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Keys to solving health problems in small ruminants: Anthelmintic resistance as a threat to sustainable nematode control

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ABSTRACT

The epidemiology of nematode parasites has changed as they have adapted to climatic and management changes and as a consequence of the inappropriate use of anthelmintic drugs. This adaptability is conferred by large, polymorphic genomes and r-reproductive strategies. A significant net effect of these factors has been the emergence of anthelmintic resistance. Consequently, blueprint control programmes have failed and suboptimal sheep productivity due to nematode parasites has become commonplace. The focus of veterinary nematode control in intensively managed sheep flocks and goat herds must shift from attempts to eliminate parasite populations, towards the adoption of management and anthelmintic drug treatment strategies aimed at maintaining adequate standards of health in the face of a low level of challenge. Conventional parasitological methods are useful for the diagnosis of disease and for monitoring of nematode management over time, but they lack the sensitivity needed to mitigate effects of climate and management on population genetics of the parasites. The publication of a draft genome and transcriptome for the model nematode parasite, *Haemonchus contortus*, affords opportunities for post genomic research to identify sensitive molecular markers to evaluate resistance management strategies and potential candidates for novel control methods.

1. Introduction: the importance of small ruminant production

Small ruminant farming has an important role to play in meeting the challenge of sustainable global food security. It is necessary to consider small ruminant production as part of a global food producing industry, and to acknowledge that efficient production from each sector of this industry is essential to meet the needs of the worlds growing human population that currently exceeds 7 billion. When addressing production efficiency, resources must be used in a manner that minimises environmental footprints, meets high standards of animal welfare and is socially acceptable. It is therefore necessary to understand and address: effects of population growth itself; demands of urbanisation and affluence; consequences of climate change; and hitherto irresponsible use of drugs and chemicals. These considerations are equally pertinent to the control of helminth parasites, which include many of the primary animal health constraints to small ruminant health and production. For example: population growth itself increases the need to manage disease to achieve more efficient food production from reducing resources; affluence associated with urbanisation increases demands for luxury food products such as sheep and goat meat, while reducing the land area for production; climate change has a profound effect on pathogens with free living stages in the environment; while the hitherto irresponsible use of medicines has resulted in the emergence of antimicrobial and anthelmintic drug resistance.

Goats are important because they naturally feed by browsing, therefore utilising poor quality nutrients to produce food, but are also suited to being kept under intensive or semi-intensive grazing or conserved forage management systems. Sheep are important due to their ability to convert short pastures efficiently into meat. Different breeds and types of small ruminants have been adapted and selected to suit specific climates and environmental resources and their potential as a means of alleviating poverty in diverse, often seasonally resource-poor, environments is well recognised (Pollott and Wilson, 2009). However, this potential is seldom realised, due to failure to translate research and development of sustainable husbandry and health management, in particular helminth parasitism, into efficient utilisation of natural resources.

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2. Nematode (roundworm) parasites as the foremost constraint to economic small ruminant production

Nematode parasites are amongst the most important production-limiting diseases of ruminant livestock worldwide. *Teladorsagia circumcincta*, *Haemonchus contortus*, *Trichostrongylus vitrinus*/*colubriformis* and *Nematodirus battus* are of particular relevance. These parasites cause a range of diseases in their hosts, from diarrhoea to anaemia, and cause significant economic losses to farmers and their keepers in terms of reduced production and treatment costs, as well as being a major welfare issue for the infected animals. They also reduce production efficiency, thereby potentially raising food prices and damaging the environment. Gastrointestinal trichostrongyle nematodes have direct life cycles, involving non-parasitic environmental egg, first, second and third stage larvae, and parasitic third and fourth stage larvae, and dioecious, sexually reproducing adults. The biology of these parasites is, therefore, influenced by both environmental and host factors, which must be accounted for when planning for their control.

The aim of all approaches to nematode control is to limit the host challenge to a level which does not compromise performance or welfare, while at the same time enabling the development of protective immunity. Sustainable nematode control in individual flocks or herds must, therefore, be underpinned by knowledge of the farming system and of the relationship between pasture contamination, the availability of infective larvae and the build up of infection in animals. For example, a health plan for nematode control in lambs which will be grazed on a particular field during the summer must include consideration of: consequences of prior autumn and winter grazing management and climate on the size of the overwintered infective larval population; potential influences of anthelmintic drug treatments of periparturient ewes, ewe nutrition and the lambing percentage on ewe faecal egg output onto that field; and effects of anthelmintic drug treatments, nutrition and grazing management on autoinfection of the field by the lambs themselves. In the face of the economic impact of nematode parasites and the complexity of the principles underpinning their control, most farmers and ruminant livestock keepers, worldwide, rely upon the use of anthelmintic drugs in an unsustainable attempt to eliminate the parasites.

3. Sustainable roundworm control

Nematode control is compromised by the parasites' adaption to climatic and management changes and hitherto irresponsible use of anthelmintic drugs. Nematode parasites have large genomes, with large numbers of genes and extraordinarily high levels of polymorphism and r-reproductive strategies giving rise to high biotic potential. The latest assembly of the *H. contortus* genome is about 320 mb, with about 22,000 protein coding genes (Laing et al., 2013), while each female can shed more than 4000 eggs per day (Sargison, 2009). These parasites will inevitably evolve in response to both favourable and hostile conditions afforded by effects of climatic or management changes on free-living stages and exposure of parasitic stages to anthelminitic drugs, respectively.

Suboptimal sheep productivity due to nematode parasites has become commonplace in small ruminant flocks and herds during recent years, despite the adoption of previously highly successful control programmes involving the use of anthelmintic drugs. Clinical investigation of these problems and parasitological monitoring show that nematode parasite epidemiology now differs from the conventional perspective in various aspects, giving rise to unexpected scenarios such as spring teladorsagiosis in young lambs caused by high levels of overwintered infective larvae on pasture (Sargison et al., 2002); autumn nematodirosis due to the prolonged survival of third stage larvae in particular environmental niches (Sargison et al., 2012); and haemonchosis associated with development of free living stages of the parasite during opportunities presented by warm spring or autumn weather (Sargison et al., 2007; Falzon et al., 2013). These problems have arisen because the epidemiology of the parasites has changed due to a combination of interacting factors. These include: new strategies in farm and grazing management caused by the changing economics of sheep production; host immune mechanisms in response to infective larval challenge; parasite evolution; and micro- and macro-climatic variation (Kenyon et al., 2009a; Van Dijk et al., 2010). Consequently the nature and timing of prescriptive nematode evasive management or anthelmintic treatments may be inappropriate. A significant net effect of these factors has been the inevitable emergence of anthelmintic resistance. Nematode control is therefore unsustainable and the immediate challenge facing small ruminant farmers and keepers is to ensure that current measures enable economically viable sheep production for long enough to allow for the development of new strategies before the existing methods eventually fail altogether.

While fully sustainable nematode control is not possible, acceptable compromises based upon an improved understanding of the parasites' biology and detailed relevant knowledge of individual farming systems are achievable. Advances are needed in these areas to validate the interpretation of the relationships between pasture contamination, the availability of infective larvae on pasture and the accumulation of infection in sheep. Planned investigation and monitoring of animal performance is important, in order to identify and understand those conditions, management practices, aspects of parasite biology and parasite population genetics that have been adopted or have arisen to enable sustainable productivity, for example, in the face of anthelmintic resistance. Thus, iterative small ruminant flock and herd health planning is an essential first step towards sustainable nematode control.

4. Anthelmintic resistance management

Following reports of *T. circumcincta* resistance to benzimidazole, imidazothiazole and macrocyclic lactone anthelmintic groups (Sargison et al., 2001, 2010), the potential threat to future health and profitability of European small ruminantproduction is recognised, and the need for management combining effective nematode control with minimal further selection for resistance is acknowledged. Globally, anthelmintic resistance has now been reported in most small ruminant parasitic nematode species, including *N. battus* (Morrison et al., 2014) and to most drugs, including monepantel (Van den Brom et al., 2015). Advice is currently given based on the premise that alleles conferring anthelmintic resistance are already present in most sheep flocks. This can be summarised as: (i) ensuring that the nematode parasites are exposed to an effective anthelmintic drug concentration; (ii) considering the timing and frequency of anthelmintic drug treatments so that only a small proportion of the population is exposed to the anthelmintic; (iii) treating introduced animals with effective anthelmintic drugs; and (iv) monitoring for anthelmintic resistance. This advice is based entirely upon theoretical principles, hence its validity is unknown. For example: the extent to which underdosing selects for anthelmintic resistance in field situations, and whether or not the practice selects for the same mechanisms of resistance as pressures relating to the timing and frequency of drug treatments is unknown; there is a paucity of empirical knowledge pertaining to different management systems and concerning the influences of timing and frequency of treatments and proportions of animals treated on the efficacy of strategies aimed at only exposing a small proportion of the parasite population to the anthelmintic