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Modelling the benefits of a new class of anthelmintic in combination

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ABSTRACT

Since 2009 two new classes of anthelmintics have been registered for use in sheep in New Zealand. This raises challenging questions about how such new actives should be used, not only to minimise the development of resistance to them, thereby ensuring their availability as effective treatments for as long as possible, but also to minimise the further development of resistance to the other anthelmintic classes. One strategy which appears to offer considerable potential for slowing the development of resistance is the use of combinations of different anthelmintic classes, although this approach remains contentious in some countries. The potential benefit of using anthelmintics in combination is particularly relevant to two recently released anthelmintic compounds because one, monepantel, is presently only available as a single active product while the other, derquantel, is only available in combination with abamectin.

A simulation modelling approach was used to investigate the potential benefits of using anthelmintics in combination. The rate at which resistance develops to a new 'active' when used alone was compared to an equivalent compound used in combination with a second compound from an alternative class (in this case, abamectin), when various levels of resistance occur to the second active. In addition, the potential of a new active to reduce further development of resistance to the second compound in the combination was evaluated. Finally, the use of combinations as compared to sequential or rotational use patterns, in the presence of side resistance between two actives was investigated.

The modelling simulations suggest a significant advantage to both compounds when they are used in combination, especially if both initially have high efficacy. The development of resistance to the new active was delayed, although to a lesser extent, even when the efficacy of the second active in the combination was only 50%. Under a 'low-refugia' management environment resistance to all actives developed more rapidly, and the advantage of using actives in combination was reduced. When used in conjunction with other resistance management strategies, a combination containing a new active prevented further development of resistance to the older class. Using actives in combination was superior to using them individually either sequentially or in rotation, even in the presence of side-resistance between the two anthelmintic classes.

1. Introduction

Anthelmintic resistance in gastrointestinal nematode parasites is a significant threat to the productivity of sheep farming in many parts of the world (Waller, 2006; Besier, 2007). Resistance to the benzimidazole (BZ), imidazothiazole (IM) and macrocyclic lactone (ML) classes of broad-spectrum anthelmintics is now widespread around the world (Nari et al., 1996; Besier and Love, 2003; Waghorn et al., 2006; Sargison et al., 2007). Importantly, on many farms, resistance has advanced to the point where more than one nematode species are resistant to more

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than one class of anthelmintic (Besier and Love, 2003; Sargison et al., 2005; Sutherland et al., 2008), meaning that combinations of different 'actives' (active ingredients) are often required just to maintain adequate control. On some farms there is the possibility that no anthelmintics will remain sufficiently effective for parasite control. Indeed, cases where farmers were forced to remove all sheep from the property due to an inability to control parasites have been reported (Sargison et al., 2005; Blake and Coles, 2007).

In 2009, monepantel, representing a new class of anthelmintics, the amino-acetonitrile derivatives (AAD) (Kaminsky et al., 2008) was released for use in sheep in New Zealand. In 2010 a further new class of compounds, the spiroindoles, represented by derquantel, was also registered for use in sheep in New Zealand (Little et al., 2010). With the release of these new compounds, farmers in New Zealand now have access to five classes of broad spectrum anthelmintics for use in sheep, a situation which has significantly altered the threat posed by anthelmintic resistance. For the immediate future there is no concern that farmers in New Zealand will not have effective treatments with which to control parasitism in their livestock. There may however, be financial consequences associated with resistance to the older classes of actives, given that it seems inevitable that new anthelmintics will command a premium price because of the vastly increased costs of their development and registration (Waller, 2006).

The release of new anthelmintic products has raised important questions about how they should be used. Given that more than 25 years have elapsed between the launching of the last class of anthelmintic (MLs) and the AADs, it is clear that an ongoing array of new compounds coming to market should not be anticipated. It is therefore prudent that any new class of anthelmintic be used in a way that will minimise the development of resistance to it (Besier, 2007; Leathwick et al., 2009). What is also clear is that new actives offer considerable potential, in some countries at least, to extend the effective life of the older classes (for example, Leathwick and Hosking, 2009).

One option for extending the useful life of anthelmintics is to use them in combination with at least one other anthelmintic compound from another class (Smith, 1990; Barnes et al., 1995). This concept is particularly topical today because monepantel has, initially at least, been released as a single active product while derquantel is only available in combination with abamectin (Little et al., 2010). However, the use of combinations to manage anthelmintic resistance remains controversial in some countries (Coles and Roush, 1992; Van Wyk, 2001). The literature pertaining to this issue was recently reviewed by Leathwick et al. (2009). In the present studies, computer modelling is used to investigate how effective a combination, containing a new active and a member of the ML class, is likely to be for delaying the development of resistance to the new active and also to extending the useful life of the ML. How this is likely to be influenced by different levels of ML resistance is also considered. Further, the potential for side-resistance between different anthelmintic classes has recently been proposed (Mottier and Prichard, 2008), and the question of whether this nullifies the advantages offered by combination anthelmintics is also considered.

2. Materials and methods

2.1. The model

The model has been described previously (Leathwick et al., 1992, 1995) and used to investigate both parasite dynamics and the development of resistance under different management practices (Leathwick and Sutherland, 2002; Leathwick et al., 2008; Leathwick and Hosking, 2009). Briefly, the model is generic in that it simulates a mixed nematode infection, rather than individual species (Leathwick et al., 1992), and incorporates both flocks of lambs and adult ewes. The development and survival of free-living nematode stages on pasture is described for each of a suite of paddocks. When a paddock is being grazed by ewes or lambs it receives inputs of nematode eggs, based on the faecal egg output of an individual multiplied by the stocking rate, and third-stage infective larvae (L3) are removed with ingested herbage. The number of ingested L3 determines subsequent worm burdens and faecal nematode egg counts under the influence of anti-parasite immunity which develops in response to both ingestion of L3 and the presence of adult worms.

Importantly, outputs from this model have previously been compared with and found to be consistent with the results of large-scale field trials, with respect to both the development of anthelmintic resistance (Leathwick et al., 2006) and nematode epidemiology (Leathwick et al., 2008).

2.2. Simulation parameters

For all simulations reported here lambs were born in early August (late winter) and grazed with their dams, set-stocked over a set of 5 paddocks, until weaning at 12 weeks of age, in early November (late spring). Stocking density was initially 18 ewes plus 22 lambs per hectare. After weaning two alternative grazing management strategies were evaluated.

In strategy 1 (rotational grazing) the lambs were separated from their dams at weaning and thereafter continued to graze in rotation over the paddocks on which they had lambed. A smaller flock of ewes (6 ewes/ha) also rotated over these paddocks, following 14 days behind the lambs. Lamb numbers were reduced on three occasions (in February, March and April) to reflect the progressive sales of animals for slaughter. Lambs received six preventive anthelmintic treatments at 28 day intervals, commencing at weaning, to reflect normal practice by sheep farmers in New Zealand (Brunsdon and Vlassoff, 1982; Lawrence et al., 2007). This strategy was intended to represent a scenario where lambs were given routine whole flock anthelmintic treatments, but reasonable efforts were made to manage anthelmintic resistance by maintaining a reservoir of susceptible genotypes, by not giving pre- or post-lambing treatments to adult ewes (Leathwick et al., 1995, 2006) and rotationally grazing treated lambs and untreated adult ewes over the same paddocks (Leathwick et al., 2008, 2009).