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Herding the U.S. cattle industry toward a paradigm shift in parasite control

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ABSTRACT

Contemporary management of nematode parasitism in cattle relies heavily on a single class of drugs, the macrocyclic lactones (MLs). The potency and convenience of the MLs, along with the low cost of generic formulations, have largely supplanted the need for critical thinking about parasite control, and rote treatment has become the default 'strategy'. This approach to parasite control has exerted substantial pressure to select populations of nematodes that can survive recommended dosages of ML products. Although macrocyclic lactones have been available for over 30 years, putative ML resistance in U.S. cattle was not reported until fairly recently. This pattern begs the question, "Is this a new, emergent problem, or an old issue that is finally commanding some attention?"

The implications of bovine anthelmintic resistance should stimulate a paradigm shift for U.S. cattle producers and their advisors. However, there are significant obstacles to changes in current thinking. It is anticipated that cattle producers will be extremely reluctant to abandon historical practices unless they can be convinced of the value of alternatives that are communicated through targeted education, practical demonstrations, economic analyses, and scientific evidence. Historically, the management advice of practitioners has not relied strongly on parasite epidemiology, and practitioners may not have the knowledge to implement evidence-based recommendations. Pharmaceutical companies could play a significant role in helping to shape and shift the thinking about sustainable use of anthelmintics. However, their primary responsibility is to stockholders, and they have strong economic incentives for maintaining the *status quo*.

It is complicated and difficult to change attitudes and practices, and it will take more than logic or fear to shift the parasite control paradigm in the U.S. cattle industry. Achieving that goal will require collaboration among stakeholders, a consistent, straightforward and understandable message about resistance, and recommendations that are practical as well as effective. But if we hope to ultimately influence producers and their advisors, we need to be conscious of how individuals and groups change their minds.

1. Introduction

> "Let me be clear about this. It is never easy to bring about a change of mind; and it is even more difficult to replace a simple way of thinking about a matter with a more complex way." (Gardner, 2004)

Uniformity is a time-honored feature of most cattle management systems. Different age groups are housed and fed separately, and all members of a cohort are managed identically. This overarching strategy was applied to parasite control soon after the first modern anthelmintic (thiabendazole) became available for bovine use in the

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early 1960s. Within a decade of its launch, thiabendazole and other anthelmintics were being administered prophylactically to entire groups of grazing cattle to exploit the epidemiology of nematode parasitism in cattle (Cornwell et al., 1971).

Although management strategies for nematode control in livestock relied very heavily on anthelmintic drugs, the introduction of ivermectin in 1981 elevated parasite control to new levels on many fronts (Geary, 2005). This compound was the inaugural member of the macrocyclic lactone (ML) class, which also includes abamectin, doramectin, eprinomectin, and moxidectin for cattle. As a class, these drugs are extremely potent (effective at low dosages), provide very high efficacy against a broad range of nematode internal and arthropod external parasites, achieve persistent blood levels, and can prevent reinfection by certain parasites for weeks after a single treatment.

The MLs can be delivered *via* injectable, oral, or topical routes, and all have an excellent safety profile. Their unprecedented efficacy and other properties opened new markets and new management options for parasite control. Other chemical classes, such as the benzimidazoles and imidazothiazoles drifted backwards in market share. This was likely due to differences in attributes and efficacies between the new compounds and the old; notably the lengthy egg reappearance periods of the MLs and their unprecedented efficacy against internal and external parasites. Consumer preference narrowed even more when topical ML formulations increased the convenience and lowered the labor costs of treatment. Pour-ons rapidly displaced oral formulations such as drenches and boluses, and injectable formulations also lost popularity, presumably due to beef quality initiatives, and the allure of easy topical administration. Contemporary US market data reflect that MLs are the preferred anthelmintic option. In 2007, MLs represented 98% of reported sales (Fort Dodge Animal Health, personal communication, 2008), and although they have recently lost ground to the benzimidazoles, still represented 82% of sales in 2012 (Boehringer Ingelheim Vetmedica Inc., personal communication, 2013). Market percentages were similar in New Zealand in the mid-2000s (McArthur, personal communication) Interesting, imidazothiazoles merit no mention in US market information and they are only sporadically available in this marketplace.

With consumer demand restricted to a single chemical class, and a strong preference for convenient routes of administration, parasite control was often reduced to a recipe and a scheduled appointment on the farm calendar (USDA, 2010). An FAO report from 2004 noted widespread promotion of the idea that parasite control was simple and could be accomplished by using broad spectrum anthelmintics in the absence of epidemiologic considerations. Consequently, this erroneous assumption, or false sense of security, served to delay or prevent the epidemiologic studies which provide the basis for effective control recommendations (FAO, 2004).

Industry-wide dependence on the potency and spectrum of a single class of chemicals, along with complacent adoption of rote programs, provided the necessary conditions for a perfect storm. In many parts of the world, these very practices contributed to a shift in parasite populations, favoring those that carry the genetics to survive treatment with MLs. After only three decades of selection pressure, invertebrate parasites managed to circumvent the battle plan of *Homo sapiens*. It is a fair assessment that the parasites have progressed further than humankind in our interactions due to their capacity for change. Mother Nature's manifesto contains no stipulations for an 'us or them' mentality; that perspective was supplied by production agriculture. The time is long past to consider strategies for coexisting with and managing parasitism in ways that preserve and prolong the efficacy of existing and future anthelmintic classes. The purpose of this paper is twofold: (1) to offer a brief review of anthelmintic resistance in cattle; and (2) to discuss the challenges faced in encouraging awareness and change in practices so as to extend the lifespan of anthelmintic drugs in US cattle operations.

2. Nature of anthelmintic resistance

> "It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change." (Charles Darwin)

For purposes of the present discussion, anthelmintic resistance will be defined simply as a measurable decrease in the efficacy of a compound against parasitic species and stages that were previously susceptible (Coles et al., 2006). Resistance is a phenotypic manifestation of a heritable, genetic trait. The genetic bases and modes of inheritance of resistance are complex and differ widely among the various classes of compounds, but positive selection occurs whenever worms carrying resistant alleles are exposed to an anthelmintic to which they have lost their susceptibility. Individual nematodes that survive an anthelmintic treatment are afforded a transient reproductive advantage in the absence of competition by susceptible worms in the alimentary environment. This advantage persists until life cycle features prevail or anthelmintic levels wane to levels that will allow reestablishment of susceptible parasites. Resistant worms transmit their unique, heritable traits to the next generation, and thereby incrementally increase the frequency of their genetic alleles in the general population (Leathwick, 2004a). Furthermore, it may be clinically significant that the numbers of infective stages available are greater than would be present following effective therapy.

Resistant worms have no inherent advantages, such as superior fitness, until the selection pressure of anthelmintic treatment is applied. Elimination of susceptible worms affords reproductive exclusivity to the resistant surviving worms until the gut is repopulated by ingested worms. One of the most effective ways to accentuate this reproductive advantage is to continually use the same anthelmintic class. Individual worms are initially resistant to only one class of anthelmintics, so when "drug A" is used, they survive, but if "drug B" were introduced, they would be removed like the rest of the susceptible population. Thus, the reproductive advantage of resistant worms would be favored if "drug A" were used exclusively (Leathwick et al., 2001).

Another potent selection pressure is frequency of treatment. If a resistance-prone drug is used often, especially at intervals shorter than the egg reappearance period of the target parasite, susceptible genotypes will never have an opportunity to reproduce. Thus, the offspring of the entire population may arise solely from resistant worms. Yet other selection pressures for ML resistance have been attributed to the pharmacokinetic properties of this chemical class, such as its persistence and the inevitable subtherapeutic blood levels during the decay phase (Leathwick and Sutherland, 2002; Leathwick, 2004a).

3. *Refugia* and bovine resistance

"The solution to pollution is dilution."

By far, the greatest selection for resistance can be ascribed to how these drugs are used in the field. In addition to exclusive and excessively frequent application, we can add specific control strategies that exploit the persistent properties of the MLs and apply them at times when the risk of reinfection is low. One example is the recommendation to treat grazing cattle in southern temperate climates during mid-summer, when hot, dry conditions reduce infective larvae to their annual nadir. Although some target parasites are seasonally arrested within the host at this time, they are nevertheless susceptible to the activity of ML dewormers. Deworming animals and moving them to a 'clean' pasture is a strategy that may make logical sense to a producer but it has been cited frequently as a practice that can accelerate the selection for resistance (Leathwick, 2004b). Yet another example comes from Western Australia, where *Teladorsagia circumcincta* in sheep developed resistance to MLs very rapidly in response to the practice of 'summer drenching' (Besier, 1996, 2001; Besier and Love, 2003). Initially these strategies were very effective, but subsequent developments have pointed out their inherent shortcomings in terms of minimizing *refugia*.

The term *refugia* denotes any subpopulation of parasites that is not exposed to an anthelmintic at the time of treatment. This includes larval stages in the environment, parasites of herd members that were not treated contemporaneously, and parasitic stages within the animal that are not exposed to the treatment due to physiologic or pharmacokinetic factors. The subpopulation left *in refugia* represents a reservoir of unselected genes, including those which impart anthelmintic susceptibility. *Refugia* provides a source of susceptible worms to mate with resistant worms. When *refugia* is increased, the rate of resistance development will be reduced. The importance of maintaining adequate *refugia* has been confirmed by field studies with parasites of sheep (Martin et al., 1981; Waghorn et al., 2008; Leathwick, 2012), as well as by computer simulations which mimic sheep parasite dynamics (Barnes et al., 1995). Although parasite *refugia* has been promoted as potentially beneficial to bovine parasite control, no field or computer modeling studies have demonstrated the validity of this concept for bovine nematodes (Leathwick, personal communication, 2013). Given the similarity of trichostrongylids of cattle and small ruminants, it remains a useful working hypothesis to consider *refugia* as a beneficial factor in delaying bovine anthelmintic resistance.

The current practice of segregating cattle management by age class means that the parasite populations of an entire group share the same selection pressures, and few opportunities exist to maintain genetic diversity. Until definitive evidence is published, how might producers attempt to provide *refugia* for their herds? Mature cows represent a potential source that is readily at hand in breeding operations. During their second grazing season and beyond, cattle generally develop significant immunity to gastrointestinal nematodes and have minimal parasite control requirements. Leaving such animals untreated represents a source of potential *refugia*. One could allow older animals to cover pastures prior to populating them with weaned calves, so as to 'seed' the forage with eggs from untreated worms. Similarly, one could commingle weaned calves and older cows, although this runs counter to the rigorous monoculture grazing practiced by stocker producers. Selective treatment is another possibility, in which a certain proportion of the herd remains untreated, and those individuals will contribute eggs from unselected parasites to the pasture.

Leaving animals untreated is anathema to a producer who equates a parasite burden with lost production. However, Leathwick (personal communication, 2013) reports that 'nearly every sheep farmer in New Zealand is now familiar with the concept of *refugia*. Once they understand why it works, they are able to find ways to implement it in their systems.' Having experienced firsthand pushback by NZ farmers when the concept of *refugia* was first floated, it is remarkable that those once-reluctant producers are today conversant with it as a management strategy (McArthur, personal communication, 2013).

As we present the importance of anthelmintic sustainability to American cattle producers, the concept of *refugia* merits discussion as a component of a holistic parasite management strategy. Part of our challenge will be making it understandable and identifying practical options for its implementation.

4. Consequences of resistance

"A burglar who respects his art always takes his time before taking anything else." (Henry Porter)

The pathogenicity of nematode parasitism in domestic animals has a distinct quantitative component; the more parasites present, the greater the probability that disease or at least suboptimal performance will ensue. Certain parasites of cattle are widely recognized as valid pathogens when sufficient numbers are present, including *Haemonchus placei* and *Ostertagia ostertagi* in the abomasum, and *Nematodirus* spp. in the small intestine. Other genera, including *Trichostrongylus, Oesophagostomum*, and *Trichuris* could be added to this list, but these worms cause disease only infrequently in cattle. Several species of *Cooperia* (*punctata, pectinata, oncophora*, and *surnabada*) are highly prevalent in cattle less than 2 years of age (Yazwinski and Tucker, 2006). Although *Cooperia* spp. have been shown to cause disease in naïve calves following inoculation with large numbers of larvae (Satrija and Nansen, 1992), overt clinical signs rarely develop following natural infection. Rather, damage by *Cooperia* is relegated to impaired performance, measured as decreased weight gain and feed efficiency (Familton, 2001; Fiel et al., 2011; Stromberg et al., 2012), and perhaps increased susceptibility to concurrent pathogens (Parkins et al., 1990; Schutz et al., 2012).

To date, resistance of cattle nematodes in the U.S. has been reported for *Haemonchus contortus, H. placei, Cooperia punctata, C. oncophora, C. spatulata* (Gasbarre et al., 2009b), and *O. ostertagi* (Edmonds et al., 2010). In the continental U.S., *Haemonchus* is geographically restricted to southern temperate and subtropical climates. However, it can be transported to all regions *via* infected cattle, and is capable of natural amplification on North American pastures during the summer grazing season. The survival of infective stages of *Haemonchus* during northern temperate winters is tenuous, but parasitic larvae could over-winter in arrested development within the abomasa of host animals. It is also feasible that cattle could be cross-infected by *H. contortus* originating from indigenous ruminant species, such as sheep, goats, and deer. Although *Cooperia* spp. are widely disseminated among cattle populations in all climates, mature cattle usually harbor only modest numbers as a consequence of acquired immunity. *O. ostertagi* is widely distributed, but to date, resistant populations in the US have been reported from only one location in the Pacific Northwest (Edmonds et al., 2010).

In small ruminants, resistance in *H. contortus* is often accompanied by morbidity or mortality, in at least some portion of the flock. In other words, anthelmintic failures against *Haemonchus* become clinically evident. Cattle can also develop clinical haemonchosis in favorable climates and under intensive grazing conditions, but weight loss and hypoproteinemia are the usual signs, as compared to the acute anemia and death seen in sheep or goats. In horses with resistant cyathostomin nematodes, clinical signs may be very subtle or non-existent, at least in herds provided with good nutrition and stress-free management. Because equine cyathostomins are not major pathogens, anthelmintic resistance in horses often remains clinically imperceptible. The resistance situation in cattle nematodes, at least with *Cooperia* spp., bears more clinical similarity to equine cyathostomins than to the trichostrongylids of small ruminants. But, morbidity and mortality could assail the cattle industry if resistant populations of *O. ostertagi* should eventually become predominant.

5. Detection of resistance

"If we don't look, we won't find."

The only method presently available for detection of anthelmintic resistance in cattle nematodes is the fecal egg count reduction test (FECRT). The mechanics of this test are similar to FECRT performed for small ruminants and horses, but cattle present the challenge of having lower FECs than sheep and goats. No definitive guidelines have been established to standardize the FECRT procedure for bovines. Limited information is available on sample size (number of individuals or percentage of a herd), minimum pretreatment egg count for inclusion in the analysis, quantitative egg counting techniques and sensitivity thereof, or cut-off values (percentage efficacy) for determining resistance (Coles et al., 2006; Sutherland and Leathwick, 2011). Several papers have been published which compare and evaluate the effect of these variables on FECRT results (Levecke et al., 2012a,b,c,d). Another complicating factor in evaluating post-treatment FECs is the propensity of MLs to suppress fecal egg production, creating falsely elevated efficacy values in the FECRT. There can be considerable disparity between efficacy determined by FECRT and true efficacy as determined by post-mortem total worm counts (DeGraef et al., 2012; Yazwinski et al., 2013; Wrigley and McArthur, 2007).

It should also be remembered that trichostrongylid populations of cattle are diverse, and typically include genera and species that are susceptible to the anthelmintic being tested. Coproculture or polymerase chain reaction (PCR) analysis of eggs passed in feces post-treatment would help to identify the surviving genera, but quantitative extrapolation would be impossible.

In vitro assays have been evaluated to a limited extent for bovine nematodes. A larval development assay (LDA) is marketed as DrenchRite® (Horizon Technology, Roseville, Australia) for use in small ruminants, and this technology has recently been investigated for nematodes of cattle (Demeler et al., 2012). A larval migration inhibition assay (LMIA) has also been developed for trichostrongylids of sheep (Kotze et al., 2006), but it has undergone only limited appraisal for cattle nematodes (Demeler et al., 2010a,b).

Regardless of the testing methodologies available, the history of anthelmintic resistance, especially in horses, demonstrates that resistance will never be detected until one looks for it. Because the anticipated impact of resistant parasites in cattle is usually subclinical, producers cannot identify unsatisfactory performance without carefully monitoring weight gain and other production parameters. Historical performance data from recent years may not prove to be a particularly reliable yardstick, given that ML-resistant bovine nematodes apparently have been present in the U.S. since at least 2003 (Gasbarre et al., 2009b). Production records from a decade ago may provide a more accurate indicator of expected performance for individual operations, but other management changes that were implemented during the interim could confound accurate interpretation.

Resistant nematodes have caused clinical disease in some cattle herds under concentrated management. Investigation into ill-thrift and diarrhea in an intensively-grazed stocker operation in Wisconsin led to the first report of ML resistance in U.S. cattle (Gasbarre et al., 2009b). A more typical resistance scenario involves stocker cattle that appear healthy, yet achieve virtually no weight gain after grazing good quality pastures for several months (Reinemeyer, personal communication, 2013).

The impacts of anthelmintic resistance in cattle are real and significant, but are manifested chiefly in economic terms. The costs of subclinical parasitism are akin to embezzlement, wherein production potential is stolen surreptitiously, and goes unnoticed until monitoring is implemented. But whether the metrics are biologic or economic, resistance will remain undetected as long as available parameters remain unmeasured.

6. Producer resistance to change

"You keep samin' when you oughta be a'changin'." (Hazlewood/Sinatra, "These Boots Are Made for Walkin'," 1966)

It is a safe assumption that relatively few U.S. cattle producers have changed their parasite control practices in recent years. This is not surprising, given the lack of a compelling message about anthelmintic resistance. The prevalence and distribution of resistance in U.S. cattle herds remains unknown, and its impact on performance has not been adequately characterized (Kaplan, 2004).

Most producers, even those currently harboring resistant nematodes in their herds, probably perceive no need for change. Unless resistant parasites cause clinical disease, they will continue to fly under the radar until some sort of biological monitoring is adopted. But in most cattle operations, monitoring of anthelmintic efficacy and associated production responses is presumably uncommon, if not altogether rare. This assertion is corroborated by data from the 2007–2008 USDA National Animal Health Monitoring Service (NAHMS) report (USDA, 2010), which cites that only 5.7% of beef operations surveyed had performed any testing of fecal samples to evaluate parasite burdens. Furthermore, less than 1% administered dewormers on the basis of fecal testing. The NAHMS study revealed that 85% of the beef producers surveyed dewormed by schedule rather than by using diagnostic means such as fecal egg counts or weight gains (USDA, 2010). Yet another disincentive for diagnosis is the fact that generic ML formulations have rendered rote treatment far less expensive than selective monitoring.

Ardent proponents of monitoring may be non-existent in many locales. The ready, over-the-counter (OTC) availability of inexpensive cattle dewormers has kept many veterinarians out of the parasite control conversation. In the absence of diagnostic monitoring and sales revenues, parasite management offers little profit opportunity for bovine practitioners. Without motivation for local involvement, commercial advertising and pharmaceutical sales representatives will remain the major sources of information about parasite control for producers and their veterinarians.

The continued intensity of anthelmintic use despite a lack of data regarding current efficacy suggests that related management decisions are justified by what can be termed 'uncontrolled experiments.' If subjective assessments (*e.g.*, fecal consistency, appearance of cattle, poor performance) are the primary indicators of anthelmintic performance (USDA, 2010), then a producer's perceived need for change may well be low. Colloquially, "If it ain't broke, don't fix it."

This attitude suggests that producers may continue to administer anthelmintic treatments despite a lack of evidence regarding their efficacy, and some would likely persist even if the drug had been demonstrated to be worthless. Oddly, the majority of beef producers surveyed in the NAHMS study noted that efficacy was 'very important' in their criteria for selecting a deworming product, yet very few indicated that fecal testing was utilized in their operations (USDA, 2010). This implies that their evidence for efficacy is extrapolated from marketing materials or generated by subjective evaluations, both of which are poor indices of performance for any livestock population.

Perhaps production enhancement is perceived as entirely separate from anthelmintic efficacy. The properties of bovine anthelmintics that are recognized by the Food and Drug Administration are rendered succinctly in the label claims of the respective product. Typically, bovine dewormers have been approved for "removal and control" or "treatment and control" of specific internal parasites or disease conditions that they cause. In stark contrast to these specific and limited criteria, the same products are often viewed by cattle producers as performance enhancers. Exclusivity and excessive frequency, the historical practices that fostered the development of resistance to bovine anthelmintics, undoubtedly were implemented in pursuit of greater productivity and profit.

A corollary of the flawed notion that frequent anthelmintic use guarantees greater profitability is the assumption that all parasitism is therefore pathogenic, at least to the extent that any infection will have a negative economic impact even if it does not result in clinical signs of disease. This is a simplistic and inaccurate characterization of bovine parasitism, but it represents a view that has been promoted widely by pharmaceutical manufacturers for decades. This argument ignores the evidence that cattle develop effective acquired immunity against nematode infections at some point during their second grazing seasons (Ploeger et al., 1990). Thereafter, although mature cattle may not remain nematode-free, the numbers of worms they harbor, the magnitude of egg production by abbreviated adult populations, and the extent of accompanying pathogenicity are all greatly reduced (Yazwinski and Tucker, 2006).

The marketing departments and technical service divisions of many pharmaceutical companies have funded extensive efforts to document and measure the potential benefits of anthelmintic treatment in adult cattle. Thus, deworming has been reported to significantly improve milk production in dairy cattle (Nødtvedt, 2002), weaning weights of suckling beef calves, and reproductive parameters of beef cows (Cheramie, 2013; Stromberg et al., 1997). These benefits have been widely disseminated (Charlier et al., 2009), but producers must critically evaluate whether these potential outcomes represent optimal investments of management dollars in view of their inherent selection for anthelmintic resistance. Although deworming mature cows and suckling calves might provide a return on investment under certain circumstances, these same practices will always reduce *refugia* on the farm. Mature cows would develop clinical parasitism only rarely if left untreated, and those that do so under acceptable management conditions are exquisitely susceptible, and their genetics should not be perpetuated in the herd. Unlike shepherds and goatherds, many modern cattle producers have never observed clinical parasitism. So for them, worms may not represent a clear and present danger; they remain an intangible bogeyman that may or may not harm their herds.

The NAHMS survey determined that a significant number of producers administer anthelmintics to cattle either before weaning or after maturity, and thereby inadvertently reduce *refugia*. In rebuttal, one could propose a hierarchy of 'need' or potential benefit, to be gained from anthelmintic treatment in various types of cattle management. For the diverse beef industry, the greatest needs are for stocker cattle and replacement heifers, followed by herd bulls, then suckling calves, and lastly, brood cows. For dairy, the priorities are replacement heifers, weaned calves raised on pasture, and adult cattle. Cattle raised totally in confinement have minimal need for anthelmintic treatment, and feedlot calves have little to fear from nematodes if effectively dewormed upon arrival. Producers could reduce their overall expenditures on anthelmintics, and simultaneously increase *refugia*, by selectively deworming only those classes or management systems of cattle with the greatest need.

Perceptions commonly trump scientific proof, especially when finances are involved. One could predict that a significant portion of cattle producers would obstinately resist any management practices that are perceived to compromise their bottom lines. Until alternate evidence can be provided, cattle producers will not likely be willing to surrender 'guaranteed income'. Compelling reasons for change must be related and explained, and some alternative of equivalent, perceived value must be available at hand to supplant the literal cash cow of current practice. The preservation of anthelmintic efficacy, although a noble and scientifically valid principle, will not provide sufficient motivation for cattle producers to implement 'soft' management changes such as monitoring or increasing *refugia* on their farms that carry a potential cost in productivity.

What will it take to convince consumers and advisors to begin thinking about progressive parasite management? Behavior shifts when the pain of staying the same is greater than the pain of change. Rightly or wrongly, most cattle producers currently believe that anthelmintic resistance is not causing any pain in their operations (Kaplan, 2004). Until monitoring is initiated, they won't know if their favorite drug is no longer working optimally, or if they are leaving money in the pasture in terms of lost productivity. Even in New Zealand, where the conversation about resistance has been open and ongoing for some time, farmers must be given a very compelling reason to change and/or shown an alternative to current routines that is practical and feasible (Leathwick, personal communication, 2013).

The veterinary parasitology community is well aware of the threat posed by diminished efficacy of our most potent class of anthelmintics. However, those concerns cannot reach the producer until scientists and advisors develop a cohesive message about monitoring, management, and *refugia*. Among producers, a few early adopters have already heard the warning bell, and are conducting limited trials on their own premises (Gasbarre et al., 2009a,b). These progressive cattlemen need and deserve technical assistance because ultimately, they will influence their peers to a greater extent than the animal health experts.

Even with hard evidence of resistance, such as a measurable loss in production or persistent high egg counts after treatment, the human side of change must be considered. It can be very difficult to overcome the gravitational pull of tradition or peer pressure. Discussions about efficacy and resistance may be new, foreign and threatening, whereas the herd mentality of maintaining the *status quo* is familiar and reassuring.

7. Commercial resistance to change

> "... it would seem obvious that no country or industry group should consider themselves immune from the threat of anthelmintic resistance." (Sutherland and Leathwick, 2011)

The animal health industry has discovered, developed, and marketed numerous effective parasiticides for cattle over the past five decades. This collection of drugs has yielded dramatic benefits in terms of animal health and profitability, but simultaneously they generated extremely high expectations among livestock producers. One could argue that the MLs as a class have set the bar unrealistically high for future anthelmintic competitors (Geary, 2005).

All corporate entities have a responsibility to their stockholders to market their products aggressively, and the pharmaceutical industry has been extremely successful at doing so with cattle dewormers. The 2009 bovine anthelmintic market in the U.S. was estimated at $134 million (Federal Trade Commission, 2009), and the global parasiticide market is many times larger (Campbell et al., 2009). The macrocyclic lactone class comprised approximately 88% of bovine anthelmintic sales in the U.S. during 2009, and benzimidazoles captured the remainder (12%) (Federal Trade Commission, 2009).

Since 1998, however, when the first generic ivermectin formulation[1] was approved, anthelmintic manufacturers have watched their margins and markets erode due to competition from lower-cost alternatives. It is a highly prevalent notion among consumers that generic versions of any product are somehow substandard. Generic drugs in the U.S., however, must meet rigorous FDA criteria, including bioequivalence, chemical identity to the pioneer compound (*i.e.*, the first approved product of a given drug and formulation), and production in compliance with Good Manufacturing Practices. Generic competition poses a very serious challenge to pioneer manufacturers, so it should come as no surprise that they rarely disabuse consumers of their innate suspicions about generic drugs. Studies have been published in which pioneer and generic anthelmintics were compared directly (Anziani et al., 2001; Yazwinski et al., 2004, 2009a,b; Tarpoff, 2012). In some of these studies, generic ivermectin products were found to be less efficacious than the pioneer formulation (Anziani et al., 2001; Yazwinski et al., 2004). Others reported equivalent efficacy and/or negligible differences in performance (Yazwinski et al., 2004, 2009a; Tarpoff, 2012), or better average daily gains in feedlot animals treated with a generic

[1] Phoenectin, ANADA 200-219, Phoenix Scientific, St. Joseph, MO.

product (Tarpoff, 2012). In the absence of a consensus of evidence, generic competition will likely continue to be addressed by innuendo. Parasites develop resistance to drug classes and modes of activity, not to brand names, so parsing the details of generic product performance is focusing on the wrong piece of the puzzle.

In addition to technical support for their respective products, the pharmaceutical industry has long been the major provider of advice about parasite control in general. Producers receive the majority of their information from commercial advertising, and pharmaceutical sales personnel are likely the number one supplier for bovine practitioners. Both sources are obviously biased. The recommendations of industry are designed to sell the most doses or greatest volumes of product, but the majority of practitioners and nearly all producers lack the parasitologic sophistication to question or challenge such advice.

As a case in point, pharmaceutical marketing departments have done little to discourage frequent and exclusive treatment, which are the two most common facilitators of anthelmintic resistance. Furthermore, the pharmaceutical industry continues to develop and produce ML products with ever-increasing periods of persistent activity, despite a sizeable body of evidence that long-acting products increase the risk of resistance development (Leathwick, 2004a; Leathwick, personal communication, 2013).

Another prevalent commercial strategy is to contend that the passage of any nematode eggs in bovine feces is unacceptable, and that a positive fecal result augurs potential disease and hidden production losses. This assertion ignores the epidemiologic details of bovine parasitism, and immune, mature cattle and suckling calves are purported to be as much at risk of parasitic disease as stockers maintained at high density. Such misinformation has been delivered effectively for years at the local level as a companion to manufacturer-sponsored, complimentary fecal examinations. The economic benefit of deworming these classes remains debatable, but the selection pressure exerted by minimizing *refugia* is undeniable.

The pharmaceutical industry would be understandably reluctant to embrace recommendations that diminish their market share, at least until they can offer some solution in exchange. Changing the mindset of industry will be difficult, probably more so than that of producers. Although decreasing treatment intensity may prolong the lifespan of a drug, market sustainability cannot compete with short-term profits. Also, anything short of maximally exploiting the sales of a new product would sacrifice its most valuable commodity – the exclusive marketing period granted by regulatory authorities before generic competition is allowed. Stockholders ultimately dictate corporate strategy, and they demand dividends, reject martyrdom, and for the most part, do not own cattle.

8. Lessons from the New Zealand experience

> "It appears at the present time there are more reported cases of anthelmintic resistance in cattle in New Zealand than in the rest of the world combined." (Familton, 2001)

In New Zealand, the objective science community was the first to sound the warning about the presence and the perils of resistance (McKenna, 1995, 1996; Vermunt et al., 1995, 1996; West and Vermunt, 1994). The funding sources for these harbingers were producer organizations and governmental entities, and their investigations were in service to the primary industries of the country (*e.g.*, agriculture). Scientific information was disseminated in many forms – refereed articles, presentations at scientific meetings, press releases to lay publications, and meetings with producers. Because of the ubiquity of parasitism in a country that relied on grazing, New Zealand veterinarians were conversant with practical parasitology and management principles. The veterinary pharmaceutical industry was similarly active in the ongoing and regular conversation. The problem of resistance in New Zealand was discussed openly by all stakeholders. As yet that conversation is relatively quiet in the US.

In defense of the contrasts in visibility, New Zealand has the land mass of Colorado, a homogeneous climate that favors perennial grass growth, and cattle management systems that are all based on grazing. In contrast, the U.S. is vast, with huge diversity in climate and husbandry systems.

Diversity aside, the essential problem is the same, and raising awareness and stimulating change must begin with the basic conversation. As awareness and the conversation about anthelmintic resistance expanded in New Zealand, pharmaceutical companies were understandably reserved in their support of the message (McPherson, 2000; McArthur, personal communication, 2013).

Similar, objective voices are not yet being heard in the U.S., and no authoritative and knowledgeable body of expertise has stepped forward to address the challenge. Although several members of the scientific community are interested and involved in the issue of bovine anthelmintic resistance, issuance of a cohesive message has been side-tracked by arguments about the validity of FECR testing, challenges regarding the pathogenicity of certain resistant parasites, and dismissal of problem properties as atypical outliers. While knowledgeable specialists delay in developing and promoting standard recommendations, parasite populations in the field are shifting ever farther along the resistance continuum in response to indiscriminate therapeutic choices.

In New Zealand, the veterinary pharmaceutical industry gradually acquiesced to the reality of resistance because the data were irrefutable. In addition, fecal egg count monitoring by producers and their advisors was better understood and practiced more widely than it is in the U.S. It is important to note that with the revelation of resistance in NZ, sales of popular anthelmintics did not suffer as a result; their need and their role did not disappear in the face of waning efficacy. Rather, knowledge became power and instead of default thinking about treatment, more producers and their advisors took an enlightened approach to integrating anthelmintics into a parasite management program.

The prominence of anthelmintic resistance in New Zealand animal agriculture was a stimulus for the pharmaceutical industry to offer profitable problem-solvers. Once companies had developed and registered anthelmintic combinations and/or new molecules, the conversation coming from industry began to change. Obviously, a company is better served by discussing a problem if it can offer a concurrent solution. Unfortunately, competitive funding bodies in the U.S. exhibit low interest in practical parasitology. When it exists at all, the U.S. research agenda is funded by academic departments, commodity groups, and the pharmaceutical industry.

9. Implementing change

"Change is a process, not an event."

Anthelmintic resistance has posed a significant challenge to parasite control in U.S. livestock for more than three decades. Whether the target audience was small ruminant producers, horsemen, or cattle farmers, scientific authors have encouraged veterinarians to perform diagnostic testing and implement management strategies, and exhorted producers to subscribe to best practices. It is inconceivable that this issue would be novel for anyone seriously involved in animal husbandry, and many owners have experienced the consequences of resistance first-hand. In light of the significance and prominence of the resistance issue, why aren't stakeholders concerned? Why don't producers want to know more?

Of all the challenges posed by bovine anthelmintic resistance, perhaps the most daunting are those that are based in human behavior. Put simply, change is hard. As a case in point, consider situations in which the personal stakes are high and carry enormous consequences, *e.g.*, heart disease or diabetes. An alarming percentage of humans are unwilling to make lifestyle changes to improve their quality of life or even to favor survival. Noncompliant behavior is a frustrating and costly challenge for the medical community and for society at large. But, if it is so difficult to effect changes which address intimate and serious conditions, how will a livestock producer find the motivation to revamp an anthelmintic program in which the consequences of drug resistance are insidious and usually invisible?

As we endeavor to elevate awareness and to implement change in the current paradigm of parasite management, it might be instructive to step back from the specifics of this challenge and to consider general principles. The following "Seven Levers of Mind-Changing" (Gardner, 2004) have been extracted from a popular book and are annotated with examples relevant to this discussion.

The Seven Levers of Mind-Changing:

Reason – Reason is a cognitive process that identifies relevant factors, weighs their relative importance, and makes an assessment. Reason is employed whenever pros and cons are considered. The counterbalance comparison of productivity *versus* sustainability is an example of reasoned choice.

Research – The research process generates evidence-based data that support an argument or decision. Research allows end-users and professional advisors to learn from the experience of others. Research may not be sufficiently compelling to influence the average consumer, but it is absolutely essential that sound management decisions are based on evidence. As scientists, we are comfortable and conversant in the language of research and reason, and that is where we place our emphasis when trying to effect change. However, our target audience may not be able to discriminate between evidence-based data and anecdotal testimonials. Research-based messages may fail to address the producer's practical concerns and level of understanding.

Resonance – Resonance is the quality of a message that affects the end-user. To a scientist, resonance may seem 'soft,' but to a producer or consumer, it carries the 'ring of truth.' Emotion is involved. Resonance is essential for acceptance, and may arise from charismatic or influential individuals or marketing/educational campaigns. Word-of-mouth advertising creates resonance through perceived credibility. The recommendation of a peer who is a leader or an early adopter often carries greater credence among producers than that of professional advisors.

Redescriptions – The term redescriptions refers to the various methods for presenting an idea, and individual producers may respond differently to the same information if it were presented as a story, in a graphic format, or in predominantly economic terms. People learn in different ways and varying the manner in which the message is presented can broaden the reach to the audience.

Resources – The process of change is facilitated by the availability of resources that reinforce the correctness of a new direction. Appropriate resources are currently available for practitioners in the form of FECR testing, and for producers in maintenance of meticulous performance records. Future resources might include subsidized diagnostic testing, demonstration field trials, or pharmaceutical incentives.

Real world events – Real world events include anything that changes the landscape of the current problem. Examples for anthelmintic resistance include dramatic changes in weather (*e.g.*, drought) which affect parasite epidemiology, unusual patterns of morbidity or mortality, the introduction of new anthelmintics, or legislated control of anthelmintic availability, as implemented in many countries in the European Union within the past decade.

Resistances – All consumers develop strong views and perspectives that they are resistant to change. Any effort to understand the changing of minds must take into account the power of pushback, inertia, and skepticism.

Minds are more likely to be changed when the first six factors operate in concert and inherent resistances are relatively weak. Conversely, change is unlikely to evolve when resistances are strong (*e.g.*, habit, pharmaceutical marketing), and the remaining factors do not point convincingly in one direction.

10. Conclusion

In considering the various elements of this challenge, a real individual of mutual acquaintance comes to mind. He is an astute, progressive and profitable cattle producer, and a sharp veterinarian with an extensive background in applied parasitology research. He knows business. He knows science. With his exceptional awareness of resistance and its effects on productivity, how likely is he to rethink his parasite management program? His attitudes and practices may serve as a model for what we can expect from producers who are receptive to the resistance message.

As gleaned from numerous conversations and presentations, our prototype is willing to consider principles and apply best practices as long as they do not compromise productivity. He monitors efficacy in a practical fashion, and adjusts his program to suit. Many aspects of his regime could support sustainability, but nothing will be implemented unless it simultaneously promotes greater productivity. Our cattleman/veterinarian is an example of how the best-intentioned recommendations will be received in the real world. The producer's perceptions and perspective will be the decisive factor.

The readers of this paper should recognize that changing the behavior of those who are impacted by bovine anthelmintic resistance will require considerable and consistent conversation – at many levels, and by many parties. It is not a task solely for animal scientists, veterinarians, or livestock parasitologists (Bath, 2006; Molento, 2009). Rather, essential expertise also resides in the skills of educators, sociologists, marketing personnel, coaches or even religious missionaries. Abandoning current and historical behavior, with its entrenched economic motives and unconfirmed assumptions of efficacy, for a nebulous and uncertain 'greater good' (*i.e.*, sustainable efficacy) will be a hard sell, but certainly one that requires a team approach with various core competencies.

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