control disease. Consequently, we can distinguish three different purposes for within-flock modelling: (i) interpreting outbreak data (including parameter estimation); (ii) characterizing transmission scenarios; and (iii) assessing the impact of possible control strategies.

2.1. Analysing outbreak data

The first analysis of a scrapie outbreak using a transmission model was reported by Woolhouse et al. [80]. They used a susceptible-infected (*SI*) modelling approach developed in an earlier paper [71] to analyze a large outbreak of natural scrapie (137 cases among 1 307 sheep born over a period of 13 years) in a flock of Cheviot sheep. By carefully setting the values for a number of crucial parameters (in particular: horizontal transmission rate, mean and variance of the incubation period distribution, and relative susceptibility of different genotypes), they were able to reproduce the main features of the observed outbreak. What was learned from their analysis, however, extends beyond the identification of the "best-fit" parameters. In fact, the most interesting results were those that are of a more qualitative nature and that can be expected to carry over to other scrapie outbreaks, notably the following:

- Most cases arise due to horizontal (as opposed to vertical) transmission;
- Many infected sheep do not survive to show clinical signs; and
- Observed cohort dependencies in mean age of cases can be explained (in part) by an increase or decrease in the force of infection (and, hence, a decrease or increase in the average age at infection).

The modelling framework used by Woolhouse et al. [80] is a deterministic one, that is it does not describe the variation in outcome arising due to chance for any given set of parameter values. Although this limits the applicability of the model in the early and late phases of the outbreak (where stochastic effects are large due to the small number of sheep infected with scrapie), the deterministic approach is adequate during the main part of the outbreak due to the large numbers of cases. Technically, the model is formulated as a set of partial differential equations (PDE), where the partial derivatives are with respect to three continuous variables: time, age and infection load. The inclusion of the infection load variable is a means to describe the incubation process: the load is assumed to increase exponentially with time, with onset of clinical disease assumed to occur when the load reaches a threshold level; the initial infection load is drawn from a probability distribution, yielding variation in the length of the infectious period [71].

In a second analysis using the same modelling approach, the population dynamics of a subsequent scrapie outbreak in the same flock of Cheviot sheep was studied [58]. In this second outbreak, the number of cases was much lower (33 cases among 1 473 sheep born over a period of 10 years) which means that on average the force of infection was lower. It turns out that for this reason the data from this epidemic provide additional information when analyzed with the model. In particular, the analysis showed that susceptibility to scrapie was reduced in older animals: no satisfactory model fits could be obtained when assuming age-independent susceptibility. Likewise, models assuming the same incubation period distribution for all susceptible genotypes could be rejected. Both an age dependence and a genotype dependence were identified in a later, statistically more rigorous estimation of susceptibility parameters from the same outbreak data [67].

This illustrates how a modelling analysis of data from a low-incidence outbreak may reveal heterogeneities that are not apparent from a high-incidence outbreak. Both the heterogeneities identified were not necessary to obtain a good description in the analysis of the first outbreak, due to the high force of infection in that outbreak. As a result of the high incidence of infection, susceptibility differences between genotypes alone were sufficient to reproduce

between-genotype differences in age of cases, and the low mean age at infection reduced the potential to detect any decline in susceptibility with age. The modelling of the two quite different outbreaks also provides insights into which parameters are the most important determinants of the observed outbreak patterns. One major determinant identified was the frequency of homozygous susceptible genotypes in the flock; this frequency was much lower in the second outbreak, and as result the incidence was lower and peaked at a later time. By contrast, the horizontal transmission parameter hardly differed between the two outbreaks.

We thus have the paradoxical effect (from a statistical viewpoint) that a "higher" incidence of cases may render it more difficult to quantify certain transmission parameters. This paradox is also apparent from a stochastic modelling analysis of a high-incidence scrapie outbreak in a flock of Romanov sheep [39]. One of the parameters studied in this analysis was the basic reproduction number, R_0, an important summary parameter that quantifies the overall transmission potential of an infection in a population of given composition (in the case of scrapie this will be the PrP genotype composition of a flock) [37, 57]. Due to the high incidence in this outbreak, the confidence interval for R_0 was found to be very wide, that is the data were consistent with a broad range of R_0 values. Nevertheless, this analysis did succeed in quantifying other parameters. In particular, it revealed that the infected animals become infectiousness at an early stage of disease incubation.

In another modelling analysis of the same outbreak in Romanov sheep [74], the hypothesis of increased scrapie transmission during the lambing season was explored. This analysis used the same PDE framework [71] as the studies of outbreaks in Cheviot sheep [58, 80]. It was found that the observed patterns of seasonality in incidence cannot be accounted for by seasonality of births alone, providing support for the biologically plausible hypothesis of increased transmission during lambing.

In the past, the most comprehensive outbreak data originated from flocks managed by research institutes. More recent data on PrP genotypes and brain-stem test results from commercial flocks subject to statutory control measures offer new opportunities for quantitative study of scrapie transmission. One issue would be to better quantify the relationship between scrapie susceptibility and PrP genotype, a relationship that has proven difficult to study experimentally [47]. The relative susceptibility of PrP genotypes is an important model parameter in most within-flock transmission models. If the incidence is sufficiently low, the calculated genotype-specific infection attack rates are proportional to the relative susceptibility. As a result, infection attack rates observed in low-incidence outbreaks can serve as a measure of genotype-specific susceptibility. For higher attack rates, this is not the case as infection saturation effects will act differently in different genotypes; mathematical modelling is necessary to take such effects into account. It is also relevant to notice that the interpretation of attack rates from either clinical scrapie data [3] or brain-stem test data in terms of relative susceptibility to scrapie infection is not straightforward; it is complicated by differences between genotypes in terms of incubation time and also, in the case of clinical data, differences in clinical signs. Infection attack rates based on brain-stem rapid tests indicate in particular that the relative susceptibility of ARR/VRQ animals is much higher than suggested by data on clinical cases (see also [35, 36]).

2.2. Characterizing transmission scenarios

The first within-flock modelling analysis aimed at characterizing different transmission scenarios focused on calculating the basic reproduction number, R_0, for scrapie [57]. By studying the sensitivity of R_0 to various parameters and to genetic variation, their role in within-flock transmission is elucidated. One of the conclusions is that 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. The authors illustrate how the mathematical expression derived for R_0 can be evaluated from outbreak data by considering the example of a scrapie outbreak in a flock of Cheviot sheep.

In a model development paper using an ordinary differential equation (ODE) model approach (as opposed to PDE), the sensitivity of R_0 to various model parameters was studied analytically by Hagenaars et al. [37]. The derivation of an explicit (analytical) result for the dependence of R_0 on model parameters was enabled by assuming negligible vertical transmission and by making the common assumption that the genotype dependence of horizontal transmission risks can be written as the product of a relative infectiousness (determined by the genotype of the infected animal) and a relative susceptibility (determined by the genotype of the susceptible contact animal). The authors were able to show how the transmission of scrapie within a flock is determined by four key factors, one of which is the manner in which the infectiousness of an animal increases between infection and disease onset. Further approximations were made that allowed additional results to be obtained. In particular, the interplay between horizontal and vertical transmission was elucidated, as well as how model parameters determine the following properties: the level of disease-induced selection against susceptibility, the presence or absence of recurrent incidence peaks, and the average infection prevalence during an outbreak.

A further issue for exploration by modelling is how the duration of scrapie outbreaks depends on the underlying parameters. To study this issue, a stochastic modelling approach is needed, because both the early and the late phases of an outbreak are much affected by chance events. In particular, disease extinction, occurring when the last infected individual recovers or, in the case of scrapie, is removed from the population, is an intrinsically stochastic process. An exploratory analysis of how scrapie extinction (or, equivalently, persistence) properties depend on relevant model parameters [38] used the stochastic equivalent of an ODE model framework developed earlier [37], as well as branching-process approximations [37]. The properties studied included the probability of early extinction and the outbreak duration distribution. One the main results was that for a given basic reproduction number, disease extinction was most likely when late-stage infected animals are responsible for most of the transmission.

A stochastic modelling approach was also adopted by Sabatier et al. [66]. They used a discrete-time stochastic model of both the genetic composition of, and scrapie transmission within, a sheep flock to study outbreak patterns. They classified the resulting patterns into three different types: sporadic (short outbreaks), endemic (long outbreaks, with clinical cases mainly in young animals), and epidemic (long outbreaks, with clinical cases in all the age classes). One of their findings was that the overall size of an outbreak was mainly determined by the initial genetic composition of the flock, whereas the outbreak type was influenced mostly by flock management practices.

2.3. Assessing the impact of control

The third principal use of within-flock modelling is to assess the effect of scrapie control measures in a flock. These range from qualitative assessments of factors likely to influence the efficacy of control [57, 79] to quantitative analyses of control programmes in affected flocks. Woolhouse et al. [79] explore the effect of a number of generic control measures on the time evolution of an outbreak: reduction of vertical transmission, reduction of horizontal transmission, slaughter of preclinically infected sheep, and breeding with homozygous resistant rams only. Similarly, Matthews et al. [57] studied the sensitivity of R_0 to the first three control measures, showing in particular that the first measure (reduction of vertical transmission) would typically have insufficient effect to reduce R_0 to below one (as required for successful control).

The first three control measures listed above are either of a generic character (reduction of transmission) or not yet feasible on a large scale (slaughter of preclinically infected sheep). However, a control programme based on selecting ARR/ARR rams for breeding was initiated in the Netherlands some years ago. In recent years, the scrapie incidence per sheep of susceptible PrP genotype was found to be dropping, in agreement with expectations based on

mathematical modelling of the selective breeding programme[1].

In the literature on modelling the within-flock dynamics of scrapie we observe that the different modelling approaches (ODE, PDE, discrete-time) give similar main model behaviour. Much of the work is exploratory in nature, for example, no detailed transmission parameter estimates have been attempted other than for a small number of outbreaks in specific flocks. The modelling analyses of the severe outbreak in the French flock of Romanov sheep [39, 74] show that although some parameters remain highly uncertain, some of them can be meaningfully quantified: seasonality, onset of infectiousness and mean incubation period.

More and better data is now accumulating as mandatory control measures in scrapie-affected flocks produce data on genotype profiles of commercially kept flocks and also cross-sectional data on infection incidence in the different genotypes in these flocks. This will allow better estimates of the relative susceptibility of the different genotypes to be obtained, and thus enable improved models for the relationship between the PrP genotype profile of a flock and its basic reproduction number. One difficult aspect of the latter relationship is to quantify differences in infectiousness amongst genotypes. Here experiments in a controlled setting might help to give at least some clues, for example experiments measuring the level of infectivity in placenta and its dependence on ewe and lamb genotype [1].

3. TRANSMISSION OF SCRAPIE BETWEEN FLOCKS

At a regional or national scale, most scrapie transmission models have been developed with the aim of assessing existing or potential control measures, even if the actual assessment may be outside the scope of the study presented [15, 31, 75]. Control measures are mostly based on selective breeding at the flock level [32, 33, 50, 76], which aims at increasing the frequency of low-risk alleles in the national flock. Accordingly, these strategies require the genotyping of rams and, possibly, ewes. Targeting animals in flocks assumed to be at a higher risk of scrapie has also been explored [50]. Apart from selective breeding, whole-flock culling may be implemented [27, 32, 76] and the impact of delayed detection or under-reporting is explored [28]. Despite all these measures being expensive to implement, very few studies have explicitly considered costs as part of the analysis [28].

Models have also been used as integrative tools to combine fairly heterogeneous data from various sources. This allows risk factors to be identified [34] or transmission scenarios to be verified [40]. Depending on the data available and on the outbreak "stage", models may also be used to reproduce the disease history at a fairly large scale [15, 34] or to predict its potential spread at an early stage [28].

3.1. Modelling approaches

Models that take into account the transmission of scrapie between flocks offer a whole range of complexity in the representation of flocks and their interactions: from simple models in which flocks are considered as individuals in an homogeneous population [28, 34], to complex models in which the within-flock transmission dynamics are explicitly included in a heterogeneous population of flocks [15, 75]. There is an obvious trade-off between tractability and realism in these models.

In such a metapopulation approach, the modelling unit is frequently the flock as a whole. It is characterised mainly by its epidemiological state, susceptible or infected [27, 31, 34, 40], an infected flock being defined as one with either infected individuals or detected cases. An exposed state [50], corresponding to a flock with relatively high frequencies of resistant PrP genotypes and assumed to have lower prevalence of infection, or a quarantine state [28] may also be considered. A certain degree of flock heterogeneity may be included in the model, typically reflecting flock-level risk

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factors for scrapie [41, 43, 59, 62]. This may simply be variation in flock size [27] or may be a more detailed characterisation of flock size, type and region [31]; flocks may also be divided into high and low risk groups [50].

The between-flock dynamics of scrapie are driven by two major flock-level parameters: the probability of infection, based on the proportion of infected flocks, and the outbreak duration. In simpler cases, these parameters are assumed to be the same for all flocks [28, 34, 40], leading to models similar to the classical *SI* models used to describe within-flock transmission. These parameters are otherwise modulated by flock characteristics [27, 31, 50]. The probability of infection may also depend on whether scrapie is supposed to originate from animals bred in the flock or those bought-in to the flock [27]. Between-flock transmission being principally due to animal movements, this probability can be further defined as the risk for a flock to acquire infected animals and subsequently develop an outbreak [31, 50].

All the models mentioned above are relatively easy to implement and are mathematically tractable, with a reasonable number of parameters. However, they offer a simplified and implicit description of scrapie dynamics within each flock. In particular, the PrP genotype structure of the flock, which plays an important role in within-flock transmission, may be implied in the model by some flock state or characteristic, but in a static representation [31, 50].

A few models differ from this approach. The first one [33] represents the dynamics of scrapie prevalence in the British sheep population structured by age and PrP genotype. It ignores the flock structure entirely, so the resulting model is a classical *SI* model in a rather large flock. By contrast, two approaches [15, 75] both explicitly incorporate the within-flock transmission dynamics in their metapopulation model, essentially by coupling several flock-level models. In [15], these are simplified versions of the model developed by Sabatier et al. [66]. Two types of flocks are considered, sedentary or transhumant flocks, as well as three levels of genetic selection. Groups of sheep within a flock are characterised by their scrapie status and PrP genotype. Between-flock transmission occurs through trade and shared grazing. In [75], the within-flock transmission dynamics are fairly detailed and based on the model developed by Hagenaars et al. [37]. Groups of sheep within a flock are characterised by their scrapie status, PrP genotype and age, as well as their incubation stage for the infected individuals. Flocks differ by their breed, size and allelic composition, the last two being breed-dependent. Between-flock transmission occurs through breeding and trading. Moreover, the authors assume a homogeneous low-level contamination generated by all flocks.

The model developed by Durand et al. [15] is the only spatio-temporal model of between-flock scrapie transmission. Space is introduced as a one-dimensional discrete variable to localise flocks, allowing neighbouring pastures or mountain grazing ranges to be defined. In [31], space appears as a factor rather than a variable and the model is fitted to regional data.

All models assume that there is a constant number of flocks. A particular feature of two approaches [50, 75] is that their models incorporate a "birth and death process" at the flock level: flocks are dispersed and new flocks are formed from several dispersed flocks. Moreover, flocks may convert from high risk to low risk and vice versa following dispersal, and, hence, the proportions of low and high risk flocks can vary. As they represent two different PrP genotype structures, this allows the rough implementation of a selective breeding programme. In [15], selective breeding is integrated through the modelling of ram genotype frequencies, which are flock- and time-dependent and act as a control measure in the model. In [76], selective breeding is introduced through the use of resistant rams.

Most between-flock transmission models are calibrated on postal survey data or other available data sources that provide information on flock types and status. In [31], a sensitivity analysis was performed to assess the impact of parameter uncertainty. Sensitivity analyses are also performed to check the robustness of potential control measures [32, 33]. The within-flock dynamics of the simplified aggregated model used in [15] is validated by comparison with the original and detailed flock-model [66].

3.2. Results from modelling studies

In some studies, the main result is the development of the model itself [15, 31, 50, 75]. Estimates of key epidemiological parameters, such as the basic reproductive number, R_0, or the duration of the outbreak are obtained from most between-flock transmission models [27, 31, 34, 40, 50, 75]. Observed patterns and trends are compared to simulation outputs [15, 28, 31].

The effects of control measures were assessed in various studies. Results do not always converge, partly because the measures tested vary amongst studies. Gravenor et al. [28] showed that early detection is more cost-effective than whole-flock slaughter. Gubbins and Webb [32] compared four breeding strategies based on different genotyping and PrP selection levels, plus whole-flock culling. The latter was more effective, though whole-flock genotyping and selective culling also worked; in both cases, it was predicted that it would take decades to achieve scrapie eradication. Gubbins and Roden [33] assessed four breeding strategies, ranging from the EU minimum (restriction on VRQ-bearing rams) to the National Scrapie Plan for Great Britain (NSP) purebred flock scheme. All four strategies were effective but took some time before any incidence decrease was predicted to occur. They all target the VRQ allele in rams, which is sufficient to control the disease. Kao et al. [50] compared three breeding programmes that tend to increase the conversion of high risk flocks to low risk flocks: (i) a non-targeted programme, (ii) a programme that targets all high risk flocks, and (iii) a programme that targets highly infected flocks. Both targeted programmes were effective at reducing scrapie prevalence. Targeting fewer flocks is preferable, but the corresponding strategy (iii) does not eradicate high risk flocks, in contrast with strategies (i) and (ii). The recommended solution was a mixed strategy: (iii) followed by (ii) or (i). Finally, Truscott and Ferguson [76] compared the outcome of several policies with the natural course of the epidemic. The NSP Compulsory Scrapie Flock Scheme (CSFS), and the EU minimum requirements were implemented. The NSP was found to be the most effective scheme: whereas the NSP and CSFS both reduce the case incidence, the CSFS was less effective at decreasing the frequency of susceptible alleles in the national flock. In addition, they also showed that trading restrictions have a limited impact, compared to selective breeding and culling.

3.3. Discussion

Many of the studies reviewed above were presented as "preliminary", pending data collection. Data are crucial to inform models in order to produce realistic results, and a lack of data leads either to fairly complex and realistic models that are difficult to validate, or to (over)simplified models that cannot capture all transmission features.

This highlights the major problems with modelling studies which investigate the spread and control of scrapie at a regional level. On the one hand, the models required to do so are a priori more complex and, hence, more difficult to implement. On the other hand, they require more data, or data that are not readily available, to parameterize and validate the models. In particular, most modelling studies usually rely on surveys to assess the flock distribution in a region, the flock characteristics or their trading practices. The resulting spatial resolution and flock description are, hence, rather poor.

In a truly mechanistic model, between-flock transmission would be based on animal movements or very close contacts between flocks (for example, shared grazing). However, the data needed to construct such a model are seldom available, Great Britain being an exception, where sheep movements have been recorded since 2002. Another issue is tractability. Heterogeneities at the individual or flock level are likely to have an important effect on scrapie transmission, for example the PrP genotype structure within a flock, management practices or trading patterns. Too fine a structure on the sheep population, however, would only lead to very complex models that cannot easily be validated.

The availability of sheep movement data for Great Britain has given rise to studies in which the actual contact structure between flocks is used to analyse scrapie epidemiological data [29, 53]. Realistic flock networks such as the

ones proposed in these studies [29, 53] are attractive tools with which to represent the spread of scrapie between flocks. One future avenue which would be very interesting to explore is to couple such network approach with a within-flock transmission model, though a compromise would have to be sought between the integration of detailed realistic features and model tractability.

Given the lack of data with which to parameterise models for the spread of scrapie at a regional level, it is reasonable to ask what utility these models have. The main reason for developing many of the models was to assess the impact of different control strategies (Tab. II). Rather than attempt to predict the absolute impact of a strategy on the occurrence of scrapie, however, most models were used to compare the relative impact of a number of different strategies. Such an approach is likely to produce more robust conclusions because the aim is primarily to rank the strategies, not to explicitly quantify their impact.

4. INFORMING SCRAPIE SURVEILLANCE

Surveillance for scrapie is carried out throughout the EU (see, for example, [19]) with three main sources used: reported clinical cases; surveys of animals found dead on farm (fallen stock); and surveys of animals slaughtered for human consumption (abattoir surveys). However, interpretation of such surveillance data is complicated by a number of factors, for example, under-reporting of suspect cases and the dependence of the probability of detecting an infected animal on stage of incubation and PrP genotype. Mathematical models have been used to take into account these complications and, hence, interpret the data in terms of the underlying prevalence rather than the apparent prevalence or incidence (Tab. III).

The first studies developed methods to estimate the prevalence of infection in GB from the results of an abattoir survey conducted in GB during 1997–1998 [30, 78]. Both studies used a simple age-structured model for the prevalence of infection and allowed the probability of detection to vary with stage of incubation. The principal difference between the papers lay in the treatment of the data: Webb et al. [78] analysed the results for each diagnostic test independently; Gubbins et al. [30] combined all the test data in a single analysis and, in addition, allowed for less than 100% specificity for the tests. The approach adopted in [30] was used subsequently to analyse the results of abattoir surveys in 2002 and 2003 [16].

More recently, a different approach based on back-calculation methods, which integrated data from three surveillance sources (reported cases, fallen stock surveys and abattoir surveys), was developed to estimate the prevalence of sheep infected with classical scrapie in GB, initially using data for a single year (2002) [35], but subsequently using data from multiple years [36]. The critical assumption required to link all three sources of data, and those for fallen stock in particular, was that a proportion of infected animals survive to disease onset, but die before clinical signs become apparent. This is the simplest way of allowing for an increased risk of mortality in scrapie-infected animals close to the onset of disease [13, 35] (cf. [21]). In effect, this assumption implies that fallen stock surveys sample animals at or close to the onset of clinical disease.

Models developed to analyse surveillance data can also be used to address the inverse problem, namely what sample size are required to detect a given prevalence in the national flock (Tab. III). Because the 1997–1998 abattoir survey yielded so few positive samples despite being designed using standard statistical methods, Webb et al. [78] used their model to investigate the number of animals that would need to be sampled at the abattoir to detect at least five infected animals. The model of Webb et al. [78] was later extended by Hopp et al. [44] to include PrP genotype and fallen stock, and used as the within-flock component of a national surveillance model for scrapie in Norwegian sheep. The aim was to compute the sample size required to detect a specified number of infected flocks, which indicated that surveillance based on fallen stock required a considerably smaller number of sheep to be tested compared with abattoir-based surveillance. This reflects the much higher prevalence in the fallen stock compared with abattoir surveys [19, 36].

Although two different approaches were used to analyse surveillance data (i.e. those based on

[78] and those based on [35]), the models make a number of common assumptions:

(i) Animals are assumed to become infected at or close to birth. This can be justified because of the increased risk of infection in the perinatal period [22, 46] and evidence suggesting there is a decrease in susceptibility with age [67] (cf. Sect. 2.1). However, the impact of this assumption on the prevalence estimates has not been assessed.

(ii) Animals experience the same force of infection, that is the models ignore the impact of flock-level heterogeneities and flock structure on transmission. (Even though Hopp et al. [44] included flock structure, they assumed that the force of infection was the same in all flocks.) This assumption is largely made to simplify the analysis and reduce the amount of demographic data required to estimate the prevalence in the national flock (cf. the data requirements for between-flock models, Sect. 3). It would, however, be of interest to explore whether the analyses could be extended to include flock structure, as this would provide information on both holding-level and within-holding prevalence; but any such analysis is likely to be severely restricted by the available data.

(iii) The demographic structure of the underlying sheep population is assumed to be static. This is likely to be reasonable for the age structure of the population, but not for the PrP genotype frequencies, especially if a selective breeding programme is being implemented, as was case for GB after 2001. This suggests that the estimates for surveys prior to 2002 are likely not to be substantially affected by this assumption, but the analysis of surveys after this date must take the changes in the underlying PrP genotype frequencies into account (see, for example, [36]).

The principal difference between the two approaches is that the analyses in [78] and [30] ignored the effect of PrP genotype on the risk of infection, the incubation period and the probability of detection, primarily because PrP genotype data were not collected for animals sampled in the surveys. This is likely to have resulted in a spurious precision for the prevalence estimates (i.e. narrower confidence limits), because it ignores the relatively small numbers of animals sampled carrying each genotype, especially those in the higher-risk genotypes [35]. In addition, by including the effects of PrP genotype in the analysis Gubbins [35] was also able to estimate the risk of infection (rather than just that of clinical disease) and incubation period in different genotypes.

In addition to their apparent precision, the prevalence estimates themselves differ between the two approaches, though only estimates for 1997/1998 have been made using both approaches. In this case they were: up to 11% [78]; 0.22% [30]; or 0.3–0.7% [36]. However, a common observation from both approaches is that the prevalence estimates depend on the assumptions made about the ability of the test to detect infected, but preclinical animals. In particular, the later in the incubation period at which infected animals can be detected, the higher the prevalence estimates obtained. Yet this critical parameter is poorly defined. Limited data from pathogenesis studies [48, 77] suggest that it could be anywhere between the final half and final quarter of the incubation period [35]. A further complication is whether the preclinical detection period is fixed [30, 78], or whether it is a proportion of the incubation period [35, 36]. A fixed period has a mechanistic basis: it corresponds to an animal becoming detectable once a threshold level infectivity is reached [13]. A proportional one, however, is simpler to extrapolate from one PrP genotype to another.

Finally, all the analyses, except for [36], focus on data for a single year. However, the long incubation period of scrapie means that data from one year informs the prevalence in other years. Consequently, integrating data from multiple years results in more robust prevalence estimates [35, 36]. Moreover, the sample sizes required to detect a given level of prevalence will be much higher if based only on a single

year's surveillance than if based on data collected over multiple years.

5. POSSIBLE CONSEQUENCES OF BSE IN SHEEP

To date no naturally-occurring cases of BSE have been confirmed in sheep [18, 69], though one case has been confirmed in a French goat [17] with a further case suspected in a British goat [49]. Consequently, mathematical modelling of BSE in sheep has been used to address a different issue, namely to examine a hypothetical situation based on limited data (Tab. IV). In particular, two questions have been addressed: what could be the size and duration of an epidemic of BSE in sheep? What is the risk to human health posed by BSE in sheep and what could be the impact of different risk mitigation strategies? The principal focus of the various studies (Tab. IV) has been the consequences for an epidemic of BSE in British sheep, which reflects the magnitude of the BSE epidemic in cattle in GB compared with other countries [14].

Two studies examined the potential size and duration of an epidemic of BSE in British sheep [20, 51]. To describe a putative feed-borne epidemic Kao et al. [51] used an age-cohort model in which flocks were divided into two categories "lowland" and "hill and upland" to reflect different patterns of exposure to BSE-contaminated feed between these sectors. In addition, the effect of PrP genotype was included by assuming that animals homozygous for glutamine at codon 171 (QQ_{171}) had a short incubation period, heterozygous animals (i.e. QX_{171} where X is any other amino acid) had a longer incubation period, and the remaining genotypes were resistant to infection. In addition, Kao et al. [51] used a model for flock-to-flock transmission of BSE in sheep similar to one presented earlier [50] (see Tab. II) to assess the impact of horizontal transmission on the spread of BSE in sheep. By contrast, Ferguson et al. [20] developed a model that included both within- and between-farm transmission. However, within-farm transmission was included only in a much simplified manner, by assuming that resistance or susceptibility to BSE was a flock- rather than an animal-level (i.e. PrP genotype) property and that once a farm recovered from infection it could not be re-infected for a mean of 20 years.

The predictions for epidemic size were similar for both models [20, 51], with a peak prevalence of around 0.1% of flocks and 0.01% of animals, which occurred in the early 1990s. Moreover, both studies identified scenarios consistent with the available data in which BSE could be maintained at low levels in the sheep population, though this only occurred if there was sheep-to-sheep transmission of the BSE agent. However, both models also predicted a wide range of potential outcomes for the epidemics (over several orders of magnitude), especially for the long-term dynamics of BSE, which meant it was not possible to draw any robust conclusions.

In a later paper Kao et al. [52] extended their earlier approach to consider the impact of susceptibility of the putatively resistant ARR/ARR sheep, which were shown to develop clinical disease following intracerebral challenge [45]. They concluded that under most scenarios for the risk of infection in ARR/ARR animals the ability of the NSP to control sheep TSE would not be adversely affected. However, some of the more extreme scenarios, although consistent with the available data, indicated that the efficacy of the NSP could be compromised.

The risk to human health posed by an epidemic of BSE in sheep was investigated by Ferguson et al. [20] by integrating the outputs from their BSE in sheep model with one for the transmission of vCJD in humans. In particular, the potential size of a vCJD epidemic was assessed under a range of risk mitigation strategies based on the removal of tissues likely to contain BSE infectivity and restricting the age of sheep entering the food chain. More recently, Fryer et al. [25] assessed the impact of different risk mitigation strategies on the amount of infectivity entering the food chain, assuming there were four BSE-affected flocks in GB (the upper 95% confidence limit for the number of affected flocks; [69]). Both studies predicted that a BSE-infected sheep posed a greater risk to human health than a BSE-infected bovine,

because of the increased number of tissues containing infectivity in sheep and the difficulty of removing these from a carcass. Moreover, the two studies produced similar rankings for the mitigation strategies based on age restrictions, with control measures under which only animals under six months of age are allowed into the food chain identified as being the most effective. Fryer et al. [25] also considered further restrictions based on PrP genotype and found that genotype-only strategies were less effective than age-based ones, but that control measures based on both age and PrP genotype produced the greatest reductions in risk.

For all the studies which have investigated the potential consequences of BSE in sheep there was a considerable range of outcomes, reflecting the uncertainties and assumptions made in the models used, which are consequences of the limited availability of data. This raises the important question of the value of these studies (see, for example, [55, 63]). First, they allow exploration of potential scenarios, which integrate the available data, though care must clearly be taken when interpreting the model outputs and communicating them to policy makers or the general public. Second, they facilitate comparison of the relative impact of different control measures. Third, and possibly most importantly, they enable data gaps to be identified.

6. CONCLUSIONS

Mathematical modelling has made a number of important contributions to scrapie epidemiology, most notably: in understanding and quantifying transmission between animals; in assessing the impact of control measures at both the flock and national level; and in interpreting and integrating the results of scrapie surveillance.

One area in which mathematical modelling has been less successful, however, is in helping to elucidate routes of transmission. Although some studies have given attention to the interplay between horizontal and vertical transmission [37, 39, 57] or the role of an environmental reservoir for infectivity [38, 39], models cannot easily be used to identify separate transmission routes. This is essentially because a decrease in transmission via one route can be compensated for by a corresponding increase in transmission via a different route without greatly affecting the predicted course of an epidemic. Consequently, transmission routes must be explored using either transmission experiments carried out in controlled environments (as was done for scrapie transmission via milk [54]) or by using more traditional field-based approaches [11, 42]. In the case of transmission experiments, mathematical modelling has an important role to play in interpreting results and extrapolating these to the field situation (see, for example, [8]).

A surprising aspect of the modelling studies highlighted by this review is the relative lack of interaction between the different levels that have been modelled (i.e. within-flock; between flock; surveillance). For example, with few exceptions ([37] and [75, 76]; [66] and [15]) the models developed to describe the dynamics of scrapie within a flock are seldom used, even in simplified forms, as components of models for the spread of scrapie between farms, despite control measures typically being targeted at a flock level. Moreover, scrapie surveillance often provides the largest data-sets with which to estimate parameters such as the relative risk of infection or the age-at-onset in different PrP genotypes, especially those in which scrapie occurs infrequently. Yet most studies of scrapie outbreaks within flocks rely solely on the data for that outbreak to estimate all parameters in the model, even those that are genotype-specific. This is sometimes feasible for high-incidence outbreaks that have been studied in detail [39, 58, 74, 80], though even here considerable uncertainty remains about some parameters [39].

This raises a particular issue with studies of scrapie outbreaks: they focus on a small number of outbreaks in flocks run by research institutes (NPU Cheviot: [58, 80]; or INRA Langlade: [39, 74]). The incidence in these flocks is typically higher than is observed in "natural" outbreaks [61], which facilitates the detailed study of scrapie dynamics. It remains to be seen whether the higher incidence is simply a consequence of closer monitoring or is a feature of the outbreaks themselves. The limited number of outbreaks studied to date, however, makes it difficult to assess which parameters in the

models can reasonably be extrapolated to other outbreaks. For example, estimates for the relative risk of infection in different PrP genotypes for the INRA Langlade flock [74] were similar to those obtained from scrapie surveillance data for GB [35]. By contrast, there is evidence that the age-at-onset of disease is different from other "natural" outbreaks [61].

More detailed data on "natural" outbreaks have recently been published (see, for example, [60, 61]). In addition, data from compulsory action in scrapie-affected flocks (PrP genotypes and results of brain-stem tests; [65]) also provide the opportunity to further analyse the dynamics of scrapie within a flock. It will be important to use these and any other suitable data to estimate transmission and other parameters. This will make it possible to examine how parameters vary amongst flocks and how this variation depends on flock management practices, especially those which have been identified as risk factors for scrapie [41, 43, 59, 62].

Two aspects of scrapie epidemiology remain outstanding questions: the role of carriers and the impact of scrapie strains. Carriers are defined as "animals which become infected, but do not develop clinical disease in their productive life" [2]. An early modelling study did explore the potential consequences of carriers for control strategies [79], but the carrier state has received little attention in subsequent studies. Recent modelling analyses of data from surveillance data [35, 36] have, however, provided evidence that the ARR/VRQ genotype may represent a carrier state in that it has a high risk of infection (the third highest; [35]) and a long incubation period, such that infected animals seldom develop clinical disease.

Despite evidence from strain typing in mice that there is strain variation in natural scrapie [5], it is unclear how these strains impact on the epidemiology of scrapie in sheep. The issue of strains has become more important in recent years with the identification of so-called atypical scrapie [4]. There are many open questions relating to this disease. However, mathematical modelling could be used to integrate what data are available and, hence, generate hypotheses about the epidemiology of atypical scrapie (cf. the situation with BSE in sheep). Of more immediate concern is the relationship between PrP genotype and the risk of atypical scrapie, which is markedly different from classical scrapie [19]. Consequently, there is the possibility that selective breeding programmes to reduce the risk of classical scrapie could increase the risk of atypical scrapie. Mathematical models have the potential to address this issue and also to investigate whether or not breeding strategies can be devised which reduce the risk of both types of scrapie.

Finally, mathematical modelling also has an important role to play in two further areas related to disease control:

(i) There are concerns that selective breeding programmes based on PrP genotype could adversely affect production (see [72] for a review). Despite the potential consequences, little attention has been given to this possibility. Mathematical modelling could be used to assess whether this is likely to be the case (see, for example, [12, 56]).

(ii) To date control measures for scrapie rely on removing animals that are at risk of scrapie rather than those which are known to be infected. Recently, live diagnostic tests have been developed which could be used as part of a large scale control programme, for example tonsil [68], third-eyelid [64] or rectal tonsil [26] biopsy, though test performance will depend on the stage of incubation and PrP genotype of the animals being tested. Mathematical modelling will form an essential part of assessing whether or not such an approach is likely to be effective and, if so, how best to use the tests[2].

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