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Recommendations for control of gastrointestinal nematode parasites in small ruminants: These ain't your father's parasites

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Abstract

Gastrointestinal nematode parasites are the single most important health problem of sheep and goats. Traditionally, parasites have been controlled by frequent administration of anthelmintic drugs. However, the emergence of multiple-drug-resistant parasites now threatens this paradigm of control and new approaches are required. Anthelmintics can no longer be thought of as a convenient and inexpensive management tool for maximizing animal productivity. Instead, anthelmintics must be thought of as extremely valuable and limited resources that should be used prudently. In response to this changing paradigm of anthelmintic use, new recommendations for parasite control now exist. A key tenet of this approach, referred to as "Smart Drenching", is to use the best available knowledge to develop strategies that maximize the effectiveness of treatments while also decreasing the development of drug resistance. Additionally, new innovative schemes using novel and sustainable approaches must be implemented. An overall strategy that integrates these approaches is referred to as "sustainable integrated parasite management" (sIPM). However, by its very nature sIPM is much more complicated and difficult to implement than casual administration of anthelmintics. Consequently, successful implementation of sIPM will only be possible with the help and active involvement of veterinarians and other animal health professionals. Because multiple-drug resistance in parasites is now the status quo, and development of further drug resistance is almost certain to outpace the development of new anthelmintics, it is critical that this new philosophy and approach to parasite control be embraced and implemented immediately.

Key words: *Haemonchus contortus*, gastrointestinal nematodes, drug resistance, anthelmintics, parasite control

Résumé

Les nématodes gastro-intestinaux parasites constituent le plus grand problème de santé des moutons et des chèvres. Traditionnellement, les parasites sont contrôlés par l'administration fréquente de médicaments anthelminthiques. Toutefois, l'émergence de parasites multirésistants aux médicaments anthelminthiques a ébranlé ce paradigme de contrôle et forcé l'utilisation de nouvelles approches. Les anthelminthiques ne peuvent plus être considérés comme un outil de gestion pratique et peu dispendieux pour maximiser la productivité animale. Au contraire, les anthelminthiques doivent plutôt être vus comme des ressources extrêmement utiles et limitées à utiliser avec circonspection. À la lumière de ce changement de paradigme dans l'utilisation des anthelminthiques, il existe maintenant de nouvelles recommandations pour le contrôle des parasites. Un élément clé de cette approche, l'arrosage intelligent, consiste à utiliser les meilleures connaissances afin de développer des stratégies qui maximisent l'efficacité des traitements tout en réduisant le potentiel de développement de la résistance aux drogues. De plus, de nouveaux systèmes innovateurs basés sur des approches nouvelles et durables doivent être mis en place. Une stratégie générale qui intègre ces approches constitue ce qu'on appelle une gestion durable et intégrée des parasites. Néanmoins, de par sa nature, une gestion intégrée est plus compliquée et plus difficile à mettre en place qu'une simple application d'anthelminthiques. Par conséquent, la réussite du déploiement de la gestion intégrée ne sera possible qu'avec l'aide et l'implication des vétérinaires et autres professionnels de la santé animale. Parce que la multirésistance aux drogues anthelminthiques des parasites représente la nouvelle réalité et que le développement de nouvelle résistance aux médicaments va certainement aller plus vite que le développement de nouveaux anthelminthiques, il est primordial que

cette nouvelle philosophie du contrôle des parasites soit adoptée et mise en place le plus rapidement possible.

Introduction

There are many important diseases of sheep and goats, but none are as ubiquitous or present as direct a threat to the health of goats as internal parasites. Control of internal parasites is therefore of primary concern in any small ruminant health management program, and is critical to profitability. Gastrointestinal nematodes (GIN) that infect sheep and goats include *Haemonchus contortus*, *Trichostrongylus colubriformis*, *T. axei*, *Teladorsagia circumcincta*, *Cooperia* spp, *Oesophagostomum*, *Trichuris ovis*, *Strongyloides papillosus*, and *Bunostomum*. Although all of these parasites can contribute to the overall problem of gastrointestinal parasitism, it is the highly pathogenic blood-sucking parasite *H. contortus* that by far is the most prevalent and important in most regions of the United States (US), and especially in the southern states.

Diagnosis of haemonchosis is made based upon the characteristic clinical signs of anemia, submandibular edema, weight loss, and ill thrift, along with finding large numbers of trichostrongyle eggs in the feces. Female *Haemonchus* produce approximately 5,000 eggs per day, and sheep and goats can be infected with thousands of these worms. This potentially results in hundreds of thousands to millions of eggs being shed onto pasture by each animal each day. Because the life cycle is so short (< 3 weeks), this cycle (infection - pasture contamination - reinfection - more pasture contamination) can rapidly transform pastures into very dangerous places for small ruminant animals. This is especially true in the warm environment in the southern US, where transmission of *H. contortus* can occur virtually year-round in some areas.

The 2 other major species of importance are *Trichostrongylus colubriformis* and *Teladorsagia circumcincta*. Though in the US their importance tends to pale in comparison to *H. contortus*, both have the potential to cause significant production loss and disease. *Teladorsagia circumcincta* prefers cool climates, so is most likely to be a problem in the northern portions of the US. *Trichostrongylus colubriformis* is intermediate in temperature preference and does well in both cool and warm climates. Both parasites cause a more classical parasitic gastroenteritis, characterized by reduced appetite, reduced weight gain and/or weight loss, and diarrhea. In contrast, *H. contortus* rarely causes diarrhea. Because any one or all of these parasite species may be infecting an animal, it is important to determine which species are present before optimal control measures can be implemented.

As is the case for most parasitic diseases, haemonchosis is most severe in young animals during their first year on pasture. Lambs and kids need special attention to parasite control around the time of weaning, as these animals will be highly susceptible to parasitic disease and will be under considerable stress. Immunity to GI nematodes in goats is slow to develop and is incomplete, therefore even mature goats are at considerable risk. In contrast, mature dry ewes tend to have quite good immunity to GIN infection. However, any one or combination of a number of factors such as poor nutrition, concurrent disease, stress, overstocking, or pregnancy/lactation can cause a loss of immunity to parasites. It is well established that ewes and does lose much of their protective immunity to GIN around the time of kidding/lambing (-2 to +8 weeks) causing the number of parasites infecting the does to increase.[13,29] Subsequently, parasite egg production and contamination of the environment with infective larvae increases, creating a dangerous situation for the highly susceptible young kids. This phenomenon, known as the periparturient rise (PPR) is an extremely important part of the epidemiology of *Haemonchus* and must be considered when designing control programs.

Anthelmintics Used in the Control of Gastrointestinal Nematodes in Sheep and Goats

There are 3 primary classes of anthelmintics available for use in treatment of helminth infections in ruminants in the US: 1) benzimidazoles (BZ), 2) imidazothiazoles/tetrahydropyrimidines (I/T) also referred to as membrane depolarizers, and 3) avermectin/milbemycins (AM) (also referred to as macrocyclic lactones and macrolide endectocides) (Table 1). All 3 of these anthelmintic classes are broad-spectrum nematocides, but spectrum against other groups of parasites varies widely. In the US, all of the anthelmintics labeled for use in ruminants are approved for cattle, and most of the commonly used anthelmintics are labeled for sheep; however, the number of FDA-approved drugs available for use in the treatment of gastrointestinal parasites in goats is severely limited. Currently only 4 drugs are approved for use in goats; morantel,[a] thiabendazole[b] (TBZ), fenbendazole[c] (FBZ), and phenothiazine[d], with TBZ no longer marketed. This list is further limited in usefulness since drug resistance to benzimidazoles (TBZ, FBZ, and related compounds) and phenothiazine is very common. Other unapproved anthelmintics commonly used in goats include ivermectin,[e] doramectin,[f] moxidectin,[g] albendazole,[h] and levamisole.[i] Thus, extra-label use is an important issue in goats. In sheep, the 4 most commonly used anthelmintics, ivermectin, albendazole, levamsiole and moxidectin, are all FDA-approved so extra-label use of anthelmintics is not a major issue for sheep. The law does allow limited extra-label use of drugs, but such use is an exclusive privilege of the

Table 1. Commonly used anthelmintics in sheep and goats.***

Drug	Class	Approved Sheep	Approved Goats^	Dosage (mg/kg)	How supplied	Prevalence of resistance*	Meat WDT	Milk WDT For goats	Remarks
Ivermectin	AM	Yes	No	Sheep 0.2 Goats 0.4	Sheep oral drench	high	Sheep 11 days Goats 14 days**[a]	9 days**[a]	[a]WDT for goats based on use of the sheep oral drench at 0.4 mg/kg Cattle injectable formulation is not rec'd
Doramectin	AM	No	No	Sheep 0.2 Goats 0.4	Injectable	high	ND	NE	Not recommended because long residual activity promotes resistance
Moxidectin	AM	Yes	No	Sheep 0.2 Goats 0.2	Sheep oral drench	moderate	Sheep 14 days Goats 17 days**[a]	8 days**[a]	Use oral drench in sheep and goats [a]WDT for goats based on use of the sheep oral drench at 0.4 mg/kg Cattle injectable and pour-on products should never be used in goats. If the injectable is used, FARAD recommends a 120-130 day meat WDT Kills ivermectin-resistant Haemonchus
Levamisole	I/T	Yes	No	Sheep 8.0 Goats 12.0	Soluble drench powder	low to moderate	Sheep 3 days Goats 4 days**	3 days**	Toxic side effects = salivation, restlessness, muscle fasciculations Recommend weighing goats before treatment
Morantel	I/T	No	Yes	10	Feed premix	moderate	30 days	0 days	Approved for use in lactating goats Surveys for prevalence of resistance have not been performed Administering 1.5 – 2X label dose may improve efficacy. If an elevated dose is used then WDT need to be extended Rec'd using concentrated form: 0.1 lb (45gm) /100 lb BW
Fenbendazole	BZ	No[a]	Yes	Sheep 5.0 Goats 5.0[b]	Paste Suspension Feed block Mineral Pellets	high	Goats 6 days[c] (for suspension only)	0 days[c] (for suspension only)	[a]Approved in Big-horned sheep [b]Label dose is 5.0 mg/kg, but 10 mg/kg is recommended for goats [c]Listed WDT are for the 5 mg/kg dose. At 10 mg/kg, WDT should be extended to 16 days for meat and 4 days for milk**. Add 1 day to WDT for each additional day the drug is used
Albendazole	BZ	Yes	No	Sheep 7.5 Goats 15-20	Paste Suspension	high	Sheep 7 days Goats 9 days**	7 days**	Don't use within 30 days of conception Effective against Moniezia tapeworms
Monepantel	AAD	No[a]	No	2.5	Sheep oral drench	none	ND	NE	[a] Monepantel is not yet approved in the USA as of this writing, but may be approved for sheep in the near term. Since it is not approved in the USA, no WDT have yet been established. See product label. If used in goats use a 2X dose. Once approved, use responsibly and minimize use to prevent rapid development of resistance

AM = avermectin/milbemycin (macrocyclic lactone)
BZ = benzimidazole
I/T = imidazothiazole/tetrahydropyrimidine
AAD = amino-acetonitrile derivative
WDT = withdrawal time
NE = milk WDT has not been established in goats; product should not be used in lactating dairy goats
ND = meat withdrawal time has not been established. To be safe it is suggested to double cattle WDT
^Drug approval information provided is only for the United States.

*Prevalence of anthelmintic resistance in the southern and mid-Atlantic regions of the United States as of 2013. Prevalence of resistance has not been established elsewhere. The effectiveness of an anthelmintic should always be tested before being used by performing a Fecal Egg Count Reduction Test (FECRT) or DrenchRite larval development assay.
**Meat and milk withdrawal times listed in this table are based on information available from FARAD (Food Animal Residue Avoidance Databank; http://www.farad.org/) as of 6/2013. However, no guarantees can be made as to the future accuracy of this information, as recommended WDT may change over time as new pharmacologic information is obtained.
***This table is intended for veterinary use only. The FDA regards extra-label use of drugs as an exclusive privilege of the veterinary profession and is only permitted when a bona fide veterinarian-client-patient relationship exists, and an appropriate medical diagnosis has been made. The prescribing veterinarian is ultimately responsible for drug residues resulting from extra-label use of drugs. Non-veterinarians should always consult with their veterinarian before using any drug in an extra-label manner.

Table is modified from Kaplan RM. Anthelmintic therapy in an era of resistance. In: Anderson DE, Rings DM, eds. *Current veterinary therapy: food animal practice.* 5th ed. St. Louis: Elsevier, 2009:472. Used with permission.

veterinary profession and is only permitted when a *bona fide* veterinarian-client-patient relationship exists and an appropriate medical diagnosis has been made.[4] Regardless of whether anthelmintics are used following label indications or in an extra-label manner, it is important that adequate milk and meat withdrawal times are stringently adhered to (Table 1).

Anthelmintics are most effective when administered orally to small ruminants, and this is the preferred route of administration. Pour-on anthelmintics are poorly absorbed in small ruminants and have a very low bioavailability,[3] so should never be used by that route unless specifically treating for ectoparasites. A recent study in cattle clearly demonstrated that orally administered avermectin/milbemycin drugs were significantly more effective than when administered by injection or pour-on.[28] Sheep should be dosed using the appropriate label directions (all FDA-approved sheep anthelmintics come in an oral drench formulation). However, when using drugs in an extra-label manner in goats it is extremely important that the sheep or cattle (label) dose is not used. Goats metabolize anthelmintic drugs much more rapidly than other livestock and require a higher dosage to achieve proper efficacy.[17,33] Consequently, it is recommended that goats be given a dose 1.5 to 2 times higher than for sheep or cattle. A 1.5X dose (5.45 mg/lb; 12 mg/kg) is recommended for levamisole, because a 2X dose is approaching a level that may be toxic in goats. Furthermore, because of the risk of toxicity with levamisole, it is recommended that individual goats be weighed prior to treatment to determine the appropriate dose.[14] For all other anthelmintics it is recommended that a 2X dose be given to goats. However, even at a 2X dose, the bioavailability generally is still lower than in sheep or cattle at the label dose. This low bioavailability has important implications in the development of anthelmintic resistance.

Doramectin has a much longer persistence but no significant improvement in efficacy compared to ivermectin, therefore it will select for resistance more rapidly. Since resistance to either ivermectin or doramectin confers resistance to the other, and there are no approved formulations of doramectin for small ruminants, for most indications extra-label use of doramectin in small ruminants cannot be justified. However, doramectin injectable may be the treatment of choice for sheep scab (*Psoroptes ovis*) because its long persistence will clear the infection with a single treatment. Also, because of its longer persistence, doramectin would be the treatment of choice for prophylactic treatment against *Parelaphostrongylus tenuis* in camelids. Moxidectin, a milbemycin, is a very closely related compound with similar spectrum of activity, but is more lipophilic than the avermectins and therefore has an even longer persistent activity.[16] Moxidectin is also more potent against many nematodes and therefore will often kill worms that are resistant to the avermectin drugs. However, because multiple-drug resistance is such a widespread problem and moxidectin resistance now is frequently reported, moxidectin should be used only with careful consideration in order to preserve its effectiveness.

It took almost 30 years (since the introduction of ivermectin) for a new anthelmintic drug class to reach the marketplace, but recently 2 new classes of anthelmintic drugs have been marketed for use in sheep; the amino-acetonitrile derivatives (AAD; e.g. monepantel)[19] and the spiroindoles (e.g. derquantel).[29] Monepantel[j] is a broad-spectrum nematocide approved for use in sheep at 1.14 mg/lb (2.5 mg/kg). As of this writing it is not yet approved in the US, but FDA approval is expected. However, excitement regarding this new anthelmintic should be tempered by the lessons learned regarding the development of resistance to all drugs, and recent unpublished reports of resistance already occurring on goat farms in New Zealand and Australia. Thus, when this new drug is approved, it must be used carefully, appropriately and selectively to guard against the rapid development of resistance. Derquantel lacked the broad-spectrum efficacy desired for a new anthelmintic and therefore was developed in combination with abamectin, an avermectin drug. This combination provides broad-spectrum utility, efficacy against isolates of nematodes resistant to existing anthelmintics, and may help provide a means of protecting the new class from the rapid emergence of anthelmintic resistance.[29] However, at present it seems unlikely that derquantel/abamectin[k] will be marketed in the United States.

Anthelmintic Resistance: An Emerging Problem that is Changing our Approach for Controlling Gastrointestinal Nematodes in Small Ruminants

Anthelmintic resistance is defined as a heritable genetic change in a population of worms that enables some individual worms to survive drug treatments that are generally effective against the same species and stage of infection at the same dose rate. In practical terms, anthelmintic resistance is present in a population of worms when the efficacy of the drug falls below that which is historically expected, when other causes of reduced efficacy have been ruled out. Parasitic nematodes have many biologic and genetic features that favor the development of drug resistance. Short life cycles, high reproductive rates, rapid rates of evolution, and extremely large population sizes combine to give many parasitic worms an exceptionally high level of genetic diversity. This leads to certain worms having gene mutations that reduce their susceptibility to the drug.

Resistant worms can come from only 2 places; either they are home-grown or purchased inside an ani-

mal. In a flock/herd that had been managed as a closed herd since before the introduction of a new drug class, resistant worms will appear as a chance genetic event. Initially, resistant worms would be very rare, making up only a tiny percentage of total worm population on the farm. Amplification of resistance within a worm population to clinically relevant levels is typically a slow and gradual process, requiring numerous generations under drug selection (usually taking several to many years). Thus, from a practical perspective, the genetic phase of resistance develops slowly over time during which it is impossible to detect, but then increases very rapidly in its later phase, where it is then perceived as a clinical event. Alternatively, resistant worms can be purchased, thus bypassing the many years of worm evolution and drug selection necessary to reach high levels. Depending upon how many animals are purchased harboring resistant worms, treatment failures can occur practically instantly or over a relatively short period.

This has great clinical relevance because in either case, resistance can transition from undetectable, to clinically important levels over a very short period of time. Consequently, unless a surveillance program is in place that closely monitors the effectiveness of drug treatments over time, resistance will not be noticed clinically until levels of resistance are extremely high. There is also very strong evidence for the BZ and AM classes that, once resistance is diagnosed as a clinical problem, "reversion" to susceptibility likely will never occur. With levamisole, there is evidence of some degree of reversion back to susceptibility, but any reversion is likely to be short-lived.

The Scope and Prevalence of Resistance

For many years, worms were controlled in small ruminants by the frequent use of anthelmintics, and this approach was quite effective. However, we now know that this strategy has turned out to be shortsighted and unsustainable. Prior to 2000, there was little data on the prevalence of anthelmintic resistance in the US. However, since that time several studies have been performed demonstrating a serious and rapidly worsening problem; the prevalence of multiple-drug resistant nematodes (particularly *H. contortus*) now is extremely high. In 2001, we published the first report of multiple-drug resistant *H. contortus* to all 3 available drug classes in the US (moxidectin remained effective).[36] We then followed up that investigation by performing a prevalence study of anthelmintic resistance on goat farms in Georgia. Ninety percent of all farms had *H. contortus* resistant to both ivermectin and albendazole. A further 30% of farms had *H. contortus* that were resistant to levamisole.[32] Moxidectin was the only drug effective on all farms, meaning that on 30% of farms it was the only drug that was fully effective. Importantly, in 2001 moxidectin (sold at that time only as a pour-on for cattle) was a very new drug in the US, and had not been used previously on most sheep and goat farms, and had been used only a few times on several of the goat farms in the study. Thus, in 2001 one would not have expected to find resistance to moxidectin. However, around this time the use of moxidectin started becoming very popular, so we performed a follow-up study in 2003, and found that 50% of farms tested which had a history of moxidectin use over the previous 2 to 3 years had moxidectin-resistant worms.[21] Unfortunately, this situation is not static, but instead worsens every year.

To gain data on the prevalence of anthelmintic resistance on sheep and goat farms throughout the southern US, a 46-farm region-wide study was performed by the Southern Consortium for Small Ruminant Parasite Control (now known as the American Consortium for Small Ruminant Parasite Control; ACSRPC).[18] In that study, *H. contortus* from 45 (98%), 25 (54%), 35 (76%), and 11 (24%) farms were resistant to benzimidazoles, levamisole, ivermectin, and moxidectin, respectively. Resistance to all 3 classes of anthelmintics was detected on 22 (48%) farms, and resistance to all 3 classes plus moxidectin was detected on 8 farms (17%). Thus on almost 20% of all farms tested, resistance was detected to all available anthelmintics, a situation referred to as "Total Anthelmintic Failure". A more recent study performed by my laboratory in collaboration with ACSRPC members from 2007 to 2009 in the mid-Atlantic region found a further escalation of moxidectin resistance; 47% of farms had resistance.[1] Thus, in less than 8 years, prevalence of resistance to moxidectin increased from 0 to near 50%.

The rapid increase seen in moxidectin resistance is not surprising given the fact that ivermectin and moxidectin are closely related drugs that almost certainly have very similar basic mechanisms of action and resistance; evidence strongly suggests that resistance to 1 drug in the AM class confers resistance to all of them.[31,35] Dose-titration studies have demonstrated that the same resistance ratios (dose required to kill resistant worms:dose required to kill susceptible worms) exist for ivermectin and moxidectin. Therefore, ivermectin-resistant worms are technically also moxidectin-resistant. The reason that moxidectin remains effective against ivermectin-resistant worms appears to be mostly a matter of potency. Being more potent, moxidectin is still capable of killing worms that have become resistant to ivermectin. Unfortunately, this efficacy has proven to be short-lived. Therefore, on farms where moxidectin is still effective, use of this drug must be carefully managed to maintain its efficacy. Moxidectin is highly persistent in animal tissues, preventing the establishment of IVM-sensitive (IVM-S) *H. contortus* in sheep for 35 days.[1,24] Even where moxidectin had 100% efficacy

against IVM-resistant (IVM-R) adult worms, incoming IVM-R L_3 infective larvae were only killed for a few days following treatment.[22] Since the persistent activity of moxidectin prevents IVM-S L_3 from establishing for up to 5 weeks, treatment with moxidectin will allow sheep and goats to become infected with a pure IVM-R population of worms over an approximately 4-week period. In this exclusive niche, one can expect a large exchange of IVM-resistance alleles among the mating adult worms, leading to higher levels of AM resistance that would then produce moxidectin inefficacy.

Diagnosis of Anthelmintic Resistance

Given the high levels and spectrum of anthelmintic resistance that have been documented, before developing an effective control program for *H. contortus* or any other GIN parasite on a farm, it is extremely important to know the resistance status of worms on that property. Presently, this can be done only 2 ways: 1) by performing a fecal egg count reduction test (FECRT); or 2) by performing an *in vitro* larval development assay (LDA). The FECRT is presently the most commonly used means of determining whether an anthelmintic is effective on a particular property, and has the advantage that it can be done on any farm with any drug. An alternative to the FECRT is the DrenchRite[m] LDA; however, the test is not suited for in-clinic use and can only be performed in a specialized parasitology diagnostic laboratory.[n] A single DrenchRite LDA can measure and detect resistance to benzimidazole (BZ), levamisole (LEV), and avermectin/milbemycin (AM) anthelmintics from a single sample. In the DrenchRite assay, nematode eggs are isolated from feces and placed into the wells of a microtiter plate containing growth media and varying concentrations of anthelmintic. The concentration of anthelmintic required to block development of nematode larvae to the third-stage is correlated to the *in vivo* efficacy of the drug.

In deciding which test to perform, there are a number of factors to consider. The DrenchRite LDA has advantages relating to veterinarian/farmer convenience and amount of information acquired from the test. To have a DrenchRite LDA performed, a veterinarian needs only to express-mail a pooled fecal sample from goats/sheep on a farm to the laboratory performing the test. Data from the DrenchRite LDA provides a quantitative measurement of the level of resistance to all 3 major drug classes (including moxidectin). The level of resistance to each drug can also be monitored over time, thus providing information on the impending development of resistance even where the drug remains effective. One limitation of the DrenchRite LDA is that very few labs have the expertise to perform it. Another is that when results show borderline resistance, it is not possible to be sure if the drug will yield satisfactory efficacy or not.

In contrast, the FECRT provides a direct measurement of the effectiveness of the anthelmintic, though the observed efficacy is subject to high variability once it falls below 95%. Furthermore, the FECRT is performed only at a single dose (the label dose [sheep] or 1.5-2X the label dose [goats]), thus the results will only tell if you the drug is effective or not at that dose; it provides no warning of emerging resistance until the drug fails. The FECRT also requires much more time and effort by the veterinarian, as fecal samples must be collected from individually identified animals, FEC performed, treatments applied accurately, treatment records kept and entered into a spreadsheet or other analysis program, and data analyzed and interpreted.

When performing a FECRT in sheep or goats, it is suggested that guidelines published by the World Association for the Advancement of Veterinary Parasitology (WAAVP) be used,[11,o] applying practical modifications to fit the situation on the farm. Briefly, groups of 15 animals that have not been treated within the past 8 weeks are randomly allocated to treatment groups and fecal egg counts (FEC) are performed (usually using the modified McMaster technique) 10 to 14 days after treatment. If enough animals are present on the farm, multiple drugs can be tested simultaneously.

Because of the over-dispersed nature of parasitic infections where approximately 20% of the animals harbor 80% of the parasites, FEC vary widely between animals, and a small percentage have much higher FEC than the rest. Thus, there is a strong possibility of a biased or erroneous result if too few animals are used. For reasonable accuracy in the FECRT, at least 6 and preferably 10 to 15 animals should be tested for each drug. If >10 animals are included in each group, it is probable that random allocation will produce treatment groups sufficiently balanced to obtain accurate results. However, if less than 10 animals are used per group it is recommended to balance groups by level of infection. This can be achieved by performing a pretreatment FEC, but this requires a great deal of additional work and expense. If using pretreatment FEC for allocation, animals are ranked from highest to lowest eggs per gram (EPG) of feces and then blocked into groups of 2, 3, 4, or 5, depending on how many drugs are being tested. Then within each block, animals are assigned randomly to treatment or control groups. Alternatively, when *H. contortus* is the primary parasite present, we have found that treatment groups can be reliably balanced if animals are assigned to treatment group based on FAMACHA© score (see below). Therefore, if this method is used a pretreatment FEC is not needed; assignment to treatment group can be made on the spot based on the FAMACHA© score using the same system of blocking and

allocation. For example, if 3 drugs are being tested, of the first 4 animals to come through the chute with the same FAMACHA© score, each of the 4 will be assigned randomly to 1 of the 4 treatment/control groups. The process then repeats itself for the next 4 with the same FAMACHA© score.

If drugs are highly effective (>97%) or poorly effective (<60%), the results will be pretty clear even with relatively few animals. But if in the gray area (80-95%) when resistance is first emerging, variation in FEC can lead to erroneous results and incorrect conclusions. In general, the more animals tested the more accurate the results will be.

Calculations for percent reduction in FEC are performed using the following formula: (FECR% = 100[1-Xt/Xc]), where Xt and Xc are the arithmetic mean EPG in the treated (t) and nontreated control (c) groups, respectively. Software is available for free that performs all calculations and gives data interpretation.[p,q] If a FECR calculator program is used, the assignment of resistance status is based both on percent reduction and the 95% confidence intervals. If a FECR calculator program is not used, the following guidelines can be applied: reductions of greater than 95% indicate sensitivity, reductions of 90-95% indicate low or suspected resistance, and reductions of <90% indicate resistance. FECRT only yields reliable data if enough eggs are counted pretreatment to accurately measure a post-treatment reduction. Thus, if mean FEC of the animals being tested are low, then the modified McMaster method may not be appropriate and an alternative egg-counting technique with greater detection sensitivity should be used.

Smart Drenching

Despite the occasional development of new anthelmintic classes, history clearly demonstrates that the development of resistance is almost certain to outpace the introduction of new drugs. Clearly then, major changes need to be made in the way that nematode control is practiced. It is no longer acceptable for veterinarians to view GIN parasite control in terms of a "deworming program". Over the past decade a paradigm shift has occurred in how GIN parasite control must be viewed and practiced. Anthelmintics can no longer be viewed as an inexpensive management tool to be used with little thought to maximize animal productivity, but instead must be viewed as an extremely valuable and limited resource. We must balance our desire for simplicity and ease with the reality that effective long-term control of GIN will only be possible if anthelmintics are used intelligently with prevention of resistance as a goal. To address this issue, a concept referred to as 'Smart Drenching' has been introduced. Smart drenching is an approach whereby we use the current state of knowledge regarding host physiology, anthelmintic pharmacokinetics, parasite biology, dynamics of the genetic selection process for resistance, and the resistance status of worms on the farm to develop strategies that maximize the effectiveness of treatments while also decreasing the selection of drug resistance. With regard to *H. contortus*, which is almost always the most important species of GIN in small ruminants in the US, one of the most important aspects of smart drenching is a selective treatment approach based on the use of FAMACHA©.

There are some specific strategies that can and should be used to maximize the effectiveness of treatments and to prevent the development of anthelmintic resistance. Some of these are directly related to the concept of smart drenching, while others relate to general management practices. The implementation of these strategies may vary considerably depending upon 1) the primary parasite species that needs to be controlled, 2) the level and spectrum of resistance already present in a region (or farm), 3) regional/local management systems that are used, 4) farm-specific pasture and management systems, 5) type and quality of animal handling system, and 6) available labor. However, there are some general guidelines that are useful in almost all circumstances, and these are listed below. Finally, FAMACHA© must be regarded as a centerpiece of any worm control program where *Haemonchus contortus* is the primary problem.

FAMACHA© – Selective Rather than Whole-Herd Treatment

Selective treatment is a critical component of a program designed to delay the development of anthelmintic resistance. Selective treatment works by maintaining refugia in the parasite population, defined as the portion of the worm population that escapes drug selection.[38] This unselected refugia provide a pool of drug-sensitive genes, thus diluting the frequency of resistant genes in a population of worms. In practical terms with regard to small ruminant parasites, refugia would be all the eggs and larvae already on pasture at the time of treatment, and all the worms in those animals that are left untreated with anthelmintic. In general, the larger the refugia, the slower the evolution of resistance. Parasitologists now believe that one of the major factors leading to the rapid and widespread development of anthelmintic resistance is the common practice of treating all animals in the herd at one time. This practice leaves none of the worms in the flock/herd in refugia; the only eggs shed onto pasture for several weeks following treatment are from those worms that survived treatment. Furthermore, if treatments are given at a time of the year when few infective larvae are on pasture, (early in grazing season or during drought), then eggs shed by the resistant worms that survived the treatment are not greatly diluted. Thus,

resistant worms will make up a significantly larger proportion of the next generation of worms infecting the animals.

We know that worm burdens are not evenly distributed in animal populations; 20-30% of the animals harbor about 80% of the worms. These 20-30% are primarily responsible for contaminating the environment with infective larvae for all the other animals. If we could identify those 20-30% and treat only those animals, we could control the parasites, save money by reducing the number of treatments given on a herd basis, and greatly lessen the selection for resistance by maintaining an adequate refugia. The question then becomes, how can we accurately identify those animals that require treatment?

Several methods have been tested for infections with non-hematophagous species (*T. circumcincta*, *Trichostrongylus* spp),[23] but these will not be addressed here as in the US *H. contortus* is almost always the most prevalent and important species infecting small ruminants. In the late 1990s, a clinical on-farm system for classifying animals into categories based upon level of anemia was developed in South Africa.[9,39] Since anemia is the primary pathologic effect from infection with *H. contortus*, this system, called FAMACHA©, can be an effective tool for identifying those animals that require treatment. To use FAMACHA©, farmers observe the color of ocular mucus membranes and compare this color to a laminated card with illustrations of eyes from sheep at different levels of anemia. The card is calibrated into 5 categories: 1 = red, non-anemic; 2 = red-pink, non-anemic; 3 = pink, mildly-anemic; 4 = pink-white, anemic; 5 = white, severely anemic. Though initially developed for use in sheep, FAMACHA© has also been validated for goats.[41] Prior to its introduction to the US, the ACSRPC performed a validation study of FAMACHA© on both sheep and goat farms, finding that the system worked very well under southern US conditions.[20] Based on this study, a set of guidelines was developed for its use.[r]

Results of that study indicated that treatment can be safely withheld until animals score as 4s or 5s as long as animals are in good body condition and good overall general health, are examined frequently (e.g., every 2 weeks), and good husbandry is used to identify animals in need of treatment (e.g., unthrifty, anorexic, lagging behind, bottle jaw) between FAMACHA© examinations. When a PCV cutoff of ≤ 15 was used as critical value for necessitating treatment, and all animals scored as 4s and 5s were treated, the percentage of false negatives (animals that had a PCV ≤ 15 but were scored as a 3, 2 or 1) was 0.5% and 0.6% for sheep and goats, respectively. At this level, death from anemia would be a very rare occurrence as long as the suggestions mentioned above were used to identify these few animals in need of treatment that were not detected with FAMACHA©. Using this approach the number of anthelmintic treatments administered will be greatly reduced, resulting in diminished selection pressure for resistance and a concomitant reduction in drug costs. In that same study, if only animals with eye scores of 4 and 5 were treated, 14% of sheep and 31% of goats would have received anthelmintic. However, it is recommended that this scheme should only be applied to adult animals. Lambs and kids have comparatively small blood volumes and can progress rapidly from moderate to severe anemia. This precaution should also be extended to ewes and does during the periparturient period, since these animals have decreased immunity to GIN and high nutritional demands. These animals, and others that may be stressed by disease, have access to inadequate nutrition or are in poor body condition, should always be treated if scored as 3s.

An alternative approach could be to treat all 3s, 4s and 5s. This will result in many more treatments being given to non-anemic animals, but will virtually eliminate the possibility that an anemic animal will fail to receive treatment. Also, because many animals scored as 3s still have high FEC, treating this group will greatly reduce egg contamination of pastures. Although many more treatments will be given, significant refugia will be maintained and the evolution of anthelmintic resistance should still be slowed considerably. On farms where resistance testing shows that several drugs are still effective, treating all 3s, 4s and 5s would be a safer approach and will result in better worm control. Many animals will still be left untreated, thereby supplying a significant level of refugia.

On farms where low to moderate levels of resistance has been diagnosed to 1 or more drugs (60-95% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these "less-effective" drugs either singly or in combination on all animals scored as 3s. Using drugs that are less effective in this group should not cause clinical problems to develop because the few 3s that are moderately anemic and in need of treatment should receive a sufficient reprieve from infection until the next FAMACHA© examination, and the majority of the 3s which are not anemic do not really need to be treated. This strategy will help preserve the efficacy of the drugs that are still fully effective by saving them only for the 4s and 5s, and also will help to minimize egg contamination of pastures.

In addition to the benefits of reducing drug costs and delaying the development of anthelmintic resistance, use of FAMACHA© can also help to improve the genetic resistance of individual herds or flocks.[8] Analyses of data in our study revealed highly significant correlations between PCV, eye score, and FEC. It has been established previously that host resistance

to infection with *H. contortus* measured on the basis of FEC and PCV is a moderately heritable trait,[2] and it has been demonstrated that the same animals tend to exhibit the highest FEC and lowest PCV on each occasion that they are measured.[6] Importantly, data from recent investigations examining the heritability of resistance and resilience of Merino sheep to infection with *H. contortus* indicate a high heritability for the clinical estimates of FAMACHA© scores.[39] Since it can be expected that the same animals will require frequent treatments, and this trait of parasite susceptibility will be passed to the next generation, FAMACHA© can be a very useful tool for identifying animals to be culled. Removing the most susceptible animals from the breeding pool each year will have the long-term effect of improving the overall innate genetic resistance and/or resilience of the herd or flock to *H. contortus*. Such progress could never be made using traditional anthelmintic treatment approaches.

While it appears simple and straightforward to examine ocular mucous membranes and assign animals to the proper category, experience in South Africa and here in the US has shown that training and experience is required to use this system effectively. It is critical that users of FAMACHA© receive proper training and understand the risks of incorrect use of this system (e.g. animal mortalities) and necessary precautions that should be taken. Of particular importance is training in the proper technique for examining the ocular mucous membrane. If poor technique is used, then results will be suboptimal. It must also be remembered that there are several other important gastrointestinal (GI) nematodes that cause disease besides *Haemonchus contortus*. In warm climates they tend to have minor importance relative to *H. contortus*, but in cooler climates they can be very important. FAMACHA© is only useful to detect animals in need of treatment due to infections with *H. contortus*, and cannot be used to detect worm infections with these other GI worms. In the cooler northern states, *Trichostrongylus colubriformis* and *Teladorsagia circumcincta* can be important small ruminant pathogens. It is important not to forget about these other worms, and this is an important reason to periodically monitor FEC even when using FAMACHA©.

FAMACHA© is distributed under the auspices of the South African Veterinary Association. Professor GF Bath (project coordinator for FAMACHA© in South Africa) has required that distribution in the US can be made only through the ACSRPC via the laboratory of Dr. Kaplan (University of Georgia), and that FAMACHA© cards are only to be sold directly to veterinarians or other trained animal health professionals.[8] These individuals are expected to provide training in the proper use of the FAMACHA© system prior to re-selling the cards, and must sign a statement indicating their acceptance of this responsibility.

Know the Resistance Status of the Worms Infecting the Herd

With the prevalence of resistance so high, it is critical that anthelmintic efficacy be determined on each farm, and be monitored every 1 to 2 years. Even when the prevalence of resistance is high, there are some farms where drugs are still effective. These farms would gain considerable benefit by using these drugs. Therefore, drugs should not be excluded from use just because resistance is common. On the contrary, one does not want to use drugs that are ineffective. The only way to determine this is to perform a test. Tests need to be performed regularly, as levels of resistance can rapidly escalate and cross the clinical threshold from effective to ineffective.

When using the FAMACHA© method, it becomes even more important to know the resistance status of the farm because animals are not treated until they show signs of anemia. If anthelmintic treatments had been applied at frequent intervals prior to using FAMACHA©, resistance may have been masked, especially if a rotation of drugs was used. In contrast, if treatment is withheld until animals are anemic and a drug that has moderate to poor efficacy due to worm resistance is used, then deaths may occur. This is a prime example of why training is required prior to using the FAMACHA© system.

Keep Resistant Worms off the Farm

Anthelmintic resistant worms can come from only 2 sources; either they are home-grown or they are purchased. Unfortunately, resistant worms come free of charge with new additions; this is a very common means of spreading the drug resistance problem. It is therefore extremely important for sheep and goat producers not to buy and introduce resistant worms to their farm. All new additions to the herd or flock should be quarantined in a dry lot (without any grass) or on concrete and aggressively dewormed upon arrival. The current recommendation is that once new additions are acclimated to the new surroundings, they should then be held without feed for 24 hours and dewormed sequentially on the same day with moxidectin, levamisole, and albendazole. After 14 days, a FEC or fecal float should be performed and the animal should only be allowed to enter the herd if the fecal is negative. If this triple-drug treatment fails to remove all parasites, then the animal needs to be kept in confinement until no more eggs are shed. If a 14-day quarantine is not possible, animals should be confined to pens for a minimum of 48 hours following treatment before being moved to pasture. However, this is a risky approach. After the animal is released from quarantine,

it should be placed on a pasture previously grazed by sheep or goats (large refugia) and should NEVER be placed on a clean or safe pasture that has not had sheep or goats on it in the recent past. In countries where monepantel has been approved and is for sale, this drug has proven useful as a quarantine treatment. However, as of this writing monepantel is not approved in the US, so no specific recommendations can be made.

Administer the Proper Dose

Every dose of anthelmintic should be given with the goal of maximizing the killing of worms. Several studies have demonstrated that sheep/goat producers often underestimate the weight of their animals and therefore underdose them. Underdosing exposes worms to sublethal doses of drug, which increase the selection for resistance. This is an especially high-risk practice in goats, who metabolize the drugs much more rapidly than other livestock. Animals should be weighed individually or dosed according to the heaviest animals in the group (except for levamisole in goats, where overdosing can be risky), and dosing equipment should be frequently checked for accuracy.

Utilize Host Physiology to Maximize Drug Availability and Efficacy

Anthelmintic efficacy is directly related to the duration of contact between drug and parasite. With all other factors being constant, by simply extending the contact time, efficacy of many anthelmintics is improved. Knowledge of host physiology can therefore be used to increase drug efficacy. When orally treating a ruminant it is critical that the full dose lodges in the rumen. Once in the rumen, the duration of drug availability as it is absorbed from the rumen and flows to more distal sites of absorption is largely dependent on the flow rate of the digesta.[15] Since rumen volume remains relatively constant, there is an inverse relationship between feed intake and digesta residence time. Simply restricting feed intake for 24 hours prior to treatment decreases the rate of digesta transit and increases drug availability and efficacy. This effect has been demonstrated in both pharmacokinetic studies and field efficacy trials, where this strategy significantly increased the efficacy of fenbendazole against benzimidazole field-resistant strains of GI nematodes.[15] Withholding of feed should always be done when using a BZ drug, and is helpful when using ivermectin. With moxidectin and levamisole it is not necessary to withhold feed, as it is unlikely that an increase in efficacy will be seen.

Proper technique when drenching animals is also very important. All anthelmintics administered orally should be delivered over the back of the tongue. Presenting a drench to the buccal cavity, rather than into the pharynx/esophagus, can stimulate closure of the esophageal groove with significant drench bypassing the rumen.[34] Absorbed drug concentrations may be higher initially, but are of such short duration that efficacy is reduced.[16] Special dosing syringes and extenders that attach to regular syringes are sold by several sheep supply companies, and should be routinely used. Without any additional cost or effort, these 2 recommendations have the potential to significantly improve drug efficacy, thereby prolonging the useful life of today's anthelmintics, and should be used as a matter of course.

Repeat Dosing

As mentioned above, increasing the duration of contact between drug and parasite can significantly increase efficacy. This also can be accomplished by administering 2 doses, 12 hours apart. Repeat dosing can be used as an alternative to withholding feed, or even better, in addition to withholding feed. In 1 study, the efficacy of fenbendazole increased from 50% when administered as a single dose, to 92% when 2 doses were administered 12 hours apart.[42] This approach is most likely to yield benefit when using a BZ drug. It is recommended to wait a full 24 hours before re-dosing when using levamisole.

Rotation of Anthelmintics

Rotation is an overblown concept that gives farmers (and veterinarians) a false sense that they are actually doing something worthwhile in terms of resistance prevention. The common practice of rotating drugs with each treatment does little to slow the development of resistance, but causes resistance to develop simultaneously to more than 1 drug. When more than 1 anthelmintic class is effective, it has been thought in the past that performing annual (slow) rotation is beneficial in terms of delaying resistance. However, there is no direct evidence for this, and recent computer models indicate no benefit of rotation in the long term. Consequently, in recent years many parasitologists believe that rotation should not be used. Instead, it is recommended that an anthelmintic be used until it is no longer effective, and then drugs should be switched. The main rationale behind this approach is that it will become obvious when a drug no longer works, so the farmer will always be aware of his/her situation. If a rotation is used, resistance develops slowly to all drugs and the farmer is unaware of this emerging problem until multiple-drug resistance is severe. Whether rotation is used or is not used, it is important to understand that rotation is not a replacement for proper resistance-prevention measures. Another factor that impairs any benefit to rotation is that many farmers do not know which products are in which drug class. There are many drugs with different brand names that belong to the same drug class - rotation between different products within the same drug

class will do nothing to slow down resistance. Rotation also becomes moot when only 1 drug is effective, a situation that is becoming increasingly common.

Combination Anthelmintics – Dosing with 2 or More Different Drugs at the Same Time

There are 2 main justifications for the use of combinations: 1) to enable the effective control of nematodes in the presence of single or multiple drug resistance, and 2) to slow the development of resistance to the component anthelmintic classes.[27] Computer modeling studies consistently show that there is a significant advantage to the use of combinations over the use of single actives in delaying the development of anthelmintic resistance. These benefits are the result of the additive efficacy produced by multiple anthelmintics administered at the same time. This, then, slows the development of resistance in a parasite population by reducing the number of resistant genotypes that survive treatment. Fewer resistant worms survive because multiple alleles conferring resistance to all the component anthelmintic classes must be present in the same parasite for survival, and such individual parasites are rare.[7] Fewer resistant survivors means there is a greater dilution of resistant genotypes by the unselected parasites in refugia, and the greater this dilution the slower the development of resistance. Managing refugia to dilute out these survivors is critical, however, because any survivors will be multiple-resistant to all drugs used in the combination.

Although expensive and not routinely practiced in the US because there are no commercial formulations of combination anthelmintics available at present, this approach deserves further attention in light of the current situation, and the possibility of new anthelmintic classes entering the marketplace. In Australia and New Zealand, use of combination anthelmintics is the normal practice on farms, and has been for a number of years.

Reduce the Frequency of Treatment Through the Use of Sound Pasture Management

Good pasture management can also go a long way in preventing resistance by minimizing the dependence on anthelmintics. Anthelmintics alone will not successfully control parasites in the face of poor management and animal husbandry. Managing pastures so that safe grazing areas are available will permit animals to be moved to a safe (low-contamination) area, reducing the number of treatments that are needed. It is important, however, that the animals not be treated immediately before the move to safe pasture unless a proportion of the animals are left untreated, as treating and moving to clean/safe pasture can rapidly accelerate the development of resistance on a farm.[27]

Goats are natural browsers, and parasite transmission is greatly reduced when animals are browsing because they are ingesting forage farther from the ground. Thus browse areas, particularly where there are plants growing with good nutritive value, should be used as much as possible. The numbers of animals on the farm must also be matched with the amount of pasture and the quality of the forage on that pasture. Overstocking increases the amount of fecal/larval contamination, and can often make control of *H. contortus* nearly impossible. Reducing stocking rates to appropriate levels will decrease the number of parasites that sheep and goats are exposed to, and will also improve the quality and quantity of forage available to the animals. Multiple-species grazing can also be a considerable help in controlling GIN parasites. Most parasites are host-specific, thus cattle and/or horses can be co-grazed with sheep/goats, or pastures can be rotated among the various livestock species. Cattle or horses will ingest the sheep/goat infective larvae without harm and visa versa. Using this simple biological approach can produce great benefits.

Novel Non-Chemical Approaches

In response to the crisis posed by drug-resistant parasites, researchers and extension personnel who have the responsibility of providing parasite control advice to the small ruminant industry have come to realize that total reliance on chemical control for parasites is no longer a viable strategy, and new innovative schemes using sustainable approaches must be implemented. There are a number of new non-chemical technologies for GIN parasite control that are being used now and will continue to become increasingly important both in the short- and long-term future.[30] These include vaccines,[25] nutritional supplementation,[12] nematophagous fungi,[26] bioactive forages,[5] copper oxide wire particle boluses,[10] and various genetic approaches. Each of these approaches provide specific benefits; however, none of these by themselves is likely to provide an answer to the problems of parasite control. Instead an integrated approach, sometimes referred to as 'sustainable integrated parasite management' (sIPM) that combines several of these novel methods, together with limited but intelligent use of anthelmintics, will be necessary.[37,40] Veterinarians and small ruminant owners must be prepared to keep up to date with new developments that are certain to materialize in the coming years as these novel approaches are further developed and validated.[t]

Therefore, at the present time we are unfortunately left with few well-tested options other than good management and intelligent chemical control with anthelmintics. However, in the meantime, in response to this changing paradigm of anthelmintic use, new recommendations for parasite control have been proposed. The basis of this approach is to use the knowledge we have about the parasite, the animal, and the drugs to

develop strategies that maximize the effectiveness of treatments while also decreasing the development of drug resistance. The term "Smart Drenching" is often used to describe this approach to worm control.

Conclusion

New novel anthelmintics will be developed in the future, and this will help in the short term. However, it is almost certain that the development of anthelmintic resistance will continue to outpace the introduction of any new drugs. Consequently, the days of being able to control GIN in small ruminants using a "deworming program" by treating the entire herd/flock with anthelmintics at frequent intervals are at an end. Specific strategies are presented in this paper that can and should be used to maximize the effectiveness of treatments, while also reducing the rate with which anthelmintic resistance develops. However, a sIPM program combining multiple modalities is much more complex and difficult to implement than is a traditional "deworming program". Due to the complexities of instituting such programs, successful implementation will only be possible with the help and active involvement of small ruminant veterinarians and other animal health professionals.

Endnotes

[a]Rumatel® Pellets, Durvet Inc., Blue Springs, MO
[b]Omnizole®, no longer marketed
[c]Safe-Guard®, Panacur®, Merck Animal Health, Summit, NJ
[d]Feno-Drench Suspension®, no longer marketed
[e]Ivomec®, Merial Ltd., Duluth, GA
[f]Dectomax®, Zoetis, Florham Park, NJ
[g]Cydectin®, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO
[h]Valbazen®, Zoetis, Florham Park, NJ
[i]Prohibit®, AgriLabs, St. Joseph, MO
[j]Zolvix®, Novartis Animal Health, Inc., Basel, Switzerland
[k]Startect®, Zoetis, Florham Park, NJ
[l]Jackson-O'Brien, submitted
[m]Dr Jennifer Gill, Microbial Screening Technologies, Smithfield, Australia
[n]For more information on submitting a sample for DrenchRite LDA see acsrpc.org, or contact Sue Howell at University of Georgia at jscb@uga.edu
[o]New guidelines for FECRT are currently under development by a WAAVP subcommittee, and are expected to be published in the near future. These will then supersede the recommendations referenced in Coles et al. (1992)
[p]A. Cameron, RESO fecal egg count reduction analysis spreadsheet. AusVet Animal Health Services, University of Sydney, Sydney, Australia 2000. Based on calculations developed by Martin PJ, Wursthorn L, 1991. RESO faecal egg count reduction test calculator, CSIRO, Animal Health, Melbourne, Australia.
[q]University of Zurich, http://www.math.uzh.ch/as/?calc
[r]See FAMACHA© Information Guide at www.acsrpc.org
[s]Information and inquiries regarding obtaining FAMACHA© cards are available at acsrpc.org or by sending an email to famacha@uga.edu
[t]Additional information on novel approaches to parasite control can be found at the American Consortium for Small Ruminant Parasite Control website www.acsrpc.org.

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