A mechanistic model of developing immunity to *Teladorsagia circumcincta* infection in lambs

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SUMMARY

Acquired immunity influences the severity of parasitic disease, but modelling the effects of acquired immunity in helminth infections has proved challenging. This may be due to a lack of suitable immunological data, or to the perceived complexity of modelling the immune response. We have developed a model of *T. circumcincta* infection in domestic sheep that incorporates the effects of acquired immunity on parasite establishment and fecundity. A large data set from commercially managed populations of Scottish Blackface sheep was used, which included relationships between IgA activity and worm length, and between worm length and fecundity. Use was also made of a recently published meta-analysis of parasite establishment rates. This realistic but simple model of nematode infection emulates observed patterns of faecal egg counts. The end-of-season faecal egg counts are remarkably robust to perturbations in the majority of the parameters, possibly because of priming of the immune system early in the season, reducing parasite establishment and growth and, therefore, faecal egg counts. Lowering the amount of early infection leads to higher end-of-season egg counts. The periparturient rise in egg counts in ewes appears to have an important role in supplying infection for the priming of the immune response. This feedback in the immune priming suggests that nematode infections may be difficult to eliminate.

Key words: *Teladorsagia circumcincta*, sheep, nematode, acquired immunity, establishment, fecundity, faecal egg count, IgA.

INTRODUCTION

Nematode infection is a major disease in ruminants (Perry and Randolph, 1999), and *Teladorsagia circumcincta* is the dominant species affecting sheep in the UK. Not only does nematode infection in farmed animals adversely affect welfare, it also imposes constraints on the efficiency of livestock production and is the most costly endemic disease affecting domestic sheep populations (Nieuwhof and Bishop, 2005). Control measures currently depend on regular anthelmintic treatments, which are simple and cost-effective. However, the appearance of anthelmintic resistance in parasite populations (Yue *et al*. 2003; Bartley *et al*. 2004; Sargison *et al*. 2007) means that alternative methods of nematode control are needed before sheep farming in its present form becomes unsustainable (Sayers and Sweeney, 2005; Stear *et al*. 2007).

Control methods include grazing management (Githigia *et al*. 2001; Niven *et al*. 2002), protein supplementation (Coop and Kyriazakis, 2001; Houdijk *et al*. 2005) and selective breeding for host resistance (Bishop and Stear, 1997; Stear *et al*. 2001). While there are no commercially available vaccines, in the future, vaccination could help to control nematodes (Knox *et al*. 2003; Hein and Harrison, 2005).

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No single control measure is likely to be totally satisfactory, and a combination of methods may be needed for efficient control. However, exploring all the potential combinations through experimentation would be a complex and costly procedure. Assessment of combinations of control methods requires models that integrate knowledge of the immune response to infection with knowledge of the parasite life cycle on pasture. The development of such a model provides a step towards the assessment of 2 groups of control strategies: those that act to reduce host exposure to the parasite (e.g. grazing management), and those that aim to improve the host response to infection (e.g. supplementary feeding, selective breeding).

The model presented here incorporates our understanding of nematode fecundity and establishment, and also considers density-dependent constraints on worm growth and egg production. Model predictions are tested against data collected in the field (Stear *et al*. 2006). This simple model of immune effector mechanisms incorporated with a model of the parasite life cycle on pasture reproduces observed patterns of faecal egg counts across a season.

MATERIALS AND METHODS

Model overview

The model used data obtained over 4 years (1992–1995) from populations of straightbred Scottish

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Blackface sheep from a commercial upland farm in Scotland. The major effector mechanisms in nematode infections of sheep are IgA-mediated suppression of fecundity and mast cell-mediated control of parasite numbers. The data were used to estimate the relationships between IgA activity and worm length (Henderson and Stear, 2006), and between worm length and fecundity (Stear and Bishop, 1999). Although mast cell degranulation has been associated with a reduction in the number of *T. circumcincta* (Stear *et al.* 1995*c*), the development of type I hypersensitivity reactions in sheep is not very well understood, and we have used the results of a recent meta-analysis of parasite establishment (Gaba *et al.* 2006).

The model by Bishop and Stear (1997) was adapted to incorporate empirical data to model the interaction between developing immunity and parasite fecundity and establishment. The model can be summarized by 2 equations, one describing worm numbers in the host, and the other the number of infective larvae contaminating the pasture. The model updates daily, and lambs are assumed to be born on day $t=0$.

$$M_t = M_{t-1}(1 - m_3) + I_{t-j}E_t \quad (1)$$

The calculation of the worm burden on any particular day, M_t, (Equation (1)) can be separated into 2 terms. The first term, $M_{t-1}(1-m_3)$, describes the number of worms surviving at day t given the worm burden at t-1 and an adult mortality rate of m_3. The second term, $I_{t-j}E_t$, describes the new infection, and is the product of the number of infective larvae ingested, I, and the nematode establishment, E. Here, j is the pre-patent period, that is the period before infection in the host becomes evident, and captures the time interval from larval ingestion to maturity of the adult parasite. The number of infective larvae ingested on any day, I_t, is directly related to the larval availability on pasture on that day, L_t in Equation (2).

$$L_t = L_{t-1}(1-m_2) + (S_{t-u} + M_{t-u}n_{t-u})(1-m_1)^u \quad (2)$$

Larval availability on pasture, L, is also the sum of 2 terms; one describing the daily mortality of infective larvae, which occurs with rate m_2, and the other describing the appearance of new infective larvae on pasture. The product $M_{t-u}n_{t-u}$ is the number of eggs produced per lamb, where n is the fecundity of the adult worms. Here, fecundity is specified per adult worm; the actual number of eggs produced per female worm would be double this value, assuming a 1:1 sex ratio. We also take into account the ewes' deposition of eggs on pasture, denoted by S. The life stages from the egg up to, but not including, the infective stage die at a daily rate m_1. The number of days spent in these stages is denoted by u. The units of L are larvae per lamb.

Host immunity

We assume that the immune response is driven by the ingestion of infective larvae, with a delay between first exposure and the initiation of the response of z days. The increase in total response on day t is assumed to be directly proportional to the number of larvae ingested on day t-z, with constant of proportionality ρ. Pre-existing activity stimulated by previously ingested larvae is assumed to decay exponentially with half-life τ. Thus, IgA activity, which mediates the immunological control of parasite fecundity, is given by Equation (3), where τ_1 is the half-life of IgA activity and ρ_1 is the immune response related to IgA production.

$$\mathrm{IgA}_t = 0{\cdot}5^{1/\tau_1}\mathrm{IgA}_{t-1} + \rho_1 I_{t-z} \quad (3)$$

Establishment

The available data do not allow us to relate the development of mast cell responses to establishment (which we have defined as the percentage of ingested larvae that develop into adult worms). We have therefore modelled an establishment control factor (ECF) whose activity has the half-life τ_2 and a response factor ρ_2 as shown in Equation (4).

$$\mathrm{ECF}_t = 0{\cdot}5^{1/\tau_2}\mathrm{ECF}_{t-1} + \rho_2 I_{t-z} \quad (4)$$

We assume that the establishment decreases over time as the lambs' immune systems develop. To simulate this decrease in establishment, we model an ECF that increases as host immunity develops. By using the meta-analysis published by Gaba *et al.* (2006), we can estimate the range over which establishment can be expected to vary in pasture-fed lambs as immunity develops. From this we have produced a function for establishment dependent on the acquisition of immunity in the host as shown in Equation (5), where E_{early} is the parasite establishment for lambs newly introduced to infected pasture, and E_{late} is the establishment at the end of the grazing season.

$$E_t = E_{\mathrm{late}} + \left(E_{\mathrm{early}} - E_{\mathrm{late}}\right)e^{-\mathrm{ECF}_t} \quad (5)$$

Nematode fecundity

The results from Stear *et al.* (1995*c*) were used to fit a function for worm length, l, in cm based on IgA activity and adult worm burden (M), as shown in Equation (6).

$$l = \alpha - \beta\log_{10}(\mathrm{IgA} + 1) - \gamma\log_{10}(M+1) \quad (6)$$

Similarly, results from Stear and Bishop (1999) were used to produce a relationship for fecundity, n (eggs worm^{-1} day^{-1}), based on worm length, shown in Equation (7). As an example, for a typical range of worm lengths from 0·7 cm to 1·2 cm the number of eggs produced daily ranges from approximately 17 to 228.

$$n = \varepsilon l^{\omega} - 1 \quad (7)$$

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Combining Equations (6) and (7), allows us to express the fecundity of adult nematodes in terms of worm burdens and IgA activity in the host. Coefficients are listed in Table 2.

Nematode mortality

The model includes 3 mortality rates to cover 3 periods of the nematode life cycle. These 3 periods are defined by the changes in environment as nematodes transition from faeces to herbage to host. Mortality in the life stages from egg to L2 is captured by m_1, mortality in the L3 stage by m_2, and mortality in the L4 and adult stages by m_3.

Lamb live weight

SAS statistical software was used to fit the mean live weight of lambs weighed at 28-day intervals throughout a season (Bishop *et al*. 1996) to the Gompertz equation (8) following Macciotta *et al*. (2004).

$$W_t = \theta \exp\left[\mu(1 - e^{-\kappa t})/\kappa\right] + \phi \tag{8}$$

The weight, W, increases in accordance with a growth rate, μ, which is itself modified by a decay parameter, κ. The Gompertz equation is preferred over the generalized logistic equation for fitting growth rates, as it overcomes the possibly inappropriate symmetry of the latter. To fit the data, an intercept, ϕ, was subtracted from all the weights to ensure the curve went through the origin. The coefficients are listed in Table 2, and at the end of the season a lamb weighs approximately 27 kg. We do not include production penalty related to worm burden in our calculation of weight as it is beyond the scope of this paper, and the relationship between production costs of worm burden and increased immunity is unclear. Additionally, the purpose of the growth curve is simply to act as a proxy for intake and faecal output.

Maternal deposition of eggs on pasture and initial larval availability

Infection in the lambs is initiated by larvae that have survived on the pasture from the previous season, L_0, and by the deposition of nematode eggs onto pasture by ewes, S. Though adult sheep with a fully developed immune system usually have very low faecal egg counts (Bishop and Stear, 2001), periparturient ewes exhibit greatly increased egg counts (Jackson *et al*. 1988). To model this effect, we assume an initial rate of egg deposition by the ewes at $t = 0$ that decreases linearly to zero after three months.

Ingestion of larvae and faecal egg counts

The larval availability on pasture is only one factor affecting the number of larvae ingested by a lamb, the others being herbage consumption and the amount of herbage per sheep on the pasture. The number of larvae ingested, I, is given in Equation (9).

$$I_t = \frac{L_t Q_t D}{H} \tag{9}$$

The stocking density of lambs on pasture, D, is measured in lambs ha^{-1}. The herbage density, H, is measured in kg dry matter (DM) ha^{-1}.

We assume that the amount of herbage consumed, Q, is a function of live weight, and therefore the mass consumed in kilograms is given by Equation (10), with the coefficients listed in Table 2.

$$Q_t = v\left(W_t - \phi\right) \tag{10}$$

The growth curve was also used to predict the mass of faeces produced daily by the developing lambs, on the assumption that the amount of faeces produced, f, is 20 g for every kg of lamb body weight. Therefore, the faecal egg count, c, of a lamb on any particular day is given by Equation (11).

$$c_t = \frac{n_t M_t}{W_t f} \tag{11}$$

Anthelmintic treatment

Sheep are usually treated with anthelmintics to control nematode infections. Here, we assume that treatment begins at $t = 29$ and continues at 28-day intervals, and is 100% effective. We also assume that treatment is only given to lambs, and ewes remain untreated.

Comparison with observed faecal egg counts

Data from Stear *et al*. (2006) together with further unpublished data collected at the same time were used as a basis for testing the model. These data were collected from Scottish Blackface sheep over a number of years (1992–1995). Faecal samples were taken at 28-day intervals, and all lambs were treated with a broad-spectrum anthelmintic immediately after sampling.

Parameters

Table 1 summarizes the parameter values. The mortality rate of 0·23 for the pre-infective nematode life stages, m_1, was obtained from Learmount *et al*. (2006), and derived from data published by Niezen *et al*. (1998). These data were collected from various plant species in New Zealand, in an environment experiencing similar temperature ranges and levels of moisture to the regions of Scotland.

For the mortality rate of the infective stage, m_2, the value of 0·008 was obtained from Kao *et al*. (2000) with reference to data from Gibson and Everett (1972). It is interesting to note the marked difference

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Table 1. Summary of parameters and variables, and their values used to produce the output shown in Fig. 1a

	Definition	Value	Units	Reference
M	Adult worm burden	See (1)	worms lamb^{-1}	
L	Larval availability	See (2)	infective larvae lamb^{-1}	
IgA	IgA activity	See (3)	optical density units	
ECF	Establishment control factor	See (4)	—	
E	Establishment	See (5)	—	Gaba *et al*. (2006)
l	Worm length	See (6)	cm	
n	Density-dependent worm fecundity	See (7)	eggs adult^{-1} day^{-1}	Stear *et al*. (1995*c*) Stear and Bishop (1999)
W	Lamb live weight	See (8)	kg	Bishop *et al*. (1996)
I	Larvae ingested	See (9)	infective larvae day^{-1}	
Q	Pasture intake	See (10)	kg DM day^{-1}	
c	Faecal egg count	See (11)	eggs g^{-1}	
m_1	Mortality rate of pre-infective larvae on pasture	0·23	day^{-1}	Learmount *et al*. (2006) Niezen *et al*. (1998)
m_2	Mortality rate of infective larvae on pasture	0·008	day^{-1}	Kao *et al*. (2000) Gibson and Everett (1972)
m_3	Mortality rate of adult nematodes	0·0307	day^{-1}	Kao *et al*. (2000) Hong *et al*. (1986)
L_0	Initial larval availability	10,000	infective larvae lamb^{-1}	
S	Maternal deposition of eggs on pasture	Linear decrease from 250,000 at $t=0$ to 0 at $t=84$	eggs lamb^{-1} day^{-1}	
j	Pre-patent period	14	days	Stear *et al*. (1995*a*)
u	Time from egg to infective stage	21	days	Urquhart *et al*. (1996)
f	Amount of faeces produced per kilogram of lamb body weight	20	g day^{-1}	
D	Stocking density	35	lambs ha^{-1}	Waller *et al*. (1981)
H	Herbage density	1,200	kg DM ha^{-1}	Waller *et al*. (1981)
τ_1	Half-life of IgA activity	8·1	days	Henderson (2002)
ρ_1	IgA response factor	$8{\cdot}61\times10^{-6}$	infective larva^{-1}	
τ_2	Half-life of establishment response	8·1	days	Henderson (2002)
ρ_2	Establishment response factor	$1{\cdot}00\times10^{-4}$	infective larva^{-1}	
z	Time for initiation of immune response	7	days	

Table 2. Summary of coefficients, their values and related parameters

Coefficient	Value	Related parameter
α	1·0103	Worm length, l
β	0·4536	
γ	0·0310	
ε	96·516	Worm fecundity, n
ω	4·7452	
θ	$3{\cdot}6\times10^{-5}$	Live weight, W
μ	0·614	
κ	0·0471	
ϕ	10·18	Live weight, W, and herbage consumed, Q
v	0·109	Herbage consumed, Q
E_{early}	0·4	Establishment, E
E_{late}	0·0	

between this mortality rate and that of the earlier life stages. The relatively high value of 0·23 compared to 0·008 may be due to susceptibility to predation by fungi and habitat disturbance in the earlier life stages. When the nematode leaves the faeces, it also undergoes physiological changes that make it more resilient.

For parasites that have been ingested and become established in the host, we use the value of 0·0307 for the daily mortality rate (m_3), obtained from Kao *et al*. (2000) with data from Hong *et al*. (1986).

The maternal contribution to larval availability is set to an initial value of 250 000 eggs deposited per lamb per day. In other words, assuming each ewe gives birth to twins, 500 000 eggs per ewe per day. If we assume an average Blackface ewe weighs 50 kg and the production of 20 g of faeces per kg as with lambs, then this equates to a faecal egg count of 500 eggs per gram (epg).

Pasture intake increases in line with lamb growth. Here we assume that consumption increases from zero at birth to a maximum of about 1·5 kg DM of pasture when growth begins to level off at about 24 weeks of age. We modelled pasture intake increasing from birth.

A value of 35 lambs ha^{-1} was used for the stocking density, D. Herbage density, H, was given the value 1200 kg ha^{-1} (Waller *et al*. 1981). For the parameters

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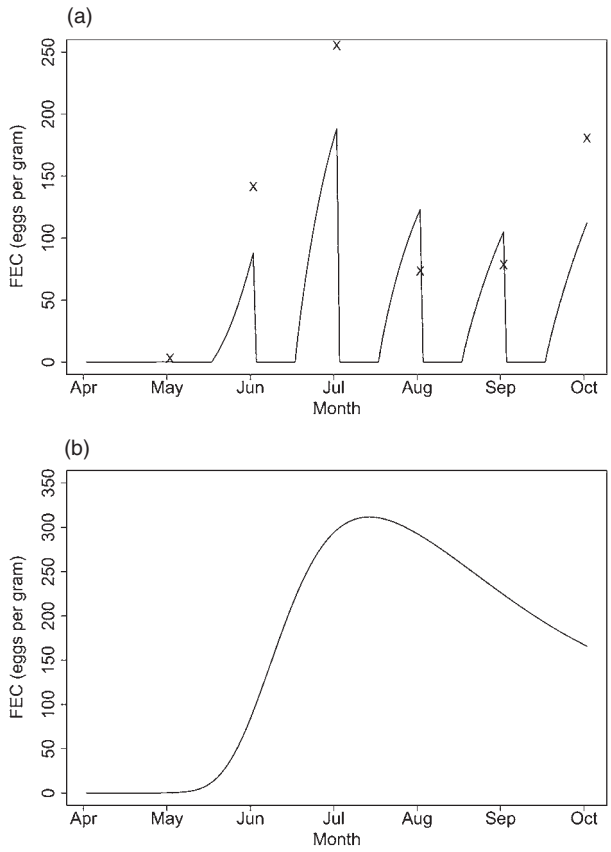

Fig. 1. (a) A comparison of output from the model with geometric means of empirical faecal egg count data (X): May 3, Jun 142, Jul 255, Aug 73, Sep 79, Oct 181. Parameters used are given in Table 1. Periods of zero egg counts follow treatments with anthelmintic. End-of-season establishment is 0·070. (b) The progression of faecal egg counts through the season when no anthelmintic treatment is given. Parameters used are given in Table 1. End-of season establishment is 0·015.

relating directly to the parasite, we used a value of 21 days for the development time from egg to infective stage, u (Urquhart *et al*. 1996), and a value of 14 days for the pre-patent period, j (Stear *et al*. 1995*a*). Stocking density is one parameter in the model that we consider free, in that it is not dictated by biological constraints but rather by farming practice. Therefore, this is one parameter that is likely to vary from farm to farm.

For parameterization of the immune response, data from Henderson (2002) were used to obtain an estimate of 8·1 days for the half-life of plasma IgA (τ_1). This same value was used for the response controlling establishment in the model (τ_2). To fit the model output to the empirical data, a best-fit analysis in which a range of values for the IgA- and establishment-related response parameters (ρ_1 and ρ_2, respectively) were trialled to find those that provided the minimum value of the sum of the squares between simulated and measured faecal egg counts at the 4 measurement points between June and September. It was not our intention to fit the majority of parameters to the empirical data, but rather to match the qualitative increase and decline of faecal egg counts through a season. Although the observed data showed a rise in faecal egg counts in October, this is believed to be due to eggs produced by parasite species other than *T. circumcincta*, therefore this point was excluded from the analysis. Data points for measured IgA values and estimated establishment were also included in the analysis. Three data points (August, September and October) were taken from Strain *et al*. (2002), and were used to obtain a least squares best-fit output in combination with faecal egg counts and establishment as described above. Based on data from Gaba *et al*. (2006), we set the establishment in naive lambs to be 0·4 (E_{early}) and used a single data-point estimate of 0·1 in September with which to obtain the best-fit output by varying E_{late}.

RESULTS

The model reproduced the observed magnitude and time-course of faecal egg counts (Fig. 1a), excluding the October measurement when other parasite species are assumed to be contributing to this number. In a simulation where anthelmintics were not administered, the peak geometric mean egg count was increased by approximately two thirds, and egg count declined more slowly in the second half of the season (Fig. 1b).

The breakdown of the contributions made to total larvae on pasture over time shows that the contribution from the ewes dominates the larval availability until late in the season (Fig. 2a). Although the ewes were removed at 12 weeks (indicated by the vertical line), their contribution (dotted line) to the total larval availability (solid line), exceeds that of the lambs' (dashed line) throughout the season as a consequence of the large numbers of eggs deposited by the ewes and the length of time eggs, pre-infective and then infective larvae are able to survive on pasture. As the ewes were not subject to anthelmintic treatments (treatment times indicated by triangles), there is relatively little impact of the treatment on the level of infective larvae on pasture.

In the absence of deposition of eggs by ewes, faecal egg counts were substantially lower and rose gradually during the full course of the grazing season (Fig. 2b).

Immune response

IgA activity (Fig. 3a) peaks later in the season followed by a slight decline. As we assume that IgA production is a function of the quantity of larvae ingested, there is no sharp fall in IgA following anthelmintic treatment. The decline in establishment over the season is shown in Fig. 3b.

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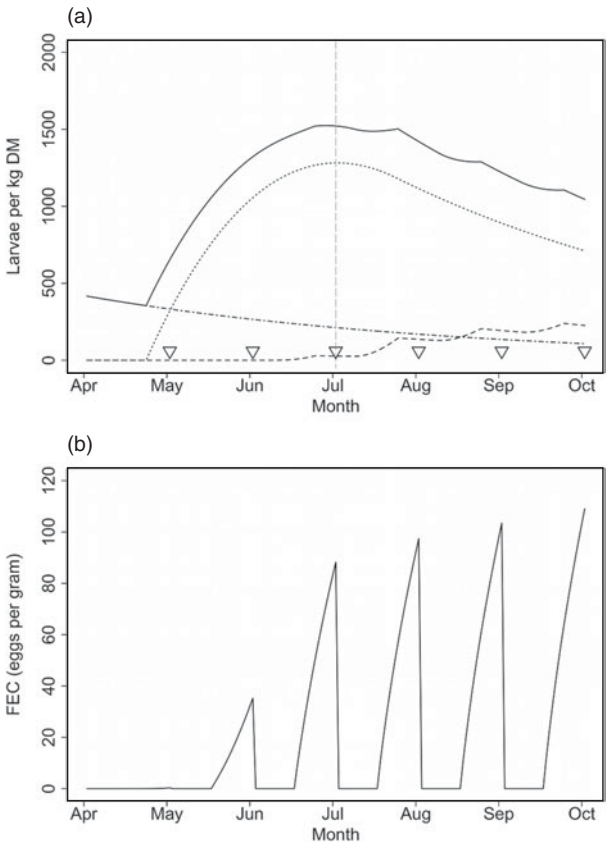

Fig. 2. (a) Breakdown of the contributions made to total larvae (solid line) on pasture from ewes (dotted line), lambs (dashed line) and over-wintered larvae (dash-dotted line). Triangles mark points of anthelmintic treatment, and the vertical dashed line marks the point at which ewes no longer deposit any new eggs on pasture. (b) Faecal egg counts obtained when using the parameters in Table 1, but assuming no deposition of eggs by ewes. End-of-season establishment is 0·273.

Sensitivity analyses

A series of sensitivity analyses were performed for several of the model parameters; one parameter was varied across a range of values while all other parameter values were kept as in Table 1.

Mortality rate of pre-infective larvae, m_1

For m_1, at the first peak in June we observe a large effect on faecal egg counts from a relatively small change in mortality rate (Fig. 4a). We can see that lower mortality rates lead to higher faecal egg counts. Interestingly, however, at the end of the season it was actually the higher mortality rates that produced the higher egg counts. This difference is due to the rate of acquisition of host immunity; when lambs are exposed to large numbers of larvae early on, the rate of establishment and parasite growth will decline more rapidly. Consequently, faecal egg count will reduce more rapidly. With a mortality rate of 0·20, the faecal egg counts do not exhibit the typical mid-season peak, with the peak being a month earlier.

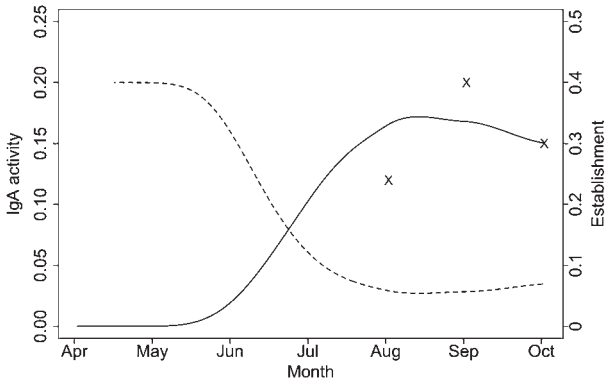

Fig. 3. The progress of IgA activity through the season as driven by exposure to infective larvae through pasture grazing (solid line), and the decline in parasite establishment (dashed line). X indicates empirical IgA data for comparison. These plots were obtained using the parameters in Table 1.

Mortality rate of infective larvae, m_2

In contrast to mortality of pre-infective larvae, the mortality rate of the infective larval stage, m_2, can be varied over a much wider range without a major impact on faecal egg counts (Fig. 4b). Similarly to m_1, at the end of the season the lowest faecal egg count is derived from the lowest mortality rate.

Mortality rate of established adults, m_3

The mortality of established adult worms, m_3, also has little influence on faecal egg counts. For example, in July, when we observe the season peak in faecal egg counts, there is less than a doubling in egg count when m_3 is decreased 100-fold (Fig. 4c). In our model, the development of immunity is related to the number of larvae ingested. Therefore, the reduced number of adult nematodes has no effect on the development of immunity.

Maternal deposition of eggs on pasture, S

The initial number of eggs deposited by ewes was allowed to vary, but declined to zero over the same period. Early in the season, greater deposition of eggs by ewes lead to higher faecal egg counts in the lambs (Fig. 4d). However, higher early infection lowers faecal egg counts in mid-season, and by October the peaks are the reverse of those seen in June. Although this model only considers a single season, this pattern could generate robust year-to-year dynamics.

Stocking density, D

High stocking densities lead to initially high faecal egg counts, but we observe ultimately lower faecal egg counts at the end of the season and higher egg counts when stocking density is lowered (Fig. 4e).

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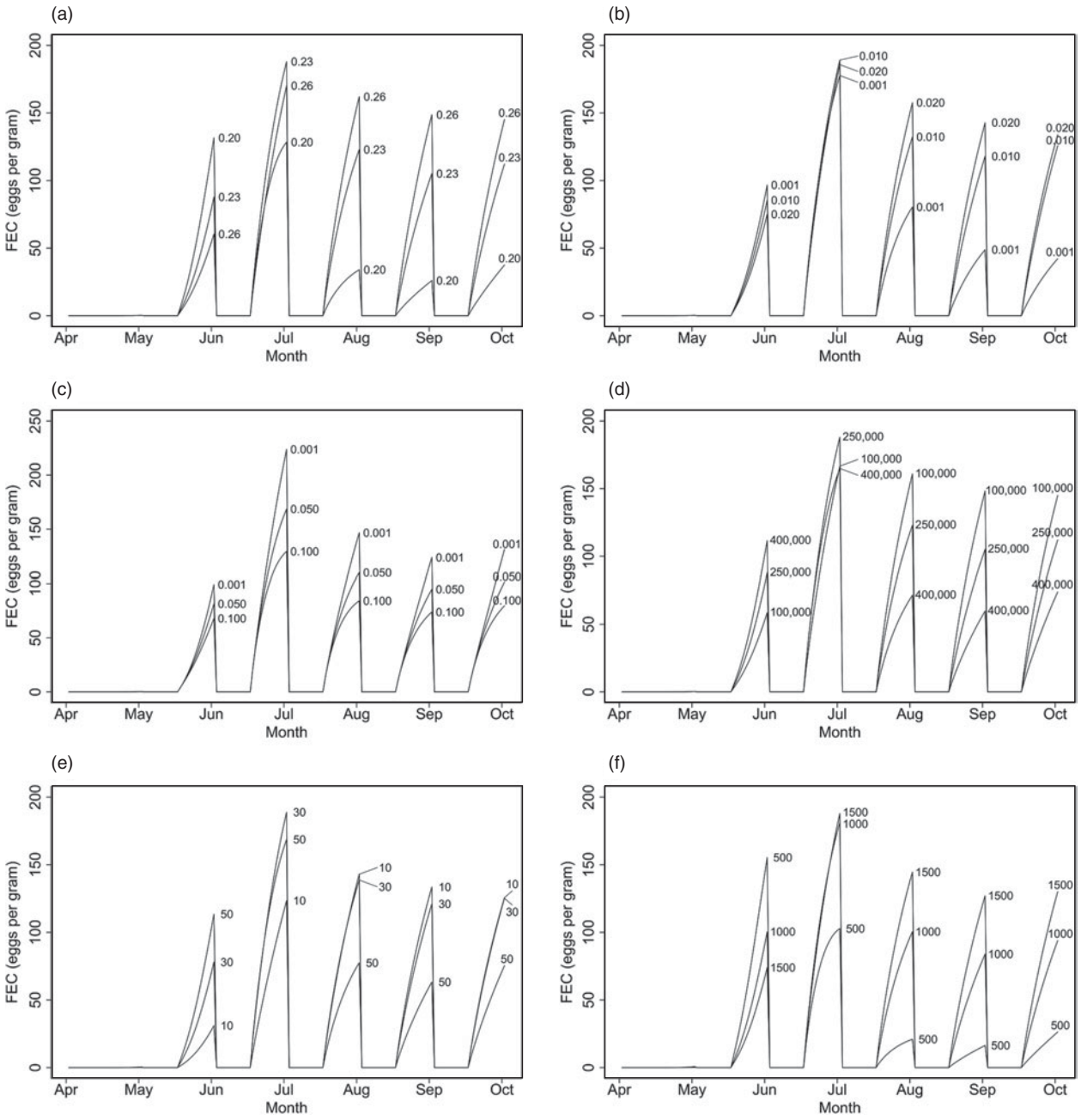

Fig. 4. Sensitivity analyses of various model parameters: (a) mortality rate of pre-infective stages, $m1$; (b) mortality rate of infective stage, $m2$; (c) adult mortality rate, $m3$; (d) maternal deposition of eggs on pasture, S; (e) pasture stocking density, D; (f) pasture herbage density, H.

Herbage density, H

Increasing herbage density decreases infection potential, as there will be fewer infective larvae per kg DM of herbage for any given number of larvae on pasture (this is assuming that larvae are evenly distributed along the herbage length, and do not migrate towards the tip). This is reflected in the faecal egg counts generated by the model (Fig. 4f). With the lower value of 500, the faecal egg counts do not show the typical mid-season peak, but instead peak a month earlier.

Establishment and faecal egg counts

To examine the relationship between establishment and faecal egg counts, the end-of-season establishment was recorded for all of the simulations shown in Fig. 4. The plot of end-of-season establishment against end-of-season faecal egg count (Fig. 5) shows how increasing egg counts are related to increased establishment up to a plateau level of around 0·15 establishment and 145 epg. After this point, egg counts appear to fall with increasing establishment because of reduced intake leading to both lower egg

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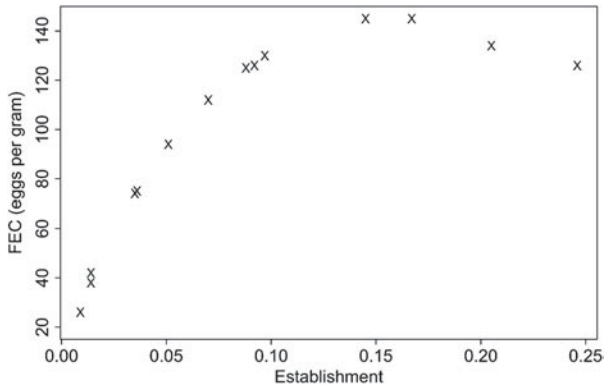

Fig. 5. End-of-season faecal egg counts from Fig. 4 plotted against their corresponding end-of-season establishment. (Values for $m3$ have been omitted, as this parameter has no direct effect on establishment).

counts and reduced stimulation of the immune response. The corresponding establishment rates for m_3 in Fig. 4 have not been included in Fig. 5, as this parameter is related to the already established adult worms and so has no direct effect on establishment.

Response to potential control strategies

By varying certain parameters of the model we were able to explore the potential effects of applying particular strategies to control the infection of lambs by nematodes. We chose to look at 4 different control strategies. Reducing the stocking density is one means by which lambs will be exposed to reduced numbers of infective larvae, and this was simulated simply by lowering the stocking density parameter, D. Reducing the number of eggs deposited by ewes, either by treating them with anthelmintics or removing them from the pasture earlier, will also expose the lambs fewer larvae, and this method of control is simulated by varying parameter S. Another way to reduce the exposure of lambs is to remove infective larvae from the pasture sooner by increasing their mortality rate (m_3). An alternative to reducing exposure to infection is to increase the immune response, e.g. by nutritional supplementation or selective breeding, and this is related to the parameters ρ_1 and ρ_2.

From these simulations, control strategies aimed at reducing exposure (related to parameters S, D and m_2) could lead to increased end-of-season faecal egg counts, except in the case of extreme reduction in stocking density (Fig. 6). However, strategies to improve the immune response could lead to reduced faecal egg counts in all cases.

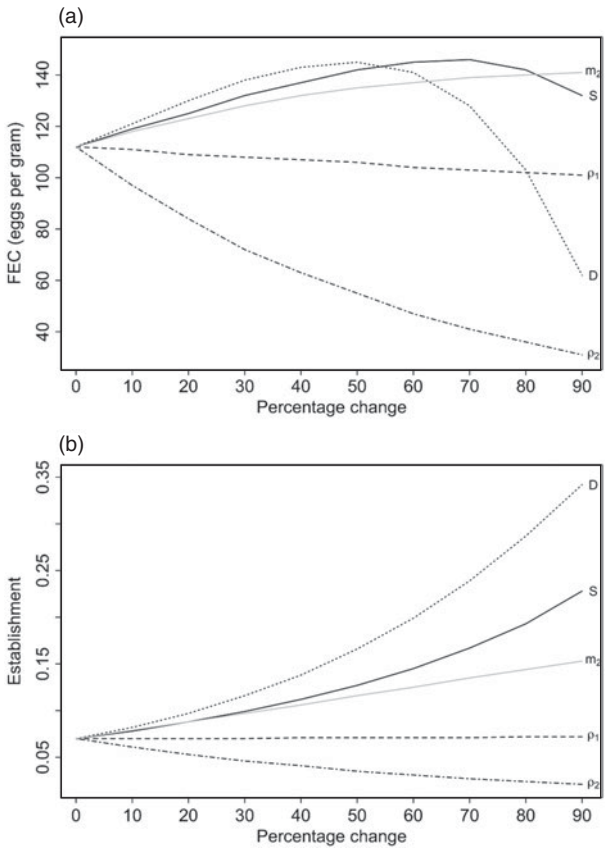

Fig. 6. The results of varying the values of 5 parameters from those given in Table 1 to simulate the effects of applying particular control strategies. The percentage change is a decrease for parameters S and D, and an increase for m_1, ρ_1 and ρ_2. End-of-season faecal egg counts are shown in (a) and establishment in (b).

DISCUSSION

We have modelled the course of nematode infection in newborn lambs over the grazing season. In particular, we have explicitly modelled the role of IgA and density dependence in regulating parasite fecundity and used a recent meta-analysis to parameterize the rate of parasite establishment. We chose to restrict the model to lambs because *T. circumcincta* infection is most prominently a problem in developing lambs and not in adults, except for ewes during the periparturient period; additionally, we were interested in modelling the developing immune system rather than immunologically mature animals.

Although we have set stocking density at a realistic value for the modelled flocks, this could be regarded as a free parameter of the model that can be adjusted to capture much of the variation between flocks. This model produces a good qualitative fit to empirical faecal egg count data, with a relatively sharp rise in egg counts seen early in the season, peaking mid-season, and then declining steadily throughout the remainder of the season.

In an earlier study, Anderson and May (1978) discussed several approaches to modelling the dynamics of host-parasite interactions. Many more models have investigated the interactions between nematode parasites and their ruminant hosts since the review by Smith and Grenfell (1985) of the

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population biology of *Ostertagia ostertagi*, and these have been thoroughly reviewed (Roberts, 1995; Cornell, 2005). More recently, Learmount *et al.* (2006) have described a model that includes flock dynamics and environmental parameters, and Louie *et al.* (2007) and Vagenas *et al.* (2007*a*,*b*) present models that consider the interaction between parasitism and sheep growth. Acquired immunity in the host has also been modelled, where it is assumed to increase over time as a consequence of exposure to infective larvae, and manifests itself as a combination of constraints on establishment, fecundity and the survival of adult parasites (Anderson and May, 1985; Roberts and Grenfell, 1991). Although the importance of host-acquired immunity has long been recognized, there are few models addressing in detail the immuno-epidemiology of farmed ruminants. However, we now have a clearer understanding of the development of acquired immunity and the mechanisms involved in within-host regulation of parasite burden, length and fecundity (Stear *et al.* 1995*c*, 1996). Detailed analyses show that there are 3 key features of the host response in sheep. First, immunity is acquired in response to exposure and develops in 2 stages, with lambs initially regulating worm growth and fecundity, and then worm number (Seaton *et al.* 1989). Second, variation among hosts in IgA production and local eosinophilia accounts, in a statistical sense, for most of the variation in worm growth and fecundity (Strain *et al.* 2002; Stear *et al.* 2004; Henderson and Stear, 2006). Third, much of the variation in worm number in deliberate infections is associated with variation in IgE activity and the number of degranulated mucosal mast cells (globule leucocytes, GL) which affect establishment and mortality (Stear *et al.* 1995*c*).

The maternal contribution to the total larval availability on pasture dominates throughout the season. Indeed, the lambs do not begin to make any contribution at all until the end of June, a delay that is due to a combination of the nematode development time, u, and the pre-patent period, j, coupled with the small initial ingestion rates at the start of the season. The maternal deposition of eggs on the pasture is an important means by which the concentration of larvae on pasture is maintained before the lambs themselves begin to make a significant contribution, which supports previous observations (Urquhart *et al.* 1996).

Our model is robust to perturbations in the majority of the parameters used in that it displays a characteristic increase and decline in faecal egg counts through a season, possibly because of early priming of the immune system; a particular characteristic of this model is the importance of early infection rate in determining the ultimate faecal egg count. As the immune response is stimulated by the ingestion of infective larvae, then the sooner a lamb is exposed to infection, and the greater the number of larvae, then the more rapidly parasite establishment and growth will be suppressed. This mechanism has a regulatory effect on host worm burdens, and acts to constrain faecal egg counts later in the season even if the initial infection rate is relatively high. The tendency for initially high faecal egg counts to produce lower egg counts later in the year was observed by Stear *et al.* (1995*b*), and suggests that the increased deposition of eggs by ewes during the periparturient period may be useful in stimulating the development of immune responses.

The robustness of this host-parasite system may be a consequence of the long coevolution between host and parasites. Nematodes of the subfamily *Ostertaginiae* are widely distributed among the *bovidae* and *cervidae*, which suggests that these nematodes and their ancestors have been infecting sheep and their ancestors for millions of years. Indeed, it may be that such an evolved system may act to reduce selective pressures on both host and parasite. These characteristics of the system also suggest that the control of nematode infection will be challenging.

We have considered the effects of applying particular control strategies to this model system by varying parameters that may respond to such strategies. These have shown that methods such as anthelmintic treatment of ewes or those that would increase the mortality of infective larvae could actually lead to higher faecal egg counts at the end of the season. This is because these control measures reduce exposure levels and ultimately delay the development of the immune system. Moderate reduction in lamb stocking density also produces higher end-of-season egg counts, but there is a significant decline in egg counts at very low stocking density. By varying the parameters directly related to the immune response, we see a consistent reduction in faecal egg counts with improved response. We also see that the response related to the suppression of establishment has a much larger effect in reducing egg counts than does the response controlling nematode fecundity. These results suggest that the most effective method of controlling nematode infection in lambs would be to improve the immune response, either with programmes of selective breeding or by nutritional supplementation.

The simple model presented here does not incorporate observed heterogeneity in individual response to infection, in worm burdens and in faecal egg counts. However, to fully assess the relative merits of combinations of control measures, such as selective breeding or vaccination, will require an individual-based model. We have also made the simplifying assumption that control of establishment and fecundity develop at the same rate; a more sophisticated model that allows for differential development rates may shift the dominant source of robustness from immune priming to density dependence.

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In summary, we have constructed a realistic but relatively simple model of nematode infection in sheep based on the immune mechanisms associated with protection. This model emulates the pattern of faecal egg counts seen in the field, and is remarkably robust to perturbations in most of the observed parameters.

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