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Worm control in sheep in the future☆

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ABSTRACT

Endoparasitic infestations cost the livestock industry many millions of pounds each year through losses in productivity and the costs of control measures. Effective control of these endemic ubiquitous diseases is important, particularly given the expanding world population and the expectation of an increasing demand for ruminant products. Currently, these debilitating ruminant infestations can be controlled prophylactically by using chemotherapy, immunomanipulation and/or management of the grazing environment, but most farmers currently rely upon having effective anthelmintics. Unfortunately, studies on the incidence and prevalence of anthelmintic resistance throughout the world suggest that production systems that are wholly reliant upon intensive chemotherapy/prophylaxis are not sustainable. Current research is examining chemical strategies that will provide good worm control and will also enable the conservation of efficacy of our current and any novel anthelmintics. Maintaining an infra- and supra-population of worms *in refugia* (i.e., unexposed to anthelmintics) is accepted by most veterinary parasitologists as the best means of maintaining the genes for susceptibility within the parasite population. Maintained susceptibility within a parasite population can be achieved in a variety of ways, all of which utilise a targeted treatment approach to some extent. Whole flock targeted treatment can be optimised using faecal egg count monitoring and individuals can have targeted selective treatments administered on the basis of morbidity markers, such as anaemia, production efficiency assessed by liveweight gain or milk production. There is also a growing interest in bioactive forages, which can have both direct anthelmintic effects and/or indirect anthelmintic effects, where the benefit derives from nutritional effects which boost the host immune responses against nematodes. In the future, arguably the most exciting area is that of immunomanipulation, where current advances in genomics and proteomics offer scope for the development of vaccines and genetic or bio-markers associated with infection or effective immunity. We have been able to identify and select genetically resistant animals for many years by using phenotypic markers for endoparasitism, but it is only recently that the first genetic marker for host resistance has become available. Further research is also needed to identify better phenotypic and genotypic markers for resilience, since in some production systems this may be a more desirable trait than resistance. The implementation of an integrated approach to control to develop sustainable control strategies represents a formidable challenge for the sheep industry. This integrated approach will require well-informed veterinarians; advisors and researchers will need to find the tools to support the practitioners, as well as to find ways of delivering them in an affordable way. Although at present these demands may seem both unobtainable and unaffordable, the development of collaborative multidisciplinary research programmes coupled with advancing high throughput technologies offers the prospect of real progress in this area in future.

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1. Introduction

In attempting to consider the future of worm control in sheep, we inevitably need to consider both our past and our current situation. Two of the most useful and perhaps contextually relevant thoughts on the matter come from Sigmund Freud who considered "*Only a good-for-nothing is not interested in his past*" and Friedrich Nietzsche who stated that "*Every past is worth condemning*".

2. Where we were and where we are now

Helminth infestations currently cost the global small ruminant livestock industry many millions of dollars annually through their major effects upon food intake, digestion, absorption and utilisation. These effects lead to poor skeletal and muscular tissue development and concomitant reductions in fertility, wool and milk production. Under certain circumstances, helminth infestations can result in high mortalities, but more often there effects are on morbidity; subclinical nematode infestations in sheep alone have been estimated to cost the UK sheep industry more than GBP 84 million (Nieuwhof and Bishop, 2005). At present, these diseases are largely controlled by using anthelmintics; the world-wide annual expenditure on anthelmintics is over USD 3 billion and in the UK alone over GBP 70 million are spent each year on these drugs. However, the increasing prevalence of parasite populations resistant to these drugs, suggests that intensive chemoprophylaxis is not a sustainable control strategy (Jackson and Miller, 2006). Multiple drug resistant populations of *Haemonchus*, *Teladorsagia* and *Trichostrongylus*, the three economically most important species of nematodes infecting small ruminants, have been recorded in tropical, subtropical and in temperate regions of the world including Europe (Jackson and Coop, 2000; Waller, 2003; Kaplan, 2004; Wolstenholme et al., 2004; Jabbar et al., 2006; Ganter, 2008; Papadopoulos, 2008). Resistance against triclabendazole (Overend and Bowen, 1995), the most effective and widely used flukicide, has also been reported in Europe (Mitchell et al., 1998; Thomas et al., 2000; Moll et al., 2000; Alvarez-Sanchez et al., 2006). When the first broad-spectrum anthelmintics were first developed some 40–50 years ago (McKellar and Jackson, 2004), their advent heralded in an age when the damaging effects of nematode infestations could be controlled very simply and cheaply. For several decades after their introduction, their effectiveness was exploited to enable producers to intensify productivity within their systems. Initially the focus of producers was simply "effective worm control", which was achieved by using anthelmintics therapeutically and prophylactically in suppressive control regimes. At those times, simple cost–benefit analyses could be used to demonstrate increases in yield obtainable from having available effective anthelmintics. Many people in the 1960s, 1970s and 1980s assumed that the animal health industry could and would continue to produce a regular stream of anthelmintics with novel modes of action. However, following the introduction of the macrocyclic lactones in the 1980s, we have needed to wait two decades for the introduction of a new drug action compound, monepantel (Kaminsky et al., 2008). The emergence of widespread resistance against the three broad-spectrum drugs has led to the recognition that simply relying upon intensive suppressive chemical control strategies may not be a sustainable approach. Today, the veterinarian/advisor and farmer need to consider the issue of "effective worm control" within a context of sustainability.

3. Where are we going?

Given the wide regional variation that exists between sheep management systems and the different parasites that inhabit them, it is hardly surprising that there are no universally applicable "blueprint" approaches to the control of nematode infestations. This in turn, means that farmers, their veterinarians and/or specialist advisors have to choose worm control strategies that suit the unique situation that each farm presents in terms of its prevalent parasites, their epidemiology and the structure and management of the farm. In developing this aspect of flock health planning, there are many options (Krecek and Waller, 2006) that can be exploited, which can be broadly categorised as being (a) chemical, (b) environmental or (c) immunological. In the short- to medium-term, it is likely that the sheep industry will rely mostly upon anthelmintics to control nematode infestations. There are several reasons for this. Firstly, the debilitating effects of nematode infestations are essentially challenge-dependant phenomena and given the inherent variability of parasite biology, we will always need the therapeutic capacity that only anthelmintics can supply. The second reason concerns the issue of practicability, anthelmintics are simple, cheap, safe and – at least prior to the advent of resistance – their successful application did not necessarily require a detailed understanding of parasite biology and epidemiology.

4. Chemical management

This year has seen the first launch of a new drug more than 25 years after the launch of the first macrocyclic lactone. The new compound, monepantel, has a novel receptor target in a broad range of nematode species (Hosking et al., 2008, 2009; Kaminsky et al., 2009; Sager et al., 2009). Also, there has been the launch of a long-acting moxidectin formulation for sheep. The best way to incorporate these new compounds and formulations into sustainable worm control strategies is an issue for the industry. One obvious application for monepantel is as a quarantine drench, using a single product to replace the combinations that have previously been recommended for this purpose in Australia (Dobson et al., 2001) and in the UK (Abbott et al., 2004) as a way of reducing the risk of importing resistance with bought in sheep. When not being used as a quarantine drench, but in routine control, it is also important that any new products are not used exclusively, but rather in conjunction with remaining effective products, in order to conserve susceptibility within parasite supra-populations (Van Wyk and Bath, 2002; Abbott et al., 2004; Pomroy, 2006).

Genetic markers for resistance are required in order to be able to monitor changes in resistance allele frequencies.

Although we have tubulin SNPs for the benzimidazoles, we still need markers for drugs in the imidazothiazole/tetrahydropyrimidine and the macrocyclic lactone families. This need has been recognised prior to the launch of monepantel, where the genetic changes that confer resistance have been described in both *Caenorabditis elegans* and *Haemonchus contortus* (Rufener et al., 2009).

It is now widely accepted (Van Wyk, 2001; Besier, 2008; Jackson and Waller, 2008) that the sustainability of chemically based worm control strategies is dependent upon ensuring that some proportion of the population remains unexposed to treatment ("*in refugia*"). This can be achieved by targeting treatments either towards the whole flock at a time when there is some *refugia* or some set proportion of the flock at those times when there is none. A targeted selective treatment approach relies upon the ability to identify individuals that will in some way benefit from treatment. Although a variety of different markers can be used to direct targeted selective treatments, the most commonly used ones are based on either morbidity/production indices, which identify individuals most susceptible to disease or parasitological markers which, at times, may provide some indication of an individual's susceptibility to infection and/or some capacity to spread that infection. The best known example of an approach with targeted selective treatments is the FAMACHA© system, pioneered in South Africa by F. Malan and J. van Wyk. This system, which is widely used in *Haemonchus* endemic regions, uses the colour of the ocular membranes as an indicator of anaemia to identify individuals at risk of haemonchosis (Bath et al., 1996; Van Wyk et al., 2006). In the earliest studies using FAMACHA©, on irrigated pastures in South Africa only about one third of the animals were found to need any treatments. An alternative targeted selective treatments strategy is to direct individual treatments to obtain a parasitological benefit, such as reduced pasture contamination. The realisation that high milk producing dairy goats also had the highest faecal egg counts led researchers in France to use individual milk production data for targeted selective treatments; in so doing managed to substantially reduce anthelmintic treatment with no negative impact upon productivity (Hoste et al., 2002).

Research in the project PARASOL (www.parasol-project.org) sponsored by the European Union and involving eight European and two African participants, has examined a range of different regionally appropriate markers for targeted selective treatments in both small and large ruminants. Sheep studies in the temperate European countries of France and the United Kingdom have shown that individual liveweight gain can be used to optimise treatments.

In a 3-year long study at Moredun Institute, different regimes (including targeted selective treatments) were applied and compared and individuals were treated according to efficiency of production measured by bodyweight gain (Greer et al., 2007). That group had comparable weight gains to both the neo-suppressively (monthly)-treated and strategically treated groups, despite having used around half of the anthelmintic used in the monthly treated animals. Moreover, the average efficacy of the anthelmintic used in the trial was maintained in the targeted selective treatments-group, whereas it fell by almost 18% in the neo-suppressively treated group. In the same study, the group of animals that were treated therapeutically on the basis of overt signs of parasitism had significantly lower weight gains than the targeted selective treatment-group, the monthly treated group and the strategically treated group.

These studies have provided the first proof of concept that liveweight gain may be used as an indicator for individual anthelmintic treatment, further large scale field trials are required to refine and optimise the system. In western European countries, where labour costs are high, this approach requires some investment in automatic weighing/shedding and in electronic identification systems. However, these costs can be offset against reduced anthelmintic costs and in the maintenance of susceptibility within the parasite populations. To date, no one has attempted to determine the value of maintained parasite susceptibility, but researchers have usually attempted to define the costs of anthelmintic resistance in terms of lost productivity, wasted anthelmintic and labour costs, etc. (Brunsdon and Vlassoff, 1982; Brunsdon et al., 1983; Larsen et al., 2006; Roger, 2008). Although these "resistance" components can simply be considered as being additive factors in calculating the cost of resistance, they do not provide any estimate of the value or cost of maintaining susceptibility. This is because of the additional costs associated with the managemental changes possibly required to manage worm control in the face of multiple resistance.

The use of bioactive forages as a means of nematode control might be thought to offer in effect a whole "new" range of anthelmintics in the form of the plant secondary metabolites that provide direct anthelmintic activity (Hoste et al., 2008). However some caution is necessary when considering this managemental intervention, since in some cases the active compounds and their toxic effects have yet to be identified and quantified. It is also possible that the transport and metabolic mechanisms that resistant parasites successfully use to regulate conventional anthelmintics might also operate against these metabolites. If this is indeed the case, then there might be some selection at resistant loci as a direct result of using these forages.

The emergence of multiple resistance and the need to conserve the efficacy of our anthelmintics has provided some of the impetus for the present research on managing the grazing environment and optimising immunological approaches to control, as means of reducing our reliance upon anthelmintics.

5. Management of grazing environment

Pasture rotations have always been a feature of sheep production systems and grazing management in various guises has been used to as a way of minimising the threat of nematode infestations for over 40 years. Although management of the grazing environment is an important weapon in the armoury for worm control, its successful implementation on farm requires detailed understanding of the farm and of the parasites on it. This complexity together with demands that grazing management makes upon types of stock and use of pasture, acts as a powerful deterrent, undoubtedly being among the reasons why grazing management is generally less well exploited.

Michel (1969) first described the dose (with an effective anthelmintic) and move (to a clean or minimally contaminated pasture) strategy as a means of controlling gastrointestinal nematodes in calves. Since then, there have been a large number of studies examining the use of cropping and aftermaths (Brunsdon, 1980), rotational grazing (Barger, 1999), "clean grazing" (Mitchell and Fitzsimons, 1983) and alternate hosts (Southcott and Barger, 1975) to reduce the size of the challenge from pasture. The use of grazing management in the control of gastrointestinal nematodes has also been the subject of a number of informative reviews (Waller, 1993; Barger, 1996, 1999).

Grazing management systems that operate without anthelmintics, such as the clean grazing system (Mitchell et al., 1984), which involve annual sheep, cattle and conservation rotations can be very effective, but only function well within very tightly defined circumstances. Whenever grazing management is used in conjunction with anthelmintics, then some care has to be taken to ensure that there is sufficient *refugia*, since if animals are dosed when there are few unexposed worms on pasture or in the host, there can be a strong selection for drug resistance. The summer drenching program promoted in southern Australia, where treatments were given at a time when few larvae were on pasture has been shown to accelerate the development of ivermectin resistance (Swan et al., 1994).

An alternate approach to the management of the free living parasite populations has been the use of predatory fungi, such as *Duddingtonia flagrans* (Waller and Faedo, 1996; Larsen, 1999). This approach gives very useful reductions in larval yield from faeces under optimum conditions, when fungal growth and larval development are synchronous, however, the findings from field studies performed around Europe have been variable (Eysker et al., 2006). As a direct consequence of this lack of consistency, research investigating this approach has declined in recent years, reducing the likelihood that there will be a commercially available product that sheep farmers can use.

6. Immunological management

The various immunological approaches to control can also be used to reduce reliance upon anthelmintics and can thus help to maintain anthelmintic susceptible populations. Immunomanipulation through optimized nutrition (Coop and Kyriazakis, 2001; Athanasiadou et al., 2008), the selection of resistant or resilient animals (Hunt et al., 2008) and/or vaccination (Smith, 2008) all offer some advantage in reducing the numbers of anthelmintic treatments that animals require.

Host acquired immunity is one of the most important factors influencing epidemiological differences between the various gastrointestinal nematode parasites and the host plane of nutrition is a crucial element that influences its development and maintenance. Marked between-farm differences in the "nutritional environment" ensure that there is no single "off the peg" approach that can be applied across all farms in a region. In developing single farm solutions, the veterianrian/advisor has an array of tests that can be used to identify macro- and micro-element deficiencies.

The ability to select either resistant (animals that mount effective immune responses against worms) or resilient animals (animals that perform well under worm challenge) has been an area of interest for many years. In several countries it is now possible to obtain estimated breeding values based upon faecal egg count data. Selection for resistance and resilience has traditionally been made using different phenotypic traits (Hunt et al., 2008) that provide some indication of the extent of infection (resistance) or of the impact of infection upon performance (resilience). Phenotypic susceptibility to *Haemonchus* identified using the FAMACHA© system has been shown to be heritable and has been used as a phenotypic marker for selective breeding in Brazil (Molento, 2007). Other morbidity markers used in the targeted selective treatments approach might also provide a suitable phenotypic marker upon which to base breeding decisions, particularly those concerned with exclusion of animals with extreme susceptibility to infection or disease.

In recent years, there have been some advances in the identification of genetic markers, which associate with host resistance and which should accelerate progress in breeding for resistance. The first test DNA test for parasite resistance has been developed and released for use in New Zealand (http://www.catapultsystems.co.nz) and we should expect further tests to come online in the next few years. However, the promising advances made in the areas of quantitative trait loci mapping and/or whole genome selection will need to be matched by a better capacity to determine phenotypes particularly during the research phase (Hunt et al., 2008). There are several reasons for this; firstly the biological mechanisms underpinning resistance are complex and subject to extremes in variance depending upon a range of factors, including nutrition, exposure to infection and breed/genotype. Secondly, immunoregulatory mechanisms have multiple pathways and the genes involved in them may also be involved in other apparently unrelated mechanisms.

The rapid development of genetic screening technologies has enabled considerable advances to be made in this area, but we are still some way from being able to integrate these DNA markers into the breeding management of commercial flocks. We also need to know how best to target this resource in our flocks and will obviously need high throughput affordable screening systems to enable this implementation of this exciting approach.

The economically important gastrointestinal nematodes of sheep have been the subject of sub-unit vaccine research for over 20 years (Smith, 2008). The fact that it has been possible to develop sub-unit vaccines for some ticks (Willadsen et al., 1992) and cestodes (Lightowlers et al., 2003) provides proof of concept of this approach to parasite control. Due to its commercial potential, research in this area is usually shrouded in secrecy, however several candidate antigens offering adequate protection in trials using native antigens have been identified for the sheep parasite *Haemonchus* and the cattle nematode *Ostertagia* (Smith, 2008). As yet, attempts to use the recombinant versions of these native antigens have not proved to be successful and this remains a major stumbling block in the progress towards vaccination. Despite this, researchers in this area are convinced that it will be possible to produce subunit vaccines for species such as *Haemonchus* and *Ostertagia*.

7. Conclusions

It seems reasonable to assume that worm control in sheep in the future will become a more complex issue requiring the veterinarian to move away from a simple over reliance upon anthelmintics as the sole means of control. If we are to get sustainable control regimes, then there are a number of challenges that the farming industry, researchers and practitioners will have to meet. Whilst there are a number of established and developing approaches that the practitioner will be able to draw upon in future, the challenge will always be to do so working with sheep an animal of low economic value where there is inevitably a small margin between economic investment and return. The fact that the sheep industry in Europe is a traditional industry, which does not assimilate change rapidly, provides a further complication. However, if the research community can meet the challenge of developing improved high throughput diagnostic technologies then it may provide affordable tools that the practitioner needs. Finally, the main challenges to the veterinary profession in many countries are firstly to re-establish and then maintain involvement with the farmer and to ensure that adequate training in parasitology is available at both undergraduate and postgraduate level.

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