



## Research paper

## Zero-inflated hierarchical models for faecal egg counts to assess anthelmintic efficacy

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## ABSTRACT

The prevalence of anthelmintic resistance has increased in recent years, as a result of the extensive use of anthelmintic drugs to reduce the infection of parasitic worms in livestock. In order to detect the resistance, the number of parasite eggs in animal faeces is counted. Typically a subsample of the diluted faeces is examined, and the mean egg counts from both untreated and treated animals are compared. However, the conventional method ignores the variabilities introduced by the counting process and by different infection levels across animals. In addition, there can be extra zero counts, which arise as a result of the unexposed animals in an infected population or animals. In this paper, we propose the zero-inflated Bayesian hierarchical models to estimate the reduction in faecal egg counts. The simulation study compares the Bayesian models with the conventional faecal egg count reduction test and other methods such as bootstrap and quasi-Poisson regression. The results show the Bayesian models are more robust and they perform well in terms of both the bias and the coverage. We further illustrate the advantages of our proposed model using a case study about the anthelmintic resistance in Swedish sheep flocks.

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## 1. Introduction

Gastrointestinal nematodes are parasitic worms that survive in livestock hosts, such as sheep, cattle and horses. The infection is common in the livestock populations in some regions (Waruiri et al., 2001; Mortensen et al., 2003; Pfukenyi et al., 2007; Tariq, 2014; Zanzani et al., 2014). Such infection can lead to numerous problems including reduction in skeletal growth, live-weight gain and milk yield (Houtert and Sykes, 1996), which can impose great economic burden on ruminant production (Perry and Randolph, 1999). The regular administration of anthelmintic treatments is a widely used method to control the infection. It aims not to eliminate the infection, but to reduce the infection intensity and prevent transmission (Levecke et al., 2012a). However, anthelmintic resistant nematodes appeared in different regions across the globe since late 1950s (Kaplan, 2004). The extensive use of anthelmintic treatments has led to an increasing problem of anthelmintic resistance. Once a resistance is detected, alternative treatments are needed in order to avoid any further production losses. Accurate

and reliable methods to assess the treatment efficacy are thus essential to effectively control and monitor the infection.

The widely used faecal egg count reduction test (FECRT) was established in the early 1990s (Coles et al., 1992). It is a straightforward method to calculate the reduction in faecal egg counts (FECs), by comparing the mean pre-treatment and post-treatment FECs. For sheep and goats, if both the percentage reduction in mean FECs is less than 95% and the corresponding lower confidence limit is less than 90%, then the anthelmintic resistance is declared to be present. A standard method to obtain the FECs, the modified McMaster counting technique, is detailed in the guideline of the World Association for the Advancement of Veterinary Parasitology (WAAVP) (Coles et al., 1992). New WAAVP guidelines are not yet developed, but Levecke et al. (2017) have made recommendations to improve and standardize the FECRT.

Although the FECRT and the McMaster technique were widely used in practice, some limitations have been pointed out in recent years. First of all, the McMaster counting technique introduces substantial variability in the results which is not accounted for in the FECRT (Torgerson et al., 2012). As a consequence of this, the estimated efficacy were found to be quite variable particularly for the samples with low pre-treatment FECs and efficacy in the range between 90% and 95% (Miller et al., 2006). The use of refined techniques with a high analytical sensitivity such as

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FLOTAC (Giuseppe et al., 2010) and Cornell-Wisconsin (Egwan and Slocombe, 1982) can reduce but not eliminate the variability (Torgerson et al., 2012; Levecke et al., 2012b). Secondly, the distribution of egg counts is typically aggregated or overdispersed within the host population (Grenfell et al., 1995). Levecke et al. (2012a) evaluated the FECRT under different scenarios, highlighted that test results should be interpreted with caution when the sample size is small and the aggregation level is high. There were several attempts to propose more elaborate statistical models in the past years. Torgerson et al. (2005) assumed a negative binomial distribution for the counts, and used parametric bootstrap to calculate the confidence interval (CI) of the FECs reduction. More recently, methods have emerged that formulate the problem in a Bayesian framework. Denwood et al. (2010) considered a Poisson-gamma distribution for the counts, with the post-treatment mean linked to the pre-treatment mean via a scale factor. The inference is then done using Markov chain Monte Carlo (MCMC). Dobson et al. (2012) proposed a novel way to determine the confidence limits of the FECs reduction using Jeffrey intervals, which is derived from Bayesian procedures using a non-informative prior, however it requires high counts and high analytical sensitivity. Paul et al. (2014) proposed a hierarchical model that uses binomial distribution to capture the counting variability, and a Poisson-gamma distribution to model the overdispersion. The posterior median for the reduction and its 95% highest posterior density (HPD) interval is used for its point and interval estimate respectively. An easy-to-use web interface was implemented and made available online (Torgerson et al., 2014). However the models themselves were not published and well-documented. Levecke et al. (2015) proposed another Bayesian model with a slightly different formulation. It used a Poisson distribution to capture the variability in the counting process and a negative binomial distribution to capture the overdispersion. The Bayesian models do not only provide credible intervals on the reduction, but also generate posterior distributions for each of the model parameters, hence offering a probabilistic view on the efficacy rather than a yes or no answer. To the best of our knowledge, a common assumption made by those recent Bayesian models is that all animals in an infected population are exposed. However, Denwood et al. (2008) showed the underlying distribution of the nematodes FECs can be zero-inflated negative binomial (ZINB). The zero-inflation component can arise as a result of the unexposed livestock in an infected population. Models with zero inflation have already been used in the context of disease mapping (Vounatsou et al., 2009; Soares Magalhães et al., 2011).

In this paper, we propose zero-inflated Bayesian hierarchical models to estimate the reduction in FECs. We build on the models in Paul et al. (2014) and explicitly formulate the model structures. The models account for the extra variabilities that arise from both the sampling process and the between-animal variations. In addition, the models allow for extra zero counts by introducing the zero-inflation components. Overall, the models are more flexible and are suitable for a wide range of scenarios. The rest of this paper is organized as follows. Section 2 briefly reviews the conventional FECRT and efforts made to modify it. Section 3 introduces the zero-inflated Bayesian hierarchical models. Section 4 conducts a simulation study, where the bias and coverage of the estimated FECs reduction are compared across different methods. In Section 5, a case study is used to illustrate the proposed methods for estimating the reduction in FECs, where anthelmintic resistance was investigated in Swedish sheep flocks. Finally, Section 6 concludes with a discussion.

## 2. Faecal egg count reduction test

The FECRT was suggested in the WAAVP guideline for estimating the reduction in FECs and its corresponding CI (Coles et al.,

1992). In order to reduce the counting variability, using groups of at least 10–15 animals was suggested. In addition, the mean pre-treatment FECs should be at least 150 epg, otherwise the FECRT can give unreliable results.

Suppose a group of  $n_T$  animals received anthelmintic treatment and a group of  $n_C$  animals serves as control. The percentage reduction in FECs can be calculated as:

$$\text{Percentage reduction} = 100 \times \left(1 - \frac{\bar{x}_T}{\bar{x}_C}\right), \quad (1)$$

where  $\bar{x}_T$  and  $\bar{x}_C$  denote the mean counts of the treatment and the control group. Assuming independence, the estimated asymptotic variance of the log ratio is given by

$$\text{Var} \left( \log \frac{\bar{x}_T}{\bar{x}_C} \right) = \frac{s_T^2}{n_T \bar{x}_T^2} + \frac{s_C^2}{n_C \bar{x}_C^2}. \quad (2)$$

where  $\bar{x}_T$  and  $\bar{x}_C$  denote the means of random samples,  $s_T^2$  and  $s_C^2$  denote the sample variance of the treatment and the control group counts. The variance can be used to construct an approximate 95% CI of the log ratio using the 97.5% and the 2.5% quantile of a Student's  $t$ -distribution with  $n_T + n_C - 2$  degrees of freedom. The CI for the log-ratio can be then transformed back to obtain the 95% CI for the estimated reduction. The WAAVP guideline (Coles et al., 1992) states that for sheep and goats, the resistance is present if (i) the percentage reduction in FECs is less than 95% and (ii) the corresponding lower 95% confidence limit is less than 90%. If only one of these two criteria is met, then resistance is suspected. Different thresholds have been suggested for other livestock.

Over the past years, modified versions of the FECRT have been proposed in the literature. Wood et al. (1995) suggested to use the geometric mean in the FECRT instead of arithmetic mean. Davison and Hinkley (1997) suggested the 95% CI can also be calculated using nonparametric bootstrap. In the unpaired design, there is one group of animals that receives the treatment and another group is chosen to act as the control group. McKenna (1990) suggested that instead of taking samples from two groups of animals, the pre-treatment counts from the treatment group can be used as the baseline, hence eliminated the need of a distinct control group. We refer to this as the paired design. In this case, the FECRT becomes inappropriate since it does not take the paired structure into account in calculating the variance.

## 3. Bayesian hierarchical models

There are two designs that can be used for detecting anthelmintic resistance in a livestock population. For each design, we propose a zero-inflated Bayesian hierarchical model to estimate the reduction in FECs.

### 3.1. The unpaired design

Suppose we have two groups of animals from the same population, a control group with size  $n_C$  and a treatment group with size  $n_T$ . A faecal sample from each animal is collected and counted with an analytical sensitivity  $f_i$ , where  $i$  is the index of each animal in the corresponding group. We assume the counts belong to the same species, more specifically the counts follow a unimodal distribution. For notational simplicity, we assume every sample has the same analytical sensitivity, hence the index in  $f_i$  is dropped for the rest of the paper. The faecal sample is thoroughly mixed after dilution, hence we assume the eggs are homogeneously distributed within each sample. A proportion of the diluted sample  $p = 1/f$  is then counted. Denote the raw number of eggs in the diluted sample of the  $i$ th control animal as  $Y_i^{*C}$ , with  $i = 1, 2, \dots, n_C$ . Given the true number of eggs per gram of faeces  $Y_i^C$ , the raw count  $Y_i^{*C}$  follows a

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