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Invited article

Investigating anthelmintic efficacy against gastrointestinal nematodes in cattle by considering appropriate probability distributions for faecal egg count data

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ABSTRACT

The Faecal Egg Count Reduction Test (FECRT) is the most widely used field-based method for estimating anthelmintic efficacy and as an indicator of the presence of anthelmintic resistant nematodes in cattle, despite never having been validated against the gold standard of controlled slaughter studies. The objectives of this study were to assess the normality of cattle faecal egg count (FEC) data and their transformed versions, since confidence intervals used to aid the interpretation of the FECRT, are derived from data assumed to be normally distributed, and violation of this assumption could potentially lead to the misclassification of anthelmintic efficacy. Further, probability distributions and associated parameters were evaluated to determine those most appropriate for representing cattle FEC data, which could be used to estimate percentage reductions and confidence limits. FEC data were analysed from 2175 cattle on 52 farms using a McMaster method at two different diagnostic sensitivities (30 and 15 eggs per gram (epg)) and a sensitive centrifugal flotation technique (SCFT) with a sensitivity of 1 epg. FEC data obtained from all egg count methods were found to be non-normal even upon transformation; therefore, it would be recommended that confidence or credible intervals be generated using either a Bootstrapping or Bayesian approach, respectively, since analyses using these frameworks do not necessarily require the assumption of normality. FEC data obtained using the SCFT method were best represented by distributions associated with the negative binomial and hence arithmetic means could be used in FECRT calculations.

Where FEC data were obtained with less sensitive counting techniques (i.e. McMaster 30 or 15 epg), zero-inflated distributions and their associated central tendency were the most appropriate and would be recommended to use, i.e. the arithmetic group mean divided by the proportion of non-zero counts present; otherwise apparent anthelmintic efficacy could be misrepresented.
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1. Introduction

For over 60 years the control of helminth parasites, due to their ever growing impact on animal health and welfare (Crofton, 1966; Vlassoff and McKenna, 1994; Corwin, 1997; Molento, 2009; Voort et al., 2013; Charlier et al., 2014), has increasingly relied on the use of anthelmintics. Many products are available worldwide and, for cattle, most are marketed for both treatment and prevention of helminthoses with the majority categorised into one of three broad-spectrum classes: benzimidazoles (1-BZ), imidazothiazoles (2-LV) and Macrocyclic Lactones (3-ML) (Taylor, 2010). Consequential to their continued use have been reports of apparent resistance to one or more of these classes of anthelmintics. Worldwide, the numbers of cattle herds thought to have been exposed to anthelmintic resistant helminths are not as alarming as the numbers for sheep flocks (Sangster, 1999; Kaplan, 2004; Wolstenholme et al., 2004; Waller, 1997) though resistance has been reported in Australia, New Zealand, parts of Europe and in some parts of the United States of America (Waghorn et al., 2006; Demeler et al., 2009; El-Abdellati et al., 2010; Edmonds et al.,

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2010; Sutherland and Leathwick, 2011). Although there have been no widespread reports of resistant helminths in cattle in the United Kingdom (UK), sporadic cases have been reported in the dose-limiting species, *C. oncophora* (Stafford and Coles, 1999; Sargison et al., 2009). Indeed, the true representation of resistance is difficult to assess mainly due to inconsistencies in treatment dose administrations, faecal sample collection and handling methods, faecal egg counting techniques used, associated experimental designs (Taylor, 2012) and the lack of robust methods for determining anthelmintic resistance under field conditions i.e. the lack of field data supported by controlled slaughter studies, or the availability of validated molecular and *in-vitro* methods for cattle nematodes.

Efficacy can be defined as a quantitative measure of the effectiveness of a drug intended to produce a desired effect (Vidyashankar et al., 2012). A fully effective anthelmintic is expected to reduce FECs to zero after administration of the anthelmintic. The most reliable method for determining anthelmintic efficacy is the controlled anthelmintic efficacy test, whereby animals are artificially infected, treated, then slaughtered and worm burden counts performed (Powers et al., 1982), but are not practicable in the field. It is common to assume that any apparent lack of efficacy is due to anthelmintic resistance – but this apparent resistance can be the result of anthelmintic failure due to other factors, most commonly under-dosing due to inaccurate estimation of bodyweight (Taylor et al., 2002). The most common method used to investigate anthelmintic resistance is the Faecal Egg Count Reduction Test (FECRT) (Coles et al., 1992, 2006). However, this test has not been validated against slaughter studies and the European Medicines Agency (EMA) regards this test as an estimation of efficacy, and not confirmation of resistance (EMA, 2014). True resistance must be confirmed through laboratory slaughter studies, potentially supported by molecular level studies, or methods such as egg hatch tests (Vidyashankar et al., 2012).

Faecal egg counts (FECs) provide an indirect measure of the worm burden present in cattle herds (and other livestock) since experimental studies have shown that there is a weak, positive correlation between FEC data and actual worm burden (Eysker and Ploeger, 2000). These counts, usually reported as the number of worm eggs per gram (epg) of faeces, can be obtained via a variety of methods. The McMaster technique and its modifications (Gordon and Whitlock, 1939; Whitlock, 1948; MAFF, 1986) are the most widely used and offer different egg detection limits, i.e. diagnostic sensitivities, typically ranging from 15 to 100 epg. For FEC methods with a high worm egg detection limit (low diagnostic sensitivity), a zero FEC may not necessarily correspond to no eggs being present; this is more likely to mean that the counting technique is not sufficiently sensitive to be able to detect any eggs present at or around the threshold of the egg detection limit. This is likely to result in false/excess zeros being present in FEC data and these can reduce the value of the arithmetic mean, i.e. the central tendency of the negative binomial distribution (Shaw and Dobson, 1995; Morgan et al., 2005; Denwood et al., 2008; Levecke et al., 2012), which is currently recommended for use in calculating percentage reductions when conducting a FECRT.

Areas of interest that exist, with regards to the statistical aspects of the FECRT, include the use and identification of appropriate experimental study designs (Lyndal-Murphy et al., 2014) and the analysis of FEC data (Presidente, 1985; Dobson et al., 2009). The objective of this study is concerned with the latter, since the purpose of this study was to determine whether or not current guidelines on parameter estimates and confidence intervals for estimating apparent anthelmintic efficacy are appropriate, using FEC data collected through an extensive field study. Firstly, the asymptotic assumption of normality of data, on which the confidence intervals are based, was assessed using these data. Secondly, various discrete probability distributions, such as *compound* distributions other than the negative binomial, were fitted to the data to determine the most appropriate distributions for representation. Based on the results, recommendations of possible alternative calculations are given.

2. Materials and methods

2.1. Field studies

All data used were collected between 1st September 2011 to 28 February 2015, i.e. over three full grazing seasons, from both dairy and beef farms throughout England. Farms were selected on the basis that they had adequate handling facilities and had not treated their first year grazing cattle with an anthelmintic prior to turn-out to pasture.

2.1.1. Study design

Composite group faecal samples were collected approximately every two weeks from cattle on farms until the group mean FEC reached >150 epg. Once groups had reached this threshold, they were enrolled into a FECRT study. This threshold was chosen as it was unlikely to be high enough to cause clinical disease in individual animals, but still high enough for a robust FECRT assessment (Coles et al., 1992, 2006). These FEC screenings were carried out with ten cattle being sampled per forty cattle on a farm, where possible, and approximately 50 grams of faeces were retrieved from each individual animal. Composite samples from ten animals, each containing 3 grams of faeces from each were then examined using the Modified McMaster technique with a diagnostic sensitivity of 15 epg (MAFF, 1986).

For the FECRT, cattle at the start of the study (Day 0) were systematically allocated to either treatment or control groups as they came through the cattle crush. Fresh faecal samples were collected from all animals, placed into zip-lock bags, labelled with the individual ear tag numbers and refrigerated. Cattle in the treatment groups were dosed based on the individual body weights (kg), measured using either weightape or by electronic weigh scales, where available, using dose rates based on 10 kg increments (3-ML) or 13 kg increments (1-BZ). All cattle were returned to the same pastures so that they were subject to the same parasite challenge. Further faecal samples were collected 14 days post-treatment (Day 14). Control animals, which were not treated on Day 0, were treated after obtaining faecal samples on Day 14. Blinding of the laboratory technicians was maintained during faecal egg counting. On-farm treatments were administered using products either from the 1-BZ or 3-ML class of anthelmintics. The choice of anthlelmintic used was based on farm history and previous anthelmintic use. From the BZ group, an oral drench product containing fenbendazole (Panacur 10% Oral Solution™, MSD Animal Health, 7.5 mg fenbendazole/kg bodyweight) was used on 12 groups of cattle; and from the ML group, doramectin injection (Dectomax Injection for Cattle and Sheep, Elanco Animal Health Ltd, 200 mcg doramectin/kg bodyweight) was used on 19 groups of cattle, doramectin pour-on (Dectomax Pour-On for Cattle, Elanco Animal Health, Ltd, 500mcg/kg bodyweight) was used on 8 groups of cattle, ivermectin injection (Ivomec Classic Injection for Cattle and Sheep, Merial Animal Health, Ltd., 200mcg/kg bodyweight) and ivermectin pour on (Ivomec Classic Pour-On for Cattle, 500mcg/kg bodyweight) were also used on 15 and 7 groups of cattle, respectively. A positive or negative control group was used on all pastures, excluding those where pour-on products were used due to the likelihood of cross-contamination of controls with pour-on products. In total, 15 negative control groups were used. Treatment groups varied in size on farms throughout the study, with some farms having more than

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