



## Research paper

# Which is the best phenotypic trait for use in a targeted selective treatment strategy for growing lambs in temperate climates?



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## ABSTRACT

Targeted selective treatment (TST) requires the ability to identify the animals for which anthelmintic treatment will result in the greatest benefit to the entire flock. Various phenotypic traits have previously been suggested as determinant criteria for TST; however, the weight gain benefit and impact on anthelmintic efficacy for each determinant criterion is expected to be dependent upon the level of nematode challenge and the timing of anthelmintic treatment. A mathematical model was used to simulate a population of 10,000 parasitologically naïve Scottish Blackface lambs (with heritable variation in host-parasite interactions) grazing on medium-quality pasture (grazing density = 30 lambs/ha, crude protein = 140 g/kg DM, metabolisable energy = 10 MJ/kg DM) with an initial larval contamination of 1000, 3000 or 5000 *Teladorsagia circumcincta* L<sub>3</sub>/kg DM. Anthelmintic drenches were administered to 0, 50 or 100% of the population on a single occasion. The day of anthelmintic treatment was independently modelled for every day within the 121 day simulation. Where TST scenarios were simulated (50% treated), lambs were either chosen by random selection or according to highest faecal egg count (FEC, eggs/g DM faeces), lowest live weight (LW, kg) or lowest growth rate (kg/day). Average lamb empty body weight (kg) and the resistance (R) allele frequency amongst the parasite population on pasture were recorded at slaughter (day 121) for each scenario. Average weight gain benefit and increase in R allele frequency for each determinant criterion, level of initial larval contamination and day of anthelmintic treatment were calculated by comparison to a non-treated population. Determinant criteria were evaluated according to average weight gain benefit divided by increase in R allele frequency to determine the benefit per R. Whilst positive phenotypic correlations were predicted between worm burden and FEC; using LW as the determinant criterion provided the greatest benefit per R for all levels of initial larval contamination and day of anthelmintic treatment. Hence, LW was identified as the best determinant criterion for use in a TST regime. This study supports the use of TST strategies as benefit per R predictions for all determinant criteria were greater than those predicted for the 100% treatment group, representing an increased long-term productive benefit resulting from the maintenance of anthelmintic efficacy. Whilst not included in this study, the model could be extended to consider other parasite species and host breed parameters, variation in climatic influences on larval availability and grass growth, repeated anthelmintic treatments and variable proportional flock treatments.

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## 1. Introduction

Reduced drug efficacy due to the emergence of anthelmintic resistance (Kaplan, 2004; Wolstenholme et al., 2004; Jabbar et al., 2006; Papadopoulos et al., 2012) threatens the sustainability of livestock systems (van Wyk et al., 1997; Waller, 2006a; Besier,

2007; Papadopoulos, 2008), prompting the proposition of a variety of non-chemotherapeutic control options (Besier and Love, 2003; Waller, 2003; Sayers and Sweeney, 2005; Jackson and Miller, 2006; Stear et al., 2007; Torres-Acosta and Hoste, 2008). Unfortunately, these do not provide sufficiently effective parasite control without chemotherapeutic support (van Wyk et al., 2006). Thus, anthelmintics remain an indispensable component of nematode control programs, further supported by their low cost and ease of use (Kenyon and Jackson, 2012). As such, integrated parasite control programs must deliver efficacious control whilst minimizing

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negative effects on drug efficacy in a manner that meets the risk profile of sheep producers.

Anthelmintic treatments are directed towards the infra-population of nematodes (parasitic stages within the host) thereby leaving the supra-population (pre-parasitic stages on pasture) *in refugia* (unexposed to anthelmintics) (van Wyk, 2001; Soulsby, 2007; Besier, 2012), providing a reservoir of more susceptible genotypes which dilute the progeny of resistant nematodes surviving anthelmintic treatment (van Wyk et al., 2006). Anthelmintic treatment is known to select for resistance in proportion to the nematode population *in refugia* (Martin et al., 1981; Michel, 1985), and consequently practices such as administering anthelmintics prior to a move to a low worm-risk pasture should be carefully managed (Martin et al., 1985; Waghorn et al., 2009). Whilst grazing management (Waller, 2006b) and the host immune response (Laurenson et al., 2012a) affect nematode epidemiology, environmental conditions experienced by the supra-population are the predominant factor impacting upon the nematode population *in refugia* (Stromberg, 1997; O'Connor et al., 2006; van Dijk et al., 2010; Morgan and van Dijk, 2012; Rose et al., 2015). Consequent fluctuations in the level of pasture contamination have led to the proposal of targeting whole flock treatments (TT, targeted treatment) at times when the supra-population provides a large *refugia* pool (Kenyon et al., 2009; Kenyon and Jackson, 2012), coinciding with periods in which the hosts will be exposed to a high level of infective larval challenge.

Further, the infra-population is known to be over-dispersed, such that the majority of the parasitic burden is aggregated within a small percentage of the host population (Barger, 1985; Sréter et al., 1994; Gaba et al., 2005). In practical terms, anthelmintic treatment can therefore be directed towards the individuals within a flock with the heaviest parasitic burden (Gallidis et al., 2009; Stafford et al., 2009; Gaba et al., 2010). Targeted selective treatment (TST) can thereby reduce the number of anthelmintic treatments administered to a flock and increase the nematode population *in refugia* by leaving a proportion of the infra-population untreated (van Wyk et al., 2006; Kenyon et al., 2009). As such, TST strategies require the ability to identify individuals for anthelmintic treatment. Genetic and genomic approaches have previously been proposed; however, in the absence of reliable genetic markers across populations, phenotypic traits were found to be preferable to estimated breeding values as the larval challenge experienced by an individual may be dis-similar to its family members due to large environmental effects (Laurenson et al., 2013a). A variety of clinical pathophysiological indicators have also been proposed and implemented; including various diarrhoea scores (Larsen et al., 1994; Larsen and Anderson, 2000; Cabaret et al., 2006; Broughan and Wall, 2007; Ouzir et al., 2011; Bentounsi et al., 2012), body condition score (Russel, 1984; Besier et al., 2010; Cornelius et al., 2014), anaemia score/FAMACHA<sup>®</sup> (Malan et al., 2001; Vatta et al., 2001; van Wyk and Bath, 2002; Kaplan et al., 2004; Molento et al., 2009; Ouzir et al., 2011; Bentounsi et al., 2012), and combinational indexes such as The Five Point Check<sup>®</sup> (Bath and van Wyk, 2009). However, these clinical indicators rely on visual assessment and are therefore prone to subjective errors (Greer et al., 2009). Additionally, anaemia is indicative of haematophagous nematodes (i.e. *H. contortus*) or liver fluke infections, and thus not suitable for use as an indicator of the *T. circumcincta* and *Trichostrongylus* spp. infections predominant in temperate climates (van Wyk et al., 2006). Further, it may be considered preferable to treat animals prior to overt clinical signs becoming apparent.

Subclinical indicators of gastrointestinal parasitism can identify between-animal variation in host resistance (suppression of nematode challenges via an immune response; Bishop and Morris, 2007) and resilience (ability to withstand the pathogenic effects of nematode challenge; Bisset and Morris, 1996). Faecal egg count (FEC) has

previously been used as a measure of host resistance (Woolaston and Baker, 1996; Morris et al., 1997; Kemper et al., 2010). TST based on treating animals with the highest FEC thereby reduces egg deposition and consequently the larval challenge experienced by the grazing flock (Kenyon et al., 2009; Kenyon and Jackson, 2012) and the associated impacts on performance (Coop et al., 1982, 1985; Holmes, 1987; Fox, 1997; Stear et al., 2003). Hence, FEC has previously been implemented as a determinant criterion for TST (Cringoli et al., 2009; Gallidis et al., 2009). In contrast, measures of host resilience provide a more direct welfare approach as only the least resilient animals are treated (Cabaret et al., 2009; Berrag et al., 2009; Kenyon et al., 2009; Kenyon and Jackson, 2012). Indicators of host resilience previously implemented as determinant criteria for TST include live weight (Leathwick et al., 2006a,b), weight gain (Stafford et al., 2009; Gaba et al., 2010; Bentounsi et al., 2012), production efficiency/HappyFactor<sup>TM</sup> (Greer et al., 2009; Busin et al., 2013, 2014; Kenyon et al., 2013), and milk production (Hoste et al., 2002; Cringoli et al., 2009; Gallidis et al., 2009; Gaba et al., 2010).

Evaluation of these determinant criteria has predominantly focussed on the productive impact of implementing TST regimes (e.g. Busin et al., 2014). Few studies have explored the impact upon anthelmintic efficacy (Leathwick et al., 2006b; Kenyon et al., 2013), due to the difficulty in measuring changes in anthelmintic resistance over short time periods (Gilleard, 2006; Besier, 2012). As such, computer simulation modelling has been suggested as a method of developing appropriate *refugia* strategies (Besier, 2012; Kenyon and Jackson, 2012), thereby reducing the necessity for expensive and time-consuming experimental trials.

The aim of this study was to use a mathematical model to compare the subclinical phenotypic traits proposed as determinant criteria for TST regimes, and investigate the impact of initial pasture larval contamination (*T. circumcincta* L<sub>3</sub>/kg DM) and day of anthelmintic treatment on sheep performance and the emergence of anthelmintic resistance.

## 2. Materials and methods

### 2.1. Mathematical model

The mathematical model of Laurenson et al. (2013b) describes the impact of host nutrition, genotype and *T. circumcincta* gastrointestinal parasitism on a population of growing lambs, and includes the impact of anthelmintic treatment on host performance, nematode epidemiology and the emergence of anthelmintic resistance.

#### 2.1.1. Individual lamb module

A schematic diagram describing the structure of the individual lamb module is provided in Fig. 1. In brief, each lamb attempted to ingest sufficient nutrients to meet protein and energy requirements for desired growth and maintenance, as defined by its genotype (Emmans, 1997; Wellock et al., 2004). However, if the nutritional quality of available herbage was poor then resource intake may be constrained by the maximum gut capacity (Lewis et al., 2004). Grazing led to the concurrent ingestion of infective larvae (L<sub>3</sub>) from pasture, modelled as a function of herbage intake and pasture larval contamination (Laurenson et al., 2012b). Within the host, ingested larvae matured (following a pre-patent period; Coop et al., 1982), established, produced eggs and died, as determined by rates for establishment, density-dependent fecundity and mortality (Bishop and Stear, 1997; Louie et al., 2005). Parasitic burdens within the host were assumed to result in an endogenous protein loss (Yakoob et al., 1983), modelled as a function of larval challenge and worm mass (Vagenas et al., 2007a). To counteract this, the host was assumed to invest in an immune response causing decreased

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