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Modelling responses to selection for resistance to gastro-intestinal parasites in sheep

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Abstract

This paper describes a general framework which enables responses to selection for resistance to gastro-intestinal parasites in sheep to be stochastically modelled. The model incorporates between-animal variation for pasture intake, the proportion of larvae ingested from the pasture which survive to become adults, the fecundity of the mature worm, along with density-dependent control of this trait and the mortality rate of the worms. The between-animal variation for each component is partitioned into genetic, permanent and temporary environmental components which vary with age. Infection rates are estimated from existing pasture larval contamination and new contamination from infected animals. Using this framework, selection for reduced mean faecal egg count was practised, in silico, for a period of 10 years. Several general patterns emerged. First, a curvilinear response to selection was observed, with responses initially being large then declining over time. Mean faecal egg count declined from approximately 500 to 140 eggs per g in 10 years and worm burdens and pasture larval contamination showed similar patterns of response. The initial responses to selection were approximately 1·7 times that predicted by quantitative genetic theory because the epidemiology of the disease changed as the animals' genetic resistance improved. A method of partitioning selection responses into components due to the altered genotypes of the animals and components due to altered disease epidemiology is outlined. Secondly, the faecal egg count distribution became more aggregated, or skewed, as selection progressed. Thirdly, correlating pasture contamination levels across years (carry-over effects) resulted in even greater apparent responses to selection. Finally, regular anthelmintic treatment reduced mean faecal egg counts but did not alter the patterns of response to selection, indicating that selective breeding should be feasible under a variety of anthelmintic regimes.

Keywords: *disease resistance, epidemiology, parasites (gastrointestinal), selection, sheep.*

Introduction

Gastro-intestinal parasitism presents a major constraint on livestock production, resulting in reduced animal performance and welfare, along with increased costs associated with both anthelmintic and management control measures. Resistance to gastro-intestinal parasitism in sheep has been shown to be heritable (e.g. Baker *et al.*, 1991; Woolaston *et al.*, 1991; Bishop *et al.*, 1996) with heritabilities for faecal egg count (FEC), a convenient measure of resistance to gastro-intestinal parasites, being of the order of 0·2 to 0·3. This suggests that selection for increased resistance may be used as a long-term control measure, in addition to existing management strategies.

However, predicting responses to selection for decreased FEC, in grazing ruminants, is not straightforward. Measured FEC is the result of a complex series of interactions between the parasite and the host, it commonly shows a negative binomial rather than a normal distribution and FEC levels also indicate the likely reinfection probabilities of other animals grazing the same pasture. Thus, in the situation of continual reinfection, interactions exist between animals in terms of their expression of resistance and this contravenes the normal (unstated) assumption made when calculating likely rates of genetic response that animals express their traits independently of each other. A possible consequence of these interactions between animals is that selection

which alters mean FEC over several years may also alter the epidemiology of the disease, as suggested by Barger (1989).

This paper addresses the issues of responses to selection for disease resistance and possible effects on disease epidemiology. Using gastro-intestinal parasitism in sheep as a case study, this paper aims to define a framework which may be used to model the effects of selection for disease resistance. Having defined the framework, the model will be investigated by means of stochastic simulation and likely patterns of selection responses will be calculated.

Material and methods

Epidemiological model

A model will be defined in general terms, then tailored to the specific example of gastro-intestinal parasitism in sheep. Unlike most previous attempts to model nematode populations, the model will concentrate on the interactions between the animal host and the pathogen, keeping epidemiological aspects of the model deliberately simple. Whilst it is recognized that external factors such as weather conditions are of overriding importance in defining potentially infective parasite populations, they are outwith the scope of this model.

(i) Basic model and equilibrium assumptions. Consider a simple infection where there is a constant infection rate of the host (I), a constant mortality rate of the adult parasite (m) and the number of adult parasites at time t is $M(t)$ (Anderson and May, 1992). Therefore:

$$dM_{(t)}/dt = I - mM_{(t)}$$

with solution:

$$M_{(t)} = M^*(1-e^{-mt}) \qquad (1).$$

Under this model the infection rate of a population of hosts will rise monotonically with time until it reaches an equilibrium value, $M^* = I/m$.

This concept may be extended to consider actual interactions between the parasite and the host. In the simplest form for gastro-intestinal parasites, three major factors may be defined: (i) *establishment* (E), i.e. the proportion of ingested larvae which survive to become adult parasites; (ii) *fecundity* (n), the number of eggs laid per adult worm per day (assuming a constant sex ratio); and (iii) *mortality* (m), the daily death rate of the adult worm, as defined above. With great simplification, and assuming constant weather conditions, the free-living stage of the parasite may be summarized by the following parameters: the probability that the egg hatches and develops to form a third stage lavae and is ingested at time t (y), and the mortality rate of the free living stage of the parasite (z).

An actual epidemic of the disease is assumed to be triggered by an initial ingestion rate of a high concentration of infective larvae (L_o). In practice, this may be caused by pasture contamination with infected larvae by periparturient ewes or by 'favourable' weather conditions resulting in dormant larvae becoming active. Therefore, the following model may be defined to take into account both the initial infection and, after time, continual reinfection:

$$M_{(t+1)} = M_{(t)}(1-m) + L_{(t-j)}E \qquad (2)$$

where $L_{(t-j)}$ is the ingestion rate of larvae j time units ago, where j is the time assumed for larvae, which become established, to reach adulthood, and summing over time

$$L_{(t)} = L_o(1-z)^t + \sum_{i=0}^{t} M_{(i)}\, n\, y(1-z)^i \qquad (3).$$

Under this model, the parasitic population will reach an equilibrium which can be defined as follows:

$$M^*_{(+1)} = M^*_{()}(1-m) + \sum_{i=0}^{j} M^*_{(\quad j-i)}\, n\, y(1-z)^i E \qquad (4).$$

This equation holds true whilst:

$$m = nEy/z = nEp \qquad (5)$$

where p is the overall probability of an egg hatching and developing to third larvae stage and being ingested before it dies. If this relationship breaks down, then the parasite population (M) quickly approaches either zero (extinction) or infinity (a runaway epidemic).

Although there may be a threshold above which the worm burden is fatal to the host, it is assumed that this threshold is not exceeded in unselected populations of lambs.

(ii) Density dependent constraints. Consider the situation of an outside perturbation of the worm population, e.g. biocide from anthelmintic treatment. The above model will once again establish an equilibrium worm burden, but a lower level than previously. This is at odds with observed field data, where a similar equilibrium appears to be re-established. Moreover, the model is also very

sensitive to breakdowns in the assumptions, with irreversible epidemics, or entire loss of the parasitic population, occurring. Population regulation of the parasite may be controlled to a large extent by density dependent constraints, which may act at any of the *establishment, fecundity* or *mortality* levels, whereby the levels of any one of these stages is an inverse function of the worm population present.

Density dependent constraints may be simply modelled for *fecundity*, i.e. for worm densities greater than average, *per capita* fecundity decreases and *vice versa* for below average worm densities. This both stabilizes the recursive equations given above, as well as ensuring that when perturbations hit the worm population the population returns towards the pre-perturbation level. Setting a constraint that the total egg production per animal rises with increasing worm burden, then the density dependent effects acting on fecundity (n) may be modelled as being proportional to worm burden (M):

$$n \propto M_{(t)}{}^{b} \qquad (6)$$

where the exponent b defines the strength of the density dependent effects, such that $0 \quad b > -1$.

(iii) Between-animal variation. The factors above describe the dynamics of the population mean. The model now has to be extended to an individual animal basis. Between-animal variation exists for worm burden and FEC, with FEC most commonly showing a negative binomial distribution. It is 'overdispersed', with a small number of animals having high FECs and thus being responsible for a large proportion of the pasture infection. Between-animal variation can conceivably exist for *establishment, fecundity* and *mortality*, with each being a manifestation of the animal's immune response to the infection. Between-animal variation for *fecundity*, as a trait of the animal, may be thought of largely as between-animal variation in adult worm size, since the correlation of worm length and eggs per worm is very high (Stear *et al.*, 1995b).

The forms of the distributions of the between-animal variation for *establishment, fecundity* and *mortality* are unknown, however they should be defined such that measured FEC has an empirical distribution similar to the negative binomial. Preliminary assumptions, made in the absence of information to the contrary, are that *establishment* and *mortality* are normally distributed (mean values are E and m, respectively), and that *fecundity*, being a biological count measurement, has a Poisson distribution (mean = n).

Further variation between animals exists for the number of ingested larvae per day and FEC measurement error. The number of larvae ingested per day is comprised of two components — first, pasture intake and secondly, sampling of larvae off the pasture. Pasture intake is assumed to be a normally distributed trait, being zero in very young lambs and rising to a plateau in lambs 4 months and older. For an animal with a given food intake, the number of larvae ingested per day due to sampling effects is a biological count, and hence may be assumed to be a Poisson variable (mean at time t = $L_{(t)}$, where $L_{(t)}$ is proportional to the animals food intake at time t). Measurement errors in FEC may be assumed to be proportional to the true (unknown) FEC, i.e. the measurement scaling error is normally distributed (mean = 1·0).

(iv) Development of immunity. Exposure to the parasite population will result in lambs developing immunity, i.e. they will improve their ability to suppress *establishment* and *fecundity* and increase *mortality*. Two components to this may be considered. First, the mean level of immunity for the population as a whole will improve with time. Secondly, genetic differences between animals in *establishment, fecundity* and *mortality* will become apparent (see below), representing differences between animals in their immunocompetence. The increase in mean immunity is assumed to follow a pattern similar to that presented by Roberts and Grenfell (1991), rising from zero in young lambs to essentially a plateau in lambs 4 months and older. Thus, under these assumptions the increase in pasture intake with age in young lambs effectively balances the increase in immune ability.

(v) Partitioning animal variation. The animal controlled components, *establishment, fecundity, mortality* and pasture intake, may be assumed to be both genetically and environmentally controlled in lambs, with both the mean levels and the degree of genetic variation between animals reflecting the immune status of the population (see above). Heritabilities may thus be defined for these traits such that the heritability for FEC is similar to that observed in field situations. *Establishment, fecundity, mortality* and pasture intake are assumed to be genetically uncorrelated. Further partitioning of between animal variation into permanent environmental components, associated with either the whole lifetime or a particular season, and temporary environmental effects, mimicking time trends and chance effects for individual animals is also necessary. Modelling these permanent and temporary environmental effects serves two purposes: it allows realistically low repeatabilities between FEC measured within the same season (e.g. r 0·5) and it also models the observed phenomenon of the correlation between FEC

measurements decreasing as the time interval between measurements increases (Stear *et al.*, 1995c).

(vi) Defining initial infection rates. The model outlined above describes the course of an infection in a static host population within one season. When considering the effects of selection, and hence changes in infection rates across seasons, an issue arises as to the definition of the initial infection rate at the start of each season. An arbitrary function, $f(LC,w)$ may be used to define the mean pasture larval count at the start of a season as a function of that present at the end of the previous season, accounting for the genotypes and immune status of animals grazing the pasture in the interim. These will be termed carry-over effects. For example, if $w = 0$ then the initial infection rate each season is constant, whereas if $w = 1$, the initial infection rate is directly proportional to the previous season's larval count.

Model investigation

The use of the model outlined above for the prediction of responses to selection for reduced FEC in lambs was investigated using stochastic simulation. The parameters of the model were set so that heritabilities and mean values for FEC mimicked results obtained for unselected Scottish Blackface lambs naturally infected with *Ostertagia circumcincta* (Bishop *et al.*, 1996).

(i) Mean values. L_0, m, n, E and p were defined such that mean FEC and adult worms burdens were close to 500 eggs per g and 2500 worms, respectively, prior to selection. Setting $E = 0{\cdot}6$, $m = 0{\cdot}06$, $n = 100$ (i.e. 500 eggs per g × 500 g faeces per day per 2500 worms) requires $p = 0{\cdot}001$ for equilibrium conditions to hold. Setting $L_0 = 1000$ achieved the desired mean infections. A constant L_0 was assumed for every year during the selection procedure. This represents the case, for example, where periparturient ewes graze the pasture prior to the lambs and these ewes are either unselected (in the initial years of selection) or unaffected by the selection (in later years). Additional scenarios were also investigated where L_0 was directly proportional to mean pasture contamination from the previous year, and where L_0 was mid way between these two extremes.

(ii) Density dependent effects. b was set to either 0, –0·25 (weak effects) and –0·5 (strong effects), for different simulation runs, following results of S. C. Bishop and M. J. Stear (unpublished data) and values presented for humans by Anderson and May (1992).

(iii) Component trait variation. A coefficient of variation of 0·3 was defined for *establishment*, *mortality* and food intake. Setting the *fecundity* mean to 100 automatically defines the coefficient of variation to be 0·1, as it is a Poisson variable, somewhat lower than for *establishment* and *mortality*. Experimental data (S. C. Bishop and M. J. Stear, unpublished data) suggest that this underestimates the variability in this trait. Moreover, assuming mean *fecundity* to be 100 resulted in unrealistic, i.e. too large, values for the negative binomial aggregation parameter (k), when this distribution was fitted to FEC. A solution was found to this problem by redefining n to be 10, rescaling the conversion from total daily egg output to eggs per g, so that mean FEC remains close to 500 eggs per g, and altering p to 0·01 so that an equilibrium was still maintained.

(iv) Animal effects. h^2 values were set to 0·2 for *establishment*, *fecundity* and *mortality*. Results of Bishop *et al.* (1996) were mimicked such that genetic control of these three traits was only apparent after 3 months of age, i.e. prior to 3 months all h^2 values were zero. Prior to 3 months the permanent environment effect (conceptually defined as a maternal c^2 effect) was set to 0·3 for all traits, and after 3 months it was reduced to 0·15. Food intake was assumed to have a constant heritability of 0·2 and a permanent environment effect of 0·15.

(v) Population structure. A simple population structure was used, for ease of calculations. A flock of 500 ewes was simulated, mated to 25 rams, with each ewe producing twins. Males were selected on FEC (see below) and used for only one breeding season at 7 months of age. Females were selected at random. Ewes were for randomized mating each year, mated first at 7 months of age and culled at random such that they had a maximum flock life of three parities.

(vi) Simulation procedure. Each year the model was run for lambs from 30 to 180 days of age. Individual genetic, phenotypic and environmental values were simulated for each trait for every lamb, as described above, with mean L values estimated from equation (3) after averaging pasture contamination effects across the whole flock. Mean FEC, averaged from samples taken on days 120, 150 and 180 was used as the selection criterion, this being a period during which heritabilties are significantly different from zero (Bishop *et al.*, 1996) and thus there are differences between animals in immunocompetence. Using these values the best 25 ram lambs every year were selected. Ten years of selection were practised and 20 replicates were run for each scenario, this being sufficient to show general patterns.

(vii) Comparing selection responses to expectation. Comparison of observed and expected responses to selection may be done by two methods. First, from

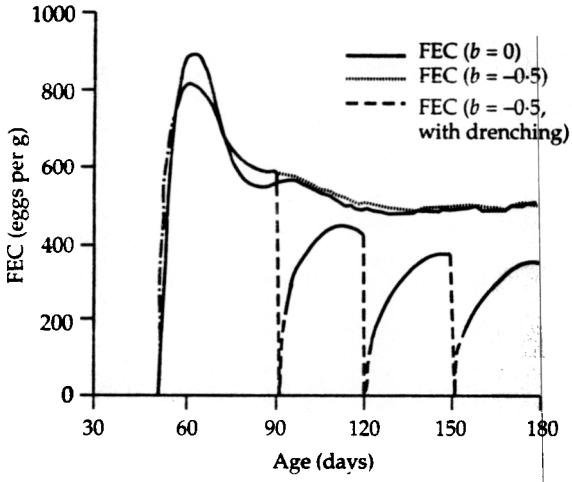

Figure 1 Faecal egg count (FEC) profiles in unselected sheep for different density-dependent effects and with anthelmintic treatment at 90, 120 and 150 days.

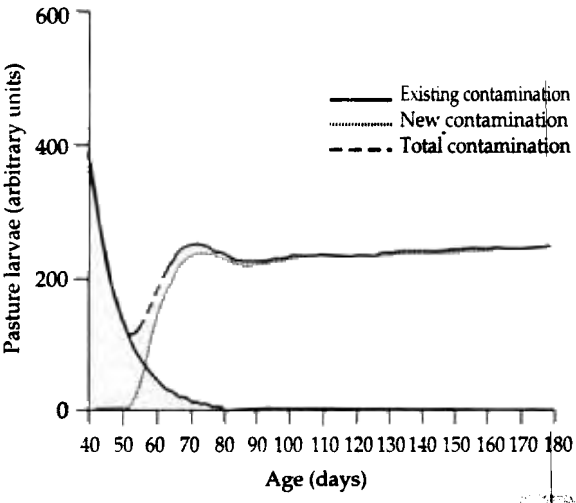

Figure 2 Pattern of pasture larval contamination.

quantitative genetic theory, i.e. $R = h^2S$, where S is the achieved selection differential and the h^2 value describes the base population. This simple approach is effective for the first generation, however it becomes more complicated in subsequent generations as the genetic and phenotypic variances change. Secondly, expected responses to selection may be inferred from the mean values for *establishment*, *fecundity* and *mortality* available from the model, each generation. Suppose unselected and selected animals are each given a dosage of a known number of infective larvae, then these mean values

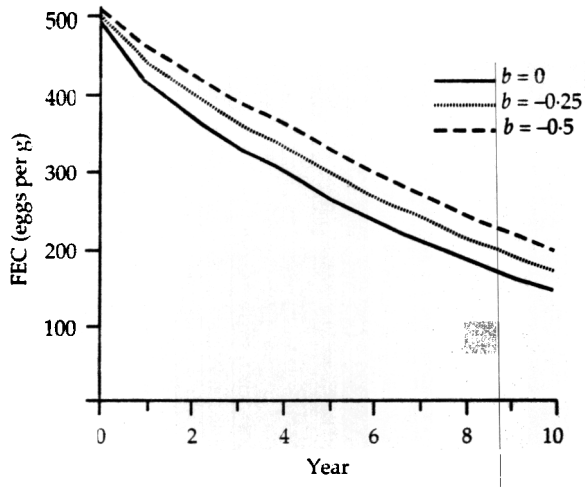

Figure 3 Responses to selection for reduced faecal egg count (FEC), assuming no carry-over effects between years.

can be used to calculate the approximate daily mean FEC values for the two groups. Comparison of the expected mean values relative to those observed from the model will determine how much of the response is genetic and how much is environmental (epidemiological) in origin.

Results

The behaviour of the model across a season for unselected animals is shown for undrenched animals (b = 0 and –0·5) and for lambs regularly drenched with a short-acting anthelmintic targetted at adult worms (b = 0·5) in Figure 1. Altering the density dependent b value has little effect on population means. However introducing a regular drench does result in an overall lowering of FEC values. Associated pasture larval contamination is shown in Figure 2, for untreated lambs.

Responses to selection for decreased mean FEC over a period of 10 years are shown in Figure 3 for density dependent exponents of b = 0, –0·25 and –0·50, mean worm fecundity of n = 10 and no carry-over effects from one year to the next in pasture larval contamination (w = 0). No anthelmintic treatment is given in this scenario. Selection responses show a general curvilinear pattern especially in the early years of selection, initially being large then decreasing and becoming more linear with time. Increasing the density dependent effect on worm fecundity decreased the responses to selection.

Using the GENSTAT package (Lawes Agricultural Trust, 1983), parameters from the negative binomial distribution were fitted to FEC values taken prior to

Table 1 *Negative binomial parameters for FEC distributions (replicate 1 data)*

	Measurement age (months)	Mean	*k*	Variance	Probability†
Before selection	4	489	3·89	71838	<0·05
	5	497	3·54	79628	<0·05
	6	500	3·46	81534	>0·50
	mean	497	7·00	38391	<0·05
After 10 years of selection	4	244	1·16	35168	<0·01
	5	121	1·23	7935	<0·01
	6	71	1·32	3450	<0·01
	mean	145	2·97	6698	>0·05

† Probability of fitting negative binomial distribution.

selection in the first replicate and to FEC values after 10 years of selection in the final replicate (Table 1). The fit of the negative binomial distribution was generally poor, only giving an adequate empirical description of FEC for two of the eight examples. However, the *k* values which describe the aggregation of the distribution were similar to those commonly observed in field data (e.g. Smith and Guerrero, 1993; Stear *et al.*, 1995a). In the cases where the negative binomial distribution was a very poor fit ($P < 0{\cdot}01$) it was because there were more zero FEC values observed than would be predicted from the fitted parameter values. Two important results are apparent in Table 1. First the distribution of FEC becomes more aggregated with selection, as mean FEC decreases. This is illustrated in Figure 4, where

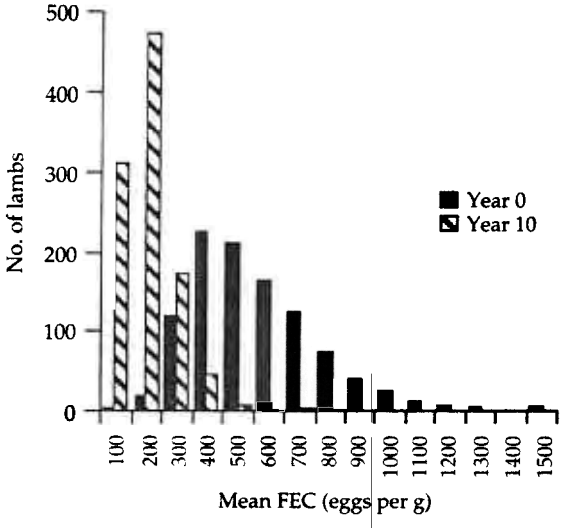

Figure 4 Distribution of mean faecal egg count (FEC) in 6-month-old lambs, before and after 10 years of selection for reduced FEC.

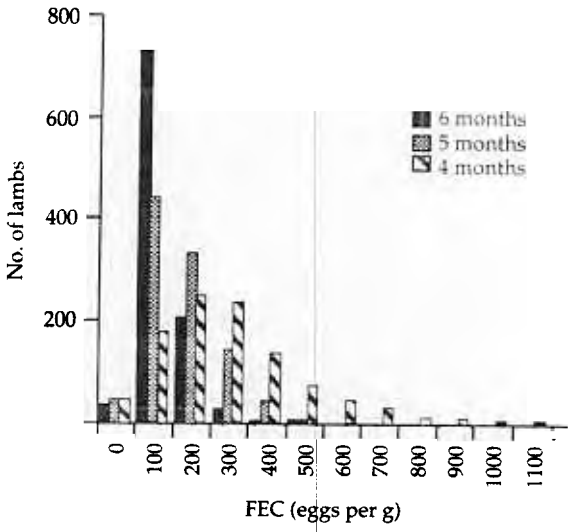

Figure 5 Distribution of faecal egg count (FEC) in lambs at different ages, after 10 years of selection.

the distribution of mean FEC before and after selection is plotted. Secondly, after effective selection has been practised and animals with superior genotypes exist in the flock, both the mean and variance of FEC decrease across the season, as illustrated in Figure 5. This results from both an increased immunocompetence of the selected animals and a consequent decreased reinfection rate.

After taking log transformations, the heritability of mean FEC in unselected animals in replicate 1 was 0·41, and the mean heritability for a single FEC was 0·19. These values dropped to 0·14 and 0·07, respectively, after 10 years of selection. The mean correlation between the three FEC measurements on which selection decisions were made was 0·25, in unselected animals.

Correlated responses to selection were also observed for worm burden and pasture larval contamination. Again, curvilinear responses to selection were apparent for both traits, and increasing the density dependent effects reduced the responses to selection. The relative reduction in worm burden was approximately half of that for mean FEC but the relative reduction in pasture larval contamination was almost as great as that for FEC.

Unlike the curvilinear responses in FEC, the responses to selection in the component traits of *establishment*, *fecundity* and *mortality* were essentially linear. Clearly, absolute responses are dependent on the assumptions made about the variability and

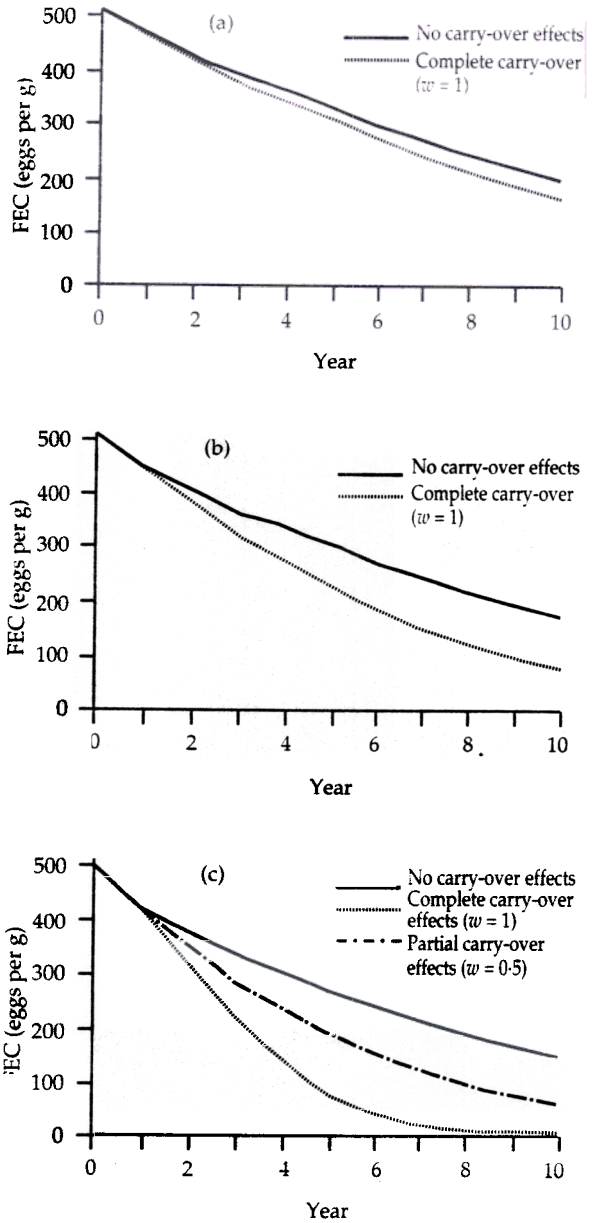

Figure 6 Carryover effects on selection response (a) for b = 0·5; (b) for b = –0·25; (c) for b = 0.

heritability for each component, however all three components will respond to selection on FEC provided that they show genetic variation during the time period the FEC measurements are being made. A more general observation was that imposing density-dependent effects on *fecundity* had a large effect on the other two components, significantly

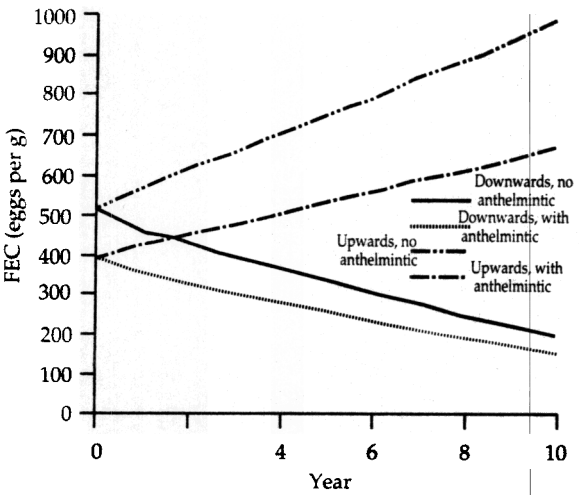

Figure 7 Comparison of divergent selection on faecal egg count (FEC) with and without anthelmintic treatment.

reducing the selection responses in *establishment* and *mortality*, yet it slightly increased the response in *fecundity*. This is explicable by the observation that such density-dependent effects will have the general effect of negating variation in other component traits. Consider *establishment*, the greater the value of this trait the greater the number of worms present in the host and hence the greater the impact of the density-dependent effect. A similar line of reasoning explains the sensitivity of mortality density-dependent effects. Food intake did not alter with selection for b = 0. However, the presence of density-dependent effects resulted in a small increase in food intake, as larval intake and total faecal output are proportional to intake but total egg output is modulated by the density-dependent effects.

The influences of carry-over effects between years in pasture larval contamination are presented in Figures 6a, 6b and 6c. With strong density-dependent effects (Figure 6a) the influence of carry-over effects on selection responses is small. It is only in the presence of weak or no density-dependent effects (Figures 6b and 6c) that the definition of carry-over effects becomes important. Clearly, the situation of L_0 being directly proportional to the previous season's pasture larval contamination gives unrealistic selection responses in the absence of density-dependent effects, however it is also unlikely that such integrity of pasture management could be maintained for several years on a farm containing a mixture of selected and unselected sheep, including periparturient ewes.

Consider selection during a rigorous anthelmintic treatment regime where the lambs are drenched immediately following the faecal sampling on days 90, 120 and 150 with a short-acting anthelmintic killing only adult worms resident in the sheep. The pattern of FEC for unselected animals under this scenario is shown in Figure 1 (for $b = -0.5$). Responses to selection for lambs under this treatment regime are shown in Figure 7, compared with those obtained for the same b value but with no drenching. The responses obviously differ, with lower mean FEC at all stages for the drenched flock of animals. However, the ratio of mean FEC in the drenched flock to that in the undrenched flock stays almost constant at 0·76 (±0·01), each year. Therefore, the nature of the response to selection for decreased FEC is unaffected by whether the animals are selected in a drenched or an undrenched environment. Moreover, the mean values for *establishment*, *fecundity* and *mortality* did not differ significantly between the two scenarios.

Also shown in Figure 7 are responses for selection for increased FEC, with and without anthelmintic treatment. These selection responses are linear, in contrast to the curvilinear responses for downwards selection. Only under the assumptions of no anthelmintic treatment and no density-dependent effects is a runaway epidemic predicted by the model.

The issue of whether the responses achieved in decreasing mean FEC were greater than predicted by quantitative genetic theory was addressed, firstly, using the equation $R = h^2S$, where S is the achieved selection differential. For generation 1 (replicate 1), the observed response was 1·72 times the expected response, using the heritability for untransformed mean FEC, and 1·67 times the expected response if the heritability of mean log-transformed FEC was used. Therefore, observed responses are considerably greater than expected, at least in early generations, indicating that selection has indeed altered the epidemiology of the disease.

The mean values for *establishment*, *fecundity* and *mortality* were also used to infer the relative contributions of genetics and epidemiology to the observed responses to selection in early and later generations. Consider results for $b = 0.0$, with no carry-over effects between years in larval contamination. Conceptually dosing unselected and selected animals with 1000 infective larvae results in approximately 119 eggs per g on day 21 for unselected animals and 55 eggs per g for selected animals. This is a genetic reduction to 0·46 of the original value, whereas the observed reduction was from 493 to 141, i.e. to 0·29. Therefore, after 10 years of selection, proportionately 0·76 of the reduction was genetic and 0·24 was due to the change in the environment. After 1 year of selection the relative contributions were 0·51 and 0·49, implying that the epidemiological effect was greater in the early years of selection, for the assumptions made in this example. Relating the initial larval challenge at the start of each season to pasture larval contamination from the previous season will increase the contribution of the epidemiological influences to the apparent selection responses.

Discussion

This paper has described a very general framework which enables individual animal variation in resistance to gastro-intestinal parasites to be modelled. This model has many potential uses, of which investigating responses to selection under different scenarios, as investigated here, is but one. No attempt has been made to make the model sophisticated from either a parasitological or host immunity viewpoint, as this has been successfully achieved by other authors (e.g. Gettinby *et al.*, 1989; Barnes and Dobson, 1990; J. A. Beecham *et al.*, unpublished data). Many of the published models describing parasite infections have been weather-based (Barnes and Dobson, 1990; Gettinby and Byrom, 1991) and have concentrated on how external factors affect parasite populations and hence likely infection rates. Some have also investigated selection for anthelmintic resistance in the parasite (Gettinby *et al.*, 1989; Barnes and Dobson, 1990). However, little attempt has hitherto been made to model specific interactions between the parasite and individual hosts within a population, as is done in this paper.

The performance of the model described in this paper is of course limited by the generality of the assumptions made. Between-animal variation in faecal egg count has been well described for a variety of host populations infected by a variety of parasites. Less well described, at the population level, are the component traits of *establishment*, *fecundity* and *mortality* as well as other important regulating factors such as density-dependent effects. Although some information is available to describe mean values of the component traits, little information is available on their variability between animals (including distributional properties), heritabilities, maternal effects (and their duration) and other repeatable sources of variation.

The results described in this paper will of course change as the assumptions regarding the component traits change with more experimental information. However, some properties which may be general have emerged.

First, a curvilinear response to selection is observed for FEC and to a lesser extent for true worm burden and pasture larval contamination. Responses to selection are initially large, then decline and become more linear. However, as described above, they are greater than predicted by quantative genetic theory. Density-dependent constraints appear to act to reduce selection responses, as they reduce between-animal variation for the traits under consideration. Reduced pasture contamination will benefit both the selected animals and also any unselected animals grazing the same pasture.

Secondly, the distribution of FEC becomes more aggregated over time. This is equivalent to the distribution becoming more skewed, resulting in selection differentials decreasing. However, as the distribution becomes more aggregated proportionately fewer animals are contributing a disproportionate number of eggs onto the pasture, hence culling of 'wormy' animals may become relatively more effective than in unselected animals. This possibility must be balanced by the relatively low repeatability of FEC within a season and requires further investigation. For selected animals, FEC also decreases within a season, this being a function of both an increased immunocompetance and lower resulting reinfection rates.

Thirdly, carry-over effects of pasture larval contamination from one year to the next have large effects on apparent selection responses in the absence of density-dependent effects but were largely cancelled out when strong density-dependent effects were present. These carry-over effects are perhaps the most difficult aspect of the system to model adequately and represent an area where this model could usefully interface with models describing animals management and the free-living stages of the parasite.

Finally, selection under regimes of no anthelmintic treatment compared with regular treatment results in different mean FEC values but similar patterns of response. Moreover, responses in the component traits (*establishment*, *fecundity* and *mortality*) are unaffected by the dosing regime.

Experimental verification of the results predicted by the model described in this paper are difficult to come by. Published selection experiments for reduced faecal egg count in sheep appear either to have offered sheep a fixed experimental dosage of larvae (e.g. Windon, 1990; Woolaston and Piper, 1996), or in the case of natural infections they have generally run divergently selected sheep together (Baker *et al.*, 1991). Whilst these are robust experimental protocols, they do not mimic selection under commercial conditions where the entire flock would be selected in the same direction and epidemiological factors would be important. It is this commercial situation that the model in this paper attempts to mimic. For these results to be predictive, however, the flock must remain closed or purchased sires and/or semen must come from equally resistant sources. A flock which allows importation of susceptible animals after several years of selection will negate some of the benefits of the several years worth of selection. Clearly, it is necessary to define circumstances under which epidemiological benefits are likely to be realized.

Although there appear to be no published experimental verifications of the epidemiological effects of selection, two simulation studies (Barger, 1989; Windon, 1990) have addressed this problem, comparing 'susceptible' and 'resistant' sheep using the model of Barnes and Dobson (1990). Both studies found that 'resistant' sheep had lower worm burdens which led to a markedly reduced pasture larval contamination, in broad agreement with the results in this paper. Moreover, the 'resistant' sheep required less anthelmintic intervention.

The results presented in this paper have general implications which are much wider than the simple situation of selecting sheep for resistance to worms, i.e. what are the epidemiological consequences of selecting domestic animals for resistance to infectious diseases? If the finding of an interaction between selection responses and the epidemiology of the disease in question is generally true, then the benefits of selecting for disease resistance relative to selecting for production traits will have been underestimated by animal breeders. This could have important consequences for future selection objectives. Clearly, there is a need to develop theory which combines genetics with epidemiology and enables us to predict such responses to selection. The arguments in this paper have been couched in terms of traditional selection techniques, however they will apply equally well to possible marker assisted selection. Therefore, results presented here further highlight the importance of mapping and utilizing disease resistance alleles in domestic animal populations.

Further work is required to verify and develop the results suggested in this paper. Numerous refinements can be made to parasitological and epidemiological aspects of the model or, alternatively, this model could be interfaced with other models which provide a more detailed description of animals' immune mechanisms, the parasite life cycle and environmental factors affecting it (e.g. those of Barnes and Dobson, 1990, and

Beecham *et al.*, 1994). Other problems of interest which should be addressed include (i) defining an optimal balance between the selection of resistant animals and the culling of 'wormy' animals, (ii) the incorporation of production traits into the model and (iii) consideration of the effect of selection on the required frequency of drenching which will influence the rate development of anthelmintic resistance amongst the parasite. Finally, as mentioned above, there is a need to develop a general theoretical framework linking quantitative genetics and epidemiology.

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