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A systematic review and meta-analysis of factors associated with anthelmintic resistance in sheep

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ABSTRACT

Background: Anthelmintic drugs have been widely used in sheep as a cost-effective means for gastro-intestinal nematode (GIN) control. However, growing anthelmintic resistance (AHR) has created a compelling need to identify evidence-based management recommendations that reduce the risk of further development and impact of AHR.
Objective: To identify, critically assess, and synthesize available data from primary research on factors associated with AHR in sheep.
Methods: Publications reporting original observational or experimental research on selected factors associated with AHR in sheep GINs and published after 1974, were identified through two processes. Three electronic databases (PubMed, Agricola, CAB) and Web of Science (a collection of databases) were searched for potentially relevant publications. Additional publications were identified through consultation with experts, manual search of references of included publications and conference proceedings, and information solicited from small ruminant practitioner list-serves. Two independent investigators screened abstracts for relevance. Relevant publications were assessed for risk of systematic bias. Where sufficient data were available, random-effects Meta-Analyses (MAs) were performed to estimate the pooled Odds Ratio (OR) and 95% Confidence Intervals (CIs) of AHR for factors reported in ≥2 publications.
Results: Of the 1712 abstracts screened for eligibility, 131 were deemed relevant for full publication review. Thirty publications describing 25 individual studies (15 observational studies, 7 challenge trials, and 3 controlled trials) were included in the qualitative synthesis and assessed for systematic bias. Unclear (i.e. not reported, or unable to assess) or high risk of selection bias and confounding bias was found in 93% (14/15) and 60% (9/15) of the observational studies, respectively, while unclear risk of selection bias was identified in all of the trials. Ten independent studies were included in the quantitative synthesis, and MAs were performed for five factors. Only high frequency of treatment was a significant risk factor (OR = 4.39; 95% CI = 1.59, 12.14), while the remaining 4 variables were marginally significant: mixed-species grazing (OR = 1.63; 95% CI = 0.66, 4.07); flock size (OR = 1.02; 95% CI = 0.97, 1.07); use of long-acting drug formulations (OR = 2.85; 95% CI = 0.79, 10.24); and drench-and-shift pasture management (OR = 4.08; 95% CI = 0.75, 22.16).

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While there is abundant literature on the topic of AHR in sheep GINs, few studies have explicitly investigated the association between putative risk or protective factors and AHR. Consequently, several of the current recommendations on parasite management are not evidence-based. Moreover, many of the studies included in this review had a high or unclear risk of systematic bias, highlighting the need to improve study design and/or reporting of future research carried out in this field.

1. Introduction

Gastro-intestinal nematodes (GINs) cause significant disease in grazing sheep worldwide, with important economic repercussions to the sheep industry (Coles, 2001; Stear et al., 2011; Knox et al., 2012). The advent of broad-spectrum anthelmintic drugs in the early 1960s offered an affordable and simple means to manage GINs. As a result, these drugs rapidly became the mainstay for GIN control (Zajac, 2006; Sargison, 2011). However, this routine use has led to the development of Anthelmintic Resistance (AHR), whereby anthelmintic drugs have reduced or no effectiveness against GINs present within animals (Morgan and Coles, 2010).

Anthelmintic resistance has been documented in most sheep-rearing countries, including Australia (Suter et al., 2004), New Zealand (Waghorn et al., 2006), North, Central and South America (Maroto et al., 2011; Torres-Acosta et al., 2012; Falzon et al., 2013), Africa (van Wyk et al., 1999), Asia (Kumar and Yadav, 1994; Ancheta et al., 2004) and Europe (Papadopoulos et al., 2012). Moreover, countries which have publications on multiple cross-sectional studies over time, such as Brazil (Echevarria et al., 1996; Sczesny-Moraes et al., 2010), New Zealand (Kettle et al., 1981; Waghorn et al., 2006) and the United Kingdom (Cawthorne and Cheong, 1984; Bartley et al., 2003; Mitchell et al., 2010), reported a worsening situation, with an increase both in AHR prevalence and in the number of GIN species affected. Multiple-drug resistance is also increasing (Sargison et al., 2007; Voigt et al., 2012; Martínez-Valladares et al., 2013), while a recent report by Scott et al. (2013) documented the first case of resistance to monepantel, a novel drug-class which has only been commercially available since 2009.

To prevent further development of AHR, a better understanding of the management practices associated with resistance is required (Sangster, 1999; Coles, 2001; Morgan, 2013). Early recommendations for sustainable parasite control were either based on evidence regarding key molecular processes involved in selection for resistance (Dobson et al., 2001), or simulation models (Leathwick et al., 1995). In recent years, several observational studies (Suter et al., 2004; Lawrence et al., 2006; Hughes et al., 2007; Calvete et al., 2012) and clinical trials (Leathwick et al., 2006; Leathwick et al., 2008; Waghorn et al., 2008, 2009) have been performed to investigate the association between putative risk factors and AHR. While all these studies may provide valuable information in isolation, they sometimes describe conflicting results. By way of example, mixed-species grazing has been described as both a protective and risk factor for AHR in different studies (Eddi et al., 1996; Lawrence et al., 2006). Thus, there is a need for better evidence regarding the effect of management practices on AHR.

The importance of evidence-based medicine is now widely recognized, whereby practitioners are encouraged to base their decisions less on clinical intuition and experience, and more on high quality evidence (McGovern et al., 2001; Schoenfeld, 2008; Petrie and Watson, 2013). Systematic Reviews (SRs) and Meta-Analyses (MAs) are considered to provide the most substantive clinical evidence (Clarke, 2008; Moayyedi, 2008; Moher et al., 2010). As opposed to narrative reviews, SRs follow explicitly defined methods that guide the search and inclusion criteria, thus ensuring a transparent and repeatable process (Greenhalgh, 1997; Sargeant et al., 2006). Moreover, SRs require the critical appraisal of included publications, which helps to identify sources of systematic bias that might influence the observed associations, and to interpret the results accordingly (Higgins et al., 2011a). Lastly, the quantitative synthesis of the results, when possible, allows for a more precise estimate of the effect and improves the external validity of the results (Lean et al., 2009).

The aim of this systematic review and meta-analysis was to identify, evaluate, and synthesize primary literature reporting the effect of selected factors associated with AHR in sheep. The rationale for this study was to generate information to help producers and veterinarians make evidence-based decisions and recommendations regarding sustainable use of anthelmintic drugs and management of GINs.

2. Materials and methods

2.1. Research question, definitions, and protocol

This SR was conducted to identify management practices associated with AHR in sheep. The population was defined as the ovine species or sheep, while goats were excluded. The interventions of interest were management practices that have been putatively associated with AHR, either in the literature or by experts; a list of all considered management practices and their respective definitions is presented in Tables 1 and 2. The outcome was AHR in sheep GIN of economic importance (i.e. *Haemonchus* sp., *Trichostrongylus* spp., *Teladorsagia*/*Ostertagia* sp., *Oesophagostomum* sp., *Chabertia* sp., *Nematodirus* spp. and *Cooperia* spp.), where AHR was diagnosed using either the in vivo fecal egg count reduction test (FECRT) or the in vitro larval development assay (LDA), egg hatch assay (EHA) or tubulin binding assay (TBA). Relevant comparators were those publications reporting one or more groups receiving: (i) no treatment or

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