PEER REVIEWED

Evaluation of generic injectable ivermectin for control of nematodiasis in feedlot heifers

T. A. Yazwinski[1], *PhD;* **C. A. Tucker**[1], *PhD;* **D. G. Miles**[2], *DVM, MS;* **J. L. Reynolds**[1], *MS;* **L. L. Jones**[1]*;*
J. A. Hornsby[1], *BS;* **M. T. Smith**[3], *MS;* **B. E. Martin**[3]
[1]*Department of Animal Science, University of Arkansas, Fayetteville, AR 72701*
[2]*Veterinary Research & Consulting Services, LLC, Greeley, CO 80634*
[3]*Harris Ranch Feeding Company, Coalinga, CA 93210*
Corresponding author: Dr. Yazwinski, Tel.: 479-575-4398, E-mail address: yazwinsk@uark.edu

Abstract

Nematode parasitism of feedlot cattle has received very little research attention. It is assumed that anthelmintics administered at feedlot entry are effective and that feedlot conditions preclude post-treatment infection by helminths. Given the paucity of information about feedlot nematodiasis, the current research project was conducted. During October of 2010, 104 animals were selected at random from approximately 1600 beef heifers received at one feedlot in California and penned as a group. Of those, 96 were administered a generic, injectable formulation of ivermectin at label dose, while the remaining eight animals were left as untreated controls. Controls and eight randomly selected treated animals were necropsied for parasite quantifications at eight weeks post-treatment. At the end of the feeding period (approximately 135 days post-treatment), parasite quantifications were performed on nine animals selected at random from the remaining 88 animals. Fecal samples were periodically collected from cattle in the feedlot during the study. As evidenced by reductions in both fecal egg count and parasite quantifications at necropsy, a lack of drug efficacy was apparent for *Cooperia* and *Ostertagia*, and suspect for *Haemonchus* infections.

Key words: bovine, feedlot, nematode, generic ivermectin, efficacy

Résumé

Le parasitisme par les nématodes chez les bovins en parc d'engraissement n'a pas été le sujet de beaucoup d'études. On assume que le traitement antihelminthique administré à l'arrivée des animaux est efficace et que les conditions dans le parc empêchent l'infection post-traitement par les helminthes. Ce projet a été développé en raison du peu d'information sur la nématodiase dans les parcs d'engraissement. En Octobre 2010, un total de 104 animaux ont été choisis au hasard d'une population d'approximativement 1600 bouvillons de bœuf regroupés tous ensemble dans un parc d'engraissement de la Californie. De ce nombre, un total de 96 individus ont reçu une formulation générique et injectable d'ivermectin à la dose recommandée tandis que les huit animaux restants n'ont rien reçu et servaient de témoins. La nécropsie des témoins et de huit individus traités choisis au hasard a été faite pour quantifier le nombre de parasites huit semaines suivant le traitement. Le nombre de parasites a aussi été évalué chez neuf individus choisis au hasard parmi les 88 animaux restants à la fin de la période d'engraissement (approximativement 135 suivant le traitement). Des échantillons fécaux étaient recueillis périodiquement des bovins du parc durant l'étude. À la lumière de la réduction du nombre d'œufs fécaux et du décompte des parasites à la nécropsie, un manque d'efficacité de la drogue était apparent pour les infections causées par *Cooperia* et *Ostertagia* et soupçonné pour celles causée par *Haemonchus*.

Introduction

Treatment of feedlot cattle for nematode parasitisms during arrival processing is an accepted management practice. It is assumed that parasitisms will negatively impact feed conversions, disease prevention, and profitability. A major consideration when selecting the anthelmintic is the cost of treatment. It can be tempting to select an inexpensive product and assume that drug efficacy does not correlate with drug cost. There are, however, significant differences in the efficacy of products used for nematode control.[22] These differences are the result of the initial spectrum of activity of the parasiticide as well as subsequent development of resistance in the targeted populations of helminths.[7] Further complicating anthelmintic selection is the degree of animal resistance, the geographic location where the animals grazed prior to feedlot entry, time of year, and animal management.

The more important nematode genera, *Ostertagia*, *Cooperia*, and *Haemonchus*, often vary in abundance, inhibition (*Ostertagia*), and degree of anthelmintic resistance. All these variations contribute greatly to the eventual efficacy of the treatment administered at feedlot arrival. The current study was conducted to gain information on nematode burdens of California cattle arriving at the feedlot, as well as the efficacy of a generic formulation of ivermectin, the standard parasiticide used during arrival processing at the feedlot.

Materials and Methods

Timetable of Events

A timetable detailing the dates and events in the study is shown in Table 1. Crossbred beef heifers from California, ranging in weight from 685 to 960 lb (311 to 436 kg) at feedlot entry, were used in the study. A study pen was established with 96 heifers treated according to label instructions with a generic, injectable formulation of ivermectin[a] (0.09 mg/lb; 0.2 mg/kg BW) at the time of enrollment into the study. Eight animals were left as untreated controls. Approximately one month post-treatment, the eight untreated animals (controls) and eight treated animals were shipped to the University of Arkansas and housed in challenge-free conditions for approximately three weeks prior to harvest and parasite collections.

Randomization

Approximately 1600 mixed breed beef heifers arrived into the California feedlot from October 06 through October 19, 2010. During arrival processing, every 15th heifer that passed through the processing chute was enrolled into the study until a total of 104 head were selected. Every 13th heifer in the pen of 104 study heifers was enrolled as an untreated control.

Parasitology

Fecal samples for parasite egg counts were collected rectally from study animals as described in Table 1. For each fecal sample, a modified single-centrifugation, magnesium sulfate flotation procedure was employed for the counting of all nematode eggs per gram of feces (sensitivity of one egg per gram).[5] In addition, feces collected just prior to harvest of animals shipped to Arkansas were processed for egg counts and cultured for isolation and identification of third-stage larvae.[12] Identification of nematode genus cannot be accurately done by observing eggs,[2,17] therefore coproculturing was done to correlate live and sacrificed animal observations.

Isolation and quantification of nematodes obtained after animal harvest were done according to current guidelines.[19] Aliquots of abomasum and small intestine contents and soaks were obtained from the 16 animals harvested in Arkansas and nine randomly selected heifers harvested in California. All soaks of cleaned small intestines were done for six hours prior to aliquot collection; abomasum soaks conducted in California were also done for six hours. Abomasum soaks conducted in Arkansas were done for 12 hours prior to aliquot collections. After appropriate sieving of content and soak aliquots, residues were stereoscopically viewed at 10-40X magnification for parasite identification and counting.

Statistics

Fecal egg counts were subjected to statistical analysis.[13] Prior to analysis, the counts were transformed to the log 10 (X+1) to reduce variability. Significance was determined with repeated t-tests at the 0.05 level of probability. Parasite counts at necropsy were not analyzed for significant differences between any two sets of animals, as the accepted minimal threshold

Table 1. Timetable for the study evaluating the efficacy of generic, injectable ivermectin for the control of nematodes in a California feedlot.

Date	Event
October 06-19, 2010	Approximately 1600 head of mixed breed beef heifers arrived at a feedlot in California, with a weight range of 685 to 960 lb. 104 study animals were selected at random, with 96 head treated at enrollment and eight left as untreated controls. Fecal samples collected as animals were enrolled in the study.
November 11, 2010	Fecal samples were collected from all 104 heifers in the study.
November 14, 2010	Eight untreated and eight treated calves were shipped to the University of Arkansas.
November 15, 2010	Calves arrived in Arkansas and given ad lib hay and water. Fecal samples were collected.
November 29, 2010	Fecal samples were collected from the 16 heifers at the University of Arkansas.
December 06-09, 2010	Animals were harvested in Arkansas for parasite retrieval and counts.
February 11, 2011	Fecal samples were collected from the 88 heifers remaining in the California feedlot.
February 25, 2011	At the end of the feeding period in California, nine GI tracts were obtained at random during the harvest of the remaining 88 animals for parasite retrieval and counts.

for parasiticide effectiveness (≥ 90%) was clearly not achieved in the study.

Results and Discussion

Fecal egg counts expressed as strongyle eggs per gram of feces (EPG) are summarized in Table 2 for animals that remained in California for the duration of the feeding period and study. Egg counts from fecal samples taken at the time of treatment with generic ivermectin, shortly after treatment, and towards the end of the feeding period differed significantly between time points ($P < 0.05$). Judging from these egg counts alone, it can be inferred that anthelmintic treatment was effective and that long-term housing under feedlot conditions resulted in continued reduction of worm burdens without reinfection, as evidenced by continued low egg counts. However, data obtained from animals shipped to the University of Arkansas (Tables 3 and 4) demonstrate a lack of efficacy for the parasiticide used in the study. Also, the diet fed in the feedlot appeared to restrict worm fecundity, which was reflected by low egg counts. Depressed egg counts for untreated cattle housed in a drylot feedlot has been reported by others.[9]

Table 2. Strongyle, fecal egg count (EPG) summary for 88 beef heifers that remained in a California feedlot.

Date	Mean (SD)	Min	Max
October 06-19, 2010[d]	48.0[a] (67.6)	0	457
November 11, 2010	8.4[b] (16.8)	0	84
February 11, 2011	1.8[c] (5.2)	0	29

[a,b,c]Means with different superscripts are significantly different as determined at $P < 0.05$ with transformed data [$\log_{10}(X+1)$].
[d]Heifers were treated with generic injectable ivermectin when enrolled into the study.

Strongyle fecal egg counts for cattle shipped to Arkansas after treatment with generic ivermectin in California are summarized in Table 3. At each sampling point, there was no significant difference in EPG between treatment groups. The cattle were maintained in a challenge-restricted environment from the time of treatment to necropsy, therefore the return of fecal egg counts in both treated and control animals to levels seen on the day of anthelmintic treatment is interpreted to result from the stressful haul from California to Arkansas, as well as the change from the concentrate ration fed in the California feedlot to the *ad libitum* hay ration in Arkansas. Both stress and diet have been shown to significantly impact gastrointestinal parasitisms of ruminants.[1,14]

On a mean treatment group basis, calculated per-genus EPG counts obtained during necropsy of cattle transported to the University of Arkansas are given in Figure 1. These egg counts were calculated by multiplying the treatment group mean necropsy strongyle egg counts by the treatment group mean coproculture larvae counts as percentages. Therefore, this figure depicts the treatment group-specific fecundities of *Cooperia*, *Ostertagia*, and *Haemonchus*, and presumably the sizes of the respective adult nematode populations for animals in the treatment and control groups. From these data, it appears that *Ostertagia* populations were diminished by treatment, whereas *Haemonchus* and *Cooperia* populations were not.

A summary of quantified nematode burdens for control and treated animals harvested at the University of Arkansas is given in Table 4. For an anthelmintic to be considered efficacious it must reduce a targeted worm burden by ≥ 90%.[19] Additionally, in the conduct of a control study (animal harvest study), at least six animals in the untreated group must be infected with the targeted

Table 3. Fecal egg count (EPG) summary for 16 beef heifers shipped to the University of Arkansas.

Date	Control[a] (N=8)			Treated[a] (N=8)		
	Mean (SD)[b]	Min	Max	Mean (SD)[b]	Min	Max
October 06-19, 2010	32.3 (37.3)	2	95	84.3 (66.4)	1	183
November 11, 2010	3.8 (6.4)	0	18	18.6 (29.6)	0	86
November 15, 2010	32.1 (35.6)	2	98	66.3 (85.2)	5	259
November 29, 2010	45.0 (73.3)	2	223	24.5 (18.6)	1	51
December 06-09, 2010	64.4 (72.0)	7	219	56.4 (52.9)	12	160

[a]Control animals received no treatment or placebo. Treated animals were administered generic injectable ivermectin when enrolled into the study.
[b]Treatment group mean EPG values did not differ significantly ($P < 0.05$) for any date during the study as determined with transformed data [$\log_{10}(X+1)$].

Table 4. Summary of nematode burdens quantified for eight untreated control and eight treated beef heifers harvested in Arkansas.[a]

	No. heifers infected[b]		Total Nematodes			
			Range		Mean	
Nematode	Control	Treated	Control	Treated	Control	Treated
Ostertagia ostertagi						
- adult	8	8	1814-4350	20-8061	2702	1900
- L4	6	5	0-150	0-430	45	65
Haemonchus placei						
- adult	4	6	0-2254	0-1070	360	189
Cooperia oncophora						
- adult	5	6	0-1190	0-649	208	250
C. punctata						
- adult	7	8	0-3820	20-3540	594	638
Nematodirus helvetianus						
- adult	2	2	0-140	0-50	33	9
- L4	2	2	0-60	0-80	10	13
Trichostrongylus colubriformis						
- adult	3	3	0-22	0-20	8	8

[a]Treated heifers were administered generic injectable ivermectin at arrival into a California feedlot approximately eight weeks earlier. Control heifers were not administered an anthelmintic.
[b]Number of animals infected per eight animals sampled per treatment group.

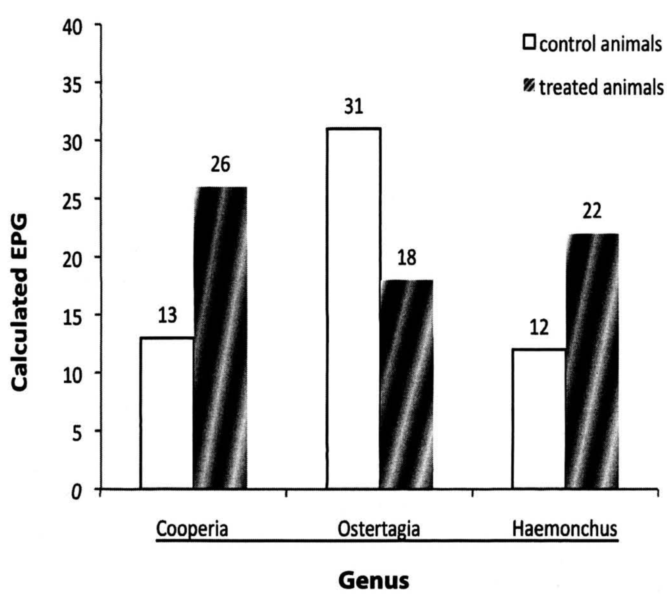

Figure 1. Calculated mean fecal egg counts (EPG) for beef heifers examined at necropsy at the University of Arkansas.

parasite if conclusions regarding drug efficacy are to be drawn.[19] Both *O. ostertagi* and *C. punctata* adults were found in at least six untreated animals, and based on treatment group arithmetic means they were reduced by 29.7 and 0.0% as a result of treatment, respectively. *C. oncophora* adults were found in five control and six treated animals, thereby failing to meet the incidence requirement for sound evaluations. Clearly however, *C. oncophora* was also ineffectually removed by the parasiticide used at feedlot entry.

Six treated animals and four untreated animals were infected with *H. placei* adults. However, more adult *Haemonchus* were found in untreated controls than in treated animals. Conversely, treated animals were passing more *Haemonchus* eggs than were the controls (Figure 1). A likely explanation for this post-treatment inverse relationship between adult worm populations and fecundity is that worms in depleted populations overcompensate for the perceived paucity in their numbers with increased reproduction.[15]

Nematodirus helvetianus and *Trichostrongylus colubriformis* were found in animals harvested at the

University of Arkansas in levels too low for any sort of interpretation relative to drug efficacies.

A summary of nematode burdens quantified for the nine study animals harvested at the end of feedlot confinement in California is presented in Table 5. Infections by *O. ostertagi, H. placei, C. oncophora*, and *C. punctata* were still present after approximately 135 days of feedlot confinement, albeit at relatively low levels (all mean infections < 300 nematodes per animal). It is doubtful that these low levels of infection negatively impacted animal performance during the feeding period. However, others have reported that lower levels of resistant parasitic nematodes, such as *Cooperia* spp, cause diminished animal condition.[10]

The routine parasiticide treatment used at arrival processing was found non-efficacious for the nematode infections present in the current study. This lack of efficacy might have been rooted in one or more of the following causes:

1. That the animals treated at receiving were treated with a macrocyclic lactone (ML) relatively close to the time of their shipment to the feedlot, thereby leaving only the ML-resistant nematodes behind.
2. That the animals were infected subsequent to their last anthelmintic treatment in the field, and that nematode infections treated at receiving were reflective of new, non-selected helminths that were indeed ML-resistant.
3. That the nematode infections remained post-treatment at the feedlot because generic formulations of MLs are less efficacious than pioneer formulations of MLs.

Table 5. Summary of nematode burdens quantified for nine beef heifers harvested at the end of the feeding period in a California feedlot.[a]

	No. infected[b]	Total nematodes	
Nematode		**Range**	**Mean**
Ostertagia ostertagi			
- adult	5	0-1300	262
- L4	1	0-40	5
Haemonchus placei			
-adult	2	0-60	9
Cooperia oncophora			
- adult	3	0-1620	205
C. punctata			
- adult	4	0-340	47

[a]Heifers were treated with generic injectable ivermectin at feedlot entry approximately 135 days earlier.
[b]Number of animals infected per nine animals sampled.

Given the lack of anthelmintic history for the study animals, and the lack of a pioneer ML treatment group in this study, the exact basis for anthelmintic failure in this study cannot be stated with complete certainty. All three reasons for the observed depressed drug efficacy suggested above are plausible and have foundation in research findings: 1) anthelmintic treatment does indeed remove susceptible forms and leave resistant individuals behind;[3] 2) reports of ML resistance in cattle have been documented in the United States (US) and abroad;[6,7] and 3) generic formulations of MLs have been shown to possess lower levels of effectiveness than their pioneer counterparts.[8,20] Correspondingly, since the exact reason(s) for the levels of efficacy seen in the current study cannot be stated with certainty, suggestions for improved anthelmintic intervention at this feedlot cannot be addressed in total.

At present in the US, combination treatments for nematode parasitisms of cattle are being employed by some, although published accounts of results are sparse.[11] The intent of this practice is to combine products which do not share parasite-specific voids in drug effectiveness. When developing a control program for nematode parasites, two populations of parasites present the most "drug-insensitive" targets for anthelmintics, populations which must be considered whenever anthelmintic intervention is attempted. The first population is inhibited *Ostertagia* (pre-type II ostertagiasis). In the US, this infection is common in the south during the summer and in the north during the winter.[18] When given at routine dose rates, benzimidazoles and imidazothiazoles do not provide effective control of this infection. The second parasite population that should be considered in planning successful anthelmintic intervention are ML-resistant nematodes which most certainly include *Nematodirus* and *Cooperia*, and possibly *Haemonchus* and *Ostertagia*. Infections by these various genera vary greatly in size and degree of resistance according to geographic location (latitude), farm, husbandry, anthelmintic history, and animal age.[21] *Nematodirus* and *Cooperia* spp nematodes primarily infect younger animals (≤ two years of age), thereby restricting most of the observed ML resistance to this age group. *Haemonchus* thrives best in the south, where it is singular amongst ruminant nematodes in ability to circumvent high temperatures and drought. *Ostertagia*, the latest nematode genus to join the ranks as ML-resistant,[4] is unfortunately not restricted by geography or animal age, and should be a consideration in anthelmintic intervention on all cattle operations.

Unfortunately, a lack of efficacy of a wide array of anthelmintics has been recently documented in the

United States.[16] In a recent controlled study conducted at the University of Arkansas, significant differences in efficacy were seen between injectable pioneer MLs, between benzimidazoles, and between injectable MLs and benzimidazoles[22] – differences which would certainly have translated into varied animal performance after treatment.

Conclusions

In the current study, a standard receiving anthelmintic was shown to be ineffective in the treatment of cattle parasitisms. Due to variation in product efficacies today, it is the recommendation of this laboratory that well planned fecal egg count reduction tests be conducted periodically at the farm level, wherein the treated animals are one to two years of age, on grass, and identified so that the same animals might be fecal sampled on the day of treatment and 14 to 21 days later. For feedlot operations, fecal egg count reduction tests appear to be invalid (due to abrupt ration changes), and alternate means of efficacy evaluation should be initiated so that this extremely expensive and intensive endpoint of animal production is not compromised by the concurrent maintenance of parasitic nematodes. Future studies should evaluate the relationship between anthelmintic efficacy and animal performance in feedlot cattle.

Endnote

[a]Noromectin, Norbrook® Laboratories Ltd (Ireland) Station Works, NEWRY, BT35 6JP, CO Down, Northern Ireland

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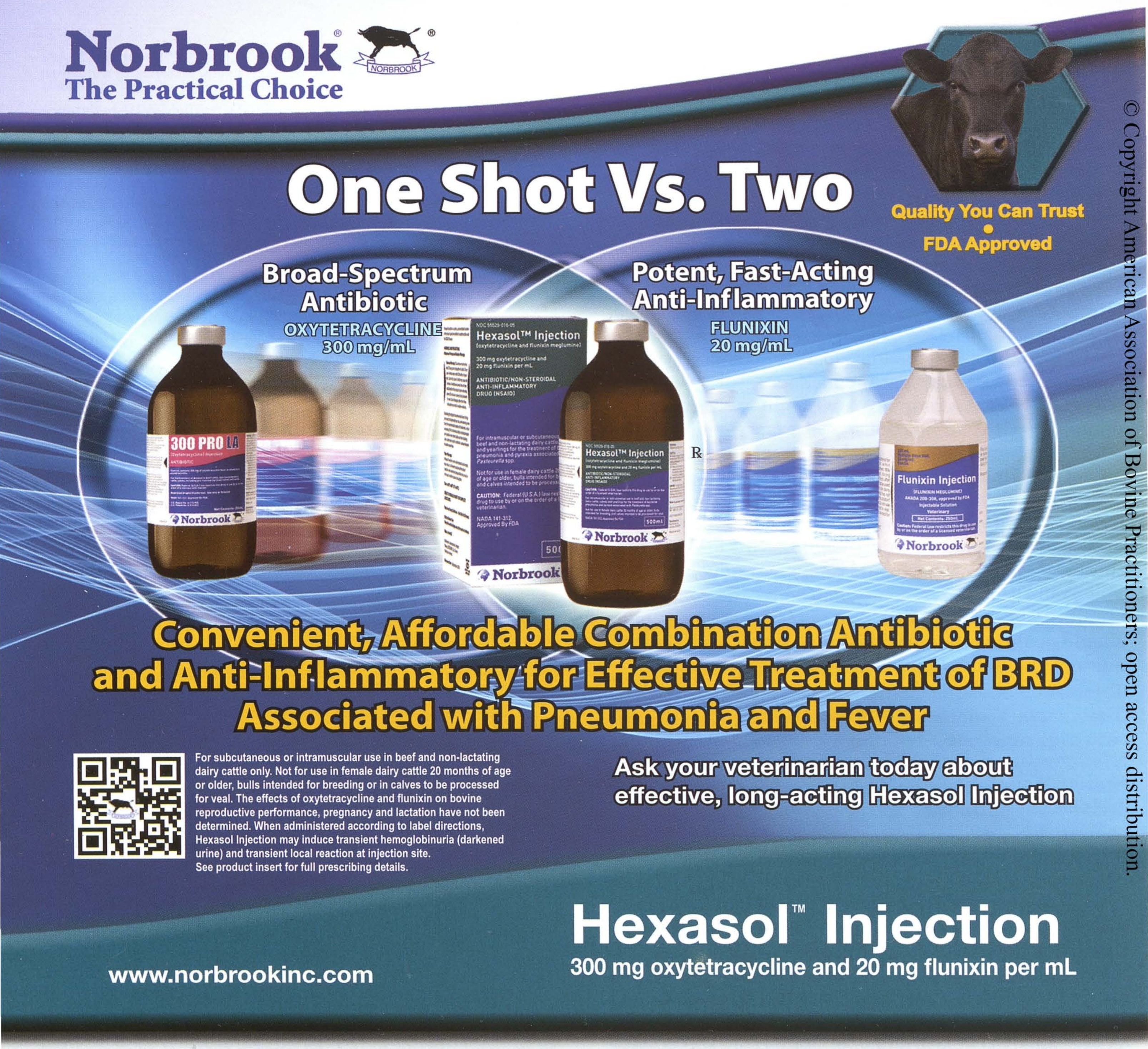

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Not for use in female dairy cattle 20 months of age or older, bulls intended for breeding, and calves intended to be processed for veal.

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INDICATIONS:
For the treatment of bacterial pneumonia associated with *Pasteurella spp.* and for the control of associated pyrexia in beef and non-lactating dairy cattle.

CONTRAINDICATIONS: Do not use in animals showing hypersensitivity to either flunixin meglumine or oxytetracycline.

WARNINGS AND PRECAUTIONS:
Withdrawal Periods and Residue Warnings
Residue Warnings: Discontinue treatment at least 21 days prior to slaughter of cattle. Do not use in female dairy cattle 20 months of age or older. Use in this class of cattle may cause milk residues. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal. Use of dosages other than those indicated may result in residue violations.

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in beef cattle and non-lactating dairy cattle may result in antibiotic residues beyond the withdrawal time.

Antibacterial Warnings
Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant pathogenic bacteria.

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