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Economic management of anthelmintic resistance: model and application*

Caris L. Pech, Graeme J. Doole and Johanna M. Pluske[†]

The increasing prevalence of anthelmintic (drench) resistance in gastrointestinal parasite populations is decreasing the profitability of the Australian sheep industry. Refugia management can delay its development by not exposing a proportion of the worm population to chemical control. A dynamic-optimisation model is used to assess the economic value of refugia for management of the worm species *Teladorsagia circumcincta* and macrocyclic lactone drenches in an application to Western Australian sheep flocks. A low rate of refugia (2 per cent) is most profitable under standard circumstances because it slows the development of resistance, but also reduces the proportion of the flock not exposed to chemical control. Frequent drench application should remain the primary method of control. However, its efficacy should be preserved through refugia management, rather than greatly reducing treatment frequency.

Key words: anthelmintic resistance, dynamic optimisation, gastrointestinal parasites.

1. Introduction

The viability of the Australian sheep industry is under threat as chemical control of gastrointestinal parasites (worms) becomes less effective with the increasing development of anthelmintic resistance. An anthelmintic, or drench, is a chemical that is used to treat infections caused by parasitic intestinal worms. Hence, anthelmintic resistance is a ‘genetically determined decline in the efficacy of an anthelmintic against a population of parasites that is generally susceptible to that drug’ (Sangster and Gill 1999, p. 141). The major cause of resistance development in Australian sheep flocks is excessive treatment frequency (Besier and Love 2003). Anthelmintics are generally regarded as providing the most cost-effective control of parasite

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populations. However, the annual cost of worms in Australia is estimated to reach \$700 million by 2010 given the sustained increase in the development of resistance (Welsman 2001).

In many cases, producers can benefit from implementing parasite management programs that consider cost effectiveness and the implications of resistance development. The integration of non-chemical methods of worm control into these programs can delay the development of resistance and/or permit the control of resistant worms. Available practices include biological control of nematode larvae, nutrition supplements and refugia (Besier and Love 2003). *Refugia* involves not exposing a proportion of the parasite population to anthelmintic treatment, thus preventing selection pressure for resistance (Van Wyk *et al.* 2006). Effective biological control of worms is presently not viable on a commercial scale. Moreover, nutrient supplementation is expensive in Western Australia, particularly in extensive farming systems. In contrast, refugia is easy to implement on-farm and appears a practical means of slowing the development of resistance (Van Wyk *et al.* 2006; Hughes *et al.* 2007).

The primary objective of this study is to investigate the optimal economic management of anthelmintic resistance in sheep flocks, with application to Western Australian conditions. This study focuses solely on refugia as a complementary strategy to chemical control because there is little understanding pertaining to its profitability. This is important as there is practical and scientific evidence highlighting its capacity to delay resistance in other farming environments (Besier and Love 2003; Hughes *et al.* 2007). A key focus is to evaluate the pattern of drench application that occurs across time under profitable management given the link between treatment frequency, use of refugia and resistance development. A dynamic-optimisation model is used to investigate the intertemporal value of refugia, which is difficult to estimate using field trials. This study appears to be the first economic analysis of the management of anthelmintic resistance, and provides valuable insight into the importance of non-chemical strategies of parasite control.

The paper is organised as follows. Section 2 outlines the development of the dynamic numerical model used in the study. Section 3 reports and discusses the results of the research. Section 4 outlines the key conclusions of this study.

2. Model

2.1 Model description

This section describes a dynamic-optimisation model to assess the economic value of refugia in sheep flocks. The model is implemented in Microsoft Excel[®] (Microsoft Corporation, Redmond, WA, USA) and an optimisation algorithm is used to identify the most-profitable pattern of drench use over time subject to different refugia strategies. The model analyses a single hectare of a field on an Australian sheep farm. Whole-farm factors can be important

in agricultural decision making, but are ignored in this model to sharpen the focus on the intertemporal problem of anthelmintic resistance. The equations describing the dynamic evolution of a worm population in Kao *et al.* (2000) are extended to incorporate anthelmintic use in the framework.

The model focuses on the worm species *Teladorsagia (Ostertagia) circumcincta*, as it is the main gastrointestinal parasite species affecting sheep in Western Australia, and resistance to two or more active ingredients of anthelmintics (i.e. multiple resistance) is evident on the overwhelming majority of farms in the State (Besier and Love 2003). Macrocyclic lactones (MLs) are the drench group represented in the model because they are the most-recently developed and commonly used anthelmintic class in Australia. Initial rates of resistance in the model are low (2 per cent), in accordance with field conditions.

In line with previous studies (e.g. Kao *et al.* 2000), the model is focussed solely on a flock of representative sheep younger than 12 months of age. In the model, the representative lambs are born at the same time at the beginning of each year and are then sold at the end of the year. The model is defined over 10 years ($y = [1, 2, \dots, 10]$) and in each year there are six periods ($t = [1, 2, \dots, 6]$) at which drenches may be used. These correspond to 98, 119, 140, 168, 196 and 256 days after the birth of the lamb. Ninety-eight days corresponds to weaning under traditional management of sheep flocks in Western Australia. Drenching times are fixed to correspond to standard use by producers.

Anthelmintic resistance is inherited in a given worm population and reversion or loss of resistance is never observed once it has entered a population (Sangster and Dobson 2002). Refugia slows the development of resistance by conserving susceptible individuals in the worm population to dilute the presence of genes conferring resistance to chemical control (Van Wyk *et al.* 2006). This slows resistance development, but also increases the worm burden in the flock, decreasing livestock production. In this study, the term refugia is used to describe the proportion of sheep not exposed to the anthelmintic (i.e. refugia in the host).

Two decision variables represent management actions that influence the worm population:

1. $u_{t,y}^1$ is a binary variable representing anthelmintic use at time t in year y .
2. u^2 represents the proportion of the sheep flock not exposed to the anthelmintic. This refugia is maintained at a constant intensity over the entire planning horizon.

The level of refugia in each model run is defined exogenously. Four possible rates of refugia are simulated: 0, 2, 5 and 10 per cent. These represent the proportions of the sheep population not exposed to the anthelmintic. Drench effectiveness declines as the number of doses of the anthelmintic applied over the planning horizon increases. However, the rate of decline depends upon the intensity of the refugia maintained by the producer. It is assumed that the host is a typical sheep and the model represents 1 ha of a farm. It is thus

problematic to define refugia in terms of the number of sheep not exposed to chemical control. Therefore, a refugia rate of n per cent is represented by reducing drench application to each sheep by n per cent. For example, the effectiveness of a given drench application is reduced by 10 per cent if a 10 per cent refugia strategy is selected.

The worm population in the model is described by two state variables:

1. $L_{t,y}$ is the density of infective nematode larvae on the pasture at time t in year y .
2. $A_{t,y}$ is the mean number of adult nematodes per host at time t in year y .
The state variable A is reset to zero at the beginning of each year with the introduction of new stock onto the field.

The evolution of the worm population is determined by a set of two inter-dependent relationships (Figure 1). The density of infective worm larvae on the pasture at any one time is determined by:

$$L_{t+1,y} - L_{t,y} = -(\rho + \beta \cdot H) \cdot L_{t,y} + q \cdot \lambda \cdot H \cdot A_{t,y}, \tag{1}$$

for $t = [1,2,\dots,5]$, $y = [1,2,\dots,10]$, $L_{1,1} = L_0$, $L_{1,y} = S \cdot L_{6,y-1}$ for $y \neq 1$, and $L_{6,10}$ free, where ρ is the rate at which larvae are lost from pasture because of reasons other than host ingestion (e.g. natural mortality), β is the rate at which larvae are eaten by a single host animal, H is the host population density (i.e. stocking rate), q is the probability that an egg develops into an infective larvae, λ is the mean rate at which an adult parasite produces eggs, L_0 is the initial worm larvae population on the pasture and S is the survival rate of worms over summer.

The mean number of adult worms per host at any one time is:

$$A_{t+1,y} - A_{t,y} = d \cdot \beta \cdot L_{t,y} - \mu \cdot A_{t,y} - (1 - u^2) \cdot A_t \cdot f(u^2) \cdot u_{t,y}^1, \tag{2}$$

for $t = [1,2,\dots,5]$, $y = [1,2,\dots,10]$, $A_{1,y} = 0$, and $A_{6,10}$ free, where d is the probability that an ingested larvae develops into an adult parasite, μ is the natural mortality rate of adult parasites and $f(u^2)$ denotes the efficacy of the anthel-

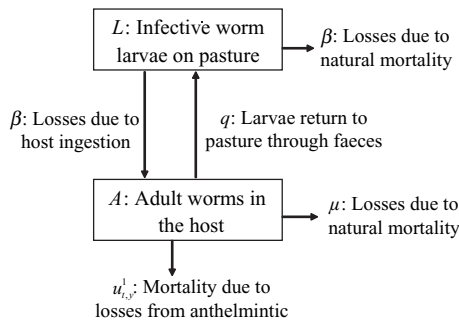


Figure 1 Diagrammatic representation of the state equations describing the evolution of the worm population.

mintic as a function of the rate of refugia adopted by the farmer. Worms in refugia prolong the use of anthelmintics by slowing the development of resistance; this is described in $f(u^2)$. However, as a proportion of the worm population is not exposed to treatment, larger worm numbers are present in the typical sheep. Accordingly, the cost of using refugia is represented by the increase in worm burden in the sheep. This enters Equation (2) through the term $1 - u^2$.

The objective of the producer is assumed to be the minimisation of costs arising from production losses because of worm burden and the cost of drench application. Thus, the objective function of the model is:

$$\min_{u_{t,y}^1} C = \sum_{y=1}^{10} (1+r)^{-y} \sum_{t=1}^6 [(1-p(A_{t,y})) \cdot l(A_{t,y}) \cdot e + p(A_{t,y}) \cdot e \cdot w + (1-u_2) \cdot c \cdot u_{t,y}^1] H, \quad (3)$$

where C is the total cost in dollars, r is the discount rate, $p(A_{t,y})$ is the probability of sheep mortality occurring because of a high worm burden, $l(A_{t,y})$ is the reduction in host liveweight because of the adult worm burden present in the host, e is the value of lamb specified per kilogram, w is the maximum possible carcass weight of a lamb and c is the cost of the anthelmintic. Each component of the objective function may be explained as follows. First, the term $(1+r)^{-y}$ is a standard discount factor representing the intertemporal aspect central to the economic analysis of resistance development. Second, the $(1-p(A_{t,y})) \cdot l(A_{t,y}) \cdot e$ component represents the cost of liveweight reduction because of the worm burden that exists in live sheep. Third, the term $p(A_{t,y}) \cdot e \cdot w$ is the cost associated with sheep dying at high worm burdens. Last, the $(1-u_2) \cdot c \cdot u_{t,y}^1$ component represents the cost of drench application adjusted for a given level of refugia to reflect the decrease in the proportion of the flock not exposed to the anthelmintic. Overall, the terms in the square brackets in Equation (3), therefore, describe the cost per lamb because of worm burden and drench application. Thus, to determine the cost of parasites per hectare, this term is multiplied by the host population density (H).

The optimisation problem faced by the producer is consequently:

$$\min_{u_{t,y}^1} C = \sum_{y=1}^{10} (1+r)^{-y} \sum_{t=1}^6 [(1-p(A_{t,y})) \cdot l(A_{t,y}) \cdot e + p(A_{t,y}) \cdot e \cdot w + (1-u_2) \cdot c \cdot u_{t,y}^1] H, \quad (4)$$

subject to:

$$L_{t+1,y} - L_{t,y} = -(\rho + \beta \cdot H) \cdot L_{t,y} + q \cdot \lambda \cdot H \cdot A_{t,y}, \tag{5}$$

for $t = [1, 2, \dots, 5]$ and $y = [1, 2, \dots, 10]$,

$$A_{t+1,y} - A_{t,y} = d \cdot \beta \cdot L_{t,y} - \mu \cdot A_{t,y} - (1 - u^2) \cdot A_t \cdot f(u^2) \cdot u_{t,y}^1, \tag{6}$$

for $t = [1, 2, \dots, 5]$ and $y = [1, 2, \dots, 10]$,

$$L_{1,1} = L_0, \tag{7}$$

$$L_{1,y} = S \cdot L_{6,y-1} \text{ for } y \neq 1, \tag{8}$$

$$A_{1,y} = 0, \text{ and} \tag{9}$$

$$A_{6,10} \text{ and } L_{6,10} \text{ free.} \tag{10}$$

2.2 Parameter estimation

The model from Section 2.1 is applied to a representative Western Australian example in this paper. This section describes the parameters used in this application.

2.2.1 Biological parameters

The standard biological values specified for each parameter in the analysis are for lambs and *T. circumcincta* populations in Western Australia (Table 1). Data of this nature for Western Australia is rare, so where it is unavailable,

Table 1 Definition and values used for model parameters

Parameter	Definition	Value	Source
ρ	Rate at which larvae are lost from pasture because of reasons other than host ingestion	0.025/day	Rounded mean from Paton <i>et al.</i> (1984) and Donald <i>et al.</i> (1978)
β	Rate at which larvae are eaten by a single host animal	4 m ² /day	Kao <i>et al.</i> (2000)
H	Host population density	10/ha	C. L. Pech (unpublished data)
q	Probability that an egg develops into an infective larva	0.0275	Mean rate from Callinan (1978)
λ	Mean rate at which an adult parasite produces eggs	54 eggs/worm/day	Gruner <i>et al.</i> (2004)
D	Probability that an ingested larva develops into an adult parasite	0.48	Barger (1989)
μ	Mortality rate of adult parasites	0.03/day	Hong <i>et al.</i> (1986)

data has been drawn where possible from studies of sheep-farming systems in regions that also possess a Mediterranean climate characterised by hot summers, mild winters and concentration of rainfall in winter (Hutchinson *et al.* 2005). In particular, it is important to note the high average rate of daily egg production by an adult parasite (λ) in Table 1, as this highlights the potential for rapid population expansion if an appropriate worm control program is not sustained.

The correlation between anthelmintic efficacy and previous use plays a key role in determining the optimal management of resistance across time. Nevertheless, this relationship is difficult to estimate given a lack of appropriate experimental data that precludes the estimation of appropriate regression functions. Accordingly, it is necessary to use a rather heuristic method to formulate an appropriate response function and explore the implications of alternative relationships in sensitivity analysis (see Section 2.4).

In the model, resistance to a given anthelmintic is assumed to be determined by a single major gene comprising two alleles at a single autosomal locus. This assumption follows other models of resistance development in intestinal parasite populations (e.g. Smith *et al.* 1999). Dobson and Besier (2004) estimated that the resistant (R) allele in *T. circumcincta* populations increases by 9.37, 3.83 and 1 per cent for 0, 2 and 10 per cent refugia rates, respectively, for the ML drench group. An approximate increase of 2.5 per cent is also determined for a 5 per cent level of refugia through linear interpolation between those functions specified for the 0 and 2 per cent refugia rates. This process is inexact, but it is required because of a lack of alternative information and a motivation to extend the results of the analysis to incorporate greater levels of refugia.

The form of the function used (δ) is $\delta = 1 - (1 + i) \sum_{t=1}^{t^*} \sum_{y=1}^{y^*} u_{t,y}^1$, where i is the percentage increase in the resistance allele described above and the nested summation terms define the total use of anthelmintics up to time period t^* in year y^* . The corresponding functions delineating the relationship between anthelmintic effectiveness and drench use are presented for various refugia rates in Figure 2. For each unit increase in the total number of drench applications, the resistance present in the worm population increases by a specified percentage. As resistance is assumed to be dominant, this results in a proportionate decline in anthelmintic effectiveness. Figure 2 displays the substantial capacity for refugia to slow the onset of resistance and that increasing, non-zero rates of refugia lead to small marginal increases in drench effectiveness.

The initial condition in the base model is 250 000 worm larvae per hectare on the pasture (i.e. $L_0 = 250\ 000$). This represents a standard density of *T. circumcincta* under Western Australian conditions.

Callinan (1978) found that very low levels of *T. circumcincta* survive over summer in dry areas, such as Western Australia. Thus, it is assumed that only 2.5 per cent of worms survive over summer in the model ($S = 0.025$).

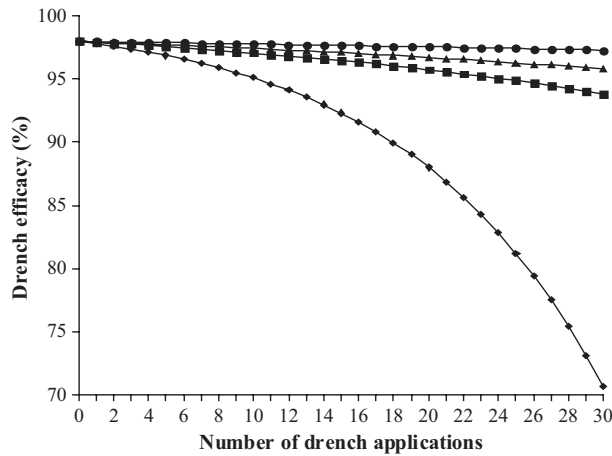


Figure 2 Drench effectiveness at (♦) 0, (■) 2, (▲) 5 and (●) 10 per cent refugia.

2.2.2 Impact of worm burden on host production

Estimation of a relationship between sheep production and worm burden, represented in the objective function as $l(A_{t,y})$, consists of two stages: (i) estimating the relationship between worm burden and feed intake, and (ii) calculating the relationship between reduction in feed intake and liveweight loss. Parasitic infection affects the host by reducing liveweight that, in severe cases, can result in host mortality. The economic effects on wool production are negligible in lambs given their low yields.

The effect of worm burden on the host's feed intake is calculated according to the method proposed by Barnes and Dobson (1990). Firstly, the number of *T. circumcincta* worms in the host is converted to *Trichostrongylus colubriformis* equivalents (TTE) using the standard rule $TTE = 2 \times T. circumcincta$. The maximum food intake for lambs is assumed to be 2 kg/head/day (Pluske and Schlink 2008). If the adult worm burden per host is less than 1000, there is no change in feed intake. As a sheep's worm burden increases from 1000 to 81 000, its food intake (z) decreases linearly from 100 to 33 per cent of the maximum intake for sheep of that age. This is defined through $z = 2.048 - 0.3493 \cdot \log_{10}(A_{t,y})$ (Barnes and Dobson 1990). For worm burdens greater than 81 000, feed intake is 33 per cent of assumed food intake. The relationship between sheep liveweight and feed intake is determined using the model of Pluske and Schlink (2008).

In severe cases of worm infection, feed intake declines to extremely low levels, resulting in host mortality. This process is incorporated using the method of Barnes and Dobson (1990). The worm burden at which all sheep die in the model is 50 000 adult worms per host (Barnes and Dobson 1990).

2.2.3 Economic parameters

This section describes the sources of the other parameters in the objective function of the model. The liveweight of a lamb with no worm burden is

37 kg. Hence, this is the maximum potential size of a sheep in the model. Liveweights are converted to carcass weights in the model to calculate the economic losses accruing to liveweight loss and mortality from worm burden. Carcass weight is assumed to be 44 per cent of liveweight. Accordingly, the maximum carcass weight of a lamb in the model at 252 days is 16.28 kg. Lamb carcasses were valued at \$3.29/kg in September 2008 (Australian Bureau for Agricultural and Resource Economics 2008); this is used as the base value in the model. Thus, with no worm burden, the maximum value of a lamb is \$53.56/head. Each dose of the ML drench costs \$0.15 for a 37 kg lamb (Department of Agriculture and Food Western Australia 2008). This cost is incurred if drenching is used in a given period and there is no refugia. A standard discount rate of 0.05 is used.

2.3 Solution process

Drench use in each time period is optimised for a given refugia level. Optimisation of the 60 binary variables (there are six potential drenching times over a planning horizon of 10 years) depicting anthelmintic use is undertaken using a genetic algorithm (GA) (Fogel 2006). The Palisade Decision Tools Evolver 5.0 (Palisade Corporation, Ithaca, NY, USA) (Nersesian 2000) is used to implement the GA in the Microsoft Excel[®] model. Optimal solutions are identified as those estimates of the optimal configuration that have not changed for 10 000 generations of the GA. The terminal condition placed on the model is $L_{1,1} \geq L_{6,10}$. This constraint ensures that the level of worm infestation at the end of the horizon is similar to its initial severity. The population of solutions maintained in the GA consists of 2000 individuals. Parameters describing the characteristics of the evolutionary process are identified within the algorithm, as these are difficult to estimate *a priori*. Each model scenario is solved five times as the model is guided by random processes and is too large for the GA to guarantee the identification of the single-best solution. This occurs because there are 2^{60} possible solutions in every scenario. The solution reported for each scenario is that with the lowest overall cost, as determined by Equation (3), found in the five runs. The solution space is so large that a global optimum cannot be identified within a practicable period of time. Thus, some minor irregularities not consistent with primary trends are occasionally observed.

2.4 Sensitivity analysis

Sensitivity analysis identifies how optimal solutions change in response to perturbations in the nominal data (e.g. drench price). The input scenarios explored, other than that concerning the rate of resistance development under alternative refugia strategies, are shown in Table 2. The optimal drench sequence is determined for each scenario for each pre-defined level of refugia through the use of the GA.

Table 2 Scenarios investigated in sensitivity analysis

Description	Low	Low-med	Standard	Med-high	High
Drench prices (\$/head)	0.120	0.135	0.150	0.165	0.180
Lamb prices (\$/kg)	2.20	2.85	3.29	3.78	4.27
Initial pasture larvae density (worms/ha)	50 000	—	250 000	—	1 000 000

Drench prices are highly sensitive to changes in industry conditions and the introduction of new drenches is likely to significantly decrease the value of older chemicals. Scenarios are selected based on realistic changes in drench price.

Lamb prices are highly variable in response to changes in demand and supply. The values are chosen based on the range of sale prices defined in the Farm Weekly magazine in the period 2004–2007.

Initial larval densities on the pasture vary substantially depending on the management of individual flocks. Initial worm densities of 50 000/ha and 1 000 000/ha are thus examined in this study.

Model output corresponding to an increase in the resistance allele over the interval [1, 2, ..., 9] per cent for each refugia level is compared with the standard solution of the model with no refugia. This analysis provides insight into the implications of poor estimation of the capacity of refugia strategies to offset resistance development.

3. Results and discussion

3.1 Evolution of the worm population

The predicted evolution of the two population variables without any anthelmintic use is presented in Figure 3. The infective larvae on the pasture increase exponentially over the planning period (Figure 3a). Larval levels on the pasture are low in summer (December and February) because of the high mortality rate of *T. circumcincta* over summer. Higher numbers of infective larvae are present on the pasture in later years because of their gradual accumulation over time. Similarly, the number of adult worms in the host increases exponentially (Figure 3b); however, numbers are reset to zero with the birth of the replacement hosts in each year.

3.2 Optimal refugia rate

Given the objective of cost minimisation in the model, optimal scenarios are those with the lowest cost. Initial resistance is assumed to be 2 per cent in the standard model (see Section 2.1). Total cost because of worm burden decreases from \$24.60/ha at 0 per cent refugia to \$20.90/ha at 2 per cent refu-

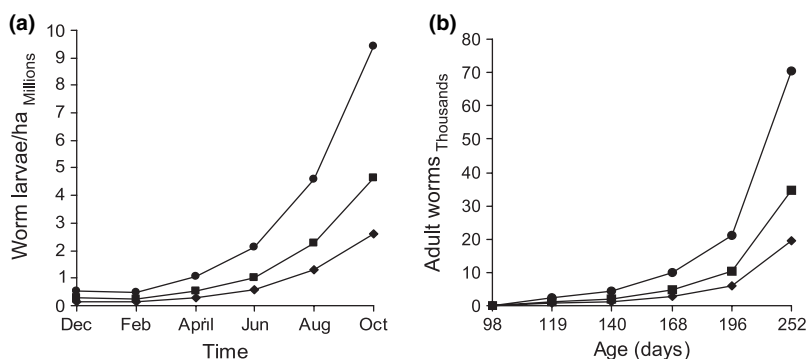


Figure 3 Worm larvae on the pasture (a) and adult worms in the host (b) in years (♦) 1, (■) 5 and (●) 10 with an initial resistance rate of 2 per cent.

gia (Table 3). However, it increases to \$21.30 and \$23.50/ha moving to 5 and 10 per cent rates, respectively. The optimality of the 2 per cent rate is due to its pronounced effect on slowing the development of resistance (Figure 2), while the income foregone because of low refugia is modest in comparison to the 5 and 10 per cent refugia rates. Even with low initial resistance levels, a refugia rate as high as 10 per cent is more valuable than no refugia at all, highlighting the significant cost of resistant parasites (Table 3). As the initial resistance rate increases, the optimal refugia level rises accordingly (Table 3) as it becomes necessary to take strong measures to slow the further development of resistance. At the higher initial resistance rate,¹ the modest marginal improvement in refugia effectiveness at refugia levels above 2 per cent is worth the higher cost. Note, however, that all modelled refugia levels are superior to zero refugia at all initial resistance levels.

The cost of resistance may be calculated by subtracting the total cost attained with resistance from the total cost computed for a scenario with no resistance. The latter is consistent with the effectiveness of the anthelmintic being fixed at its base level (98 per cent) in perpetuity. The cost of ML

Table 3 Total cost* (\$) of parasites per hectare over the 10 year horizon for different initial resistance levels at each rate of refugia

Initial resistance level (%)	Refugia level (%)			
	0	2	5	10
2 (standard value)	24.60	20.90	21.30	23.50
5	29.80	22.60	21.40	22.12
10	38.80	24.00	23.80	21.60

*Because of production losses, mortality and anthelmintic use.

¹ This result is relevant for those drench groups to which high levels of resistance are more common; for example, the Levamisole chemicals.

resistance identified in the model is \$6.80/ha. That is, assuming no refugia is used, approximately one-third of the total cost of worm infection is a direct result of anthelmintic resistance. This substantial cost highlights the importance of implementing management strategies, such as refugia, to slow its development.

3.3 Optimal drench application

The pattern of optimal drench application over time at each of the different refugia rates is presented in Figure 4. Note that generally the optimal strategy is comparable between refugia rates, and involves drenching at high rates in year 1 with application frequency more uniform over years 2 to 10. The high rates of use in year 1 are to minimise the worm population that can breed in future years. From an economic perspective, the marginal benefit of controlling worms in the initial year is higher because these individuals can breed over a longer period, relative to those worms that appear in later years.

In terms of intra-year relationships, the optimal strategy is to drench most heavily at 98, 140 and 196 days after birth (Figure 5). Drenching every second period ensures that worm burdens in the host do not reach high levels, thereby decreasing production losses, and the cost of drench application is not borne in each individual period. The need for regular drenching is motivated by worm biology. First, worms lay eggs daily, so regular drenching is important to prevent populations reaching very high levels. Second, protection of a given proportion of the worm population from chemical control in refugia increases the chance that these worms may breed. Third, even with regular control, reinfection remains a practical reality because of larval ingestion from pasture. Last, there is a strong relationship between livestock production and worm burden.

In the cost-minimising model solutions, worm burdens in individual sheep are generally kept below 500 to avoid production losses (Figure 6). However,

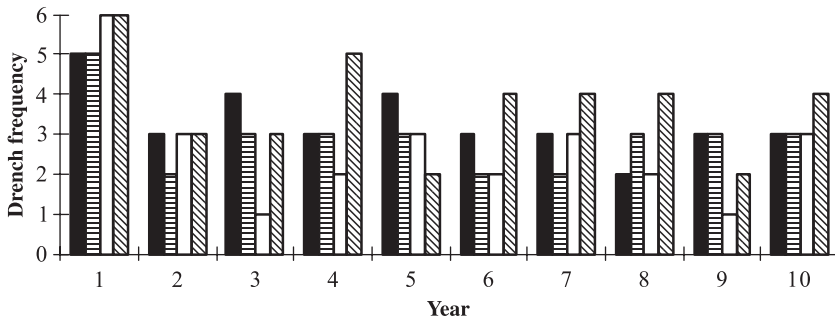


Figure 4 Optimal frequency of drench application per year at (■) 0, (≡) 2, (□) 5 and (▨) 10 per cent refugia with an initial resistance rate of 2 per cent.

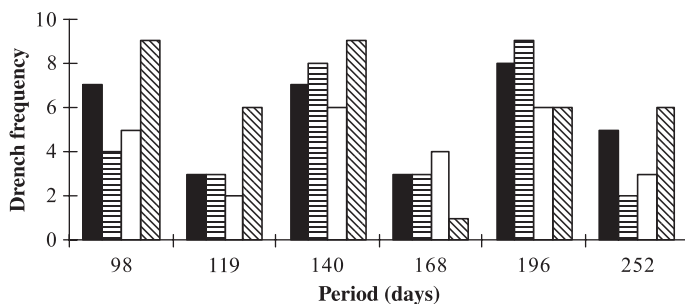


Figure 5 Frequency of drench application per period at (■) 0, (▨) 2, (□) 5 and (▩) 10 per cent refugia with an initial resistance rate of 2 per cent.

populations can reach higher levels at 252 days because they are reset to zero in the first period of the next year when a new cohort of sheep replaces the former group. Generally, drenches are applied at 140 and 196 days to avoid rapid increases in worm burdens. An exception to this is at the 10 per cent refugia level, where no drench is applied at 196 days because the worm burden is below 500 worms. However, this prompts the need to drench at 252 days to avoid production loss.

Across different refugia rates, the pattern of drench use is broadly similar. However, the number of drench applications is marginally higher at 10 per cent refugia with 37 applications, compared with 33 drench applications at 0 refugia over the 10 year horizon. A high number of drench applications is optimal at higher refugia levels because there are greater numbers of worms present, both on the pasture and in the host. Moreover, the presence of refugia lowers the cost accruing to a given drench application because of its contribution to resistance (Figure 2).

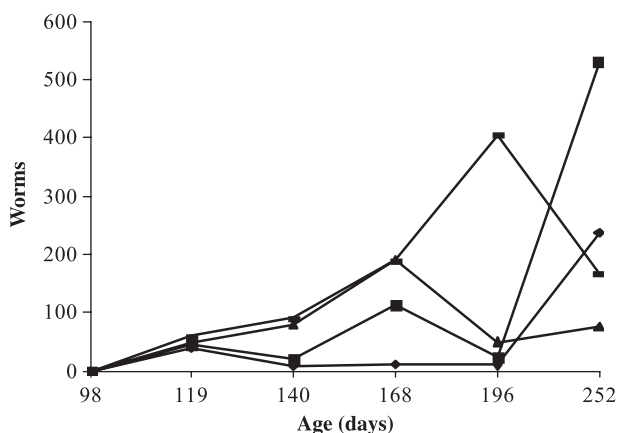


Figure 6 Adult worms in the host in year 5, based on the optimal drenching scenarios, at (◆) 0, (■) 2, (▲) 5 and (×) 10 per cent refugia with an initial resistance rate of 2 per cent.

3.4 Costs accruing to worm burdens

The division of total costs into those attributable to production losses and treatment cost for the standard parameter values at the four refugia levels is presented in Table 4. Costs arising from production loss are minimal. In fact, with 0, 2 and 10 per cent refugia, there are no costs at all accruing to production loss. However, at the 5 per cent refugia level, there is a small cost of \$2.16/ha. This contrasting result is an example of the small irregularities that can present themselves in model output when the number of possible solutions precludes identification of a global optimum and the search procedure is governed by a stochastic process. In contrast, the costs because of drench use account for the majority, if not all, of total costs. This reinforces that the optimal strategy is to manage worm burdens in the host to minimise those costs arising from production losses.

3.5 Sensitivity analysis

3.5.1 Lamb and drench prices

Total cost per hectare for changes in lamb and drench prices are presented in Table 5. Costs are more sensitive to changes in drench price than lamb price for a given level of refugia. For example, as drench prices increase from \$0.12 to \$0.18/head, total costs increase from \$18.40 to \$27.60/ha based on a 0 per cent refugia level. For the same refugia level, total costs are \$22.80/ha at a lamb price of \$2.20/kg, increasing only slightly to \$25.00/ha with a substantial increase in lamb price to \$4.27/kg (Table 5) because of an increasing optimal level of drench.

This finding arises as worm numbers in the host are the same at a consistent refugia level, regardless of the drench price (data not shown). This confirms that under optimal management it is necessary to control worm burdens so that losses in sheep production either do not occur or are minimal (see Section 3.4). Accordingly, changes in drench price have substantial impacts on total cost because the main cost incurred by farmers in the optimal solutions is that associated with chemical control. In contrast, total cost is relatively insensitive to changes in lamb price because the production losses accruing to worm populations are negligible under optimal management (Table 4).

Table 4 The cost (\$) of parasites per hectare over the 10 year horizon because of production losses and drench use at 0, 2, 5 and 10 per cent refugia

Refugia level	Costs because of production losses (\$)	Costs because of drench use (\$)
0	0	24.60
2	0	20.90
5	2.16	18.60
10	0	23.50

Table 5 Total cost* (\$) of parasites per hectare over the 10 year horizon for different drench and lamb prices at each level of refugia

Scenario	Refugia level (%)			
	0	2	5	10
Drench prices (\$/head)				
Low	18.40	16.20	16.30	17.70
Low-medium	19.10	17.00	17.80	18.80
Standard	24.60	20.90	21.30	23.50
Medium to high	25.90	21.90	23.50	23.70
High	27.60	22.90	25.60	26.70
Lamb prices (\$/kg)				
Low	22.80	18.70	20.10	21.40
Low-medium	24.40	20.20	20.00	23.20
Standard	24.60	20.90	21.30	23.50
Medium to high	24.80	21.40	22.40	23.90
High	25.00	21.60	22.90	25.40

*Because of production losses, mortality and anthelmintic use.

Total costs are more sensitive to changes in lamb prices than drench prices across different refugia rates. For example, total cost decreases from \$18.40/ha at 0 refugia to \$16.20/ha at 2 per cent refugia for low drench prices, compared with a decrease from \$22.80 to \$18.70/ha for low lamb prices. The cost of refugia is associated with liveweight loss because a proportion of the livestock population is not treated with the anthelmintic. Hence, changes in refugia intensity directly affect total cost with the change in the lamb price.

3.5.2 Initial larvae pasture density

Initial pasture larvae densities of 50 000 and 1 000 000/ha are also examined in the model. As expected, at lower initial larvae densities, costs are lower than in pastures with high initial larvae densities (Table 6). Costs are higher at greater larval densities because of the need for a greater number of drenches to control the worm population, particularly early in the time horizon. Over the 10 year horizon, it is economically optimal to apply 31 drench applications at high larvae pasture densities, compared with 27 applications at low larvae pasture densities. These results indicate that it will be

Table 6 Total cost* (\$) of parasites per hectare over the 10 year horizon for different initial larvae densities on the pasture at each level of refugia

Scenario	Value	Refugia level (%)			
		0	2	5	10
Initial larvae pasture density (worms/ha)					
Low	50 000	19.20	17.20	17.90	19.50
Standard	250 000	24.60	20.90	21.30	23.50
High	1 000 000	27.80	21.40	24.90	32.00

*Because of production losses, mortality and anthelmintic use.

profitable for farmers to minimise worm infection by grazing sheep on pastures where larval densities are low. However, recent research highlights that this practice may increase the selection pressure for resistance (e.g. Hughes *et al.* 2007). Therefore, this result should be taken with caution.

3.5.3 Rate of resistance development

Total cost for each refugia strategy grows as the rate of expected resistance development increases (Figure 7). This result is expected because such increases erode the benefit accruing to refugia, namely the capacity to offset anthelmintic resistance. Total cost for a refugia rate of 10 per cent grows rapidly, surpassing the value of the base strategy at between a 2 and 3 per cent rate of resistance development (Figure 7). In contrast, the 2 and 5 per cent refugia strategies remain more cost-effective than the use of no refugia up to a percentage increase in resistance of 7 per cent (Figure 7). Thus, the optimality of retaining low levels of refugia is very robust to the degree to which its effect on resistance development is misestimated. The cost associated with a given rate of resistance development generally increases with the intensity of refugia in Figure 7, as the reduced drenching intensity augments the costs associated with production losses.

4. Conclusions

Anthelmintic resistance has greatly reduced the profitability of sheep enterprises in Western Australia. Refugia practices involve reducing control intensity to lower selection pressure for resistance in gastrointestinal worm populations. This study presents a model designed to assess the economic value of this strategy for delaying the onset of anthelmintic resistance in Australian sheep flocks.

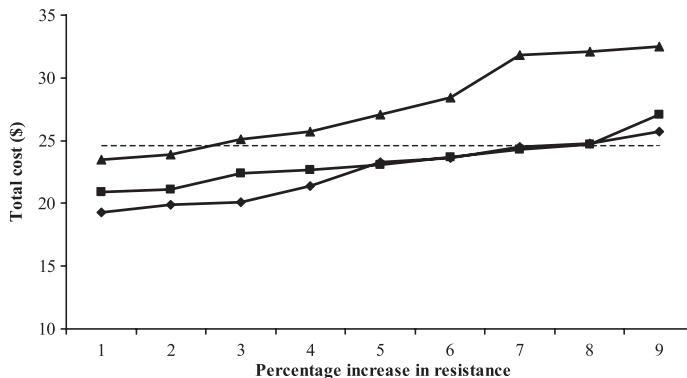


Figure 7 Total cost trajectory for (◆) 2, (■) 5, and (▲) 10 per cent refugia strategies as the percentage increase in the rate of resistance is varied. The dashed line signifies the total cost corresponding to the base scenario (i.e. no refugia, initial resistance rate of 2 per cent, and an increase in the resistance allele of 9.37 per cent).

In an application to Western Australian conditions, model output indicates that refugia strategies are of high value in a parasite management program. In the standard model, it is most profitable to leave 2 per cent of the flock undrenched. A low rate of refugia allows the effectiveness of drenches to be prolonged, while limiting host-parasite competition. Thus, producers should consider the use of refugia if they are looking to maximise long-term profit. However, attention needs to be paid to the level of resistance already present in the parasite population.

Total costs under optimal management consist mainly of control costs, rather than those accruing to production loss. This focus towards the minimisation of competition from gastrointestinal worms is motivated by their high reproductive rate and the threat of continued infection from larval uptake from pasture. This result is equivalent to that observed in the control of the weed annual ryegrass (*Lolium rigidum* Gaud.), as the competitiveness and large seed production of these plants encourage maintenance of low populations under optimal management (Doole *et al.* 2009). Moreover, the profitability of minimising competition from internal parasites is promoted by the strong relationship between livestock production and parasite burden. Consequently, it is most profitable to drench frequently to minimise production loss. This emphasises the need for farmers to monitor worm burdens in the host and implement an appropriate drench regime in response to observed levels.

Resistance to ML drenches is estimated by the model to cost around \$6.80/ha over the 10 year horizon. Therefore, approximately a third of the cost accruing to the most-profitable program to manage *T. circumcincta* consists of the impact of resistance development. This highlights the substantial cost borne by farmers who do not implement refugia and maintain intensive chemical control of gastrointestinal worms.

This study indicates that non-chemical strategies can be a profitable addition to control programs for gastrointestinal parasites in Western Australian sheep flocks. However, the model can be extended in several directions. First, analysing the profitability of a portfolio of non-chemical strategies, including breeding sheep for greater resistance to worm burden (Karlsson and Greeff 2006), would be an interesting extension. Second, research into the effects of resistance on other anthelmintic groups, especially combination drenches, and other worm species would be useful additions.

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