IMPACT OF IMPROVED HOST RESISTANCE ON WORM CONTROL IN MERINOS - A COMPUTER SIMULATION STUDY

SJ Eady[A], RJ Dobson[B] and EH Barnes[B]

[A]CSIRO Division Animal Production Armidale NSW 2350

[B]CSIRO Division Animal Production Locked Bag1 Blacktown 2148

Introduction

An evaluation of selection for host resistance to internal parasites cannot be performed in an environment independent of the life cycle of the infecting parasite. The overall effect of selection is a combination of both the direct influence of the sheep's immunity on worm burden as well as the subsequent reduction in levels of infective larvae on pasture. This makes field evaluation of progressive improvement in host resistance difficult because in most comparisons of resistant and random-bred sheep the two flocks are run together as one management group.

The drench requirements and productivity of lines of sheep divergent for resistance are being evaluated under field conditions at Armidale, NSW (Woolaston, Barger and Eady unpublished), Hamilton, Vic (Cummins unpublished) and in New Zealand (Bisset unpublished) and the results from these field trials may indicate the long term impact of breeding for resistance on worm control strategies. However, they cannot be used to predict the change in treatment that will occur over time as a normally susceptible flock increases in resistance with selection.

A complementary approach to field studies is to simulate the systems that are operating. This has been done for the relationship between sheep and *Trichostrongylus colubriformis* (Barnes and Dobson[1]). The Worm World (WW) model integrates current knowledge of the survival and development of the free-living stages of *T. colubriformis* (Barnes *et al.*[2]), establishment and survival of incoming larvae as a function of infection rate and host age (Dobson *et al.*[3]), worm fecundity (Barnes and Dobson[4]), genetics of anthelmintic resistance in the worm (Dobson *et al.*[5]) and distribution of the worm population within a flock (Barger[6]). Using this information the worm population is simulated in response to meteorological conditions, drenching, grazing management and acquired host immunity.

The WW model has been used to examine the epidemiological consequences of having a flock of resistant lambs as a result of either selective breeding or vaccination (Barger[7]). However, these simulations started with "resistant" sheep rather than simulating the gradual change in immune response that would occur over a number of years in a breeding program.

Modifications can be made to WW to enable host resistance to increase with time, in proportion to predicted genetic change in faecal egg count (FEC) from selection. The hypothesis tested is that, with selection, the number of anthelmintic treatments given to young sheep can be reduced without compromising the productivity of the animals. This paper describes modifications of the WW model to simulate improved immunity and describes the outcomes of the simulation in terms of reduced anthelmintic treatment and level of infective larvae on pasture.

Materials and methods

The WW model was used to simulate the host-parasite relationship between sheep and *T. colubriformis*, to predict the number of anthelmintic treatments required by selected sheep in order that they achieve a similar level of production to that seen in random-bred sheep on Wormkill (Dash[8]). A comparison of number of deaths was also made for random-bred and selected sheep.

The climatic data used for the simulation was from Armidale, on the New England Tablelands in NSW. The simulation ran for 20 years using weather data for the period 1959-1976, with the weather data from 1959 and 1960 used twice (in years 1 and 2 and years 19 and 20 of the simulation). Ten "replicate" simulations of selected and unselected sheep were run by commencing weather data in years 1, 3, 5 ...19.

The simulation comprised two management groups, the first being breeding ewes (plus lambs) and the second their offspring after weaning. Groups compared were young sheep, born on 15 September, from 7 weeks of age through to 12 months of age. Anthelmintic treatment in young sheep comprised 3 drenches, on 22 December, 22 February and 24 April, as per the recommendations of Wormkill. The ewe flocks received anthelmintic treatment on 31 August and 22 December in all years of all simulations and their anthelmintic requirements and worm burdens were not compared. There was no decrease in the efficiency of anthelmintic treatment over time. In the first year ivermectin was used and in the second year a benzimidazole + levamisole combination was used. This two year drench rotation was repeated throughout the simulation.

To simulate the selection response for decreased FEC, the parameters given in Table 1 were all simultaneously changed in proportion to predicted selection response for log FEC. The model also included a stress period associated with weaning and this was reduced with selection with a target value of zero.

Table 1 Resistance parameters changed

Parameter	Description	Initial value	Target value
Y_o	Proportion of larvae that establish in helminthologically naive sheep.	0.65	Determined by Pt
Pt	Proportional return to Y_o when immune response is impaired.	1.0	0.48
TWB	Threshold level of adult worm burden per sheep to trigger host immune response.	3532	1695
MINAGE	Age (wks) at which the host's capacity to develop resistance changes most rapidly.	18.76	9.00
L	Lower limit for proportion of adult worm establishment in resistant sheep.	0.10	0.048
f_{max}	Potential maximum egg production per female worm (eggs/d).	783	376
a	Proportional reduction in eggs (day^{-1}).	-0.05	-0.07

The effect of these parameter changes on FEC was validated against changes in FEC observed in flocks selected for low FEC. The model used a target value for each parameter to move towards and each target value was set as the lower value for the 99% confidence interval (where a decrease in the parameter indicated improved resistance). The assumption was made that all parameters had a coefficient of variation of 20% and from this the lower value confidence interval was calculated.

The response in log FEC was predicted from:-
Response = $((i_m + i_f) / (a_m + a_f)) \times h^2 \times \sigma_P$
i_m = selection intensity for rams
i_f = selection intensity for ewes
a_m = average generation length for rams (years)
a_f = average generation length for ewes (years)
h^2 = heritability of log FEC
σ_P = phenotypic variance for log FEC

Five percent of rams and 70% of ewes were selected for breeding. Selection intensities were calculated by the model (Linden[9]). The average generation length was 2.4 years and 3.99 years for rams and ewes, respectively. Heritability of 0.3 was assumed for log FEC. The phenotypic variance for log FEC was estimated by the model from the mean FEC and acquired flock immunity.

FEC was the sole trait under selection. The criterion for culling was a mean FEC of 500 epg when the sheep were between 3 and 14 months of age. No selection occurred if 500 epg was not reached. After meeting this requirement the response in log FEC (as a percentage of the mean at the time of selection) was calculated. This figure was used to calculate the proportional reduction in the parameters in Table 1. Each parameter was reset for the rest of the simulation. The next round of selection then further reduced the parameter values.

Young sheep (random-bred on Wormkill v's selected) were compared on the basis of the number of weeks for which adult worm burden exceeded 5000 worms. Deaths were predicted by the model. A drench program for selected sheep was formulated by an iterative procedure to give a similar number of weeks for which the adult worm burden exceeded 5000. Drenches were progressively removed commencing with the last and working back to the first in the Wormkill program. Removing earlier drenches first was investigated but not in a systematic manner.

Results

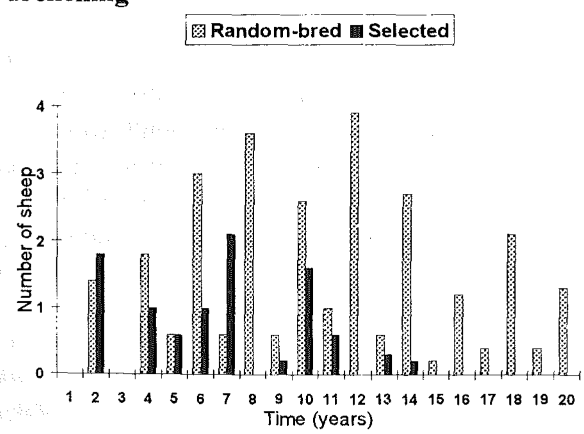
The number of drenches required each year is given in Table 2. The WW simulation predicted that the earliest a drench could be removed from the Wormkill program is in year 9 of selection (Table 2), the earliest drenching could cease is in year 13. In all replications drenching had ceased by year 19 of selection. Worm burdens in excess of 5000/sheep were minimised when the drenches were removed in the following order - April, Feb then December i.e.drenches at an older age first.

Table 2 Drenches required for resistant sheep

Yr	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Rep 9	Rep 10
1	3	3	3	3	3	3	3	3	3	3
2	3	3	3	3	3	3	3	3	3	3
3	3	3	3	3	3	3	3	3	3	3
4	3	3	3	3	3	3	3	3	3	3
5	3	3	3	3	3	3	3	3	3	3
6	3	3	3	3	3	3	3	3	3	3
7	3	3	3	3	3	3	3	3	3	3
8	3	3	3	3	3	3	3	3	3	3
9	3	3	3	3	3	3	3	3	3	2
10	2	3	3	3	2	3	3	3	3	2
11	2	2	2	3	1	3	2	3	3	2
12	1	2	1	1	1	3	1	3	2	2
13	1	2	0	1	0	3	1	2	0	1
14	1	1	0	1	0	2	1	1	0	1
15	0	1	0	0	0	2	1	0	0	1
16	0	0	0	0	0	2	0	0	0	0
17	0	0	0	0	0	1	0	0	0	0
18	0	0	0	0	0	1	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0

Deaths (averaged over all replicates) for random-bred and selected sheep are shown in Figure 1.

Figure 1 Deaths in random-bred sheep on Wormkill and selected sheep with reduced drenching



Deaths in the random-bred sheep exceeded those for selected sheep in all but year 2 and 7. There were no deaths in the selected sheep after year 14. Total deaths over the 20 years averaged 28 and 9 for random-bred and selected sheep, respectively.

Mean larval contamination on the paddock into which lambs were weaned is shown in Figure 2 for random-bred and selected sheep. A marked downward trend in L3/kg herbage dry matter was evident in the simulations with sheep selected for resistance.

Figure 2 Weaner paddock L_3 contamination

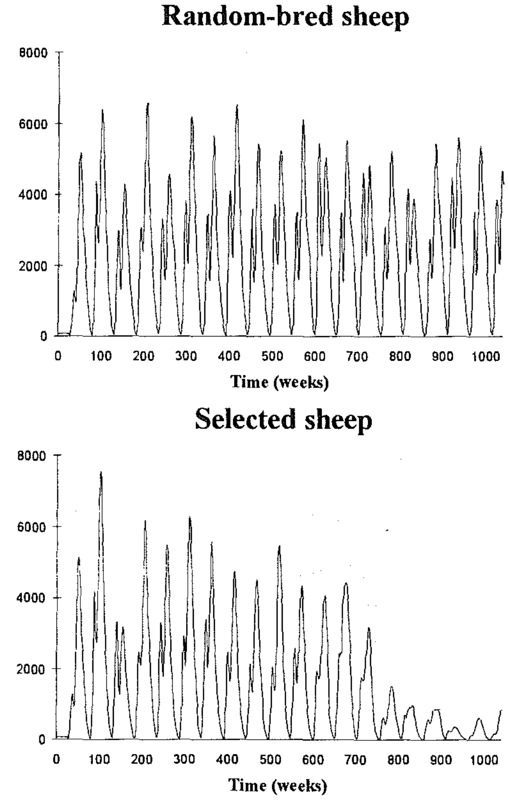


Table 3 shows the years in which the selection criterion (flock mean FEC>500 epg) was reached.

Discussion

The results from the WW simulations suggest that it is feasible to reduce the number of drenches that are required to control worms in sheep selected for resistance. In addition there may be added benefits in terms of reduced mortality. The results also indicate that selection may not need to be continued once a certain threshold of resistance and larval contamination is reached. As with the studies reported by Barger[7] the resistant sheep had lower worm burdens and FECs resulting in lower larval contamination on pasture.

In terms of minimising production losses, the most successful outcome for reducing the number of drenches resulted from removal of drenches at an older age first. This outcome is logical given that immune response is age dependent, the older sheep having greater resistance to worm establishment and fecundity. As immune response strengthened egg counts fell to the extent where the average FEC of 500 epg was not reached and selection ceased at approximately year 15, thus indicating that over a 20 year period 100% selection emphasis for FEC was not essential. Selection was solely for low FEC, which is unlikely to be feasible in practice because of the economic importance of other traits. Simulations using a lower selection pressure are warranted to give a more realistic picture of what may happen in a commercial Merino flock.

Table 3 Years in which sheep were selected

Yr	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Rep 9	Rep 10
2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
9	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
11	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
13	✓	✓	✓	✓	✓	✓		✓	✓	✓
14	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
15	✓		✓			✓		✓	✓	✓
16						✓	✓	✓		
17							✓			
18							✓			
19										
20										

The genetic and phenotypic correlations between FEC and Merino production traits (fibre diameter, fleece weight, body weight and number of lambs weaned) are generally neutral (Eady unpublished) which means FEC can be included in a breeding objective without causing unfavourable correlated responses in these traits. However, the inclusion of a new trait results in loss of selection pressure for other traits. In a commercial ram breeding enterprise achieving 50% of the possible gain in FEC reduces improvement in production merit by approximately 13%, while 70% of possible gain in FEC reduces production merit by 29% (Pocock *et al.*[10]). It is feasible to include FEC in a breeding objective and this is being undertaken by a number of ram breeders in the Merino industry.

It must be recognised that reduced larval contamination on pasture grazed by selected sheep made an important contribution to the lower worm burden and need for fewer drenches in these sheep. This is in addition to the improvement in host immune response preventing establishment of incoming larvae. Should the resistant sheep be moved from their "home" paddocks into paddocks with a normal level of contamination, then it may be necessary to resume drenching for adequate worm control until such time as the resistant sheep are able to reduce the level of infective larvae. However, reversion to a nil drench situation should occur more rapidly than observed in these simulations as the sheep would be more resistant.

The simulations did not allow for any changes in the fitness of the worm population, either in terms of developing anthelmintic resistance or increasing virulence in response to improved host immunity. The issue of increasing anthelmintic resistance needs to be addressed as this is the driving force behind many breeders embarking on selection for resistance. Escalating anthelmintic resistance in the worm population is likely to increase the advantage of resistant genotypes over random-bred sheep. WW has the capacity to model the frequencies of genes for anthelmintic resistance in the worm population, and further simulations investigating the impact of such worm selection are warranted.

Conversely, increased virulence of the parasite, as a response to improved host immunity, has the potential to reduce benefits that may arise from host selection. However, with sheep and their nematode parasites there has been little evidence to suggest this will occur. Studies designed to monitor worms bred in resistant or susceptible lines of sheep for 14 (Woolaston *et al.*[11]) and 29 generations (Woolaston unpublished) have shown no divergence in reproductive fitness in the worms. Based on these results including changes in parasite virulence in the model is not indicated.

The results from the simulations reported here should be viewed as preliminary for a number of reasons. The only parasite population simulated was *T. colubriformis* and the matching of productivity for random-bred sheep and selected sheep was on the basis of the total number of weeks during which adult worm burdens exceeded 5000. This trait was chosen as there is experimental evidence that production in young sheep is not compromised until the adult worm burden exceeds 5000 (Major and Royal[12]; Steel *et al.*[13]). There is little information available on how production is further compromised as the burden increases over 5000 or how consecutive weeks of greater than 5000 worms effect production compared to isolated weeks. There is some experimental evidence to suggest which parameters in the model should be varied with increasing host resistance (Dineen and Windon[14]; Dobson *et al.*[15]; Gray *et al.*[16]) but little is known about the relative changes, with selection, in the biological characteristics described by these parameters.

Conclusions

Results from these simulations are encouraging, predicting that selection for low FEC will over a 10-15 year period lead to reduced reliance on anthelmintics for worm control. However, there remains a tremendous body of work to be done to validate the changes made to the parasitological and host immunity parameters in the WW model. Then the evaluation of selection strategies and the management of resistant animals can be investigated with more confidence. The use of the WW simulation model will be critical to gaining some understanding of how breeding for worm resistance will interact with the epidemiology of the disease.

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References

1 Barnes EH and Dobson RJ Population dynamics of *Trichostrongylus colubriformis* in sheep: computer model to simulate grazing systems and the evolution of anthelmintic resistance *International Journal for Parasitology* 1990; 20: 823-831

2 Barnes EH, Dobson RJ, Donald AD and Waller PJ Predicting populations of *Trichostrongylus colubriformis* infective larvae on pasture from meteorological data *Int J Parasit* 1988; 18: 767-774

3 Dobson RJ, Donald AD, Barnes EH and Waller PJ Population dynamics of Trichostrongylus colubriformis in sheep: model to predict the worm population over time as a function of infection rate and host age. *Int J Parasit* 1990; 20: 365-373

4 Barnes EH and Dobson RJ Population dynamics of Trichostrongylus colubriformis in sheep: mathematical model of worm fecundity *Int J Parasit* 1990; 20: 375-380

5 Dobson RJ, Griffiths DA, Donald AD and Waller PJ A genetic model describing the evolution of levamisole resistance in *Trichostrongylus colubriformis*, a nematode parasite of sheep. *IMA J Math App Med & Biol* 1987; 4: 279-293

6 Barger IA The statistical distribution of trichostrongylid nematodes in grazing lambs *Int J Parasit* 1985; 15: 645- 649

7 Barger IA Genetic resistance of hosts and its influence on epidemiology *Vet Parasit* 1989; 32:21-35

8 Dash KM Control of helminthosis in lambs by strategic treatment with closantel and broad-spectrum anthelmintics. *Aust Vet J* 1986; 63: 4-8

9 Linden D Short note: An approximate formula for selection intensity *Silvae Genetica* 1986; 35:249

10 Pocock MJ, Eady SJ and Abbott KA Nemesis in action - breeding for worm resistance *Proceedings Aust Assoc Anim Breed Genet* 1995; 11:74-78

11 Woolaston RR, Elwin RL and Barger IA No adaptation of Haemonchus contortus to genetically resistant sheep *Int J Parasit* 1992; 22:377-380.

12 Major GW and Royal WM Anthelmintic treatment of ewe and lamb in relation to parasitism and production *Proc Aust Soc Anim Prod* 1974; 10: 174-178

13 Steel JW, Symons LEA and Jones WO Effects of level of larval intake on the productivity and physiological and metabolic responses of lambs infected with Trichostrongylus colubriformis *Aust J Agric Res* 1980; 31:821-838

14 Dineen JK and Windon RG The effect of acquired resistance on adult worms of *Trichostrongylus colubriformis* in lambs *Int J Parasit* 1980; 10: 249-252

15 Dobson RJ, Waller PJ and Donald AD Population dynamics of *Trichostrongylus colubriformis* in sheep: the effect of host age on the establishment of infective larvae *Int J Parasit* 1990; 20: 353-357

16 Gray GD, Presson BL, Burgess SK and Adams DB Responses of genetically resistant Merino lambs to artificial and naturally acquired infections of Haemonchus contortus *Final Report of Project UNE 12P WRDC* 1992; pp 1-9