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Research paper

Managing anthelmintic resistance—Variability in the dose of drug reaching the target worms influences selection for resistance?

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ABSTRACT

The concentration profile of anthelmintic reaching the target worms in the host can vary between animals even when administered doses are tailored to individual liveweight at the manufacturer's recommended rate. Factors contributing to variation in drug concentration include weather, breed of animal, formulation and the route by which drugs are administered. The implications of this variability for the development of anthelmintic resistance was investigated using Monte-Carlo simulation. A model framework was established where 100 animals each received a single drug treatment. The 'dose' of drug allocated to each animal (i.e. the concentration-time profile of drug reaching the target worms) was sampled at random from a distribution of doses with mean *m* and standard deviation *s*. For each animal the dose of drug was used in conjunction with pre-determined dose-response relationships, representing single and poly-genetic inheritance, to calculate efficacy against susceptible and resistant genotypes. These data were then used to calculate the overall change in resistance gene frequency for the worm population as a result of the treatment. Values for *m* and *s* were varied to reflect differences in both mean dose and the variability in dose, and for each combination of these 100,000 simulations were run. The resistance gene frequency in the population after treatment increased as *m* decreased and as *s* increased. This occurred for both single and poly-gene models and for different levels of dominance (survival under treatment) of the heterozygote genotype(s). The results indicate that factors which result in lower and/or more variable concentrations of active reaching the target worms are more likely to select for resistance. The potential of different routes of anthelmintic administration to play a role in the development of anthelmintic resistance is discussed.

1. Introduction

The number of reports documenting the presence of anthelmintic resistance in nematode parasites of cattle have increased in recent years, although to what extent this reflects an increase in surveillance rather than an increase in prevalence remains unclear (Sutherland and Leathwick, 2011). Resistance appears to be most common in the relatively non-pathogenic *Cooperia* spp. (Waghorn et al., 2006; Sutherland and Leathwick, 2011; Cotter et al., 2015), however, the recent confirmation of macrocyclic lactone (ML) resistance in the highly pathogenic *Ostertagia ostertagi* (Demeler et al., 2009; Edmonds et al., 2010; Rendell, 2010; Geurden et al., 2015; Waghorn et al., 2016) suggests that a review of current worm control strategies in cattle, and the implementation of management practices capable of slowing the further development of resistance, is overdue in many countries. However, although there have been many years of research dedicated to understanding the factors selecting for resistance in parasites of sheep and goats (Leathwick et al., 2009; Leathwick and Besier, 2014) equivalent studies in cattle are noticeably lacking. Hence, there are almost no resistance management practices which have been derived, or validated, through studies in cattle. Further, although there are now numerous resistance management practices being implemented in sheep flocks around the world (Leathwick and Besier, 2014), it remains unclear to what extent these can be extrapolated to cattle.

One of the major differences between parasite control practices in sheep and cattle is the routes by which anthelmintics are administered. Anthelmintics are generally administered to sheep as oral drenches while cattle are normally treated via the topical (pour-on) or injectable routes. A recent study by Leathwick and Miller (2013) compared the efficacy and plasma profiles of the ML moxidectin administered to cattle by all three of these routes (i.e. oral, injection and pour-on) and found significant differences in both the mean efficacies of the treatments and the variability in efficacy between treated animals. Because this study compared the same active (moxidectin) administered by different routes against the same worm populations, it was hypothesised that the measured differences in efficacy reflect differences in the

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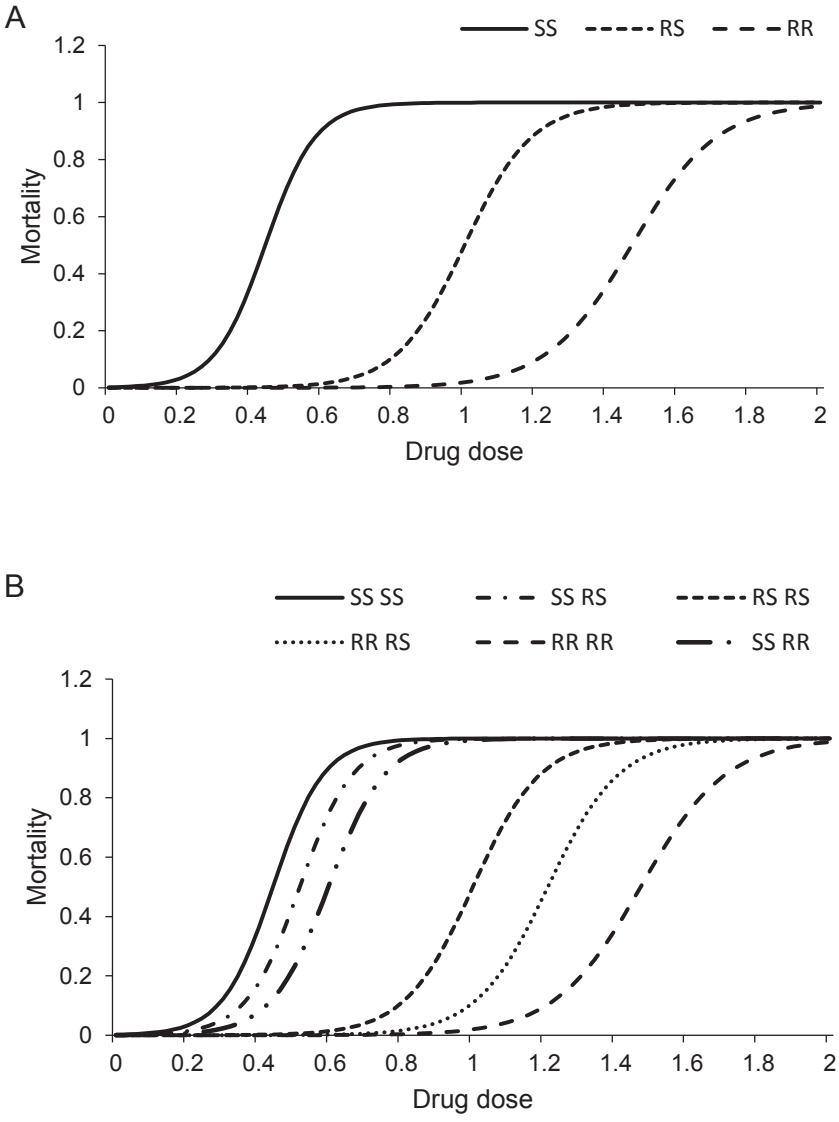

Fig. 1. Dose mortality curves from Eq. (1) for the single gene model a) and the two gene model b) using the coefficients from Table 1. Note that some curves have the same coefficients and so the dose-mortality lines are super-imposed.

delivery of active drug to the target worms in the gastrointestinal tract. Interestingly, the observed differences in efficacy were not consistent with the drug concentration-time profiles measured in plasma, indicating that plasma profile is not a good indicator of efficacy, or by inference the drug concentration reaching the target worms in the gastrointestinal tract. This conclusion is supported by studies in other hosts where different routes of administration have resulted in sizeable differences in drug concentrations in the target organs and/or worms and these have correlated with efficacy (Bogan and McKellar, 1988; Gokbulut et al., 2010; Lloberas et al., 2012). Given that different routes of administration can result in differences in drug concentration reaching the target worms, and its variability, an obvious question is whether this has implications for selection for anthelmintic resistance? This question was raised specifically by Gasbarre (2014) who speculated that the large variation in the amount of drug entering and distributed throughout the animal when treatment is by the pour-on route, could be a factor in selection for resistance in cattle parasites.

It is widely accepted that suboptimal dosing of anthelmintics will lead to the development of resistance (Prichard et al., 1980; Smith et al., 1999; Van Zeveren et al., 2007; Lespine et al., 2012) and indeed resistant worm populations have been selected by this method (Martin, 1989; Van Zeveren et al., 2007; Bartley et al., 2015). As a consequence, in some countries vigorous efforts have been made to ensure that farmers don't treat animals at below the manufacturer's recommended dose rate (Besier and Hopkins, 1988; Taylor, 2012; McMahon et al., 2013). However, sub-optimal dosing, at least to a proportion of the worm population, can also potentially occur through administering a drug in a manner which results in high variability in dose reaching the target worms. Logically, this is also likely to select for resistance. However, the potential of high variability in the dose of drug reaching the target worms to select for anthelmintic resistance has not previously been formally investigated, and it is difficult to conceive how this might be measured empirically. Therefore, the purpose of this study was to investigate the implications of suboptimal dosing, achieved either through a reduced mean dose or through a wider variation in dose of anthelmintic reaching the target worms, on the development of anthelmintic resistance.

2. Materials and methods

Monte-Carlo simulation was used to investigate the effect of variations in the concentration of drug reaching the target worms on the resistance gene frequency in a worm population over a single anthelmintic treatment. A model framework was established in which 100 animals each received a single treatment with an anthelmintic. The dose of drug allocated to each animal was sampled at random from a normal frequency distribution with mean (m) and standard deviation (s). For each animal the efficacy of treatment was calculated using a