



## Short communication

## Can we use genetic and genomic approaches to identify candidate animals for targeted selective treatment

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## ABSTRACT

Estimated breeding values (EBV) for faecal egg count (FEC) and genetic markers for host resistance to nematodes may be used to identify resistant animals for selective breeding programmes. Similarly, targeted selective treatment (TST) requires the ability to identify the animals that will benefit most from anthelmintic treatment. A mathematical model was used to combine the concepts and evaluate the potential of using genetic-based methods to identify animals for a TST regime. EBVs obtained by genomic prediction were predicted to be the best determinant criterion for TST in terms of the impact on average empty body weight and average FEC, whereas pedigree-based EBVs for FEC were predicted to be marginally worse than using phenotypic FEC as a determinant criterion. Whilst each method has financial implications, if the identification of host resistance is incorporated into a wider genomic selection indices or selective breeding programmes, then genetic or genomic information may be plausibly included in TST regimes

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## 1. Introduction

Targeted selective treatment (TST) has previously been proposed as a means of reducing the rate at which anthelmintic resistance develops, and consequently prolonging effective parasite control in livestock systems reliant upon anthelmintic drugs (van Wyk et al., 2006). TST strategies reduce the number of anthelmintic treatments administered (and thereby the selective pressure for anthelmintic resistance), by selectively treating only those animals that will benefit most from treatment (Kenyon et al., 2009). As such, TST strategies require the ability to identify those animals within a flock that are most susceptible to parasitism.

Previously, Laurenson et al. (2013) used a mathematical modelling approach to compare various phenotypic traits as determinant criteria for TST and concluded that

compared to live weight or weight gain, faecal egg counts (FEC) led to higher levels of flock performance for a given percentage of animals drenched. However, FEC is prone to variation arising from a number of sources which may obscure the identification of susceptible animals for TST including faecal output (Niezen et al., 1998), differences in the genetic growth attributes of the host population (Stear et al., 1996) and sampling errors (Stear et al., 2009).

The ability to identify genetically resistant animals has previously been an area of interest for use in selective breeding programmes (Stear et al., 2001). Traditionally this has been achieved using phenotypic traits (Kemper et al., 2010), however it is now standard practice to obtain estimated breeding values (EBV) for individual animals based upon individual and relatives' FEC data, combined with knowledge of animals' pedigree. Using EBV for FEC may thereby provide a method of reducing the noise due to the factors described above, and give a better indication of the underlying host resistance. Further, with dense single nucleotide polymorphism (SNP) chips available for sheep, it is now possible in principle to obtain genomic

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predictions of nematode resistance without the requirement for a phenotype on the candidate animal (Meuwissen et al., 2001; Kemper et al., 2011); this is currently routine for production and health traits in the dairy industry.

Prior to costly and logistically demanding field studies, a mathematical modelling approach may provide an indication of the potential of using EBV for host resistance to parasites, based on FEC data or genetic markers, as determinant criteria in a TST regime. The aim of this simulation study was to evaluate the potential of using EBV based on phenotypic traits (FEC) or genetic markers for host resistance as determinant criteria for a TST regime, and compare results to other criteria, such as FEC.

## 2. Materials and methods

The mathematical model of Laurenson et al. (2013) was used as the basis of this study. The model describes the impact of host nutrition, genotype and gastro-intestinal 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. Between-animal variation was included in animal growth attributes (optimal growth rate and body composition at maturity), maintenance requirements, and the ability to mount an immune response (rate of acquisition, as well as initial and final rates for host-controlled establishment, mortality and fecundity). Initial input parameters describing these traits were assumed to be normally distributed and all input traits, other than those associated with host resistance, were assumed to be uncorrelated (Doeschl-Wilson et al., 2008). Resistance traits (i.e. establishment, mortality and fecundity) were assumed to be strongly correlated ( $r=+0.5$ ), as a function of overlapping effector mechanisms (such as components of the Th2 immune response) (Jenkins and Allen, 2010).

Whilst host and parasite descriptions within model can be parameterized to represent different hosts (e.g. different sheep breeds) as well as nematode species, in this instance host growth characteristics were parameterized such that trait means and between-animal variance matched those of Bishop et al. (1996) and Bishop and Stear (1997) for Scottish Blackface lambs, and parasitological parameters matched those of Coop et al. (1982) for lambs infected with *Teladorsagia circumcincta*. However, it should be noted that the concepts and principles presented in this paper may be considered generally applicable to other nematode species and to nematode infections in other host species such as cattle and goats.

A population of 10,000 lambs, generated from mating 250 sires to 5000 dams according to a pre-determined mating structure, was simulated to be grazing on a medium-quality pasture (AFRC, 1993) at a density of 30 lambs/ha for 4 months from weaning to 6 months of age. This large population size was chosen to ensure that trait means at each time point were estimated with precision, avoiding the need for statistical analyses of the outputs. With this population size, the expected standard error of each mean value within the simulation is  $\sigma/100$ , where  $\sigma$  is the trait standard deviation at that time point. Therefore, even with extremely variable traits such as FEC, which have

a coefficient of variation close to 100%, the standard error of the mean will only be 1% of the mean value.

The lambs were assumed to be initially parasitologically naïve and the initial larval contamination of pasture was set at 3000 *T. circumcincta* larvae/kg DM (Coop et al., 1982), and the frequency of the recessive allele that confers anthelmintic resistance (R) in the parasite was initially set to 0.01 (Barnes et al., 1995). Anthelmintic drenching was assumed to reduce the population of infective larvae and adult nematodes resident within a host by 99% for heterozygous (RS) and homozygous susceptible genotypes (SS), and by 1% for homozygous resistant genotypes (RR). The frequency of the R allele was tracked in the parasite population, assuming standard Mendelian inheritance.

Basing TST on lamb EBV for FEC poses a problem of potential incompatibility. In the circumstance where only a proportion of animals are treated (i.e. TST), anthelmintic intervention only impacts upon the FEC of treated animals yet affects the estimation of breeding values for the entire population. Therefore, we propose three solutions to this problem. Firstly, the EBV for FEC may be based on the parental average EBV (pEBV) for the entire growth period, where the parental EBVs for FEC have been estimated in a system where all animals have been treated the same. Consequently, pEBV was calculated by simulating the population of lambs over a single grazing season in the absence of any anthelmintic treatment. The FEC of each lamb (including a sampling error with a variance of 20% (Stear et al., 2009)) was recorded on days 30, 60, 90 and 120. Sire and dam EBVs for FEC were then calculated from the log-transformed FEC ( $\ln(\text{FEC} + 1)$ ) data of the lamb population using an animal model in ASReml (Gilmour et al., 2009), correcting for day of sampling. Individual lambs were then assigned the average of their parental EBVs. Thus, this approach assumes that the lamb population arose from a breeding programme for which parental EBVs were available.

Secondly, the EBV for FEC may be based on only the first FEC sampling occasion (fEBV) before animals are selectively treated. Thus, fEBV was calculated from log-transformed FEC data (including sampling error) recorded prior to the first anthelmintic treatment using an animal model in ASReml (Gilmour et al., 2009). Phenotypic FEC measurements were assumed to be taken 5 days prior to anthelmintic treatment to allow for the samples to be processed and analysed.

Thirdly, it may be assumed that we already know the lamb EBV for FEC, this approach may be considered to equate to perfect genomic selection. Therefore, an individual lamb true EBV for FEC (tEBV) was calculated from log-transformed FEC data (without sampling error) recorded on days 30, 60, 90 and 120 in the absence of anthelmintic treatment, using an animal model in ASReml (Gilmour et al., 2009), correcting for day of sampling.

To evaluate the potential of using these differing EBVs for FEC to identify susceptible animals for TST, the population of lambs was simulated for a single grazing season with anthelmintic treatment administered only on day 30 (Laurenson et al., 2013), and the proportion of the lamb population given anthelmintic treatment was investigated at each of the 10th percentiles (0%, 10%, 20%...90%,

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