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A scrapie epidemic in Cyprus

M. B. GRAVENOR[1,2]*, P. PAPASOZOMENOS[3], A. R. McLEAN[1,4] AND G. NEOPHYTOU[3]

[1] *Institute for Animal Health, Compton Laboratory, Compton, Berkshire, RG20 7NN, UK*
[2] *Swansea Clinical School, University of Wales Swansea, Swansea, SA2 8PP, UK*
[3] *Department of Veterinary Services, Animal Health and Welfare Division, 1417 Nicosia, Cyprus*
[4] *Department of Zoology, University of Oxford, Oxford, OX1 3PS, UK*

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SUMMARY

Scrapie is endemic in the sheep flocks of many countries, but good epidemiological information on this disease is scarce. Data on the initial stages of an epidemic are even more rare. We describe the ongoing epidemic of scrapie in Cyprus that has been tracked since it began in the mid-1980s. The early stages of the spread of scrapie from farm to farm, between 1985 and 2000, is analysed with a simple mathematical model. The flock-to-flock basic reproductive number (R_0) for the spread of scrapie was estimated at between 1·4 and 1·8. The impact of interventions on the control of the epidemic are discussed from an epidemiological and economic point of view. Early identification of scrapie cases on farms can have a large impact on the number of farms affected. The long period before detection of disease in a flock means that policies based on whole-flock slaughter can be inefficient in preventing spread. Under a range of scenarios, a concentration of resources on early detection and quarantine may be more effective in terms of both the costs and control of the epidemic.

INTRODUCTION

Scrapie is a fatal disease of sheep and goats. It is a member of a group of diseases known as transmissible spongiform encephalopathies (TSE) that include bovine spongiform encephalopathy (BSE) and human Creutzfeldt–Jakob disease (CJD). The infectious process, in which the infectious agent itself is believed to be a modified host protein [1], has yet to be fully characterized but results in progressive debilitating neurological illness after a prolonged asymptomatic incubation period. Infection can pass from sheep to sheep via horizontal and vertical routes [2]. Transmission might also occur from contaminated pasture [3].

* Author for correspondence.

Scrapie has been reported worldwide [4]. Losses in affected flocks are highly variable ranging from 1% annual mortality to over 20%. Although there has always been some stigma associated with incidence of scrapie, death of individual animals has until recently been the main measure of loss. However, scrapie infection can now limit the international trade in live sheep and other ovine products. Affected farms and areas suffer losses due to decreased value of breeding stock and the need for eradication or control programmes. In the wake of the BSE epidemic in the United Kingdom, there is a greater drive for producers, and if possible countries, to become scrapie free.

Control of scrapie is hampered by the incubation period, often several years long. Pre-clinical testing is available [5] but not widespread. Imported sheep and goats may require certification of a scrapie-free

history, and undergo an extended quarantine and monitoring period. Scrapie control within a flock is also complicated by the long incubation period, and a lack of understanding of the relative importance of the transmission routes. Control has traditionally involved slaughter of the infected and related animals [6]. Measures now focus on the important role of susceptibility genes [7] and the role of the placenta as a source of the infectious agent [8]. Certain common polymorphisms in the *PrP* gene are associated with strong resistance to scrapie whilst others appear to be highly susceptible [9]. Breeding programmes are now the preferred method for scrapie control [10, 11] and it is advised that lambing premises are promptly cleansed.

Models for the within-flock spread of scrapie have been proposed, and data from individual and specially maintained flocks analysed [12–18]. However, there have been limited opportunities to describe the early stages and development of a new epidemic on a large scale. Prior to 1985, scrapie had never been recorded in Cyprus. Two cases were confirmed in February 1985 (described in [19]). It soon became clear that these cases marked the beginning of an epidemic of scrapie on the island, and the number of affected farms increased exponentially. By the year 2000, 201 farms had been infected. Here, these years of the epidemic are analysed with a simple mathematical model that allows an estimate of the rate of spread of scrapie between farms. We focus on control strategies that involve whole-flock slaughter and ask why extensive efforts over the first 14 years were unable to control the epidemic. Control options are discussed in terms of their impact on the epidemiology, and their relative costs in the future.

MATERIALS AND METHODS

Scrapie in Cyprus

The data analysed here consists of monthly incidence of affected farms over the period 1985–2000. It remains unclear exactly when and how the disease entered Cyprus. Indigenous wild Cypriot sheep may be relatively resistant (G. Neophytou, unpublished results), and it is possible that scrapie was introduced during the recent importation of live animals as an attempt to upgrade sheep flocks. No information is available on scrapie in the north of the island.

The predominant transmission route between farms is likely to be the trade in live animals. Due to the long incubation period, scrapie-infected animals that appear healthy can be bought and sold. Trade in live sheep occurs regularly between all five districts of Cyprus. Sheep from one farm may potentially infect sheep from another farm if grazing grounds are shared, however neighbouring farms tend not to mix in this manner.

Control of scrapie in Cyprus

Over the period analysed here, control of scrapie is based around preventing spread from farms with confirmed cases. An on-going information campaign followed the initial detection of the disease in 1985. Both farmers and government veterinarians received information on identification of clinical symptoms of scrapie. All suspect sheep are confiscated, slaughtered and tested for scrapie using histopathology [19]. Full compensation is paid for all confiscated animals. Following confirmation, a case farm is banned from trading in live animals for at least 3 years after the last case was detected. It is not compulsory to slaughter the whole flock. Within-flock control is based on continual removal of all suspect animals and culling of animals related to cases, a traditional means of scrapie control. This may lead to slaughter of the whole flock (in some cases of high within-flock incidence), and when this occurs the farm may not be restocked for a period of at least 3 years, though in practice this period may be much longer.

On a national scale, more recent control efforts have focused on the use of genotyping to identify resistant stock and introduction of breeding programmes using these animals. A 'bank' of resistant rams is being developed, and these animals are used as replacements in scrapie-affected flocks. Prior to 2000, few genotyping results were available, and control efforts were uniform over time (hence our choice of years for the analysis of the initial rate of spread). Since then, although some genotype information has been collected, it has not reached large-scale levels. The impact of genotyping will be continually assessed over the coming years, but it is not expected to have a substantial impact until 2004 and beyond.

A mathematical model of the initial outbreak

The following model is a simplified description of the spread of scrapie between Cypriot farms. The total number of farms at-risk is divided into four categories: unaffected with scrapie but susceptible to the introduction of disease (X); affected with scrapie but

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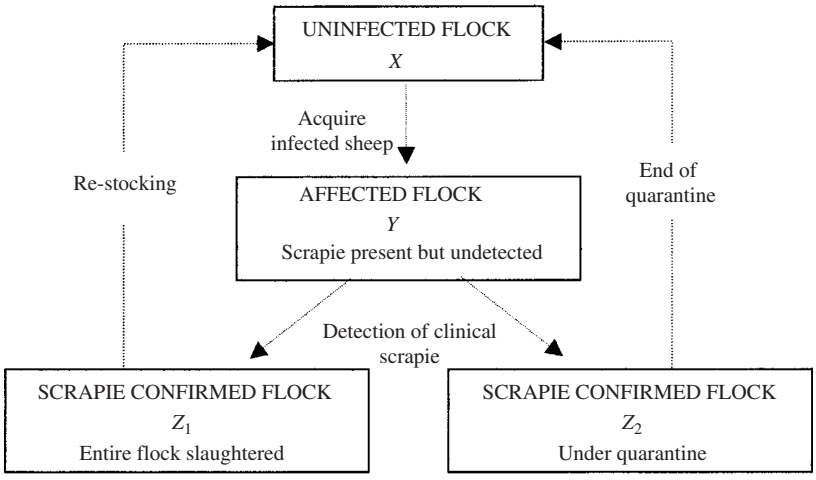

Fig. 1. Schematic of model structure. The category that a flock belongs to changes between four classes. Unaffected and susceptible flocks (X) acquire scrapie animals by trading (at random) with affected flocks. Initially an affected flock remains undetected (Y). Detection of a case occurs at a rate α, following passive surveillance by farmer and government vets. A proportion $(1-p)$ farms are quarantined and can still in theory spread scrapie (Z_2). All sheep in a proportion of p scrapie-confirmed farms are slaughtered. Flocks return to the unaffected category at the rates μ_1 (restocking following slaughter) and μ_2 (after quarantine period).

not identified as such due to incubation of the disease in sheep or misdiagnosis (Y); and farms with confirmed cases of scrapie (Z_1 and Z_2). When a case of scrapie is confirmed on a farm, either the whole flock is slaughtered (Z_1) or the flock is banned from trading animals while control methods are employed (Z_2). The model is illustrated in Figure 1 and the following equations describe the rate of change of the four populations.

$$\frac{dX}{dt} = -X(\beta_1 Y + \beta_2 Z_2) + \mu_1 Z_1 + \mu_2 Z_2,$$

$$\frac{dY}{dt} = X(\beta_1 Y + \beta_2 Z_2) - \alpha Y,$$

$$\frac{dZ_1}{dt} = p\alpha Y - \mu_1 Z_1,$$

$$\frac{dZ_2}{dt} = (1-p)\alpha Y - \mu_2 Z_2.$$

Here the farm is the unit of study, and the total number of farms is a constant N. Predominantly, farms become affected from buying infected sheep from farms that harbour infection but have not yet detected it (Y). Infection may possibly pass from flocks that have confirmed cases and have not been entirely culled (Z_2), either through direct contact (shared grazing) with neighbouring farms or if the ban on trading live animals is not adhered to.

Mixing of farms with respect to buying and selling sheep is assumed to be homogenous, and infection occurs at a rate proportional to the product of susceptible and affected farms. The constant β is a transmission coefficient and characterizes the degree of infectiousness of an affected farm. Since the main route of infection is from farms that have not detected scrapie, β_1 is likely to be greater than β_2. If quarantine measures are 100% effective, $\beta_2 = 0$ (i.e. if farms with confirmed cases never spread scrapie). It is assumed that flocks that acquire an infected sheep, but recover completely before any cases are detected have a negligible impact on the between-farm spread.

When a first clinical case of scrapie is detected, the farm moves to one of the confirmed categories. This occurs at a rate α, hence α^{-1} is the average time between the first infected animal appearing in a flock and confirmation of the outbreak. A proportion, p, of confirmed case flocks are slaughtered entirely, the remaining $1-p$ are banned from trading live animals. Following confirmation of cases, there is a period before the farm eliminates scrapie (culling infected animals and certain bloodlines). For slaughtered flocks this is the average time for restocking (μ_1^{-1}), for quarantined flocks this is the average time for elimination of infection and trading to restart (μ_2^{-1}). In practice the time for elimination of disease and resumption of trading is expected to be considerably more than 3 years.

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Here, R_0 is the average number of flocks that acquire scrapie from the first affected flock (type Y) in an otherwise entirely scrapie-free farm population. In order for the epidemic to be controlled, R_0 must be less than 1, and the magnitude of R_0 determines the degree of difficulty in controlling an outbreak. In terms of the model parameters,

$$R_0 = \frac{\beta_1 N}{\alpha} + (1-p)\frac{\beta_2 N}{\mu_2}.$$

The small size of the farming community and the well integrated nature of trading networks has underlined our assumption of homogenous mixing. (Also, the initial spread of the disease did not appear to be localized.) However, detailed spatial information on the epidemic is currently being collected that will allow the testing of the model assumptions, and expansion of the model to include a spatial component. In particular, information on trading networks is being collected that may be used to analyse recent patterns in the epidemiology.

Estimation of parameter values

The model parameters can be estimated by fitting the model to the time-series of monthly cases observed in Cyprus or if possible from independent data. The behaviour of a model simulation is determined by the parameter values and the number of farms in each model compartment at the start of the epidemic. At $t=0$, the number of confirmed cases is 0 ($Z_{1(0)} = Z_{2(0)} = 0$). The number of undetected affected farms at the start of the epidemic ($Y_{(0)}$) is unknown and must be estimated from the data in addition to the unknown parameters. It follows that the initial number of susceptible farms is $X_{(0)} = N - Y_{(0)}$.

Independent estimates are available for the parameters, p, and approximately for α. In Cyprus approximately half of all flocks with confirmed cases were slaughtered entirely, therefore p was set at 0·5. α^{-1} is the average detection period and is therefore related to the incubation period of scrapie in individual sheep (approximately 2 years). It is, however, likely to be shorter if a farm buys a sheep in the latter stages of infection, longer if animals tend to be slaughtered or sold before displaying symptoms or if symptoms are overlooked. For a new disease it is unlikely that the average detection period will be significantly less than the disease incubation period, and it is also likely to have a highly variable distribution (here an exponential is implied). We explored the fit of the model for a range of detection period (α^{-1}) values of between 2 and 5 years.

Using the assumed values of α and the known value for p, the fit of the model simulation to the cumulative monthly incidence data was explored for combinations of values of β_1, β_2 and $Y_{(0)}$. A numerical optimization routine was used to provide the maximum-likelihood estimates for β_1, β_2 and $Y_{(0)}$, assuming Poisson-distributed observations. Over the period of interest, few farms had resumed trading following slaughter or quarantine, and baseline values of 0·1 were used for μ_1 and μ_2. Sensitivity of output to this assumption was tested by repeating the analyses for $\mu_i = 0{\cdot}2$–$0{\cdot}07$. Results reported below were not found to be sensitive to these parameter values.

Long-term behaviour of the epidemic and control

With the estimated parameter values, the model was used to explore the long-term behaviour of the epidemic. After an initial rise, the numbers of farms in each category tend towards equilibrium values, where the proportion of farms affected is $1 - 1/R_0$. In the model, control of the disease is based around adjusting the values of three parameters. The proportion of farms slaughtered (p), the efficacy of preventing spread from quarantined farms that are not fully slaughtered (inversely related to β_2) and the time taken to detect cases on affected farms (α^{-1}). The relative effects of interventions that target these parameters were explored as follows. The model was fitted to the data up to the year 2000 as described above, model simulations were then run into the future with all combinations of parameters from the following ranges: $0{\cdot}0 \leqslant p \leqslant 1{\cdot}0$, $1 \leqslant \alpha^{-1} \leqslant 2$, and $0 \leqslant \beta_2/\beta_1 \leqslant 0{\cdot}17$. Primary output from the model, for each combination of parameters, was R_0 and the cumulative number of farms affected with scrapie over the next 5 years. β_1 and $Y_{(0)}$ were always fixed at the estimates described above, and initial conditions used for the extended simulations were the predicted values of X, Y, Z_1 and Z_2 at the beginning of 2000.

Estimating costs of control methods

It is possible that an intervention that significantly reduces the number of affected farms is prohibitively expensive. If estimates can be made of the cost of control measures, these can be combined with the estimates of the impact on the epidemic to minimize the size of the epidemic for a given expenditure. Precise estimation of costs is not possible, however

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for a range of assumptions suggestions for optimal strategy can be generated. The aim here is to compare the merits of slaughtering whole flocks with interventions that reduce the detection period, after which quarantine and selective slaughter only is maintained.

Compensation costs are relatively easy to estimate, but still require a number of assumptions. At the end of the period of interest (in this case 5 years), for a given combination of parameters let the cumulative number of farms having detected scrapie (since 2000) be Z_{tot}. Compensation is paid for all animals in those farms in which the whole flock is slaughtered (pZ_{tot}) and all suspect animals confiscated from the rest of the affected farms [$(1-p)Z_{\text{tot}}$]. We estimate compensation for whole-flock slaughter simply from the average number of sheep in an affected flock ($n_{\text{sheep}}=130$). Compensation on farms with sheep under quarantine is more likely to be paid over a number of years, as suspect sheep are gradually detected. Let n_{conf} be the average number of suspect sheep confiscated from a flock under quarantine. If compensation paid is a Cypriot pounds (£CYP) per sheep, the total compensation paid is $apZ_{\text{tot}}n_{\text{sheep}}$ for whole-flock slaughter, plus $a(1-p)Z_{\text{tot}}n_{\text{conf}}$ for quarantined farms.

The number of sheep confiscated from quarantined farms can potentially increase indefinitely, so that in some cases the compensation paid may exceed the amount that would have been paid on whole-flock slaughter at the detection of the first case. One flock that at any one time consisted of around 140 sheep in fact lost 191 suspect animals over the period 1993–1998. In general however, the majority of cases are found only in the first few years of quarantine, and scrapie is eliminated through slaughter of breeding lines (that may involve genotype information). Using the farms initially affected up to 1993 only, we estimated that the number of confiscated sheep on quarantined farms is on average 56% of the flock size at first detection of scrapie. Based on an average flock size of 130, we therefore use a value of 73 sheep for n_{conf}. All costs here are expressed in £CYP. In 2000, the average compensation paid per sheep is $a=60$.

Interventions that reduce the detection period are based on the inspection of farms by government vets and increasing scrapie awareness, and are much more difficult to cost. Here we investigate three scenarios. First, since government veterinarians already visit all farms for purposes other than scrapie control and education campaigns have already been implemented, the costs for keeping the detection period (α^{-1}) at ≈ 2 years (*status quo*) are not considered. Secondly, the

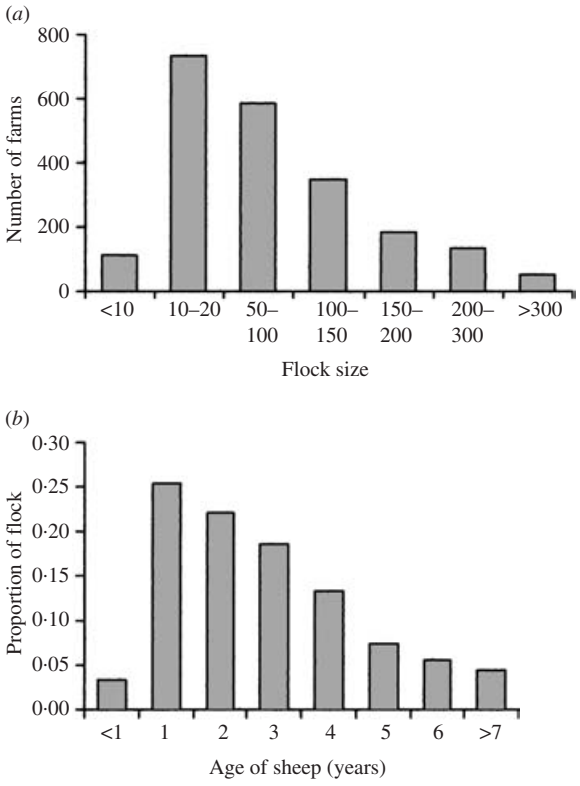

Fig. 2. (*a*) Distribution of sheep flock sizes on Cypriot farms (estimated in 1998). (*b*) Average age structure of a Cypriot sheep flock (estimated in 1998, from a sample of 20).

costs of reducing the detection period to 18 months are assumed equivalent to one additional visit to all farms where scrapie has not been detected. Thirdly, it assumed that two additional visits per farm per year are required to reduce the detection period to 1 year. The costs are based on a 4-h visit by one government vet at £CYP 8.50 per hour.

Given these assumptions, costs were calculated for model simulations with each of the parameter combinations described above. The costs of maintaining β_2 at a particular value are not considered here.

RESULTS

Scrapie in Cyprus

There are over 2000 sheep farms in Cyprus. The distribution of farm size is an important demographic characteristic in Cyprus. Most farms hold small numbers of sheep (Fig. 2*a*). Although often in very close proximity, they remain distinct units. Since sheep are used for milk and meat industries, the typical age-structure of a flock shows a relatively high proportion of older animals (Fig. 2*b*), which may

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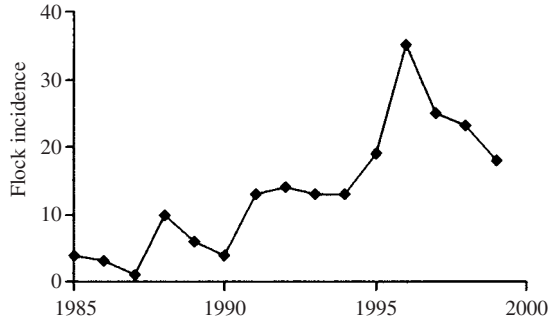

Fig. 3. Number of newly confirmed scrapie-affected flocks in Cyprus 1985–2000.

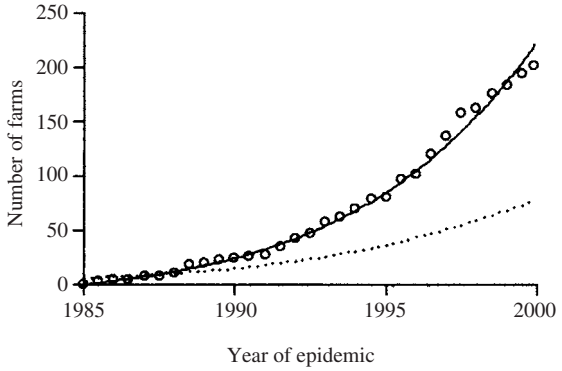

Fig. 4. Fit of model to data using baseline parameter estimates. The best fitting simulation of model cumulative confirmed cases (Z_1+Z_2) is plotted against observed monthly cumulative farms with detected scrapie (circles). The dotted line plots the estimated number (not cumulative) of farms harbouring undetected scrapie-infected animals at each time-point ($Y_{(t)}$). $\beta_1=31{\cdot}4\times10^{-5}$, $Y_{(0)}=6$, $\beta_2/\beta_1=0{\cdot}034$, $\alpha=0{\cdot}5$, $\mu_1=\mu_2=0{\cdot}1$, $p=0{\cdot}50$. $R_0=1{\cdot}5$.

aid the detection of clinical scrapie. The number of scrapie-affected farms per year up to the beginning of 2000 is given in Figure 3. Cases had appeared in all five districts of Cyprus within 7 years, and even in the early years, cases would appear simultaneously on different areas of the island. Although affected farms tended to be slightly larger than the overall mean farm size, there were no significant changes in the size of affected farms as the epidemic progressed. There appears to be a peak in 1996, when 1·7% of susceptible flocks had a confirmed case, but cases have since remained consistently high.

Goats

Of the sheep farms, 1352 also keep goats, and there are an additional 2086 goat farms in Cyprus. Scrapie infection in Cypriot goats was first confirmed in 1986 [20]. The epidemiology of scrapie in goats is not considered here. However, we note that the dynamics of the disease in goats is likely to be highly dependent on sheep scrapie. Of the 37 farms detecting cases in goats only 2 did not keep sheep ($\chi^2_{1\ \text{d.f.}}=48$, $P<0{\cdot}001$). It is possible that these infections resulted from transmission from sheep rather than trade in infected goats. If this is true, R_0 for goats is likely to be less than 1 in the absence of sheep.

Estimates of R_0

The best fit of the model to the epidemic was found for relatively low average detection periods ($\alpha^{-1}=$ 2 years). Parameter estimates (with 95% confidence intervals) were $\beta_1=31{\cdot}4\times10^{-5}$ (28·8–32·7), $\beta_2=3{\cdot}4\%$ of β_1 (0–17) and $Y_{(0)}=6$ (5·4–6·6). Therefore, at the time of the first confirmed case, there was an estimated six other farms harbouring scrapie-infected animals. These parameters generate an R_0 of 1·5 (1·4–1·8). The fit of the model to the data with this baseline parameter set is shown in Figure 4. We note that the above values of β_1 and $Y_{(0)}$ are consistent with those obtained from a fit of a simplified version of the model to the very first few years' data (prior to 1990), when all cases were very likely to have arisen from undetected affected farms and during which it could be assumed, therefore, that $\beta_2=0$. The impact of spread from farms with confirmed cases can only be seen later in the epidemic. The small estimate for β_2/β_1 suggests quarantine measures are fairly effective, but the upper confidence limit for this ratio (17%) shows that this group of farms could still have an impact.

Even with a low value of R_0, the equilibrium predicted number of farms confirmed with scrapie, and under quarantine or slaughter is high (586). This equilibrium however, will take a very long time to be reached [21] and is based on the premise that parameter values in the future are not influenced by control measures. It should be regarded only as a maximum estimate, particularly after changes to control due to genetic information, and model forecasts of this kind should only be made over short time-periods. Of more interest is the prediction of the number of non-case farms that currently harbour undetected scrapie. At the early stages of the epidemic the majority of infections are in this farm category. Even in 2000, there are predicted 78 undetected scrapie farms. Even if all transmission between flocks was halted in 2000, the minimum size of the outbreak would be almost 300 farms.

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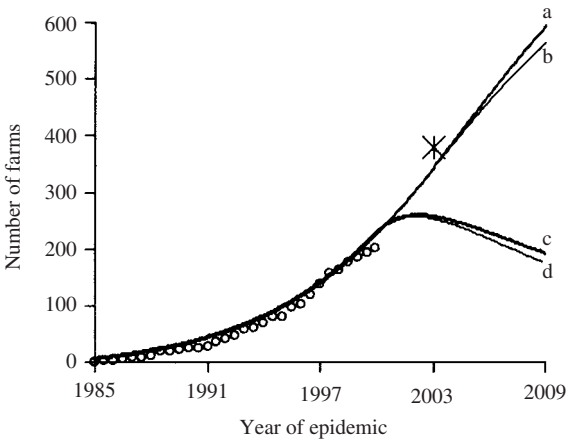

Fig. 5. Modelling future trends in confirmed case farms under different control policies. Control measures introduced in 2000. (a) No change. (b) Increased whole-flock slaughter, $p=1{\cdot}0$. (c) Reduced detection period, $p=0{\cdot}5$, $\alpha^{-1}=1$ year. (d) Combined whole-flock slaughter and reduced detection period, $p=1{\cdot}0$, $\alpha^{-1}=1$ year. Baseline parameters (fit up to 2000 data only, circles) as in Figure 4. The observed cumulative incidence by the beginning of 2003 is marked by the cross (see Discussion).

Long-term behaviour of the epidemic: impact of control strategies

Using the baseline estimates of β_1, β_2 and $Y_{(0)}$, we explored the effect of varying the parameters p and α on the total numbers of farms affected after a given period of time. Figure 5 (line a) plots the expected number of farms affected over the next 9 years. Also plotted are three different hypothetical control strategies implemented in 2000. The proportion of whole flocks slaughtered could be increased to 100% (Fig. 5, line b), or increased active surveillance could reduce the detection period to 1 year (Fig. 5, line c). Both these measures are implemented in Figure 5 (line d).

Figure 5 suggests that increasing the culling policy to above the current 50% has a small impact on the magnitude of the epidemic, whilst a reduction in the detection period may have much greater effect. Doubling p reduces the number of flocks affected after 9 years to only 95% of the expected number, whilst halving the detection period reduces it to 32%. Although the mixed policy has the greatest impact on the epidemic, the result of culling all affected flocks has little extra effect above that of reducing the detection period. These observations can be explained by the impact of changes in parameters on R_0. In the absence of a reduced detection period, increasing the proportion of slaughtered flocks cannot reduce R_0 below 1. With p set at 0·5, a halving of the average detection period reduces R_0 to 0·8. Even in the absence of a flock-slaughter policy ($P=0$), an R_0 of less than 1 can be achieved by reducing the detection period to 1 year.

Long-term behaviour of the epidemic: cost considerations

Figure 6 compares the impact of equivalent control strategies on both the size of the epidemic and the estimated yearly cost of the strategy. Combinations of α and p are considered at two values of β_2/β_1. From the model simulations, the cumulative number of newly affected farms and the cost of their control were calculated over 5 years. The graphs are contour maps on the p and α plane, the contours represent equal numbers of affected flocks (top) and equal costs per year (bottom).

In Figure 6 (left-hand panels), simulations were run using the best estimate of β_2/β_1 (0·034). Since β_2 is very small, whatever the value of the detection period, the affected farm contours are almost parallel with the p axes. Increasing the proportion of whole flocks slaughtered therefore has little effect on the epidemic size (top), but greatly increases the expenditure (bottom). In contrast, increasing the detection rate serves to reduce the cumulative affected farms from 260 to 180. This is achieved for a relatively small increase in costs, and achieves an R_0 value of less than 1 (0·68).

In Figure 6 (right-hand panels), β_2/β_1 is set at its upper confidence limit (17%). In this case, for a fixed value of α slaughtering all flocks has some impact on the size of the epidemic. Again, however, it comes at a high cost, and even for slaughter of all flocks ($p=1$), R_0 always remains above 1 unless the detection period is also reduced to 19 months ($\alpha=0{\cdot}63$).

For a fixed available expenditure, the farm and cost contours can be superimposed (not shown) to suggest the policy that has the greatest impact on the epidemic. At a low β_2/β_1, the returns for extra expenditure above the policy of minimum detection period ($\alpha=1$) and minimum slaughter ($p=0$) are negligible. Even with a high β_2/β_1 for low- or mid-range budgets, the number of affected farms is minimized by choosing a policy with a high detection rate and low proportion of whole flocks slaughtered. Optimal combinations of p and α at the highest expenditure can be obtained from the graphs, but the returns for the extra cost of slaughter diminish rapidly.

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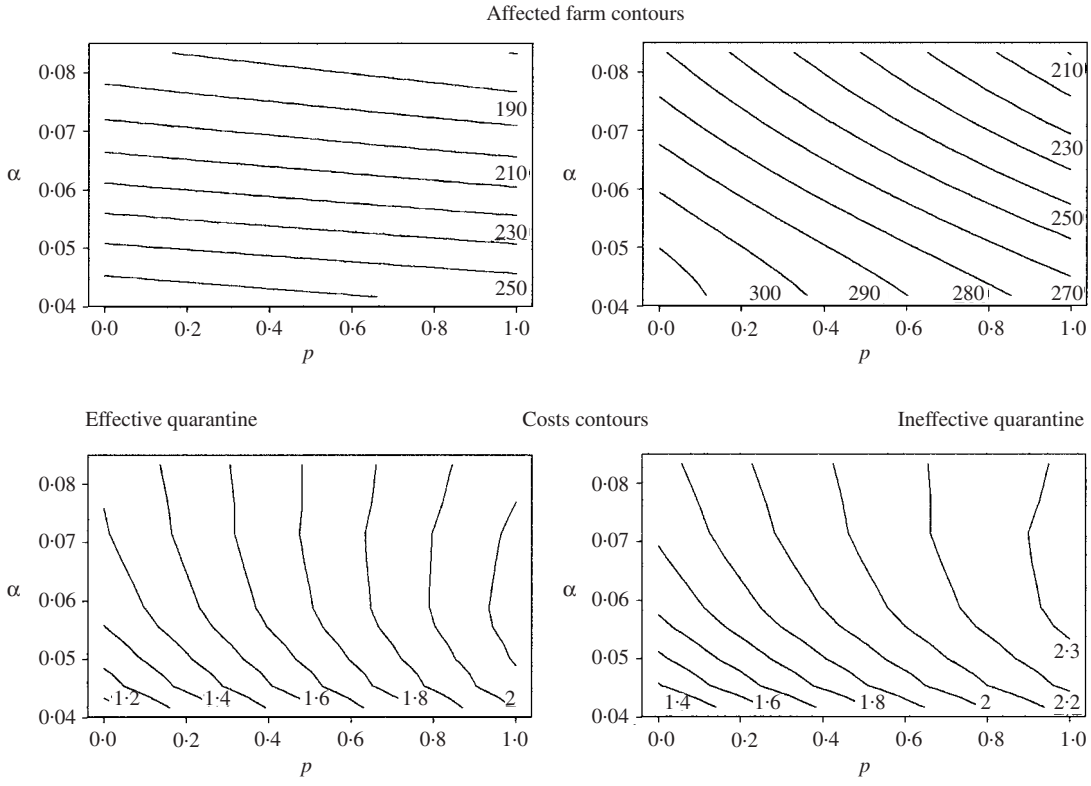

Fig. 6. Contour maps to compare costs and impact of different control strategies. The control strategy is defined by a combination of p (proportion of whole scrapie flocks slaughtered) and α (detection rate per month, where α^{-1} is the average detection period in months). Contours represent combinations of p and α that lead to equivalent cumulative affected farm numbers (top) or costs (bottom). Simulations were run for 5 years from 2000, using (left-hand panels) $\beta_2/\beta_1 = 0{\cdot}034$ (baseline estimate, effective quarantine), (right-hand panels) $\beta_2/\beta_1 = 0{\cdot}17$ (ineffective quarantine). Costs estimated in £CYP million.

DISCUSSION

Following the BSE epidemic in cattle, there is a pressing need in a number of countries for efficient control and ultimately eradication of scrapie from sheep flocks. Previous, often intensive control programmes have foundered, and we cannot point to a clear-cut example of successful large-scale scrapie control. One reason for this is that, outside the laboratory, scrapie remains an obscure disease. Its epidemiology is not well documented or understood. Recent efforts in the United Kingdom have concentrated on estimating basic parameters such as prevalence [22], farm-level risk factors [23–25] and force of infection [26, 27]. These factors apply to an approximately endemic situation, where scrapie has been present for hundreds of years. The on-going collection of data on Cyprus provides an important source of information on the initial development of an epidemic, and the impact of control measures based on whole-flock slaughter.

A recent increase in scrapie cases does not necessarily reflect a new epidemic. This pattern may be due to increased awareness of TSEs. Subsequent decreases in scrapie incidence may similarly be associated with increasing stigma associated with this group of diseases. A number of factors lead us to believe the Cyprus epidemic is not such an artifact. Most important are the structures of the sheep and veterinary industry. Despite thousands of positive sheep confirmed in Cyprus, no cases have yet been documented in indigenous breeds. The introduction of foreign breeds began recently in an attempt to increase yield, and a large number of animals were imported from countries where scrapie has been recorded. Veterinary support for almost all Cypriot farms is supplied from centralized government services. Surveillance is aided further by the size of the island and the number of farms, many of which are in close proximity.

In the first 15 years since scrapie was first recorded, over 9% of Cypriot sheep flocks experienced a case. The rate of increase implies a flock-to-flock R_0 of approximately 1·5. We estimate that in 2000 around 80 farms harboured infected but undetected animals, and that the increase in incidence should therefore

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continue. The fit of a simple epidemic model suggests that quarantine measures (that include confiscation of large numbers of suspect animals) are effective once the disease has been detected on a farm.

After collating the most up-to-date data, the model predictions have proved accurate. The highest yearly incidence was in 2003, and by the beginning of the year the cumulative incidence had reached 378 flocks. This is very close to the extrapolations from the fit to the early data generated here, and assuming no changes to the control policy (see Fig. 5, line a). The apparent reduction in incidence from 1997 to 1999 proved short term, and as suggested by the model (Fig. 4), large numbers of flocks must have been harbouring undetected scrapie infections at this time.

Over the period of this study, scrapie was not under control in Cyprus despite extensive efforts. This is likely to be due to a prolonged period during which scrapie-infected sheep are present on a farm but remain undetected. During this time the disease can spread to other flocks via trade and possibly direct contact. The modelling exercise suggests that slaughtering whole flocks may have little impact on the spread of scrapie, and at a considerable expense. At present, even the slaughter of all flocks with detected cases does not reduce R_0 below 1, hence the detection period must be reduced.

Our cost estimations give only a rough indicator of the economics of scrapie control. There are likely to be hidden costs in both the estimates of a slaughter policy and detection period reduction (for example transport and laboratory costs). Further, predictions too far into the future using such simple models will be unreliable. However, we are interested here in general conclusions. During a large outbreak it is clear that the costs of compensation for confiscated sheep will rapidly escalate and there are at best diminishing returns to increasing the proportion of whole flocks slaughtered. Previous experience, in the United States for instance [28, 29] also suggests caution with this approach, particularly when budgets are limited.

The scenarios that describe reductions in the detection period are hypothetical. Passive surveillance, via veterinary visits and education campaigns should have some impact, but there is no guarantee that some of the low values for detection time used here are attainable. The recent advances in pre-clinical testing for scrapie offer the potential for active surveillance [30] and the greatest hope for reducing the detection period. Experiments have shown that in certain genotypes the signs of infection can be detected in the tonsils of live sheep more than 18 months before clinical signs normally appear. Costs for this approach might be considerable but could be recovered by reductions in the proportion of whole-flock slaughter. Random sampling could be improved upon by taking samples from farms identified as high risk, or possibly the use of sentinel animals of highly susceptible genotypes. Costs aside, in many circumstances this may offer the best opportunity of reducing R_0 significantly below 1.

In line with recent experience with foot-and-mouth disease [31–33] the interval between a flock becoming infected and detected is critical. But in contrast to foot-and-mouth disease, the long scrapie incubation period means whole-flock slaughter will be highly inefficient since the disease is likely to have already spread from the flock before detection. Selective cull remains necessary during the quarantine period. Its efficiency could be greatly increased if genotype information is available, by identifying susceptible animals and removing those potentially incubating the disease. Such genetic information will of course have an impact wider than the individual farm level, if the animals can be used to increase the level of resistance of the national flock. The new breeding programmes will be monitored in Cyprus over the coming years.

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