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Invited Review

Anthelmintic resistance in equine nematodes

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ABSTRACT

Anthelmintics have been applied indiscriminately to control horse nematodes for over 40 years. Three broad-spectrum anthelmintic classes are currently registered for nematode control in horses: benzimidazoles (fenbendazole, oxibendazole), tetrahydropyrimidines (pyrantel) and macrocyclic lactones (ivermectin, moxidectin). Generally, control strategies have focused on nematode egg suppression regimens that involve the frequent application of anthelmintics to all horses at intervals based on strongyle egg reappearance periods after treatment. The widespread use of such programmes has substantially reduced clinical disease, especially that associated with large strongyle species; however, high treatment frequency has led to considerable selection pressure for anthelmintic resistance, particularly in cyathostomin species. Field studies published over the last decade indicate that benzimidazole resistance is widespread globally in cyathostomins and there are also many reports of resistance to pyrantel in these worms. Cyathostomin resistance to macrocyclic lactone compounds is emerging, principally measured as a reduction in strongyle egg reappearance time observed after treatment. Ivermectin resistance is a further concern in the small intestinal nematode, *Parascaris equorum*, an important pathogen of foals. These issues indicate that horse nematodes must now be controlled using methods less dependent on anthelmintic use and more reliant on management practices designed to reduce the force of infection in the environment. Such strategies include improved grazing management integrated with targeted anthelmintic administration involving faecal egg count (FEC)-directed treatments. The latter require that the supporting diagnostic tests available are robust and practically applicable. Recent research has focused on maximising the value of FEC analysis in horses and on optimizing protocols for anthelmintic efficacy testing. Other studies have sought to develop diagnostics that will help define levels of pre-patent infection. This review describes recent advances in each of these areas of research.

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1. The issue of horse nematodes

Horses worldwide are exposed to an array of gastrointestinal nematodes. Animals that graze contaminated pasture, and which are not treated with effective anthelmintics, can accumulate large numbers of worms. The most prevalent of these are members of the small strongyle group, the cyathostomins (Ogbourne, 1976; Bucknell et al., 1995; Gawor, 1995; Kuz'mina, 2012; Relf et al., 2013). When the total burden of cyathostomins is high, they can seriously compromise the health of affected individuals (Mair, 1994; Matthews, 2008; Matthews, 2008, 2014). Substantial burdens (i.e. several million) of immature cyathostomins can encyst in the large intestinal wall and it is thought that these stages can persist for years (Murphy and Love, 1997). These stages, in particular early third stage larvae (EL3), are relatively insensitive to most anthelmintics available (Monahan et al., 1996). In temperate areas of the northern hemisphere, cyathostomin larvae encyst primarily during the autumn and winter and can comprise up to 90% of the total burden (Dowdall et al., 2002). When these larvae re-emerge in large numbers from the gut wall, a fatal colitis, larval cyathostominosis, can develop (Giles et al., 1985).

Several other nematode species infect horses and other equids, but the prevalence of these species is usually lower than that of cyathostomins (Relf et al., 2013). The most important non-cyathostomin species affecting horses older than one year is *Strongylus vulgaris.* This nematode can cause non-strangulating intestinal infarction leading to severe colic and was the major parasitic threat to equine health before the advent of broad-spectrum anthelmintics, in particular, the macrocyclic lactones (Reinemeyer and Nielsen, 2009). In younger horses (i.e. those less than 2 years-old), the small intestinal ascarid, *Parascaris equorum*, can be a substantial risk, producing both respiratory and intestinal signs of disease (Cribb et al., 2006). The lungworm, *Dictyocaulus arnfieldi* (MacKay and Urquhart, 1979), and the liver fluke, *Fasciola hepatica* (Owen, 1977), can undergo life cycle development in horses and lead to clinical signs; these are a particular hazard in horses that co-graze with, or graze pastures recently populated by, more permissive hosts such as donkeys and ruminants, respectively. There are few published studies describing the factors that affect the prevalence and abundance of the various parasitic nematode species of horses. A recent publication identified that a lack of rotational grazing practices (between age groups or host species) was associated with a higher prevalence of cyathostomin egg excretion on Thoroughbred stud farms (Relf et al., 2013). In the same study, higher levels of strongyle egg shedding (i.e. >200 eggs per gram) in faeces were observed to be significantly associated with a number of factors, with a recent history of treatment with fenbendazole identified as the most significant factor. The latter observation may be linked to the fact that there is a high prevalence of benzimidazole resistance in cyathostomin populations (see below).

Since the 1960s, nematode control has followed interval treatment regimens involving the frequent administration of anthelmintic products at intervals based on strongyle egg reappearance periods (ERP). These periods were defined for each chemical class of compound at the time of licensing (Parry et al., 1993; Kaplan and Nielsen, 2010). Such interval treatment programmes have been successful in substantially reducing the prevalence of strongyle infections and the incidence of large strongyle-associated disease. On the flip side, these programmes have made a substantial contribution to the development of anthelmintic resistance, particularly in cyathostomin species (Kaplan, 2004). Should anthelmintic resistance levels worsen, there will be limited scope for control, as no new classes of compound appear to be under development for use in horses in the short to medium term. Based on comparative studies on sheep nematodes (Jackson and Coop, 2000), reversion to anthelmintic sensitivity is unlikely to occur once populations are measured as anthelmintic resistant by conventional means such as the faecal egg count reduction test (FECRT). For these reasons, more sustainable methods of nematode control are now required, these being based on a requirement to treat animals predisposed to larger burdens to prevent clinical disease, balanced with a need to reduce treatment frequency to preserve anthelmintic efficacy. In the last decade, regulations in the European Union (EU) require that anthelmintics be classified as prescription-only drugs. Currently, the legislation is interpreted differently across the EU, with strictest implementation in Denmark where anthelmintic administration is based on diagnostic evidence of infection (Nielsen et al., 2012). Deployment of such diagnostic-based control strategies requires that robust and practical support tools are available. Coprological analysis for nematode eggs is central to this strategy, but this method is incapable of discriminating pre-patent infection. With the extended pre-patent period of several strongyle species, there is a requirement for diagnostic tests that detect and quantify levels of immature stages. A number of antigens are under investigation as diagnostic markers for detecting pre-patent cyathostomin (McWilliam et al., 2010) and *S. vulgaris* (Andersen et al., 2013a) infections. Until these are available, FEC-directed treatments will need to be balanced with anthelmintics applied strategically to target pathogenic larvae (Matthews, 2008).

2. Anthelmintic resistance

Interval-based treatment programmes, which have been used extensively in the equine industry, will be expected to select resistance alleles within nematode populations (Kaplan and Nielsen, 2010). Resistance to the earlier registered anthelmintics, the benzimidazoles and the tetrahydropyrimidines, has been reported many times in cyathostomin populations across the world, and resistance to both of these classes in single populations is a common observation in field studies (Kaplan et al., 2004; Traversa et al., 2009; Traversa et al., 2012). As fenbendazole resistance in cyathostomins is virtually ubiquitous in many regions (Osterman Lind et al., 2007; Traversa et al., 2012; Lester et al., 2013b; Relf et al., 2014; Stratford et al., 2014b), this anthelmintic should not be recommended for use in control of these infections in these areas. Perhaps surprisingly, despite the substantial reliance on ivermectin and moxidectin for equine nematode control in the last 30 years, resistance, measured as a reduction in FEC of less than 90–95% at 14–17 days after treatment, has been reported infrequently. Nevertheless, there have now been several reports of reduced strongyle egg ERP after ivermectin or moxidectin administration in a number of countries (von Samson-Himmelstjerna et al., 2007; Molento et al., 2008; Lyons et al., 2009; Lyons et al., 2010; Rossano et al., 2010; Lyons et al., 2011; Lyons and Tolliver, 2013; Canever et al., 2013; Relf et al., 2014). Reduced ERP is believed to provide an early indicator of a shift in a nematode population's sensitivity towards resistance (Sangster, 2001) and so this provides a warning as to the likely long-term effect of macrocyclic lactone compounds in horses.

Ivermectin resistance measured as low FEC reduction after treatment has been reported with regularity in *P. equorum* populations (Boersema et al., 2002; Hearn and Peregrine, 2003; Stoneham and Coles, 2006; Craig et al., 2007; Schougaard and Nielsen, 2007; von Samson-Himmelstjerna et al., 2007; Reinemeyer, 2012). These findings are unsurprising given the excessively frequent use of ivermectin in foals on stud farms. Control of ivermectin resistant *P. equorum* populations can theoretically be achieved using