

***Anthelmintic Resistance:
An Examination of its Growing
Prevalence in the U.S. Cattle Herd***

*Executive Summary of the 2005
Anthelmintic Resistance Roundtable*



INTRODUCTION

When livestock producers use anthelmintic parasite-control products in their herd and fail to see a response, there are a number of factors to consider. Was the timing of use appropriate to minimize re-infection? Did the dosage match the weight of the animals? Or did the product fail to achieve a response because the parasite population has become resistant to the dewormer of choice?

The demands of maximizing production have led today's beef and dairy producers to adopt preventive control measures that include regular treatment of their cattle with an anthelmintic parasite-control product during the grazing season. This intensive management approach combined with environmental factors and dosing practices is believed to have resulted in the selection of parasites resistant to some classes of anthelmintic products.

Parasite resistance is a potentially costly problem and will likely continue to be a concern within the United States beef and dairy industries.

Anthelmintic resistance in cattle is becoming a worldwide problem. But, until recently, there was little or no documented research on parasite resistance to commonly used bovine anthelmintics in the United States. Meanwhile, countries with livestock numbers comparable to the United States have reported occurrences of resistance in areas where cattle producers extensively used dewormers. Parasite resistance is a potentially costly problem and will likely continue to be a concern within the United States beef and dairy industries.

To address this information void, Intervet, a leading global animal-health company, brought together the top experts in the field of parasitology for an in-depth, roundtable discussion on anthelmintic resistance in the United States.

As host of the 2005 Anthelmintic Resistance Roundtable, Intervet sought to open a dialog about resistance, its diagnosis, its economic effect on the U.S. cattle industry and solutions to prevent it.

This executive summary was generated from comments made during the five-hour roundtable discussion held in conjunction with the 2005 American Association of Veterinary Parasitologists (AAVP) annual convention in Minneapolis, Minn.

PARTICIPANTS:

Dwight Bowman, Ph.D. — *professor of parasitology, Cornell University*

Don Bliss, Ph.D. — *parasitologist at the MidAmerica Agricultural Research Center, Madison, Wis.*

Tom Craig, D.V.M. — *professor of parasitology, Texas A&M*

Louis C. Gasbarre, Ph.D.— *immunologist and research lead with USDA-ARS*

Bill Kvasnicka, D.V.M. — *parasitologist (retired Extension Veterinarian University of Nevada)*

Gil Myers, Ph.D. — *Myers Parasitology Services, Magnolia, Ky.*

Jim Miller, D.V.M. — *professor of parasitology, Louisiana State University*

Cliff Monahan, D.V.M., Ph.D. — *professor of parasitology, The Ohio State University*

MODERATOR:

Bert Stromberg, Ph.D. — *professor and associate dean for research and graduate programs, University of Minnesota College of Veterinary Medicine*

RESISTANCE IN THE U.S CATTLE HERD

To date, research of anthelmintic resistance around the world has focused primarily on sheep and goats. Researchers in the United States have documented resistance in horses as well. But only in the past couple of years have reports of resistance in U.S. cattle herds been documented and presented to the veterinary community.

One of the first cases documented in the United States was described by Dr. Lou Gasbarre, research leader with USDA's Agricultural Research Service, and Larry Smith, DVM, Smith Research and Development, Inc., Lodi, Wis., who studied a Wisconsin background operation where the owner noticed an apparent decrease in the effectiveness of his strategic anthelmintic program. Upon evaluating parasite loads, it was noted that treatment with ivermectin injectable, moxidectin pour-on, doramectin injectable, eprinomectin pour-on or albendazole oral did not result in parasite burden reductions of at least 80 percent.

"In the past two to three years, it has become evident that the modern anthelmintics upon which the American cattle industry relies have begun to show diminished efficacy," said Dr. Don Bliss, parasitologist at the MidAmerica Agricultural Research Center, Madison, Wis., who has monitored thousands of fecal samples from cattle throughout the United States over the past 20 years. Bliss said he sees examples of anthelmintic resistance on a daily basis.

HOW TO DIAGNOSE RESISTANCE

During the roundtable, a general consensus was developed that the fecal egg count reduction test (FECRT) remains the most practical tool to help parasitologists identify resistance to anthelmintics by nematodes.

"The FECRT can be used to examine whether or not we are seeing loss of efficacy with these drugs," said Dr. Dwight Bowman, professor of parasitology at Cornell University.

He pointed out that when they came onto the market, the drugs had to prove their efficacy in order to get approval.

Gasbarre noted that while fecal egg counts are a good measure of what is happening in groups of animals, it is not reliable in an individual animal. "If you are going to evaluate a failure based on just a couple of animals, I think you would be misusing the technology," said Gasbarre. "If you are going to look at a single animal, it should be tested by multiple samples, not just once."

In addition to what tests are used, the panel noted that a consistent method of testing is also important.

"Like a lot of parasitologists, I felt that if we got our samples seven days after treatment, we had a representative sampling," explained Dr. Gil Myers, owner of Myers Parasitology Services in Magnolia, Ky.

"We now know that with the avermectins, for example, we really need to be sampling about 14 days after treatment. We don't understand all the reasons for that, but in studies from Ohio, the results at 14 days were entirely different than at seven days. There were many more parasitized animals and many more parasite eggs found. In contrast, the cattle that were treated with the Safe-Guard® (fenbendazole) or Panacur® product, there's no difference between day 7 and day 14 egg counts."

It appears that avermectins do not kill adult worms as fast as benzimidazoles.

It was noted that USDA statisticians believe 17 animals, no matter what the herd size, is a good sample number. The test group, however, should consist of animals of similar age. Focusing on younger animals also provides the most accurate measure of parasite worm load, according to the expert panel.

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IDENTIFYING RESISTANCE

While the FECRT is a valuable tool to measure the parasite burden within an animal, the test itself doesn't define resistance. The panelists gathered at the Anthelmintic Roundtable discussed in detail not only what resistance is, but also what it is not.

"Resistance is selected for because it is a genetic switch. You are not changing something in the worm," explained Bowman. "By giving dewormers, we are not inducing resistance, we are simply providing an environment for the resistant [parasites] to flourish and multiply."

Dr. Cliff Monahan, professor of parasitology at The Ohio State University, further explained that users of dewormers are not creating mutants. "We are merely creating an environment where that particular genetic makeup survives," he said. "If we look at some of the drug treatments where it is 99.9 percent effective, .1 percent of the [parasites] survive, and they now have carte blanche to reproduce. So their genetic pool becomes the dominant pool."

The panel noted that resistance is not the development of "superworms." "I define resistance as the failure of an anthelmintic to adversely affect helminthes in a specific host as efficiently as it formerly had done so," added Dr. Tom Craig, veterinarian at Texas A&M University.

When a producer administers a parasite-control product and fails to see a result, the efficacy of that product is in question. To the producer, it was a product failure. The question becomes, why was the product not efficacious? Was it excessive parasite burden? Was the proper dose given for the animal's body weight? Was the timing wrong, allowing for re-infection through grazing? Or had the resistant parasites in the herd reached damaging levels?

CAUSES OF RESISTANCE DEVELOPMENT

Nematodes with the genetic makeup to withstand treatment are given the opportunity to flourish when susceptible nematodes are eliminated. It appears, however, that several environmental factors affect how quickly or how often resistant parasites flourish.

"We see a great deal of herd variation, and this stands to reason because no two cattle operations are managed the same or is their history of dewormer use the same," said Myers.

How producers handle the cattle, their stocking rate, age of cattle, pasture contamination level at the start of grazing and weather conditions all help determine parasite challenges more than location. It is generally accepted that the greater the parasite challenge, the harder it will be to have successful treatment. Preventing seasonal buildup of parasite contamination is important to preventing parasite resistance from developing within the animals.

Adding to the discussion on environmental factors, Dr. Jim Miller, professor of parasitology at Louisiana State University, noted that anthelmintic resistance is not contained to a certain region or area of the country. He noted that when dealing with resistance, one must look at the individual farm involved because what goes on there can be different from what goes on right down the road.

Of concern to the livestock industry when it comes to resistance is that there are limited tools in the parasite control toolbox. Only three major anthelmintic families are used in the United States, the endectocides, which are ivermectin, doramectin, eprinomectin and moxidectin; the benzimidazoles, which primarily include fenbendazole, oxfendazole and albendazole; and the imidazoles, which include levamisole and morantel tartrate. Use of imidazoles is very limited leaving only two classes to be used extensively.

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Frequent and repeated use of the same drug class of anthelmintic was determined to be a considerable risk factor for development of resistance. It was noted that producers are missing opportunities for improved production by deworming just with endectocides because of poor efficacy and the increased opportunity for resistance.

Another risk factor discussed by the panel was the effect of subtherapeutic drug levels on the survivability of resistant worms. It was reasoned that some parasites survived subtherapeutic levels of treatment that would have been eradicated by exposure to a full dose of the drug. The panel had concerns about endectocides that persist in the animal and pasture environment at low levels for an extended duration of time.

It was also noted that endectocide pour-ons have created a phenomenon of low and variable blood-serum levels compared with injectable formulations, which may allow resistant parasites to flourish. Inconsistent absorption rates and improper dosing compound the problem.

Myers pointed out that there are two simple practices that producers can do to decrease the risk of anthelmintic resistance. “Know the weights of the animals you are treating, and make sure you are treating them with the proper amount of the drug,” he said. “The literature clearly indicates that under-dosing can lead to drug resistance.”

The panel also sought to address what effect persistent activity — when a drug is present in the animal or environment for a prolonged period of time — had on the potential development of resistance.

Dr. Bill Kvasnicka, parasitologist and retired extension veterinarian from the University of Nevada, noted that persistent anthelmintic activity trials published as far back as 1995 discussed prolonged decreasing of blood levels. “This feature may protect animals from re-infection from some nematodes for up to four weeks or longer,” he noted, “but slowly decreasing concentrations of anthelmintic in an animal can select for resistance.”

“I have had the opportunity to test nearly every pour-on product sold today,” said Bliss. “Based on what I’ve found and what the World Association for the Advancement of Veterinary Parasitology (WAAVP) standards are for a dewormer, I believe we are seeing true parasite resistance with the endectocide pour-ons.

“We’ve had the persistent doramectin (Dectomax®) products out in the market now for maybe 10 years or less,” continued Bliss. “We are seeing a number of reports of worldwide potential resistance product failure. Persistent products may very well trigger resistance more quickly.

In contrast, fenbendazole (Safe-Guard) has been on the market for over 20 years with only one or two reports of anthelmintic resistance. Safe-Guard works fast and doesn’t linger in the animal or the environment for a prolonged period of time.

Gasbarre noted that from a theoretical standpoint, the more selective pressure you place on a population, the more likely you are to select for traits that confer an advantage. So if the loss of efficacy is due to selection of a different population, any enhancement of persistence or long-lasting selection theoretically would result in resistance arising even faster.

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PROJECTING AN IMPACT

As producers increase their use of anthelmintics and expose them to more parasites, more resistant parasites likely will evolve.

“We find parasites are present on nearly all operations and are one of the most important deterrents to efficient production that producers have to deal with,” noted Bliss. “The most recent production-based deworming trials show that as cattle become more efficient in terms of their genetic potential, the more important parasites become in terms of the economic loss sustained.”

Resistance takes a long time to develop, and it is a gradual process, said Myers. “The process takes time, and producers are not going to have a real clear-cut red light go on and say ‘Bingo, the worms are resistant.’ That’s not going to happen. What we will see, and what producers are beginning to report, is ‘The calves are just not gaining.’”

Monahan said he believes the spread of the drug resistance across the country will be under the radar for most producers. “But when it hits an individual producer it won’t be a gradual loss of productivity,” he said. “It’s going to hit the individual producer extremely hard.”

“I believe producers are using anthelmintics more and more because they are convinced of the profitability of using them, added Gasbarre. “Any increased number of times that parasites are exposed to drugs should select for more resistance.”

The panel agreed that as the trend toward more intensive operations continues, the industry could expect to see the problem of anthelmintic resistance grow.

Also of concern is that parasites have a negative effect on immunity, according to research done by Gasbarre and his team at the USDA Bovine Functional Genomics Laboratory.

Research has shown that while parasite burdens can trigger an immune response in cattle, response can ultimately shut down immune response to other infectious agents. The roundtable participants recognized that the economic value of having a strong immune system in animal production is extremely high for today’s high-performance cattle. The effect of parasites on the immune system is another example of how important it is to have the dewormers working properly.

LOOKING AHEAD

Livestock producers have become accustomed to being able to control parasites with easy-to-use and inexpensive anthelmintic dewormers, so the economic impact of uncontrolled parasites in livestock does not register as a top priority. Meanwhile, modern management practices that include higher stocking densities and intensive grassland management mean parasites potentially represent a more serious threat than they did before the introduction of broad-spectrum anthelmintics.

It is unlikely that any new anthelmintics will be introduced in the near future, so loss of efficacy of existing products could pose severe problems for the cattle industry. Anthelmintic resistance is already a serious problem in some parts of the world, not just in sheep and goats but also in cattle. With that in mind, the participants of the Anthelmintic Resistance Roundtable identified important next steps necessary to address and slow the advancement of resistance in the U.S. cattle herd.

First, the panel determined that a standardized protocol for testing parasite burden should be established within the cattle industry against which all deworming practices can equally be measured and evaluated. The panelists agreed that a committee should be set up to identify the best testing protocol.

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Second, the panel recommended that a shared database is needed to effectively monitor resistance development.

“I think it is important that we understand and we get some kind of handle on exactly how widespread the issue of drug resistance is in this country,” said Gasbarre. “There have been a couple of published reports and other anecdotal reports, but we really don’t have any idea of what is really out there. We don’t know what drugs work where, and why they still work, and why the ones that don’t work don’t work.”

Third, it was agreed that increased awareness is necessary to encourage producers to work with their veterinarians to monitor what their dewormer is doing by testing their herd regularly in a consistent manner.

Participants noted that producers within the industry may not recognize the significance of resistance problems until it hits them in the pocketbook, but producers need to be educated and made aware of the warning signs for anthelmintic resistance.

“I don’t think anything is going to happen until they recognize the problem themselves,” explained Gasbarre. “But I think we can make them aware that this is a potential problem that they ought to look for. Otherwise, they won’t notice it until it’s too late.”

Fourth, the panel concluded that an updated protocol for strategic deworming is needed. It was noted that a parasite control program that seeks total suppression leads to resistance development at a rapid pace. A program to reduce pasture contamination and keep the parasite population at an economically acceptable level would extend product efficacy and maintain profitability in the long run.

A second meeting of leading parasitologists and veterinary researchers will be held in August 2006 to serve as a workshop for addressing resistance issues identified by the Anthelmintic Resistance Roundtable.

Related Research on Anthelmintic Resistance

- Barnes, E.H., Dobson, R.J., Stein, P.A., LeJambre, L.F., Lenane, I.J. 2001. Selection of different genotype larvae and adult worms for anthelmintic resistance by persistent and short-acting avermectin- and moxidectin-selected strains. *Int. J. Parasitol.* 31, 720-727.
- Bliss, D.H., Kvasnicka, W.G., 2004. Failure of avermectins to control an outbreak of parasitic gastro-enteritis in a cow/calf herd *Proceedings of the 49th American Association of Veterinary Parasitologists*. Philadelphia, July 24-28 (Abstract 42).
- Coles, G.C., Jackson, F., Pomroy, W.E., Prichard, R.K., von Samson-Himmelstjerna, G., Silvestre, A., Taylor, M.A., Vercruyse, J., 2006. The detection of anthelmintic resistance in nematodes of veterinary importance. *Vet. Parasitol.* 136: 167-185.
- Gasbarre, L.C., Smith, L.L., Lichtenfels, J.R., Pilitt, P.A., 2004. The identification of cattle nematode parasites resistant to multiple classes of anthelmintics in a commercial cattle population in the US. *Proceedings of the 49th American Association of Veterinary Parasitologists*. Philadelphia, July 24-28 (Abstract 44).
- Myers, G.H., 2005. Avermectin Resistance in an Ohio Beef Cattle Herd. *Proceedings of the 50th American Association of Veterinary Parasitologists* Minneapolis, MN. (Abstract 44).
- Smith, L.L., L.C. Gasbarre, 2005. Effect of single or combinational drug treatment on EPG values in a commercial cattle operation harboring nematode parasites resistant to multiple classes of anthelmintics. *Proceedings of the 50th American Association of Veterinary Parasitologists*. Minneapolis, MN. (Abstract 47).

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