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Face facts : drenching with anthelmintics for worm control selects for drug resistance – and no excuses!

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ABSTRACT

Worm anthelmintic resistance is entering the final phase, where nothing remains with which to control worms at a level commensurate with profitable animal production. In Brazil, for instance, moxidectin alone or in combination with other compound(s) has failed in numerous cases in sheep and goats, and in New Zealand combined treatment of goats with moxidectin plus a benzimidazole and levamisole failed completely against *Trichostrongylus* and *Ostertagia* spp. Cattle follow closely behind, with a recent survey in Argentina indicating a prevalence of 55 % of worm populations resistant to ivermectin.

It is suggested that the solution for sustainable Integrated Parasite Management is use of systems of Targeted Selective Treatment (TST) to optimise application of the phenomenon of refugia for reduced worm selection. However, due to reticence of farmers and their advisors, the required major paradigm shift will be very difficult to achieve. To overcome this, it is suggested that dedicated software be developed for specific decision support at farm level, as detailed as the intervals between TST evaluations of a given flock/herd of animals and percentages of animals to examine and treat.

The conclusion reached is to face the fact that no excuse regarding animal production or farmer reticence will expunge the reality that conventional worm control is leading to intractable resistance; optimum, not maximum production is the prerequisite.

INTRODUCTION

First and foremost in a discussion of anthelmintic resistance it needs to be emphasised that at present anthelmintic usage is a sine qua non for helminth management; because of insufficient efficacy no alternative method can replace, but only complement it.

To the average farmer and his/her advisor, serious anthelmintic resistance (AR) can be likened to the attitude of many people to serious car accidents or cases of housebreaking - it happens only to others and not to yourself or immediate family. Similarly, AR is only a real problem for those persons who drench “too much”, or only in *Haemonchus* spp. and only in small ruminants, i.e., not in the less lethal non-bloodsucking scour-causing worms of developed countries or in any of the worms of cattle. Even a case of resistance so severe that the paper in which it was reported nine years ago was entitled “How long before resistance makes it impossible to control some field strains of *Haemonchus contortus* with any of the modern anthelmintics?” (Van Wyk *et al*., 1997), did not draw much attention. At that stage almost no overt resistance had developed to moxidectin and certain other drugs also seemed to be holding out reasonably well. The farmer and his advisor could therefore look the other way; it was a problem for others, especially since the scour-causing worm species of developed countries were not nearly as lethal as *Haemonchus* spp., the principal worm species involved in pronounced AR at that time.

The standard reaction of the farmer when confronted with a viable alternative, such as the conservation of drug efficacy by treating in relation to faecal egg counts instead of rigidly adhering to a set strategic drenching programme and to avoid drenching at times when severe selection for resistance would take place (for instance, immediately before a move to “clean” pastures), is endless excuses. These revolve around ease of application and possible losses in animal production, but the question of what losses would be likely to occur when drugs were no longer effective against a given worm population (Van Wyk, 2001), is given almost no consideration.

The resistance situation has, however, changed dramatically over the past decade; the old stalwarts, including moxidectin, are failing virtually day by day, with little hope of relief in view regarding the development of new anthelmintics with unrelated activity. Even if an unrelated new anthelmintic group were to be discovered now, it is unlikely that it would reach the market within a decade and if it is used in similar fashion to its predecessors, it is soon likely to fail. For instance, within three years of ivermectin being launched on the international market for use in sheep, the first cases of resistance were encountered (Carmichael *et al*., 1987; Van Wyk & Malan, 1988; Van Wyk *et al*., 1989). There is also the inherent danger that by the time the particular compound becomes available there will be such a demand from farmers who are no longer able to manage worms, that it will be over-utilised without regard to selection for AR. An additional consideration is that the manufacturer may be tempted to recoup its huge investment very rapidly by maximising sales before other competition may materialise or the patent rights lapse.

Ontogeny of anthelmintic resistance

With few exceptions, early drenching programmes such as the better known "Wormkill" of Australia (Dash *et al*., 1985) were strategic in nature, applied when there were few worms in refugia (i.e. unexposed to any control measures) on pasture, and were based primarily on chemical prophylaxis to prevent a build-up of parasites on pasture (Michel, 1969). This approach, initiated almost a century ago when Theiler (1912) suggested that *Haemonchus contortus* could be eradicated if sheep were drenched (with a mixture of an arsenical dip for external parasites and copper sulphate) and moved to worm-free pasture, seemed the most logical since it was the most cost effective and efficient. It was also supported by genetic theory, since the expectation was that because of the exceptionally high efficacy of the modern anthelmintics, the few resistant survivors would "…be depleted enough to reduce the amount of genetic variability [which would] make the response to selection less effective" (Le Jambre, 1978).

When the first cases of resistance against the anthelmintics currently available on the international market started to surface (Drudge *et al*., 1964) and for some time thereafter, the phenomenon was largely disregarded. Warnings to the effect that it could become a serious problem (Van Wyk, 1985; 1990), were generally met with scepticism, especially in the light of the unceasing, impressive armoury of new anthelmintics reaching the market. However, costs of discovering and developing anthelmintics for registration soared so much as to discourage the search for unrelated new ones. McKellar (1994) estimated the cost of developing and registering a broad-spectrum anthelmintic at US$230 million. In the light of the fact that the efficacy of anthelmintic drugs had apparently remained largely intact against the helminths of cattle and that there were too few small ruminants in developed countries globally to foot such an enormous bill, the present impasse has developed. We are now on the verge of it becoming impossible to continue with small ruminant production on pasture on some farms in many countries in as widely separated regions as the Americas, Africa and Asia (Van Wyk *et al*., 2006).

Extent of anthelmintic resistance

After a multitude of reports on resistance to the various anthelmintic acitivity groups; of the different compounds within each group; and eventually even on a population of *H. contortus* multiply resistant to all five of the activity groups available at the time (Van Wyk *et al*., 1997), numerous surveys indicated extremely high prevalences of serious multiple resistance, in South Africa (Van Wyk *et al*., 1997), Argentina (Eddi *et al*., 1996), Brazil (Eschevarria *et al.,* 1996), Paraguay (Maciel *et al*., 1996) and Uruguay (Nari *et al*., 1996) in South America (Table 1). A break-down of the results in South Africa (Van Wyk *et al*., 1999) yielded the disturbing information that some populations of *Haemonchus* spp. were less than 60 %, and others even less than 40 %, susceptible to compounds from all four of the anthelmintic groups involved, including ivermectin (Table 2).

TABLE 1: Resistance of *Haemonchus* spp. of sheep to various anthelmintics: comparison of South Africa with four South American countries (Van Wyk *et al.*, 1999)

Country	Survey farms(n)	Anthelmintic: % resistant farms [1]						
		Benz	Iver	Lev	Rfx	Clos	Benz + Lev	Overall
South Africa[2]	80	79	73	23	89	-	-	98 [7]
Paraguay [3]	37	70	67	47	-	-	-	?
Uruguay [4]	242	61	1	29	-	-	-	93 [8]
Brazil [5]	182	68	7	19	-	20	15	97 [8]
Argentina [6]	65	37	2	8	-	-	5	46 [8]

[1] Benz – benzimidazole ; Iver – ivermectin ; Lev – levamisole ; Rfx – rafoxanide ; Clos - closantel

[2] Van Wyk *et al.* (1999); [3] Maciel *et al.* (1996); [4] Nari *et al.* (1996); [5] Echevarria *et al.* (1996); [6] Eddi *et al.* (1996)

[7] Geometric mean reduction, according to Presidente (1985); when analysed by the RESO method (Anonymous, 1989), all three South African surveys show resistance on 100 % of the commercial farms investigated

[8] Analysed according to the RESO method (Anonymous, 1989)

TABLE 2: Populations of *Haemonchus* spp. resistant to compounds from all four anthelmintic groups tested (benzimidazoles, imidazothiazoles, macrocyclic lactones and substituted salicylanilides-plus-phenols) in South Africa (Van Wyk *et al*., 1999)

Farms (n)	Anthelmintic efficacy (%)		
	<95 %	<60 %	<40 %
	% of worm strains		
80	20,2	6,2	2,4

Moxidectin - a forlorn last hope ?

Due to high prevalence of resistance to nearly all other comounds, Moxidectin, subtly suggested as belonging to a different activity group than ivermectin, has thus been considered the last stand in the face of development of uncontrollable worm resistance (Kieran, 1994, queried by Rothwell & Rolfe, 1994; Cesar Torrano, 2003). However, moxidectin is also starting to fail globally in small ruminants (Leathwick, 1995; Love *et al*., 2003; Hughes *et al*., 2004; Sutherland *et al*., 2004; Thomaz-Soccol *et al*., 2004; West *et al*., 2004a; 2005) and resistance to it has reached a high prevalence in Brazil, with some cases of complete failure even when administered together with other compounds (Table 3 - C.S. Sotomaior *et al*., Personal Communication, 2005). While there are certainly differences in the pharmacokinetics of the ivermectin and moxidectin, this failure of the latter was to be expected (Van Wyk, 2001) because of widely disseminated, high levels of resistance to ivermectin and side-resistance between moxidectin and ivermectin, as demonstrated practically irrefutably by Shoop (1993), Shoop *et al*. (1993), Conder *et al*. (1993) and Watson *et al*. (1996) and an absence of any convincing evidence to the contrary. It is possible that differences in overkill at therapeutic dosage levels could be responsible for differences in the dominance of the heritability of resistance to the two compounds. To quote Roush & McKenzie (1987), "…dominance is a property of phenotypic characters and not of alleles". And (Leathwick *et al*., 2001): "If a similarly high percentage of heterozygous (RS) worms are killed by a given dose of drug as are homozygous susceptible (SS) worms, the R gene is said to be recessive". Hence, in contrast, at lower dosages which do not remove RS worms, AR can be expected to be dominant.

On the other hand, a slower rate of selection for AR is not necessarily desirable unless utilised pre-emptily in sustainable parasite management (*s*IPM) programmes. As pointed out by Van Wyk (2001), the resistance that can be expected to develop after selection with moxidection at the present therapeutic dosage rate will be worse than that with ivermectin; when resistance has developed to the latter, moxidectin can still control the population concerned as long as further selection for resistance is prevented as far as possible, but not vice versa. This has since been confirmed by Le Jambre *et al*. (2005), who reported that both ivermectin and moxidectin were totally ineffective against moxidectin-R populations of *T. colubriformis* and *H. contortus*. In other words, resistance that develops after use of ivermectin can serve as a timely warning and may act as a stimulus for the farmer(s) concerned to change to sustainable, refugia-friendly systems of worm management before moxidectin is affected to the same degree.

TABLE 3: Worm populations found in a survey in Paraná State, Brazil, to be less than 80 % susceptible to moxidectin drenched either alone or together with other compounds (Sotomaior *et al*., personal communication, 2006)

Worm populations	Moxidectin alone	Moxidectin + other [1]
No. < 80 % susceptible	21	6
No. < 30 % susceptible	6	0
Mean	47.8 %	54.8 %
Range	0-74 %	0-77 %

[1] Moxidectin + Closantel and/or Moxidectin + Nitroxynil

Anthelmintic resistance in the worms of cattle

With few exceptions the resistance described above was limited to helminths of small ruminants, while comparatively little work had been done on the worms of cattle. Despite a stern warning by Waller (1997; 2003) that cattle worms had already reached levels of resistance similar to those at which the worms of small ruminants had been a decade earlier; and despite a growing number of reports of worm resistance against various anthelmintics in cattle, there have been few reports of investigations into the prevalence of AR to the common compounds in worms of this host species. New Zealand appeared to be at the forefront of development of resistance in bovine helminths (West *et al*., 1994b; Vermunt *et al*., 1995; Hosking *et al*., 1996; McKenna, 1996), but the South American countries now seem to have taken the lead as regards the extent of AR in cattle worms, even if perhaps it only concerns investigating the problem more systematically.

In 2004 Anziani *et al*. (2004) reported resistance of helminths of cattle to the benzimidazole and macrolactone anthelmintics, Coronado *et al*. (2003) reported total failure of ivermectin against *Cooperia* sp. infection in cattle in Venezuela, and very recently Caracostantogolo *et al*. (2005) found disturbing support for Waller's (1997) statement (above) on the likelihood of the phenomenon also becoming a serious problem in grazing cattle. In a survey of 69 farms in Argentina they found 55 % of worm populations to be resistant to ivermectin. Surprisingly, the prevalence of resistance to the other compounds was considerably lower (Table 4), but it is common knowledge that the macrocyclic lactones are used intensively in South American countries, with large numbers of generic products containing ivermectin for use in cattle in their markets.

TABLE 4: Anthelmintic resistance prevalence in the worms of cattle in Argentina - survey of 69 farms (Caracostantogolo *et al*., 2005)

Compound	Prevalence of resistance (%)
Ivermectin	55
Fenbendazole	10
Levamisole	7
Multiple resistance	9

Leathwick *et al*. (2001) admirably summarised the reality of AR in New Zealand, but the question remains as to what extent the warnings and suggestions have been heeded. These authors emphasise that, because of differences in epidemiology and farming practices, recommendations for management of resistance cannot be literally extrapolated from Australia (or, indeed, from any other country). However, it is equally important to realise that the principles of development of AR are universal, irrespective of any "excuse", such as the necessity of profitable animal production.

Refugia - the key to worm resistance

Van Wyk (2001) posed the question as to why there was a lack of emphasis on the well-known phenomenon of refugia (the non-exposure of some parasites of a given population to a certain control measure, for instance free-living stages of worms on pasture when their hosts are dewormed). Despite it having been shown previously to have a direct effect on the selection for AR (Martin *et al*., 1981; Martin, 1985; 1989), often being mentioned in passing in papers on worm control in the face of drug resistance, it was seldom included and almost never stressed in the final recommendations for countering resistance, whether in human or veterinary medicine (Van Wyk, 2001). In addition, highly deleterious practices, such as strategic drenching of all animals at the time of a move to "safe" or "clean" (worm-free) pasture or intensive drenching at the beginning and/or end of a given worm season, both of which had been shown at least two decades previously to select strongly for AR (Martin, 1981; 1989), were not condemned.

Through comparison of the phenomenon of refugia with other commonly recommended strategies such as under-dosing and reduced drenching frequency for countering resistance, Van Wyk (2001) concluded that refugia is the most important factor in selection for AR; that farmers should be educated to consider refugia above all else in deciding when and with what to drench; and that strategies such as to drench all animals shortly before a move to "safe" or "clean" pasture should be "condemned and never recommended" - in other words, that an extensive paradigm shift was required from previous practices. By pointing out that "widespread resistance to all existing broad spectrum anthelmintic chemical classes is an inevitable consequence of current drenching practices", Leathwick *et al*. (2001) lend strong support for such a drastic paradigm shift. They also emphasise amongst others that to drench as a means to produce "safe" pasture is likely to select rapidly for AR and that the number of anthelmintic drenches is not necessarily a reliable indicator of selection pressure, since both number and timing are the operative factors.

Targeted Selective Treatment

A range of possibilities is available for utilising the phenomenon of refugia optimally under field conditions. Chief among these is Targeted Selective Treatment (TST), the targeting of only those hosts for treatment which are unable to manage current worm challenge unaided, instead of blanket treatment either strategically or whenever some become ill. Granted a susceptible worm population, the untreated animals continue to produce an undiminished number of unselected susceptible worm eggs, compared to a small number of eggs produced by those worms which are resistant to the products used in the treated hosts.

The principle on which TST is based, is gross over-dispersion of burdens of nematodes of farm animals, with the major portion of the worms in the population occurring in a small percentage of the hosts (Barger, 1985). Similarly disparate are the reactions of these hosts to the effects of the different worm burdens due to inherent differences in the resilience of individual animals to the pathological effects of infection.

FAMACHA© clinical evaluation of anaemia

By capitalising on the well-known variation in the colour of the ocular mucous membranes of sheep exposed to *Haemonchus* challenge from a deep red, through shades of pink, to practically white terminally, the FAMACHA© system was developed for the clinical classification of the anaemia of haemonchosis. After the principle had been shown by Malan *et al*. (2001) to be successful for identifying animals for treatment that were unable to cope unaided with reigning worm challenge, the FAMACHA© system was developed (Bath *et al*., 1996) and its results largely validated under field conditions (Van Wyk & Bath, 2002). The introduction of a colour chart facilitated the classification of the observed conjunctival colour changes. A big advantage of the system is that with BLUP (Best Linear Unbiased Production) analysis of preliminary data (thus far only from a single farm), use of the FAMACHA© system for measuring the ability of sheep to withstand infection with haematophagous worm species appears to be practically on a par with that of the haematocrit technique and slightly higher than that of faecal worm egg counts (Van Wyk, unpublished observations, 2005). A special advantage of the FAMACHA© system for developing countries is that it can be applied even by virtually illiterate persons.

In the FAMACHA© validation trials mentioned, it was not uncommon to find that as large a proportion as 70 % of dry ewes and 45 % of lactating ewes on pastures ideal for haemonchosis, required no anthelmintic treatment during an entire *Haemonchus* season, while a very small percentage of the remainder needed up to four salvage treatments over the same period (Malan *et al*., 2001; Van Wyk & Bath, 2002). The FAMACHA© system will also identify sheep suffering from anaemia that results from conditions other than haemonchosis, and this will lead to some unnecessary drenching. However, in the trials conducted to date, only fasciolosis has been a complication in this respect and it is likely that the system will also be applicable to this condition (Van Wyk, personal observations, 2001). Fears have been expressed that under conditions of TST a continual build-up of worm numbers will occur over time. However, it is encouraging that this has not been experienced to date even after up to six years of application of the system on farms in the subtropical regions where most of the testing has been done. What remains to be investigated, however, is whether similar results will be obtained when methods other than FAMACHA© are applied for TST (see below) in temperate climates where non-bloodsucking worm species predominate and can reach very high levels on pasture under conventional farming conditions, with up to 117,000 worms developing from infective larvae ingested in a single day by young calves while grazing (Table 5).

In addition to South Africa, the FAMACHA© system is being used in a host of other countries, among which Brazil (Sotomaior *et al*., 2003a; 2003b; Molento *et al*., 2004a) and southern USA (Mortensen *et al*., 2003; Kaplan *et al*., 2004) stand out.

Body Condition Scoring

While the FAMACHA© system is applicable only to haematophagous worm species, preliminary tests indicate that Body Condition Scoring may hold potential for TST against the non-haematophagous, so-called scour-causing worm species, *T. colubriformis* and *Ostertagia*

TABLE 5: Estimation of levels of pasture larval contamination (as judged from worm burdens in selected tracer calves)

Reference	Age of tracer calf when turned out	Worm burden per day of grazing [1]		
		Ostertagia spp.[2]	*Cooperia* spp.[3]	Total burden [4]
1. Borgsteede & Eysker (1987)	3 months	(a) 32 557	(a) 85 214	(a) 117 771
		(b) 24 614	(b) 44 714	(b) 96 328
		(c) 24 443	(c) 25 925	(c) 50 371
2. Eysker *et al*. (1998)	+/- 4 months	(a) 6 050	(a) 97 079	(a) 103 129
		(b) 15 914	(b) 59 314	(b) 75 228
		(c) 16 871	(c) 52 229	(c) 69 100
3. Eysker *et al*. (1992)	3-4 months	(a) 8 825	(a) 79 625	(a) 88 450
		(b) 7 125	(b) 40 550	(b) 47 675

1 Total worm burden divided by number of days spent on pasture
2 Mainly *Ostertagia ostertagi*
3 Mainly *Cooperia oncophora*
4 Excluding a few other worm species recovered from these calves

circumcincta (Van Wyk & Bath, 2002). It has the disadvantage that it is subject to a very wide range of disease conditions and problems such as malnutrition and practically every disease that has an effect on animal production. However, it has a distinct advantage over weighing in that it is independent of body size, is quicker and involves relatively little labour input. On the other hand, the method has not been tested nearly as thoroughly as the FAMACHA© system for identifying animals which are overly susceptible to worm challenge, and this should be given high priority.

Automated TST in developed countries

Because of the high labour input required, both FAMACHA© and Body Condition Scoring are generally impractical for use in cattle or, in developed countries, for any but small herds or flocks of small ruminants. Furthermore, at present there is no other system available for applying TST in cattle. Nevertheless, it is possible that changes in body weight (Average Daily Gain – ADG) over short periods may provide an index of the effects of non-bloodsucking worm species of both small ruminants and cattle, or possibly even of haemonchosis and/or fasciolosis in these hosts. This, together with systems such as radio frequency identification, holds much potential for computerised automation, for use where labour is scarce and expensive (Van Wyk *et al*., 2006), and should be tested to be able to make TST available under these conditions.

Treat-&-Stay

An important adjunct to TST for ensuring optimum utilisation of the phenomenon of refugia is to treat animals and then to leave them on the infected pasture thereafter, so that they become re-infected with unselected worms, in order to dilute the gene pool of the survivors of the drug treatment. However, several problems complicate this approach. Most importantly, drug formulations such as the ultra-longacting ivermectin and moxidectin and various slow release preparations with extremely long residual action make this approach ineffective for ensuring the required numbers of worms in refugia. In fact, for *Haemonchus* spp. in small ruminants, treatment even at the start of the worm season with the recent ultra-long-acting formulation of moxidectin, with a registered claim in South Africa of 133 days high efficacy against incoming infective larvae, will largely prevent development of susceptible infective larvae in grazing small ruminants over the entire season. In other words, only the more highly resistant helminths will be able to develop and will form the core of the new generation in the successive worm season. On the other hand, development of host immunity towards the end of a given worm season will also prevent much re-infection even after treatment with compounds with no appreciable residual efficacy.

Move-Then-Treat

In order to overcome the problems inherent in the Treat-&-Stay approach, Molento *et al.* (2004b) suggest that by treating animals only some time after having been moved to "safe" or "clean" pasture, it can be ensured that unselected worms will populate the new pasture, thus giving rise to a population of worms in refugia before the animals are treated. The time interval before treatment can be varied in relation to the estimated levels of infection of the animals at the time of the move, to manage levels of parasites in refugia practically at will. In addition, if combined with an applicable system of TST, the reduction in selection for drug resistance can be expected to be dramatic.

A major paradigm shift is required

It is most likely the majority of farmers today enjoyed at least two decades of trouble-free, uncomplicated worm control based practically completely on application of chemicals in set drenching programmes before there was any general suggestion that AR could become the threat it has become today. And, ironically, most of these farmers probably not only do not fully grasp the extent of the threat, but are also managing well with the present anthelmintics on their farms, especially considering that with relatively intensive treatment it is only when more than about 50 % of a given worm population is resistant to a given drug that a farmer is likely to experience clinically-observable loss in production. In addition, a large proportion of advisors to the farmers are similarly unaware of the extreme effect AR can eventually have on animal production and have also not become aware of methods of *s*IPM that can be employed to allay the problem (Van Wyk *et al*., 1997; 2006).

Problems with adoption of a paradigm shift

Against the background of ignorance of a large proportion of advisors to farmers in both developed and developing countries, of new developments in the field of parasite management, it is not surprising that the few people who are expounding the "no-excuses" paradigm shift required to slow selection for AR are apparently (as judged from common recommendations globally) experiencing little to no success. Meanwhile farmers are being bombarded by the media, strikingly illustrated by two recent examples from

South Africa. In May, 2003 a full colour advertisement propounded eight anthelmintic drenches (five of which comprised of closantel alone or in combination with other drugs) for sheep on improved pasture (Anonymous, 2003) and in March 2006, an article quoting a veterinary advisor, contains the recommendation that farmers drench pregnant ewes and then wait for a few days before moving them to pasture that had not been grazed for "a long time" (Van Rooyen, 2006) – a practice which is anathema to sustainable worm management (Martin, 1985; Van Wyk, 2001). At the same time AR is escalating relentlessly and by the time the farmer desperately beseeches help, nothing remains with which to come to his or her aid (Van Wyk *et al*., 1997; 2006).

An important reason for this failure is inability of the seriously diminished numbers of dedicated helminthologists in the world both to do the necessary work to develop methods for countering the escalating resistance on one hand, and to mount the huge effort required for convincing the farmers and advisors on the other. It is compounded by the fact that all forms of integrated parasite management are more complex than conventional methods of control based practically only on chemicals.

Automated technology transfer to farmers and advisors

Van Wyk (2003) and Van Wyk *et al*. (2006) suggest that through the use of new available technology it is possible to overcome the problem of lack of sufficient infrastructure for the training required for both farmers and their advisors to be brought up to date with the latest developments in the field of worm management in modern methods of *s*IPM. The suggestion is that special software be developed, aimed at very specific worm management decision support concerning factors such as intervals between evaluation of sheep by the various methods for TST, the classes of animals and percentages of flocks/herds to be examined, the categories to be treated and drug formulations to use/not to use in relation to whether the animals need to be moved to new pastures. In this way the need for sufficient training for sophisticated systems of worm management can be bypassed in the respect that weighing up of the effect of operative factors will be done by computer evaluation of basic epidemiological data. In the process of application the farmers and their advisors will also be trained indirectly through observation of the decisions generated by computer. In addition, the system will offer the chance for future changes in approach to be incorporated without the need for expensive and labour-intensive training of all the people involved in the network of worm management at that time.

CONCLUSIONS

The question which has to be faced now (rather belatedly at that) by practically everyone involved in worm management, either as farmer at ground level or as advisor, whether in small ruminants, cattle, horses or other grazers, is what the result will be if the situation is reached where no drugs remain with which to control gastrointestinal helminths. Will it be possible to farm profitably even with cattle if worm burdens as illustrated in Table 5 are considered….

There can be no doubt or indeed any excuse for disregarding the fact that the writing is on the wall concerning AR - at present there are only relatively few farmers, but their numbers are growing, who will probably have to cease farming with grazing domestic animals unless drastic action is taken in an attempt to avoid uncontrollable worm populations.

REFERENCES

Anonymous, 1989: Anthelmintic resistance. *Report of the Working Party for the Animal Health Committee of the Standing Committee on Agriculture, SCA Technical Report Series No. 28, Canberra*

Anonymous. 2003: *Landbouweekblad*, 30 May 2003: p33

Anziani, O.S.; Suarez, V.; Gugliomone, A.A.; Warnke, O.; Grande, H.; Coles, G.C. 2004: Resistance to benzimidazole and macrocyclic lactone anthelmintics in cattle in Argentina. *Veterinary parasitology 122*: 303-306

Bath, G.F.; Malan, F.S.; Van Wyk, J.A. 1996: The "FAMACHA©" Ovine Anaemia Guide to assist with the control of haemonchosis. *In*: Anonymous, Proceedings of the 7th Annual Congress of the Livestock Health and Production Group of the South African Veterinary Association, Port Elizabeth, South Africa: 5pp

Barger, I.A. 1985: The statistical distribution of trichostrongylid nematodes in grazing lambs. *International journal for parasitology 15*: 645-649

Borgsteede, F.H.M.; Eysker, M. 1987: Strains of cattle parasites in The Netherlands with different propensities for inhibited development. *Veterinary parasitology 24*: 93-101

Caracostantogolo, J.; Castaño, R.; Cutullé, Ch.; Cetrá, B.; Lamberti, R.; Olaechea, F.; Ruiz, M.; Schapiro, J.; Martinez, M.; Balbiani, G.; Castro, M. 2005: Evaluación de la resistencia a los antihelminticos en ruminates en Argentina. En Resistencia a los Antiparasitarios Internos en la Argentina, Estudio FAO Producción y Sanidad Animal, Organización de las Naciones Unidas para la Agricultura y la Alimentación, Roma 2005.

Carmichael, I.; Visser, R.; Schneider, D.; Soll, M. 1987: *Haemonchus contortus* resistance to ivermectin. *Journal of the South African Veterinary Association 58*: p93

Cesar Torrano, J. 2003: Mode of action and resistance mechanisms of moxidectin and macrocyclic lactones. *In*: Proceedings. *Vth international seminar in animal parasitology, October 1-3, Merida, Yucatan, Mexico*: 105-113

Conder, G.A.; Thompson, D.P.; Johnsson, S.S. 1993: Demonstration of co-resistance of *Haemonchus contortus* to ivermectin and moxidectin. *Veterinary record 132*: 651-652

Coronado, A; Escalona, J.; Henriquez, H.; Mujica, F.; Suarez, C. 2003: Ivermectin resistance in naturally *Cooperia* sp. infected heifers in Lara State, Venezuela. *In*: Proceedings. *Vth international seminar in animal parasitology, October 1-3, Merida, Yucatan, Mexico*: 67-71

Dash, K.M.; Newman, R.L.; Hall, E. 1985: Recommendations to minimise selection for anthelmintic resistance in nematode control programmes. *In*: Anderson, N.; Waller, P.J. *ed.* Resistance in Nematodes to Anthelmintic Drugs. *Australian Wool Corporation Technical Publication 1985*: 161-169

Drudge, J.H.; Szanto, J.; Wyant, Z.N.; Elam, G. 1964: Field studies on parasite control in sheep: comparison of thiabendazole, ruelene and phenothiazine. *American journal of veterinary research 25*: 1512-1518

Echevarria, F.; Borba, M.F.S.; Pinheiro, A.C.; Waller, P.J.; Hansen, J.W. 1996: The prevalence of anthelmintic resistance of sheep in Southern Latin America: Brazil. *Veterinary parasitology 62*: 199-206

Eddi, C.; Caracostantogolo, J.; Peña, M.; Schapiro, L.; Marangunich, L.; Waller, P.J; Hansen, J.W. 1996: The prevalence of anthelmintic resistance of sheep in Southern Latin America: Argentina. *Veterinary parasitology 62*: 189-197

Eysker, M; Boersema, J.H.; Cornelissen, J.B.W.J.; Kooyman, F.N.J.; De Leeuw, W.A. 1992: *Dictyocaulus viviparous* in calves: effect of rotational grazing on the development of infections. *Veterinary parasitology 41*: 127-135

Eysker, M.; Van der Aar, W.M.; Boersema, J.H.; Githiori, J.B.; Kooyman, F.N.J. 1998: The effect of repeated moves to clean pasture on the build up of gastrointestinal nematode infections in calves. *Veterinary parasitology 76*: 81-94

Hosking, B.C; Watson, T.G.; Leathwick, D.M. 1996: Multigeneric resistance to oxfendazole by nematodes in cattle. *Veterinary record 138*: 67-68

Hughes, P.L.; McKenna, P.B.; Murphy, A. 2004: Resistance to moxidectin and abamectin in naturally acquired *Ostertagia circumcincta* infections in sheep. *New Zealand veterinary journal 52*: 202-204

Kaplan, R.M.; Burke, J.M.; Terrill, T.H.; Miller, J.E.; Getz, W.R.; Mobini, S.; Valencia, E.; Williams, M.J.; Williamson, L.H.; Larsen, M.; Vatta, A.F. 2004: Validation of the FAMACHA© eye color chart for detecting clinical anaemia in sheep and goats on farms in southern United States. *Veterinary parasitology 123*: 105-120

Kieran, P.J. 1994: Moxidectin against ivermectin-resistant nematodes - a global view. *Australian veterinary journal 71*: 18-20

Leathwick, D.M. 1995: A case of moxidectin failing to control ivermectin resistant *Ostertagia* species in goats. *Veterinary record 136*: 443-444

Leathwick, D.M.; Pomroy, W.E.; Heath, A.C.G. 2001: Anthelmintic resistance in New Zealand. *New Zealand veterinary journal 49*: 227-235

Le Jambre, L.F. 1978: Anthelmintic resistance in gastrointestinal nematodes of sheep. *In*: Donald, A.D.; Southcott, W.H.; Dineen, J.K. *ed.* The epidemiology and control of gastrointestinal parasites of sheep in Australia. *Commonwealth Scientific and Industrial Research Organization, Australia* [Shiels Printing, Mt Waverley]: 109-120.

Le Jambre, L.F.; Geoghegan, J.; Lyndal-Murphy, M. 2005: Characterization of moxidectin resistant *Trichostrongylus colubriformis* and *Haemonchus contortus*. *Veterinary parasitoloy 128*: 83-90

Love, S.C.J.; Neilson, F.J.A; Biddle, A.J.; McKinnon, R. 2003: Moxidectin-resistant *Haemonchus contortus* in sheep in northern New South Wales. *Australian veterinary journal 81*: 359-360

Maciel, S.; Giménez, A.M.; Gaona, C.; Waller P.J.; Hansen J.W. 1996: The prevalence of anthelmintic resistance of sheep in Southern Latin America: Paraguay. *Veterinary parasitology 62*: 207-212

Malan, F.S.; Van Wyk, J.A.; Wessels, C.A. 2001: Clinical evaluation of anaemia in sheep: early trials. *Onderstepoort journal of veterinary research 68*: 195-174

Martin, P.J., 1985: Nematode control schemes and anthelmintic resistance. *In*: Anderson, N.; Waller, P.J. *ed.* Resistance in nematodes to anthelmintic drugs. *CSIRO Division of Animal Health. Australia Wool Corporation*: 29-40.

Martin, P.J. 1989: Selection for thiabendazole resistance in *Ostertagia* spp. by low efficiciency anthelmintic treatment. *International journal for parasitology 19*: 317-325

Martin, P.J.; Le Jambre, L.F.; Claxton, J.H. 1981: The impact of refugia on the development of thiabendazole resistance in *Haemonchus contortus. International journal for parasitology 11*: 35-41

McKellar, Q.A., 1994: Chemotherapy and delivery systems – helminths. *Veterinary parasitology 54*: 249-258

McKenna, P.B.: 1996: Anthelmintic resistance in cattle nematodes in New Zealand: is it increasing? *New Zealand veterinary journal 44*: p96

Michel, J.F. 1969: The epidemiology and control of some nematode infections in grazing animals. *In*: Dawes, B. *ed. Advances in parasitology 7*: 211-282

Molento, M.B.; Tasca, C.; Gallo, A.; Ferreira, M.; Bononi, R.; Stecca, E. 2004a: Método FAMACHA como parâmetro clínico individual de infecção por *Haemonchus contortus* em pequenos ruminantes (FAMACHA guide as an individual clinical parameter for *Haemonchus contortus* infection in small ruminants). *Ciências Rural, Santa Maria 34*: 1139-1145

Molento, M.B.; Van Wyk, J.A.; Coles, G.C. 2004b: Sustainable worm management. *Veterinary record, July 17*: 95-96

Mortensen, L.L.; Williamson, L.H.; Terrill, T.H.; Kircher, R.A.; Larsen, M.; Kaplan, R.M. 2003: Evaluation of prevalence and clinical implications of anthelmintic resistance in gastrointestinal nematodes in goats. *Journal of the American Veterinary Association 223*: 495-500

Nari, A.; Salles, J.; Gil, A.; Waller, P.J.; Hansen, J.W. 1996: The prevalence of anthelmintic resistance of sheep in Southern Latin America: Uruguay. *Veterinary parasitology 62*: 213-222

Presidente, P.J.A. 1985. Methods for detection of resistance to anthelmintics. *In*: Anderson, N.; Waller, P.J. *ed.* Resistance in nematodes to anthelmintic drugs. *CSIRO Division of Animal Health, Australian Wool Corporation Technical Publication:* 13-27

Rothwell, J.T.; Rolfe, P. 1994: Moxidectin against ivermectin-resistant nematodes - a global view. *Australian veterinary journal 71*: p158, with Kieran's reply (*Australian veterinary journal 71*: 158-159)

Roush, R.T.; McKenzie, J.A. 1987: Ecological genetics of insecticide and acaricide resistance. *Annual review of entomology* 32: 361-380

Shoop, W.L. 1993: Ivermectin resistance. *Parasitology today 9*: 154-159

Shoop, W.L.; Haines, H.W.; Michael, B.F.; Eary, C.H. 1993: Mutual resistance to avermectins and milbemycins: oral activity of ivermectin and moxidectin against ivermectin-resistant and susceptible nematodes. *Veterinary record 133*: 445-447

Sotomaior, D.S.; Caldas, J.S.; Iark, P.; Benvenutti, T.; Rodrigues, N. 2003a: Utilizacao do método FAMACHA© em caprinos utilización del sistema FAMACHA© en caprinos. *In*: Proceedings *III Congreso Latinamericano de especialistas en pequenos ruminantes y camelidos Sulamericanos, held at Vina del Mar, Chile, 7-9 may 2003*: 3pp

Sotomaior, C.; Milczewski, V.; Morais, F.R.; Schwartz, M.G. 2003b: Evaluation of FAMACHA© system: accuracy of anaemia estimation and use of the method on commercial sheep flocks. *In*: Anonymous: Proceedings *V^th^ international seminar in animal parasitology. October 1-3, 2003, Merida, Yucatan, Mexico*: 61-65

Sutherland, I.A.; Brown, A.E.; Leathwick, D.M.; Bisset, S.A. 2004: Resistance to prophylactic treatment with macrocyclic lactone anthelmintics in *Teladorsagia circumcincta*. *Veterinary parasitology 115*: 301-309

Theiler, A. 1912: Voorlopig rapport omtrent het ingeven van Cooper's Dip en blaauwsteen aan schapen op een zuurveldplaats. *Landbouw journaal van die Unie van Zuid-Afrika*, *August 1912, Bulletin No. 48*: 14pp

Thomaz-Soccol, V.; Souza, F.P. de; Sotomaior, C.; Castro, E.A.; Milszewski, V.; Mocelin G.; Pessoa e Silva M. do C. 2004: Resistance of gastrointenstinal nematodes to anthelmintics in sheep (*Ovis aries*). *Brazilian archives of biology and technology 47*: 41-47

Van Rooyen, C. 2006: Beplan fyn vir teelsukses. *Landbouweekblad 31 March, 2006*: 26-27

Van Wyk, J.A. 1985: The epidemiology and control of gastrointestinal nematode infestation of sheep and cattle in South Africa. I. The historic role of Onderstepoort and a short discussion of present research priorities. *Onderstepoort journal of veterinary research 52*: 215-219

Van Wyk, J.A. 1990: Occurrence and dissemination of anthelmintic resistance in South Africa, and management of resistant worm strains. *In:* Boray, J.C.; Martin, P.J.; Roush, R.T. *ed.* Resistance of parasites to antiparasitic drugs. *Round table conference held at the VIIth international congress of parasitology, Paris, August 1990*: 103-113

Van Wyk, J.A. 2001: Refugia - overlooked as perhaps the most potent factor concerning the development of anthelmintic resistance. *Onderstepoort journal of veterinary research 68*: 55-67

Van Wyk, J.A. 2003: Think refugia or lose the battle against drug resistance. *In*: Proceedings *Vth international seminar in animal parasitology, October 1-3, Merida, Yucatan, Mexico*: 39-47

Van Wyk, J.A.; Bath, G.F. 2002: The FAMACHA© system for managing haemonchosis in sheep and goats by clinically identifying individual animals for treatment. *Veterinary research 33*: 509-529

Van Wyk, J.A.; Hoste, H.; Kaplan, R.M.; Besier, R.B. 2006: Targeted selective treatment for worm management - how do we sell rational programs to farmers? *Veterinary parasitology*: In press

Van Wyk, J.A.; Malan, F.S. 1988: Resistance of field strains of *Haemonchus contortus* to ivermectin, closantel, rafoxanide and the benzimidazoles in South Africa. *Veterinary record 123*: 226-228

Van Wyk, J.A.; Malan, F.S.; Gerber, H.M.; Alves, R.M.R. 1989: The problem of escalating resistance of *Haemonchus contortus* to the modern anthelmintics in South Africa.

Onderstepoort journal of veterinary research 56: 41-49

Van Wyk, J.A.; Malan, F.S.; Randles, J.L. 1997: How long before resistance makes it impossible to control some field strains of *Haemonchus contortus* in South Africa with any of the anthelmintics? *Veterinary parasitology 70*: 111-122

Van Wyk, J.A.; Stenson, M.O.; Van der Merwe, J.S.; Vorster, R.J.; Viljoen, P.G: 1999: Anthelmintic resistance in South Africa: surveys indicate an extremely serious situation in sheep and goat farming. *Onderstepoort journal of veterinary research 66*: 273-284

Vermunt, J.J.; West, D.M.; Pomroy, W.E. 1995: Multiple resistance to ivermectin and oxfendazole in *Cooperia* species of cattle in New Zealand. *Veterinary record 137*: 43-45

Waller, P.J. 1997: Anthelmintic resistance. *Veterinary parasitology 72*: 391-412

Waller, P.J. 2003: The future of anthelmintics in sustainable parasite control programs for livestock. *Helminthologia 40*: 97-102

Watson, T.G.; Hosking, B.C.; Leathwick, D.M. 1996: Ivermectin-moxidectin side resistance by *Ostertagia* spp. isolated from goats and passaged to sheep. *Veterinary record 138*: 472-473

West, D.M.; Pomroy, W.E.; Leathwick, D.M. 2004a: Multiple resistance in *Trichostrongylus* and *Teladorsagia* (*Ostertagia*) in goats to oxfendazole, levamisole and moxidectin, and inefficacy of trichlorfon. *New Zealand veterinary journal 52*: 298-299

West, D.M.; Vermunt, J.J.; Pomroy, W.E.; Bentall, H.P. 1994b: Inefficacy of ivermectin against *Cooperia* spp. infection in cattle. *New Zealand veterinary journal 42*: 192-193

West, D.M.; Pomroy, W.E.; Leathwick, D.M. 2005: *Trichostrongylus* and *Teladorsagia* (*Ostertagia*) in goats with multiple resistances to all sheep anthelmintic groups - how do we control them? *New Zealand journal of zoology 32*: p284.