PEER REVIEWED

Treatment efficacy of tildipirosin or tulathromycin for first treatment of naturally occurring bovine respiratory disease in a commercial feedlot

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Abstract

Tildipirosin was compared to tulathromycin for treatment of bovine respiratory disease (BRD) in feedlot cattle. Six hundred calves identified with BRD by feedlot pen riders with a rectal temperature ≥ 104.0°F (≥ 40°C) and no previous treatments of disease were randomly allocated to treatment with either tildipirosin or tulathromycin in a 1:1 ratio within lot. Eligible lots included 2 different risk categories: 1) calves with low or moderate risk of developing BRD that did not receive a metaphylactic antimicrobial at arrival, or 2) calves determined to be at high risk of developing BRD that were administered a metaphylactic antimicrobial (tilmicosin) at arrival processing. Calves were returned to their home pen immediately after treatment and were monitored for 60 days. All enrolled animals which died during the study were necropsied by a veterinarian or trained feedlot personnel. Data were evaluated with generalized linear mixed models including lot as random effect comparing treatment groups and metaphylaxis status. No differences were observed (P>0.12) in health outcomes between the 2 treatment groups. Also, there were no differences in first treatment success or case fatality rate in calves with differing metaphylaxis status. Tildipirosin and tulathromycin were both effective antimicrobials for first treatment of BRD in medium- to low-risk populations of feedlot cattle.

Key words: bovine respiratory disease, BRD, feedlot, tildipirosin, tulathromycin, treatment

Résumé

La tildipirosine a été comparée à la tulathromycine pour le traitement du complexe respiratoire bovin (CRB) chez des bovins en parc d'engraissement. Les employés du parc ont identifié le CRB chez les veaux lorsque la température rectale était plus grande ou égale à 104.0°F (≥ 40°C). Un total de 600 veaux avec CRB et sans traitement au préalable pour la maladie ont été alloués au hasard à l'un des deux traitements (tildipirosine ou tulathromycine) en gardant un rapport de 1:1 dans chaque lot. Les lots éligibles incluaient deux catégories de risque possibles : 1) les veaux avec un risque faible ou modéré de développer le CRB et qui n'avaient pas reçu d'antibiotiques en métaphylaxie à l'arrivée, 2) les veaux à risque élevé de développer le CRB et qui avaient reçu un traitement antibiotique en métaphylaxie (tilmicosine) à l'arrivée. Les veaux étaient retournés à leurs enclos respectifs immédiatement après le traitement et ont été suivis pendant 60 jours. Tous les animaux inclus qui sont morts durant l'étude ont été nécropsiés par un vétérinaire ou par des employés formés du parc. Les données ont été évaluées avec des modèles linéaires mixtes généralisés incluant le lot comme effet aléatoire et le traitement et le statut en métaphylaxie comme effets fixes. Il n'y a pas eu de différence dans les résultats de santé (P > 0.12) entre les deux traitements. De plus, il n'y a pas eu de différence entre le succès au premier traitement ou le taux de létalité selon le statut en métaphylaxie. La tildipirosine et la tulathromycine étaient des antimicrobiens tout aussi efficace l'un que l'autre pour le premier traitement contre le CRB dans des populations de bovins en parc d'engraissement à risque faible ou modéré.

Introduction

Bovine respiratory disease (BRD) continues to be the most common and economically significant disease affecting the beef industry.[10] Costs attributable to BRD include the cost of treatment, increased mortality risk, decreased performance, and loss of carcass value.[3,4,11,21,25] Management strategies, vaccinations, and anti-infective products are used in an attempt to decrease incidence and severity of BRD.

The 2011 National Animal Health Monitoring System (NAHMS) survey of beef feedlots determined that > 93% of cattle were administered injectable respiratory vaccines, while antimicrobial metaphylaxis was administered to 21.3% of the cattle placed in the feedlot.[27] Both of these risk

mitigation practices have previously been shown to reduce incidence of BRD; however, BRD still occurs despite these practices.[20,23,26,28] In the same NAHMS survey, 16.2% of feedlot cattle were diagnosed with clinical BRD.[15,22,27] Cattle with BRD are commonly administered antimicrobial therapy. Several factors are used when selecting from antimicrobial options for treatment of BRD, including but not limited to efficacy, price, duration of action, and withdrawal period.

Tildipirosin has been evaluated for treatment of BRD.[9,16] Also, mixed treatment comparison meta-analyses have been performed evaluating tildipirosin against other commercially available antimicrobials for treatment of BRD[18,19] and metaphylaxis control of BRD.[1] These meta-analyses were performed with no direct comparisons of tildipirosin to other antimicrobials. Although indirect comparisons provide reasonable estimates, additional research is needed to determine treatment efficacy of tildipirosin in naturally occurring BRD cases compared to tulathromycin. Dodd et al reported improved first-treatment success, reduced BRD mortality, and reduced total mortality in calves treated with tulathromycin compared to tildipirosin in heifer calves with a high incidence of acute respiratory morbidity.[6] This population of calves experienced 75.9% respiratory morbidity in the first 10 days-on-feed (DOF), and represents only a small percentage of cattle on feed in typical commercial feedlots. The primary objective of this study was to compare treatment efficacy of tildipirosin to tulathromycin for first treatment of BRD and any association to subsequent health outcomes in a commercial feedlot placing calves at low to moderate risk of developing BRD. A secondary objective of the study was to compare health outcomes in calves initially treated for BRD ≥ 21 DOF that received metaphylactic tilmicosin at arrival processing compared to calves which did not receive a metaphylactic antimicrobial during arrival processing.

Materials and Methods

The study was performed at a commercial feedlot facility located near Montezuma, Kansas. The study began November 3, 2017 and concluded May 15, 2018. All procedures were approved by the Merck Animal Health Institutional Animal Care and Use Committee prior to study initiation.

Sample size

Bovine respiratory disease case fatality rate[7] was considered the primary outcome for this study and used to determine sample size estimates. Sample size was based on the ability to identify a difference of 7 percentage points with a baseline of 7%. Alpha was set at 0.05, and beta set to 0.20 using a commercial software package,[a] resulting in 300 calves per treatment group.

Animal enrollment

Calves were observed daily by pen riders for identification of BRD based upon subjective evaluation including physical appearance, attitude, gauntness, nasal discharge, and reluctance to move. Calves were removed from the home pen and moved to a hospital for confirmatory diagnosis and either enrollment into or exclusion from the study.

All calves identified by pen riders as having clinical signs of BRD were evaluated by a veterinarian (MET) prior to enrollment. Inclusion criteria for the study were rectal temperature ≥ 104.0°F (≥ 40°C), no previous treatments for disease, estimated > 60 days to harvest, and absence of clinical signs of disease in other organ systems. Eligible lots either did not receive a metaphylactic antimicrobial or did receive a metaphylactic antimicrobial at arrival processing (tilmicosin[b] 6 mg/lb [13.2 mg/kg] of body weight (BW) subcutaneously (SC); 2.0 mL/100 lb [45.5 kg] of BW). The decision whether or not to metaphylactically treat individual lots at arrival processing was made by feedyard personnel based upon subjective risk classification of the cattle at arrival into the feedlot. All lots of cattle in the feedlot were eligible to be enrolled based upon meeting the metaphylaxis processing inclusion criteria. Calves in lots that received a metaphylactic antibiotic were not eligible for inclusion in the study until ≥ 21 DOF. Once calves were enrolled from an individual lot, all first BRD treatments which met the inclusion criteria were enrolled into the study. There was a tentative eligible population of 56,178 calves at the time of this study, based upon lot inclusion criteria and enrollment period.

Calves meeting inclusion criteria were randomized in a 1:1 ratio to 1 of 2 treatment groups within each lot: tildipirosin[c] (TIL) (1.81 mg/lb [4 mg/kg] BW; 1 mL/100 lb of BW SC in left neck) or tulathromycin[d] (TUL) (1.13 mg/lb [2.5 mg/kg] BW; 1.1 mL/100 lb of BW SC in left neck) by different personnel (MET) than pen riders. An enrollment form was created to assign calves to treatment group in pairs within a lot; random numbers were assigned to each blank. The lowest random number within a pair was assigned to TIL[c] and the highest random number was assigned to TUL[d] within each pair. The first calf which met the case definition was assigned to the treatment group assigned to the first blank on the enrollment form. The next calf from the same lot which met the case definition was assigned to the second blank on the enrollment form. Calves were randomized to have treatments evenly distributed within lot; duplicate ear tags were used to identify each calf. Individual body weight and rectal temperature were collected for all calves enrolled, and were recorded in a feedlot animal health computer system.[e] Calves treated for BRD were returned to their home pen. Calves were monitored for 60 days to determine subsequent health outcomes by feedlot personnel blinded to the experimental treatment.

BRD retreatments

A 5-day post-treatment interval (PTI) was used for both the TIL and TUL treatment groups. Calves were eligible for retreatment if identified with clinical signs of BRD by pen riders, had a rectal temperature of ≥ 104.0°F (≥ 40°C)

and/or lost body weight from first treatment, and met or exceeded the PTI. All pen riders were blinded to treatment group. Calves requiring a second treatment for BRD were administered florfenicol[f] (18.14 mg/lb [40 mg/kg] of BW SC; 6 mL/100 lb BW). A 3-day PTI was used after the second treatment, and calves requiring a third treatment for BRD were administered enrofloxacin[g] (4.50 mg/lb [9.92 mg/kg] BW SC; 4.5 mL/100 lb of BW).

Gross necropsies

A gross necropsy was performed by a veterinarian or trained feedlot personnel on all enrolled animals which died during the study. A cause of death was determined for all calves that died during the monitoring period.

Feed, housing, and water

Calves were fed diets formulated to meet or exceed National Research Council maintenance requirements. Rations consisted of steam flaked corn, wet distillers' grains, ground alfalfa hay, chopped corn stalks, supplement, and ground prairie hay. No feed-grade antimicrobials labeled for control of BRD were fed to calves during the study. Calves were housed in dirt floor pens consistent with commercial feedlot operations. Water was provided *ad libitum* through an automatic float-activated system.

Data management

Data from all calves which died due to causes other than BRD, or required additional treatments not related to BRD, were removed prior to analysis. Binary variables were created for treatment successes and case fatality rate health outcomes. Treatment success was defined as not requiring additional treatment for BRD, and surviving the 60-day monitoring period. Case fatality rate was defined as the percentage of calves treated that died of BRD during the 60-day monitoring period. Treatment death interval was calculated from days of first treatment for BRD to the day of death for calves that died of BRD.

Statistical analyses

Data were imported into a commercial software package.[a] Continuous outcomes (enrollment body weight, enrollment rectal temperature, body weight at second treatment, rectal temperature at second treatment, body weight at third treatment, rectal temperature at third treatment, and treatment death interval) were evaluated with linear mixed models. Binary outcomes (treatment successes and case fatality rate) were evaluated using generalized linear mixed models. All models included a fixed effect of treatment group and random effect of origin lot. Differences exhibiting a P value ≤ 0.05 were considered statistically significant. Health outcomes were evaluated using a generalized linear mixed model where treatment, metaphylaxis status, and treatment by metaphylaxis status were used as fixed effects, and lot of origin was used as a random effect.

Results

A total of 600 calves were enrolled into the study (TIL n = 299; TUL n = 301). Seven calves were removed prior to analysis due to conditions not directly associated with BRD (TIL n = 4; TUL n = 3). Two calves with digestive disorders and 2 with heart failure were removed from the TIL group. One calf in the TUL group died of thromboembolic meningoencephalitis, 1 died of atypical interstitial pneumonia, and 1 calf sustained a shoulder injury during reimplant. These calf removals occurred prior to the end of the 60-day monitoring period, leaving 295 head in the TIL group for analysis, and 298 head in the TUL group. A total 430 calves were not administered a metaphylactic antibiotic at arrival, and 163 calves were administered tilmicosin during arrival processing and were enrolled with ≥ 21 DOF.

No differences in treatment success or case fatality rate were identified between the 2 treatment groups (Table 1). The statistical models evaluating body weight, rectal temperature, and treatment success at third treatment would not converge when constructed as described above, therefore the random effect for origin lot was removed from these models. There were no significant interactions between treatment group and metaphylaxis status for all health outcomes (P≥0.10; Table 2). Rectal temperature (P=0.02) at enrollment and rectal temperature at third treatment for BRD (P=0.02) were greater in calves not administered tilmicosin upon arrival processing compared to calves treated metaphylactically with tilmicosin at arrival processing (Table 3). No other differences in health outcomes were identified in the evaluation of metaphylaxis status.

Discussion

Results from this study indicate there were no differences in health outcomes in calves treated with tildipirosin compared to tulathromycin for first treatment of BRD. Judicious use of antimicrobials requires studies to follow cattle and evaluate treatment efficacies.[5] To the authors' knowledge, this is the first study to compare health outcomes for cattle which were metaphylactically administered tilmicosin on arrival and treated for BRD ≥ 21 DOF compared to calves which were not metaphylactically treated during arrival processing.

Results of the current study differ from a previous study comparing tildipirosin and tulathromycin for BRD treatment.[6] However, this may be explained by the referent populations used in each study. Dodd et al enrolled 75.9% of a high-risk contiguous arrival group over a 10-day period,[6] and the current study enrolled calves over a 133-day period from a feedlot population at low- to moderate-risk for developing BRD. Calves enrolled in the study by Dodd et al would likely be administered antimicrobials during arrival processing to reduce BRD in most commercial feedlot settings.[14] The average BRD incidence is 16.2%, and the frequency of lots with greater than 75% BRD morbidity is small.[24,27] The referent

Table 1. Model-adjusted least square means (± SE) of health outcomes for first treatment of bovine respiratory disease (BRD) by treatment group. *P*-value displayed is main effect of treatment group. Model included random effect for origin lot.

Outcome	Tildipirosin*	Tulathromycin†	*P*-value
Number of observations, *n*	295	298	-
Enrollment body weight, lb	799.44 ± 10.15	802.91 ± 10.15	0.71
Enrollment rectal temperature, °F	104.71 ± 0.04	104.68 ± 0.04	0.62
First treatment success,‡ %	80.72 ± 2.42	80.59 ± 2.44	0.97
BRD second treatment, %	15.25 ± 2.09	13.42 ± 1.97	0.52
Body weight at second treatment, lb	743.46 ± 24.99	773.46 ± 26.67	0.36
Rectal temperature at second BRD treatment, °F	104.35 ± 0.07	104.39 ± 0.08	0.68
Second treatment success,‡ %	64.46 ± 7.30	70.20 ± 7.49	0.58
BRD third treatment, %	2.68 ± 0.93	3.73 ± 1.10	0.47
Body weight at third treatment,§ lb	676.73 ± 38.62	735.63 ± 45.28	0.34
Rectal temperature at third BRD treatment,§ °F	104.35 ± 0.20	104.48 ± 0.17	0.62
Third treatment success,‡,§ %	27.27 ± 13.43	62.50 ± 17.12	0.12
BRD case fatality rate, %	6.17 ± 1.95	5.93 ± 1.95	0.89
Treatment death interval, d	21.98 ± 3.48	14.46 ± 3.43	0.13

* Tildipirosin, Zuprevo®, Merck Animal Health, Whitehouse Station, NJ

† Tulathromycin, Draxxin®, Zoetis Animal Health, Parsippany, NJ

‡ Treatment success defined as not requiring additional treatment for BRD and not dying of BRD within the 60-day monitoring period.

§ Third treatment outcomes did not include random effect for origin lot, as no lots had multiple observations in calves treated 3 times.

Table 2. Model-adjusted least square means (± SE) of health outcomes for first treatment of bovine respiratory disease (BRD) by treatment group and lot metaphylaxis with tilmicosin status. Model included random effect for origin lot. *P*-value is for treatment group by metaphylaxis interval. Eligible lots were not metaphylactically administered an antimicrobial during arrival processing program, or were metaphylactically administered tilmicosin* (2.0 mL/100 lb of body weight) upon arrival to the feedyard with ≥ 21 days on feed for first pull for BRD.

Outcome	Tildipirosin† No metaphylaxis	Tildipirosin† Metaphylaxis	Tulathromycin‡ No metaphylaxis	Tulathromycin‡ Metaphylaxis	*P*-value
Number of observations, *n*	218	77	212	86	-
Enrollment body weight, lb	811.84 ± 11.81	765.66 ± 19.25	806.56 ± 12.01	793.59 ± 18.48	0.12
Enrollment rectal temperature, °F	104.77 ± 0.05	104.53 ± 0.09	104.70 ± 0.05	104.61 ± 0.08	0.25
First treatment success,§ %	81.72 ± 2.76	77.95 ± 4.76	78.37 ± 2.98	86.10 ± 3.80	0.11
BRD second treatment, %	14.22 ± 2.37	18.18 ± 4.40	15.57 ± 2.49	8.14 ± 2.95	0.07
Body weight at second treatment, lb	774.81 ± 30.08	677.41 ± 43.53	780.30 ± 29.22	762.47 ± 62.63	0.33
Rectal temperature second BRD treatment, °F	104.26 ± 0.09	104.54 ± 0.13	104.37 ± 0.09	104.39 ± 0.19	0.28
Second treatment success,§ %	63.17 ± 9.16	67.19 ± 12.69	76.26 ± 7.88	42.06 ± 19.59	0.16
BRD third treatment, %	4.13 ± 1.35	2.60 ± 1.81	2.36 ± 1.04	3.49 ± 1.98	0.42
Body weight at third treatment,‖ lb	731.00 ± 38.99	532.00 ± 63.68	708.20 ± 49.32	781.33 ± 63.68	0.10
Rectal temperature third BRD treatment,‖ °F	104.25 ± 0.17	105.10 ± 0.28	104.24 ± 0.22	104.53 ± 0.28	0.25
Third treatment success,§,‖ %	33.33 ± 15.71	0.00 ± 0.00	60.00 ± 21.91	66.67 ± 27.22	0.27
BRD case fatality rate, %	5.90 ± 2.09	6.81 ± 3.19	6.04 ± 2.15	5.54 ± 2.76	0.72
Treatment death interval, d	25.63 ± 4.31	15.67 ± 5.88	14.76 ± 4.19	13.88 ± 6.02	0.38

* Micotil®, Elanco Animal Health, Greenfield, IN

† Tildipirosin, Zuprevo®, Merck Animal Health, Whitehouse Station, NJ

‡ Tulathromycin, Draxxin®, Zoetis Animal Health, Parsippany, NJ

§ Treatment success defined as not requiring additional treatment for BRD and not dying of BRD within the 60-day monitoring period.

‖ Third treatment outcomes did not include random effect for origin lot, as no lots had multiple observations in calves treated 3 times.

population in the current study may be more representative of the majority of commercial feedlot cattle.

Meta-analyses have been conducted evaluating treatment efficacy of different antimicrobials used for metaphylaxis[1,17] and BRD treatment.[18,19] These meta-analyses show advantages for using tulathromycin instead of tildipirosin for both BRD treatment and metaphylaxis, but the studies included for meta-analyses were commonly performed on high-risk cattle. Summarized results of meta-analyses of high-risk studies are only relevant to other similar referent populations. High-risk cattle experience greater treatment failure compared to low-risk cattle, but the difference be-

Table 3. Model-adjusted least square means (± SE) of health outcomes for first treatment of bovine respiratory disease (BRD) by lot metaphylaxis (with tilmicosin*) status. *P*-value displayed is main effect of metaphylaxis status. Model included random effect for origin lot.

Outcome	No metaphylaxis	Metaphylaxis	*P*-value
Number of observations, *n*	430	163	-
Enrollment body weight, lb	809.29 ± 10.56	780.95 ± 16.60	0.15
Enrollment rectal temperature, °F	104.74 ± 0.04	104.57 ± 0.06	0.02
First treatment success,† %	80.00 ± 1.93	82.21 ± 3.00	0.54
BRD second treatment, %	14.88 ± 1.71	12.88 ± 2.62	0.54
Body weight at second treatment, lb	772.86 ± 22.90	713.18 ± 38.59	0.19
Rectal temperature at second BRD treatment, °F	104.31 ± 0.07	104.52 ± 0.12	0.12
Second treatment success,† %	61.98 ± 10.75	68.78 ± 5.88	0.57
BRD third treatment, %	3.26 ± 0.86	3.07 ± 1.35	0.91
Body weight at third treatment,‡ lb	706.36 ± 35.13	688.00 ± 58.78	0.79
Rectal temperature at third BRD treatment,‡ °F	104.82 ± 0.14	104.28 ± 0.23	0.02
Third treatment success,†,‡ %	42.86 ± 0.13	40.00 ± 21.91	0.91
BRD case fatality rate, %	6.02 ± 1.84	6.16 ± 2.43	0.95
Treatment death interval, d	19.32 ± 3.00	15.41 ± 4.60	0.48

* Micotil®, Elanco Animal Health, Greenfield, IN

† Treatment success defined as not requiring additional treatment for BRD and not dying of BRD within the 60-day monitoring period

‡ Third treatment outcomes did not include random effect for origin lot, as no lots had multiple observations in calves treated 3 times

tween the risk classification is less with greater DOF.[2] Performing studies in medium- to low-risk populations of cattle provides data for future meta-analyses evaluating outcomes by risk classification.

Interestingly, there were no observed differences in health outcomes among calves not administered metaphylaxis upon arrival compared to calves which were administered tilmicosin metaphylaxis and subsequently pulled for BRD ≥ 21 DOF. Additionally, there were no significant ($P>0.05$) interactions between treatment group and metaphylaxis status. Metaphylaxis has been shown to shift the nasopharyngeal microbiota and antimicrobial susceptibility profile of BRD pathogens.[13,29] Additionally, nasopharyngeal microbiota and the antimicrobial susceptibility profile of BRD pathogens have been shown to change within the first 2 DOF[12] and between feedlot arrival and 90 DOF.[8] Additional work is needed to establish any association to clinically relevant outcomes, such as treatment failures, chronic animals, and mortality, and the results of in vitro antibiograms.

One limitation of this study was that calves were only monitored for 60 days post-enrollment, and no performance outcomes were collected. Sample size was determined based upon a large case fatality rate difference between treatment groups; however, clinically there appears to be minimal differences between treatment groups in the medium- to low-risk population of cattle evaluated. The power for identifying a difference in outcomes by metaphylaxis status was less than treatment comparison; however, these results provide initial results for further studies. Additional research is needed to evaluate treatment efficacies using antimicrobials that are in the same class as those used in a metaphylactic program.

Conclusions

No health differences were identified in calves treated with tildipirosin compared to tulathromycin for first treatment of BRD or between calves receiving a metaphylactic antibiotic compared to calves that did not. Tildipirosin and tulathromycin were effective antimicrobials for first treatment of BRD in the medium- to low-risk populations of cattle.

Endnotes

[a] R Studio Team 2016, Boston, MA
[b] Micotil®, Elanco Animal Health, Greenfield, IN
[c] Zuprevo®, Merck Animal Health, Whitehouse Station, NJ
[d] Draxxin®, Zoetis Animal Health, Parsippany, NJ
[e] Animal Management System, Animal Health International, Greeley, CO
[f] Nuflor®, Merck Animal Health, Whitehouse Station, NJ
[g] Baytril®, Bayer Animal Health, Shawnee, KS

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References

1. Abell KM, Theurer ME, Larson RL, White BJ, Apley M. A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease in beef cattle. *J Anim Sci* 2017; 95:626-635.
2. Avra TD, Abell KM, Shane DD, Theurer ME, Larson RL, White BJ. A retrospective analysis of risk factors associated with bovine respiratory disease treatment failure in feedlot cattle. *J Anim Sci* 2017; 95:1521-1527.
3. Brooks KR, Raper KC, Ward CE, Holland BP, Krehbiel CR, Step DL. Economic effects of bovine respiratory disease on feedlot cattle during backgrounding and finishing phases. *Prof Anim Sci* 2011; 27:195-203.
4. Cernicchiaro N, White BJ, Renter DG, Babcock AH. Evaluation of economic and performance outcomes associated with the number of treatments after an initial diagnosis of bovine respiratory disease in commercial feeder cattle. *Am J Vet Res* 2013; 74:300-309.
5. DeDonder KD, Apley MD. A review of the expected effects of antimicrobials in bovine respiratory disease treatment and control using outcomes from published randomized clinical trials with negative controls. *Vet Clin North Am Food Anim Pract* 2015; 31:97-111.
6. Dodd CC, Bechtol DT, Waite A, Corbin M, Renter DG. A randomized trial to compare the efficacy of tildipirosin and tulathromycin for initial treatment of bovine respiratory disease in naturally exposed commercial feedlot heifers. *Bov Pract* 2018; 52:39-45.
7. Dohoo I, Martin W, Stryhn H. Measures of disease frequency. In: *Veterinary epidemiologic research*. 2nd ed. Charlottetown, PEI, Canada: AVC Inc, 2009; 73-90.
8. Erickson N, Ngeleka M, Lubbers BV, Trokhymchuk A. Changes in the rates of field isolation and antimicrobial susceptibility of bacterial pathogens collected from fall-placed feedlot steers between arrival at the feedlot and 90 to 120 days on feed. *Bov Pract* 2017; 51:165-173.
9. Freedom of Information Summary. NADA 141-334 Zuprevo 18 – Original Approval. 2012. Available at https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/892. Accessed June 29, 2018.
10. Galyean ML, Perino LJ, Duff GC. Interaction of cattle health/immunity and nutrition. *J Anim Sci* 1999; 77:1120-1134.
11. Gardner BA, Dolezal HG, Bryant LK, Owens FN, Smith RA. Health of finishing steers: effects on performance, carcass traits, and meat tenderness. *J Anim Sci* 1999; 77:3168-3175.
12. Holman DB, Timsit E, Amat S, Abbott DW, Buret AG, Alexander TW. The nasopharyngeal microbiota of beef cattle before and after transport to a feedlot. *BMC Microbiol* 2017; 17:70.
13. Holman DB, Timsit E, Booker CW, Alexander TW. Injectable antimicrobials in commercial feedlot cattle and their effect on the nasopharyngeal microbiota and antimicrobial resistance. *Vet Microbiol* 2018; 214:140-147.
14. Ives SE, Richeson JT. Use of antimicrobial metaphylaxis for the control of bovine respiratory disease in high-risk cattle. *Vet Clin North Am Food Anim Pract* 2015; 31:341-350.
15. Lee TL, Terrell SP, Bartle SJ, Reinhardt CD, Apley MD, Rethorst D, Thomson DU. Current feedlot cattle health and well-being program recommendations in the United States and Canada: the 2014 feedlot veterinary consultant survey. *Bov Pract* 2015; 49:124-131.
16. Menge M, Rose M, Bohland C, Zschiesche E, Kilp S, Metz W, Allan M, Ropke R, Nurnberger M. Pharmacokinetics of tildipirosin in bovine plasma, lung tissue, and bronchial fluid (from live, nonanesthetized cattle). *J Vet Pharmacol Ther* 2012; 35:550-559.
17. Nautrup BP, Ilse Van Vlaenderen D, Decker M, Cleale RM. Antimicrobial drug use for control and treatment of bovine respiratory disease in US feedlot cattle: A meta-analysis of comparative studies versus tulathromycin. *Bov Pract* 2017; 51:1-13.
18. O'Connor AM, Coetzee JF, Silva Nd, Wang C. A mixed treatment comparison meta-analysis of antibiotic treatments for bovine respiratory disease. *Prev Vet Med* 2013; 110:77-87.
19. O'Connor AM, Yuan C, Cullen JN, Coetzee JF, da Silva N, Wang C. A mixed treatment meta-analysis of antibiotic treatment options for bovine respiratory disease - An update. *Prev Vet Med* 2016; 132:130-139.
20. Perino LJ, Hunsaker BD. A review of bovine respiratory disease vaccine field efficacy. *Bov Pract* 1997; 31:59-66.
21. Schneider MJ, Tait RGJ, Busby WD. An evaluation of bovine respiratory disease complex in feedlot cattle: Impact on performance and carcass traits using treatment records and lung lesion scores. *J Anim Sci* 2009; 87:1821-1827.
22. Terrell SP, Thomson DU, Wileman BW, Apley MD. A survey to describe current feeder cattle health and well-being program recommendations made by feedlot veterinary consultants in the United States and Canada. *Bov Pract* 2011; 45:140-148.
23. Theurer ME, Larson RL, White BJ. A systematic review and meta-analysis of commercially available vaccine effectiveness against bovine herpes virus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza-type 3 virus in cattle for bovine respiratory disease complex. *J Am Vet Med Assoc* 2015; 246:126-142.
24. Theurer ME, Renter DG, White BJ. Using feedlot operational data to make valid conclusions for improving health management. *Vet Clin North Am Food Anim Pract* 2015; 31:495-508.
25. Theurer ME, White BJ, Larson RL, Schroeder TC. A stochastic model to determine the economic value of changing diagnostic test characteristics for identification of cattle for treatment of bovine respiratory disease. *J Anim Sci* 2015; 93:1398-1410.
26. Tripp HM, Step DL, Krehbiel CR, Moberly HK, Malayer JR. Evaluation of outcomes in beef cattle comparing preventive health protocols utilizing viral respiratory vaccines *Bov Pract* 2013; 47:54-64.
27. USDA. Part IV: Health and health management on US feedlots with a capacity of 1,000 or more head. 2011. Accessed July 3, 2018.
28. Wileman BW, Thomson DU, Reinhardt CD, Renter DG. Analysis of modern technologies commonly used in beef cattle production: Conventional beef production versus non-conventional production using meta-analysis. *J Anim Sci* 2009; 87:3418-3426.
29. Zaheer R, Cook SR, Klima CL, Stanford K, Alexander T, Topp E, Read RR, McAllister TA. Effect of subtherapeutic vs therapeutic administration of macrolides on antimicrobial resistance in *Mannheimia haemolytica* and enterococci isolated from beef cattle. *Front Microbiol* 2013; 4:1-14.