REVIEW ARTICLE

Alternatives to anthelmintics for the control of nematodes in livestock

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SUMMARY

Efficient and welfare-friendly livestock production demands the control of nematode infection. Current control measures rely upon anthelmintic treatment but are threatened by the widespread evolution of drug-resistance in parasite populations. Several methods have been advocated to control nematodes without relying on effective anthelmintics. These include grazing management, biological control, nutritional supplementation, vaccination, and genetic approaches. Each method has its advantages and disadvantages. There are several grazing management schemes that can reduce the severity of infection but they are insufficient on their own to control infection. Biological control includes the use of predatory fungi to control nematode populations and the use of pasture species that can reduce the intensity of infection. Fungi can control nematodes but the current requirement for daily feeding means that this approach will be most useful for animals that are handled daily. Feeding supplementary protein can control nematode infection. The method is simple but can be expensive and may not be cost-effective for some marginal enterprises. Genetic approaches include the use of resistant breeds and selective breeding. Some breeds will thrive in conditions that kill animals from other breeds but substitution of resistant breeds is not always feasible. Selective breeding is effective and inexpensive but requires a high level of expertize. The most appropriate method or set of methods to minimize the adverse consequences of nematode infection may vary among farms.

Key words: nematode, grazing management, biological control, nutrition, genetics, vaccination, parasite control.

INTRODUCTION

Nematode infection threatens the health and welfare of livestock and compromises the efficiency of livestock production. Nematodes are possibly the major disease challenge facing ruminants (Perry and Randolph, 1999). They are ubiquitous and have a major impact on all production areas (Urquhart *et al*. 1987). Essentially all grazing livestock are exposed to infection.

Nematodes cause disease and can kill but perhaps their major economic impact is their reduction of growth in young lambs (Coop *et al*. 1977). The severity of disease and the loss of production depend upon the intensity of infection, immunity of the host and its relative nutritional status (Coop and Kyriazakis, 2001; Stear *et al*. 2003). The intensity of infection is influenced by the weather and management factors such as stocking rate, frequency of anthelmintic treatment and the number of times animals are moved to less contaminated pastures. Host immunity is strongly influenced by genetic factors but also depends upon age, nutrition and history of exposure. Relative nutritional status depends not only on past and current diet, especially protein intake (Coop and Kyriazakis, 2001) but also upon the intensity of infection.

Anthelmintics offer a simple, cheap, cost-effective method of controlling nematodes. They kill existing parasites and reduce the production of eggs. Therefore they can prevent disease in infected animals and reduce the intensity of future infection in infected animals and their offspring. The widespread application of anthelmintics has transformed the livestock industries, especially cattle and sheep. Indeed without effective anthelmintics the livestock industry could not exist in its current form (Stear *et al*. 2000*b*).

There are 3 major classes of drugs used to control nematodes in livestock: benzimidazoles (such as albendazole sulphoxide), nicotinic agonists (such as levamisole) and macrocyclic lactones (including

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ivermectin). Unfortunately, resistance is evolving in nematode populations to all 3 classes of anthelmintic (Bartley *et al.* 2004). Therefore there is an increasingly urgent need to develop alternative or supplementary methods of nematode control. These methods fall into 5 categories: grazing management, biological control, nutrition, vaccination and genetic approaches. A recurring theme in this review is that improved understanding of the underlying science leads to more effective and sustainable methods of nematode control. Therefore each section contains a brief summary of our current knowledge.

The aim of this review is to describe the advantages and disadvantages of existing methods for nematode control that can be used in place of anthelmintics. This review complements and extends recent reviews (Sayers and Sweeney, 2005; Waller and Thamsborg, 2005). It does not cover developments that might lead to nematode control in the future but these have been reviewed recently (Hein *et al.* 2001; Knox, 2004).

Many different species of nematodes are pathogenic and they differ in their natural history, epidemiology and pathology (Urquhart *et al.* 1987). The mixture of species differs among different climates and much unnecessary confusion has been caused by the incautious extrapolation of results from one nematode species or one production system to another. The emphasis in this review is on nematodes of sheep in temperate climates, especially *Teladorsagia circumcincta* as this is among the best understood of all host-parasite interactions. Where appropriate, contrasts will be drawn with other species of nematode and host.

In the UK and other temperate climates, the dominant nematode of sheep is *T. circumcincta* but most lambs are infected with a mixture of species, including Nematodirus spp., Cooperia spp. and Trichostrongylus spp. In other countries the situation is different. For example, in Poland, Trichostrongylus spp., *Haemonchus contortus* and *T. circumcincta* are the most prevalent species (Moskwa *et al.* 1998; Gorski *et al.* 2006).

GRAZING MANAGEMENT

Most of the nematodes that parasitize the gastrointestinal tract of livestock have simple direct life-cycles (Urquhart *et al.* 1987). For *T. circumcincta*, adult worms mate in the abomasum and eggs are passed in the faeces. Eggs hatch in the faeces and the first-stage larvae then moult into the second stage. These stages feed on bacteria in the faeces. The third-stage larvae retain the second stage cuticle which prevents dessication but also means that these larvae are unable to feed. Third-stage larvae move out, or are washed out, of the faeces onto pasture; although some nematodes may leave the faeces on discharged fungal spores (Robinson, 1962; Bizzell and Ciordia,

1965). The dispersal of larvae from faeces is largely dependent on sufficient water from dew or rainfall to allow larvae to migrate (Stromberg, 1997). In addition to horizontal movement onto pasture, larvae may also move vertically both up grass and other plants to increase their chances of being ingested by grazing animals and also down into the soil. The type of forage species available influences the rate of vertical migration (Niezen *et al.* 1998) while soil may act as a haven and protect nematodes from adverse weather (Waghorn *et al.* 2002).

For the free-living stages, the rate of development and the probability of survival are strongly influenced by the weather, especially temperature and moisture (Callinan, 1978). Interestingly, the optimum temperature and moisture for quickest development may vary among different locations according to the prevailing weather (Kao *et al.* 2000). The suggestion here is that parasites adapt to the prevailing local conditions and the most useful recommendations for nematode control will require local studies and local knowledge.

The main aim of most current grazing schemes is to maximize the use of available pasture for livestock grazing. Ideally, grazing management schemes should also reduce the number of infective third-stage larvae available to infect grazing animals. The options include reduced deposition of eggs, reduced larval development and survival as well as provision of clean pasture. One area of concern in the development of grazing management schemes is that the methods available to count the number of eggs in faeces and to determine the number of infective larvae on pasture are somewhat inaccurate and rather imprecise (Gettinby *et al.* 1985; Stear *et al.* 1996).

Stocking density

One possible option to reduce the amount of infective nematodes on pasture is to reduce the number of animals in a given area. Fewer egg-producing hosts could lead to lower levels of pasture contamination and hosts may be able to avoid grazing near faeces where contamination is likely to be highest (Stromberg, 1997). However, the rate of larval development and the probability of larval survival may be dependent on the density of larvae and reduced numbers of eggs deposited need not produce proportionate reductions in the availability of infective larvae. In addition, livestock production, especially sheep, is not particularly profitable and many producers would find farming unprofitable and unsustainable at lower stocking densities.

Alternating use of pasture

Historically, many farms kept a mixture of stock, especially horses, and grew crops. The current trend to single enterprise farms has the unintended

consequence of allowing larval numbers to increase due to the same field being grazed by the same species year on year. This exposure to increased numbers of larvae increases the severity of infection. Alternating crops and livestock would reduce the intensity of infection as would the use of different livestock species. For example, only a few nematodes such as *Trichostrongylus axei*, are able to infect different species such as sheep, horses and cattle. While care is needed to prevent the build up of multi-host nematodes, mixed infections are the most pathogenic (Stear *et al.* 2003) and reducing the species mix is likely to be beneficial in itself. Alternating livestock species is inappropriate for closely related species such as sheep and goats because most nematodes that can infect one species can also infect the other. Although recent molecular analysis indicates, that at least some *T. circumcincta* found in goats may not be the same species as *T. circumcincta* described in sheep (Leignel *et al.* 2002).

Another option is to rotate young and older animals. Older animals are generally less susceptible to infection and have lower faecal egg counts. Consequently, rotating older and younger animals might reduce the build up of infective larvae. However, older animals also produce more faeces and this could outweigh the lower concentration of eggs per gram of faeces (Stromberg, 1997).

Move to clean pasture

Another procedure is to move vulnerable animals onto less contaminated fields. The obvious difficulty of preventing the build up of parasitic larvae was to some extent solved by treating animals with anthelmintic before the move. This treat and move strategy has much to recommend it but does suffer from the disadvantage that any larvae that survive treatment will contain a high frequency of drug resistance alleles and their progeny will dominate the parasitic nematode community (Sutherland *et al.* 2002).

Rotational grazing

A further option to reduce the intensity of nematode infection is rotational grazing. Here, rather than allowing all animals to graze the available pasture, the pasture is divided into sections that are grazed sequentially. In the absence of grazing animals, infective nematode larvae cannot find a host and eventually die. Ideally, by the time animals return to the first section, most of the infective larvae have died. The rate at which third-stage larvae die depends upon the species and the climate (Callinan *et al.* 1982). Some nematode species, such as *H. contortus*, that are able to survive in tropical and subtropical conditions do better at higher temperatures than species such as *T. circumcincta* that are adapted for cooler climates. For the cattle nematode,

Ostertagia ostertagi, survival is lower in adverse conditions such as the hot summers of Louisiana but is relatively high in temperate climates (Stromberg, 1997).

Rotational grazing is plausible but not very effective (Stromberg and Averbeck, 1999) due to the long life of infective larvae in all but the most extreme conditions (Callinan *et al.* 1982) and the fact that ingestion of larvae is more harmful at certain times of the year. For example, in the UK, lambs infected before June can have relatively large numbers of worms but lambs infected later in the grazing season produce fewer eggs due to the development of host immunity and the suppression of egg output (Gibson and Everett, 1972; Michel, 1985).

In future, good grazing management may come to mean controlling nematodes as well as making the most of the available grass. Many grazing management schemes have much in their favour and in certain parts of the world, including Scotland, they are widely used (Gettinby *et al.* 1987). However, on their own they are unlikely to provide adequate nematode control but more detailed research is needed to determine specific recommendations for each geographical area.

BIOLOGICAL CONTROL

All species have their population growth constrained by abiotic factors, especially weather and food, or biotic factors – essentially parasites, predators and competitors – or by a combination of both. Nematodes are a large and successful phylogenetic group with a large number of organisms that prey on them (Waller and Faedo, 1996). Their predators are obvious candidates for biological control and a series of trials have shown that the nematode-trapping fungus *Duddingtonia flagrans* has the ability to reduce the number of infective larvae on pasture and reduce the intensity and severity of infection (Waller *et al.* 2004*b*). There appear to be no deleterious effects on non-parasitic, soil-dwelling nematodes (Knox *et al.* 2002). The use of predatory fungi represents a promising option for nematode control. For optimal control, the diet needs daily supplementation with fungal material during periods of nematode control (Waller and Thamsborg, 2005). The requirement for daily feeding of fungal spores is the main drawback in the use of predatory fungi.

An alternative method of biological control is to influence the rate of faecal breakdown and burial. The free-living stages of parasitic nematodes develop in faeces and an increased rate of faecal degradation could expose larvae to inclement weather (Williams and Warren, 2004). Alternatively, too slow a rate of faecal degradation could impede the movement of infective larvae onto pasture (Vlassoff *et al.* 2001). Faecal degradation is dependent upon the type of forage (Niezen *et al.* 1998; Williams and Warren,

2004), the density and spatial distribution of faeces (Williams and Warren, 2004) as well as, possibly, the presence of grazing sheep (Williams and Warren, 2004). In a separate study in New Zealand, the burial of faeces by dung beetles enhanced larval recovery consistent with the hypothesis that soil can provide a protective haven for parasitic larvae (Waghorn *et al.* 2002).

Sheep grazing pastures containing some plant species, such as chicory (*Cichorium intybus*) and birdsfoot trefoil (*Lotus corniculatus*), have lower egg production than sheep grazing pastures lacking these species (Waller and Thamsborg, 2005). Possible mechanisms include increased protein or trace element supply to the host which would increase host immunity and reduce pathology by enhancing tissue repair; decreased development or survival of free-living stages; reduced ingestion or survival of infective larvae or direct toxicity to nematodes (Marley *et al.* 2003). Birdsfoot trefoil contains condensed tannins, plant polyphenols that may have a direct effect on nematodes (Waller and Thamsborg, 2005), although the effect appears to vary among species (Waller and Thamsborg, 2005) with *T. circumcincta* and *H. contortus* less susceptible than *T. colubriformis*.

The use of plant species containing products that influence nematode establishment and survival is attractive but the results are quite variable; for example the development of *Trichostrongylus* spp. in faeces from lambs fed birdsfoot trefoil was inconsistent in two different years (Marley *et al.* 2003). More research is needed before this approach can be recommended.

CONTROL OF PARASITIC STAGES

The 3 remaining methods of nematode control are nutritional supplementation, vaccination and utilization of genetic resistance. These methods aim to control the parasitic stages within the host, largely by enhancing the immune response. This section therefore starts with a review of nematode life-history within the host, again with an emphasis on *T. circumcincta*.

The larvae that are ingested by grazing sheep, start to exsheath in the rumen, then rapidly move into the gastric glands and develop into fourth-stage stage larvae. After leaving the gastric glands, the young adults live, mate and develop on the surface of the abomasal mucosa within the protective mucus layer. The environment is the major influence on the speed of nematode development. Within the host, the major determinant of environmental quality is the protective immune response. Nematodes in resistant hosts lay fewer eggs (Stear and Bishop, 1999), these eggs may be less viable (Jorgensen *et al.* 1998) and ingested larvae take longer to develop into adult worms; in naïve hosts this may take only 13 days but

as long as 56 days in previously exposed animals (Stear *et al.* 1995). The situation is similar in other gastrointestinal nematodes although the sites of development and the time needed to develop vary among species (Urquhart *et al.* 1987).

NUTRITIONAL SUPPLEMENTATION

Infection with *T. circumcincta* causes a relative protein deficiency (Armour *et al.* 1966; Coop *et al.* 1985; Coop *et al.* 1982). Clinical signs can be prevented or reduced when animals are fed supplementary protein before and during infection (Coop *et al.* 1995).

The usefulness of supplementary feeding of sheep has also been demonstrated for *H. contortus* (Abbott *et al.* 1984, 1986, 1988; Wallace *et al.* 1999) as well as the small intestinal species *Trichostrongylus colubriformis* (Bown *et al.* 1991; Kambara *et al.* 1993; van Houtert *et al.* 1995; Kyriazakis *et al.* 1996) and *Nematodirus battus* (Israf *et al.* 1996).

Interestingly, dietary supplementation with urea also enhances resistance and resilience to *T. colubriformis* (Knox and Steel, 1999) as well as resilience to *T. circumcincta* (Wallace *et al.* 1998); Stear *et al.* 2000 *a*) presumably because bacteria in the rumen convert urea into amino acids and protein that are subsequently digested by the host. This suggests that cheap sources of non-protein nitrogen could be used instead of expensive proteins to supplement diets.

Supplementary feeding with additional protein enhances the immune response to *T. circumcincta* (Coop *et al.* 1995; Strain and Stear, 2001). Supplementary dietary protein also enhances the immune response to *H. contortus* (Strain and Stear, 2001) and *T. colubriformis* (Kambara *et al.* 1993). The modulation of host resistance to nematode infection by supplementary feeding has been extensively reviewed (Coop and Kyriazakis, 2001; Stear *et al.* 2003; Sykes and Coop, 2001). Presumably, additional dietary protein also enhances the ability of the infected host to repair mucosal damage.

Pregnant or lactating ewes often show an increased faecal nematode egg output during the periparturient period although the timing can vary among studies. The rise in egg count has been attributed to a relaxation in host immunity and appears to be more severe for *T. circumcincta* than *T. colubriformis* (Donaldson *et al.* 1998) *H. contortus* (O'Sullivan and Donald, 1973; Gibbs and Barger, 1986) or *T. vitrinus* (Jackson *et al.* 1988).

This periparturient rise plays a critical role in the epidemiology of infection. Feeding supplementary protein can influence nematode egg output and the number of established *T. circumcincta* (Donaldson *et al.* 1998; Houdijk *et al.* 2001 *a, b*, 2003).

In addition to the effect of supplementary protein a number of trace elements have been shown to

influence host resistance to nematode infection, including iron, zinc, copper and molybdenum (Koski and Scott, 2003). An intermediate level of trace elements may be optimal for nematode control (Koski and Scott, 2003). Trace elements are obviously important but the value of supplementing the diet with trace elements may vary among farms (Waller *et al.* 2004*a*) and even among sheep on the same field. Differences among farms may arise due to differences in the availability of trace elements in the soil and in pasture. Genetic variation in trace element metabolism exists (Wiener, 1979; Littledike and Young, 1993) and could lead to differences among animals in the effect of supplementation.

Supplementary feeding is a successful method of nematode control. The barriers to more widespread adoption of this solution are largely financial; both the cost of supplements and the extra labour required.

VACCINATION

Perhaps no area of nematode control has been as extensively reviewed as vaccination (Emery, 1996; Smith, 1999; Dalton *et al.* 2003; Knox *et al.* 2003; Vercruysse *et al.* 2004). Vaccine development has used 3 strategies: attenuated vaccines (Bain, 1999), vaccines based on natural immunity (Meeusen and Piedrafita, 2003) and the hidden antigen approach (Knox *et al.* 2003).

The only commercially available vaccines against nematodes are irradiated larval vaccines against bovine and ovine lungworm (Bain, 1999; Newton and Munn, 1999). Irradiated larval vaccines against gastrointestinal nematodes do not generate immunity in lambs, presumably because the mechanisms of immunity in lungs and tissues differ from the mechanisms operating in the gastrointestinal tract. However, irradiated larval vaccines do protect older sheep against *H. contortus* but older sheep are not naturally susceptible to gastrointestinal nematodes, presumably because they develop effective mechanisms to control adult worms, such as mast cell-mediated hypersensitivity (Stear *et al.* 1999). Possibly, irradiated larval vaccines provoke natural mechanisms and cannot work if natural mechanisms to control adult worm number are absent. Vaccination of older animals could help to control nematodes (Bain, 1999) but these vaccines are not commercially available.

The second phase of vaccine development was the search for parasite molecules that are recognized by the host during natural or deliberate infection. Sheep vary in their response to infection, and the molecules preferentially recognized by resistant rather than susceptible hosts are logical candidates. Although various preparations have evoked high levels of resistance, so far no single naturally recognized parasite molecule has been shown to produce high levels of resistance (Yatsuda *et al.* 2005). During natural infection, livestock recognize a wide variety of parasite molecules (Hilderson *et al.* 1993; Schallig *et al.* 1994; McCririe *et al.* 1997) and resistance appears to require the recognition of a broad range of parasite molecules (Stear *et al.* 2005).

The third stage of vaccine development was the search for hidden antigens; these are molecules expressed by the parasite that can generate immune responses but do not normally do so, possibly because host cells are not exposed to these molecules. Proteins from the gastrointestinal tract of the parasite are logical candidates and 2 preparations H11 and H-gal-GP have been shown to generate effective immunity in field trials (Knox *et al.* 2003). Unfortunately, extraction of sufficient proteins directly from the parasite gastrointestinal tract is impractical. Vaccines based on recombinant molecules would potentially be safe, stable and cheap to produce (Vercruysse *et al.* 2004) and so the aim now is to generate recombinant molecules. However, there are still serious hurdles to this approach. In particular, antigens that induce protective immunity as native parasite molecules do not do so when expressed as recombinant molecules. Intensive research, including the use of a variety of different expression systems, is ongoing to try and solve these problems (Knox *et al.* 2003).

UTILIZATION OF GENETIC VARIATION

There are 3 strategies for utilizing genetic variation: selection among breeds, cross-breeding and selection within breeds (Nicholas, 1987). These 3 strategies will be considered in turn.

Variation among breeds

A comparison of different breeds for resistance to *H. contortus* has clearly shown that some sheep breeds are much more resistant to this parasite than other breeds. In Kenya, the indigenous Red Maasai is more resistant than imported breeds such as the Dorper, which is itself a cross between the Dorset and the Black-headed Somali breed (Mugambi *et al.* 1996; Baker *et al.* 1999; Nguti *et al.* 2003). In Louisiana and Florida, the Gulf Coast Native breed is more resistant than other breeds such as the Suffolk (Bahirathan *et al.* 2000). The St Croix (Gamble and Zajac, 1992) and Barbados Blackbelly (Yazwinski *et al.* 1979, 1981) from the Caribbean are also remarkably resistant to haemonchosis.

There have been fewer comparisons of different breeds for resistance to other nematodes. An early report with a small number of animals suggested breed differences in resistance to *T. circumcincta* (Stewart *et al.* 1937). More recent research has suggested that sheep of the Texel breed are more

resistant than sheep of the Suffolk breed (Good *et al.* 2006).

Differences among breeds are conceptually the easiest way to exploit genetic variation. Farmers with sheep that suffer from haemonchosis can obtain replacements from a more resistant breed. There has been some concern over productivity. In areas of endemic disease, animals from indigenous resistant breeds are often smaller than animals from imported susceptible breeds; possibly because animals need to allocate resources to fighting infection and repairing damage. Despite their smaller size, the resistant animals can be more productive than their larger susceptible contemporaries (Baker *et al.* 2003).

However, even when there is a clear commercial advantage to one breed, farmers can be reluctant to switch breeds and funding for farmer education is often scarce. Australia has one of the most efficient and effective agricultural industries in the world, but even here, it took a long time and a great deal of effort to persuade farmers to use breeds with superior resistance to the cattle tick *Boophilus microplus* (Parsonson, 1998). Ticks are much more visible than nematodes, which suggests that even more effort may be needed to encourage farmers to use breeds with superior resistance to nematodes.

Cross-breeding

There has been surprisingly little research into the production of cross-bred animals for enhanced resistance to nematodes although Border Leicester × Merino sheep are more resistant to nematodes than purebred Merinos (Donald *et al.* 1982). Most research has been done with beef cattle and a variety of breeds have been created by cross-breeding, some of which, such as the Belmont Red, appear to have superior resistance to nematode infection (Mackinnon *et al.* 1991). Given the superior resistance of Texel to Suffolk sheep, and the widespread use of these 2 breeds as terminal sires in cross-breeding schemes (Simm, 1998), there is an obvious need to compare the performance of their cross-bred progeny. In New Zealand, McEwan has reported that Texel × Romney sheep have lower egg counts than straightbred Romney sheep (Niezen *et al.* 1996).

Selection within breeds

In some situations, breed substitution is not an option because one breed is markedly more productive than other breeds. The most obvious examples are the Australian wool industry with the Merino and the dairy industry in the western world. Here the best way to exploit genetic variation is to select within a breed (Kloosterman *et al.* 1978; Gray *et al.* 1987).

Setting up a selection scheme involves 3 steps: choosing what character or characters we wish to improve (selection objective), choosing the criteria to measure (selection criterion) and the relative weighting of the traits (selection index) (Nicholas, 1987).

The response to selection depends in part upon the proportion of the total variation that is due to the average effects of genes; this is known as the heritability (Nicholas, 1987). Faecal egg counts are widely used to measure resistance to nematode infection. A wide variety of studies have shown that the heritability of single faecal egg counts following natural or deliberate infection is in the range of 0·2 to 0·4 in sheep (Bisset *et al.* 1992; Sreter *et al.* 1994; Gruner *et al.* 2001; Morris *et al.* 2000) and also in cattle (Leighton *et al.* 1989; Stear *et al.* 1990; Morris *et al.* 2003). These heritabilities are similar in magnitude to the heritability of milk production in dairy cattle or the heritability of growth rate in beef cattle (Nicholas, 1987). These heritabilities also indicate relatively rapid responses to selection for reduced faecal egg count.

The response to selection is somewhat complicated because the selected animals produce fewer eggs than unselected animals. Consequently, there is a concomitant improvement in the environment as pasture contamination is reduced. The combined effect of selection is to reduce the intensity of infection and to suppress egg output by infected hosts that further reduces the intensity of infection. The response to selection has been modelled (Bishop and Stear, 1997). This model demonstrated remarkably rapid responses to selection with a 2- to 5-fold reduction in faecal egg counts over 10 years. However, the results from modelling need to be treated with some caution. The weather can affect the intensity of nematode infection and, as acknowledged by the authors, this model does not take variations in the weather into account. In addition, some of the underlying assumptions about host immunity and density dependence have still to be tested.

The heritability of a single egg count increases with age; 6 to 7-month-old lambs show higher heritabilities than younger lambs and 1 to 2-month-old lambs show no heritable variation in egg count (Bishop *et al.* 1996). Faecal nematode egg counts are fairly imprecise and taking multiple counts on each sample or taking samples from animals at different ages would increase the heritability and hence the rate of response to selection (Stear *et al.* 1996).

In addition to faecal egg count, there are other markers available that could be used to supplement or even replace faecal egg count. Markers come in 2 types: those based on phenotypic measurements, such as antibody activity (Douch *et al.* 1996), are known as indicator traits. Those based on genetic polymorphisms are known as genetic markers. Molecular markers can be indicator traits based on specific molecules such as parasite-specific IgA activity against fourth-stage larvae (Strain *et al.* 2002)

or molecular genetic markers such as the G2 allele of the *DRB1* locus of the ovine major histocompatibility complex (Schwaiger *et al.* 1995).

Several markers for nematode resistance have been identified (Sayers and Sweeney, 2005). Indicator traits include packed red cell volume (Gray *et al.* 1987), parasite-specific IgA activity (Strain *et al.* 2002), pepsinogen activity (Stear *et al.* 1999) and eosinophilia (Stear *et al.* 2002). Care is needed in the use of indicator traits. For example, markers based on immune responsiveness, such as IgA activity or eosinophilia, will only indicate resistance in older animals that have been exposed to nematode infection and have had time to develop protective immune responses (Doligalska *et al.* 1999). If the population has had heterogeneous exposure to nematodes, the most heavily exposed individuals may show the strongest immune responses and harbour the most parasites. Also, markers based on pathology, may not be appropriate for all nematodes. For example, pepsinogen activity reflects the activity of abomasal but not intestinal nematodes (Stear *et al.* 1999), while packed red cell volume is useful for bloodsucking nematodes such as *H. contortus* but not for other species that do not cause anaemia such as *T. circumcincta* and *T. colubriformis*.

Molecular genetic markers are likely to be more robust than indicator traits (Dominik, 2005). However, they may not show consistent associations with indicator traits, such as faecal egg counts. Only necropsies from carefully monitored infections provide reliable assessment of parasite resistance and great care will be required to distinguish reliable genetic markers from markers showing chance associations in field trials.

There are 2 confirmed genetic markers for *T. circumcincta*: the major histocompatibility complex (Schwaiger *et al.* 1995; Paterson *et al.* 1998; Charon *et al.* 2002; Sayers *et al.* 2005; Stear *et al.* 2005) and the interferon gamma locus (Coltman *et al.* 2001). Although in both cases, the causative mutations have still to be identified.

The major histocompatibility complex may also be a marker for resistance to *T. colubriformis* (Hulme *et al.* 1993) but probably not for *H. contortus* (Cooper *et al.* 1989; Blattman *et al.* 1993; Crawford *et al.* 1997). A genome scan for resistance to *T. colubriformis* identified a potential marker on chromosome 6 (Beh *et al.* 2002) while association analyses by the same group reported an association between reduced faecal egg counts and a deletion upstream of the constant region of immunoglobulin E. However, this association was not confirmed in follow-up studies. Other markers probably exist but due to the commercial potential of genetic markers, full details are unavailable.

Two independent markers can provide a check on each other and selection schemes for resistance to *H. contortus* in Australia have used both packed red cell volume and faecal egg counts while selection schemes in New Zealand, where *T. colubriformis* dominates the egg count, have used antibody activity and faecal egg count. Interestingly, in Scottish lambs with predominantly *T. circumcincta* the relationship between egg count and worm number is convex (Bishop and Stear, 2000); lambs with very high numbers of adult *T. circumcincta* produce fewer eggs than lambs with a lower number of nematodes. Therefore, faecal egg counts are not reliable indicators for the number of *T. circumcincta*. There is perhaps a need to incorporate additional markers for this species as in Australia and New Zealand.

Rather than selecting for resistance to infection or disease, it may be better to select for the ability to perform and produce meat, milk or wool during exposure (Morris *et al.* 2003), a trait known as resilience (Clunies Ross, 1932; Albers *et al.* 1987). Commercial selection schemes include both markers of resistance and markers of productivity and this will select for both resistance and resilience. The problem is to decide upon the relative weighting of the chosen measures of resistance, resilience and productivity. For an optimal response to selection the relative economic value of the traits measured and their genetic correlations are required. For natural, predominantly *T. circumcincta* infection, 2 independent trials in Scotland (Stear *et al.* 1997) and Poland (Bouix *et al.* 1998) have shown strong and favourable genetic correlations between egg counts and growth rate. In contrast, under Australian and New Zealand conditions genetic correlations tend to be weaker and unfavourable (Bisset *et al.* 1992; McEwan *et al.* 1995; Eady *et al.* 1998). In Australian cattle, the magnitude and sign of the genetic correlation varies between the wet and dry season (Mackinnon *et al.* 1991). This appears to be yet another area where different nematode species give different results.

The relative economic value of nematode resistance or faecal egg count is not obvious. A recent study estimated the cost of various diseases and concluded that nematode infection was the most costly disease of sheep in the UK (Nieuwhof and Bishop, 2005). Anthelmintic treatment of nematode infection is currently cost-effective but as nematodes evolve resistance to anthelmintics, treatment will become less effective and the economic impact of nematodes will increase. In the extreme case an inability to control nematodes could make livestock farming unprofitable. The emphasis to be given to nematode resistance relative to productivity in selective breeding schemes is an area where more research and modelling is needed.

Utilization of genetic variation has much to commend it. It is safe, cheap, effective and probably as sustainable as any other method. Farmers who already breed livestock could readily incorporate nematode control into the selection index. Farmers

who merely keep rather than breed livestock could consider resistance or resilience when they buy in replacement stock. The main disadvantage in the use of genetic variation is that it requires expertise in quantitative genetics to implement most efficiently and this is an area where many but not all farmers and advisors are lacking.

COMBINATION OF METHODS

This review of existing methods of nematode control has concluded that there are a variety of methods available but no one method can be recommended to the exclusion of all others. Therefore there may be a role for a combination of methods but somewhat surprisingly there has been very little research in combinations of different methods. One combination that has been investigated is diet and genetic resistance.

The effect of dietary protein supplementation was investigated in animals from the relatively resistant Scottish Blackface breed and the relatively susceptible Finn-Dorset (Abbott *et al*. 1985). Following deliberate infection with *H. contortus*, the severest effects were found in the relatively susceptible Finn-Dorset sheep on the low protein diet (Abbott *et al*. 2000). Interestingly, in the resistant breed, pathogenesis was not influenced by diet and resistant animals on the low diet behaved similarly to susceptible animals on the high diet. (Abbott *et al*. 2000). Greater effects of diet in genetically susceptible animals were also reported in a comparison of Hampshire Down and Scottish Blackface (Wallace *et al*. 1995, 1996). Similar results were found in selectively-bred Merino ewes (Kahn *et al*. 1999). Most of the research on diet and genetics has been with *H. contortus*, but a trial with Scottish Blackface lambs that were deliberately infected with 10 000 *T. circumcincta* 3 times a week for 9 weeks then slaughtered suggested that a combination of acquired resistance and dietary supplementation would be most effective at controlling infection with *T. circumcincta* (Stear *et al*. 2000 *a*).

CONCLUSION

Several methods exist for nematode control but each method has its strengths and weaknesses. No single method can be recommended for all farms. Each farm may need to select the most appropriate combination of procedures from the available options. Additional research is needed, particularly in the application and adaptation of proposed methods to local circumstances.

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