LS02-143

Evaluation of prevalence and clinical implications of anthelmintic resistance in gastrointestinal nematodes in goats

Lars L. Mortensen, DVM; Lisa H. Williamson, DVM, MS; Thomas H. Terrill, PhD; Robin A. Kircher, BS; Michael Larsen, PhD; Ray M. Kaplan, DVM, PhD

Objective—To determine prevalence of resistance to all anthelmintics that are commonly used to treat gastrointestinal nematodes (GINs) in goats.

Design—Prospective study.

Animals—777 goats.

Procedure—On each farm, goats were assigned to 1 of 5 treatment groups: untreated controls, albendazole (20 mg/kg [9.0 mg/lb], PO, once), ivermectin (0.4 mg/kg [0.18 mg/lb], PO, once), levamisole (12 mg/kg [5.4 mg/lb], PO, once), or moxidectin (0.4 mg/kg, PO, once), except on 3 farms where albendazole was omitted. Fecal samples were collected 2 weeks after treatment for determination of fecal egg counts (FECs), and percentage reductions were calculated by comparing data from anthelmintic-treated and control groups. Nematode populations were categorized as susceptible, suspected resistant, or resistant by use of guidelines published by the World Association for the Advancement of Veterinary Parasitology.

Results—Resistance to albendazole was found on 14 of 15 farms, and resistance to ivermectin, levamisole, and moxidectin was found on 17, 6, and 1 of 18 farms, respectively. Suspected resistance to levamisole and moxidectin was found on 4 and 3 farms, respectively. Resistance to multiple anthelmintics (albendazole and ivermectin) was found on 14 of 15 farms and to albendazole, ivermectin, and levamisole on 5 of 15 farms. Mean overall FEC reduction percentages for albendazole, ivermectin, levamisole, and moxidectin were 67, 54, 94, and 99%, respectively.

Conclusions and Clinical Relevance—Anthelmintic resistance in GINs of goats is highly prevalent in the southern United States. The high prevalence of resistance to multiple anthelmintics emphasizes the need for reexamination of nematode control practices. (*J Am Vet Med Assoc* 2003;223:495–500)

Gastrointestinal nematode (GIN) parasites are the single greatest problem for the health and productivity of goats in the southern United States. A 7-year review (July 1993 to July 2000) of clinical cases at Auburn University Veterinary Medical Teaching Hospital in Alabama found that parasite control was the primary reason that 70% of sheep and 91% of goats were examined and treated by hospital clinicians.[1,2] Although many species of parasites contribute to the overall problem of gastrointestinal parasitism, *Haemonchus contortus* is the most prevalent, pathogenic, and economically important.[3] During the past 40 years, the primary means of controlling *H contortus* has been the frequent administration of anthelmintics. Unfortunately, intensive use of and virtual total reliance on anthelmintics for control of GINs has led to worldwide development of anthelmintic-resistant nematode populations, which is recognized globally as the single greatest problem for grazing small ruminant production.[4] In South America[5,6] and South Africa,[7] the prevalence of resistance to anthelmintic drugs has reached alarming proportions and threatens the future viability of small ruminant production.

During the past 35 years, numerous case reports and studies on the prevalence of anthelmintic resistance have been published from countries throughout the world. In contrast, there have been few publications on anthelmintic resistance in the United States. The first reports of anthelmintic resistance in the United States were against phenothiazine[8,9] (1957) and **thiabendazole** (TBZ; 1964) in *H contortus* in sheep.[10,11] In 1988, resistance to 3 different benzimidazole anthelmintics (TBZ, **fenbendazole** [FBZ], and mebendazole) was reported in a herd of dairy goats in Pennsylvania,[12] and in 1990, the first report[13] of resistance to **ivermectin** (IVM) in the United States was made in a herd of Angora goats in Texas. A few years later, resistance to **levamisole** (LEV) was reported in this same Texas herd.[14] A second report[15] of resistance to IVM in *H contortus* in sheep was made in 1994 in Louisiana, and in 2000, resistance to multiple anthelmintics (IVM, LEV, and FBZ) was reported in a

From the Danish Center for Experimental Parasitology, Department of Veterinary Microbiology, Section for Parasitology, Royal Veterinary and Agricultural University, DK-1870 Frederiksberg C, Denmark (Mortensen, Larsen); Departments of Large Animal Medicine (Williamson) and Medical Microbiology and Parasitology (Kaplan), College of Veterinary Medicine, University of Georgia, Athens, GA 30602; and School of Agriculture, Home Economics and Allied Programs, Agricultural Research Station, Fort Valley State University, Fort Valley, GA 31030 (Terrill, Kircher). Dr. Mortensen's present address is Ringe Dyreklinik, 5 Gørtlervej, DK-5750 Ringe, Denmark.

Dr. Mortensen was a veterinary student at the time of the study.

Supported in part by the American Dairy Goat Association, The University of Georgia Veterinary Medical Experiment Station, and a USDA Capacity Building Grant (award No. 99-38814-8306).

Presented in part at the Novel Approaches Third International Conference, Moredun Research Institute, Edinburgh, Scotland, July 2002; and the 47th Annual Meeting of the American Association of Veterinary Parasitologists, Nashville, Tenn, July 2002.

The authors thank Sue B. Howell, Tselane Ware, Betty Jo Rumph, and Lisa Westberry for technical assistance.

Address correspondence to Dr. Kaplan.

goat herd in Virginia.[16] In a recent report,[17] resistance to IVM, doramectin, albendazole (ABZ), morantel, FBZ, and a combination of IVM and ABZ was reported in Georgia in a study involving 90 Spanish meat goats and 40 Nubian cross goats in 2 selected herds.

When making broadly applicable recommendations on parasite control, it is not the sporadic occurrence of resistance that is important but rather the prevalence of such resistance. As already noted, there have been several published reports of individual-farm occurrences of anthelmintic resistance in the United States; however, the prevalence of anthelmintic resistance against the 3 major groups of anthelmintics (macrocyclic lactones, benzimidazoles, and imidazothiazoles) remains unknown. To date, the only study[18] of prevalence of anthelmintic resistance in GINs reported in the United States was published more than 10 years ago, before the recent worldwide increase of nematodes that are resistant to multiple anthelmintics. That study, performed on sheep production units in North Carolina, reported resistance to FBZ in 6 of 13 flocks, with *H contortus* being the predominant species. No resistance was reported against LEV, pyrantel pamoate, or IVM; however, the cutoff values used in the study for establishing resistance were very conservative. Considering the present global problem of lack of anthelmintic efficacy against GINs of small ruminants, the recent reports of resistance to multiple anthelmintics from the southern United States, and the high frequency of anecdotal reports of treatment failure, it is important that the prevalence of resistance in GINs of goats be studied in the southern United States. The purpose of the study reported here was to determine the prevalence of resistance to all anthelmintics that are commonly used to treat GINs in goats.

Materials and Methods

Goats—Seventeen goat farms in Georgia and 1 goat farm in South Carolina were included in this study of which 15 were meat producers and 3 were combined meat and dairy producers. Criteria used to select farms were ≥ 50 goats and verbal commitment of cooperation by the owner. Eight farms were selected from a pool of 57 farms that responded to a farm management and parasite control questionnaire sent to dairy and meat goat producers, and 10 additional farms were selected by other means. All 10 of these farms also completed questionnaires. Farms were located in 13 counties throughout Georgia, with representative farms from all physiographic regions of the state including the northern mountainous, central piedmont, and southern coastal plain regions (Fig 1). An additional farm was in the southern coastal region of South Carolina. Numbers of goats per farm varied from 50 to 565. All goats used in this study were not treated with an anthelmintic for at least 4 weeks before pretreatment fecal collection. This was done to assure that goats were infected with sufficient GIN burdens to perform the study and that the infections were indicative of the overall nematode population in the individual farm habitat, unbiased by recent treatment. Management of farms was not altered; all goats grazed on pasture and were given feed containing supplements as per normal procedures for each individual farm. Ten breeds of goats were on the selected farms; 64% of all goats for which breed information could be obtained were Boer or Boer crosses.

Experimental protocol—The fecal egg count reduction (FECR) test was conducted according to guidelines established by the World Association for the Advancement of Veterinary Parasitology (WAAVP) for evaluating the efficacy of anthelmintics in ruminants.[19] Fecal samples were collected 2 to 10 days before treatment, and fecal egg counts (FECs) were performed by use of a modified McMaster technique with a sensitivity of 50 eggs/g.[20] Goats with FECs < 200 eggs/g were excluded from the study, and when sufficient young or female goats were available, mature bucks were also excluded. On each farm, all goats that were included in the study were stratified by sex, ranked by pretreatment FEC, and blocked into groups of 5 such that the 5 female (or male) goats with the highest FECs were in the first block, the next 5 highest in the second block, and so on. Within each block, goats were randomly assigned to 1 of 5 treatment groups: untreated controls, ABZ[a] (20 mg/kg [9.0 mg/lb], PO, once), IVM[b] (0.4 mg/kg [0.18 mg/lb], PO, once), LEV[c] (12 mg/kg [5.4 mg/lb], PO, once), or moxidectin[d] (MOX, 0.4 mg/kg [0.18 mg/lb], PO, once). Because none of these anthelmintics have a label approval for goats, doses were selected on the basis of data in the anthelmintic pharmacologic literature, which indicates that goats metabolize drugs much faster than sheep or cattle, resulting in decreased bioavailability.[21-28] At the doses used in this study (1.5 to 2X the label dose for sheep), all 4 of the anthelmintics are highly effective against susceptible isolates of GINs of goats.

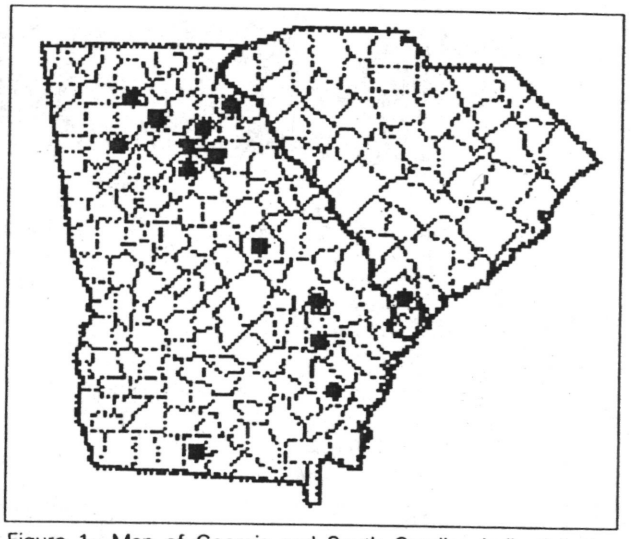

Figure 1—Map of Georgia and South Carolina indicating the location (black dot) by county of 1 or more farms that participated in a study of anthelmintic resistance of gastrointestinal nematodes in goats.

Ten goats were assigned to each treatment group; however, the overall mean number of goats tested per group was 8.9 because certain goats were removed from the study. The most common reasons for removing goats from the study were life-threatening parasite burdens that required immediate treatment (with an anthelmintic other than that of their assigned treatment group) and goats not present on the days of treatment or posttreatment sampling. When it was necessary to remove a goat from the study, the other goats in the same 5-goat treatment allocation block were also removed to keep the treatment groups balanced and remove any bias that might be introduced into the data set. All anthelmintics were stored at approximately 22°C except LEV, which was stored at 4°C after preparation (from powder). All anthelmintics were administered orally into the pharynx by use of separate syringes for each anthelmintic. Immediately before treatment, all goats were weighed with a digital portable scale, and doses were calculated according to body weight. Ten to 14 days after treatment, fecal samples from all goats were col-

lected per rectum and stored at 4°C until FECs were performed. For each farm, cultures of nematode larvae were prepared from pooled feces of goats in the control group. Infective larvae (ie, L_3 stage) were recovered, and genus of the larvae was identified.[29]

Statistical analyses—Mean percentage reductions in FEC were calculated for treatment groups on each farm by use of a computer program[c] on the basis of the formula

$$FECR = 100[1-Xt/Xc]\%$$

where Xt and Xc are the arithmetic mean eggs per gram in the treated (t) and nontreated control (c) groups, respectively. This program also calculated 95% confidence intervals. Results were interpreted according to the WAAVP guidelines; resistance was present if the FECR was < 95% and the lower 95% confidence limit was < 90%; if only 1 of these 2 criteria was met, resistance was suspected.

Results

Gastrointestinal nematodes resistant to ABZ were found on 14 of 15 farms, with mean FECR of 64% (median, 70%; range, 0 to 88%) on farms with resistance (Fig 2). Tests for resistance to IVM, LEV, and MOX were performed on 18 farms. Resistance to IVM was detected on 17 farms, with mean FECR of 42% (median, 36%; range, 0 to 93%). On 3 of the farms, IVM was completely ineffective in reducing FEC (0% reduction). Levamisole resistance was found on 6 farms, with mean FECR of 84% (median, 89%; range, 58 to 93%). Suspected resistance to LEV was found on 4 additional farms, all with a 97% reduction in numbers of eggs. Resistance to MOX was found on 1 farm (mean FECR, 94%), and suspected resistance was found on 3 farms (mean FECR, 96%).

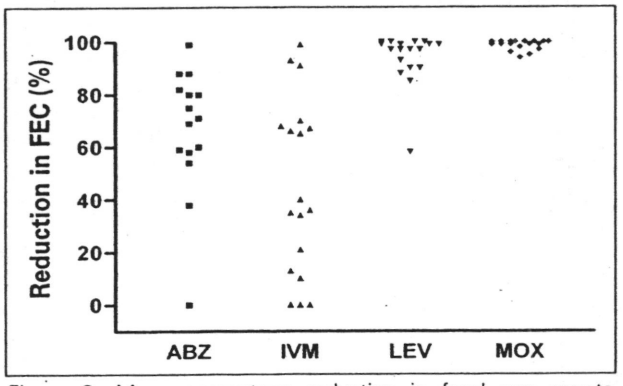

Figure 2—Mean percentage reduction in fecal egg counts (FECs) in goats on farms with anthelmintic resistance after treatment with albendazole (ABZ; n = 15 farms), ivermectin (IVM; 18), levamisole (LEV; 18), and moxidectin (MOX; 18).

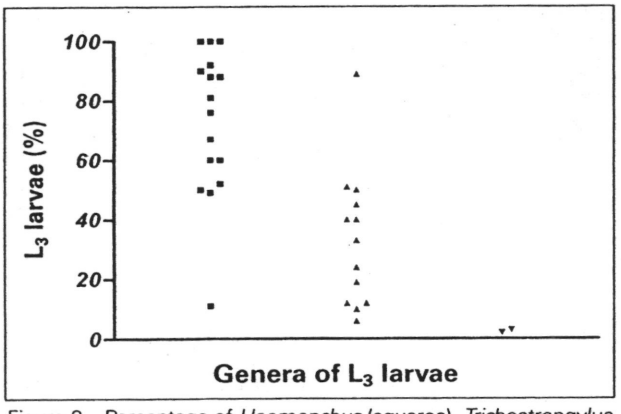

Figure 3—Percentage of *Haemonchus* (squares), *Trichostrongylus* (triangles), and *Oesophagostomum* (inverted triangles) third-stage larvae (L_3) recovered from larval cultures from pooled feces from goats that were not treated with anthelmintics (controls) on 18 farms. One hundred larvae from each culture were identified to genus.

Resistance to multiple anthelmintics (ABZ and IVM) was found on 14 of the 15 farms where both of these drugs were tested simultaneously, and resistance to ABZ, IVM, and LEV (representing all 3 groups of anthelmintics tested) was found on 5 of 15 farms. Only 1 farm had parasites that were fully susceptible to all anthelmintics tested. The overall mean reductions in FEC on all farms for each treatment group were 67 (ABZ), 54 (IVM), 94 (LEV), and 99% (MOX). Larvae recovered from cultures of nematode larvae from pooled feces revealed that *H contortus* (73%) and *Trichostrongylus colubriformis* (27%) were the predominant species, accounting for > 99% of all L_3 larvae (Fig 3). Low numbers of *Oesophagostomum* larvae were seen on a few farms. On the basis of larval recoveries, *H contortus* was the major species on all farms but 3, and *H contortus* accounted for ≥ 80% of all L_3 larvae on half the farms.

Discussion

Results of this study indicate that an extremely serious situation for nematode parasite control is emerging in goats in the southern United States. Gastrointestinal nematodes that are resistant to multiple anthelmintics are highly prevalent, and the situation appears to be rapidly worsening. Resistance to both IVM and ABZ was found on 14 of 15 farms, with mean FECR of only 42 and 64%, respectively. Levamisole was much more effective; however, resistance or suspected resistance was still found in GINs on 10 of 18 farms. Although the overall efficacy of LEV remains fairly high against GINs of goats, LEV has only rarely been used as an anthelmintic in goats in the southern United States. Of the 18 farms, only 6 had used LEV in the past 5 years. Of those 6 farms, 4 had used LEV in only 1 of the past 5 years, and 2 farms had used LEV in 2 of the past 5 years. Parasites on both farms with a history of use of LEV for 2 of the previous 5 years had resistance to this anthelmintic, and 1 of the these farms had the lowest efficacy for LEV of any farm in this study (FECR, 58%).

Resistance to MOX was found in GINs on 1 farm, and suspected resistance was found in GINs on 3 farms. However, we suspect that the farm with nematodes resistant to MOX may have had resistance because of technical error, since only 1 of 9 treated goats had a positive FEC result (≥ 1 egg on McMaster slide [> 50 eggs/g]) following treatment. When conducting on-farm studies where experimental conditions are not highly controlled, it is not inconceivable that on rare occasions, an animal is misidentified or a sample is incorrectly labeled. However, we believe that if any technical errors were made in this study, they were few in number. Rare technical errors should have little impact on a study such as this, because

anthelmintic efficacy studies are designed with the knowledge that nematode burdens and FECs vary greatly among animals. To compensate for this variation, FECR calculations are made on the basis of group means, and in this study, virtually all treatment groups had 8 to 10 goats. A rare data error would have little impact on the results from most farms; only in an instance such as this, where FECs were 0 in all goats but 1, would such an error have a major impact on the interpretation of the data. We have no evidence that an error was made on that farm and are only speculating on the basis of the results. The 3 farms with suspected resistance to MOX that had multiple goats with FEC of > 50 eggs/g after treatment are high cause for concern, because MOX has only recently been used as an anthelmintic in goats. In this study, 9 of 18 farms had used MOX in the past 1 to 2 years. Three of the 4 farms that had GINs resistance or suspected resistance to MOX are included in these 9. The reduction in efficacy of MOX on these farms is a strong warning of what can be expected in the future if nematode control practices are not changed. Ivermectin was the most commonly used anthelmintic, with all farms reporting frequent use during the past 5 years.

The findings of this study suggest that the recent individual-farm reports of GINs that are resistant to multiple anthlemintics in Texas,[14] Virginia,[16] and Georgia[17] were not isolated occurrences. The goat industry is a regional enterprise with goats being constantly sold and moved across state lines (with their parasites). Considering the differences in breeds, management styles, and topographies represented by the 18 farms in this study and the fact that the 3 physiographic regions of Georgia (mountains, piedmont, and coastal plain) are representative of those topographies found throughout the southeastern United States, it is likely that the results of this study are representative for the entire southeastern United States. These data emphasize the need for development and implementation of novel and sustainable methods of nematode control to minimize anthelmintic use, thus, protecting and preserving the efficacy of the few anthelmintics that remain effective.

The market for anthelmintics in host species that are plagued by resistance (horses, sheep, and goats) is perceived by the pharmaceutical industry as being too small to sustain the great costs associated with a drug discovery program.[30] Therefore, it is extremely unlikely that new anthelmintics with novel modes of action will be developed and marketed in the foreseeable future.[31] The present situation dictates that we must balance our goal of maximizing goat productivity with the reality that effective long-term control of *H contortus* in goats 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, whereby knowledge regarding host physiology, anthelmintic pharmacokinetics, parasite biology, dynamics of the genetic selection process for resistance, and the resistance status of nematodes on the farm are used to develop strategies that maximize the effectiveness of treatments and decrease selection for anthelmintic resistance.[32]

It is important for farmers to know the efficacy of the different anthelmintics available for treatment on their farms. Performing a FECR test on the farm or sending a composite fecal sample to a laboratory capable of performing an in vitro larval development assay[f] can provide this information. Once the resistance status is known, it is important to only use anthelmintics with good efficacy and to ensure that a correct dose is administered. Because visual estimation is an unreliable method to estimate body weight, it is recommended that all goats be weighed before treatment (this is also important to prevent toxicosis with levamisole). If weighing individual goats is not feasible, doses should be assigned to all goats on the basis of the weight of the heaviest goats within the same age group. Goats are often treated as if they were sheep; however, differences in metabolism and pharmacokinetics between goats and sheep require that a higher dose be used in goats than in sheep.[24] In general, goats should receive twice the dose recommended for sheep, except for LEV, where 1.5X the sheep dose should be given because of potential toxicosis.[33,34] It is important to note that all of these usages are extralabel, and although the FDA does allow limited extralabel use of drugs, this is an exclusive privilege of the veterinary profession.

Efficacy of anthelmintics is directly related to the duration of contact between anthelmintic and parasite. To ensure sufficient anthelmintic-parasite contact time, it is important that the full dose lodges in the rumen. Administering a drench to the buccal cavity, rather than into the pharynx and esophagus, can stimulate closure of the esophageal groove with a large amount of the drench bypassing the rumen.[28] Duration of anthelmintic availability as it flows to more distal sites of absorption is largely dependent on the flow rate of the digesta.[35] Because rumen volume typically remains constant, there is an inverse relationship between feed intake and digesta residence time. Restricting feed intake for 24 hours before treatment slows digesta flow and increases anthelmintic availability and efficacy. Increasing the duration of contact between anthelmintic and parasite can also be accomplished by repeated dosings 12 hours apart. In a recent study,[16] the efficacy of FBZ increased from 50% when administered as a single dose to 92% when 2 doses were administered 12 hours apart. Other recommendations include improving pasture management, reducing stocking rates, and making improved use of areas used for browsing. These recommendations reduce the concentration of infective larvae on the pasture and subsequent need for treatment.

Rate of selection for anthelmintic resistance is significantly affected by the proportion of selected-to-unselected nematodes.[36,37] The unselected population referred to as refugia provides a pool of genes sensitive to anthelmintics, which dilutes the frequency of resistant genes and slows the evolution of resistance. Parasitologists now believe that 1 of the major factors responsible for the development of anthelmintic resistance is the common practice of treating all animals in a herd at 1 time, which leaves no nematodes in refugia.[36] However, nematode burdens are not evenly distributed; an overdispersed pattern exists in which a

small percentage of the animals harbor most of the parasites.[38,39] Drenching only those goats that require anthelmintic treatment will greatly reduce the selection for resistance by maintaining a large refugia and provides a means to improve overall genetic resistance of the herd by culling goats requiring repeated treatments. Implementation of selective treatment for *H contortus* has been prevented by lack of a simple and reliable field test for anemia. However, a clinical on-farm system[g] was recently developed in South Africa for classifying animals into treatment categories on the basis of the level of anemia.[40] Results of evaluation trials[41] in South Africa have indicated that use of this system in sheep can reduce the number of anthelmintic treatments given by up to 90%.

On the basis of the findings of this study, use of ABZ (or other benzimidazole anthelmintics) and IVM cannot be recommended for the control of GINs in goats in the southern United States unless first proven effective. For ABZ or FBZ, restricting feed intake for 24 hours before treatment or use of a repeated dosing method may increase the efficacy of these drugs sufficiently to make them useful. However, the increase in efficacy that results from this treatment method would probably not be long lived in areas where high levels of resistance are already present. In other areas of the country where levels of benzimidazole resistance may be lower, this strategy could substantially increase the effective life span of these anthelmintics. Levamisole and MOX continue to have good to excellent efficacy and are the anthelmintics of choice for goats with clinical haemonchosis. However, it is important not to assume that these anthelmintics will remain effective. Neither LEV nor MOX has been used extensively in goats in the United States; therefore, selection for resistance has been low. Furthermore, IVM and MOX are closely related anthelmintics that have the same or similar mechanisms of action and resistance. Results of dose-titration studies[42-44] have indicated that similar resistance ratios (dose required to kill resistant nematodes-to-dose required to kill susceptible nematodes) exist for IVM and MOX, proving that resistance to 1 of these anthelmintics confers resistance to the other. Therefore, nematodes resistant to IVM are technically also resistant to MOX; however, the higher potency of MOX against *H contortus* results in treatment doses that remain capable of killing nematodes that have become resistant to IVM. Unfortunately, if MOX is overused, this efficacy can be expected to be short-lived.

Goat owners can use all the best management and GIN control strategies and still have highly resistant nematodes in their herds if newly purchased goats were already infected with them. Therefore, it is important to institute a rigid treatment and quarantine program for all new goats introduced to the herd. All newly acquired goats should be dewormed with MOX and LEV on arrival and held in drylot confinement for 14 days. Fourteen days after treatment, a fecal floatation or FEC should be performed, and goats should only enter the herd if no nematode eggs are found.

This study provides evidence that the problem of anthelmintic resistance in GINs of goats is much more severe than is commonly recognized. The principal reasons for this discrepancy between perception and reality are that frequent treatments with marginally effective anthelmintics and rotation between effective and ineffective anthelmintics can often conceal resistance. Resistance is only recognized once efficacy of treatment decreases below an important threshold level that results in death of goats after treatment. The current paradigm of parasite control that relies on frequent treatment of all goats with anthelmintics requires little thought or analysis and is, therefore, easy for producers to understand and implement. In contrast, strategies that aim to reduce anthelmintic use require a greater depth of understanding of parasite epidemiology and host-parasite dynamics. Therefore, successful implementation of a smart drenching approach to parasite control will only be possible if small ruminant veterinarians take an active and leading role in the education of goat producers.

[a]Valbazen 11.36% suspension, Pfizer Animal Health, Eaton, Pa.
[b]Ivomec sheep drench 0.08% solution, Merial, Iselin, NJ.
[c]Levasol soluble drench powder, Pitman-Moore Inc, Mundelein, Ill.
[d]Cydectin pour-on for cattle, 5 mg/mL, Fort Dodge Animal Health, Fort Dodge, Iowa.
[e]Cameron A. RESO fecal egg count reduction analysis spreadsheet. Available at: www.sheepwormcontrol.com. Accessed May 5, 2003.
[f]DrenchRite larval development assay, Bioniche Animal Health, Armidale, New South Wales, Australia. US source: Department of Medical Microbiology and Parasitology, College of Veterinary Medicine, University of Georgia, Athens, Ga.
[g]FAMACHA, Livestock Health and Production Group of the South African Veterinary Association, Pretoria, South Africa. US source: RM Kaplan, Department of Medical Microbiology and Parasitology, College of Veterinary Medicine, University of Georgia, Athens, Ga.

References

1. Pugh DG, Navarre CB. Internal parasite control strategies. *Vet Clin North Am Food Anim Pract* 2001;17:231–244.
2. Pugh DG, Hilton CD, Mobini SM. Control programs for gastrointestinal nematodes in sheep and goats. *Compend Contin Educ Pract Vet* 1998;20:S112–S115, S123.
3. Craig TM. Epidemiology and control of gastrointestinal nematodes and cestodes in small ruminants. Southern United States. *Vet Clin North Am Food Anim Pract* 1986;2:367–372.
4. Waller P. Anthelmintic resistance. *Vet Parasitol* 1997;72: 391–412.
5. Echevarria F, Borba MF, Pinheiro AC, et al. The prevalence of anthelmintic resistance in nematode parasites of sheep in southern Latin America: Brazil. *Vet Parasitol* 1996;62:199–206.
6. Maciel S, Gimenez A, Gaona C, et al. The prevalence of anthelmintic resistance in nematode parasites of sheep in southern Latin America: Paraguay. *Vet Parasitol* 1996;62:207–212.
7. Van Wyk JA, Stenson MO, Van der Merwe JS, et al. Anthelmintic resistance in South Africa: surveys indicate an extremely serious situation in sheep and goat farming. *Onderstepoort J Vet Res* 1999;66:273–284.
8. Drudge JH, Leland SE, Wyant ZN, et al. Strain variation in the response of sheep nematodes to the action of phenothiazine. IV. Efficacy of single therapeutic doses for the removal of *Haemonchus contortus*. *Am J Vet Res* 1959;20:670–676.
9. Drudge JH, Leland SE, Wyant ZN. Strain variation in the response of sheep nematodes to the action of phenothiazine. II. Studies on pure infections of *Haemonchus contortus*. *Am J Vet Res* 1957;18:317–325.
10. Drudge JH, Szanto J, Wyant ZN, et al. Field studies on parasite control in sheep: comparison of thiabendazole, ruelene, and phenothiazine. *Am J Vet Res* 1964;25:1512–1518.
11. Conway DP. Variance in the effectiveness of thiabendazole

against *Haemonchus contortus* in sheep. *Am J Vet Res* 1964;25: 844–846.

12. Uhlinger C, Fetrow J, Johnstone C. A field-evaluation of benzimidazole and nonbenzimidazole drugs in a herd of dairy goats. *J Vet Intern Med* 1988;2:113–116.

13. Craig TM, Miller DK. Resistance by *Haemonchus contortus* to ivermectin in angora goats (Erratum published in *Vet Rec* 1990; 127:66). *Vet Rec* 1990;126:580.

14. Miller DK, Craig TM. Use of anthelmintic combinations against multiple resistant *Haemonchus contortus* in Angora goats. *Small Rumin Res* 1996;19:281–283.

15. Miller JE, Barras SR. Ivermectin resistant *Haemonchus contortus* in Louisiana lambs. *Vet Parasitol* 1994;55:343–346.

16. Zajac AM, Gipson TA. Multiple anthelmintic resistance in a goat herd. *Vet Parasitol* 2000;87:163–172.

17. Terrill TH, Kaplan RM, Larsen M, et al. Anthelmintic resistance on goat farms in Georgia: efficacy of anthelmintics against gastrointestinal nematodes in two selected goat herds. *Vet Parasitol* 2001;97:261–268.

18. Uhlinger C, Fleming S, Moncol D. Survey for drug-resistant gastrointestinal nematodes in 13 commercial sheep flocks. *J Am Vet Med Assoc* 1992;201:77–80.

19. Coles GC, Bauer C, Borgsteede FHM, et al. World Association for the Advancement of Veterinary Parasitology (WAAVP) methods for the detection of anthelmintic resistance in nematodes of veterinary importance. *Vet Parasitol* 1992;44:35–44.

20. Barriga O. *Veterinary parasitology for practitioners*. 2nd ed. Edina, Minn: Burgess International Group Inc, 1997.

21. Coles GC, Giordano DJ, Tritschler JP II. Efficacy of levamisole against immature and mature nematodes in goats with induced infections. *Am J Vet Res* 1989;50:1074–1075.

22. Reinemeyer CR, Pringle JK. Evaluation of the efficacy and safety of morantel tartrate in domestic goats. *Vet Hum Toxicol* 1993; 35 (suppl 2):57–61.

23. McKellar QA, Benchaoui HA. Avermectins and milbemycins. *J Vet Pharmacol Ther* 1996;19:331–351.

24. McKenna PB, Watson TG. The comparative efficacy of 4 broad-spectrum anthelmintics against some experimentally induced trichostrongylid infections in sheep and goats. *N Z Vet J* 1987;35: 192–195.

25. Hennessy D. The disposition of antiparasitic drugs in relation to the development of resistance by parasites of livestock. *Acta Trop* 1994;56:125–141.

26. Elliott DC. Removal of *Haemonchus contortus*, *Ostertagia circumcincta* and *Trichostrongylus* spp. from goats, by morantel citrate, levamisole hydrochloride, fenbendazole, and oxfendazole. *N Z Vet J* 1987;35:208–210.

27. Sanyal PK. Disposition kinetics of albendazole in goat compared to sheep. *Indian Vet J* 1997;74:213–216.

28. Sangster N, Rickard J, Hennessy D, et al. Disposition of oxfendazole in goats and efficacy compared with sheep. *Res Vet Sci* 1991;51:258–263.

29. Ministry of Agriculture, Fisheries and Food. *Manual of veterinary parasitological techniques*. London: Ministry of Agriculture, Fisheries and Food, 1977.

30. Geary TG, Sangster NC, Thompson DP. Frontiers in anthelmintic pharmacology. *Vet Parasitol* 1999;84:275–295.

31. Hennessy DR. World Association for the Advancement of Veterinary Parasitology/Pfizer Award for Excellence in Veterinary Parasitology Research—my involvement in, and some thoughts for livestock parasitological research in Australia. *Vet Parasitol* 2000;88: 107–116.

32. Hennessy DR. Physiology, pharmacology and parasitology. *Int J Parasitol* 1997;27:145–152.

33. Craig T. Control of gastrointestinal nematodes of sheep and goats in North America, in *Proceedings*. Am Assoc Small Rumin Pract Symp Health Dis Small Rumin 1996;132–139.

34. Babish JG, Coles GC, Tritschler JP II, et al. Toxicity and tissue residue depletion of levamisole hydrochloride in young goats. *Am J Vet Res* 1990;51:1126–1130.

35. Hennessy DR. Modifying the formulation or delivery mechanism to increase the activity of anthelmintic compounds. *Vet Parasitol* 1997;72:367–382.

36. Van Wyk JA. Refugia—overlooked as perhaps the most potent factor concerning the development of anthelmintic resistance. *Onderstepoort J Vet Res* 2001;68:55–67.

37. Sangster NC. Pharmacology of anthelmintic resistance in cyathostomes: will it occur with the avermectin/milbemycins? *Vet Parasitol* 1999;85:189–204.

38. Crofton HD. A quantitative approach to parasitism. *Parasitology* 1971;62:179–193.

39. Sreter T, Molnar V, Kassai T. The distribution of nematode egg counts and larval counts in grazing sheep and their implications for parasite control. *Int J Parasitol* 1994;24:103–108.

40. Bath G, Van Wyk JA. Using the FAMACHA system on commercial sheep farms in South Africa, in *Proceedings* (CD-ROM edition). 5th Int Sheep Vet Cong 2001.

41. Malan FS, Van Wyk JA, Wessels C. Clinical evaluation of anaemia in sheep: early trials. *Onderstepoort J Vet Res* 2001;68: 165–174.

42. Shoop WL, Haines HW, Michael BF, et al. Mutual resistance to avermectins and milbemycins: oral activity of ivermectin and moxidectin against ivermectin-resistant and susceptible nematodes. *Vet Rec* 1993;133:445–447.

43. Molento MB, Wang GT, Prichard RK. Decreased ivermectin and moxidectin sensitivity in *Haemonchus contortus* selected with moxidectin over 14 generations. *Vet Parasitol* 1999;86:77–81.

44. Ranjan S, Wang GT, Hirschlein C, et al. Selection for resistance to macrocyclic lactones by *Haemonchus contortus* in sheep. *Vet Parasitol* 2002;103:109–117.