Influence of therapeutic use of feedgrade tetracyclines in combination with tulathromycin metaphylaxis on animal health and performance of Holstein steer calves[1]

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ABSTRACT: Feedgrade chlortetracycline (CTC) and oxytetracycline (OTC) are approved for use in beef cattle diets for the control of bovine respiratory disease (BRD). The objectives of this experiment were to compare CTC and OTC, administered according to label, for the treatment of BRD in Holstein calves and to characterize the influence of tulathromycin metaphylaxis in combination with tetracycline treatment. Summer-placed Holstein steer calves (n = 6,800) were randomly assigned to one of four treatments (11 blocks; initial BW = 140 ± 18 kg) as they passed through the squeeze chute at initial processing in a commercial feedlot. Treatments consisted of: (i) CTC and tulathromycin metaphylaxis (CTC+TUL), (ii) OTC and tulathromycin metaphylaxis (OTC+TUL), (iii) tulathromycin metaphylaxis only (TUL), or (iv) CTC only (CTC). Cattle were fed for an average of 118 d. Tetracycline feeding was instituted based on visual assessment of the attending veterinarian in accordance with the veterinary feed directive. When applicable, CTC was fed as a topdress at a rate of 4 g CTC·steer^{-1}·d^{-1} for 5 consecutive days, beginning on 6 d on feed (DOF). Three 5-d pulses were delivered to CTC+TUL and CTC cattle, with a 48-h time lapse between pulses. Cattle on OTC+TUL were administered 4 g OTC·steer^{-1}·d^{-1} as part of a complete diet for 14 consecutive days beginning on 10 DOF. Within the first 30 d of the feeding period, BRD first pulls were reduced (P = 0.001) for CTC+TUL, OTC+TUL, and TUL relative to CTC alone. Percentage of BRD first pulls and total morbidity were lowest (P = 0.001) for CTC+TUL across the feeding period, with OTC+TUL and TUL being intermediate, and CTC alone exhibiting the highest percentage. Death loss and railers were not influenced ($P \geq 0.58$) by treatment. Dry matter intake was greater (P = 0.001) for CTC+TUL than all other treatments. Final BW and ADG were greatest for CTC+TUL, lowest for TUL alone, and intermediate for the remaining treatments ($P < 0.05$) on a deads-and-railers-out basis. Deads-and-railers-in ADG was greatest ($P < 0.05$) for CTC+TUL compared to all other treatments. Feed conversion was not influenced ($P \geq 0.22$) by treatment. In the current study, supplementation of OTC in combination with tulathromycin metaphylaxis did not benefit health over tulathromycin alone. Results suggest that CTC in combination with tulathromycin metaphylaxis reduces morbidity in Holstein steers calves, which may lead to improved performance.

Key words: bovine respiratory disease, cattle, feedgrade tetracyclines, health, metaphylaxis

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INTRODUCTION

Cattle entering the feedlot, particularly those that are lightweight and/or high risk, are more susceptible to bovine respiratory disease (BRD) than any other health challenge (Taylor et al., 2010b). In weaned dairy calves specifically, BRD is the primary cause of death; a fact that has remained unchanged in the last few decades, demonstrating a need for improvement in preventing and controlling the disease (Gordon and Plummer, 2010). BRD is multi-factorial in nature, as it involves infectious disease agents, compromised host immunity, and environmental factors that may include transport and feedlot processing activities that ultimately result in bronchopneumonia (Grissett et al., 2015). Therefore, implementing health and production strategies in lightweight cattle is necessary for reducing stress, minimizing disease, and optimizing performance (Nickell and White, 2010). Despite the improvements in managing feedlot health in recent years, the complex nature of BRD, in addition to an ever-changing landscape of government regulation, perpetuates morbidity and mortality rates in the feedlot (Windeyer et al., 2017).

One method for controlling BRD in newly received cattle is through the therapeutic use of feedgrade tetracyclines. Chlortetracycline (CTC) and oxytetracycline (OTC) are 2 naturally occurring tetracycline compounds approved for use in beef cattle diets. Feeding antimicrobials may be beneficial in decreasing the amount of "pulls" from the feedlot home pen and the associated stress of being removed and doctored (Thomson and White, 2015). Consequently, the judicial use of feedgrade antibiotics, in accordance with the VFD, may decrease the necessity for injectable antibiotics from antimicrobial classes which are categorized as "highest priority critically important antimicrobials" by the World Health Organization (third-generation cephalosporins, fluoroquinolones, and macrolides) (Agga, Schmidt, and Arthur, 2016). Aside from chemical structure, differences between OTC and CTC relate to their physical application (feed delivery), their antimicrobial properties, and their absorption into the bloodstream (bioavailability) (Agwuh and MacGowan, 2006). Feed application of the type A version of these tetracyclines differs in that OTC contains a higher concentration than CTC (220 and 440 g/kg for type A CTC and OTC, respectively), which decreases bulk in the ration, labor, and batching times when included in a complete diet, relative to CTC; however, CTC is also available as a type C product which may be administered in a top-dress application to eliminate related milling issues.

Data that compare the bioavailability and/or efficacy of CTC vs. OTC in cattle are limited. When treating non-intestinal pathogens such as BRD with oral antibiotics, it is imperative that the antimicrobial be effectively absorbed into the bloodstream to reach targeted tissues of the respiratory tract (del Castillo et al., 1998). Luthman and Jacobsson (1983) observed greater bioavailability of CTC relative to OTC (37% vs. 5%, respectively) following oral administration to non-fasted calves, concluding that CTC is more suitable than OTC for oral therapy. However, limited data exist that evaluate and compare the therapeutic use of feedgrade tetracyclines in reducing BRD, particularly in lightweight Holstein calves.

A second and more characterized method for controlling BRD in lightweight, high-risk calves is metaphylaxis, which is the mass medication of calves with antibiotics upon arrival to the feedlot (Abell et al., 2017). While metaphylaxis is effective at reducing morbidity and mortality, the prevalence and challenges associated with BRD remain, suggesting a need for additional measures for control of the disease (Ives and Richeson, 2015). Therefore, the objectives of this experiment were to compare feedgrade CTC and OTC for the treatment of BRD in Holstein calves and to characterize the influence of tulathromycin metaphylaxis in combination with the use of feedgrade tetracyclines.

MATERIALS AND METHODS

This study was conducted from July 2017 and December 2017 in a feedyard in southwestern Arizona and followed an approved protocol whereby routine management practices of the commercial feedlot are in accordance with 7 U.S.C. 54 and FASS (2010).

Cattle Arrival and Processing

Summer-placed Holstein steer calves (n = 6,800; initial BW = 140 ± 18 kg) acquired from various dairy farms in the western United States, which underwent standard dairy calf management including colostrum feeding, standard vaccination procedures, and acclimation to grain-based diets, were used in this trial. Steers were received between July 27, 2017 and August 26, 2017, allowed an average of 3 d rest (range = 1 to 5 d) with access to feed and water, prior to being randomized to one of four4 treatments as they passed through the

squeeze chute at initial processing using a chute-side personal computer containing a randomization application. As cattle exited the squeeze chute, they were sorted into one of four pens according to treatment assignment. Sort pens were then assigned to home pens via a randomization function (Excel, Microsoft Corporation, Redmond, WA). The study was comprised of 44 pens, divided into 11 blocks of four treatments each. Pens within a statistical block were provided similar area (32.3 and 39 m^2 for blocks 1 to 6 and 7 to 11, respectively) and bunk space (27.4 and 30.5 cm per animal for blocks 1 to 6 and 7 to 11, respectively) and were oriented in the same direction regarding pen slope. Water tank space was identical among pens within a statistical block (2.4 and 4.6 cm per animal for blocks 1 to 6 and 7 to 11, respectively).

Cattle were administered various products at processing, following a standardized feedlot protocol which included a dangle identification tag in each ear, 2 mL s.c. in the neck of a five-way modified-live respiratory vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN), 1 mL per naris of an intranasal respiratory vaccine (Nasalgen IP, Merck Animal Health, Madison, NJ), 2 mL s.c. in the neck of a seven-way clostridial vaccine for protection against *Clostridium* bacteria (Ultrachoice 7, Zoetis, Kalamazoo, MI), a growth implant in the middle third of caudal aspect of the ear (Synovex C, Zoetis), and 3.5 mL per animal s.c. in the neck of tulathromycin (Draxxin, Zoetis Animal Health, Kalamazoo, MI) when applicable due to treatment assignment. After processing each block of steers, sort pens within block were weighed across a platform scale before moving cattle to one of four adjacent home pens in the feedlot. Platform scale weights served as initial weights for the study.

Experimental Design and Treatments

Experimental treatments were designed to compare two different tetracycline molecules, CTC (Aureomycin, Zoetis Animal Health) and OTC (Terramycin, Phibro Animal Health, Teaneck, NJ), and to evaluate tulathromycin (Draxxin, Zoetis Animal Health) metaphylaxis on health and performance of Holstein steer calves. Cattle were assigned to one of four treatments: (i) CTC and tulathromycin metaphylaxis (CTC+TUL), (ii) OTC and tulathromycin metaphylaxis (OTC+TUL), (iii) tulathromycin metaphylaxis only (TUL), or (iv) CTC only (CTC). Tetracycline feeding was instituted based upon the assessment of the attending veterinarian in accordance with the Veterinary Feed Directive, using visual signs of anorexia, dull eyes, depression, weakness, cough, nasal discharge, watery eyes, lack of fill, stiff gait, loose feces, and increased respiratory rate. Feedgrade CTC is approved for use in beef cattle diets for control of bacterial pneumonia associated with the shipping fever complex caused by *Pasteurella* species susceptible to CTC when fed continuously at 350 mg·animal^{-1}·d^{-1}. Additionally, CTC is approved for treatment of bacterial pneumonia cause by *P. multocida* organisms susceptible to CTC when fed at 22 mg/kg BW daily for no more than 5 consecutive days. OTC is approved for treatment of bacterial pneumonia (shipping fever complex) caused by *Pasteurella multocida* susceptible to OTC fed at 22 mg/kg BW daily for 7 to 14 d.

Chlortetracycline was fed as a top-dress once daily using a commercially available type C pelleted top-dress containing 8.8 g/kg CTC, when applicable, at a rate of 4 g CTC·steer^{-1}·d^{-1} (22 mg/kg BW) for 5 consecutive days starting at 6 d on feed (DOF) (Table 1). Six DOF was chosen as the start date for CTC in an effort to maximize the concentration of CTC in lung tissue, based on results from previous studies (Wallace et al., 2009; Thomson et al., 2014). CTC and CTC+TUL calves continued to display BRD symptoms 48 h after the initial CTC pulse and were administered a second 5-d pulse of the same dose, per veterinary recommendation. Forty-eight hours following the second CTC pulse, calves continued to display BRD symptoms and were administered a third CTC pulse, again upon veterinary assessment and recommendation.

Cattle assigned to the OTC treatment were fed a complete feed formulated to provide 4 g OTC·steer^{-1}·d^{-1} (22 mg/kg BW) for 14 consecutive days starting at 10 DOF (Table 1). Ten DOF was selected to account for the starter ration fed previously, which contained an ionophore (Laidlomycin, Cattlyst, Zoetis Animal Health) not approved for combination with OTC. Actual OTC fed averaged 3.9 g·steer^{-1}·d^{-1} (range = 3.3 to 4.3 g·steer^{-1}·d^{-1}).

Complete feed was delivered once daily and consisted of steam-flaked corn, corn silage, alfalfa and sorghum-Sudan hay, tallow, corn-milling byproducts, and supplemental ingredients. All cattle were managed using the same feed management philosophy and were adapted to a finish ration using a single intermediate ration and a series of step-up feeding schedules. Laidlomycin type A (Cattlyst) was included in all diets (11.1 g/ton; dry matter basis), except during the OTC feeding period because of combination feeding restrictions.

Table 1. Treatment-dose regimen of feedgrade tetracyclines

Treatments	CTC+TUL[1]	OTC+TUL[2]	TUL[3]	CTC[4]
Item				
Tetracycline DOF[6]	Pulse[5] 1: 6 to 10 Pulse 2: 12 to 16 Pulse 3: 18 to 22	10 to 23	n/a	Pulse[5] 1: 6 to 10 Pulse 2: 12 to 16 Pulse 3: 18 to 22
Ionophore				
Pre-tetracycline phase	Laidlomycin[7]	Laidlomycin	Laidlomycin	Laidlomycin
Tetracycline phase	Laidlomycin	None	Laidlomycin	Laidlomycin
Tetracycline rest days	Laidlomycin	n/a	Laidlomycin	Laidlomycin
Post-tetracycline phase	Laidlomycin	Laidlomycin	Laidlomycin	Laidlomycin

[1]Chlortetracycline (Aureomycin type C pellet 8.8 g/kg, L.A. Hearn Company, King City, CA) fed at 4 g·steer^{-1}·d for three 5-d treatments plus metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) injection administered on arrival at 3.5 mL·steer^{-1}·d^{-1}.

[2]Oxytetracycline (Terramycin 200 type A 440 g/kg, Phibro Animal Health) fed at 4 g·steer^{-1}·d^{-1} for 14 consecutive days plus metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) injection administered on arrival at 3.5 mL·steer^{-1}·d^{-1}.

[3]Metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) administered on arrival at 3.5 mL·steer^{-1}·d^{-1}).

[4]Chlortetracycline (Aureomycin type C pellet 8.8 g/kg, L.A. Hearn Company) fed at 4 g·steer^{-1}·d^{-1} for three 5-d treatments.

[5]Animals were evaluated by a veterinarian 48 h after each treatment to determine if a subsequent second and third treatment were needed.

[6]Days on feed.

[7]Laidlomycin type A (110 g/kg), Cattlyst, Zoetis Animal Health.

Animal Health Management

Study cattle were observed daily by pen riders, between 0600 and 1000 hours, with a single pen rider examining all four pens within a statistical block when possible. Cattle were treated between 0900 and 1400 hours, with all cattle operations ceasing by 1100 hours in the month of August due to heat. All pulls within a block were treated at the same hospital facility. Cattle on CTC+TUL, OTC+TUL, and TUL experimental treatments were not eligible for pull and BRD treatment with injectable antibiotics until a 7-d postmetaphylaxis interval had been reached (Table 2). Table 3 provides the BRD injectable treatment regimen for cattle not receiving metaphylaxis. Post-treatment intervals for animals that relapsed and received additional injectable antibiotic therapy for BRD treatment were as follows: tulathromycin (Draxxin, Zoetis Animal Health), 7 d; florfenicol and flunixin meglumine (Resflor, Merck Animal Health), 4 d; danofloxacin (Advocin, Zoetis Animal Health), 3 d; OTC (Bio-Mycin 200, Boehringer Ingelheim Vetmedica, Duluth, GA), 2 d. Cattle pulled a fourth time for BRD were eligible for re-treatment with danofloxacin rather than being railed if 45 d had elapsed since receiving their last BRD treatment. Cattle were railed if requiring a fourth treatment for the same disease or if pulled for a disease for which no practical treatment plan was available at the feedyard. Florfenicol and flunixin meglumine was administered using a syringe fitted with 14 gauge x 1.9 cm needles, while all other injectable antimicrobials were administered using syringes fitted with 16 gauge x 1.6 cm needles. All antibiotics were administered s.c. according to Beef Quality Assurance guidelines. One case of treatment noncompliance was reported in the TUL treatment group; this steer received an antimicrobial labeled for treatment of BRD that was not included in the regimen in Table 2. This animal was retained in the data set during statistical analysis.

Standard feedlot protocols were implemented for the treatment of diseases unrelated to BRD and were consistent for cattle across experimental treatments. Cattle were allowed to convalesce in hospital pens for a minimum of 24 h before returning to home pens. Post-treatment interval and clinical appearance were used to determine whether cattle should return to the home pen or receive a subsequent treatment. Mortalities were subject to postmortem examination by a licensed veterinarian or trained feedlot employee. Upon study completion, steers were weighed across a platform scale before being re-implanted between 116 and 121 DOF. These pen weights served as the official final pen weights for the study.

Statistical Analysis

Data were analyzed as a randomized complete block design with pen as experimental unit. Continuous data (e.g., initial BW) were analyzed using the MIXED procedure (SAS 9.4 Inc., Cary,

Table 2. BRD[1] injectable treatment regimen for cattle receiving tulathromycin[2] metaphylaxis

Pull order[3]	Rectal temperature ≥40 °C	Rectal temperature <40 °C
1	Florfenicol and flunixin meglumine[4]	Oxytetracycline[5]
2	Danofloxacin[6]	Florfenicol and flunixin meglumine
3	Rail	Danofloxacin
4	n/a	Rail

[1]Bovine respiratory disease.

[2]Tulathromycin (100 mg/mL) administered at 3.5 mL/animal; Draxxin, Zoetis Animal Health.

[3]A post-metaphylactic interval of 7 d was imposed prior to cattle being eligible for treatment with an injectable antibiotic.

[4]Florfenicol (300 mg/mL) and flunixin meglumine (16.5mg/mL) administered at 6 mL/45.4 kg BW; Resflor, Merck Animal Health; post-treatment interval was 4 d.

[5]Oxytetracycline (200 mg/mL) administered at 4.5 mL/45.4 kg BW; Bio-Mycin 200, Boehringer Ingelheim Vetmedica; post-treatment interval was 2 d.

[6]Danofloxacin (180 mg/mL) administered at 2 mL/45.4 kg BW; Advocin, Zoetis Animal Health; post-treatment interval was 3 d.

Table 3. BRD[1] injectable treatment regimen for cattle not receiving metaphylaxis

Pull order	Rectal temperature ≥40 °C	Rectal temperature <40 °C
1	Tulathromycin[2]	Oxytetracycline[3]
2	Florfenicol and flunixin meglumine[4]	Tulathromycin
3	Danofloxacin[5]	Danofloxacin
4	Rail	Rail

[1]Bovine respiratory disease.

[2]Tulathromycin (100 mg/mL) administered at 1.13 mL/45.4 kg BW; Draxxin, Zoetis Animal Health; post-treatment interval of 7 d.

[3]Oxytetracycline (200 mg/mL) administered at 4.5 mL/45.4 kg BW; Bio-Mycin 200, Boehringer Ingelheim Vetmedica; post-treatment interval of 2 d.

[4]Florfenicol (300 mg/mL) and flunixin meglumine (16.5 mg/mL) administered at 6 mL/45.4 kg BW; Resflor, Merck Animal Health; post-treatment interval of 4 d.

[5]Danofloxacin (180 mg/mL) administered at 2 mL/45.4 kg BW; Advocin, Zoetis Animal Health; post-treatment interval of 3 d.

NC), with treatment as a fixed effect and block as a random effect. A generalized linear mixed model (GLIMMIX, SAS 9.4 Inc.) was used to analyze categorical data with the model effects described previously. Model estimation was performed using a logit scale to link events/trials responses to a binomial distribution. Initial estimates of treatment means and respective standard errors are reported on the data scale using an inverse link method (ILINK Option, SAS 9.4 Inc.). When overall treatment effect was significant ($P < 0.10$), treatment means were partitioned using Tukey's HSD post hoc analysis.

RESULTS

First BRD pulls (rectal temperature ≥40 °C) were lower ($P < 0.05$) for CTC+TUL and OTC+TUL in the first 30 DOF compared to TUL and CTC and lower ($P < 0.05$) for CTC+TUL compared to all other treatments over the entire feeding period (Table 4). Total morbidity was lowest for CTC+TUL cattle, greatest for CTC cattle, and intermediate for OTC+TUL and TUL treatments ($P < 0.05$). However, mortality, railers, and wastage (sum of mortality and railers) were not influenced ($P \geq 0.58$) by treatment.

Cattle were fed for an average of 118 d. Dry matter intake was greater ($P < 0.05$) for CTC+TUL compared to all other treatments (Table 5). Final BW and ADG were greater ($P < 0.05$) for CTC+TUL compared to OTC+TUL, TUL, and CTC and were lower ($P < 0.05$) for TUL cattle relative to OTC+TUL or CTC treatments on a deads-and-railers-out basis. On a deads-and-railers-in basis, final BW was greater ($P < 0.05$) for CTC+TUL compared to TUL or CTC alone, but was similar ($P = 0.16$) to OTC+TUL. ADG was greater ($P < 0.05$) for CTC+TUL cattle than TUL or CTC treatments with OTC+TUL animals being intermediate ($P < 0.05$) on a deads-and-railers-in basis. Treatment had no effect ($P > 0.22$) on G:F on a DM basis.

DISCUSSION

In the current study, tulathromycin metaphylaxis alone improved health over feeding CTC alone and was overall similar to OTC+TUL. Several studies have demonstrated reductions in morbidity when implementing metaphylaxis with parenteral antibiotics upon arrival of young cattle to the feedlot (van Donkersgoed, 1992; Frank et al., 2002; Macartney et al., 2003) and more specifically when administering tulathromycin on arrival (Step et al., 2007; Wellman and O'Connor, 2007). Furthermore, Rooney et al. (2005), in three separate studies, observed superior efficacy of tulathromycin at decreasing morbidity and mortality in newly received, high-risk calves compared to tilmicosin and florfenicol. Chlortetracycline alone did not improve health relative to other treatments in the current study; however, it is important to note that there was not a negative control treatment for full evaluation of its effect. Other studies have demonstrated health improvements in response to oral CTC. First pulls and morbidity were reduced in multiple earlier studies in cattle supplemented with CTC compared to negative control treatments

Table 4. Influence of feedgrade tetracycline and arrival metaphylaxis on health of Holstein steer calves

	Treatments					
Item	CTC+TUL[1]	OTC+TUL[2]	TUL[3]	CTC[4]	SEM	*P*-value[5]
No. of pens	11	11	11	11	—	—
BRD[6] first pulls ≥40 °C, % of enrolled						
First 30 DOF[7]	7.0[a]	6.8[a]	8.9[b]	13.0[c]	1.79	0.001
Entire feeding period	12.8[a]	16.2[b]	16.9[b]	19.7[c]	1.83	0.001
BRD first pulls, % of enrolled						
First 30 DOF	9.7[a]	9.3[a]	11.1[a]	15.9[b]	1.97	0.001
Entire feeding period	19.1[a]	22.8[b]	24.1[b,c]	25.8[c]	1.92	0.001
BRD relapses[8], % of all BRD first pulls	45.3	40.7	42.2	46.6	3.06	0.329
Bullers,[9] %	0.18	0.06	0.06	0.12	0.102	0.696
Skeletal morbidity, % of enrolled[10]	0.53	0.18	0.24	0.53	0.184	0.230
Other morbidity, % of enrolled	0.12	0.47	0.35	0.35	0.201	0.393
Total morbidity, % of enrolled[11]	20.0[a]	23.6[b]	24.9[b,c]	26.9[c]	1.97	0.001
Deathloss, % of enrolled						
BRD	0.93	1.17	1.46	1.17	0.303	0.576
Digestive	0.47	0.29	0.29	0.47	0.166	0.716
Other	0.46	0.58	0.35	0.29	0.196	0.581
Total	1.87	2.04	2.10	1.92	0.366	0.959
Railers, % of enrolled						
BRD	1.41	1.65	1.35	1.41	0.303	0.576
Total	1.58	1.87	1.46	1.81	0.343	0.765
DOF at time of death	49	59	48	49	6.7	0.550
DOF at time of rail	79	82	86	79	4.9	0.734
Wastage[12]	3.41	3.87	3.53	3.70	0.526	0.894

[a–c]Treatments with unlike superscripts differ ($P \leq 0.10$).

[1]Chlortetracycline (Aureomycin type C pellet 8.8 g/kg, L.A. Hearn Company) fed at 4 g·steer^{-1}·d^{-1} for three 5-d treatments beginning on day 6 plus metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) injection administered on arrival at 3.5 mL·steer^{-1}·d^{-1}; animals were assessed by a veterinarian 48-h after each treatment dose to determine if a second or third subsequent dose was necessary.

[2]Oxytetracycline (Terramycin type A 440 g/kg, Phibro Animal Health) fed at 4 g·steer^{-1}·d^{-1} for 14 consecutive d beginning on day 10 plus metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) injection administered on arrival at 3.5 mL·steer^{-1}·d^{-1}.

[3]Metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) administered on arrival at 3.5 mL·steer^{-1}·d^{-1}.

[4]Chlortetracycline (Aureomycin type C pellet 8.8 g/kg, L.A. Hearn Company) fed at 4 g·steer^{-1}·d^{-1} for three 5-d treatments.

[5]*P*-value associated with the overall effect of experimental treatment.

[6]Bovine respiratory disease.

[7]Days on feed.

[8]Cattle treated for BRD more than once.

[9]Steers repeatedly mounted by pen cohorts.

[10]Injuries or diseases related to skeletal structures of the feet, limbs, back, shoulder, and hip.

[11]Total first pulls for all diseases includes bullers.

[12]Death loss plus railers.

(Hale et al., 1967; Drake, Smart, and Smith, 1968). More recently, Thomson et al. (2014) reported improvement morbidity and re-treatment rates when feeding CTC and decoquinate to steers when compared to negative control animals. Perhaps most notable with regard to health in the current study was the improvement in health variables in cattle on the CTC+TUL treatment relative to all other treatments, as evidenced by a decrease in morbidity. This may suggest an additive effect of CTC and TUL on improving health. However, studies examining the implementation of tetracyclines fed at therapeutic doses in combination with metaphylaxis are quite limited. Wallace et al. (2009) did not observe a similar additive effect of tulathromycin and CTC on health variables when compared to diets containing no CTC; however, CTC was top-dressed for only two 5-d treatments, rather than 3, and began earlier in the feeding period (one and seven DOF) than the current study, which may indicate that the timing of the treatment doses should have been delayed for a more optimal response.

Performance overall was improved for the CTC+TUL treatment relative to other treatments and may partly be explained by the increase in DMI observed, as healthy cattle tend to consume more

Table 5. Influence of feedgrade tetracycline and arrival metaphylaxis on growth performance of Holstein steer calves

	Treatments					
Item	CTC+TUL[1]	OTC+TUL[2]	TUL[3]	CTC[4]	SEM	*P*-value[5]
No. of pens	11	11	11	11	—	—
Steers enrolled	1,700	1,700	1,700	1,700	—	—
Initial BW, kg[6]	142	141	141	141	2.45	0.70
DOF[7]	118	118	118	118	—	—
DMI, kg	5.36[a]	5.13[b]	5.08[b]	5.13[b]	0.07	0.001
Deads and railers out[8]						
Final BW, kg	301[a]	298[b]	293[c]	296[b]	3.45	0.001
ADG, kg	1.35[a]	1.33[b]	1.29[c]	1.31[b]	0.023	0.001
G:F	0.253	0.260	0.253	0.255	0.002	0.215
Deads and railers in[8]						
Final BW, kg	295[a]	291[a,b]	286[c]	288[b,c]	3.63	0.003
ADG, kg	1.27[a]	1.24[b]	1.21[c]	1.22[b,c]	0.014	0.001
G:F	0.238	0.242	0.236	0.236	0.001	0.376

[a–c]Treatments with unlike superscripts differ ($P \leq 0.10$).

[1]Chlortetracycline (Aureomycin type C pellet 8.8 g/kg, L.A. Hearn Company) fed at 4 g·steer^{-1}·d^{-1} for three 5-d treatments plus metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) injection administered on arrival at 3.5 mL·steer^{-1}·d^{-1}; animals were assessed by a veterinarian 48 h after each treatment dose to determine if a second or third subsequent dose was necessary.

[2]Oxytetracycline (Terramycin type A 440 g/kg, Phibro Animal Health) fed at 4 g·steer^{-1}·d^{-1} for 14 consecutive days plus metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) injection administered on arrival at 3.5 mL·steer^{-11}·d^{-1}.

[3]Metaphylaxis with tulathromycin (Draxxin 100 mg/mL, Zoetis Animal Health) administered on arrival at 3.5 mL·steer^{-1}·d^{-1}.

[4]Chlortetracycline (Aureomycin type C pellet 8.8 g/kg, L.A. Hearn Company) fed at 4 g·steer^{-1}·d^{-1} for three 5-d treatments.

[5]*P*-value associated with the overall effect of experimental treatment.

[6]Pen weights from cattle weighed in one or more drafts on a platform scale.

[7]Days on feed.

[8]Four percent pencil shrink applied.

feed than animals experiencing greater immunosuppression and subsequent decreased appetite. Repartitioning of nutrients away from growth and toward the immune system during an immune challenge further necessitates nutrient intake in order to minimize muscle protein degradation in immunosuppressed animals (Carroll and Forsberg, 2007). GrowSafe Technologies (GrowSafe Systems, Airdrie, Alberta, Canada) have indicated that a 30% decrease in time at the bunk occurs in newly received sick cattle and that feed intake differences are most pronounced during the first 4 d in the feedlot (Sowell et al., 1998, 1999). Effects of feeding CTC on DMI are variable across studies. Dry matter intake was increased in cattle fed CTC vs. control animals when cross-bred steers and heifers were finished on a grain-based diet that included a sub-therapeutic dosage of CTC (35 mg/kg DM; ad libitum feeding) for the duration of the trial (Beacom et al., 1988.) In contrast, no effect of CTC was observed on DMI compared to CTC in combination with sulfamethazine when fed to newly weaned calves in the feedlot for a 5-d treatment (five to nine DOF) at a rate of 6 g·animal^{-1}·d^{-1} (Gibb et al., 2006); a therapeutic dosage similar to the current study. Thomson et al. (2014) did observe an increase in DMI when feeding CTC (22 mg/kg BW) for a 5-d treatment (one to five DOF), in combination with decoquinate at 0.5 mg/kg BW. Clearly, these studies differ in dosage, feed-duration of CTC, and their respective treatment comparisons; therefore, it would be presumptuous to generalize across these trials. Furthermore, many factors contribute to DMI, such as ration composition, management conditions, disease incidence, which are likely variable across studies. Tulathromycin, when compared to other antibiotics administered to feedlot cattle, has elicited significantly lower undifferentiated fever, treatment and relapse rates, morbidity and mortality in addition to a greater DMI and ADG response, all of which are consistent with the current experiment (Booker et al., 2007). Given the results of the current study, it seems plausible that the tulathromycin in combination with CTC produced an additive feed intake response that did not occur when tulathromycin was fed in combination with OTC or when CTC or tulathromycin were administered alone. This may be a result of the health improvements observed in the CTC+TUL animals relative to other treatments.

Consistent with increased DMI was the improved final BW and ADG in CTC+TUL steers relative to other treatments, on a deads-and-railers-out basis. However, it is important to note that this improvement in ADG (1.2% and 2.4% on a deads-and-railers-in/out basis, respectively) was not reflected in improved feed efficiency, an important indicator of health status. Few studies have observed the effects of feeding CTC at a therapeutic 5-d treatment dose of 22 mg/kg of BW, while multiple studies have demonstrated improvements in ADG in cattle fed CTC at sub-therapeutic doses. Brown et al. (1975) conducted four feedlot trials in which ADG was improved over controls when CTC was fed at a rate of 70 mg·animal^{-1}·d^{-1} for the duration of the feeding period. Similarly, Beacom et al. (1988) fed CTC to finishing cattle in the feedlot at 35 mg·kg^{-1}·DM^{-1} on an ad libitum basis for the duration of the feeding period and observed increased ADG over controls. In a study where 4,325 high-risk feeder calves were fed a conventional ration plus a feed additive containing 350 mg·animal^{-1}·d^{-1} each of CTC and sulfamethazine from the time of arrival until 56 DOF, ADG was significantly improved, as were morbidity and mortality attributed to BRD (Gallo and Berg, 1995). Feeding CTC in a similar fashion to the current study, Kreikemeier et al. (1996) observed improved ADG over control cattle when feeding a therapeutic dose of CTC to newly received, high-stressed calves beginning on one DOF, for a 5-d treatment of 22 mg/kg of BW. Similarly, Thomson et al. (2014) fed a therapeutic dose of CTC (22 mg/kg BW) for a 5-d treatment beginning on either one or six DOF, depending on treatment, to newly received steer calves and observed improvements in ADG in all cattle receiving CTC vs. control animals. It should be noted here that CTC treatments in the Thomson et al. experiment received 0.5 mg/kg BW of a coccidiostat (decoquinate) in the diet for 28 d, whereas control steers did not.

Interestingly, in the current study, the TUL treatment exhibited decreased ADG compared to all other treatments when deads and railers were excluded, which further substantiates the possibility of an additive effect of CTC and tulathromycin metaphylaxis on performance. In contrast, as previously mentioned, Wallace et al. (2009) observed no differences in performance when administering tulathromycin metaphylaxis concurrent with feeding CTC; however, this is again most likely due to timing differences, in which the first CTC treatment was delayed until six DOF in the current study in an effort to maximize the concentration in the lung tissue in conjunction with tulathromycin.

An additional factor to consider is that the body of literature related to feeding CTC, OTC, or administering metaphylaxis to newly received, high-risk cattle upon arrival primarily consists of experiments conducted on beef breeds, rather than Holstein steers. Not only do dairy cattle possess different performance characteristics than typical beef breeds, such as a slightly lower ADG and greater DMI across the feeding period due to larger maintenance requirements, Holsteins are also more susceptible to environmental stressors because of their thinner hide and hair coat and less subcutaneous fat (Hulbert and Moisa, 2016). However, multiple studies have examined ex vivo immune factors and observed that after weaning, Holstein calves did not differ immunologically from their conventionally fed beef animal counterparts (Nonnecke et al., 2003; Foote et al., 2005, 2007; Ballou, 2012; Obeidat et al., 2013; Ballou et al., 2015). Nonetheless, we are not aware of any studies to date that have compared the effects of feedgrade CTC or OTC, or in combination with tulathromycin metaphylaxis, on Holstein steers entering the feedlot. It is also important to note that treatment effects are potentially more reliably interpreted in the current study due to the homogeneity of genetics among Holstein steers derived from calf ranches.

In conclusion, BRD continues to be the primary threat to newly received, high-risk feedlot cattle despite the use of metaphylaxis; therefore, it may be beneficial to administer feedgrade antibiotics in conjunction with metaphylaxis to improve health and performance of Holstein steers. Based on this study and prior research, it appears necessary to consider the timing of treatment dosing feedgrade tetracyclines relative to metaphylaxis. Feeding OTC in combination with tulathromycin metaphylaxis did not improve health over tulathromycin alone; whereas health parameters were improved when feeding CTC in combination with tulathromycin. To our knowledge, no other experiments to date have observed the effects of the therapeutic use of feedgrade tetracyclines in combination with tulathromycin metaphylaxis on Holstein steer calves. The homogeneity of genetics among Holsteins may suggest more repeatable results in the future and warrants further research of the combination of these health technologies to reduce BRD.

Conflict of interest statement. None declared.

LITERATURE CITED

Abell, K. M., M. E. Theurer, R. L. Larson, B. J. White, and M. Apley. 2017. A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease in beef cattle. J. Anim. Sci. 95(2):626–63. doi: 10.2527/jas.2016.1062

Agga, G. E., J. W. Schmidt, and T. M. Arthur. 2016. Effects of in-feed chlortetracycline prophylaxis in beef cattle on animal health and antimicrobial-resistant *Escherichia coli*. Appl. Environ. Microbiol. 82:7197–7204. doi:10.1128/AEM.01928-16

Agwuh, K. N. and A. MacGowan. 2006. Phamacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J. Antimicrob. Chemother. 58:256–265. doi: 10.1093/jac/dkl224

Ballou, M.A. 2012. Immune responses of Holstein and Jersey calves during the preweaning and immediate postweaned periods when fed varying planes of milk replacer. J. Dairy Sci. 95:7319–7330. doi:10.3168/jds.2012-5970

Ballou, M. A., D. L. Hanson, C. J. Cobb, B. S. Obeidat, M. D. Sellers, A. R. Pepper-Yowell, J. A. Carroll, T. J. Earleywine, and S. D. Lawhon. 2015. Plane of nutrition influences the performance, innate leukocyte responses, and resistance to an oral Salmonella enterica serotype typhimurium challenge in jersey calves. J. Dairy Sci. 98:1972–1982. doi:10.3168/jds.2014-8783

Beacom, S. E., Z. Mir, G. O. Korsrud, W. D. G. Yates, and J. D. MacNeil. 1988. Effect of the feed additives chlortetracyclines, monensin, and lasolocid on feedlot performance of finishing cattle, liver lesions, and tissue levels of chlortetracycline. Can. J. Anim. Sci. 68:1131–1141. doi:10.4141/cjas88-129

Booker, C. W., S. M. Abutarbush, O. C. Schunicht, G. K. Jim, T. Perrett, B. K. Wildman, P. T. Guichon, T. J. Pittman, C. Jones, and C. M. Pollock. 2007. Evaluation of the efficacy of tulathromycin as a metaphylactic antimicrobial in feedlot calves. Vet. Ther. 8:183–200.

Brown, H., R. F. Bing, H. P. Grueter, J. W. McAskill, C. O. Cooley, and R. P. Rathmacher. 1975. Tylosin and chlortetracycline for the prevention of liver abscesses, improved weight gains and feed efficiency in feedlot cattle. J. Anim. Sci. 40:207–213. doi:10.2527/jas1975.402207x

Carroll, J. A., and N. E. Forsberg. 2007. Influence of stress and nutrition on cattle immunity. Vet. Clin. North Am. Food Anim. Pract. 23:105–149. doi:10.1016/j.cvfa.2007.01.003.

del Castillo, J. R. E., J. Elsener, and G. P. Martineau. 1998. Pharmacokinetic modeling of in-feed tetracyclines in pigs using meta-analytic compartmental approach. J. Swine Health Prod. 6(5):189–202. http://www.aasp.org/shap.html

Drake, C. L., L. I. Smart, and E. F. Smith. 1968. The value of chlortetracycline (Aureomycin) and sulfamethazine fed independently and in combination to weanling beef calves following shipment. 1968 Kansas Cattlemen's Day Rep. Bull. 518, p. 61.

Foote, M. R., B. J. Nonnecke, D. C. Beitz, and W. R. Waters. 2007. High growth rate fails to enhance adaptive immune responses of neonatal calves and is associated with reduced lymphocyte viability. J. Dairy Sci. 90:404–417. doi:10.3168/jds.S0022-0302(07)72641-3

Foote, M. R., B. J. Nonnecke, W. R. Waters, M. V. Palmer, D. C. Beitz, M. A. Fowler, B. L. Miller, T. E. Johnson, and H. B. Perry. 2005. Effects of increased dietary protein and energy on composition and functional capacities of blood mononuclear cells from vaccinated, neonatal calves. Int. J. Vitam. Nutr. Res. 75:357–368. doi:10.1024/0300-9831.75.5.357.

Frank, G. H., R. E. Briggs, G. C. Duff, R. W. Loan, and C. W. Purdy. 2002. Effects of vaccination prior to transit and administration of florfenicol at time of arrival in a feedlot on the health of transported calves and detection of *Mannheimia haemolytica* in nasal secretions. Am. J. Vet. Res. 63:251–256. doi:10.2460/ajvr.2002.63.251

Gallo, G. F., and J. L. Berg. 1995. Efficacy of a feed-additive antibacterial combination for improving feedlot cattle performance and health. Can. Vet. J. 36:223–229.

Gibb, D. J., K. S., Schwartzkopf-Genswein, T. A. McAllister, B. M. A. Genswein, and M. Streeter. 2006. Effect of sub-therapeutic antibiotics and auction exposure on health, performance, and feeding behavior of weaned calves. Can. J. Anim. Sci. 86:457–460. doi:10.4141/A06-024

Gordon, P.J. and P. Plummer. 2010. Control, management, and prevention of bovine respiratory disease in dairy calves and cows. Vet. Clin. North Am. Food Anim. Pract. 26(2):243–259. doi: 10.1016/j.cvfa.2010.03.004

Grissett, G. P., B. J. White, and R. L. Larson. 2015. Structured literature review of responses of cattle to viral and bacterial pathogens causing bovine respiratory disease complex. J. Vet. Intern. Med. 29:770–780. doi:10.1111/jvim.12597

Hale, W. H., B. Taylor, B. Theurer, and H. Essig. 1967. Methods of starting new feeder calves. 1967 Arizona Cattle Feeders Day Rep., Series P-7. Tuscon, AS: University of Arizona Libraries, Special Collections.

Hulbert, L. E., and S. J. Moisá. 2016. Stress, immunity, and the management of calves. J. Dairy Sci. 99:3199–3216. doi:10.3168/jds.2015-10198

Ives, S. E., and J. T. Richeson. 2015. Use of antimicrobial metaphylaxis for the control of bovine respiratory disease in high-risk cattle. Vet. Clin. North Am. Food Anim. Pract. 31:341–50, v. doi:10.1016/j.cvfa.2015.05.008

Kreikemeier, K., G. Stokka, and T. Marston. 1996. Influence of delayed processing and mass medication with either chlortetracycline or tilmicosin phosphate on health and growth of highly stressed calves. Southwest Research-Extension Center Progress Report. 773:23–27.

Luthman, J. and S. O. Jacobsson. 1983. The availability of tetracyclines in calves. Nord. Vet. Med. 35:292–299.

Macartney, J. E., K. G. Bateman, and C. S. Ribble. 2003. Health performance of feeder calves sold at conventional auctions versus special auctions of vaccinated or conditioned calves in Ontario. J. Am. Vet. Med. Assoc. 223:677–683. doi:10.2460/javma.2003.223.677

Nickell, J. S., and B. J. White. 2010. Metaphylactic antimicrobial therapy for bovine respiratory disease in stocker and feedlot cattle. Vet. Clin. North Am. Food Anim. Pract. 26:285–301. doi:10.1016/j.cvfa.2010.04.006

Nonnecke, B. J., M. R. Foote, J. M. Smith, B. A. Pesch, and M. E. Van Amburgh. 2003. Composition and functional capacity of blood mononuclear leukocyte populations from neonatal calves on standard and intensified milk replacer diets. J. Dairy Sci. 86:3592–3604. doi:10.3168/jds.S0022-0302(03)73965-4

Obeidat, B. S., C. J. Cobb, M. D. Sellers, A. R. Pepper-Yowell, T. J. Earleywine, and M. A. Ballou. 2013. Plane of nutrition during the preweaning period but not the grower phase influences the neutrophil activity of Holstein calves.

J. Dairy Sci. 96:7155–7166. doi:10.3168/jds.2013-6699

Rooney, K. A., R. G. Nutsch, T. L. Skogerboe, D. J. Weigel, K. Gajewski, and W. R. Kilgore. 2005. Efficacy of tulathromycin compared with tilmicosin and florfenicol for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease. Vet. Ther. 6:154–166.

Sowell, B. F., J. G. P. Bowman, M. E. Branine, and M. E. Hubbert. 1998. Radio frequency technology to measure feeding behavior and health of feedlot steers. Appl. Anim. Behav. Sci. 59:277–284. doi:10.1016/S0168-1591(98)00110-5

Sowell, B. F., M. E. Branine, J. G. Bowman, M. E. Hubbert, H. E. Sherwood, and W. Quimby. 1999. Feeding and watering behavior of healthy and morbid steers in a commercial feedlot. J. Anim. Sci. 77:1105–1112. doi:10.2527/1999.7751105x

Step, D. L., T. Engelken, C. Romano, B. Holland, C. Krehbiel, J. C. Johnson, W. L. Bryson, C. M. Tucker, and E. J. Robb. 2007. Evaluation of three antimicrobial regimens used as metaphylaxis in stocker calves at high risk of developing bovine respiratory disease. Vet. Ther. 8:136–147.

Taylor, J. D., R. W. Fulton, T. W. Lehenbauer, D. L. Step, and A. W. Confer. 2010a. The epidemiology of bovine respiratory disease: what is the evidence for preventive measures? Can. Vet. J. 51:1351–1359.

Taylor, J. D., R. W. Fulton, T. W. Lehenbauer, D. L. Step, and A. W. Confer. 2010b. The epidemiology of bovine respiratory disease: what is the evidence for predisposing factors? Can. Vet. J. 51:1095–1102.

Thomson, D. U., R. S. Swingle, M. Branine, S. J. Bartle, and D. A. Yates. 2014. Effects of timing of chlortetracycline in combination with decoquinate on growth performance, health, and carcass characteristics of feeder steers. Bov. Pract. 48(2):120–128.

Thomson, D. U., and B. J. White. 2015. Feedlot production medicine. Vet. Clin. Food Anim. 31(3):11–12. doi:10.1016/j.cvfa.2015.08.001

Van Donkersgoed, J. 1992. Meta-analysis of field trials of antimicrobial mass medication for prophylaxis of bovine respiratory disease in feedlot cattle. Can. Vet. J. 33:786–795.

Wallace, J. O., C. D. Reinhardt, and D.U. Thomson. 2009. Concurrent metaphylaxis with aureomycin and Draxxin in high-risk calves has no additive effects on cattle health and performance. Kansas Agricultural Experiment Station Research Reports. doi:10.4148/2378–5977.1483

Wellman, N. G., and A. M. O'Connor. 2007. Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. J. Vet. Pharmacol. Ther. 30:234–241. doi:10.1111/j.1365-2885.2007.00846.x

Windeyer, M. C., E. Timsit, and H. Barkema. 2017. Bovine respiratory disease in pre-weaned dairy calves: are current preventative strategies good enough? Vet. J. 224:16–17. doi:10.1016/j.tvjl.2017.05.003