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Caris L. Pech

Graeme J. Doole

And

Johanna M. Pluske

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# The value of refugia in managing anthelmintic resistance: a modelling approach

Caris L. Pech<sup>1</sup>, Graeme J. Doole<sup>1</sup> and Johanna M. Pluske<sup>1</sup>

<sup>1</sup> School of Agriculture and Resource Economics, Faculty of Natural and Agricultural Sciences,  
University of Western Australia, 35 Stirling Highway, Crawley, Western Australia 6009.

**Abstract.** The increasing prevalence of anthelmintic (drench) resistance in gastrointestinal parasite populations is decreasing the profitability of the sheep industry in Western Australia (WA). A strategy, referred to as *refugia* management, has the potential to delay the development of resistant parasites by not exposing a proportion of the worm population to chemical control. A dynamic bioeconomic model is used to assess the economic value of refugia for management of the worm species *Teladorsagia circumcincta* and Macrocytic Lactone drenches in 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 cost accruing to production losses that arise from maintaining a proportion of the worm population in refugia. The optimal drenching strategy is to drench heavily early in the time horizon to minimise worm populations in subsequent years. This study highlights the optimality of minimising production losses by maintaining high levels of consistent control.

**Key words:** Anthelmintic resistance, bioeconomic model, gastrointestinal parasites, refugia, sheep, *Teladorsagia circumcincta*.

## 1. Introduction

The viability of the Western 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). Anthelmintics are generally regarded as providing the most cost-effective control of parasite populations. However, the significant increase in resistance observed over the last 20 years is

adversely affecting sheep productivity and profitability (Hein *et al.* 2001; Besier and Love 2003). Key operational factors that have been identified as promoting resistance include (1) excessive treatment frequency, (2) under-dosing and (3) the use of long-acting formulations that decline in concentration over time (see Prichard *et al.* 1980; Waller 1986; Besier and Love 2003; Jabbar *et al.* 2006; Hughes *et al.* 2007). McLeod (1995) estimated the annual cost of worms in Australia to be in excess of \$220 million.<sup>1</sup> If Australian farmers are to continue their reliance on chemical-based control methods, it is estimated that the potential annual cost of worms will be \$700 million by 2010 given the expected continued development of resistance (Welsman 2001).

It is essential that parasite management programs focus on maximising long-term profitability. This may involve either delaying resistance through drench conservation or exploiting the anthelmintic resource. The integration of non-chemical treatments for worm control into these programs has been proposed as a method of significant potential importance to delay the development of resistance and/or permit the control of gastrointestinal worms already resistant to anthelmintics. Available practices include breeding for natural resistance in sheep, grazing management, biological control of nematode larvae, nutrition supplements and refugia (see Barger 1993; Waller 1993; Sangster 2001; Besier and Love 2003). *Refugia* has been identified as a crucial component in prolonging the use of anthelmintics (Van Wyk 2001). It is defined as a situation where part of the parasite population is not exposed to anthelmintic treatment, thus escaping selection for resistance (Van Wyk 2001). Refugia was discussed by Prichard *et al.* (1980) in the early 1980s, however, its practical importance has only been identified recently (e.g. Van Wyk 2001; Besier and Love 2003; Hughes *et al.* 2007).

This study focuses on refugia as a complementary strategy to chemical control because there is little understanding pertaining to its profitability in Western Australian conditions and there is extensive evidence (e.g. Hughes *et al.* 2007) that it is the most promising method for cost-effectively slowing the development of anthelmintic resistance elsewhere. Furthermore, it is easy to implement and thus of direct relevance to many producers.

A dynamic optimisation model is used to assess the economic value of refugia for anthelmintic resistance management in Western Australian sheep flocks. This model captures

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<sup>1</sup> All dollar values are in AUD unless otherwise specified.

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the intertemporal value of refugia, which is difficult to estimate using field trials. Similar studies in the pesticide literature have focused on determining the optimal size of refugia that is necessary to reduce the selection pressure for resistance among susceptible pest populations in certain crops (e.g. Laxminarayan and Simpson 2002; Cerda 2004; Livingston 2004). These studies acknowledged the importance of refuge areas in pest-control programmes, particularly after the onset of resistance. However, in a Western Australian context, no previous studies have considered the economic value of refugia for parasite management. In addition, this appears to be the first analysis conducted worldwide that investigates the profitable management of gastrointestinal parasite resistance to chemical control in livestock populations.

The primary hypothesis of this study is that parasites in refugia will be a profitable component of long-term parasite management programs in Western Australian sheep flocks because they cost-effectively delay the development of anthelmintic resistance. The secondary hypothesis is that the biology of gastrointestinal worms will promote the regular application of anthelmintics to maintain parasite populations at low levels.

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 results of the research. Section 4 outlines the key conclusions of this study. The term “optimal” is used throughout to denote strategies that are more profitable than other alternatives. Other goals are important to farmers (Pannell *et al.* 2006), but profitability is a core focus of commercial producers.

## **2. Model**

### **2.1 Model description**

A dynamic optimisation model is developed to assess the economic value of refugia for anthelmintic-resistance management in Western Australian sheep flocks. The model is implemented in the spreadsheet program, Microsoft Excel<sup>®</sup>, and uses an optimisation algorithm to identify the most-profitable pattern of drench use over time subject to different refugia strategies. The model is defined in discrete time periods to represent the discrete nature of anthelmintic treatments.

The model analyses a single hectare of a field on a Western Australian sheep farm. Whole-farm factors are 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 evolution of the worm population in Roberts and Grenfell (1991; 1992), Kao *et al.* (2000) and Louie *et al.* (2005) are extended to incorporate anthelmintic use. The model focuses on the worm species *Teladorsagia (Ostertagia) circumcincta*, as it is the main gastrointestinal parasite species affecting sheep in WA and multiple anthelmintic resistance affects an overwhelming majority of farms in the State (Besier and Love 2003; Suter *et al.* 2004; Besier 2007). Macrocytic Lactones (MLs) are the drench group represented in this model because they are the most-recently developed and commonly-used anthelmintic class in Australia (Barger 2003). The model assumes that initial resistance rates are relatively low (2 per cent), in accordance with field conditions.

In line with standard theory (e.g. Roberts and Grenfell, 1991), the model is focussed solely on a flock of representative sheep younger than 12 months of age. Lambs and weaners are an appropriate focus since they are more susceptible to worm burden than adult sheep as their immunological response is not fully developed (Gray 1997).

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 birth of the lamb. 98 days corresponds to weaning under traditional management of sheep flocks in WA. Drenching times are fixed because they correspond to standard times used by producers.

Anthelmintic resistance is inherited in a given worm population (Prichard *et al.* 1980), and once resistance has entered a population, reversion or loss of resistance is never observed (Sangster and Dobson 2002). Refugia slows the development of resistance by allowing the conservation of susceptible individuals to dilute the progeny of resistant parasites that survive treatment (Van Wyk *et al.* 2006). 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 actions that influence the worm population. Anthelmintic use at time  $t$  in year  $y$  is denoted by the binary variable  $u_{t,y}^1$ . The use of refugia is denoted by

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$u^2$  and represents a single decision, whether or not to implement refugia 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 can be simulated: 0, 2, 5 and 10 per cent. Treatment frequency has been recognised as a major factor in the development of anthelmintic resistance (Prichard *et al.* 1980; Waller 1986; Besier and Love 2003). Therefore, drench effectiveness is directly related to the number of doses of anthelmintic that the host receives and the refugia rate. Effectiveness declines as the number of doses of the anthelmintic applied over the planning horizon increases. However, the rate of decline depends upon the proportion of the sheep population not exposed to the anthelmintic (i.e. maintained in refugia).

It is assumed that the host is a representative sheep and the model represents one hectare of a farm. It is thus problematic to define refugia in terms of the number of sheep in a flock not exposed to chemical control. For example, it is impossible to represent a 2 per cent refugia rate in a flock consisting of 10 sheep (the standard stocking rate in this analysis) using this approach. Therefore, refugia of  $n$  per cent is represented by reducing drench application to each of the representative sheep by  $n$  per cent. This is consistent with their use to describe a host population in the model.

The worm population in the model is described by two variables: the density of infective nematode larvae on the pasture at time  $t$  in year  $y$  ( $L_{t,y}$ ) and the mean number of adult nematodes per host at time  $t$  in year  $y$  ( $A_{t,y}$ ). The state variable  $A$  is reset to zero at the beginning of each year with the introduction of new stock onto the field (Louie *et al.* 2005).

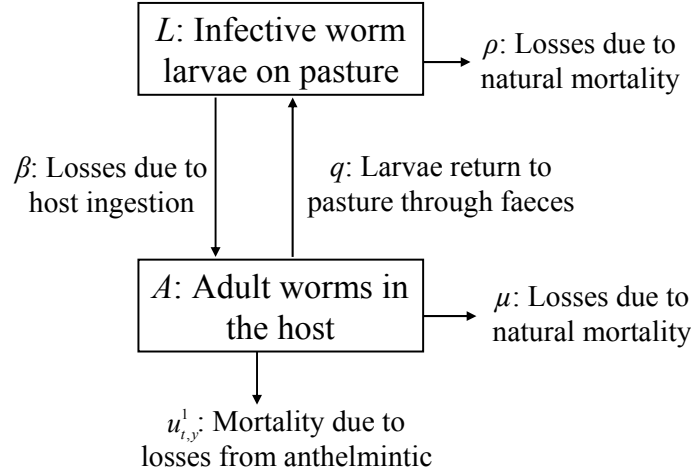
The evolution of the worm population is determined by a set of two interdependent relationships (Figure 1). The density of infective worm larvae on the pasture at any one time is determined by:

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

for

$$t = [1, 2, \dots, 5], y = [1, 2, \dots, 10], L_{1,1} = L_0 \text{ and } L_{1,y} = S \cdot L_{6,y-1} \text{ for } y \neq 1,$$

where  $\rho$  is the rate at which larvae are lost from pasture due to reasons other than host ingestion (e.g. natural mortality),  $\beta$  is the rate at which larvae are eaten by a single host animal,  $H$  is the host population density,  $q$  is the probability that an egg develops into an infective larvae,  $\lambda$  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.



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

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

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

for

$$t = [1, 2, \dots, 5], y = [1, 2, \dots, 10], \text{ and } A_{1,y} = 0,$$

where  $d$  is the probability that an ingested larvae develops into an adult parasite,  $\mu$  is the natural mortality rate of adult parasites and  $f(u^2)$  denotes the efficacy of the anthelmintic 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 host animal. Accordingly, the cost of using refugia is represented by the increase in worm burden in the host. This enters eq. (2) through the term  $1 - u^2$ .

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The interdependency between the population equations of (1) and (2) is evident. This complicates effective management as livestock can become infected from the ingestion of worms from pasture, even if regular drenching has reduced populations within the grazing animal itself.

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

$$\min_{u_{t,y}^1, u^2} C = \sum_{y=1}^{10} (1+r)^{-y} \sum_{t=1}^6 [(1-p(A_{t,y})) \cdot l(A_{t,y}) \cdot e + p(A_{t,y}) \cdot e \cdot w + (1-u_2) \cdot c \cdot u_{t,y}^1] H, \quad (3)$$

where  $C$  is the total cost in dollars,  $r$  is the discount rate,  $p(A_{t,y})$  is the probability of sheep mortality occurring due to a high worm burden,  $l(A_{t,y})$  is the reduction in host liveweight due to 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. The terms in the square brackets in eq. (3) describe the cost per lamb due to worm burden and drench application. Therefore, to determine the cost of parasites per hectare, this term is multiplied by the host population density ( $H$ ). In addition, the cost of drench application is adjusted when a given level of refugia is defined to reflect the decrease in the proportion of the flock not exposed to the anthelmintic.

## 2.2 Parameter estimation

### 2.2.1 Population parameters

The standard biological values specified for each parameter in the analysis are for lambs and *T. circumcincta* populations in WA (Table 1). Data of this nature for WA is rare, so where it is unavailable, data has been used from similar climatic regions. In particular, note in Table 1 the particularly high average rate of daily egg production by an adult parasite (54 eggs worm<sup>-1</sup> day<sup>-1</sup>) (Gruner *et al.* 2004).

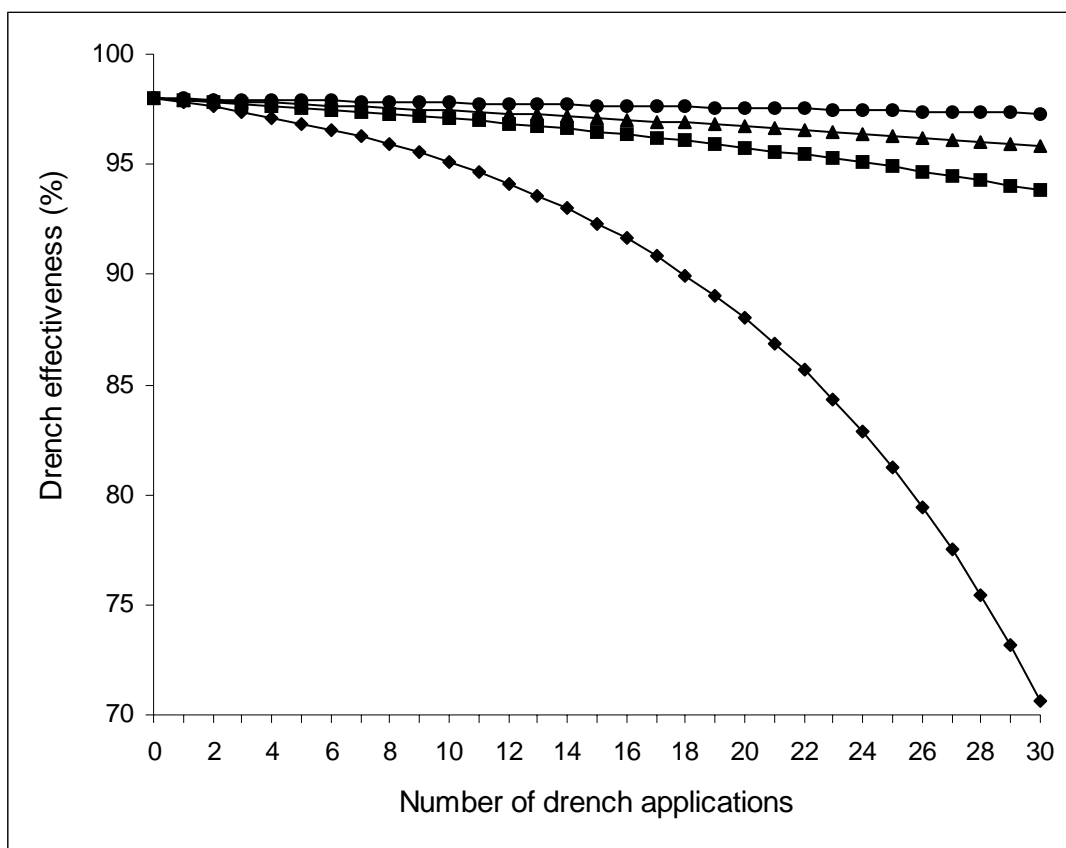
**Table 1** Definition and values used for model parameters.

Parameter	Definition	Value	Source
$\rho$	Rate at which larvae are lost from pasture due to reasons other than host ingestion	0.025 day <sup>-1</sup>	Rounded mean from Paton <i>et al.</i> (1984) and Donald <i>et al.</i> (1978)
$\beta$	Rate at which larvae are eaten by a single host animal	4 m <sup>2</sup> day <sup>-1</sup>	Kao <i>et al.</i> (2000)
$H$	Host population density	10 ha <sup>-1</sup>	Rounded mean from Brown <i>et al.</i> (1985) and White and McConchie (1976)
$q$	Probability that an egg develops into an infective larvae	0.0275	Mean rate from Callinan (1978)
$\lambda$	Mean rate at which an adult parasite produces eggs	54 eggs worm <sup>-1</sup> day <sup>-1</sup>	Gruner <i>et al.</i> (2004)
$d$	Probability that an ingested larvae develops into an adult parasite	0.48	Barger (1989)
$\mu$	Mortality rate of adult parasites	0.03 day <sup>-1</sup>	Hong <i>et al.</i> (1986)

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 percent refugia rates, respectively, for the ML drench group.

This data is used to calculate anthelmintic effectiveness as a function of drench use for various refugia rates (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. A 5 per cent refugia rate is also estimated based on the three rates presented above. The capacity for refugia to slow the onset of resistance is substantial, though the small marginal increase in drench effectiveness attained at increasing, non-zero rates of refugia is also observable (Figure 2).

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

The initial condition for the population equations is 250 000 worm larvae per hectare on the pasture (i.e.  $L_0 = 250\,000$ ). This is the standard density of *T. circumcincta* under Western Australian conditions at the time corresponding to the first management period in the model. Different initial conditions are explored using sensitivity analysis.

Southcott *et al.* (1976) and Callinan (1978) highlighted that seasonal variability is a key driver in the occurrence and severity of intestinal parasite infection. They 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 ( $S = 0.025$ ).

### 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: (1) estimating the relationship between worm burden and feed intake, and (2) 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 (Jabbar *et al.* 2006; Louie *et al.* 2007). The economic effects on wool production are negligible in lambs given their low yields and the depressed state of the Australian wool market (Kopke *et al.* 2008).

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 (R. Dobson, pers. comm., 2008):<sup>2</sup>

$$TTE = 2 \times T. circumcincta. \quad (4)$$

The maximum food intake for lambs is assumed to be 2 kg hd<sup>-1</sup> (Pluske and Schlink 2008). If the adult worm burden per host is less than 1000, there is no change in feed intake. For worm burdens greater than 81 000, feed intake is 33 per cent of assumed food 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 by Barnes and Dobson (1990) through:

$$z = 2.048 - 0.3493 \cdot \log_{10}(A_{t,y}). \quad (5)$$

The relationship between sheep liveweight and feed intake is determined using the model of Pluske and Schlink (2008). Metabolisable energy is the energy from food available to sheep for the metabolic process of maintenance and growth. The liveweight change per day is determined by the following functions:

$$\hat{W} = W_{\&} \text{ If } (\bar{E} - \frac{E}{L}) < 0, \text{ and} \quad (6)$$

$$\hat{W} = W_{\&} \text{ If } (\bar{E} - \frac{E}{L}) \geq 0, \quad (7)$$

where  $\hat{W}$  is the liveweight gain (kg day<sup>-1</sup>),  $W_{\&}$  is the predicted liveweight gain (kg day<sup>-1</sup>),  $W_{\&}$  is the predicted liveweight loss (kg day<sup>-1</sup>),  $\bar{E}$  is the metabolisable energy requirement for

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<sup>2</sup> Dr Robert Dobson, Senior Research Fellow, School of Veterinary and Biomedical Sciences, Faculty of Health Sciences, Murdoch University, Murdoch, Western Australia, Australia.

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maintenance ( $\text{MJ day}^{-1}$ ),  $E$  is the metabolisable energy of feed ( $\text{MJ day}^{-1}$ ) and  $D$  is the dry matter intake ( $\text{kg hd}^{-1} \text{day}^{-1}$ ).

Therefore, if  $(\bar{E} - ED) < 0$  the host animal will gain weight. The predicted liveweight gain ( $\text{kg day}^{-1}$ ) is described by:

$$W = 0.92 \frac{E - ED}{\hat{E}}, \quad (8)$$

where  $E$  is the metabolisable energy retained by the animal as body tissue ( $\text{MJ day}^{-1}$ ) and  $\hat{E}$  is the energy requirements for weight gain ( $\text{MJ day}^{-1}$ ).

However, if  $(\bar{E} - ED) \geq 0$  then the host animal will lose weight. The predicted liveweight loss ( $\text{kg day}^{-1}$ ) is determined by the following:

$$W = \frac{E - ED}{0.92 \tilde{E}}, \quad (9)$$

where  $\tilde{E}$  is the energy requirements for weight loss ( $\text{MJ day}^{-1}$ ).<sup>3</sup>

In severe cases of worm infection, feed intake declines to extremely low levels, resulting in host mortality (Kyriazakis 1998). Barnes and Dobson (1990) estimated host mortality of naturally infected lambs by a negative binomial distribution. This distribution has two parameters: the mean worm burden at which mortality occurs ( $m$ ), and the level of host immunity ( $k$ ). For sheep less than 6 months of age,  $k$  is equal to 10. The parameter  $k$  decreases linearly from 10 to 3 as age increases from 6 to 18 months. As specified by Barnes and Dobson (1990), the lethal level ( $m$ ) used in the model is 50 000 adult worms per host.

### 2.2.3 Economic cost and benefits

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

<sup>3</sup> A detailed description of subsequent equations and their parameters is described in Appendix 1.

burden. Carcass weight is assumed to be 44 per cent of liveweight (Kleemann 1984). 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 per kilogram in September 2008 (ABARE 2008); this is used as the base value. Thus, with no worm burden, the maximum value of a lamb is \$53.56  $\text{hd}^{-1}$ .

Additionally, there is the cost of drench application in each period. A 20 L drum of Ivomec<sup>®</sup> is valued at \$300 (Agriculture Western Australia 2008). Based on a standard dose rate of 1 mL per 4 kg of liveweight, each dose of the Macrocytic Lactone drench costs \$0.14 for a 37 kg lamb. This cost is incurred if drenching is used in a given period and there is 0 refugia. However, if there is some proportion of the flock maintained in refugia, then the cost is adjusted to reflect the proportion not receiving the anthelmintic.

Based on Doole (2008), a standard discount rate of 0.05 is used in this paper with sensitivity analysis applied to examine its impact on optimal parasite management.

### **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). The Palisade Decision Tools Evolver 4.0 (Nersesian 2000) is used to implement the GA in the Microsoft Excel<sup>®</sup> model. GAs draw an equivalence between optimisation and evolutionary processes, with feasible solutions evolved over time through breeding, random mutation and termination of less-profitable configurations (Goldberg 1989). They are an appropriate tool for the optimisation of this model given the relatively large number of binary decision variables and the availability of efficient solution software.

Optimal solutions are identified as those estimates of the optimal configuration that have not changed for 10 000 generations. The terminal condition placed on the model is  $L_{1,1} \geq L_{6,10}$ . This constraint is simple, operational and 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 optimisation consists of 2000 individuals and parameters describing combination, mutation and termination are identified within the algorithm as these are typically problem-specific and thus are difficult to estimate *a priori*. Each model scenario is solved five times as the model is

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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.

### 2.4 Sensitivity analysis

Sensitivity analysis identifies how sensitive an optimal solution is to changes in the assumed parameter values (e.g. drench price and discount rate). The scenarios explored are shown in Table 2. The optimal drench sequence is determined for each scenario for each predefined level of refugia through the use of the GA.

**Table 2** Scenarios investigated in the model.

<b>Description</b>	<b>Low</b>	<b>Low-med</b>	<b>Standard</b>	<b>Med-high</b>	<b>High</b>
Drench prices (\$ mL <sup>-1</sup> )	0.0120	0.0135	0.0150	0.0165	0.0180
Lamb prices (\$ kg <sup>-1</sup> )	2.20	2.85	3.29	3.38	4.27
Discount rate	0.01	-	0.05	-	0.10
Initial pasture larvae density (worms ha <sup>-1</sup> )	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. Thus, it is important that changes in drench price are investigated since these are the main form of control against gastrointestinal parasites. Scenarios were selected based on realistic changes in drench price.

Lamb prices are highly variable in response to changes in demand and supply. Therefore, it is important to examine their effect on parasite management. The values were chosen based on the range of sale prices defined in the Farm Weekly magazine in the period 2004–2007.

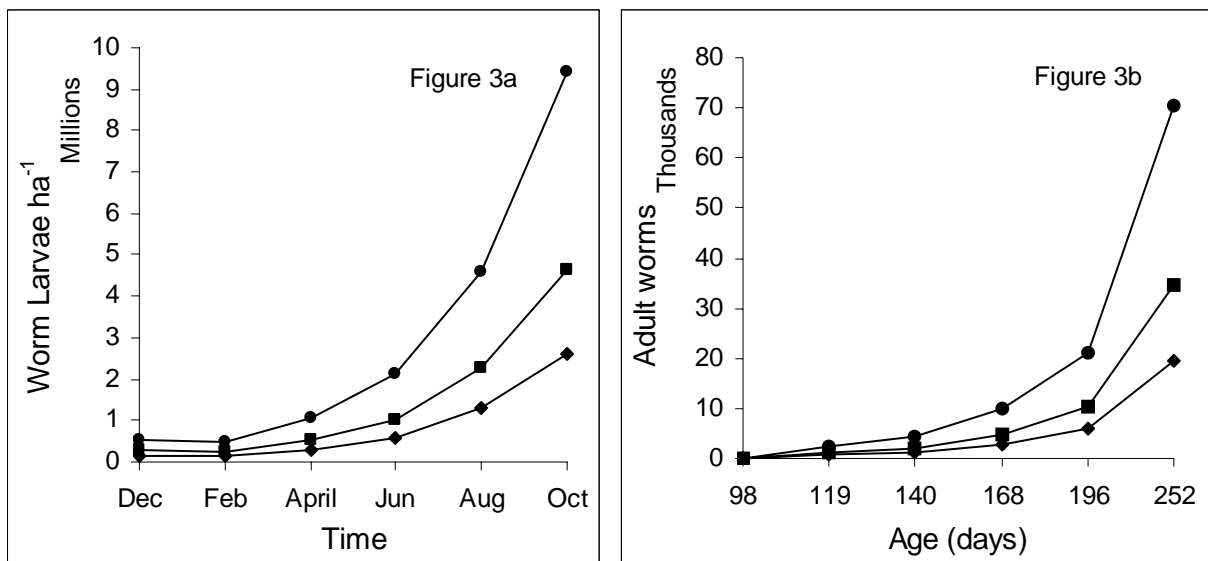
Discounting is important in the determination of optimal policies as resistance is a dynamic issue. Income earned earlier in the horizon is more valuable than that received later given the opportunity to invest these funds elsewhere in the economy. A low discount rate of 1 per cent and a high discount rate of 10 per cent are used in sensitivity analysis.

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

### 3. Results and Discussion

#### 3.1 Evolution of the worm population

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



**Figure 3** Worm larvae on the pasture (3a) and adult worms in the host (3b) in years 1 (◆), 5 (■) and 10 (●).

### 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 due to worm burden decreases from \$24.60 at 0 per cent refugia to \$20.90 at 2 percent refugia (Table 3). However, it increases from \$21.30 to \$23.50 moving from 5 to 10 per cent. The optimality of the 2 per cent rate is due to its pronounced effect on reducing the development of resistance (Figure 2), while minimising the costs accruing to higher worm infestation, 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 over time (Table 3).

**Table 3** Total cost<sup>1</sup> (\$) of parasites per hectare over the 10-year horizon for different initial resistance levels at each level 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

<sup>1</sup>Due to production losses, mortality and anthelmintic use.

The relatively low optimal rate of refugia in the standard scenario can be explained by the high initial efficacy rates that are assumed in the model. At higher initial resistance levels, the optimal refugia rate increases (Table 3) as it becomes necessary to take strong measures to slow the further development of resistance. For example, if initial resistance levels in the population are high, for example at 10 per cent, then the optimal level of refugia increases to 10 per cent (Table 3). This result is relevant for those drench groups to which high levels of resistance are more common, for example, the Levamisole chemicals (Love 2007).

Numerous studies have identified that anthelmintic resistance threatens the sustainability of the sheep industry (e.g. Prichard 1990; Waller 1997; Besier and Love 2003). The cost of resistance may be calculated by subtracting the cost attained with 0 per cent refugia in the standard model from a scenario in which the effectiveness of the anthelmintic is fixed at its

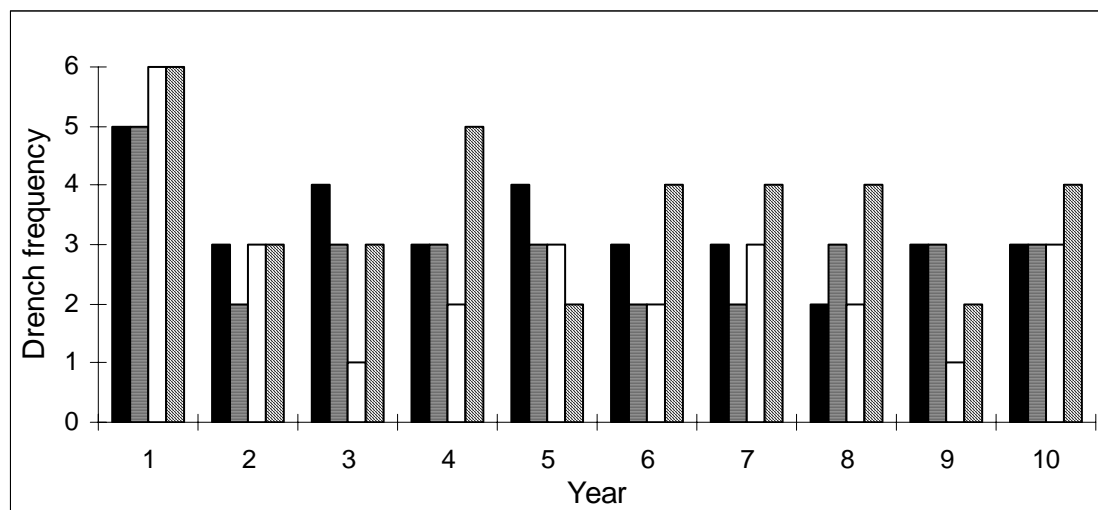
base level (98 per cent). The cost of ML resistance identified in the model is \$6.80 ha<sup>-1</sup>. That is, assuming 0 per cent refugia, approximately one-third of the total cost of worm burden is a direct result of anthelmintic resistance. This substantial cost highlights the importance of implementing management strategies, such as refugia, to slow its development.

This result supports the hypothesis that parasites in refugia are valuable in long-term parasite management in WA. Farmers should consider the use of refugia if they are looking to maximise long-term profit in their sheep flocks. This is important since refugia may in fact be of higher value than predicted by this model, as in reality farmers can select those sheep with a higher level of natural immunity to worms to leave untreated. However, attention needs to be paid to the level of resistance already present in the parasite population.

### **3.3 Optimal drench application**

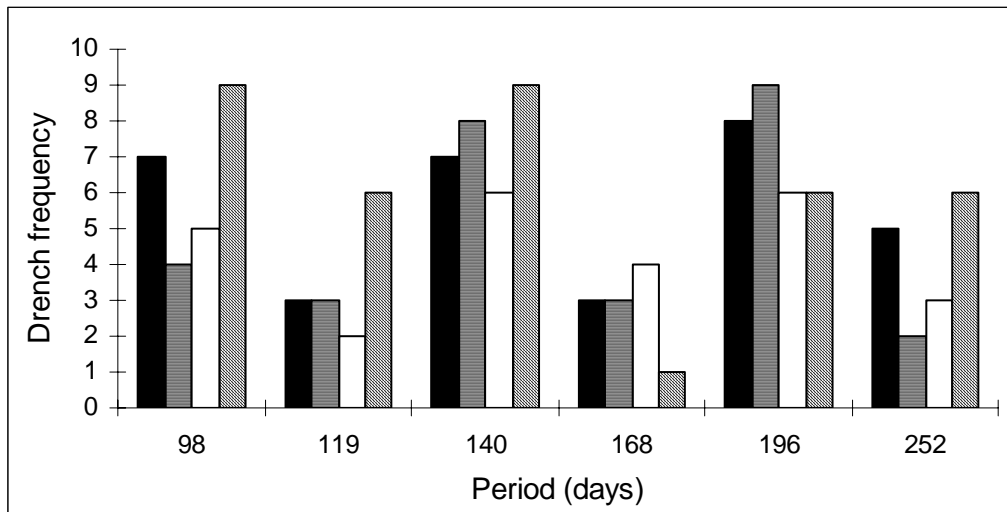
The pattern of optimal drench application over time at each of the different refugia rates is presented in Figure 4. Note that generally the optimal strategy is comparable between refugia rates, and involves drenching at high rates in year 1 with application frequency more uniform over years 2 to 10. 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. The potential for worm populations to increase rapidly in the absence of control is evident in Figure 3. This is consistent with studies of weed management (e.g. Gorrard *et al.* 1995), which recommend the use of highly-effective weed treatments in the initial years of a planning horizon to minimise seed production in subsequent periods.

### The value of refugia in managing anthelmintic resistance



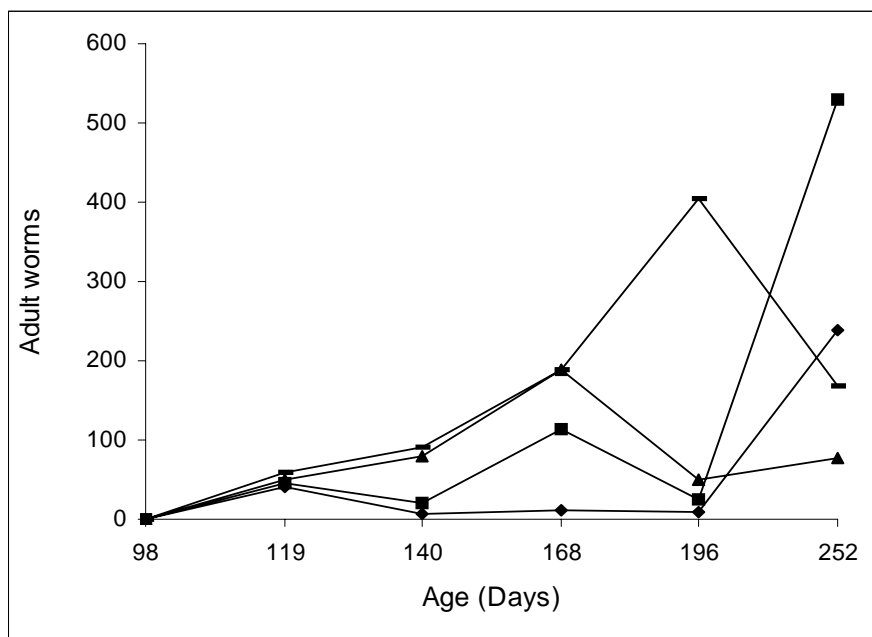
**Figure 4** Frequency of drench application per year at 0 (■), 2 (≡), 5 (□) and 10 (▨) per cent refugia.

In terms of intra-year relationships, the optimal strategy is to drench at 98, 140 and 196 days after birth (Figure 5). Drenching every second period ensures that worm burdens in the host do not reach critical levels, thereby decreasing production losses, and the cost of drench application is not borne in each individual period. The need for regular control is promoted by the biology of the worm population. Firstly, worms lay eggs daily, so regular drenching is important to prevent populations reaching very high levels. Secondly, model output shows that the capacity of worms to develop resistance necessitates refugia management. Protection of a given proportion of the worm population from chemical control increases the chance that these worms may breed. (Although it is recognised that the use of refugia will prolong drench efficacy, and therefore improve worm control over time.) Thirdly, even with regular control, reinfection remains a practical reality because of larval ingestion from pasture. This finding supports the secondary hypothesis that the biology of gastrointestinal worms will promote the regular application of effective anthelmintics to maintain parasite populations at low levels.



**Figure 5** Frequency of drench application per period (right) at 0 (■), 2 (▨), 5 (□) and 10 (▩) per cent refugia.

Worm burdens in the sheep are generally kept below 500 to avoid production losses (Figure 6). However, populations can reach higher levels at 252 days because they are reset to zero in the host in the first period of the next year. Generally, drenches are applied at 140 and 196 days to avoid rapid increases in worm burdens. An exception to this is 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.



**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.

## The value of refugia in managing anthelmintic resistance

Across different refugia rates, the pattern of drench use is 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 in terms of its contribution to resistance (Figure 2).

The recommended drench applications given here are more frequent than those recommended by the current epidemiologically-based strategic programs (see Van Wyk *et al.* 2006). However, this is consistent with earlier research that indicated that suppressing worm burdens by short-interval treatment maximised sheep production (Anderson 1972; Brown *et al.* 1985). This study extends this earlier research by highlighting that regular intermittent drench application is also most profitable for farmers. This result highlights the importance of considering economic factors in the practical management of anthelmintic resistance, and in resistance management generally.

Moreover, it is evident that it is most profitable to use refugia to slow the development of resistance, but simultaneously use regular drench applications to minimise production loss. This highlights that drenches are an integral part of parasite management given maintenance of their high efficacy with use of refugia, the strong relationship between worm burden and livestock production and also the lack of alternative non-chemical strategies that achieve a high rate of control against parasite populations. Further, these results show that optimal resistance management should focus on prolonging drench efficacy. This should be achieved by refugia management, not by reducing treatment frequency, given the capacity of worm populations to expand rapidly.

### **3.4 Costs due to worm burden**

The division of total costs into those attributable to production losses and treatment cost for the standard parameter values at the four refugia levels are 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 per hectare. In contrast, the costs due to drench use account for the majority, if not all, of total costs.

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

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

This reinforces that the optimal strategy is to manage worm burdens in the host to minimise those costs arising from production losses. This has an important implication for parasite management in WA: drenching should be applied when needed to reduce any effect that worms could have on sheep production. This is examined further in sensitivity analysis.

### 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 example, as drench prices increase from \$0.012 ml<sup>-1</sup> to \$0.018 ml<sup>-1</sup>, total costs increase from \$18.40 to \$27.60 based on a 0 per cent refugia level. For the same refugia level, total costs are \$22.80 at a lamb price of \$2.20 kg<sup>-1</sup>, increasing only slightly to \$25.00 per hectare with a substantial increase in lamb price to \$4.27 kg<sup>-1</sup> (Table 5).

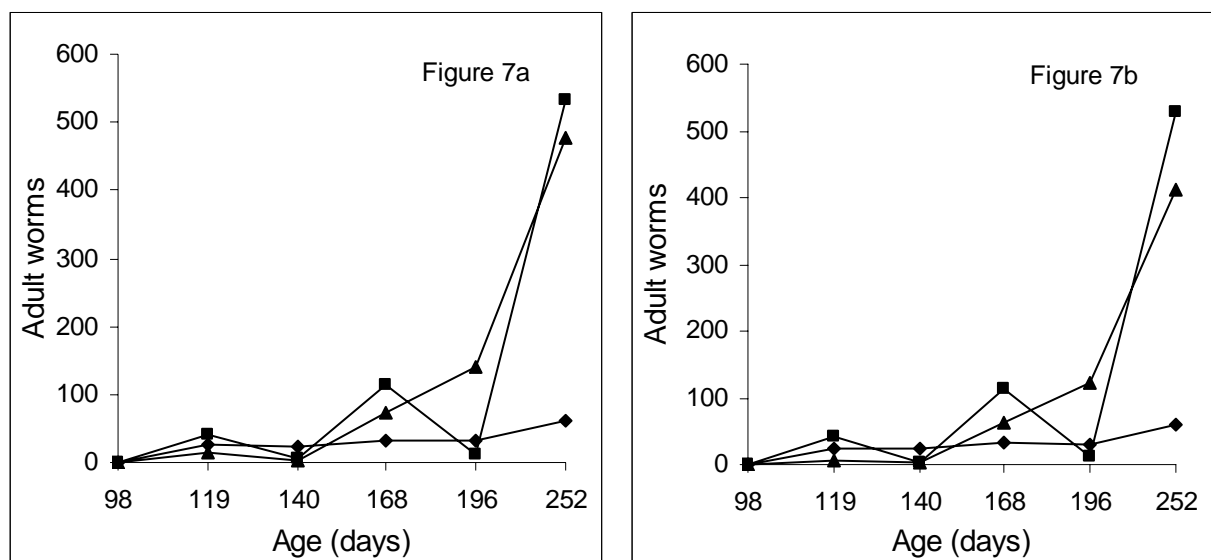
## The value of refugia in managing anthelmintic resistance

**Table 5** Total cost<sup>1</sup> (\$) of parasites per hectare over the 10-year horizon for different drench and lamb prices at each level of refugia.

Scenario	Value	Refugia Level			
		0	2 %	5 %	10 %
Drench prices (\$ mL <sup>-1</sup> ):					
<i>Low</i>	0.0120	18.40	16.20	16.30	17.70
<i>Low-medium</i>	0.0135	19.10	17.00	17.80	18.80
<i>Standard</i>	0.0150	24.60	20.90	21.30	23.50
<i>Medium to high</i>	0.0165	25.90	21.90	23.50	23.70
<i>High</i>	0.0180	27.60	22.90	25.60	26.70
Lamb prices (\$ kg <sup>-1</sup> ):					
<i>Low</i>	2.20	22.80	18.70	20.10	21.40
<i>Low-medium</i>	2.85	24.40	20.20	20.00	23.20
<i>Standard</i>	3.29	24.60	20.90	21.30	23.50
<i>Medium to high</i>	3.38	24.80	21.40	22.40	23.90
<i>High</i>	4.27	25.00	21.60	22.90	25.40

<sup>1</sup>Due to production losses, mortality and anthelmintic use.

Figures 7a and 7b show for a number of years that worm numbers in the host are the same regardless of drench price. Thus, this sensitivity analysis confirms that under optimal management it is necessary to control worm burdens so that losses in sheep production either do not occur or are minor (see Section 3.4). Accordingly, changes in drench price have substantial impacts on total cost because the main cost incurred by farmers under optimal management is the use of chemical control. A change in lamb price could intuitively have a large effect on the optimal plan as the value of control would increase. However, total cost is relatively insensitive to changes in lamb prices because the production losses accruing to worm populations are negligible under optimal management (Table 4).



**Figure 7** Adult worms in the host at low drench prices (7a) and high drench prices (7b) at years 1 (◆), 5 (■) and 9 (▲).

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

### 3.5.2 Initial larvae pasture density

Initial pasture larvae densities of 50 000 ha<sup>-1</sup> and 1 000 000 ha<sup>-1</sup> are also examined in the model. As expected, at lower initial larvae densities, costs were lower than in pastures with high initial larvae densities. For example, total cost increases from \$17.20 to \$21.40 moving from a low to a high density at 2 per cent refugia. Costs are significantly 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 to only 27 applications at low larvae pasture densities. These results infer that it will be profitable for farmers to minimise worm infection by grazing sheep on pastures where larval densities are low.

## The value of refugia in managing anthelmintic resistance

**Table 6** Total cost<sup>1</sup> (\$) of parasites per hectare over the 10-year horizon for different initial larvae pasture densities at each level of refugia.

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

<sup>1</sup> Due to production losses, mortality and anthelmintic use.

These results are supported by Hein *et al.* (2001), who identified that the most-effective way to prevent nematode parasitism in ruminants was to reduce the uptake of infective larvae from pasture. This was the justification for commercial drenching programs in the 1990s to recommend that stock highly susceptible to worm challenge (e.g. weaned lambs) should be placed onto spelled pasture to minimise the uptake of larvae (Barger 1996). However, other studies have demonstrated that this practice only increases the selection pressure for resistance (e.g. Leathwick *et al.* 2006; Hughes *et al.* 2007). Therefore, this result should be taken with caution. An interesting extension to this model may be to add a component representing the interaction between initial pasture larvae densities and the development of resistance.

### 3.5.3 Discount rate

Costs due to parasites are intuitively higher at low discount rates than at high discount rates as they are discounted to a lesser degree (Table 7). For example, for a 2 per cent refugia level, costs decrease from \$25.20 to \$17.80 as the discount rate increases from 0.01 to 0.10.

**Table 7** Total cost<sup>1</sup> (\$) of parasites per hectare over the 10-year horizon for different discount rates at each level of refugia.

Scenario	Value	Refugia Level			
		0	2 %	5 %	10 %
Discount rate:					
<i>Low</i>	0.01	28.00	25.20	26.20	26.50
<i>Standard</i>	0.05	24.60	20.90	21.30	23.50
<i>High</i>	0.10	19.00	17.80	18.40	18.80

<sup>1</sup> Due to production losses, mortality and anthelmintic use.

It could be expected that a higher discount rate would promote greater drench application in the initial years since future economic values are less important under this scenario. However, the timing of optimal drench application is insensitive to changes in the discount rate (data not shown). Intermittent control is profitable, regardless of the discount rate, because of the biology of the intestinal worm that permits their populations to expand rapidly if not properly regulated (see discussion in Section 3.3).

### **3.6 Limitations**

Whole-farm implications of drench resistance are not included in the model. However, this allows a greater focus on the intertemporal problem of anthelmintic resistance.

Climate and market variability are not included in the model. The inclusion of such factors can complicate interpretation of model output and is difficult to incorporate given the lack of information pertaining to the structure of probability distributions for important relationships. Sensitivity analysis was therefore used to overcome this limitation. However, extension of the model to include stochastic processes in future research would be interesting.

The model incorporates a single worm species and a single drench family. Other broad-spectrum drenches available on the market include Benzimidazoles and Levamisoles; however, resistance levels to these groups are comparatively high. Limiting the focus to one worm species and drench group allowed the research to consider important considerations underlying the management of resistance across time, while maintaining tractability.

Only a single non-chemical strategy for managing worm populations (refugia) is studied. In reality, producers have a selection of management strategies that they can use to reduce the development of drench resistance. The study of refugia is justified since it is a highly effective and practicable method of control and thus of potential value to many producers. In contrast, effective biological control of pasture larvae is still being developed. Moreover, nutrient supplementation is expensive, particularly given the extensive scope of many WA sheep farms. Breeding sheep to withstand worm burden is promising (Karlsson *et al.* 1995; Gray 1997; Karlsson and Greeff 2006); however, the rate of genetic progress is slow and therefore its primary value will be its combination with more direct forms of resistance management, principally refugia.

## The value of refugia in managing anthelmintic resistance

The model does not include the decline in immune response that occurs during excessive treatment (Williams 1997). This may overestimate the value accruing to regular drench application in the model. Nonetheless, the representation of important factors of worm biology that necessitate intermittent control (see Section 3.3) infer that the regular use of drenches will remain necessary, even if this immune response was indeed incorporated.

### **4. Conclusions**

Anthelmintic resistance is a serious threat to 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 uses bioeconomic modelling to assess the economic value of this strategy for delaying the onset of anthelmintic resistance in Western Australian sheep flocks.

At the parameter values used in this study, 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 minimising host-parasite competition. This supports the predominant hypothesis of the study; that maintaining worms in refugia is a valuable management strategy in sheep-farming systems in WA. Thus, farmers should be educated about this strategy and aim to implement refugia practices in their individual systems.

In the model, the pattern of optimal anthelmintic application is to drench heavily in year 1 to minimise the worm population that can breed in future years. Total costs under optimal management consist mainly of control costs, rather than those accruing to production losses. 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. Consequently, it is most profitable to drench often to keep production losses to a minimum. This is consistent with the secondary hypothesis that posits that the biology of gastrointestinal worms will promote the regular application of anthelmintics to maintain parasite populations at low levels. This result is confirmed by the high (low) sensitivity of total cost to significant changes in the drench (lamb) price.

This study produces some important implications for parasite management in WA. Firstly, and most importantly, it highlights the importance of worms in refugia for slowing the

development of resistance. Secondly, it emphasises the need for farmers to monitor worm burdens in the host and implement the corresponding drenching regime to reduce the losses accruing in sheep production.

This initial study has indicated that the use of non-chemical strategies in integrated parasite management programmes can be profitable in livestock. However, the model can be extended in several directions. Research into the effects of other anthelmintic groups, including combination drenches, could be of value. In addition, the investigation of other dominant worm species in Western Australia would be useful. In reality, producers also have a portfolio of management strategies that they can use to reduce the development of anthelmintic resistance. Exploring their implications for management would also be an interesting extension of this research.

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## Appendix

This appendix is a detailed description of the equations used to calculate the effect of feed intake on host liveweight, as outlined in Section 2.2.2.

The metabolisable energy requirement for maintenance ( $\bar{E}$ ) (MJ day<sup>-1</sup>) is:

$$\bar{E} = (0.26W^{0.75}e^{(-0.03A)})/k_m + 0.09ED, \quad (\text{A.1})$$

where  $W$  is the standard live weight of a lamb (kg),  $k_m$  is the efficiency of utilising metabolisable energy for maintenance,  $E$  is the metabolisable energy of feed (MJ day<sup>-1</sup>) and  $D$  is the dry matter intake (kg hd<sup>-1</sup> day<sup>-1</sup>).

The metabolisable energy of feed ( $E$ ) (MJ day<sup>-1</sup>) is:

$$E = \sum E_n, \quad (\text{A.2})$$

where  $E_n$  is the metabolisable energy for each feed component (MJ day<sup>-1</sup>).

The dry matter intake ( $D$ ) (kg hd<sup>-1</sup> day<sup>-1</sup>) is:

$$D = \sum (F_n \frac{D_n}{100}), \quad (\text{A.3})$$

where  $F_n$  is the amount each feed component fed fresh (kg hd<sup>-1</sup>) and  $D_n$  is the dry matter for each feed component (measured as a percentage).

The efficiency of utilising metabolisable energy for maintenance is:

$$k_m = 0.35M + 0.503, \quad (\text{A.4})$$

The metabolisable energy retained by the animal as body tissue ( $E_r$ ) (MJ day<sup>-1</sup>) is:

$$E_r = k_f ED - \bar{E}, \quad (\text{A.5})$$

where  $k_f$  is the efficiency of utilising metabolisable energy for growth.

The prediction of energy requirements for gain ( $\hat{E}$ ) (MJ kg<sup>-1</sup>) is:

$$\hat{E} = 6.7 + \hat{R} + \frac{(20.3 - \hat{R})}{1 + e^{-6(W/\bar{W} - 0.04)}}, \quad (\text{A.6})$$

where  $\hat{R}$  is the correction for feeding level when metabolisable energy intake is known and weight gain is to be predicted and  $\bar{W}$  is the standard reference weight of a lamb (kg).

The prediction of energy requirements for loss ( $\tilde{E}$ ) (MJ kg<sup>-1</sup>) is:

$$\tilde{E} = 6.7 + \hat{E} + \frac{(20.3 - \hat{E})}{1 + e^{-6(\hat{R} - 0.04)}}. \quad (\text{A.7})$$

The metabolisability of gross energy at maintenance ( $M$ ) is:

$$M = \frac{E}{GD}, \quad (\text{A.8})$$

where  $G$  is the gross energy in the feeds (MJ day<sup>-1</sup>).

The efficiency of utilising metabolisable energy for growth ( $k_f$ ) is:

$$k_f = 0.78M + 0.006. \quad (\text{A.9})$$

The correction for feeding level when metabolisable energy intake is known and weight gain to be predicted ( $\hat{R}$ ) is:

$$\hat{R} = 2\left(\frac{E}{\hat{E}} - 1\right). \quad (\text{A.10})$$

The gross energy in the feed ( $G$ ) (MJ day<sup>-1</sup>) is:

$$G = \sum \mathcal{G}_n, \quad (\text{A.11})$$

where  $\mathcal{G}_n$  is the gross energy for each feed component (MJ day<sup>-1</sup>).