The changing landscape of parasite control in small ruminants: What practitioners need to know

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Abstract

Control of gastrointestinal (GIN) parasites is of primary concern in any small ruminant health management program, and is critical to profitability of the farm. For many years, GIN were controlled by the frequent use of anthelmintics, and this approach was quite effective. However, we now know that this strategy is shortsighted and unsustainable. Anthelmintic resistance is bounding out of control, and many of the drugs relied upon for decades no longer are effective on many farms. Furthermore, 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 drug classes. Thus, anthelmintics can no longer be viewed as inexpensive management tools, but instead must be viewed as extremely valuable and limited resources. Furthermore, parasite control must no longer be equated with a deworming program. Rather, parasite control will only be sustainable if it is approached as an integrated parasite management program, where anthelmintics are only 1 of several components. Additionally, there are new strategies for how we need to use our anthelmintics, the most important of which are that treatment is given selectively to animals based on need, and multiple anthelmintics are administered as a combination treatment.

Key words: *Haemonchus contortus*, drug resistance, parasite control

Introduction

There are many important diseases of sheep and goats, but none pose a greater threat to the health of sheep and 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 in the US include *Haemonchus contortus* (Barberpole worm), *Trichostrongylus colubriformis* (black scour worm), *T. axei*, *Teladorsagia circumcincta*, *Cooperia* spp, *Oesophagostomum* (nodular worm), *Trichuris ovis* (whipworm), *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 common and important in most regions of the US.

Diagnosis of haemonchosis is made based upon the characteristic clinical signs of anemia (blood loss), bottle jaw, weight loss, and ill thrift along with finding large numbers of eggs in the feces. Female *Haemonchus* produce approximately 5,000 eggs per day and sheep/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), pastures can rapidly become very dangerous places for small ruminant animals.

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. Thus, it can be an issue in places like Michigan. *Trichostrongylus colubriformis* is intermediate in temperature preference and does well in both cool and warm climates. Both of these 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 GIN 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 a 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.[11] 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 other GIN and must be considered when designing control programs.

Anthelmintics (Dewormers) Used in the Control of Gastrointestinal Nematodes in Sheep and Goats

There are 3 primary classes of anthelmintics (dewormers) available for use in treatment of helminth (worm) infections in ruminants in the United States (USA): 1) benzimidazoles ("white wormers"; e.g. fenbendazole and albendazole), 2) membrane depolarizers (e.g. levamisole), and 3) avermectin/milbemycins (also referred to as macrocyclic lactones and macrolide endectocides; e.g. ivermectin, moxidectin). All drugs in these classes kill roundworms (nematodes), fenbendazole and albendazole kill tapeworms, and albendazole kills liver flukes. In the USA all of the anthelmintics that are labeled for use in ruminants are approved for cattle, and most of the commonly used anthelmintics are also labeled for sheep; however, the number of FDA-approved drugs available for use in the treatment of GI parasites in goats is severely limited. Currently, morantel[a] and fenbendazole[b] are the only 2 drugs approved for use in goats. This list is further limited in usefulness since drug resistance to fenbendazole is very common. Other unapproved anthelmintics that are commonly used in goats include: ivermectin,[c] doramectin,[d] moxidectin,[e] albendazole,[f] and levamisole.[g] Thus, extra-label use is an important issue in goats. In sheep, the 4 most commonly used anthelmintics, ivermectin, albendazole, levamisole, 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 veterinary profession and is only permitted when a *bona fide* veterinarian-client-patient relationship exists and an appropriate medical diagnosis has been made.[3] Without a prescription from a veterinarian with whom you have veterinarian-client-patient relationship, it technically is not legal to use these drugs in goats, since there is no label approval for use in goats. Regardless of whether anthelmintics are used following label indications or in an extra-label manner, it is important that adequate milk and meat withholding 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,[2] therefore blood and tissue levels of drug are suboptimal. Therefore, pour-ons should never be used in sheep/goats unless you are specifically treating for external parasites (lice, etc). 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.[24] Sheep should be dosed using the appropriate label directions (all FDA approved sheep anthelmintics come in an oral drench formulation). Goats also should be treated orally only, but 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.[13] 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. 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 drug resistance.

Table 1. Impact of using anthelmintics in combination on the efficacy of treatments.
Where D1 = efficacy of drug 1, D2 = efficacy of drug 2, D3 = efficacy of drug 3,
2-drug combination (C2%) = efficacy of D1+D2 = D1% + (100-D1%)*D2%
3-drug combination (C3%) = efficacy of D1+D2+D3 = C2% + (100-C2%)*D3%

Drug 1	Drug 2	Drug 3	Combination
80	80		96
80	80	80	99.2
90	90		99
90	90	90	99.9
60	95		98
60	60	95	99.2
99	99		99.99

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 in many parts of the world: monepantel[h,17] and derquantel.[25] As of this writing monepantel is not approved in the United States, and it is unknown when or even if it will be approved and sold in the US. Additionally, it seems unlikely that derquantel will be marketed in the United States. Thus, it seems that we have what we have for the foreseeable future, making the implementation of sustainable parasite control strategies increasingly important.

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 individual worms having gene mutations that reduce their susceptibility to the drug. These worms then amplify themselves in the population when under drug selection.

Resistant worms can come from only 2 places; either they are home grown or purchased inside an animal. An increase in resistance within a worm population to levels that are clinically apparent 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 noticed as the drug becomes less effective. 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 that harbor resistant worms, and other management and pasture factors, treatment failures due to drug resistance 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 until levels of resistance are extremely high. There is also very strong evidence for the benzimidazole and macrocyclic lactones 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 and of little practical benefit.

In general, resistance to 1 drug in a class of anthelmintics confers resistance to all other drugs in that same class. However, drugs do differ in their potency, therefore some drugs within a class will be more effective than others in the early stages of resistance. However, once resistance reaches high levels it is unlikely that any drug in a given class would remain effective.

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. During the period 2002 to 2009, 2 studies were performed investigating the prevalence of anthelmintic resistance on 80 sheep and goat farms in the southern and mid-Atlantic states. In the southern states (2002 to 2006) *H. contortus* from 45 (98%), 25 (54%), 35 (76%), and 11 (24%) farms were resistant to benzimidazoles, levamisole, ivermectin, and moxidectin, respectively.[16] 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". In the mid-Atlantic region study performed a few years later (2007 to 2009), the prevalence of moxidectin resistance was twice as high at 47% of farms.[12] We also have collected data (unpublished) on resistance on sheep and goat farms in other areas of the US. From 2004 to 2015 we tested 29 sheep and goat farms in Michigan and the surrounding states (Wisconsin, Illinois, Indiana, Ohio). *H. contortus* from 100%, 21%, 52%, and 14% of those farms were resistant to benzimidazoles, levamisole, ivermectin, and moxidectin, respectively. These levels are quite a bit lower than those seen in the southern and eastern states; however, these prevalences are still quite high suggesting that testing on every farm is important. It also should be noted that the data cited above are from studies performed more than 5 years ago, and testing by our laboratory clearly indicates that resistance problems worsen every year.

What resistance means with regard to drug selection – Based on surveillance of resistance by my laboratory over the past 16 years, we have a great deal of data on the level and distribution of anthelmintic resistance in the US. Based on these data we can make general statements about which dewormers can be expected to work and which can be expected not to work on a given farm. However, it must be kept in mind that these are generalities that will be true the majority of the time, but not all the time. This is because even when most farms have resistance to a given dewormer, there are some farms that do not; your farm could be in the majority or the minority. Thus I strongly recommend that you test your dewormers to determine if they are effective (see below). Nevertheless, here I provide some generalities to provide a starting point (all comments here relate to *Haemonchus* unless indicated otherwise):

1. Fenbendazole: resistance is extremely common -- it is rare to find farms where fenbendazole is highly effective against *H. contortus* in the US, and it often has virtually no efficacy at all. One should never assume fenbendazole works against *H. contortus* unless it is tested first. However, as discussed in the section below, by repeating doses and/or withholding feed you may improve the response you get. However, this drug remains effective against tapeworms at a 2X dose.
2. Albendazole: similar drug to fenbendazole and everything mentioned above for fenbendazole also holds for albendazole. However, albendazole tends to be a little more potent and thus often will provide marginally better efficacy than fenbendazole.
3. Levamisole: resistance is less common to this drug, thus levamisole is the most likely of all the available anthelmintics to remain effective. However, we

still see resistance fairly often, so one cannot safely assume this drug works – it still should be tested, especially if there is a history of using this drug on the farm.

4. Ivermectin: once the most effective dewormer ever developed, due to high levels of use ivermectin resistance is now extremely common. One should never assume ivermectin works against *H. contortus* unless it is tested first.
5. Moxidectin: this drug is closely related to ivermectin, but is more potent and thus kills ivermectin-resistant worms. However, once a farm has resistance to ivermectin, resistance to moxidectin tends to develop quickly. We have seen a rapid increase in the level and distribution of moxidectin over the past decade, especially on goat farms. Thus, any farm that has been using moxidectin for more than 2 years, or buys animals from other farms should not assume this drug is highly effective. Like with all drugs, testing is highly recommended.
6. Doramectin: this drug is very closely related to ivermectin and resistance to either ivermectin or doramectin confers resistance to the other. It is noteworthy that there are no FDA approved formulations of doramectin for small ruminants, and 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 longer persistence will clear the infection with a single treatment. Also, because of its longer persistence, doramectin would be preferred for prophylactic treatment against *Parelaphostrongylus tenuis* (brain worm) in camelids.

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[i] LDA; however, this test can only be performed in a specialized parasitology diagnostic lab[j], and currently Dr. Kaplan's lab is the only lab in the US that offers this test. However, this service may not be available for much longer. A single DrenchRite LDA can measure and detect resistance to benzimidazole, levamisole, and macrocyclic lactone 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/farmer 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. The major limitations of the DrenchRite LDA are that it requires a great deal of technician time and expertise to perform, and only 1 lab currently offers this test. Another is that when results show borderline resistance, it is impossible to be sure whether 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. In contrast, as mentioned above, the DrenchRite test could tell you that the drug is likely to still be working, but is on the borderline, suggesting resistance is around the corner. The FECRT also requires much more time and effort by the veterinarian, as fecal samples must be collected from individually identified animals at the time of treatment and again 2 weeks later, fecal egg counts (FEC) performed, treatments applied accurately, accurate treatment records kept and entered into a spreadsheet or other analysis program, and data analyzed and interpreted. Nevertheless, the FECRT is the preferred test for detecting drug resistance on the farm level because of its easy implementation.

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,[k,9] applying practical modifications to fit the situation on the farm. It is worth noting that an updated guideline is in the final stages of preparation and should be published in late 2020 or early 2021. Briefly, groups of 15 animals that have not been treated within the past 8 weeks or longer 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. If treatment groups are smaller than 15 animals, the accuracy of the FECRT may be compromised when results are in the gray

borderline/suspected resistance range (85 to 95%), however, if efficacy is very high (>97%) or low (<80%) interpretation is pretty straightforward, even with much fewer animals. See Kaplan (2020) for detailed recommendations on performing a FECRT.[19]

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 livestock producers (especially sheep/goat producers) 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 a relatively inexpensive management tool to be used with little thought to maximize animal productivity, but instead must be viewed as extremely valuable and limited resources. 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 the host animal, the properties of the drug, parasite biology, dynamics of the genetic selection processes that lead to resistance, and the actual resistance status of worms on the farm, to develop strategies that maximize the effectiveness of treatments while also decreasing the selection of further drug resistance. With regard to *H. contortus*, which is almost always the most important species of GIN in small ruminants in the USA, 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 (5) 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.[29] 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. 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.

Worm burdens are not evenly distributed in animal populations; 20 to 30% of the animals harbor about 80% of the worms. These 20 to 30% are primarily responsible for contaminating the environment with infective larvae for all the other animals. By identifying those 20 to 30% and treating 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.

Several methods have been tested for infections with non-blood-feeding species (*T. circumcincta*, *Trichostrongylus* spp),[20] but these will not be addressed here, as in the USA *H. contortus* is almost always the most prevalent and important species infecting small ruminants. In the late 1990s a clinical on-farm system called FAMACHA© for classifying animals into categories based upon level of anemia was developed in South Africa.[30] Since anemia is the primary pathologic effect from infection with *H. contortus*, this system can be an effective tool for identifying those animals that require treatment. To use FAMACHA©, farmers observe the color of ocular (eye) 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.[32] Prior to its introduction to the USA, the ACSRPC performed a validation study of FAMACHA© on both sheep and goat farms, finding that the system worked very well under southern USA conditions.[18] Based on this study, a set of guidelines was developed for its use.[1]

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. 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 (around time of lambing/kidding), since these animals have decreased immunity to GIN and high nutritional demands. These and other animals 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 be missed and fail to receive treatment. Although many more treatments will be given, adequate 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, supplying a significant level of refugia. However, on farms that are down to their last effective drug, avoiding treating the 3s, except as indicated above, would be a more sustainable approach.

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.[6] It has been established that host resistance to infection with *H. contortus* measured on the basis of FEC and red blood cell packed cell volume (PCV) is a moderately heritable trait,[1] 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.[5] 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.[30] 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 USA 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 or even poor. It must also be remembered that there are several other important GIN as mentioned previously that cause disease besides *Haemonchus contortus*. 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. It is important not to forget about *Trichostrongylus colubriformis, Teladorsagia circumcincta*, or *Oesophagostomum* spp and this is an important reason to periodically monitor FEC even when using FAMACHA©. In particular, it is important to note if diarrhea is present. *H. contortus* does not cause diarrhea, whereas with infections with these other nematode species, diarrhea is the most prominent clinical symptom.

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 (wormx.info), and currently 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.[m] 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 anthelmintic resistance being so common and widespread, it is critical that anthelmintic efficacy be determined on each farm, and be monitored every 1 to 2 years. Note that 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. Unfortunately, most farmers do not test, and thus use ineffective drugs thinking resistance is a problem their neighbors might have, but not them. However, the scientific facts prove that resistance is very widespread, and your clients likely have drug-resistant worms on their farms whether you or they think so or not. Even though the use of anthelmintic combinations is highly recommended (see below), FECRT should still be performed on each drug separately. This is the only way that an evidence-based decision can be made regarding which anthelmintics to include in the combination. Drugs with >50% efficacy are still quite useful as part of a combination, but once efficacy falls to <30% the benefit is small, and may not justify the added time and cost of including it in the combination treatment. If the combination is tested as a single treatment, there is no way to know which drug(s) are making the major contribution to that efficacy. However, one can easily calculate the expected efficacy from

a combination of treatments if the efficacy of each drug is measured separately.

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, and 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, a FEC should be performed and they should then be held without feed for 24 hours and dewormed sequentially on the same day with moxidectin, levamisole, and albendazole (all given orally). Note that if a new anthelmintic class gets approved and becomes available, then it would advisable to include that new drug in the combination. After 14 days a second 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 should be treated with copper oxide wire particles (COWP; see below) and another FEC performed 7 to 14 days later. Note that the animal will need to be kept in confinement until no more eggs are shed, and this can possibly take many months. If a 14-day quarantine is not possible, animals should be treated with both the triple dewormer combination and the COWP and then confined to pens for a minimum of 48 hours following treatment before being moved to pasture. However, this is a risky approach because if the treatment was not fully effective you have just released "super" worms onto your property that cannot be controlled. 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.

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 their animals. 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. When orally treating a ruminant it is critical that the full dose lodges in the rumen (large fermentation compartment of the ruminant stomach). Once in the rumen, the duration of drug availability as it is absorbed from the rumen and flows down the GI tract is largely dependent on the flow rate of the digesta (digested feed).[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 benzimidazole 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 (this is due to differences in pharmacokinetics).

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 mouth, rather than into the pharynx/esophagus, can result in a significant amount of the drench bypassing the rumen (and going into a different stomach compartment instead).[27] This will then cause a short duration of drug contact resulting in a reduction in efficacy.[14] 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.

Split and 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.[33] This approach is most likely to yield benefit when using a benzimidazole drug. With levamisole it is recommended to wait a full 24 hr before re-dosing. Treatment with benzimidazole drugs can be repeated for 3 days in a row as well. This may increase efficacy in the short term, but also will place a very high selection pressure for higher levels of resistance.

Rotation of anthelmintics: rotation is not recommended; it is an overblown concept that gives farmers (and veterinarians) a false sense that they are actually doing some-

thing worthwhile in terms of resistance prevention, when in fact it does little to slow the development of resistance. And given the high rates of resistance, it is likely that one will be rotating to an ineffective drug.

Combination anthelmintics - dosing with 2 or more different drugs at same time: This practice is highly recommended and should be used as a standard practice. Recent research has also demonstrated quite clearly that the use of anthelmintics in combination is a beneficial practice. In fact, in Australia and New Zealand there are few products sold as single actives; most products contain 3, 4, or 5 different anthelmintic classes (note that they have some anthelmintic classes that are not available in the US). There are 3 major benefits to using drugs in combination: (1) one gets an additive effect with each drug used, thus the efficacy of the treatment increases, sometimes dramatically (Table 1); (2) it provides improved broad-spectrum efficacy; resistance is species and drug-specific, thus a second (or third) drug may kill any species resistant to the first drug. This will then return the broad-spectrum result that one aims to achieve (and that is specified on product labels). (3) By achieving a higher efficacy, there are fewer resistant survivors, thus there is a greater dilution of resistant worms by the susceptible portion of the population. For example, if 2 drugs each with 90% efficacy are used in rotation, then each time cattle are treated 10% of the worms (resistant) survive. In contrast, if the 2 drugs are used in combination then the efficacy would be 99%; this yields 10X fewer resistant survivors (first drug kills 90%, second drug kills 90% of the remaining 10%). The end result is the anthelmintic resistance evolves more slowly. However, it is critically important that combination treatments be given selectively and not as herd-wide treatments, as refugia must be managed to gain these benefits. Without preservation of refugia, multiple-drug resistance to all the drugs used in the combination could occur rapidly.

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. In fact, if you have a severe parasite problem on your farm then you have a management problem that must be addressed. 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.[23]

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.[26] These include vaccines,[21] nutritional supplementation,[10] nematophagous fungi,[22] bioactive forages,[4] copper oxide wire particle boluses,[8] 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.[28, 31] 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.[n] An example is the recent introduction of a product[o] containing the nematophagus fungi, *Duddingtonia flagrans*. This product has the potential to be an important component of a sIPM program.[7]

Conclusion

It is likely that new novel anthelmintics will eventually be developed and sold in the future, and this will be beneficial for worm control. 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. Therefore, it is important that sheep and goat producers develop a meaningful veterinarian-client relationship with a veterinarian who is knowledgeable in small ruminants, or is willing to learn.

Endnotes

[a] Rumatel® Pellets, Durvet Inc., Blue Springs, MO
[b] Safe-Guard®, Panacur®, Merck Animal Health, Summit, NJ
[c] Ivomec®, Boehringer Ingelheim Animal Health USA Inc., Duluth, GA
[d] Dectomax®, Zoetis, Florham Park, NJ
[e] Cydectin®, Bayer Animal Health, Shawnee, KS
[f] Valbazen®, Zoetis, Florham Park, NJ
[g] Prohibit®, AgriLabs, St. Joseph, MO
[h] Zolvix®, Elanco, Greenfield, IN
[i] Dr Jennifer Gill, Microbial Screening Technologies, Smithfield, Australia
[j] for more information on submitting a sample for DrenchRite LDA see wormx.info, or contact Sue Howell at University of Georgia at jscb@uga.edu
[k] 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)
[l] see FAMACHA© Information Guide at www.wormx.info
[m] Information and inquiries regarding obtaining FAMACHA© cards are available at www.wormx.info or by sending an email to famacha@uga.edu
[n] Additional information on novel approaches to parasite control can be found at the American Consortium for Small Ruminant Parasite Control (website www.wormx.info)
[o] Bioworma®, International Animal Health Products, Huntingwood, NSW, Australia

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