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Targeted anthelmintic treatment of parasitic gastroenteritis in first grazing season dairy calves using daily live weight gain as an indicator

A. Jackson[1], K.A. Ellis[1]. J. McGoldrick[1], N.N. Jonsson[2], M.J.Stear[3], A.B. Forbes[1]

[1]Scottish Centre for Production Animal Health and Food Safety, School of Veterinary Medicine, College of Veterinary and Life Sciences; University of Glasgow, Bearsden, Glasgow, G61 1Q

[2] Institute of Biodiversity, Animal Health and Comparative Medicine, College of Veterinary and Life Sciences; University of Glasgow, Bearsden, Glasgow, G61 1Q

[3]La Trobe University, Animal, Plant and Soil Sciences, Melbourne, Australia.

Corresponding author: A.B. Forbes: Telephone +44(0)7712738530; email andrew.forbes@glasgow.ac.uk

A. Jackson's current address is: Merial New Zealand, Level 3, Merial Building, 2 Osterley Way, Auckland 2104, New Zealand

ABSTRACT

Control of parasitic gastroenteritis in cattle is typically based on group treatments with ~~appropriate~~ anthelmintics, complemented by grazing management, where feasible. However, the almost inevitable evolution of

resistance in parasitic nematodes to anthelmintics over time necessitates a reappraisal of their use in order to reduce selection pressure. One such approach is targeted selective treatment (TST), in which only individual animals that will most benefit are treated, rather than whole groups of at-risk cattle. This study was designed to assess the feasibility of implementing TST on three commercial farms, two of which were organic. A total of 104 first-grazing season (FGS), weaned dairy calves were enrolled in the study; each was~~. All animals were~~ weighed at monthly intervals from the start of the grazing season using scales or weigh-bands. A~~; a~~t the same time dung and blood samples were collected in order to measure faecal egg counts (FEC) and plasma pepsinogen, respectively. A pre-determined threshhold weight gain of ~~less than~~ 0.75 kg/day was used to determine those animals that would be treated; t~~. T~~he anthelmintic used was eprinomectin. ~~, which has persistent efficacy of 3 weeks against *Cooperia oncophora* and 4 weeks against *Ostertagia ostertagi*.~~ No individual animal received more than one treatment during the grazing season and all treatments were given in July or August; five animals were not treated at all because their growth rates consistently exceeded the threshold. Mean daily live weight gain over the entire grazing season ranged between 0.69 and 0.82 kg/day on the three farms. ~~On the two organic farms, these growth rates exceeded those recorded during the preceding grazing season.~~ Neither FEC nor pepsinogen values were significantly associated with live weight gain ~~and therefore are unsuitable markers for performance-based TST~~. Implementation of TST at farm level requires regular (monthly) handling of the animals and the use of weigh scales or tape, but can be integrated into farm management

practices. This study has shown that acceptable growth rates can be achieved in ~~young~~ FGS cattle with modest levels of treatment and correspondingly less exposure of their nematode populations to anthelmintics, which should mitigate selection pressure for resistance by increasing the size of the refugia in ~~the~~ both hosts and ~~on~~ pasture.

Key words: Targeted selective treatment, TST, parasitic gastroenteritis, PGE, cattle, eprinomectin, ~~organic~~

1. INTRODUCTION

~~The spectre of a~~Anthelmintic resistance (AR) ~~hangs like a malevolent cloud over many popular methods of parasite control and consequently resistance~~ has become a major driver for parasitology research and in tailoring advice on parasite control~~to farmers~~. In northern temperate Europe there are currently only three classes of anthelmintic that are licensed for the control of parasitic gastroenteritis (PGE) in cattle: benzimidazoles, tetrahydropyrimidines (levamisole)~~s~~ and macrocyclic lactones (MLs), none of which are available in combination with each other. The most commonly reported cases of resistance in bovine nematode parasites in Europe have been in *Cooperia* species, in which the efficacy of MLs has been shown to be sub-optimal (Geurden et al., 2015). Given that *Cooperia* spp. are ~~commonly~~ dose-limiting ~~in~~ for ~~the~~ several MLs (Vercruysse and Rew, 2002), accurate weighing of animals and ~~dose~~ administration of the correct dose is essential for efficacy and reports of resistance in which these basic criteria have not be fulfilled should be treated circumspectly. In addition there is some evidence for ML-resistant *Ostertagia ostertagi* in Europe, which has also been observed in other regions of the world (Sutherland and Leathwick, 2011; Waghorn et al., 2016). For these reasons it is paramount that practices that reduce selection pressure for resistance and conserve the longevity of the current array of cattle anthelmintics are adopted.

In New Zealand, the emergence of ML-resistant *Cooperia* was associated with high frequency (every 3-4 weeks) administration over periods of six months or longer each year in young cattle grazed intensively (Jackson et al., 2006). There is little evidence for similar use patterns in Europe, where specific risk factors for AR in cattle have not been determined. Early season strategic anthelmintic treatments have been well established in Europe and shown to provide effective control of parasitic gastroenteritis (PGE) particularly in set-stocked, weaned first grazing season (FGS) cattle (Shaw et al., 1998), but also in the second year at grass (Taylor et al., 1995). The primary objective of strategic approaches is to limit concentrations of infective larvae in the herbage throughout the grazing season by minimising worm egg output and ~~auto~~re-infection, so strategic treatments create low challenge pastures with correspondingly low refugia; this has the potential to increase the speed of selection for anthelmintic resistance (Martin et al., 1981).

Irrespective of the possible risk factors for AR in cattle nematodes, practices that reduce anthelmintic usage are likely to limit selection pressure on parasite populations. One such approach is targeted selective treatment (TST) in which, rather than the more typical, synchronous group anthelmintic treatments, individual animals are treated on the basis of a marker or markers that indicate that they will benefit from removal of their parasite burdens. Targeted selective anthelmintic treatments (TST) were initially studied in small ruminants (Kenyon et al., 2009), in which proof of concept was demonstrated insofar as disease control and animal performance could be maintained with TST at a level comparable to that seen in animals that were treated more intensively. Equally important was the demonstration that TST applied over successive years led to lower selection for resistance compared to that in lambs treated at 4-week intervals over the grazing season (Kenyon et al., 2013).

There is limited published literature regarding the use of performance-based TST approaches in cattle in the field (Charlier et al., 2014; Kenyon and Jackson, 2012). Analysis of published trial data using reporter operating curve (ROC) analysis suggested that an appropriate threshold for daily live weight gain (DLWG) in a TST regime in young cattle would be 0.75 kg/day (Hoglund et al., 2009). This figure coincides with growth rates that are required for replacement dairy heifers to reach minimal breeding weight at 15 months in order to calve at two years of age (Froidmont et al., 2013; Zanton and Heinrichs, 2005)~~, thus, DLWGs of ~0.75kg are consistent with commercial targets and farmer aspirations~~ . Weight-gain based TST approaches have provided similar results to those reported in sheep, that is to say acceptable weight gains have been maintained and the number of anthelmintic treatments has been reduced compared to routine, whole group treatments (Greer et al., 2010; Hoglund et al., 2013; McAnulty et al., 2011). It should be noted that to date, TST has only been shown to be effective in the management of PGE, furthermore, if, for example, lungworm (*Dictyocaulus viviparus*) is present and has not been controlled through vaccination, then parasitic bronchitis can thwart efforts to control PGE through TST (O'Shaughnessy et al., 2015).

A series of studies were conducted to extend the scientific evidence base for TST in cattle and to determine its on-farm feasibility (Jackson, 2012). Included in this work was an assessment of various biomarkers as potential indicators for TST, an evaluation of the accuracy and utility of weigh bands for farms that do not have access to weigh scales and implementation of a weight gain-based TST. The objective of the study described in this paper was to determine the feasibility of a weight-gain based TST in first season dairy-bred calves on three livestock farms, two of which were organic.

2. MATERIALS AND METHODS

This TST study was approved by the Ethics and Welfare Committee of the School of Veterinary Medicine, University of Glasgow.

2.1. Participating Farms

Three dairy farms located in central and south-west Scotland were recruited into the study: two organic and one conventional (Farm O1, Farm O2 and Farm C3). The three farms were a sub-set of the six farms that were involved in a monitoring study of gastrointestinal parasitism the previous year (Jackson, 2012).

2.1.1 Organic Farm 1 (O1)

Organic dairy farm 1 comprised a mixed breed milking herd, predominantly of Friesians and Ayrshires, with some Brown Swiss and Jersey crosses, calving all-year-round and grazing over 93 hectares (ha) of semi-improved grassland from April to October. All FGS cattle in the study were vaccinated against lungworm prior to turnout in late April, when the calves grazed a small paddock near the farm and were given supplementary feed. Two weeks later the calves were moved onto another pasture and subsequently were rotated every two weeks around seven different paddocks in an extensive grazing system. The previous year these fields were grazed by FGS, second season grazers (SGS) or adult dairy cattle.

In the year prior to the TST study, faecal egg counts (FEC) were taken in June and September and only calves with a FEC of ≥200 eggs per gram (epg) were treated with fenbendazole (Panacur® 10% oral suspension, MSD). The farmer had used this method of anthelmintic treatment over the previous two grazing seasons. The average DLWG in FGS calves during the year that preceded the TST study was 0.46 kg/day.

2.1.2. Organic Farm 2 (O2)

Organic dairy farm 2 covered 344 ha which supported a milking herd of 135 Ayrshire and Ayrshire cross cows; some Aberdeen Angus suckler cows and sheep were also kept on the farm. Approximately forty per cent of the dairy herd calved between November and December, the rest calved year-round; heifers calved between February and April. The FGS were turned out in early May as a group of sixty calves, which were rotationally grazed over three fields, each of ~20 ha. The year before the TST study, based on faecal egg counts, all FGS were treated with fenbendazole drench in mid-July; the treatment was repeated again at housing in late November. The average DLWG in FGS calves during the year that preceded the TST study was 0.57 kg/day.

2.1.3. Conventional Farm 3 (C3)

The conventional dairy farm milked a herd of eighty five Holstein-Friesian cows and there were also beef and sheep enterprises on the farm. Calving in the dairy herd was year round and both heifer replacements and beef x dairy calves were grazed together. The previous year, the FGS animals were not turned out until mid-July because herbage regrowth after early sheep grazing was insufficient; they were set-stocked on four hectares of land and treated with moxidectin injection (Cydectin^{tm} 10%, Zoetis) at turnout. The average DLWG in FGS calves during the year that preceded the TST study was 0.93 kg/day.

2.2 Experimental Animals

All first season grazers (FGS) on-farm were included in the study (Farm O1 n = 20, Farm O2 n = 41, Farm C3 n = 43). All animals on Farms O1 and C3 were vaccinated against *D. viviparus* (Bovilis Huskvac™, MSD) before turnout to control lungworm disease.

2.3. Experimental Design

Farms were visited in late April and early May 2010, just prior to turnout from housing onto pasture and then at 28-day intervals until housing in the autumn, except for September, when two of the farmers were unable to gather the cattle because of other farming activities. At visit 1 on all farms, each FGS animal had its live weight calculated by weigh-band (Coburn® weigh tape). On Farm C3, all FGS were also weighed on Ritchie® mechanical weigh-scales. At visit 3 in July, eight to ten weeks post-turnout, the girth of all FGS calves were measured using the weigh-band and their live weight gain from turnout calculated. If the live weight gain of an individual animal was < 0.75 kg/day they were treated with eprinomectin (Eprinex™ pour-on, Merial). At visit 4 in August, the live weight gain of the FGS over the previous four weeks was calculated. Animals that had not been treated previously and were growing < 0.75 kg/day were treated with eprinomectin.

Because e~~E~~prinomectin has persistent activity of twenty-eight days against *O. ostertagi* and 21 days against *C. oncophora* (Cramer et al., 2000), ~~the two most common species contributing to PGE in FGS in northern Europe. Thus, following treatment, FECs would be expected to be minimal for 6-7 weeks, this being the sum of persistent activity and a typical pre-patent period of ~3 weeks for *O. ostertagi* and *C. oncophora*. For this reason,~~

animals previously treated at visit 3 were not treated again at visit 4, irrespective of their DLWG in the interim, as this would have meant treating within the effective pre-patent period and this can potentially exert a high selection pressure for AR. As farmers had requested a month off from sampling in September on farms O1 and O2, no treatments were given on this visit (5) on Farm C3. No treatment was planned for visit 6 at housing.

2.3.1. Laboratory Analysis

Each calf had a blood sample taken by jugular or coccygeal venepuncture into an EDTA tube for serum pepsinogen analysis (all visits) and a faecal sample taken *per rectum* obtained at visits 2, 3, 4, 5 and 6 for faecal egg count, lungworm and liver fluke monitoring. Larval culture was performed on faeces collected during visit 3. Further details of the standard laboratory techniques used can be found in a ~~companion~~ previously published paper (Ellis et al., 2011).

2.3.2. Statistical Analysis

The Spearman’s rank correlation test was used on non-normally distributed data to investigate any associations with live weight gain. Statistical analysis of the data was performed using Excel, Minitab 16 for Windows and SAS University edition (SAS Institute, Cary, N. Carolina). The association of bodyweight or growth rate with faecal egg count (FEC) or pepsinogenaemia (Pep) was assessed by repeated measures variance analysis. The proc mixed procedure in SAS was used and the model fitted the effects of farm, sample date, test variable (FEC or Pep) and the interaction between sample date and test variable. Several variance structures were tested including unstructured, compound symmetry and heterogeneous autoregressive of order 1. The best fitting model was chosen using four criteria: residual log likelihood, Akaike's information criterion (AIC), the finite-population corrected AIC and Bayes Information criterion (BIC). For both faecal egg count and plasma pepsinogen concentration, a heterogeneous autoregressive structure provided the best fit.

3. RESULTS

3.1. Live weight Gain

Mean live weight gains (± Standard Deviation) over the grazing season for all FGS animals in the study were:

- Farm O1 0.69 ± 0.28 kg/day (weighband)
- Farm O2 0.82 ± 0.13 kg/day (weighband)
- Farm C3 0.75 ± 0.23 kg/day (weigh scale)

The cattle on the conventional farm were heavier (277 kg) at turnout than those on the organic farms (190 and 167 kg), but the growth curves of cattle on all three farms were similar and DLWG was distributed normally amongst all the animals (Figure 1).

3.2. Faecal Egg Count

No results are available from t~~T~~he faecal samples taken from the cattle on the organic farms on visit 6 as they were stored incorrectly~~poiled~~ after collection~~ in the laboratory~~. The majority of faecal egg counts on all farms over the grazing season were less than 200 epg (Figure 2), though at the July sampling a peak individual count of 1200 epg was observed on one of the organic farms (O1). There were significant differences among the farms (p=0.007). Consistent with results on the same farms sampled the previous year, faecal egg counts showed no significant association with growth rate (p=0.605) and there was no interaction between FEC and sample date (p=0.177).

3.3 Larval Culture

Using standard techniques and keys (MAFF, 1986; van Wyk et al., 2004), l~~L~~arval culture and ~~speciation~~ identification was undertaken on dung samples collected at visit 3 in July, corresponding to the middle of the grazing season before anthelmintic treatment. The results are tabulated in Table 1. The majority of larvae cultured were *C. oncophora*, the remainder were *O. ostertagi*.

3.4. Pepsinogen

Plasma pepsinogen concentrations were at baseline on visit I prior to turnout; thereafter concentrations increased on all farms over the grazing season, though the majority of values remained at ≤2 IU (Figure 3). The differences among farms in the mean pepsinogen response were not significant (p=0.051), although cattle farm O1 had high plasma pepsinogen concentrations at housing (3.2 ± 1.7 iu/l). Consistent with results on the same farms sampled the previous year, plasma pepsinogen concentrations showed no association with growth rate (p=0.409) and there was no interaction between pepsinogen and sample date (p=0.131).

3.5. Targeted Selective Anthelmintic Treatment

None of the animals on any farm were treated more than once over the grazing season; all the treatments were administered in either July or August according to individual DLWG over the preceding 28 days.

- Farm O1 18 in July; 1 in August; 1 animal not treated at all
- Farm O2 29 in July; 8 in August; 4 animals not treated at all
- Farm C3 18 in July; 25 in August

~~5.~~4. DISCUSSION

The basic premise for DLWG-based TST is that, providing nutrition is not limiting and that no other identifiable causes of ill-health are present, then the individual growth rate of weaned calves (or lambs) at pasture is linearly and consistently related to the impact of gastrointestinal parasitism (Greer et al., 2009) through its effect on appetite, feed intake, protein metabolism and nutrient partitioning (Forbes et al., 2000; Fox, 1997). In ~~order to incorporate the quality and quantity of the herbage available into the implementation of TST, in~~ sheep systems an algorithm named the Happy Factor™ has been developed (Greer et al., 2009), which~~. This~~ adjusts the target DLWG to the availability and quality of the herbage. This approach has not yet been used in cattle TST, where the assessment of pasture is typically undertaken either subjectively by observation, or quantitatively through the use of standard techniques to measure~~ments of~~ herbage mass and/or sward height (Lambert et al., 2004). Individual DLWG alone was used as the determinant for treatment in this study, though samples were also taken for parasitological examination in order to gain further knowledge of their interrelationships.

~~5.1. Biomarkers~~

~~Faecal egg counts and plasma pepsinogen concentrations were analysed throughout the grazing season and an evaluation of their correlation with live weight gain was undertaken as both have been advocated for use in targeted selective anthelmintic regimes (Charlier et al., 2014).~~

~~5.1.1. Faecal Egg Counts~~

As in the preceding year (Jackson, 2012), there were no significant associations between FEC and DLWG. This result is not surprising, given that FECs in young cattle in temperate regions with an *Ostertagia*/*Cooperia* dominant nematode fauna, whether in experimental infections or under field conditions, have shown no consistent or linear relationship with worm burdens or animal performance (Brunsdon, 1969, 1971; Michel, 1969).

An analysis was performed of the number of calves that would have been treated with anthelmintic at visit 3 if FECs were used as an indicator using an arbitrary threshold of ≥250 epg. The results show only ten FGS had FEC of ≥250 epg, all on Farm O1. Overall, 54 calves, growing <0.75 kg/day would not have been treated with anthelmintic had FEC been used as an indicator.

~~5.1.2 Larval culture~~

Cooperia spp. larvae predominated in the faecal cultures conducted in July, but these results do not necessarily reflect the worm burdens in the animals at the time (Brunsdon, 1968, 1971). The results of the pepsinogen assays suggest that *O. ostertagi* ~~nematodes~~ was~~were~~ having a greater impact over the second half of the grazing season.

~~5.1.3 Pepsinogen~~

Consistent with results from the preceding year (Jackson, 2012), there were no significant correlations between plasma pepsinogen concentrations and DLWG. Pepsinogen provides a direct measure of abomasal dysfunction and is closely associated with abomasal pathology and intra-luminal *O. ostertagi* populations (Michel et al., 1978). It is perhaps surprising that it is not more closely correlated with growth rate, but this h~~w~~as also been observed in other field studies in temperate regions (Brunsdon, 1969, 1971, 1972) and may be due to co-infection with the intestinal species of *Cooperia* in FGS calves, which can also impact growth rate, singly (Armour et al., 1987) or in combination with *O. ostertagi* (Parkins et al., 1990), but *Cooperia* spp. do not typically provoke an increase in pepsinogen.

4~~5.2. Performance-based Targeted Selective Anthelmintic Treatment~~

~~5.2.1. Growth rate~~

The current trial was primarily a feasibility study for TST on commercial farms, so ~~there are~~ no contemporary comparisons were possible, however cattle growth rates from the previous year are available for each farm and these provide a basis on which to assess the impact of TST. Despite some concurrent (non-parasitic) respiratory disease, the mean growth rate of the FGS cattle on the conventional farm C3 was ≥0.75 kg/day over the grazing season, which was the target, though less than the previous year when, using a long-acting anthelmintic and over a shortened grazing season, the growth rate was 0.93 kg/day. On the organic farm O2 the average growth rate under the TST regimen exceeded 0.75 kg/day and this was considerably higher than in the previous year (0.57 kg/day). Although the growth rate on organic farm O1 was less than target, at 0.69 kg/day it was again higher than that of the previous grazing season when it was 0.46 kg/day. On neither of the organic farms were there any major changes in nutritional or grazing management between years.

~~5.2.2. Anthelmintic use~~

The number of animals treated (all) on the conventional farm was the same using TST as it was the previous year, but the potential exposure to discriminating doses of anthelmintic was reduced with TST through the asynchronous, mid/late season administration of eprinomectin, which has persistent activity of 28 days against *O. ostertagi*, compared to moxidectin 10%, which has 120 days of persistent activity against this species. On organic farm O2, all FGS calves were treated once in July the previous year with fenbendazole, which has no persistent activity, whereas under the TST regimen, all bar four animals were treated in July or August, with eprinomectin, so arguably ~~the~~ anthelmintic selection pressure could have increased under TST. Similarly, o~~O~~n organic farm O1, only two calves were treated the previous year with fenbendazole, while 19/20 animals were treated with eprinomectin under TST, however~~,~~ on both organic farms~~,~~ the FGS growth rates were higher under the TST regime.

In order to assess the effect of TST in satisfying the joint objectives of achieving satisfactory growth rates while limiting selection pressure for anthelmintic resistance, modellers have introduced a factor named 'benefit per R', abbreviated to BPR (Laurenson et al., 2016). This is calculated from a ratio between the average weight gain benefit (AWGB) arising from whatever control measures have been used and the increase in anthelmintic resistance allele frequency (IRAF) under that system; both are calculated over the duration of the grazing season. This approach was used initially in sheep and has subsequently extrapolated to cattle (Berk et al., 2016), in which it was shown that the use of a DLWG threshold as an indicator for anthelmintic treatments in TST was the approach that optimised BPR.

4~~5~~.3. Concluding remarks

Applying a performance-based TST in the field was shown to be feasible through the use of weigh bands, albeit this measurement requires adequate restraint of animals. Gathering and handling young stock can be a critical factor in commercial dairy herds, where replacement heifers are often grazed on pastures away from the main farm and where handling facilities may be rudimentary and inadequate for monthly individual animal assessments. Wider adoption of some of the technologies that are already used by some sheep farmers, such as electronic identification (EID), weigh-scales with integrated software and automatic shedding gates (McBean et al., 2016) would all facilitate the adoption of TST in cattle. Faecal egg count and plasma pepsinogen concentration were found to have no significant association with live weight gain and showed high levels of variability amongst individuals within the management groups, so cannot be recommended if one of the primary objectives for parasite control in youngstock is to maintain growth rates that are commensurate with farm objectives and industry standards.

On the organic farms, where anthelmintic treatment was already minimal, DLWG was increased compared to the previous grazing season to rates that are considered to be more compatible with optimum life-time performance in heifer replacements (Wathes et al., 2014). Although organic principles eschew the priority of performance in medication decisions, poor growth is virtually a universal indicator of illness in young animals, commonly through mechanisms that include anorexia (Exton, 1997; Hart, 1990), then it seems that monitoring DLWG should be compatible with the organic ethos in promoting animal welfare.

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Tables

Table 1. Percentage of *O. ostertagi* and *C. oncophora* larvae cultured from faecal samples collected pre-treatment in July (visit 3) on each farm.

Figures

- Figure 1. Normal distribution (Kolmogorov-Smirnov test $p>0.150$) of live weights of animals throughout study.
- Figure 2. Skewed distribution (Kolmogorov-Smirnov test $p<0.01$) of individual faecal egg counts (FEC) throughout study.
- Figure 3. Skewed distribution (Kolmogorov-Smirnov test $p<0.01$) of individual plasma pepsinogen (PEP) throughout study.

Targeted anthelmintic treatment of parasitic gastroenteritis in first grazing season dairy calves using daily live weight gain as an indicator

A. Jackson[1], K.A. Ellis[1]. J. McGoldrick[1], N.N. Jonsson[2], M.J.Stear[3], A.B. Forbes[1]

[1]Scottish Centre for Production Animal Health and Food Safety, School of Veterinary Medicine, College of Veterinary and Life Sciences; University of Glasgow, Bearsden, Glasgow, G61 1Q

[2] Institute of Biodiversity, Animal Health and Comparative Medicine, College of Veterinary and Life Sciences; University of Glasgow, Bearsden, Glasgow, G61 1Q

[3]La Trobe University, Animal, Plant and Soil Sciences, Melbourne, Australia.

Corresponding author: A.B. Forbes: Telephone +44(0)7712738530; email andrew.forbes@glasgow.ac.uk

A. Jackson's current address is: Merial New Zealand, Level 3, Merial Building, 2 Osterley Way, Auckland 2104, New Zealand

ABSTRACT

Control of parasitic gastroenteritis in cattle is typically based on group treatments with anthelmintics, complemented by grazing management, where feasible. However, the almost inevitable evolution of resistance in parasitic nematodes to anthelmintics over time necessitates a reappraisal of their use in order to reduce selection pressure. One such approach is targeted selective treatment (TST), in which only individual animals that will most benefit are treated, rather than whole groups of at-risk cattle. This study was designed to assess the feasibility of implementing TST on three commercial farms, two of which were organic. A total of 104 first-grazing season (FGS), weaned dairy calves were enrolled in the study; each was weighed at monthly intervals from the start of the grazing season using scales or weigh-bands. At the same time dung and blood samples were collected in order to measure faecal egg counts (FEC) and plasma pepsinogen, respectively. A pre-determined threshhold weight gain of 0.75 kg/day was used to determine those animals that would be treated; the anthelmintic used was eprinomectin. No individual animal received more than one treatment during the grazing season and all treatments were given in July or August; five animals were not treated at all because their growth rates consistently exceeded the threshold. Mean daily live weight gain over the entire grazing season ranged between 0.69 and 0.82 kg/day on the three farms. Neither FEC nor pepsinogen values were significantly associated with live weight gain. Implementation of TST at farm level requires regular (monthly) handling of the animals and the use of weigh scales or tape, but can be integrated into farm management practices. This study has shown that acceptable growth rates can be achieved in FGS cattle with modest levels of treatment and correspondingly less exposure of their nematode populations to anthelmintics, which should mitigate selection

pressure for resistance by increasing the size of the refugia in both hosts and pasture.

Key words: Targeted selective treatment, TST, parasitic gastroenteritis, PGE, cattle, eprinomectin,

1. INTRODUCTION

Anthelmintic resistance (AR) has become a major driver for parasitology research and in tailoring advice on parasite control. In northern temperate Europe there are currently only three classes of anthelmintic that are licensed for the control of parasitic gastroenteritis (PGE) in cattle: benzimidazoles, tetrahydropyrimidines (levamisole) and macrocyclic lactones (MLs), none of which are available in combination with each other. The most commonly reported cases of resistance in bovine nematode parasites in Europe have been in *Cooperia* species, in which the efficacy of MLs has been shown to be sub-optimal (Geurden et al., 2015). Given that *Cooperia* spp. are dose-limiting for several MLs (Vercruysse and Rew, 2002), accurate weighing of animals and administration of the correct dose is essential for efficacy and reports of resistance in which these basic criteria have not be fulfilled should be treated circumspectly. In addition there is some evidence for ML-resistant *Ostertagia ostertagi* in Europe, which has also been observed in other regions of the world (Sutherland and Leathwick, 2011; Waghorn et al., 2016). For these reasons it is paramount that practices that reduce selection pressure for resistance and conserve the longevity of the current array of cattle anthelmintics are adopted.

In New Zealand, the emergence of ML-resistant *Cooperia* was associated with high frequency (every 3-4 weeks) administration over periods of six months or longer each year in young cattle grazed intensively (Jackson et al., 2006). There is little evidence for similar use patterns in Europe, where specific risk factors for AR in cattle have not been determined. Early season strategic anthelmintic treatments have been well established in Europe and shown to provide effective control of parasitic gastroenteritis (PGE) particularly in set-stocked, weaned first grazing season (FGS) cattle (Shaw et al., 1998), but also in the second year at grass (Taylor et al., 1995). The primary objective of strategic approaches is to limit concentrations of infective larvae in the herbage throughout the grazing season by minimising worm egg output and re-infection, so strategic treatments create low challenge pastures with correspondingly low refugia; this has the potential to increase the speed of selection for anthelmintic resistance (Martin et al., 1981).

Irrespective of the possible risk factors for AR in cattle nematodes, practices that reduce anthelmintic usage are likely to limit selection pressure on parasite populations. One such approach is targeted selective treatment (TST) in which, rather than the more typical, synchronous group anthelmintic treatments, individual animals are treated on the basis of a marker or markers that indicate that they will benefit from removal of their parasite burdens. Targeted selective anthelmintic treatments (TST) were initially studied in small ruminants (Kenyon et al., 2009), in which proof of concept was demonstrated insofar as disease control and animal performance could be maintained with TST at a level comparable to that seen in animals that were treated more intensively. Equally important was the demonstration that TST applied over successive years led to lower selection for resistance compared to that in lambs treated at 4-week intervals over the grazing season (Kenyon et al., 2013).

There is limited published literature regarding the use of performance-based TST approaches in cattle in the field (Charlier et al., 2014; Kenyon and Jackson, 2012). Analysis of published trial data using reporter operating curve (ROC) analysis suggested that an appropriate threshold for daily live weight gain (DLWG) in a TST regime in young cattle would be 0.75 kg/day (Hoglund et al., 2009). This figure coincides with growth rates that are required for replacement dairy heifers to reach minimal breeding weight at 15 months in order to calve at two years of age (Froidmont et al., 2013; Zanton and Heinrichs, 2005). Weight-gain based TST approaches have provided similar results to those reported in sheep, that is to say acceptable weight gains have been maintained and the number of anthelmintic treatments has been reduced compared to routine, whole group treatments (Greer et al., 2010; Hoglund et al., 2013; McAnulty et al., 2011). It should be noted that to date, TST has only been shown to be effective in the management of PGE, furthermore, if, for example, lungworm (*Dictyocaulus viviparus*) is present and has not been controlled through vaccination, then parasitic bronchitis can thwart efforts to control PGE through TST (O'Shaughnessy et al., 2015).

A series of studies were conducted to extend the scientific evidence base for TST in cattle and to determine its on-farm feasibility (Jackson, 2012). Included in this work was an assessment of various biomarkers as potential indicators for TST, an evaluation of the accuracy and utility of weigh bands for farms that do not have access to weigh scales and implementation of a weight gain-based TST. The objective of the study described in this paper was to determine the feasibility of a weight-gain based TST in first season dairy-bred calves on three livestock farms, two of which were organic.

2. MATERIALS AND METHODS

This TST study was approved by the Ethics and Welfare Committee of the School of Veterinary Medicine, University of Glasgow.

2.1. Participating Farms

Three dairy farms located in central and south-west Scotland were recruited into the study: two organic and one conventional (Farm O1, Farm O2 and Farm C3). The three farms were a sub-set of the six farms that were involved in a monitoring study of gastrointestinal parasitism the previous year (Jackson, 2012).

2.1.1 Organic Farm 1 (O1)

Organic dairy farm 1 comprised a mixed breed milking herd, predominantly of Friesians and Ayrshires, with some Brown Swiss and Jersey crosses, calving all-year-round and grazing over 93 hectares (ha) of semi-improved grassland from April to October. All FGS cattle in the study were vaccinated against lungworm prior to turnout in late April, when the calves grazed a small paddock near the farm and were given supplementary feed. Two weeks later the calves were moved onto another pasture and subsequently were rotated every two weeks around seven different paddocks in an extensive grazing system. The previous year these fields were grazed by FGS, second season grazers (SGS) or adult dairy cattle.

In the year prior to the TST study, faecal egg counts (FEC) were taken in June and September and only calves with a FEC of ≥200 eggs per gram (epg) were treated with fenbendazole (Panacur® 10% oral suspension, MSD). The farmer had used this method of anthelmintic treatment over the previous two grazing seasons. The average DLWG in FGS calves during the year that preceded the TST study was 0.46 kg/day.

2.1.2. Organic Farm 2 (O2)

Organic dairy farm 2 covered 344 ha which supported a milking herd of 135 Ayrshire and Ayrshire cross cows; some Aberdeen Angus suckler cows and sheep were also kept on the farm. Approximately forty per cent of the dairy herd calved between November and December, the rest calved year-round; heifers calved between February and April. The FGS were turned out in early May as a group of sixty calves, which were rotationally grazed over three fields, each of ~20 ha. The year before the TST study, based on faecal egg counts, all FGS were treated with fenbendazole drench in mid-July; the treatment was repeated again at housing in late November. The average DLWG in FGS calves during the year that preceded the TST study was 0.57 kg/day.

2.1.3. Conventional Farm 3 (C3)

The conventional dairy farm milked a herd of eighty five Holstein-Friesian cows and there were also beef and sheep enterprises on the farm. Calving in the dairy herd was year round and both heifer replacements and beef x dairy calves were grazed together. The previous year, the FGS animals were not turned out until mid-July because herbage regrowth after early sheep grazing was insufficient; they were set-stocked on four hectares of land and treated with moxidectin injection (Cydectin^{tm} 10%, Zoetis) at turnout. The average DLWG in FGS calves during the year that preceded the TST study was 0.93 kg/day.

2.2 Experimental Animals

All first season grazers (FGS) on-farm were included in the study (Farm O1 n = 20, Farm O2 n = 41, Farm C3 n = 43). All animals on Farms O1 and C3 were vaccinated against *D. viviparus* (Bovilis Huskvac^{TM}, MSD) before turnout to control lungworm disease.

2.3. Experimental Design

Farms were visited in late April and early May 2010, just prior to turnout from housing onto pasture and then at 28-day intervals until housing in the autumn, except for September, when two of the farmers were unable to gather the cattle because of other farming activities. At visit 1 on all farms, each FGS animal had its live weight calculated by weigh-band (Coburn® weigh tape). On Farm C3, all FGS were also weighed on Ritchie® mechanical weigh-scales. At visit 3 in July, eight to ten weeks post-turnout, the girth of all FGS calves were measured using the weigh-band and their live weight gain from turnout calculated. If the live weight gain of an individual animal was < 0.75 kg/day they were treated with eprinomectin (Eprinex™ pour-on, Merial). At visit 4 in August, the live weight gain of the FGS over the previous four weeks was calculated. Animals that had not been treated previously and were growing < 0.75 kg/day were treated with eprinomectin.

Because eprinomectin has persistent activity of twenty-eight days against *O. ostertagi* and 21 days against *C. oncophora* (Cramer et al., 2000), animals previously treated at visit 3 were not treated again at visit 4, irrespective of their DLWG in the interim, as this would have meant treating within the effective pre-patent period and this can potentially exert a high selection pressure for AR. As farmers had requested a month off from sampling in September on farms O1 and O2, no treatments were given on this visit (5) on Farm C3. No treatment was planned for visit 6 at housing.

2.3.1. Laboratory Analysis

Each calf had a blood sample taken by jugular or coccygeal venepuncture into an EDTA tube for serum pepsinogen analysis (all visits) and a faecal sample taken *per rectum* obtained at visits 2, 3, 4, 5 and 6 for faecal egg count, lungworm and liver fluke monitoring. Larval culture was performed on faeces collected during visit 3. Further details of the standard laboratory techniques used can be found in a previously published paper (Ellis et al., 2011).

2.3.2. Statistical Analysis

The Spearman's rank correlation test was used on non-normally distributed data to investigate any associations with live weight gain. Statistical analysis of the data was performed using Excel, Minitab 16 for Windows and SAS University edition (SAS Institute, Cary, N. Carolina). The association of bodyweight or growth rate with faecal egg count (FEC) or pepsinogenaemia (Pep) was assessed by repeated measures variance analysis. The proc mixed procedure in SAS was used and the model fitted the effects of farm, sample date, test variable (FEC or Pep) and the interaction between sample date and test variable. Several variance structures were tested including unstructured, compound symmetry and heterogeneous autoregressive of order 1. The best fitting model was chosen using four criteria: residual log likelihood, Akaike's information criterion (AIC), the finite-population corrected AIC and Bayes Information criterion (BIC). For both faecal egg count and plasma pepsinogen concentration, a heterogeneous autoregressive structure provided the best fit.

3. RESULTS

3.1. Live weight Gain

Mean live weight gains (± Standard Deviation) over the grazing season for all FGS animals in the study were:

- Farm O1 0.69 ± 0.28 kg/day (weighband)
- Farm O2 0.82 ± 0.13 kg/day (weighband)
- Farm C3 0.75 ± 0.23 kg/day (weigh scale)

The cattle on the conventional farm were heavier (277 kg) at turnout than those on the organic farms (190 and 167 kg), but the growth curves of cattle on all three farms were similar and DLWG was distributed normally amongst all the animals (Figure 1).

3.2. Faecal Egg Count

No results are available from the faecal samples taken from the cattle on the organic farms on visit 6 as they were stored incorrectly after collection. The majority of faecal egg counts on all farms over the grazing season were less than 200 epg (Figure 2), though at the July sampling a peak individual count of 1200 epg was observed on one of the organic farms (O1). There were significant differences among the farms ($p=0.007$). Consistent with results on the same farms sampled the previous year, faecal egg counts showed no significant association with growth rate ($p=0.605$) and there was no interaction between FEC and sample date ($p=0.177$).

3.3 Larval Culture

Using standard techniques and keys (MAFF, 1986; van Wyk et al., 2004), larval culture and identification was undertaken on dung samples collected at visit 3 in July, corresponding to the middle of the grazing season before anthelmintic treatment. The results are tabulated in Table 1. The majority of larvae cultured were *C. oncophora*, the remainder were *O. ostertagi*.

3.4. Pepsinogen

Plasma pepsinogen concentrations were at baseline on visit I prior to turnout; thereafter concentrations increased on all farms over the grazing season, though the majority of values remained at ≤2 IU (Figure 3). The differences among farms in the mean pepsinogen response were not significant (p=0.051), although cattle farm O1 had high plasma pepsinogen concentrations at housing (3.2 ± 1.7 iu/l). Consistent with results on the same farms sampled the previous year, plasma pepsinogen concentrations showed no association with growth rate (p=0.409) and there was no interaction between pepsinogen and sample date (p=0.131).

3.5. Targeted Selective Anthelmintic Treatment

None of the animals on any farm were treated more than once over the grazing season; all the treatments were administered in either July or August according to individual DLWG over the preceding 28 days.

- Farm O1 18 in July; 1 in August; 1 animal not treated at all
- Farm O2 29 in July; 8 in August; 4 animals not treated at all
- Farm C3 18 in July; 25 in August

4. DISCUSSION

The basic premise for DLWG-based TST is that, providing nutrition is not limiting and that no other identifiable causes of ill-health are present, then the individual growth rate of weaned calves (or lambs) at pasture is linearly and consistently related to the impact of gastrointestinal parasitism (Greer et al., 2009) through its effect on appetite, feed intake, protein metabolism and nutrient partitioning (Forbes et al., 2000; Fox, 1997). In sheep systems an algorithm named the Happy Factor™ has been developed (Greer et al., 2009), which adjusts the target DLWG to the availability and quality of the herbage. This approach has not yet been used in cattle TST, where the assessment of pasture is typically undertaken either subjectively by observation, or quantitatively through the use of standard techniques to measure herbage mass and/or sward height (Lambert et al., 2004). Individual DLWG alone was used as the determinant for treatment in this study, though samples were also taken for parasitological examination in order to gain further knowledge of their interrelationships.

As in the preceding year (Jackson, 2012), there were no significant associations between FEC and DLWG. This result is not surprising, given that FECs in young cattle in temperate regions with an *Ostertagia*/*Cooperia* dominant nematode fauna, whether in experimental infections or under field conditions, have shown no consistent or linear relationship with worm burdens or animal performance (Brunsdon, 1969, 1971; Michel, 1969).

An analysis was performed of the number of calves that would have been treated with anthelmintic at visit 3 if FECs were used as an indicator using an arbitrary threshold of ≥250 epg. The results show only ten FGS had FEC of ≥250 epg, all on Farm O1. Overall, 54 calves, growing <0.75 kg/day would not have been treated with anthelmintic had FEC been used as an indicator.

Cooperia spp. larvae predominated in the faecal cultures conducted in July, but these results do not necessarily reflect the worm burdens in the animals at the time (Brunsdon, 1968, 1971). The results of the pepsinogen assays suggest that *O. ostertagi* was having a greater impact over the second half of the grazing season.

Consistent with results from the preceding year (Jackson, 2012), there were no significant correlations between plasma pepsinogen concentrations and DLWG. Pepsinogen provides a direct measure of abomasal dysfunction and is closely associated with abomasal pathology and intra-luminal *O. ostertagi* populations (Michel et al., 1978). It is perhaps surprising that it is not more closely correlated with growth rate, but this has also been observed in other field studies in temperate regions (Brunsdon, 1969, 1971, 1972) and may be due to co-infection with the intestinal species of *Cooperia* in FGS calves, which can also impact growth rate, singly (Armour et al., 1987) or in combination with *O. ostertagi* (Parkins et al., 1990), but *Cooperia* spp. do not typically provoke an increase in pepsinogen.

4

The current trial was primarily a feasibility study for TST on commercial farms, so no contemporary comparisons were possible, however cattle growth rates from the previous year are available for each farm and these provide a basis on which to assess the impact of TST. Despite some concurrent (non-parasitic) respiratory disease, the mean growth rate of the FGS cattle on the conventional farm C3 was ≥0.75 kg/day over the grazing season, which was the target, though less than the previous year when, using a long-acting anthelmintic and over a shortened grazing season, the growth rate was 0.93 kg/day. On the organic farm O2 the average growth rate under the TST regimen exceeded 0.75 kg/day and this was considerably higher than in the previous year (0.57 kg/day). Although the growth rate on organic farm O1 was less than target, at 0.69 kg/day it was again higher than that of the previous grazing season when it was 0.46 kg/day. On neither of the organic farms were there any major changes in nutritional or grazing management between years.

The number of animals treated (all) on the conventional farm was the same using TST as it was the previous year, but the potential exposure to discriminating doses of anthelmintic was reduced with TST through the asynchronous, mid/late season administration of eprinomectin, which has persistent activity of 28 days against *O. ostertagi*, compared to moxidectin 10%, which has 120 days of persistent activity against this species. On organic farm O2, all FGS calves were treated once in July the previous year with fenbendazole, which has no persistent activity, whereas under the TST regimen, all bar four animals were treated in July or August, with eprinomectin, so arguably anthelmintic selection pressure could have increased under TST. Similarly, on organic farm O1, only two calves were treated the previous year with fenbendazole, while 19/20 animals were treated with eprinomectin under TST, however on both organic farms the FGS growth rates were higher under the TST regime.

In order to assess the effect of TST in satisfying the joint objectives of achieving satisfactory growth rates while limiting selection pressure for anthelmintic resistance, modellers have introduced a factor named 'benefit per R', abbreviated to BPR (Laurenson et al., 2016). This is calculated from a ratio between the average weight gain benefit (AWGB) arising from whatever control measures have been used and the increase in anthelmintic resistance allele frequency (IRAF) under that system; both are calculated over the duration of the grazing season. This approach was used initially in sheep and has subsequently extrapolated to cattle (Berk et al., 2016), in which it was shown that the use of a DLWG threshold as an indicator for anthelmintic treatments in TST was the approach that optimised BPR.

4.3. Concluding remarks

Applying a performance-based TST in the field was shown to be feasible through the use of weigh bands, albeit this measurement requires adequate restraint of animals. Gathering and handling young stock can be a critical factor in commercial dairy herds, where replacement heifers are often grazed on pastures away from the main farm and where handling facilities may be rudimentary and inadequate for monthly individual animal assessments. Wider adoption of some of the technologies that are already used by some sheep farmers, such as electronic identification (EID), weigh-scales with integrated software and automatic shedding gates (McBean et al., 2016) would all facilitate the adoption of TST in cattle. Faecal egg count and plasma pepsinogen concentration were found to have no significant association with live weight gain and showed high levels of variability amongst individuals within the management groups, so cannot be recommended if one of the primary objectives for parasite control in youngstock is to maintain growth rates that are commensurate with farm objectives and industry standards.

On the organic farms, where anthelmintic treatment was already minimal, DLWG was increased compared to the previous grazing season to rates that are considered to be more compatible with optimum life-time performance in heifer replacements (Wathes et al., 2014). Although organic principles eschew the priority of performance in medication decisions, poor growth is virtually a universal indicator of illness in young animals, commonly through mechanisms that include anorexia (Exton, 1997; Hart, 1990), then it seems that monitoring DLWG should be compatible with the organic ethos in promoting animal welfare.

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Tables

Table 1. Percentage of *O. ostertagi* and *C. oncophora* larvae cultured from faecal samples collected pre-treatment in July (visit 3) on each farm.

Figures

- Figure 1. Normal distribution (Kolmogorov-Smirnov test $p>0.150$) of live weights of animals throughout study.
- Figure 2. Skewed distribution (Kolmogorov-Smirnov test $p<0.01$) of individual faecal egg counts (FEC) throughout study.
- Figure 3. Skewed distribution (Kolmogorov-Smirnov test $p<0.01$) of individual plasma pepsinogen (PEP) throughout study.

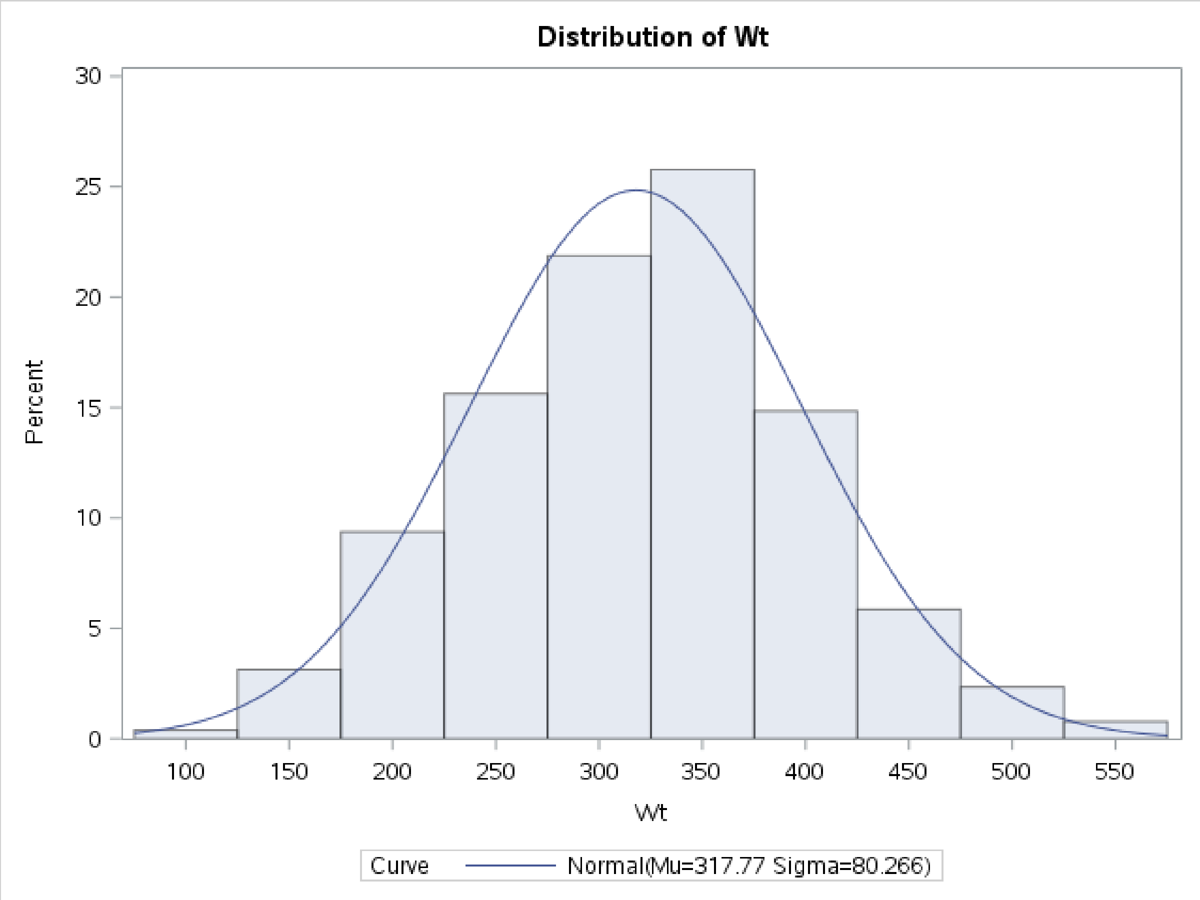
Table

Table 1. Percentage of *O. ostertagi* and *C. oncophora* larvae cultured from faecal samples collected pre-treatment in July (visit 3) on each farm.

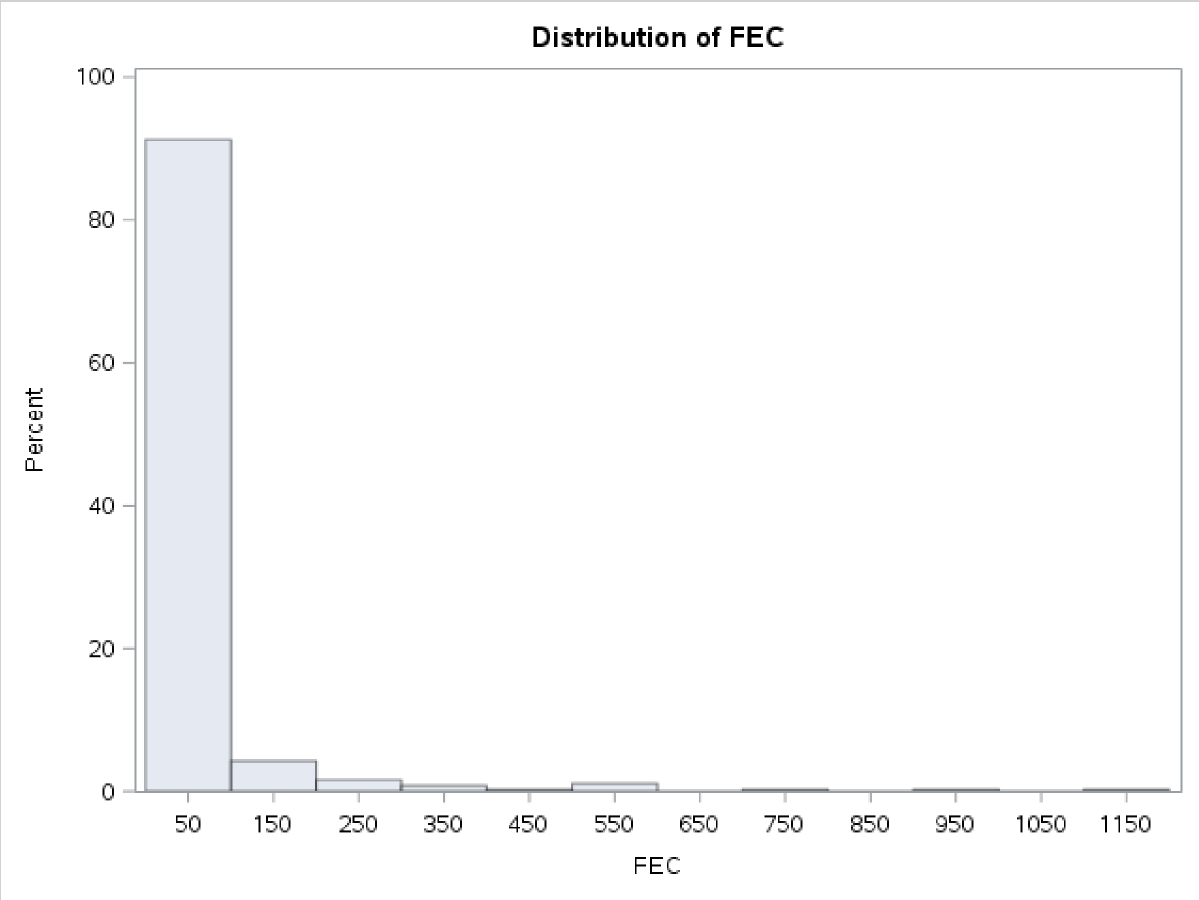
Farm	*O. ostertagi*	*C. oncophora*
C3	18%	82%
O1	21%	79%
O2	4%	96%

Figure

Figure 1. Normal distribution (Kolmogorov-Smirnov test p>0.150) of live weights of animals throughout study



- Figure 2. Skewed distribution (Kolmogorov-Smirnov test $p<0.01$) of individual faecal egg counts (FEC) throughout study.



- Figure 3. Skewed distribution (Kolmogorov-Smirnov test p<0.01) of individual plasma pepsinogen (PEP) throughout study.