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Will there be any more classical scrapie cases in sheep in Great Britain? A modelling study to predict future cases

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Abstract

The aim of this study was to apply a back-calculation model to Great Britain (GB) classical scrapie surveillance data, and use this model to estimate how many more cases might be expected, and over what time frame these cases might occur. A back-calculation model was applied to scrapie surveillance data between 2005 and 2019 to estimate the annual rate of decline of classical scrapie. This rate was then extrapolated to predict the number of future cases each year going forward. The model shows that there may be yet further cases of classical scrapie in GB. These will most likely occur in the fallen stock scheme, with approximately a 25% probability of at least 1 further scrapie positive, with a very low probability (~0.2%) of having up to three additional scrapie positives. This highlights the difficulty of completely eliminating all further cases, even in the presence of very effective control measures.

Scrapie is a fatal neurodegenerative disease of sheep [1]. Although it had long been endemic in Great Britain (GB) with no evidence that it posed a risk to humans, its similarity with bovine spongiform encephalopathy (BSE) and fears that scrapie could be masking a BSE outbreak in sheep, led to a number of control measures being introduced across the EU. These involved both targeted culling of affected flocks and breeding for genetic resistance, to increase the proportion of sheep with the ARR allele of the PrP gene, which was associated with scrapie resistance. More recently, 'atypical' scrapie was discovered in Norway and subsequently in several other EU member states [2], although this may not be infectious [3], and the focus of the present study is classical scrapie. The controls implemented led to a significant decrease in scrapie occurrence in GB with the lack of any clinical suspect cases and year on year falls in the number of active surveillance scrapie positives [4].

Given the efforts that have been made to control scrapie in GB, it is useful to know the likely number of future cases that could be expected. Greater understanding of the potential number of future cases is also useful for the purpose of monitoring scrapie cases to determine whether the outbreak is declining as expected, and will assist in correct interpretation of the epidemiological situation should future cases arise. Also knowledge of whether any future cases are expected is useful to discussions with other countries about resumption of international trade in sheep and sheep products, especially where such trade ceased as a result of the BSE epidemic in UK.

Therefore the aim of this study was to predict the number and possible timing of future cases of classical scrapie in GB, and determine which of the surveillance streams they will most likely occur, using a modelling approach and a previously developed model.

Scrapie cases in GB, to be included in the model, were taken from three different surveillance streams. First, clinical suspects that were confirmed positive, taken from the Scrapie Notifications Database (SND), that contains data on all scrapie cases confirmed in GB since scrapie became a notifiable disease in 1993. Second, data from an annual fallen stock survey, where a sample of animals that had died on farm are tested. And third, data from an annual abattoir survey of apparently healthy sheep. The model was applied to annual data from these surveillance streams between 1 January 2005 and 30 June 2019.

Based on the level of resistance/susceptibility to classical scrapie, the 15 allelic variations at codons 136 154 and 171 of the ovine PrP gene present in GB breeds were grouped in five categories, from type I to type V. These were, in decreasing order of resistance, as follows:

- Type 1 (ARR/ARR) most resistant
- Type 2 (ARR/AHQ, ARR/ARH, ARR/ARQ) resistant but need careful selection,
- Type 3 (AHQ/AHQ, AHQ/ARH, AHQ/ARQ, ARH/ARH, ARH/ARQ, ARQ/ARQ) little resistance,
- Type 4 (ARR/VRQ) susceptible
- Type 5 (AHQ/VRQ, ARH/VRQ, ARQ/VRQ, VRQ/VRQ) highly susceptible.

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For the purposes of the denominator of the surveillance data, genotype was not recorded for all animals tested, but rather a sample of negatives was genotyped each year. The overall proportion of each genotype was assumed to be equal in proportion to the sampled genotype each year. This genotype sampling was stopped in 2017, so genotype distributions for 2018 and 2019 were assumed equal to that of 2017.

A back-calculation model was used to estimate the scrapie infection prevalence and trend. Basically, this approach involves estimating the number of sheep infected in order to observe the number detected by the various surveillance streams, taking into account the size and age distribution of the sheep population, incubation period by genotype, sensitivity of the diagnostic test and the likelihood of ending up in each surveillance stream. The model has been described in full elsewhere [4]. The key output of the model was the infection prevalence, which was estimated via an exponential trend i.e. $A\exp(-B\ \text{year})$, where A was the prevalence in 2005 and B was the exponential rate of decline. Most of the key parameters were estimated from GB data previously [4] and were kept the same for the present study. This includes the incubation period by NSP genotype group, which had been estimated from reported cases in the SND database, and the sensitivity of the rapid test relative to the stage of the incubation period, applied to animals tested through active surveillance. There were also a number of parameters that were estimated along with the infection prevalence as part of the back-calculation model, and updated estimates of these were generated as part of the estimation process. These were (i) the relative risk of infection (to NSP group V) by NSP genotype group, (ii) the proportion of infected sheep entering the healthy slaughter stream and (iii) the rate of under-reporting of clinical suspects. The latter two were important as they would influence the effectiveness of each surveillance stream. For the proportion of healthy sheep entering the healthy slaughter stream, a linear temporal trend was investigated to explore any change in this over time. Finally, the model was used to test whether there was any significant difference between the level of scrapie infection or the trend in reduction of scrapie over time at the GB nation level. This would help determine whether future cases were more likely to occur in one particular nation, and whether control measures were equally effective between the GB nations. This was done via estimating the parameter A at the nation level (to determine any difference in the prevalence of scrapie in 2005), and B at the nation level (to determine any difference in the reduction of scrapie since 2005). To do this, the data on the number tested and number positive in each surveillance stream was separated into nation level using the farm county, parish, holding (CPH) identifier. For confirmed clinical suspect cases, this was available for all positives ($n = 319$), for fallen stock there were two cases that did not have farm location data (90 cases in GB dataset, 88 at the nation level), and for the abattoir survey, there were seven cases that did not have farm location data (32 cases in GB dataset, 25 at the nation level). For the negatives, the majority of fallen stock samples had identifiable farm locations (98.3%), but the abattoir survey samples are not sourced directly from the farms so a relatively high proportion of these had unknown farm locations (35%). The total number of samples per nation was adjusted upwards for each surveillance stream proportionately to account for those samples with unknown farm locations. Statistical significance of the parameters A and B at the nation level was tested using a likelihood ratio test.

For the model to estimate the likely final year in which a scrapie case would be observed, a similar approach to that applied to BSE in a previous study was adopted [5]. The estimated trend of the infection prevalence, derived from 2005–2019 data, was projected forward to provide prevalence estimates for future years. It was assumed that the number tested in each stream in the future would remain similar to the current rates i.e. approximately 13 500 fallen stock tested and 5000 abattoir survey tested per annum. The year of the final scrapie case was estimated by simulating the number of cases each year, with 10 000 replicates, assuming a Poisson distributed number of cases in each stream, with expected value given by the back-calculation model.

The estimated infection prevalence of scrapie in 2005 (i.e. the starting prevalence for the exponential decline model) was given by 0.03 (95% confidence interval (CI): 0.028–0.036), and the rate of exponential decline each year was given by −0.33 (95% CI: −0.42 to −0.28). This indicates a decline in infection prevalence from 3% in 2005 down to 0.03% in 2019, a decline of 99% between those years.

The risks of classical scrapie infection in animals with genotypes of NSP types I–IV, relative to type V (highly susceptible), were estimated to be: 0, 0.0008, 0.07 and 0.17, respectively. There was no evidence of any trend over time in terms of the proportion of infected sheep sent to healthy slaughter (parameter determining time dependence of the proportion of infected sheep sent to healthy slaughter having 95% CI −0.13 to 0.11), with infected sheep having a 22% probability of ending up in the healthy slaughter scheme (95% CI: 19–23) and 78% (95% CI: 77–81) in fallen stock.

There was a significant difference in the scrapie infection prevalence in 2005 ($P < 0.001$) between England, Wales and Scotland. Wales had the highest prevalence (0.045 (95% CI: 0.044–0.048)), followed by England (0.032 (95% CI: 0.031–0.034)), and Scotland the lowest prevalence (0.012 (95% CI: 0.0008–0.015)). However, there was no significant difference between the rate of decline between the different nations of GB ($P = 0.25$), suggesting no evidence of any differences in the effectiveness of control measures between the nations. The finding that England and Wales have higher scrapie infection prevalence than Scotland is consistent with the findings of an earlier study [6], although that study was based on data on confirmed clinical cases, which rely on farmer reporting. The present study also includes active surveillance data, which will reduce the dependency of the findings on reporting rates, although not eliminate it entirely as the reported cases still make up the majority of the cases. The reasons for differences in infection prevalence between the different parts of GB are unclear. A recent study showed no clear increase in genetic susceptibility of Wales and England over Scotland [7], and an earlier study exploring environmental and farm-level risk factors, which could potentially explain differences [6], only included England and Wales. It remains possible that some of the patterns of higher prevalence in certain areas relate to historic patterns of transmission.

The model estimated a low probability of future abattoir survey positives (Fig. 1a), with only a 2% likelihood of having one positive, and negligible probability of having two. There was a much greater likelihood of fallen stock scrapie positives, with approximately a 25% probability of at least one further scrapie positive, with a very low (~0.2%) of having up to three additional scrapie positives.

The model estimated very low rates of reporting in recent years since there have been no reported cases of confirmed clinical cases

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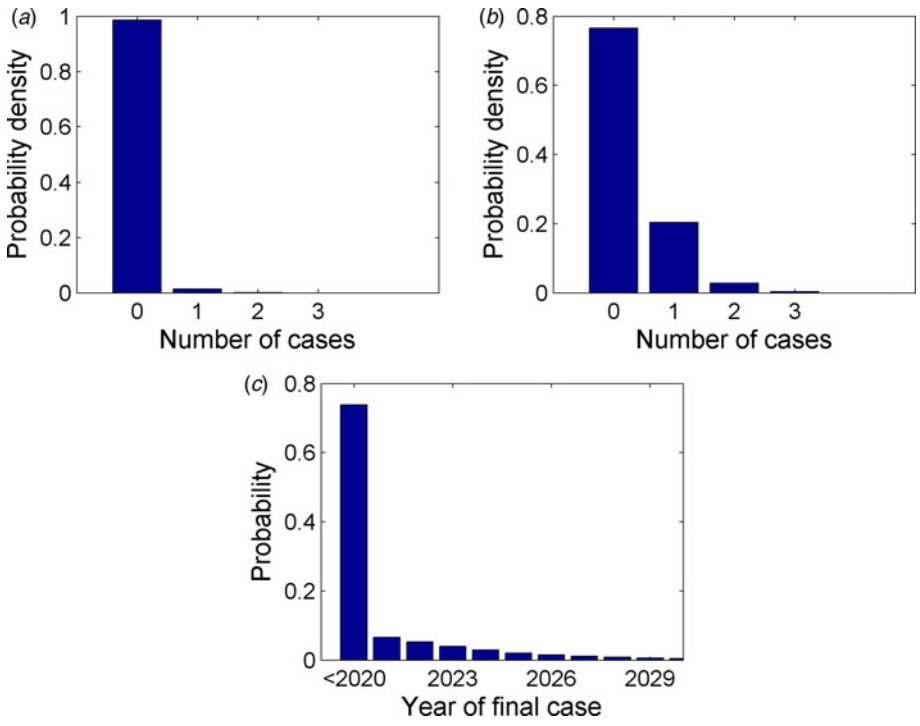


Fig. 1. Predicted number of future cases of classical scrapie in Great Britain using a back-calculation model from a) the annual abattoir survey and b) the annual fallen stock survey. A histogram giving the predicted year of the final case in fallen stock is given in c).

of classical scrapie since 2011, with almost negligible likelihood of suspect cases now being reported (down to approximately 1 in a million). The model did estimate that clinical cases are likely to still be occurring, with an expected number of sheep expected to reach clinical onset of scrapie of 138 nationally in 2019.

In terms of the timing of any future cases, although for the abattoir survey cases beyond 2019 were unlikely, they did occur in the model simulations, even occurring up to 2029 in the simulations (with a 1 in 10 000 probability). For the fallen stock, a similar pattern of declining likelihood of cases occurring as the year increased, but with rare occurrences of a case up to 2030 and beyond, but with very low probability (Fig. 1b).

The present study indicates that despite the very low prevalence and the effectiveness of the control measures for scrapie in GB, there is still the possibility of further cases, especially in the fallen stock stream. This underlines the difficulty of eradicating all cases of a low prevalence, difficult to detect pathogen, especially where the animal populations are large. Even with the very low infection prevalence in 2019 (0.03%), the large domestic sheep population (20.5 million), means that there is still in the region of 6000 sheep infected in GB. Whether such sheep are ultimately detected by the surveillance operating in GB will depend on a number of chance events, such as their possible inclusion in active or passive surveillance and their stage of incubation period if so, which will determine whether they are detectable.

The back-calculation model using data up to 2019 estimated a 28% annual reduction in scrapie infection prevalence each year. A previous application of this model using data up to the end of 2012 showed a mean reduction of 31% per annum [4]. This slight lowering of the estimated rate of reduction has been influenced by the occurrence of a recent case of classical scrapie, detected in the fallen stock scheme in 2019; re-estimation of the rate of decline without this case resulted in an estimated reduction similar to the 2012 estimate. As cases become rarer, each additional case may have large influence on the model estimates of the rate of decline, although they would not affect the overall pattern of statistically significant exponential decline, as long as such exponential decline remains the true pattern of scrapie decline.

The estimated rate of under-reporting from the model is extremely low, and this combined with the low prevalence of scrapie means that it is not expected that any further cases will be identified through the passive surveillance stream. Nevertheless, even with the low prevalence of scrapie there are still sheep reaching clinical onset, thus it is not impossible in principle that further scrapie infected sheep could be identified through this route.

Model estimates that the majority of infected animals end up in fallen stock scheme (~78%) rather than in healthy slaughter. This is an important finding as it indicates that targeting detection through the fallen stock scheme is more efficient than sampling the healthy slaughter, in agreement with other studies [8], although the fallen stock scheme has been shown to suffer from geographical farm size bias [3]. It is in contrast to BSE, where preclinically infected cattle are more likely to be destined for healthy slaughter than fallen stock in GB [9], highlighting how different production systems and species may influence farmer behaviour and decision making.

The model shows that there may be yet further cases of classical scrapie in GB. These will most likely occur in the fallen stock scheme, and if so will most likely be only one further case, occurring before 2030. This highlights the difficulty of completely eliminating all further cases, even in the presence of very effective control measures.

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Data availability statement. Some of the data that support the findings of this study are openly available at gov.uk: https://www.gov.uk/government/publications/sheep-tse-surveillance-statistics. For the remaining data please

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contact the authors. Approval for release will be required from Defra and the Scottish and Welsh governments through the Privacy Impact Team.

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