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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).