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The Happy Factor treatment threshold, used to determine Targeted Selective Treatment decisions for lambs, is transferable between farms

D.W. McBean [a],*, A.W. Greer [b], F. Kenyon [a]

[a] Moredun Research Institute, Pentlands Science Park, Bush Loan, Penicuik EH26 0PZ, Scotland, United Kingdom
[b] Faculty of Agriculture and Life Sciences, P.O. Box 85084, Lincoln University, Lincoln 7647, New Zealand

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ABSTRACT

Weight gain-based treatment decision-making has been shown to successfully reduce the number of anthelmintic treatments without compromising production as part of a Targeted Selective Treatment (**TST**)-based worm control strategy in sheep. The effects of using an efficiency threshold (Standard Threshold (**ST**)) developed on one farm were examined to establish whether there was a need to tailor the threshold for individual farm conditions. The Standard Threshold had been used on a number of farms, and data from these trials were used here. The ideal threshold (Estimated Treatment Threshold) for each farm was calculated using the same method as the original threshold, and the effect on the number of treatments given and subsequent productivity was estimated. Estimated treatment thresholds were calculated to be higher on all farms including the original, resulting in increased numbers of treatments due. The effect of the increased number of treatments was calculated to have no effect on productivity however, and it was concluded that the ST was sufficient, at least initially, for successful implementation of TST and that further refinement could be made using locally derived data if required.

Implications

Anthelmintic resistance is a threat to animal production globally. Reducing the number of anthelmintic treatments given slows the development of resistance. Weight gain-based TST is a method of reducing treatments by identifying and targeting animals which will benefit from treatment by calculating growth targets for lambs. This study aimed to ensure that TST can be implemented reliably and effectively by understanding the transferability of the treatment threshold developed on one farm to another, and the effect on treatment and productivity that changing thresholds would produce.

Introduction

The growing threat of anthelmintic resistant gastrointestinal nematode infections to sustainable sheep production has been widely documented (Waller, 1999; Papadopoulos et al., 2012; Torres-Acosta et al., 2012). While there is no realistic prospect of halting the development of resistance within the parasite population, refugia-based techniques such as Targeted Selective Treatment (**TST**) can slow the reduction in efficacy (Kenyon et al., 2013). This is achieved by leaving some animals untreated within a flock and treating only those individuals which require it (Van Wyk, 2001), in contrast with the normal practice of blanket treating all animals in a flock. The key to a successful TST is dependent on correctly identifying those animals at risk of parasite-caused reduction in productivity and relies on accurate and appropriate measures of animal health in order to make suitable treatment decisions (Van Wyk and Bath, 2002; Kenyon et al., 2009). Furthermore, for TST to be viable on farm, these measures must be made pen-side and allow for instant treatment decisions to be made as it is unlikely that farms will adopt measures requiring further handling or gathering of animals due to cost and inconvenience (Kenyon et al., 2009).

Weight-based TST using the Happy Factor™ fits these criteria and has previously been shown to slow the development of resistance in previously susceptible populations (Greer et al., 2009; Kenyon et al., 2013) by reducing anthelmintic exposure and maintaining susceptible parasites in refugia, yet not compromising productivity. Happy Factor™ TST uses individual animal weight predictions to determine animals requiring treatment, based on single animal failures to reach a predicted weight threshold. The value of this threshold, however, is key to successful TST in order to minimise production losses arising from missed beneficial treatments (**MBTs**), while at the same time reducing unnecessary treatments as far as possible (Hodgkinson et al., 2019). In developing the target prediction model, individual animal production efficiencies were calculated as a proportion of the maximum theoretical weight gain attainable by each lamb given its size and food availability according to the formula described by Greer et al. (2009). Receiver

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* Corresponding author.
E-mail address: dave.mcbean@moredun.ac.uk (D.W. McBean).

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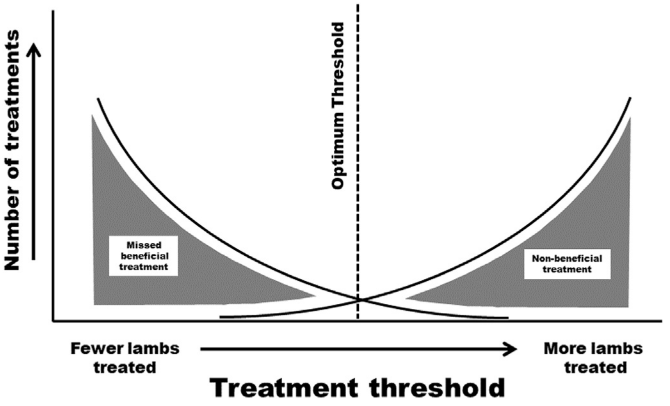

Fig. 1. Ideal treatment threshold for Happy Factor Targeted Selective Treatment in lambs.

operator characteristic (**ROC**) curve analysis of efficiency data generated by lambs prior to and following anthelmintic treatment was used to determine the optimum threshold at which treatment should be given in order to treat as many animals which would benefit from treatment as possible while avoiding animals already performing well and which would derive no benefit from the treatment, thus retaining a population of unexposed parasites in refugia (Greer et al., 2009).

Although the method has been applied with apparent success on a number of different farms (McBean et al., 2016), each of these studies used a standard Happy Factor™ threshold of 0.66, which was calculated on a single farm with Scottish Blackface lambs when the model was first described. It is possible that the optimum threshold changes depending upon sheep breed, pasture type or locality. Indeed, the use of the Happy Factor™ TST in Coopworth lambs in New Zealand (Greer et al., 2010) found that the ideal threshold to be higher at 0.74, suggesting that different farming systems may require adjustment of the threshold for TST to be optimised. Fig. 1 demonstrates a schematic of the ideal threshold for TST treatment, where the minimum number of treatments given that would not benefit the animal and the maximum number of treatments that would benefit the animal are administered. The consequence of different optimal treatment thresholds is that the technique may cause treatments to be missed where they would prove beneficial leading to production losses or that an excess number of treatments are applied resulting in higher selection pressure for resistance. Should this be the case, it could require an individual farm approach to calculating the threshold value to maximise the usefulness of TST as a management approach. This in itself could prove a barrier to farmer uptake. For the effective adoption of TST by farms using different breeds with potentially different weight gains, as well as different pasture and land types, it is necessary to examine data from a range of sheep farms to identify which, if any, factors affect the optimum thresholds and assess the viability of transferring the current parameters for weight gain-based TST to adopters of the approach.

This study used data from anthelmintic-treated animals on 5 farms which had trialled this TST approach previously (McBean et al., 2016) to examine whether the standard threshold (**ST)** determined in a previous study (Greer et al., 2009) is applicable to farms in multiple locations with differing conditions and animal breeds. This was conducted by applying the method used in the original development to data sets from several farms in Scotland and calculating the number of beneficial treatments given or missed under several proposed treatment thresholds.

Material and methods

Study data

Data from four farms used in previous TST experiments were used in this study (Table 1) as they provided the necessary environmental and productivity data required for efficiency calculations. Data used were from all suitable treatment points where animals received a planned whole-group anthelmintic treatment. Farms 1 to 3 were previously described in McBean et al. (2016); however, farm 2 in that study provided insufficient data for use here. Accordingly, farms 3 and 4 from that study become farms 2 and 3 in this paper. Farm 1 was a long-term study comprising several anthelmintic treatment strategies during 6 years on a research farm operated by Moredun Research Institute. Farm 3 was a mixed upland and hill research farm mimicking a fat lamb production system, while Farms 2 and 4 were purely commercial farms trialling TST. Farm 3 was stocked with two separate breeds, and these were analysed separately here as farm 3a (Scottish Blackface) and farm 3b (Lleyn). Studies on Farm 4 have been previously described (Busin et al. 2013 and 2014), and data from both experiments on the farm were used in this study, considered as two separate years and used here as farm 4a (2013) and farm 4b (2014).

Table 1
Farm summary with farm type, breed of lambs, anthelmintic class and number of observations.

Farm	Type	Breed	Drug compound	Number of observations
1	Lowland	Blackface/Texel	Ivermectin	1 723
2	Lowland	Suffolk Crossbred	Levamisole	78
3a	Hill	Scottish Blackface	Levamisole	130
3b	Upland	Lleyn	Levamisole	104
4a	Upland	Texel crossbred	Ivermectin	85
4b	Upland	Texel crossbred	Ivermectin	135

In order to avoid bias from using TST animals, for this analysis, animal data were only used from blanket-treated control groups. Examination of drug efficacy and productivity gains showed that any treatment where the drug efficacy was below 70% was ineffective at improving productivity (data not shown) and such data were disregarded. This situation only occurred on Farm 1, and all other farms were using effective drenches with efficacy in excess of 95%. Weight data from anthelmintic-treated animals were used to calculate individual animal efficiency at converting available food to growth using the model described by Greer et al. (2009). Briefly, the model calculates the energy utilisation of the animal (efficiency) over a set time period using the formula:

$$\text{Efficiency} = (1-((\text{MEg}-\text{NE})/\text{MEI})/\text{PI})/\text{TE}$$

Where MEg is the energy available for growth, NE is the net energy, MEI is the potential metabolisable energy intake from the pasture quality (estimated here) and pasture mass, PI is the proportion of maximum intake and TE the mean ambient temperature. The TE data, for both this and the previous studies, were taken from UK Meteorological Office monthly regional averages (http://www.metoffice.gov.uk/climate/uk/summaries/datasets#Yearorder, accessed as required). A sensitivity analysis of the effect of temperature on the thresholds has shown that there is little effect of temperature within the ranges typically found in Scotland (10–15 °C, Greer et al., 2009). Temperatures for Farm 1 and 4b are presented here as the mean as the data used derives from more than one individual month. Pasture mass data incorporated into the model were collected using a Grassmaster II pasture mass meter (Novel Ways Inc. New Zealand) with measurements taken every 5 paces in a w-pattern throughout the pasture on dates roughly midway between sampling times.

Estimated Treatment Threshold calculation

All suitable weight data from each farm were used; three weight sampling points prior to, at time of, and post anthelmintic treatment were used to calculate the growth rates and individual animal efficiency values before and after treatment using the Happy Factor model described by Greer et al. (2009). Treatments were deemed beneficial if the post-treatment efficiency of the animal exceeded that prior to treatment. The efficiency data prior to treatment and the corresponding change in efficiency post-treatment were then used to calculate ROC curves (Prism V.6, Graphpad Software Inc.) where an increase in efficiency was deemed as a positive treatment and no change or decrease as a negative response to treatment. ROC generates a table of % Sensitivity and % Specificity for each predictor, and here the sum of the Sensitivity and Specificity values (Youden's J statistic, Youden, 1950) was used to identify the optimum treatment threshold value (Estimated Treatment Threshold, **ETT**), deemed to be the value where the sum was greatest. More commonly, specificity is created from the false positive rate as 1-Specificity, in which case the threshold would be generated from the lowest value of 1-Specificity, but the method used here (Graphpad) will generate the same values, albeit as a percentage value rather than a proportion. Previously, the treatment threshold value was deemed to be 0.66 of the theoretical maximum weight gain in a preliminary study using pilot data on the farm described here as Farm1 (Greer et al., 2009) and is used here as the ST.

Estimation of treatment numbers using Standard and Estimated Treatment Threshold regimes

Treatment under TST was simulated by calculating the number of treatments which would have been administered using either the ST or the ETT. The number of treatments which would have been saved compared with whole-group treatment, the difference in treatment numbers between each threshold and the number of beneficial treatments which would have been missed by using the standard rather than the ETT were determined. McNemar's chi-squared test (R-studio, R Core Team) was used to analyse the difference between Standard and ETT treatment numbers.

Estimation of productivity effects of Standard and Estimated Treatment Threshold regimes

The effect on productivity of using TST at either ST or ETT was estimated. Post-treatment productivity was deemed to be either the actual post-treatment weight gain would the animal have been treated under TST, or for animals which would not have been treated, the pre-treatment weight gain.

Assessment of beneficial and non-beneficial treatments

Weight targets for each animal were calculated using treatment threshold values of 0.5, 0.55, 0.6, 0.66, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95 and 1.0. The numbers of treatments which would have been beneficial, but not administered (MBT) under TST conditions, were estimated as the number of animals with a greater efficiency than the treatment threshold prior to treatment, but still benefitted from treatment through a further increase in efficiency. Animals which would have received treatment under TST by being less efficient than the threshold, yet did not show a beneficial increase in animal performance (Non-Beneficial Treatment, **NBT**), were derived for all treated animals and are also shown in Fig. 2. The ideal threshold would be located at or near the intersection of MBT and NBT as demonstrated in Fig. 1.

Results

Calculation of treatment thresholds for individual farms

The results from the ROC analysis including Area under curve (**AUC**) and ETT are shown in Table 2. Area under curve ranged from 0.64 to 0.93, with the lowest values on farm 3. Carter et al. (2016) suggest that a minimum AUC of 0.7 indicates a reasonable predictive outcome, which is not met for either Farm 3a or 3b. All other farms had AUC in excess of 0.8 which is considered as good or excellent as a predictive tool. The Estimated Treatment Thresholds generated from the highest combined sensitivity and specificity (lowest value of 1-specificity) ranged from 0.71 to 0.84.

Effect of standard and calculated treatment thresholds on estimated treatment outcomes

Actual treatments administered and estimates of treatment numbers under the two TST thresholds are shown in Table 3. While all farms would have received fewer treatments under TST using either the ST of 0.66 or ETT, compared with whole flock treatment, there was also a difference ($P < 0.005$) between number of treatments using the two threshold values on all of the farms, with the higher ETT threshold leading to corresponding higher numbers of treatments required.

Of these further treatments under ETT, at least some would have been beneficial on Farms 1 (122 of 250 additional treatments), 2 (all 13), 3a (36 of 58) and 3b (28 of 67), but not on farms 4a (0 of 10) and b (0 of 16).

Effect of standard and calculated treatment thresholds on post-treatment productivity estimates

The mean pre-treatment and estimated post-treatment weight gains for lambs treated under Standard and ETT TST are shown in Table 4.

Pre-treatment weight gains ranged from 93.4 to 266.8 g/day, and actual post-treatment weight gains were significantly higher ($P < 0.05$) than pre-treatment for all farms except Farm 3a and b and 4a where post-treatment growth rates were lower than pre-treatment.

Use of the ST gave estimated post-treatment weight gains from 185.1 to 285.3 g/day and 160.9 to 287.0 g/day at ETT. The difference between the growth rates at Standard or ETT was small on most of the farms where an increase was estimated (farms 1,4a and 4b) of between 1.1 and 9.2 g/day, while farm 2 estimated an increase in growth of 21.6 g/day when using ETT over Standard. The actual mean growth rates on both farm 3a and 3b declined post-treatment, and this led to reductions in estimated growth of 20.6 and 45.2 g/day when more treatments were given under ETT than Standard. Farm 4a also saw a post-treatment reduction in productivity, but this did not have the same effect on the growth estimates.

Effect of different treatment thresholds on the percentage of missed and non-beneficial treatments administered

The treatment decisions which would have been made using a range of treatment thresholds were calculated for all animals. The number of beneficial and NBTs expressed as a percentage of the flock is shown in Fig. 2. Most farms followed the expected pattern demonstrated in Fig. 1, with the exception of farm 2, in that the majority of animals benefitted from the treatment, and there were very few treatments that did not result in some increase in productivity. For the farms following the expected trend, the ETT was close to the intersection between MBT and NBT with the exception of farm 3b.

Discussion

While the use of TST on these farms has been explored and found to be successful in reducing anthelmintic input (McBean et al., 2016) and at the same time avoiding negative impact on lamb productivity, it is necessary to confirm that the treatment threshold parameter was optimised for the farms involved. By simulating the use of TST in a group of animals which were all treated, it was possible to examine the benefit or otherwise in lambs which were treated regardless of production or parasitism levels and retrospectively analyse the effect an alternative TST treatment threshold would have had on anthelmintic use. In doing so, this study confirms the previous findings that all farms would have experienced considerable reductions in anthelmintic use

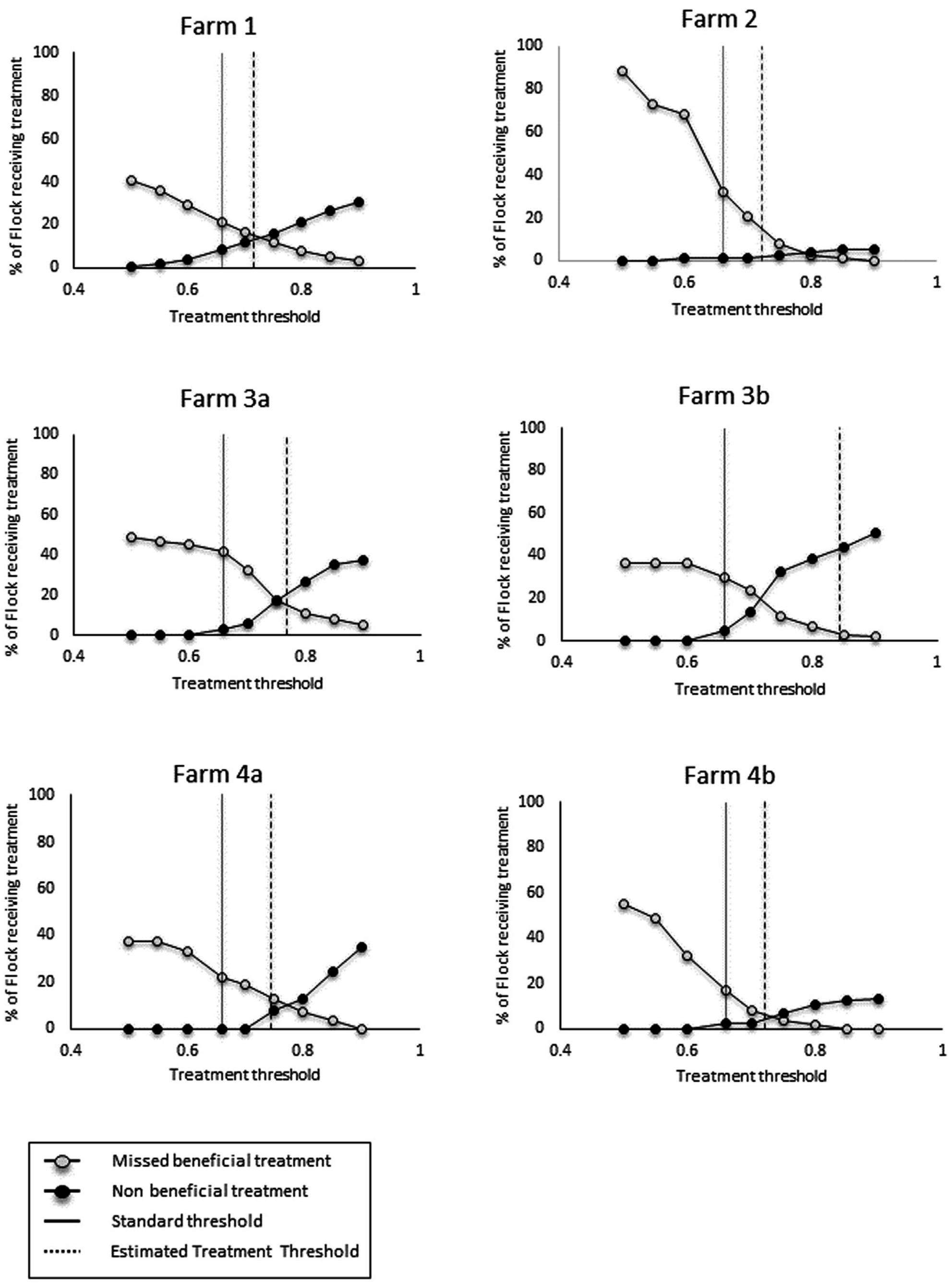

Fig. 2. Percentage of lamb flocks receiving non-beneficial treatments or missing beneficial treatments at various treatment thresholds, plus standard and estimated treatment thresholds.

Table 2
Number of treatments administered to lambs used for Receiver Operator Characteristic (ROC) analysis which were beneficial and non-beneficial in terms of post-treatment increase in efficiency. Mean production efficiency pre- and post-treatment (proportion of maximum theoretical productivity) with SD in brackets. Area under curve and Estimated Treatment Thresholds (ETT) calculated from ROC analysis with the Sensitivity and Specificity of the cut-off value used as ETT (%).

Farm	Beneficial treatments	Non-beneficial treatments	Pre-treatment efficiency		Post-treatment efficiency		Area under ROC curve	%Sensitivity at ETT	%Specificity at ETT	ETT
			Mean Proportion	SD	Mean Proportion	SD				
1	959	764	0.70	0.22	0.76	0.22	0.802	75.4	69.7	0.72
2	74	4	0.65	0.12	0.92	0.12	0.801	83.6	80	0.72
3a	64	66	0.78	0.11	0.77	0.12	0.692	71.9	60.6	0.77
3b	38	66	0.77	0.11	0.74	0.11	0.641	92.1	33.3	0.84
4a	34	51	0.82	0.15	0.74	0.13	0.891	82.4	78.4	0.75
4b	114	21	0.58	0.16	0.84	0.16	0.933	93.9	85.7	0.72

Table 3
Estimated lamb treatment numbers using Targeted Selective Treatment (TST) at standard and Estimated Treatment Threshold (ETT) thresholds, * signifies statistically significant difference ($P < 0.05$) between treatments given at Standard and ETT thresholds.

Farm	Actual number of treatments under whole-group treatments	No. treatments at standard threshold		No. treatments at ETT threshold		Extra treatments using ETT over standard TST	
		Total	% reduction	Total	% reduction	Total	Beneficial
1	1723	748	56.59	953*	44.69	205	122
2	78	49	37.18	62*	20.51	13	13
3a	130	14	89.23	72*	44.61	58	36
3b	104	12	88.46	79*	24.03	67	28
4a	85	15	82.35	25*	70.59	10	0
4b	135	94	30.37	110*	18.52	16	0

Table 4
Pre-treatment mean lamb weight gains, estimated post-treatment weight gains under Standard or Estimated Treatment Threshold (ETT), actual mean weight gains following whole group treatment.

Farm	Pre-treatment (g/day)	Post-treatment estimated mean weight gain (g/day)		Actual post-treatment weight gain (g/day)
		Standard threshold	ETT	Whole-group treatment
1	129.5	185.1	186.2	135.8
2	123.7	268.3	289.9	286.1
3a	202.2	205.2	184.6	141.2
3b	207.9	205.3	160.1	131.8
4a	266.8	285.3	287	182.3
4b	93.4	259.3	268.5	249.7

in the animals examined here by using TST, regardless of which of these treatment thresholds were used. In support of this, simulated reductions in the numbers of anthelmintic treatments ranged from a 30% reduction in Farm 4b to 89% reductions on farm 3a when the ST of 0.66 was used and between 18.5% in Farm 4b and 70% in Farm 4a when the ETT was used. Although the data sets provided here do not allow for the impacts on the development of anthelmintic resistance to be established, any reduction in anthelmintic use can reasonably be expected to assist in slowing resistance development through the provision of refugia sourced from animals that did not receive treatment.

All of the farms were found to have a higher ETT than the Standard treatment threshold. While some differences may be expected given the confounding factors, such as breed, temperature, pasture quality and location, all of which may influence the potential animal productivity and thus the production efficiency estimated through the Happy Factor, this suggests that the ST may in fact be too low. Similarly, a study in New Zealand using the same methodology on Coopworth lambs which found the ideal threshold to be 0.74, which led in that study to 85% of treatments proving of benefit (Greer et al., 2010). Some confidence in the calculated ETT values here can be drawn by the consistently high AUC from the ROC analysis which indicates successful discrimination between true positives and false negatives. In fact, the lowest AUC and sensitivity were observed on farms 3a and 3b, which is likely to reflect that samplings on this farm were longer duration apart than other farms (mean duration between pre-treatment and treatment weighings of 36.9 and 36.7 days for 3a and 3b, respectively, and post-treatment of 20.7 for both a and b) when compared with the other farms which all weighed animals at 14 day intervals except Farm 2 which was 21 days pre-treatment and 16 days post-treatment. This increase in duration increases the effect of confounding factors in animal efficiency outwith the anthelmintic treatment on the calculation of efficiency. Furthermore, the ETT threshold consistently indicated <25% of the flock would have missed a beneficial treatment, while <10% of the flock would have received a NBT (Fig. 2). By comparison, the proportion of the flock that would have either missed a beneficial treatment or received a NBT when using the standard treatment threshold was more variable, ranging from 20 to 60% and 0 to 15%, respectively. It is somewhat surprising that there was a difference between ETT and STs on farm 1 where the ST was originally developed. The reasons for this are unclear as the same methodology used to calculate the standard treatment threshold was used for calculation of the ETT, but this may reflect several changes on the farm. There was a change in breed on this property from Scottish Blackface to Texel cross which is reputed to have a greater production potential, anthelmintic use on the farm during the period resulted in reduced efficacy on some areas and the pasture itself was poorer in nutritional quality. This would suggest the need for periodic monitoring of the appropriateness of treatment threshold values to ensure they represent the production potential of the flock as environmental conditions or flock genetics change.

The increased ETT compared with ST led to higher numbers of treatments on all farms as many animals were at a pre-treatment efficiency between the Standard and ETT levels. While this may suggest that a higher threshold should be implemented across the board, the question of whether these extra treatments were of value is dependent on those treatments resulting in production gains. This was variable across the farms, with all of the extra treatments on farm 2 proving beneficial, yet none on farms 4a and 4b having any impact on productivity. The other farms had between 41 and 62% of these extra treatments prove beneficial. That all of the extra treatments were beneficial on Farm 2 may be explained by the fact that of the actual treatments given, all but 5 of the 78 resulted in positive gains in efficiency suggesting an extremely effective whole flock treatment was administered. The increase in threshold, and consequently higher numbers of treatments, is supported by the plots of missed beneficial and NBTs (Fig. 2), where all farms had the intersection of plots close to the ETT, with the exception of Farm 3b. It is unclear why this farm differed here, but it may reflect a poor relationship between pre-treatment efficiency and treatment outcome, possibly as a result of other endemic production limiting factors in the flock.

We attempted to assess the effect of the treatment thresholds by estimating post-treatment growth rates, using the pre-treatment rate for animals untreated under the TST thresholds, as no data from untreated animals was available. This poses the risk of the results being unreliable when growth rates are affected by factors other than parasitism. This was the case here, where three of the farms experienced large reductions in growth rate post-treatment. With this issue, it was felt that this method is unreliable in predicting post-treatment outcomes from implementing TST on farm. Indeed, the results suggest that on farms 3a and 3b, the combination of increased treatments (which led to more actual post-treatment gains being included in the estimates) and a reduced post-treatment weight gain led to an indication that part flock TST treatment would lead to higher growth rates than the actual whole flock treatment.

We can be confident about the results from treated animals, as all data used here were generated from treated lambs; however, there is expected to be greater variation in the figures used for the untreated animals. The results indicated differences in post-treatment weight gains when ETT was used rather than ST on four of the six farms. However, in reality, the estimates from untreated animals were likely to be unreliable. This is highlighted by the fact that actual whole flock treatments resulted in lower gain rates than part flock treatments. Further to this, the progression of infection in untreated animals would result in reduced efficiency during the post-treatment period, also confounding the estimate value. Difficulties in this prediction method notwithstanding, on Farm 1, moving from ST to ETT would have increased the number of treatments by 205, with 122 of these being notionally beneficial. In practice however, the benefit of these treatments was predicted to be small and result in a gain of only 1.1 g/day/animal compared with Standard TST treatment. The value of this limited weight gain of only 30.8 g over 28 days must be taken in the wider context of the aim of TST in reducing drug treatments and maintaining refugia with the aim of prolonging anthelmintic efficacy.

Overall, it may be concluded that the use of the ST, although not optimal in all cases, was sufficient on the farms studied for use, at least initially, in a TST scheme. Not only would this largely provide the benefits of TST in terms of reduced drug application but would also provide the data and opportunity required for further refinement of the treatment threshold, allowing for farm- and animal-specific characteristics.

Ethics approval

Not applicable.

Data and model availability statement

None of the data were deposited in an official repository. Data are available to reviewers.

Author ORCIDs

David McBean https://orcid.org/0000-0001-7956-3145.
Andrew Greer https://orcid.org/0000-0002-1479-3297.
Fiona Kenyon https://orcid.org/0000-0002-8073-0382.

Author contributions

David McBean: Conceptualization, Methodology, Formal analysis, Investigation, and Writing – original draft.

Andrew Greer: Methodology and Writing – review & editing.

Fiona Kenyon: Investigation and Writing – review & editing.

Declaration of interest

None.

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