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Research paper

Computer modelling of anthelmintic resistance and worm control outcomes for refugia-based nematode control strategies in Merino ewes in Western Australia

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ABSTRACT

This study utilised computer simulation modelling (Risk Management Model for Nematodes) to investigate the impact of different parasite refugia scenarios on the development of anthelmintic resistance and worm control effectiveness. The simulations were conducted for adult ewe flocks in a Mediterranean climatic region over a 20 year time period. Factors explored in the simulation exercise were environment (different weather conditions), drug efficacy, the percentage of the flock left untreated, the timing of anthelmintic treatments, the initial worm egg count, and the number of drenches per annum. The model was run with variable proportions of the flock untreated (0, 10, 20, 30, 40 and 50%), with ewes selected at random so that reductions in the mean worm burden or egg count were proportional to the treated section of the flock. Treatments to ewes were given either in summer (December; low refugia potential, hence highly selective) or autumn (March; less selective due to a greater refugia potential), and the use of different anthelmintics was simulated to indicate the difference between active ingredients of different efficacy. Each model scenario was run for two environments, specifically a lower rainfall area (more selective) and a higher rainfall area (less selective) within a Mediterranean climatic zone, characterised by hot, dry summers and cool, wet winters. Univariate general linear models with least square difference post-hoc tests were used to examine differences between means of factors. The results confirmed that leaving a proportion of sheep in a flock untreated was effective in delaying the development of anthelmintic resistance, with as low as 10% of a flock untreated sufficient to significantly delay resistance, although this strategy was associated with a small reduction in worm control. Administering anthelmintics in autumn rather than summer was also effective in delaying the development of anthelmintic resistance in the lower rainfall environment where all sheep were treated, although the effect of treatment timing on worm control effectiveness varied between the environments and the proportion of ewes left untreated. The use of anthelmintics with higher efficacy delayed the development of resistance, but the initial worm egg count or number of annual treatments had no effect on either the time to resistance development or worm control effectiveness. In conclusion, the modelling study suggests that leaving a small proportion of ewes untreated, or changing the time of treatment, can delay the onset of anthelmintic resistance in a highly selective environment.

1. Introduction

The widespread and increasing severity of anthelmintic resistance is considered the greatest threat to efficient sheep nematode (worm) control on a global basis (Kaplan and Vidyashankar, 2012). It is therefore critical to maintain the effectiveness of the current anthelmintic classes that are still effective, and that of any new anthelmintics that may be released (Kaminsky et al., 2008; Little et al., 2010; Leathwick and Besier, 2014). A major factor contributing to the development of anthelmintic resistance in livestock nematodes is the practice of treating all animals in the flock in situations with little refugia, i.e. parasites not exposed to anthelmintics (Besier and Love, 2003; Leathwick et al., 2009). Subsequent to

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whole flock treatments, the only eggs shed onto pasture are from worms that survived treatment and where there is no refugia as free-living stages on pasture, rapid selection for resistance is likely (Van Wyk, 2001; Kaplan, 2010).

Investigations into sustainable parasite control have included “refugia-based” management strategies, which aim to minimise the development of resistance by ensuring the survival of sufficient nematodes with susceptible genotypes to dilute resistant individuals surviving anthelmintic treatment (Van Wyk, 2001; Kenyon et al., 2009; Leathwick and Besier, 2014). In the Mediterranean-environment region of southern Western Australia, where *Trichostrongylus* spp. and *Teladorsagia circumcincta* are the predominant gastrointestinal nematodes, strategic anthelmintic treatments are commonly used in the hot and dry summer period where they impose heavy selection for anthelmintic resistance (Besier and Love, 2003). Two main refugia-based approaches to worm control have been investigated for this environment, both specifically intended for use in mature sheep (Besier, 2012). These involve either a whole-flock treatment to all sheep in autumn (when conditions for survival of free living stages are more favourable than in summer) in order to avoid the heavy resistance selection pressure of summer treatments (Woodgate and Besier, 2010), or a “targeted selective treatment” (TST) approach by which a proportion of a flock is left untreated in summer to retain non-selected (i.e. not anthelmintic exposed) worms in the population (Besier et al., 2010). Both approaches have implications for the likely acceptability to sheep farmers, due to concerns partly over the practicality of implementation, but especially for the effectiveness of parasite control of strategies which require the retention of worm populations in refugia. To achieve wide uptake, it is necessary to demonstrate that the recommended strategies provide a substantial benefit regarding the reduction in the development of anthelmintic resistance, but without a significant loss of worm control efficacy.

Field investigations in Western Australia have confirmed that a TST strategy based on the selection of ewes for treatment (or otherwise) using body condition score is a practical procedure and does not jeopardise wool production when applied in adult sheep flocks in this environment (Besier et al., 2010), or adversely affect body weight or condition score (Cornelius et al., 2014, 2015b). However, field studies to determine the longer-term effects on the development of anthelmintic resistance and impacts on worm control effectiveness in the flock into the future are difficult and expensive to conduct in real time. This study utilised computer simulation modelling to investigate the impact of different refugia scenarios on anthelmintic resistance and worm control effectiveness outcomes in adult ewe flocks in a Mediterranean climatic region over a 20 year time period. The modelled scenarios allow comparisons between timing of treatment (summer or autumn), different proportions of a flock left untreated, different locations within the region, and for anthelmintics with different resistance status. The aim of this study was to describe effects of refugia-based nematode control methods on worm control effectiveness and development of anthelmintic resistance, with the goal of developing appropriate worm control programs for a range of sheep management situations and environments that achieve the objectives of both efficiency and sustainability.

2. Materials and methods

2.1. Model—Risk Management Model for Nematodes (RMMN)

The model, previously described by Dobson et al. (2011a,b) was initially developed in FORTRAN for a DOS computing platform and more recently translated (Dobson, pers. com) to use in Excel under a Windows operating system (Microsoft, 2015).

2.2. Simulated sheep management

The model assumptions were that ewes were grazed at a stocking rate of 12 dry sheep equivalent per hectare (DSE: unit of measure to compare feed requirements or farm carrying capacity based on a two-year-old, 45 kg Merino wether or non-pregnant/lactating ewe). Ewes rotated between two paddocks each year, changing paddocks in December and back again in April. Lambs were born in June and ran with the ewes until weaned into a separate paddock in October. This cycle continued annually for 20 years. Periods of stress that can diminish the immune response of ewes to worms were taken into account in the model, including that of the peri-parturient relaxation of immunity during early lactation following lambing. Anthelmintic treatments were given to ewes as specified. Lamb treatments were always given at weaning (October) and in summer (December) with the same types of drenches that were used for the ewes in that year. Anthelmintic resistance and worm control effectiveness were assessed across worm populations in the entire flock (ewes and progeny), including the contribution of the lambs through cycling worm populations that originated in the ewes before and following treatment.

Output from the model included two measures: years to anthelmintic resistance and mean worm control effectiveness (as a percentage). Dobson et al. (2011b) provides a full description of how these measures are estimated and how deaths from concurrent nematode infections were estimated, based on model predictions of adult worm burdens. ‘Years to anthelmintic resistance’ indicates the time taken for the resistance (R) allele gene frequency to reach 50% in the infective larval population on pasture. ‘Worm control effectiveness’ is a similar concept to drug “efficacy” with higher effectiveness score representing better control, measuring the weighted average reduction in worm burden, egg counts, production penalty and deaths from an untreated control group over a number of years (Dobson et al., 2011b).

2.3. Factors simulated

Six factors were explored in the simulation exercise (Table 1): percentage of the flock left untreated, timing of anthelmintic treatments, number of drenches per annum, anthelmintic drugs used, environment (different weather conditions) and initial ewe faecal worm egg count (WEC). This gave rise to 480 separate 20-year simulations.

2.3.1. Proportion of flock left untreated

The model was run with variable proportions of the flock untreated (0, 10, 20, 30, 40 and 50%; Table 1), with ewes selected at random so that potential reductions in the mean worm burden or egg count were proportional to the treated percentage of the flock. This refugia strategy aims to allow unselected adult worm populations in sheep to contaminate pasture.

2.3.2. Time of treatment

To simulate the strategy of changing the time of strategic anthelmintic treatment of ewes from a highly selective to a less selective time of year, the model was run with treatments to ewes either in summer (December; low refugia potential i.e. few if any infective larvae on pasture, hence highly selective) or autumn (March; less selective due to a greater refugia potential) (Table 1 and Table 2). Lambs were treated to a standard program regardless of ewe treatments, with a treatment at weaning (October) and then in summer (December).