An Evaluation of Concomitant Therapy for the Treatment of Arrival Fever in Feedlot Calves at Ultra-High Risk of Developing Undifferentiated Fever/Bovine Respiratory Disease

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ABSTRACT

A field study was conducted at four commercial feedlots in the United States to compare the relative efficacy of two treatment programs for the treatment of arrival fever (AF) in feedlot calves at ultra-high risk (UHR) of developing undifferentiated fever/bovine respiratory disease (BRD): concomitant Excede® Sterile Suspension for Cattle (Zoetis, Parsippany, New Jersey) and Draxxin® (Zoetis) (**CT**) versus Resflor Gold® (Merck Animal Health, Intervet Inc., Madison, New Jersey) (**RESF**). In this study, 1126 animals with AF were randomly allocated to experimental group and followed from allocation until exit from the feedlot, with the individual animal as the experimental unit. The first AF relapse, second AF relapse, and overall chronicity rates were reduced in the **CT** group as compared to the **RESF** group (absolute differences of 15.28%, $P < 0.001$; 6.52%, $P = 0.011$; and 0.36%, $P <$

0.001; respectively). In addition, the overall mortality, BRD mortality, metabolic mortality, and other causes mortality rates were lower in the **CT** group as compared to the **RESF** group (absolute differences of 9.59%, 6.75%, 0.71%, and 1.42%, respectively; $P < 0.001$). Average daily gain (allocation to 120 days on trial) was higher in the **CT** group as compared to the **RESF** group (difference 10.29%, $P < 0.001$). In summary, this commercial field trial conducted in UHR calves demonstrated that concomitant administration of Draxxin and Excede for the treatment of initial AF cases was shown to substantially reduce morbidity and mortality (approximately a 50% reduction in overall mortality to feedlot exit), which has meaningful positive impacts on animal welfare.

INTRODUCTION

Bovine respiratory disease (BRD), also commonly referred to as undifferentiated fever (UF) and historically known as "shipping fever," continues to be one of the most common animal health concerns in commercial feedlot production.[1-3] Although beef feedlot operations have become more sophisticated in managing health problems, significant economic losses from BRD continue to be related to morbidity and mortality rates, reduced feedlot performance, and metaphylactic and therapeutic regimen costs.[2] According to recent data from the United States Department of Agriculture National Animal Health Monitoring System, overall mortality on surveyed feedlots with a capacity of 1,000 animals and greater has increased from 1.1% in 1994 to 1.6% in 2011.[4] In 2009, the economic losses attributable to BRD were estimated to cost the North American cattle industry greater than $500 million US annually.[5] A more recent retrospective study involving 73,067,534 cattle showed a similar increasing trend in overall mortality in lots that closed from January 2005 to September 2014, with BRD mortality comprising 47% of total mortality.[6]

Arrival fever (AF) is a diagnosis used to identify animals that are sick at the time of feedlot arrival, and is defined as a lack of abnormal clinical signs referable to organ systems other than the respiratory tract and a rectal temperature ≥ 104.0ºF (≥ 40.0°C) at the time of feedlot arrival. In calves at ultra-high risk (UHR) of developing UF/BRD, those animals diagnosed as having AF exhibit an increased mortality risk (approximately 2-3 times higher) compared to non-AF animals from the same cohorts (authors' observations based on unpublished data). The increased mortality risk seen in this population represents a significant animal welfare concern (*7*, authors' observations), and an economic liability. Therefore, it is important to seek the most efficacious, practical, and cost-effective treatment strategies, based on high quality field trial data, for animals diagnosed with AF.

Florfenicol + flunixin meglumine (Resflor Gold®, Merck Animal Health, Intervet Inc., Madison, New Jersey) is an antimicrobial non-steroidal anti-inflammatory product licensed in the United States (US) for the treatment of BRD, associated with *Mannheimia haemolytica*, *Histophilus somni*, *Mycoplasma bovis*, and *Pasteurella multocida* infections, as well as BRD associated pyrexia in beef cattle.[8] Resflor has been determined to be an effective product for the treatment of initial UF in feedlot cattle in western Canada,[9] and extrapolation of these data has led to its use as a treatment for initial AF in the US and Canada (authors' observations).

Despite these advances in the early diagnosis and treatment of AF, clinical outcomes and animal welfare remain a concern in calves at UHR of developing UF/BRD. When coupled with increasing concerns over antimicrobial resistance and the lack of novel antimicrobial development, there is an ever-increasing need to focus on treatment strategies that improve clinical outcomes and focus on antimicrobial stewardship. One such strategy is the use of antimicrobial combinations[10,11] or antimicrobial cycling[12] as a form of "concomitant therapy".

In determining the appropriate pairing of drug combinations for use as concomitant

therapy, the ultimate objective would be to use drugs that in combination exhibit a synergistic effect.[11] Evidence from the human literature indicates that combination therapy may be more appropriate and provide improved *in vitro* susceptibility for patients infected with resistant organisms.[13,14] It seems logical to extrapolate the *in vitro* susceptibility approach to cattle populations. However, commercial production practices at the time of feedlot arrival make culture and sensitivity testing impractical. Thus, AF treatment protocols are developed empirically in most commercial feedlot production scenarios.

In human pediatric patients, specific combination therapies have been shown to be both appropriate and effective for empirical treatment of serious bacterial infections.[15-17] In addition, combination therapies comprised of at least two antimicrobials with different mechanisms of action have been associated with increase survivability in adult patients treated for septic shock.[18] As a result, it seems logical that similar therapeutic approaches might produce the same results in UHR feedlot cattle diagnosed with AF.

Tulathromycin (Draxxin®, Zoetis, Parsippany, New Jersey) is a semi-synthetic macrolide antibiotic licensed in the US for the treatment and control of BRD associated with *M. haemolytica, P. multocida*, *H. somni*, and *M. bovis*, the treatment of infectious bovine keratoconjunctivitis associated with *Moraxella bovis*, as well as the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*.[8] In calves at UHR of developing UF/BRD, administration of Draxxin metaphylactically at the time of feedlot arrival is currently the most effective approach for decreasing morbidity and mortality during the feeding period.[19-21] Ceftiofur crystalline free acid sterile injectable suspension (Excede® Sterile Suspension for Cattle, Zoetis) is an antimicrobial product licensed in the US for the treatment and control of BRD associated with *M. haemolytica, H. somni*, and *P. multocida* infections, as well as the treatment of bovine foot rot associated with *F. necrophorum* and *P. levii* in beef cattle.[8] Administration of Excede metaphylactically on arrival in calves at UHR of developing UF/BRD has previously been determined to be effective.[19,22] In addition, Excede has been shown to be an effective product for treatment at the time of initial UF diagnosis in calves at UHR of developing UF/BRD following metaphylactic Draxxin.[23]

The objective of this study was to compare the relative efficacy of two treatment programs for AF in feedlot calves at UHR of developing UF/BRD: concomitant Draxxin and Excede vs Resflor Gold. Based on findings in the human literature, the authors hypothesized that concomitant administration of two long-acting antimicrobials from different antimicrobial classes at the time of initial AF diagnosis would result in improved animal health outcomes, and ultimately, a higher standard of animal welfare.

MATERIALS AND METHODS

General Overview

In this commercial field trial, male and female calves were randomly allocated at the time of initial AF diagnosis to one of two experimental groups: **CT** or **RESF**. Study animals were sent to commercial feedlot production pens and commingled with non-study animals immediately after initial AF treatment. Animals were followed from allocation (initial AF diagnosis) until exit from the feedlot, with the individual animal as the experimental unit. Outcome variables were measured to evaluate the relative effects of the AF treatment programs on animal health and feedlot performance. Statistical analyses were used to determine the probability of whether differences in outcome variables between the experimental groups were due to differences in the treatment regimens or random chance.

All procedures involving live animals were approved by the Feedlot Health Animal Care Committee (ACC), a certified holder of a Certificate of Good Animal Practice, and in accordance with guidelines put forth

by the Canadian Council on Animal Care (2009), with informed consent from the animal owners.

Study Facilities

The study was conducted at four commercial feedlots in the US with one-time capacities of approximately 15,000 animals, 15,000 animals, 80,000 animals, and 7000 animals for Site 1, Site 2, Site 3, and Site 4, respectively. The basic designs of the feedlots are representative of standard designs used in the US. Animals were housed in either open-air, dirt-floor pens that are arranged side by side with central feed alleys, or open-sided, slatted-floor pens arranged side by side in monoslope concrete barns with single-side feed alleys. There are three to five animal handling facilities located at each site. Each facility has a hydraulic chute equipped with an individual animal scale, a chute-side computer with individual animal data collection and management software (*i*FHMS©, Feedlot Health, Okotoks, Alberta), and separation alleys to facilitate the return of animals to designated pens. Open-air containment pens are located adjacent to each facility.

Study Animals

Candidate animals for the study were auction market-derived, mixed beef breed male and female calves at UHR of developing UF/BRD that arrived at the feedlot between April 13, 2013 and December 3, 2014, and met the following individual-animal criteria at the time of initial AF diagnosis:

1. an absence of abnormal clinical signs referable to organ systems other than the respiratory tract
2. an elevated rectal temperature ≥ 104.0°F (≥ 40.0°C) at the time of feedlot arrival.

- At the time of feedlot arrival, each animal received health and production products as per standardized commercial feedlot practices. In addition to the study of specific antimicrobials administered at time of initial AF diagnosis as described in the Experimental Design section below, all study animals received:
  - individual animal identification
  - a pentavalent modified-live viral (MLV) vaccine
  - an *M. haemolytica* toxoid
  - a topical avermectin

  Site specific arrival products included:
  - a multivalent clostridial bacterin-toxoid (Sites 1 and 2)
  - an *H. somni* bacterin (Sites 1 and 4)
  - an oral fenbendazole dewormer (Sites 2 and 4)
  - a trivalent MLV intranasal vaccine (65 animals from each experimental group at Site 2)
  - a growth implant in the middle third of the ear (Sites 2 and 3).

Heifers received an abortifacient either at feedlot arrival or at first re-handle (average approx. 23 days on feed [DOF] for heifers receiving abortifacient(s) at first re-handle) as per the standard procedures at their respective sites (100% of heifers at Sites 1, 2, and 4; 40.5% of heifers at Site 3). The heifer management protocol was standardized across experimental groups within a site. Intact bull calves received a tetanus toxoid and were banded, either at the time of feedlot arrival or at time of first re-handle (average approx. 25 DOF for bulls banded at first re-handle).

Following arrival, animals were revaccinated and implanted as per standardized feedlot protocols. With the exception of the initial AF antimicrobials administered as per the Experimental Design, all animals within a processing group/production lot at each site received the same commercial products at arrival and all re-handle events.

Experimental Design

In this commercial field trial, animals were blocked by gender and randomly allocated at the time of initial AF diagnosis on an individual animal basis in blocks of two animals using a proprietary computer-generated allocation table to one of two experimental groups: **CT** or **RESF**. Animals in the **CT** group received a subcutaneous

(SC) injection of Draxxin in the neck region at a rate of 2.5 mg/kg body weight (BW) (1.13 mL/100 lb BW) and a SC injection of Excede in the base of the ear at a rate of 6.6 mg/kg BW (1.5 mL/100 lb BW) once at the time of initial AF treatment. Animals in the **CT** group had a post-treatment interval (PTI) of 10 days before they were eligible for additional antimicrobial therapy. Animals in the **RESF** group received a SC injection of Resflor Gold in the neck region at a rate of 40.0 mg florfenicol + 2.0 mg flunixin meglumine/kg BW (6.0 mL/100 lb BW) once at the time of initial AF therapy. Animals in the **RESF** group had a PTI of 3 days before they were eligible for additional antimicrobial therapy.

The treatment protocol for first AF relapse therapy in both experimental groups was SC enrofloxacin (Baytril® 100, Bayer Healthcare LLC, Animal Health Division, Bayer Inc., Shawnee Mission, Kansas) in the neck region at a rate of 7.7 mg/kg BW (3.5 mL/100 lb BW) once at the time of first relapse therapy. The treatment protocol for second AF relapse therapy in the **RESF** group was SC Draxxin in the neck region at a rate of 2.5 mg/kg BW (1.13 mL/100 lb BW) once at the time of second relapse therapy, whereas, the treatment protocol for second AF relapse therapy in the **CT** group was SC Resflor Gold in the neck region at a dosage of 40.0 mg florfenicol + 2.0 mg flunixin meglumine/kg BW (6.0 mL/100 lb BW) once at the time of second relapse therapy. The treatment protocol for third AF relapse therapy in the **RESF** group was SC Excede in the base of the ear at a rate 6.6 mg/kg BW (1.5 mL/100 lb BW) once at the time of third relapse therapy, whereas the treatment protocol for third AF relapse therapy in the **CT** group was SC oxytetracycline dihydrate (Noromycin 300 LA, Norbrook Inc., Lenexa, Kansas) in the neck region at a dosage of 30 mg/kg BW (4.5 mL/100 lb BW) once at the time of third relapse therapy. The PTI before animals were eligible for second and third AF relapses was 3 days for animals in both groups. All individual treatment doses were determined based on BW at the time of the respective AF relapse therapy.

Study animals were housed in commercial feedlot pens and followed from the time of initial AF diagnosis until exit from the feedlot (at Site 3, exit was defined as 120 days post-allocation), with the individual animal as the experimental unit.

Feeding Program

Water and standard mixed complete feedlot diets, formulated to meet or exceed the National Research Council nutritional requirements for beef cattle, were offered *ad libitum* throughout the feeding period. At each site, study animals were conditioned to a high-concentrate diet utilizing multiple transition diets. Animals remained on the high-concentrate diets until the time of exit from the feedlot. Diet formulations and diet changes were based on commercial feedlot protocols and were standardized across experimental groups within a site. Feedlot diets were blended in truck-mounted mixer boxes equipped with electronic load cells. Diets were delivered to the pens once or twice daily as per the standard feeding procedures at each site.

Animal Health

Experienced animal health personnel, blinded to the experimental status of each individual animal, observed the study animals once or twice daily for evidence of disease. Animals deemed to be "sick" by the animal health personnel, based on subjective criteria such as general appearance, attitude, gauntness, reluctance to move, etc., were individually sorted from pen mates, moved to the hospital facility, diagnosed, and treated as per the standard feedlot protocol for all diseases other than AF. Animals diagnosed with AF were treated as per the Experimental Design. The treatment events, including the treatment date, the presumptive diagnosis, drug(s) administered, and dose(s) used were recorded using *i*FHM*S*.

The case definition for AF was a lack of

Table 1. *Definitions and calculations for individual animal-level variables from a study evaluating concomitant therapy for the treatment of arrival fever in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease*

Animal Health Rates		
First AF Relapse Treatment	=	# of animals treated for first AF relapse divided by the # of animals treated for initial AF
Second AF Relapse Treatment	=	# of animals treated for second AF relapse divided by the # of animals treated for first AF relapse treatment
Chronicity	=	# of animals with chronic disease (all causes) divided by the # of animals allocated
Wastage	=	# of animals with chronic disease (all causes) that did not die divided by the # of animals allocated
Overall Mortality	=	# of mortalities (all causes) divided by the # of animals allocated
BRD Mortality	=	# of mortalities due to BRD divided by the # of animals allocated
HS Mortality	=	# of mortalities due to histophilosis divided by the # of animals allocated
Lameness Mortality	=	# of mortalities due to lameness divided by the # of animals allocated
Metabolic Mortality	=	# of mortalities due to metabolic disease divided by the # of animals allocated
Other Causes Mortality	=	# of mortalities (causes other than those previously listed) divided by the # of animals allocated
Ancillary Production Variables		
Initial Weight	=	individual gross live weight of animals at allocation
Re-handle Weight	=	individual net live weight of animals at last re-handle (30 to 120 days on trial, inclusive)
Weight Gain	=	net re-handle weight minus gross initial weight and represents weight gain of animals from allocation to last re-handle
Days on Trial	=	last re-handle date minus the allocation date and represents the # of days on trial at last re-handle
Feedlot Performance Variables		
ADG	=	weight gain divided by the # of days on trial

1. # = number, AF = arrival fever, BRD = bovine respiratory disease, HS = lesions consistent with Histophilus somni infection, ADG = average daily gain.
2. Animals were allocated at initial AF diagnosis (arrival).

abnormal clinical signs referable to organ systems other than the respiratory tract and a rectal temperature ≥ 104.0ºF (≥ 40.0°C) at the time of feedlot arrival. All animals identified to be displaying clinical signs of BRD by animal health personnel subsequent to initial AF therapy were defined as relapses. Relapse treatment required an absence of abnormal clinical signs referable to organ systems other than the respiratory tract. The maximum number of AF treatments permitted for all animals on the study was four. That is, once an animal was treated as a third AF relapse, no further therapy for AF occurred. Animals identified as "sick" subsequent to third AF relapse therapy were deemed to be "chronics." Also, animals that were unsuitable to be returned to their designated feedlot pens, based on subjective appraisal of the attitude and appearance of each animal, were deemed to be "chronics." Chronics that did not die during the study were defined as wastage. All other diseases were treated as per standard feedlot protocols provided by the consulting veterinarians.

A gross necropsy examination was performed on each dead animal by trained per-

Table 2. *Animal health data summary up to 120 days on trial from a study evaluating concomitant therapy for the treatment of arrival fever in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease*

	Experimental Group		
Animal Health Variable	**CT**	**RESF**	***P* - value**
Morbidity			
First AF Relapse Treatment* (%)	23.98	39.61	< 0.001
Second AF Relapse Treatment (%)	37.78	43.05	0.131
Chronicity (%)	1.78	2.66	0.085
Wastage (%)	0.89	1.78	0.014
Mortality			
Overall Mortality (%)	8.70	17.05	< 0.001
BRD Mortality (%)	5.86	12.79	< 0.001
HS Mortality (%)	0.53	0.89	0.176
Metabolic Mortality (%)	0.18	0.18	N/A
Other Causes Mortality (%)	2.13	3.20	< 0.001

1. Animals in the CT group (563 animals, 4 sites) received a subcutaneous (SC) injection of Draxxin® Injectable Solution (Zoetis, Parsippany, New Jersey) at a rate of 2.5 mg/kg body weight (BW) and a SC injection of Excede® Sterile Suspension for Cattle (Zoetis) at a rate of 6.6 mg/kg BW at treatment for initial arrival fever (AF). Animals in the RESF group (563 animals, 4 sites) received a SC injection of Resflor Gold® (Merck Animal Health, Intervet Inc., Madison, New Jersey) at a rate of 40.0 mg florfenicol + 2.0 mg flunixin meglumine/kg BW at treatment for initial AF. Animals were followed from first AF treatment up to 120 days on trial with the final weight captured at the last re-handle event.
2. Data were analyzed using the GENMOD procedure of SAS® (Version 9.3, SAS Institute Inc., Cary, North Carolina) using Poisson regression in a log linear model for experimental group effects and correcting for clustering of disease (site) with generalized estimating equations. In addition, gender was included in the models for "Overall Mortality" and "BRD Mortality" as a fixed effect, as it was statistically significant at the P < 0.050 level.
*3. *A significant interaction existed between site and experimental group for first AF relapse rate. The mean first AF relapse rate for the CT and RESF groups at Site 1 were 31.03% and 44.83%, respectively (P = 0.142); Site 2 were 17.71% and 36.16%, respectively (P < 0.001); Site 3 were 32.07% and 41.30%, respectively (P = 0.145); and Site 4 were 4.76% and 47.62%, respectively (P = 0.028).*
4. N/A = not available; some animal health models would not converge due to the small number of events
5.AF = arrival fever, BRD = bovine respiratory disease, HS = lesions consistent with Histophilus somni infection.

sonnel. In some instances, a Feedlot Health veterinarian conducted the post-mortem examination on site and determined the cause of death based on the findings of clinical history and gross post-mortem examination. In other instances, trained personnel prosected the dead animals using a standardized method to capture appropriate digital images as outlined in the written necropsy protocol provided by Feedlot Health. Subsequently, all digital images were electronically transferred to Feedlot Health and the cause of death for each dead animal was determined based on clinical history and gross post-mortem examination by a Feedlot Health veterinarian. All animals that died were weighed by feedlot personnel.

Data Collection and Management

Over the course of the trial, all individual animal feedlot data were collected using *i*FHM*S*, including individual animal weights at allocation and routine feedlot re-handling events. All study data were entered or electronically imported into a spreadsheet program (Microsoft® Office Excel 2010, Microsoft Corporation, Redmond, Washington), collated, and verified. Outcome variables describing animal health, ancillary production, and feedlot performance were calculated for each individual animal. Definitions and formulae used to calculate outcome variables are summarized in Table 1. Due to the fact that cases at Site 3 could only be followed up to 120 days post-allocation, the animal health data

Table 3. Animal health data summary to feedlot exit from a study evaluating concomitant therapy for the treatment of arrival fever in feedlot calves at ultra-high risk of developing undifferentiated fever/ bovine respiratory disease*

	Experimental Group		
Animal Health Variable	**CT**	**RESF**	***P* - value**
Morbidity			
First AF Relapse Treatment** (%)	24.51	39.79	< 0.001
Second AF Relapse Treatment (%)	37.68	44.20	0.011
Chronicity (%)	2.66	3.02	< 0.001
Wastage (%)	1.60	1.95	0.719
Mortality			
Overall Mortality (%)	9.95	19.54	< 0.001
BRD Mortality (%)	6.22	12.97	< 0.001
HS Mortality (%)	0.53	1.07	0.142
Lameness Mortality	0.00	0.18	N/A
Metabolic Mortality (%)	0.36	1.07	< 0.001
Other Causes Mortality (%)	2.84	4.26	< 0.001

1. Animals in the CT group (563 animals, 4 sites) received a subcutaneous (SC) injection of Draxxin® Injectable Solution (Zoetis, Parsippany, New Jersey) at a rate of 2.5 mg/kg body weight (BW) and a SC injection of Excede® Sterile Suspension for Cattle (Zoetis) at a rate of 6.6 mg/kg BW at treatment for initial arrival fever (AF). Animals in the RESF group (563 animals, 4 sites) received a SC injection of Resflor Gold® (Intervet Inc., Schering-Plough Animal Health, Roseland, New Jersey) at a rate of 40.0 mg florfenicol + 2.0 mg flunixin meglumine/kg BW at treatment for initial AF.

2. Data were analyzed using the GENMOD procedure of SAS® (Version 9.3, SAS Institute Inc., Cary, North Carolina) using Poisson regression in a log linear model for experimental group effects and correcting for clustering of disease (site) with generalized estimating equations. In addition, gender was included in the models for "Overall Mortality" and "BRD Mortality" as a fixed effect, as it was statistically significant at the P < 0.050 level.

*3. *Animals at site 3 were followed from allocation up to 120 days on trial*

*4. **A significant interaction existed between site and experimental group for first AF relapse treatment. The mean first AF relapse rate for the CT and RESF groups at Site 1 were 31.03% and 44.83%, respectively (P = 0.142); Site 2 were 18.82% and 36.53%, respectively (P < 0.001); Site 3 were 32.07% and 41.30%, respectively (P = 0.145); and Site 4 were 4.76% and 47.62%, respectively (P = 0.028).*

5. N/A = not available; some animal health models would not converge due to the small number of events.

6. AF = arrival fever, BRD = bovine respiratory disease, HS = lesions consistent with Histophilus somni infection.

were summarized both from allocation to 120 days post-allocation and from allocation to feedlot exit (with 120 days post-allocation used as feedlot exit at Site 3). Ancillary production and feedlot performance outcomes up to 120 days post-allocation were summarized for animals with a re-handling weight 30 or more days after allocation, excluding animals that died and animals sent for salvage slaughter.

Statistical Analysis

Data were analyzed using a commercially available analytical software program (SAS® for Windows, Release 9.3, SAS Institute Inc., Cary, North Carolina) to compare the **CT** group to the **RESF** group. Statistical analyses were used to determine the probability of whether differences in outcome variables between the experimental groups were due to differences in the treatment regimens or random chance. Baseline variables were tested as covariates of the ancillary production, feedlot performance, and animal health variables, and included in those final models if statistically significant ($P < 0.050$).[24] The baseline, ancillary production and feedlot performance data were analyzed using the GENMOD procedure in SAS using normal regression in a linear model for experimental group effects and adjusted for intra-site clustering of observations using generalized estimating equations.[24] The animal health data were analyzed using the GENMOD procedure in SAS using Poisson regression in a log linear

Table 4. *Baseline, ancillary production and feedlot performance data summary up to 120 days on trial from a study evaluating concomitant therapy for the treatment of arrival fever in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease*

Experimental Group				
Production Variable	**CT**	**RESF**	**Standard Error**	***P* - value**
Initial Weight (lb)	450.1	448.8	± 5.2	0.286
Initial Weight – Performance* (lb)	448.9	458.3	± 5.7	0.017
Re-handle Weight (lb)	666.6	656.9	± 14.8	0.041
Weight Gain (lb)	209.3	190.9	± 18.8	< 0.001
Days on Trial (day)	90.3	89.5	± 5.3	0.309
Average Daily Gain (lb/day)	2.25	2.04	± 0.12	< 0.001

1. Animals in the CT group (563 animals, 4 sites) received a subcutaneous (SC) injection of Draxxin® Injectable Solution (Zoetis, Parsippany, New Jersey) at a rate of 2.5 mg/kg body weight (BW) and a SC injection of Excede® Sterile Suspension for Cattle (Zoetis) at a rate of 6.6 mg/kg BW at treatment for initial arrival fever (AF). Animals in the RESF group (563 animals, 4 sites) received a SC injection of Resflor Gold® (Intervet Inc., Schering-Plough Animal Health, Roseland, New Jersey) at a rate of 40.0 mg florfenicol + 2.0 mg flunixin meglumine/kg BW at treatment for initial AF. Animals were followed from first AF treatment up to 120 days on trial with the final weight captured at the last re-handle event.

2. Data were analyzed using the GENMOD procedure of SAS® (Version 9.3, SAS Institute Inc., Cary, North Carolina) using normal regression in a linear model for experimental group effects and correcting for clustering of disease (site) with generalized estimating equations. In addition, gender was included in the models for "Weight Gain", "Days on Trial" and "Average Daily Gain" as a fixed effect, as it was statistically significant at the P < 0.050 level.

*3. *Initial Weight – Performance represents the average individual initial weight for animals used in Weight Gain and Average Daily Gain calculations.*

4. Animals were included in ancillary and performance analyses if they were not sent for salvage slaughter, did not die, and had a re-handle event 30 or more days after allocation.

model for experimental group effects and correcting for intra site clustering of disease with generalized estimating equations.[24]

RESULTS

There were 1314 animals with arrival fever allocated to the study. However, animals were removed from the study for not receiving the correct product(s) at allocation (110 animals) or for risk classification other than UHR (78 animals), leaving a total of 1126 animals in the final data set. The final data set included 174 animals allocated at Site 1 (9 females, 165 males), 542 animals allocated at Site 2 (66 females, 476 males), 368 animals allocated at Site 3 (205 females, 163 males), and 42 animals allocated at Site 4 (42 females).

The animal health summary up to 120 days on trial is presented in Table 2. The first AF relapse rate was lower in the **CT** group as compared to the **RESF** group (absolute difference 15.63%, $P < 0.001$). However, a significant interaction existed between site and experimental group with regards to first AF relapse rate. The direction of the differences in first AF relapse rates between the experimental groups was consistent across sites, but there were large differences in the magnitude of the response.

The mean first AF relapse rate for the **CT** and **RESF** groups at:

- Site 1 were 31.03% and 44.83%, respe**ct**ively ($P = 0.142$)
- Site 2 were 17.71% and 36.16%, respectively ($P < 0.001$)
- Site 3 were 32.07% and 41.30%, respectively ($P = 0.145$)
- Site 4 were 4.76% and 47.62%, respectively ($P = 0.028$).

There was no difference detected in second AF relapse rate between the experimental groups at the $P < 0.050$ level. The overall wastage rate was reduced in the **CT**

group as compared to the **RESF** group (absolute difference 0.89%, $P = 0.014$). While not significant, there was a strong trend toward a lower overall chronicity rate in the **CT** group as compared to the **RESF** group (absolute difference 0.88%, $P = 0.085$). The overall mortality, BRD mortality, and other causes of mortality were lower in the **CT** group as compared to the **RESF** group (absolute differences 8.35%, 6.93%, and 1.07%, respectively; $P < 0.001$). No differences in histophilosis mortality or metabolic mortality rates were detected between the experimental groups at the $P < 0.050$ level.

The animal health summary to feedlot exit is presented in Table 3. The first AF relapse and second AF relapse rates were reduced in the **CT** group as compared to the **RESF** group (absolute differences 15.28%, $P < 0.001$ and 6.52%, $P = 0.011$). A significant interaction existed between site and experimental group with regard to first AF relapse rate. The direction of the differences in first AF relapse rates between the experimental groups was consistent across sites, but there were large differences in the magnitude of the response.

The mean first AF relapse rate for the **CT** and **RESF** groups were:

- Site 1, 31.03% and 44.83%, respectively ($P = 0.142$)
- Site 2, 18.82% and 36.53%, respectively ($P < 0.001$)
- Site 3, 32.07% and 41.30%, respectively ($P = 0.145$)
- Site 4, 4.76% and 47.62%, respectively ($P = 0.028$).

The overall chronicity rate was lower in the **CT** group as compared to the **RESF** group (absolute difference 0.36%, $P < 0.001$). The overall mortality, BRD mortality, metabolic mortality, and other causes mortality rates were lower in the **CT** group as compared to the **RESF** group (absolute differences of 9.59%, 6.75%, 0.71%, and 1.42%, respectively; $P < 0.001$). No differences in overall wastage, histophilosis mortality, or lameness mortality rates were detected between the experimental groups at the $P < 0.050$ level.

The baseline, ancillary production, and feedlot performance data summary up to 120 days on trial is presented in Table 4. The experimental groups were considered homogenous ($P \geq 0.050$) with respect to average initial weight. Average daily gain (ADG) was higher in the **CT** group as compared to the **RESF** group (difference 10.29%, $P < 0.001$). This resulted in higher re-handle weights (difference 1.48%, $P = 0.041$) and weight gain from allocation to re-handle (difference 9.64%, $P < 0.001$) in the **CT** group compared to the **RESF** group. There was no difference ($P \geq 0.050$) in average days on trial at re-handle between the two experimental groups.

DISCUSSION

The objective of this study was to compare the relative efficacy of concomitant Draxxin and Excede to that of Resflor Gold for the treatment of AF in feedlot calves at UHR of developing UF/BRD. The average initial AF treatment rate in 87 candidate lots of animals for this study was 5.55% (range: 0.46% to 21.03%). While the increased mortality rate in this AF population is viewed as a welfare concern (*7*, authors' observations) and an economic liability. The early detection of UF/BRD in these animals (at the time of feedlot arrival) also presents a significant opportunity for the development and evaluation of therapeutic approaches that could have meaningful impacts on animal health, welfare, and feedlot performance. Both Draxxin[19-21] and Excede[19,22,23] have previously been validated as effective for the prevention and/or treatment of UF/BRD and represent molecules from different antimicrobial classes: macrolides and beta-lactams, respectively. Thus, these two antimicrobials were logical choices to be included in a concomitant therapy regime.

Administration of concomitant Draxxin and Excede for treatment of initial AF resulted in substantially lower first AF relapse, wastage, overall mortality, BRD mortality, and other causes mortality rates up to 120 days on trial. Similarly, concomitant Draxxin and Excede resulted in substantially

lower first AF relapse, second AF relapse, chronicity, overall mortality, BRD mortality, metabolic mortality, and other causes mortality rates from allocation to feedlot exit. Even though a subset (368/1126; 32.7%) of the study animals were only followed up to 120 days on trial, the absolute difference in overall mortality rate between the two experimental groups was larger when measured to feedlot exit (9.59%) than the absolute difference in overall mortality rate measured up to 120 days on trial (8.35%). This suggests that not only did concomitant therapy for the treatment of initial AF reduce overall mortality rates, but this effect was sustained throughout the feeding period. Furthermore, the absolute difference in overall mortality observed to feedlot exit and the increased absolute difference in overall mortality to feedlot exit relative to 120 days on trial are likely conservative estimates for the effect of the concomitant program, as animal health outcomes for Site 3 were fixed between the two summaries.

In addition to the animal health outcomes discussed above, administration of concomitant Draxxin and Excede for treatment of initial AF resulted in improved ADG up to 120 days on trial (difference 10.29%, $P < 0.001$) as compared to the administration of Resflor Gold. No lung lesion quantification was performed in the present study and it was not possible to determine individual animal dry matter intake (DMI). Therefore, the authors can only speculate as to the mechanism(s) involved in the increased ADG observed in the group receiving concomitant therapy. Multiple studies have characterized a correlation between the presence of lung lesions at slaughter and decreased ADG during the feeding period,[25-28] and it is possible that the improvement in ADG may be explained by a reduction in lung lesions as a result of concomitant therapy. Alternatively, the difference in ADG may simply be a function of improved general health in this group throughout the feeding period leading to an increased DMI.

Mannheimia haemolytica is one of the most common pathogens isolated from both clinically symptomatic and asymptomatic cattle in the feedlot[29,30] as well as lung lesions at the time of post-mortem, particularly those of a more acute nature.[31] Although sampling methodology, timing of sample collection, and disease status of the animals sampled can have significant impacts on the prevalence of specific pathogens, *M. haemolytica* continues to be considered one of the primary bacterial pathogens associated with BRD in the feedlot.[30]

Previous studies describing the resistance profiles of *M. haemolytica* have generated variable results, largely considered to be due to regional differences and case selection, such as pre-treatment versus post-treatment samples.[32] In a recent study of randomly sampled animals on arrival and again during various times during the feeding period in western Canada, over 87% of *M. haemolytica* isolates were pan-susceptible.[30] In addition, very few tulathromycin resistant (2/2989) or ceftiofur resistant (2/2989) isolates were identified.

In contrast, a second study of *M. haemolytica* isolates from BRD submissions to a diagnostic laboratory yielded resistance to three or more common antimicrobials in 42%, 46%, and 63% of isolates from 2009, 2010, and 2011, respectively.[33] These diagnostic submissions represent animals that had succumbed to fatal BRD, and it is not possible to determine if treatment selected for multidrug resistance or if multidrug resistance contributed to treatment failure. While these are observational data and caution must be exhibited when interpreting them, the second study highlights a potentially concerning trend of increasing *M. haemolytica* multidrug resistance in isolates from BRD submissions.[32,33] Concern over increased antimicrobial resistance requires the development of strategies that combat resistance. The substantial improvements in clinical outcomes observed with concomitant therapy in the present study may be evidence that this is a strategy that may be successful in overcoming or preventing

multidrug resistance at some level.

One possible method for improved clinical outcomes with concomitant therapy is by exploiting the phenomenon of collateral sensitivity, in which bacteria or cancer cells, when developing resistance to one drug, develop increased sensitivity to another drug.[12,34,35] *In vitro* studies have shown that *Escherichia coli* strains resistant to a particular antimicrobial can exhibit increasing sensitivity to one or more other antimicrobials.[12,34] With respect to the drug classes in the present study (macrolide and beta-lactam), Imamovic et al[12] did not observe in vitro collateral sensitivity in *E. coli* (ie, *E. coli* strains resistant to the beta-lactams tested were no more sensitive to the macrolide tested and vice versa). However, it is important to note that collateral sensitivity profiles are likely specific to each pathogen of interest,[12] and it has been previously demonstrated that resistance profiles in non-type specific *E. coli* do not predict resistance profiles in *M. haemolytica* isolates from the same animal.[36] As such, *E. coli* resistance research may not be generalizable to the common pathogens associated with BRD, and the phenomenon of collateral sensitivity could still possibly explain the improved health outcomes observed in the concomitant group in the present study.

The vastly improved animal health and animal welfare outcomes observed in the present study indicate that the concomitant administration of Draxxin and Excede is very effective for treating AF (largely attributed to BRD) in a clinical setting. Previous *in vitro* evaluation of the efficacy of these two antimicrobials on isolates of *P. multocida* and *M. haemolytica* did not produce a synergistic *in vitro* effect.[37] However, the correlation between *in vitro* evaluation and in vivo clinical effect is unknown. Moreover, neither Draxxin nor Excede were evaluated individually in the present study; therefore, the relative *in vivo* effects of concomitant therapy compared to monotherapy with these antimicrobials cannot be determined.

In summary, the selection of antimicrobials to be used for concomitant therapy should consider factors such as duration of therapy, antimicrobial class, targeted pathogen, collateral sensitivity profiles, antimicrobial stewardship, and the risk of antimicrobial resistance development. However, it is perhaps more important to continually seek cost-effective therapies for UF/BRD that improve clinical outcomes and animal welfare. In the present study, concomitant administration of Draxxin and Excede for the treatment of initial AF cases was shown to substantially reduce morbidity and mortality (approximately a 50% reduction in overall mortality to feedlot exit), which obviously has meaningful positive impacts on animal welfare. Future large pen commercial research should focus on identifying and evaluating alternative therapeutic approaches, including strategic use of concomitant therapy, that further improve clinical outcomes for UF/BRD and animal welfare. Whenever possible, these studies should also investigate the effects that these treatment strategies have on antimicrobial resistance/susceptibility.

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