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# ANTHELMINTIC RESISTANCE AND ITS IMPORTANCE IN THE CONTROL OF NEMATODE PARASITISM OF SMALL RUMINANT LIVESTOCK IN THE TROPICS / SUBTROPICS

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## SUMMARY

Livestock raised in the humid tropics are exposed to a wide range of helminth parasites which are responsible for enormous losses in productivity, and often high levels of mortality, particularly in young animals. Control methods rely almost exclusively on the use of anthelmintic drugs. Frequency of use depends on the farmers desire to treat his animals and/or his ability to pay for the drugs. However there is an increasing tendency for farmers to resort to treatment with their greater understanding of the losses caused by parasites and particularly due to the fact that cheap, generic drugs are becoming more readily available. As a result, anthelmintic resistance in helminth parasites has developed, but its importance varies between parasite taxa, between parasites of different host species and between different regions/ countries in the tropics. By far the greatest problem with anthelmintic resistance is associated with the nematode parasites of small ruminants, particularly with *Haemonchus contortus*, a major pathogen of sheep and goats throughout the humid tropical/sub-tropical regions of the world. The worst situation is generally in the large-scale sheep farming countries within these regions (continents of Africa, South America, and Australia). Generally speaking, resistance in the Asian countries is not as serious, although individual countries have major problems (eg. Malaysia, Fiji). Evidence is clear-cut that anthelmintic resistance is increasing - in prevalence, magnitude and spectrum. Unfortunately there is a tendency to seek a solution when it is too late, when total anthelmintic failure has occurred. However, some adjuncts and/or alternatives to parasite control are available, but none in isolation will solve the problem, nor will they offer immediate respite. The way to sustainable nematode parasite control in the future is to incorporate a range of control options into an Integrated Pest Management (IPM) package for nematode parasites of livestock.

Keywords: anthelmintic resistance, control options, nematode parasites, sheep, goats, tropics

## INTRODUCTION

Internal parasitism constitutes one of the greatest disease problems in grazing livestock worldwide (Perry and Randolph, 1999). Immunity to helminth parasites develops slowly, it is labile, and its maintenance is dependent upon a good nutritional state of the animal. Consequently, parasites are ubiquitous wherever livestock are kept and impose a constant, often high infectious pressure on animals particularly in the humid tropics / sub-tropics (Waller, 1999).

Worm infections in grazing livestock are almost always a mixture of species. All have deleterious effects and collectively lead to chronic ill-thrift. Economic evaluations repeatedly show that the major losses due to parasites are on animal production, rather than on mortality. Recent estimates of the annual costs of internal parasites to the sheep industries in Australia, South Africa and Uruguay were found to be USD122$\times 10^6$ (Mcleod, 1995), USD45 $\times 10^6$ (Horak pers. comm.) and USD41.8 $\times 10^6$ (Nari *et al.* 1997), respectively.

A major constraint to more effective control of nematode parasites of small ruminant livestock (sheep and goats), is the development of anthelmintic resistance. Recently, the World Organisation for Animal Health (Office International des Epizooties: OIE) commissioned a survey to determine the status of parasiticide resistance in livestock worldwide (Nari and Hansen, 1999). Of the 151 member countries, responses were obtained from 77 (55% response). The parasites considered to be of greatest importance to the livestock in each country were in rank order worms (73% of respondent countries), ticks, mange mites, flies and lice. Control of these pests was almost entirely by the use of chemicals. Resistance had been diagnosed in 55% of the responding countries. Of these, 86% had diagnosed anthelmintic resistance, 50% ixodicide resistance and 31% insecticide resistance. An important note was that these estimates were considered conservative, as 27% of countries mentioned a lack of capabilities, infrastructure, and/or interest in assessing the significance of these problems.

For anthelmintics used to control nematode parasites of small ruminants, high levels of resistance now exist to two (ie. benzimidazoles and imidothiazoles) of the three main broad spectrum anthelmintic groups (Waller, 1997a). However resistance to the only remaining group, the macrocyclic lactones, is now rapidly increasing (Sangster, 1999).

## ANTHELMINTIC RESISTANCE WHAT'S SO SPECIAL ABOUT THE TROPICS / SUB TROPICS?

Although anthelmintic resistance is a global issue

(Nari and Hansen, 1999), it is generally considered to be of greater threat in the warmer regions of the world. For the sake of this presentation, I define this region as lying between latitudes 30° north and 30° south lying outside the Tropics of Cancer and Capricorn, respectively.

This includes virtually the whole of the African continent, South West and South East Asia, Central and Equatorial America and the northern half of Australia.

*The nature of economic development*

The tropical / subtropical region of the world, encompasses a large proportion of the world accorded "developing nation" status by the United Nations (Anon, 1991), thus requiring special assistance. With the advent of modern broad-spectrum anthelmintics, mortality of livestock attributed to nematode parasitism has become very rare in the temperate regions of the world. Not so in the tropics / subtropics. In the extreme situations of subsistence farming, where anthelmintics are either unaffordable, or of such inferior quality, that they are not used by the stock owner, high rates of mortality cause by internal parasites are still commonplace, particularly in countries of the African and Asian continents (Anon, 1992; Griggs, 1996).

However, many livestock owners in the tropics / subtropics now use anthelmintics. This has become much more the case since patent protection of all the currently available broad spectrum anthelmintics has lapsed, resulting in burgeoning marketing of generic anthelmintic products. Quality assurance was an absolute pre-requisite for the parent companies, but now they have to competeon the deregulated market against companies with these "look alike" products. The outcome for the farmers superficially seems favourable, with not only a greater range, but also much cheaper, products. However many instances of poorly manufactured, or counterfeit, generic products have been reported. This is particularly so in the developing countries, which cannot provide the resources to monitor product quality and to prosecute offenders (Wanyangu *et al.* 1994; Waller *et al.* 1996). Also, as a result of this unfair competition, there are instances of highly reputable companies marketing substandard products in this region of the world (van Wyk *et al.* 1995). Thus in most instances, freeing-up the anthelmintic market in the tropics / subtropics has not been in the farmers' best interests. As poor quality products assume a significant market share, then not only do the farmers waste their money, by failing to control parasites in their animals, but they hasten the selection process for anthelmintic resistance.

*The relative importance of small ruminant livestock*

This region has large, and in many countries, still increasing populations of small ruminants. It is of interest to note the changing demographics of livestock over recent years (see Table 1)Over the past decade, the populations of sheep have substantially decreased (~ 18%) in the developed countries, whereas there has been a commensurate percentage increase (~ 22%) in the developing countries. This could be attributed to the decline in the wool industry, which negatively impacted on the sheep populations of countries such as Australia and New Zealand, but the increase in the latter would be largely due to a response, particularly in the Asian countries, of national policies aimed at becoming self-sufficient in livestock products. Much of this recent expansion would be by farmers with no tradition, or experience, of managing sheep production.

Despite the importance, and the numerical abundance, of the sheep and goats in this region of the world, it is a sobering thought to remember that these industries account for a very small share of the world veterinary parasiticide market (Waller, 1997b). Thus there is little incentive for the international pharmaceutical industry to develop new anthelmintics for the small ruminant anthelmintic market, particularly when one realises that the research and development costs, and the risks of failure, are exponentially increasing (Waller, 1997c).

*The relative importance of parasite species*

*Haemonchus contortus* is overwhelmingly the most important internal parasite of small ruminants (sheep and goats) in the tropical/subtropical regions of the world (Anon, 1991, Anon, 1992). This blood-sucking parasite is responsible for acute outbreaks with high mortality, particularly in young animals. In Kenya alone, it has been estimated that it causes losses in the order of USD 26

**Table 1: Animal inventory in developing & developed countries during 1975 to 1995**

| | Developing Countries | | | Developed Countries | | |
|---|---|---|---|---|---|---|
| | 1975 | 1995 | Increase % | 1975 | 1995 | Increase % |
| Inventory (million) | | | | | | |
| Cattle | 739 | 942 | +27 | 448 | 364 | -19 |
| Sheep | 523 | 639 | +22 | 523 | 428 | -18 |
| Goats | 389 | 607 | +56 | 24 | 32 | +33 |
| Pigs | 382 | 598 | +56 | 302 | 302 | 0 |

*Source* : Schillorn Van Veen

million each year (Anon, 1999). It is probably the only nematode parasite of sheep and goats that can be accurately diagnosed without the aid of laboratory testing. Signs of acute anaemia are obvious, past history (particularly weather conditions) and discounting other less common conditions (eg. fasciolosis, theileriosis etc.), will strongly suggest clinical haemonchosis. This parasite has very high biotic potential (egg production by female parasites) and at times when transmission of this parasite is favoured (warm and wet), losses can occur in all classes of animals. On a worm-for-worm basis, *H. contortus* is generally considered the most pathogenic parasite of small ruminants (Soulsby, 1986). Although it occurs in mixed infections with other nematode parasites, it invariably dominates the faecal worm egg counts and often approaches 90% of worm egg contamination on pastures under prevailing conditions of high temperature and humidity. Whilst this parasite enjoys such environmental conditions in the free-living stage, it is poorly adapted to cold and dry conditions (Levine, 1963). Thus it declines in importance, further north and south of the boundaries outlined above, in the temperate regions of the world.

*The nature of livestock management*

In contrast to the livestock systems of the temperate regions, where varying degrees of housing and /or zero grazing are practised, ruminant livestock production in the tropics / sub tropics is characterised by year-round grazing on pasture. Thus larval pickup from pasture is more-or-less continuous and all livestock are likely to be infected.

In many regions in the tropics / subtropics communal grazing is the norm. Thus there is little or no for opportunity individual farmers to practise any form of parasite control, unless there is widespread compliance the same practices by the whole community.

*Parasite population dynamics*

As stated by Hugh McL Gordon, one of the 'fathers' of modern applied veterinary parasitology, internal parasites "work by the weather" (Gordon, 1948). The severity of disease is dictated by the degree of larval pickup, or challenge, from pasture. This is determined by temperature and humidity. If either of these environmental variables is unfavourable (ie. temperature and/or humidity too low) then discontinuities in the translation process from egg hatch to infective larval availability on pasture, can occur. Thus, both temperature and rainfall are important parameters controlling this process in the temperate regions of the world, whereas in the tropics/subtropics, the limiting environmental variable is only rainfall because temperatures are always high enough to facilitate this process. Consequently, in the humid tropics/subtropics, the environmental pasture conditions are favourable, more or less continuously. Whereas in the temperate regions there are often times when 'bottlenecks' occur in the larval translation process, which not only reduce larval pickup, but can be exploited in parasite control programmes.

*The "Drench Gun" mentality*

Whilst livestock owners in many countries of the tropics / subtropics lack the financial resources, knowledge, or the will, to treat their animals with drugs, there are also many countries in this region where quite the opposite is the case. Because of the importance of *H. contortus,* and the very high efficiency of the broad spectrum anthelmintics against this parasite, the concept of suppressive drenching of sheep and goats became firmly entrenched in many countries of the tropics / subtropics where this parasite is endemic. Frequent (every 4 6 weeks), and often haphazard treatment became commonplace. As a legacy major problems of resistance now occur not only in *H. contortus,* but for other important parasites of small ruminants as well (Waller, 1997a). The ultimate disastrous scenario exists in certain regions of Brazil, Paraguay and South Africa where farmers have abandoned farming of sheep and goats because of failure to keep animals alive and producing because of anthelmintic resistance (Maciel *et al*. 1996; van Wyk, 1990).

## COPING WITH THE PROBLEM

Undoubtedly the problem of anthelmintic resistance in nematode parasites (specifically *H. contortus*) of sheep and goat populations in the tropics / subtropics is large and inexorably increasing. The message is clear if sheep and goat raising is to continue, and hopefully flourish in this region, then serious changes in the way in which they are managed need to be made. There are examples of ways this may be effected:

*Breeding approaches*

Many of the indigenous breeds of sheep and goats in the wet tropics and subtropics have over the centuries been exposed to strong survival pressure for parasite resistance. The formidable combination of malnutrition, environmental stress, long-term and often massive larval challenge and limited relief by way of effective anthelmintic treatment, would have imposed the harshest conditions for selection, resulting in survival of the fittest. As a consequence some of the most innately resistant breeds of sheep (eg. Red Maasai, St. Croix, Barbados Blackbelly, Javanese thin tail) and goats (Djallonke, Small East African) are found in the humid tropics / subtropics (Baker, 1996). However they were often considered to be inferior with respect to productivity and performance, compared with the popular breeds that have been developed in the temperate regions of the world. When attempts were made to introduce and cross breed with the 'exotic' temperate breeds in the tropics, major problems were encountered. No account was paid to the need for local adaptation, not only to the climate and feed supply, but also to parasite challenge. The smaller frame and higher fecundity of many of the indigenous

breeds has now shown that if productivity is assessed on an area basis, rather than on an individual animal basis, then the local breeds can easily hold their own with the exotic breeds as well as possessing the important adaptive traits for them to survive in the tropics. Steps are now being taken to reverse the trend in animal breeding in the tropics and nucleus flocks of indigenous breeds are being established in the humid tropics to provide breeding stock.

*Grazing strategies*

Many worm control recommendations have been developed in the temperate regions of the world to improve the efficiency of control that are based on combining anthelmintic treatment with some form of grazing management (Barger, 1997). In comparison, there are relatively few examples of such schemes in the tropics/ subtropics, even though in this region their potential may be even greater. This is because although the development of the free living stages is generally faster and more successful in the tropics / subtropics than in the temperate regions, their longevity is much shorter. Studies in the wet tropical climates of several Pacific Island countries showed that peak larval concentrations of *H.contortus* and *Trichostrongylus* spp. occurred on pasture about one week after contamination but fell to barely detectable levels within 46 weeks (Banks *et al.,* 1990; Barger *et al.,* 1994). A grazing system was developed to exploit these findings for the control of parasites in small ruminants. It consisted of 10 paddocks, easily, cheaply and effectively established by using solar powered fencing. Each paddock was grazed in sequence for 3.5 days then spelled for 31.5 days. This grazing period had to be less than one week to prevent auto-infestation and 3.5 rather than 4 days was chosen so that the stock movements were made at the same times and the same days each week (Barger *et al.* 1994). Egg counts of goats which grazed in the rotational system were less than half those of similar set stocked goats on an adjacent area. In addition, the set stocked goats required nearly four times more anthelmintic treatments than the rotationally grazed animals, over the course of a year. But most dramatically, there were indications that it may have been possible to dispense with anthelmintic treatment entirely in the rotational grazing system. A very similar programme was tested and found to succeed in Malaysia (Chandrawathani, 1997). These excellent examples of practical parasite control systems readily lend themselves to adoption in many areas throughout the tropics/subtropics. However, a cautionary note must be heeded for those designing schemes for environments which are cooler and/or dryer than the above. Development and survival times of the free-living stages of these parasites are almost certain to be longer than those recorded in the Pacific islands and Malaysia. Before launching into similar rotational grazing schemes, it is important to have a good understanding of the local ecology of the free-living stages.

Unfortunately, the reality is that these simple and practical grazing management systems tend to be abandoned, not because they ultimately fail, but because livestock owners consider that they require more effort compared with simply suppressively drenching their stock (Manuel 1996). The message of impending total anthelmintic failure in these countries and the need for farmers to adopt sustainable parasite control practices is not being heeded or reinforced. In the temperate regions of the world considerable benefits have been achieved in worm control for both sheep and cattle parasites by interchange grazing between these two species of livestock. These grazing management strategies exploit host specificity, whereby parasite species that are pathogenic in one host species either do not infect the alternative host, or are less pathogenic and prolific. Typical procedures involve alternation of the separate host species at intervals from two to six months (Barger and Southcott, 1978; Donald *et al.* 1987), with anthelmintic usually but not always (Donald *et al.* 1987) given at times of alternation. These trials proved to be very successful, with parasitism and production of young sheep given only one or two drenches annually being equivalent to that of suppressively treated (1224 times / year) sheep over a three year period. However, care must also be exercised in adopting these schemes in the tropics and the subtropics. Similar benefits may result from interchange grazing, but the grazing intervals almost certainly need to be shorter. Furthermore, control of *H. contortus* may prove difficult. In the more temperate regions this species can cycle in calves, but they rapidly acquire natural immunity to become refractory to infection by 12 months of age (Southcott and Barger, 1975). In the tropics this age resistance is slower to develop, or may never occur. For example, in Paraguay there was no indication that cattle had acquired significant immunity after two years of grazing (Benitez-Usher *et al.* 1984).

*'Famacha'and the control of H. contortus*

Parasite populations are typically over-dispersed in naturally infected herds, or flocks, of grazing livestock. In other words, in any aggregation of animals, a few individuals have disproportionately high parasite burdens, whilst a relatively large number of animals have few worms and some with possibly no worms. Thus not only good parasite control, but also reduced selection for resistance, should occur if only those individuals which carried the high worm burdens, and by implication, responsible for the greatest amount of pasture contamination, were treated (Barger, 1985). The "Farmacha"system developed in South Africa is based on this premise (Malan and van Wyk, 1992). It is focussed on the management of *H. contortus* infections in sheep and in goats, based on the clinical identification of developing anaemia in individual animals within a flock.

One important feature of the system is that it is equally applicable to all levels of the farming community.

The visual appraisal of anaemia by inspecting the conjunctiva of the eye, is linked to an identification chart. Therefore literacy is not a requirement, and it has been found that very limited training is needed for farmers to

master the procedure. Famacha is equally applicable to the control of *H. contortus* throughout the moist tropics / sub-tropics of the world where this parasite is endemic. However, it is essential that farmers are made clearly aware that this system is only applicable to *H. contortus* infections. Other important nematode parasite species need to be closely monitored, particularly *Trichostrongylus* and *Ostertagia* spp. The South African workers also warn about the re-emergence of *Oesophogostomum columbianum*, which may follow a major reduction in drenching, after decades of suppressive anthelmintic treatment (Malan and van Wyk, 1992).

*Biological control*

In contrast to the conventional methods of nematode parasite control which focus on the parasitic stages within the animal, biological control is targeted at the free-living stages on pasture. It is aimed at exploiting the nematode destroying properties of certain microfungi, particularly *Duddingtonia flagrans*. This fungus has the ability to survive gut passage of ruminants, as resting spores. These then rapidly germinate and spread on fresh dung and capture infective larvae before they migrate to pasture to complete the parasite life cycle once ingested by the grazing animal. Rapid progress has been made and current studies at these laboratories are investigating various means of fungal delivery (Grønvold *et al.* 1996; Waller and Faedo, 1996). Although most of this work has been carried out in Australia and Denmark, considerable research activity is underway in countries of the tropics / subtropics, such as in Brazil, Fiji, India, Indonesia, Kenya, Malaysia and Mexico.

Not only is there a special need to develop cheap, sustainable, non-chemotherapeutic alternatives to worm control in small ruminants in the tropics / subtropics, but biological control would be particularly suited to the conventional animal management practices of night housing in this region of the world. Animals are often provided with some form of feed supplementation when housed and fungal material could either be co-administered or grown directly on the supplement if it consists of plant by-product material.

*Ethno-veterinary preparations and condensed tannins*

Anthelmintic medication has its origin in the use of plant products and extracts. Examples that are found in the historical literature include jallop, quassia, areca nut, cloves, aloes, garlic, curcubit seeds, castor oil, male fern and oil of chenopodium. In general, these were hazardous concoctions with low anthelmintic activity, especially in ruminant species, and they rapidly disappeared from veterinary use with the advent of the safer, more effective synthetic anthelmintic compounds.

However, there has been a resurgence of interest in traditional health practices in both the industrialised and developing countries of the world (Hammond *et al.*, 1997; Waller *et al.*, 2001). In animal health, this interest encompasses ethno-botany and the use of herbal remedies. However, although there is a large and diverse range of herbal de-wormers available, the scientific validation of the purported anthelmintic effects of many of these products is still lacking.

## DISCUSSION

Livestock production systems in the tropical / subtropical regions of the world face ever increasing demands for products to cope with not only the human population explosion, but an even greater and legitimate need to improve levels of human nutrition. This needs to be accomplished in situations where the land available to raise livestock is declining because of pressure on space by the even greater imperatives and priorities associated with housing and cropping. Clearly the only way to meet the need for greater livestock products is to increase the productivity for individual animals and/or to intensify production. Attempts to achieve this have met with major constraints, not least of which are the greater problems associated with the control of gastro-intestinal parasitism. Control of nematode parasites has depended on the ready availability of cheap and effective anthelmintics, but no longer can this be assured. The spectre of widespread and high level resistance to all the available broad spectrum anthelmintics is now looming large, particularly for the goat and sheep producers in the tropics / subtropics. The solution is neither simple nor easily achieved. Livestock owners cannot expect new, alternative drugs to become available in the immediate future. Nor can they reasonably be expected to solve their problems individually. Major changes need to be made to the way in which nematode parasite control is tackled in the future. This will depend on co-ordinated, continued and committed education and technology transfer from scientists to advisors and in turn, to the producers. A commitment by the pharmaceutical industry towards this goal is also an essential requirement.

Much has been written and said, but there has been little action, towards meeting these objectives. Of course, it is unrealistic to assume that there will be a simultaneous and synchronous initiation and progress towards sustainable nematode parasite control in small ruminants across the tropical/subtropical regions. Nevertheless a start must be made. There have been some excellent examples, outlined above, of methods by which parasite control can be improved in small ruminants in these regions. These should form the foundation of education and extension programmes, where appropriate. There is difficulty in obtaining long-term funding for these programmes, but such resources need not be large. Experience in Australia has shown that the promotion of regional worm control programmes of sheep which led to high levels of adoption by producers could be achieved by the activities of very few, but very dedicated, individuals. Similar models could be adopted elsewhere. Donor bodies that support research and development activities in the tropics and subtropics

need to become aware of the looming crisis in nematode control, particularly in small ruminants, and then in turn recognise that funding technology transfer is the most pressing and cost-effective requirement for dealing with this problem.

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**RINGKASAN**

*ANTHELMINTIC RESISTANCE AND ITS IMPORTANCE IN THE CONTROL OF NEMATODE PARASITISM OF SMALL RUMINANT LIVESTOCK IN THE TROPICS / SUBTROPICS*

Ternakan yang dipelihara di kawasan tropika lembap terdedah kepada pelbagai parasit helmin yang bertanggungjawab terhadap kerugian besar produktiviti, dan selalunya kematian berlaku pada kadar yang tinggi, terutamanya di kalangan anak haiwan. Kaedah pengawalan hanya bergantung kepada penggunaan drug antelmintik. Kekerapan penggunaannya bergantung kepada kehendak penternak untuk merawat ternakannya dan/atau keupayaannya membayar kos drug tersebut. Walaubagaimanapun, terdapat pertambahan kecenderungan di kalangan penternak untuk merawat ternakan mereka selepas memahami kerugian yang disebabkan oleh parasit dan terutamanya, kemudahan untuk mendapat drug yang lebih murah lagi generik. Dengan itu, berlaku ketahanan terhadap antelmintik oleh parasit helmin, tetapi kepentingannya berbeza di antara taksa parasit, di kalangan parasit pelbagai spesies perumah dan di antara kawasan/negara tropika. Setakat ini, masalah terbesar dengan ketahanan antelmintik dikaitkan dengan parasit nematod ruminan kecil, terutamanya *Haemonchus contortus*, yang merupakan patogen utama biri-biri dan kambing di rantau tropika lembap/ sub-tropika. Keadaan yang teruk amnya berlaku di negara yang menternak biri-biri secara besar-besaran (benua Afrika, Amerika Selatan, dan Australia). Pada amnya, ketahanan antelmintik di negara Asia tidaklah serius, sungguhpun setiap negara di Asia mempunyai masalah besar (contoh Malaysia dan Fiji). Bukti jelas menunjukkan bahawa ketahan antelmintik sedang bertambah dari segi prevalens, magnitud dan spektrum. Malangnya, berlaku kecenderungan untuk mencari penyelesaian apabila sudah terlambat, iaitu apabila telah berlaku kegagalan antelmintik secara menyeluruh. Walaubagaimanapun, terdapat beberapa tambahan dan/atau alternatif terhadap pengawalan parasit, tetapi apabila digunakan secara berasingan, ia tidak dapat menyelesaikan masalah tersebut ataupun menawarkan apa jua kelegaan. Untuk masa hadapan, cara lestari untuk kawalan parasit nematod ialah menggabungkan pelbagai opsyen kawalan ke dalam pakej Pengurusan Serangga Bersepadu untuk parasit nematod ternakan.