A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease in beef cattle[1,2]

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ABSTRACT: The objective of this project was to evaluate the effects of antimicrobials approved for parenteral metaphylactic use in feeder and stocker calves on morbidity and mortality for bovine respiratory disease with the use of a mixed treatment comparison meta-analysis. An initial literature review was conducted in April 2016 through Pubmed, Agricola, and CAB (Commonwealth Agricultural Bureau) for randomized controlled trials for metaphylaxis antimicrobial administered parentally to incoming feedlot or stocker calves within 48 h of arrival. The final list of publications included 29 studies, with a total of 37 trials. There were 8 different metaphylactic antimicrobials. Final event outcomes were categorized into bovine respiratory disease (BRD) morbidity cumulative incidence d 1 to ≤ 60 of the feeding period, BRD morbidity cumulative incidence d 1 to closeout of the feeding period, BRD mortality cumulative incidence d 1 to closeout of the feeding period, and BRD retreatment cumulative incidence morbidity d 1 to closeout of the feeding period. Network meta-analysis combined direct and indirect evidence for all the event outcomes to determine mean odds ratio (OR) with 95% credibility intervals (CrIs) for all metaphylactic antimicrobial comparisons. The "upper tier" treatment arms for morbidity d 1 to ≤ 60 included tulathromycin, gamithromycin, and tilmicosin. For BRD mortality cumulative incidence d 1 to closeout and BRD retreatment morbidity d 1 to closeout, classifying the treatment arms into tiers was not possible due to overlapping 95% CrIs. The results of this project accurately identified differences between metaphylactic antimicrobials, and metaphylactic antimicrobial options appear to offer different outcomes on BRD morbidity and mortality odds in feedlot cattle.

Key words: antimicrobial, bovine respiratory disease, meta-analysis, metaphylaxis, mixed treatment comparison

INTRODUCTION

Bovine respiratory disease (**BRD**) complex is a well-documented, multi-faceted disease syndrome involving environmental factors, host factors, and management practices affecting the health and performance of feedlot calves (Kelly and Janzen, 1986; Smith, 1998). Marketing and shipment of cattle are associated with stress prior to feedlot arrival, which increases the risk for BRD of fed cattle (Lofgreen et al., 1978; Camp et al., 1981). Mass medication, also known as metaphylaxis, has been used to prevent BRD in groups of cattle arriving at feedlots with over half of United States feedlots using metaphylaxis on at least some groups of cattle near the time of feedlot arrival (USDA, 2011).

Multiple antimicrobials are currently available and used metaphylactically to decrease negative effects of BRD in groups of feedlot cattle, and the decision to implement a specific antimicrobial is dependent on the efficacy and cost effectiveness (Nickell and White, 2010). Clinical trials have been conducted to investigate the efficacy of antimicrobials for the treatment and control of BRD, and metaphylaxis uses have been investigated as a method to reduce morbidity and mortality associated with BRD in feedlot cattle (DeDonder and Apley, 2015; Ives and Richeson, 2015). Meta-analysis and systematic reviews of the available literature have been previously performed to summarize published clinical trials for antimicrobial treatment of clinical BRD cases and for specific antimicrobials used metaphylactically, but no systematic review or meta-analysis has been published that summarizes clinical trials for all approved parenterally administered metaphylactic antimicrobials (Van Donkersgoed, 1992; Wellman and O'Connor, 2007; Wileman et al., 2009; Nickell and White, 2010).

A mixed treatment comparison (**MTC**) meta-analysis can assess indirect comparisons between antimicrobials where an actual clinical trial was not performed (Higgins and Whitehead, 1996; Lu and Ades, 2004; Jansen et al., 2011). The indirect comparison have been proven to be realistic estimates of disease risk when direct estimates are not available (O'Connor et al., 2016). The MTC of meta-analysis has been done frequently in the human medical field (Mills et al., 2009; Roever and Biondi-Zoccai, 2016; Shao et al., 2016), and has previously evaluated antimicrobial efficacy for treatment of BRD (O'Connor et al., 2013). The objective of this research was to evaluate the effect of parenterally administered metaphylactic antimicrobials approved for feeder and stocker calves on morbidity and mortality due to BRD using a MTC meta-analysis. These results should aid in the understanding of the effect of metaphylactic antimicrobial options on clinically important BRD outcomes.

MATERIALS AND METHODS

Literature Search

An initial literature review was conducted in April 2016 by a reviewer (**KA**) using, AGRICOLA (all years available), Commonwealth Agricultural Bureau (all years available), and Pubmed (all years available) for retrieval of topics relevant to the objective. The search terms included [beef OR cattle OR cow or OR bovine OR steer OR heifer OR calf OR calves] AND [metaphyl* OR prophylactic]. An initial search revealed a total of 3753 papers. Titles of peer reviewed papers published in English that included the search terms were examined

for relevance. The initial search process was repeated with another independent reviewer (**RL**). Abstracts of relevant manuscripts were reviewed, and if agreed relevant, the full manuscript was acquired. Relevant manuscripts obtained by both reviewers were compared and only those relevant to the objective were fully reviewed. A third party reviewer was utilized if a disagreement between the first 2 reviewers occurred over the relevance of a manuscript. Studies were excluded if randomization was not reported. In addition, metaphylaxis antimicrobial had to be administered parentally to incoming feedlot or stocker calves within 48 h of arrival. Studies using young, lightweight veal or dairy calves were excluded; however, if age, weight, or type of cattle were specifically described and were consistent with cattle arriving at U.S. feedlots, the study was included in the analysis. Metaphylactic administration had to be the only treatment variable. Only naturally occurring BRD was used as study outcome and challenge studies were excluded from the analysis. Blinding was reported in 24 trials, and was not reported in 16 trials, all trials were included in the statistical analysis regardless of blinding criteria. In 2 trials, blinding was reported to have not been possible due to the person implementing the BRD treatment protocol having prior knowledge of previous antimicrobials administered metaphylactically (Van Donkersgoed, 2012; Van Donkersgoed and Merrill, 2013a).

Data Extraction

Outcome data comparing a metaphylactic antimicrobial to another antimicrobial or a control within each trial within each study was extracted (Larson and Step, 2012; Theurer et al., 2015). If a study contained multiple trials, the data from each trial were extracted separately. All data for each trial were extracted by a single reviewer (KA), and verified by a second reviewer (RL). A treatment arm was considered a different antimicrobial for each trial. For example, if a trial consisted of antimicrobial A and B, this trial included two different treatment arms. For each trial, the following data were extracted: the interventions (antimicrobial) for each treatment arm, the number of animals enrolled in each treatment arm, and event occurrence for each treatment arm (Table 1). Event occurrence included morbidity, retreatment morbidity, and mortality related to BRD. Data were aggregated between treatment arms within a trial if the difference between those treatment arms was due to a difference in the post metaphylactic interval or route of antimicrobial administration. For example, if the difference between 2 antimicrobial groups was the dosage of the antibiotic (tilmicosin 10 mg/kg and 20 mg/kg), then antimicrobials were aggregated to a single antimicrobial group (tilmicosin; Corbin et al., 2009). Also, if the difference between 2

Table 1. Data extracted from 37 individual trials and 29 studies included in the mixed treatment comparison meta-analysis for each outcome event

Treatment arms	Number of animals	EU/group[1]	Wt[2] (kg)	BRD morb to 60[3]	BRD morb to closeout[4]	BRD mort to closeout[5]	BRD retreat to closeout[6]	Trial
ceftiofur/gamithromycin	1853	931/922	205	354/295	–	–	–	(Amrine et al., 2014)
control/gamithromycin	87	44/43	582	12/8	–	–	–	(Baggott et al., 2011)
control/gamithromycin	242	121/121	390	32/8	–	–	–	(Baggott et al., 2011)
control/gamithromycin	227	114/113	430	32/6	–	–	–	(Baggott et al., 2011)
tilmicosin/oxytetracycline/ tulathromycin	9910	3304/3302/ 3304	300	–	464/562/113	62/84/10	179/218/26	(Booker et al., 2007)
tilmicosin/ceftiofur	11,605	3870/7735	256	–	1116/2120	423/626	713/1222	(Booker et al., 2007)
control/tilmicosin	1000	200/800	207	–	68/164	27/54	23/58	(Corbin et al., 2009)
control/tilmicosin	997	200/797	265	–	137/374	1/14	53/107	(Corbin et al., 2009)
control/tilmicosin	64	32/32	224	23/15	–	–	–	(Duff et al., 2000)
control/oxytetracycline	1793	893/900	120	71/30	–	–	–	(Fazzio et al., 2015)
control/florfenicol	60	30/30	230	13/10	–	–	–	(Frank et al., 2002)
control/florfenicol	42	21/21	230	12/9	–	–	–	(Frank et al., 2002)
control/tilmicosin	57	28/29	170	13/0	–	–	–	(Galyean et al., 1995)
control/tilmicosin	116	58/58	191	19/7	–	–	–	(Galyean et al., 1995)
control/tilmicosin	121	62/59	232	27/7	–	–	–	(Galyean et al., 1995)
control/tilmicosin	400	200/200	273	113/51	123/60	0/2	12/8	(Guthrie et al., 2004)
control/TMS/oxytetracycline	900	300/300/300	325	139/133/97	172/169/140	10/9/6	–	(Harland et al., 1991)
control/gamithromycin	308	154/154	293	64/34	–	–	–	(Lechtenberg et al., 2011)
control/gamithromycin	159	53/106	256	34/15	–	–	–	(Lechtenberg et al., 2011)
control/florfenicol	108	54/54	271	16/18	–	–	–	(Martin et al., 2007)
control/tilmicosin	199	100/99	215	54/15	–	–	–	(McClary and Vogel, 1999)
control/tilmicosin/ oxytetracycline	1806	601/602/603	300	254/117/157	–	–	–	(Morck et al., 1993)
tilmicosin/tulathromycin	293	147/146	219	100/48	–	20/5	–	(Nickell et al., 2008)
control/gamithromycin	250	125/125	350	43/6	–	–	–	(Rossi et al., 2010)
oxytetracycline/ gamithromycin	470	235/235	345	34/4	–	–	–	(Rossi et al., 2010)
tulathromycin/ gamithromycin	1136	568/568	325	83/53	–	–	–	(Rossi et al., 2010)
control/tilmicosin	305	154/151	337	35/8	–	–	–	(Schumann et al., 1990)
control/tilmicosin	205	103/102	269	21/2	–	–	–	(Schumann et al., 1991)
tilmicosin/oxytetracycline	10,989	5494/5495	281	–	1064/1239	77/85	409/454	(Schunicht et al., 2002)
tilmicosin/ceftiofur	385	194/191	–	14/18	–	–	–	(Step et al., 2007)
control/tilmicosin/ tulathromycin	2336	783/784/769	312	–	112/45/16	24/11/8	–	(Tennant et al., 2014)
tulathromycin/ gamithromycin	2529	1266/1263	230	274/361	–	–	–	(Torres et al., 2013)
tilmicosin/gamithromycin	5000	2500/2500	312	–	480/320	10/15	81/44	(Van Donkersgoed, 2012)
tilmicosin/tildipirosin	4500	2250/2250	336	–	608/338	20/20	79/54	(Van Donkersgoed and Merrill, 2013a)
control/tilmicosin	4314	2157/2157	348	–	259/173	9/2	53/33	(Van Donkersgoed and Merrill, 2013b)
tilmicosin/tulathromycin	4494	2250/2244	274	–	315/67	5/1	28/7	(Van Donkersgoed et al., 2008)
control/tilmicosin	1096	550/546	259	298/165	317/185	23/9	50/22	(Vogel et al., 1998)

[1]Experimental units per antimicrobial group.

[2]Allocation weight in kilograms.

[3]BRD morbidity cumulative incidence d 1 to $\leq$ 60 of the feeding period.

[4]BRD morbidity cumulative incidence d 1 to closeout of the feeding period.

[5]BRD mortality cumulative incidence d 1 to closeout.

[6]BRD retreatment cumulative incidence d 1 to closeout.

treatments with the same antimicrobial was due to post-metaphylactic interval (ceftiofur 3 PMI and 7 PMI), then antimicrobials were aggregated to a single antimicrobial group (ceftiofur; Booker et al., 2006).

BRD morbidity included calves that were enrolled in the trial and had to be treated for BRD. The protocol for BRD diagnosis needed to be described in the report, and had to include rectal temperature, clinical signs consistent with BRD, and administration of an antimicrobial. If this protocol was not outlined, the corresponding author was contacted for clarification of the protocol to diagnose BRD. Two corresponding authors were contacted and responded for clarification. If the results were given as a percent of animals in each treatment arm, then the event occurrence was extracted based on the total number of animals enrolled in that trial for each of the treatment arms. If the numerator and denominator used to calculate the percent could not be distinguished, the data were excluded in the analysis.

BRD retreatment morbidity was classified as animals initially diagnosed with BRD and treated with an antimicrobial that required an additional antimicrobial for BRD. If mortality data were not provided in the trial, or BRD mortality could not be distinguished from the overall mortality events, the mortality data were excluded in the analysis.

Treatment periods were established as either d 1 to $\leq$ 60 of the feeding period or d 1 to the end of the feeding period, and a single event could be classified as occurring in both treatment periods. The end of the feeding period is referred to as closeout. Day 1 included the day the metaphylactic treatment was given. If the monitoring period of the study was less than 60 d, the data were only included in the d 1 to $\leq$ 60 of the feeding period category. Trial days ranged from 7 to 60 d and this variability was accounted for in the analysis. If a trial included event results from d 1 to $\leq$ 60 over multiple periods, the event results closest to 60 d was included. Any trial data that did not fall into one of these categories were excluded.

Multiple Treatment Comparison Analysis

The effectiveness of each individual treatment arm for the BRD morbidity d 1 to $\leq$ 60 was examined using the binomial likelihood, complimentary log-log link, random-effects model for combining direct and indirect evidence in mixed treatment comparisons using a Bayesian approach as previously described (Higgins and Whitehead, 1996; Lu and Ades, 2004; Dias et al., 2010). This model assumes that the outcome for BRD morbidity d 1 to $\leq$ 60 is time dependent, and based on the differing lengths of each treatment arm the time until an event occurs has an exponential distribution (Dias et al., 2011). Differing days at risk were accounted for BRD morbidity

d 1 to $\leq$ 60, for example if a trial period was 14 d, the days at risk would be 14/60 = 0.23 d at risk. Trial days were only accounted for in trials included in the BRD morbidity d 1 to $\leq$ 60 outcome. The effectiveness of each individual treatment arm for BRD morbidity, BRD mortality, and BRD retreatment d 1 to $\leq$ closeout was examined using the binomial likelihood, logit link, random-effects model for combining direct and indirect evidence in mixed treatment comparisons using a Bayesian approach similar to d 1 to $\leq$ 60 d evaluation. (Higgins and Whitehead, 1996; Lu and Ades, 2004; Dias et al., 2010). This model assumes that the proportional odds assumption holds, that all trials occur within the same time period, and further days at risk would not affect the differences between events (Dias et al., 2011). The code was called through WinBUGS with R to fit the model with the R2Winbugs package (Dias et al., 2011).

A homogeneous variance was assumed and uniformed priors were used for the standard deviation, σ for each of the BRD morbidity d 1 to $\leq$ 60 d, BRD morbidity d 1 to closeout, BRD mortality d 1 to closeout, and BRD retreatment morbidity d 1 to closeout models. Two uniform standard deviation priors were compared for each individual outcome model, σ ~ uniform (0, 5) vs. σ ~ uniform (0, 2), and based on narrower credibility intervals (**CrIs**) and lower deviance information criterion (DIC), σ ~ uniform (0, 5) was used in the final code. Gelman-Rubin diagnostics were performed to determine best convergence for chains (Gelman and Rubin, 1992). A total of 2 chains were used for each model, each with 120,000 iterations, with the first 20,000 iterations discarded. The output from the code was the posterior mean for odds ratio between the treatment arm comparisons with corresponding 95% CrIs. Treatment arms with the least OR and with corresponding overlapping 95% CrIs were classified as "upper tier." Treatment arms with the greatest OR and with corresponding overlapping 95% CrIs were classified as "lesser tier." Treatment arms in between the greatest and least OR and with corresponding overlapping 95% CrIs were classified as "middle tier."

RESULTS

After initial screening for relevant titles and abstracts, a final list of 170 publications was retrieved and evaluated. From these publications, 29 studies, with a total of 37 trials met all inclusion criteria. The length of the trial periods ranged from 7 to 293 d. Only BRD morbidity cumulative incidence is reported for treatment period d 1 to $\leq$ 60 of the feeding period and all event outcomes (BRD morbidity, mortality, and retreatment morbidity) are reported for treatment period d 1 to closeout.

Figure 1 shows a network of the different treatment arms included for each individual event outcome. BRD
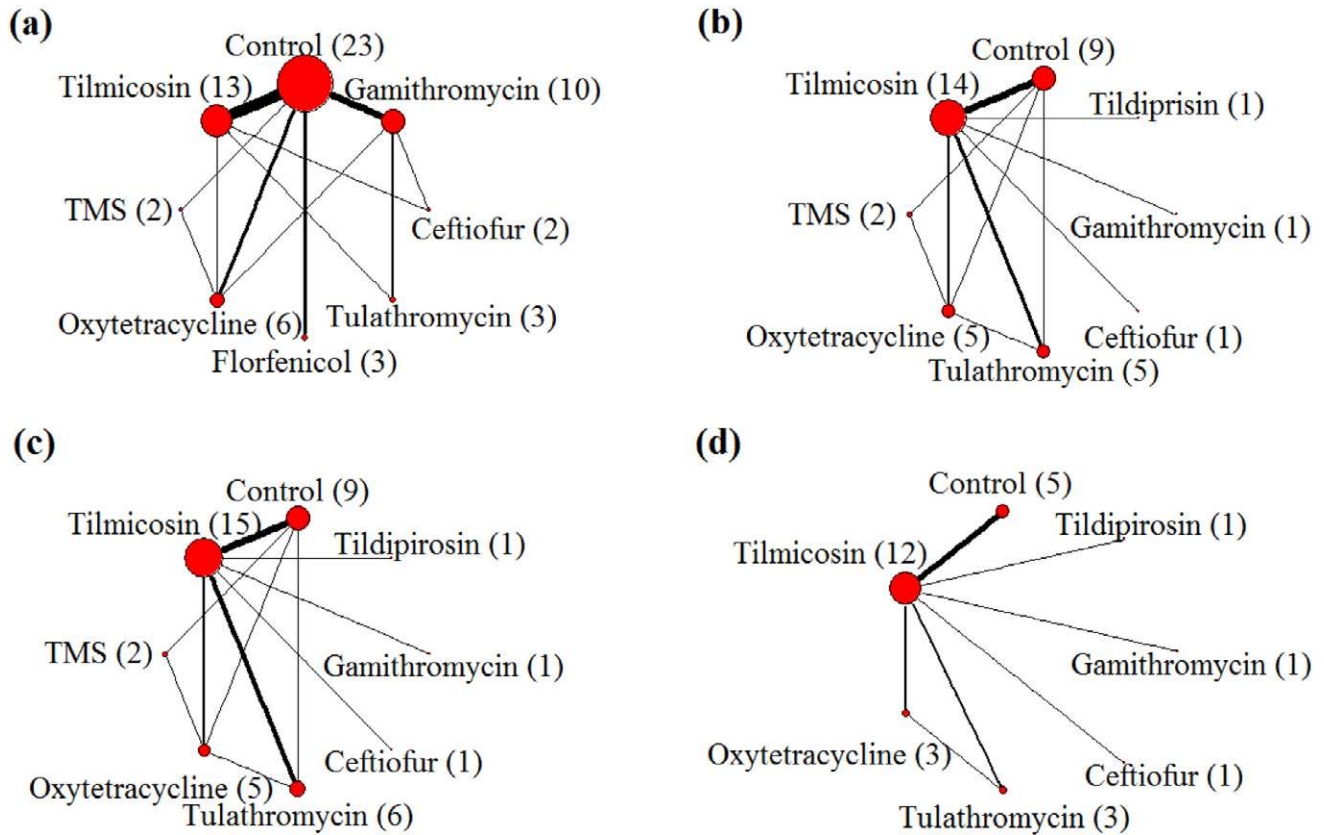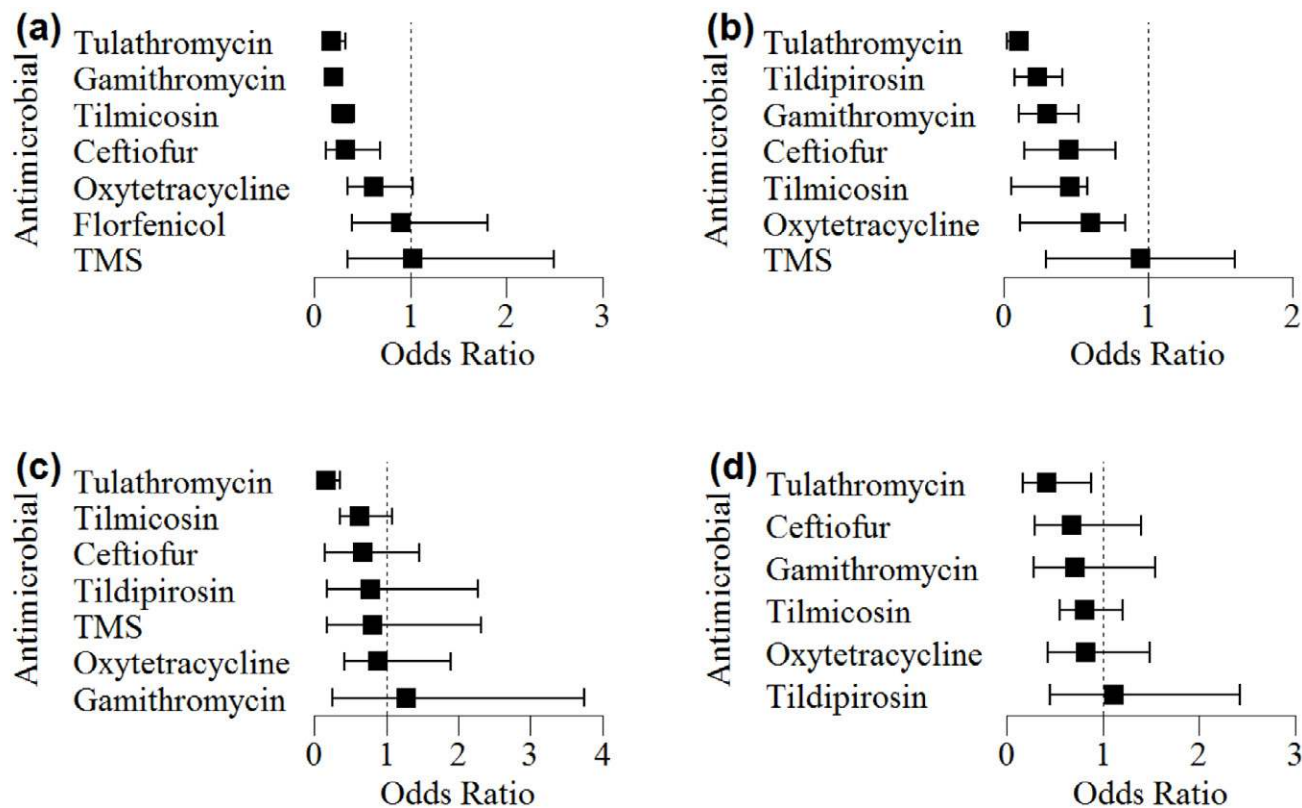
Figure 1. Network of treatment arms for the metaphylactic antimicrobial for BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period (a), BRD morbidity cumulative incidence d 1 to closeout of the feeding period (b), BRD mortality cumulative incidence d 1 to closeout (c), and BRD retreatment morbidity cumulative incidence d 1 to closeout (d) in the mixed treatment comparison meta-analysis. The width of the lines corresponds to the number of direct comparisons between antimicrobials, the size of the dot indicates the number of antimicrobials within each arm, and number in parenthesis corresponds to the number of comparisons for each antimicrobial.

morbidity cumulative incidence d 1 to ≤ 60 included 62 treatment arms from 27 trials, BRD morbidity cumulative incidence d 1 to closeout included 37 treatment arms from 13 trials, BRD mortality cumulative incidence d 1 to closeout included 40 treatment arms from 14 trials, and BRD retreatment morbidity cumulative incidence d 1 to closeout included 26 treatment arms from 11 trials (Fig. 1). The maximum number of treatment arms within a trial were 3 (Harland et al., 1991; Morck et al., 1993; Booker et al., 2007; Tennant et al., 2014), all other trials contained 2 treatment arms. There were a total of 8 different metaphylactic antimicrobials (Table 1). All treatment arms were included in 4 or more trials except florfenicol, tildipirosin, and TMS. Florifenicol had 3 trials, tildipirosin had 1 trial, and TMS had 1 trial included. A placebo control was present in 25 trials.

Forest plots of the mean odds ratio (**OR**) comparisons between antimicrobial and control with 95% CrIs for each event outcome are shown in Fig. 2. The dotted line in the center of each forest plot designates the OR equal to 1. If the OR are equal to 1, odds of the event occurrence are the same for the antimicrobial compared to the control; if odds are less than 1, the odds for the event occurrence are greater for the con-

trol compared to the antimicrobial; if odds are greater than 1, the odds for the event occurrence are greater for the antimicrobial compared to the control. BRD morbidity cumulative incidence d 1 to ≤ 60 "upper tier" treatment arms were tulathromycin, gamithromycin, and tilmicosin. The "middle tier" included ceftiofur and oxytetracycline, and the "lesser tier" included florfenicol and TMS. Morbidity cumulative incidence d 1 to closeout "upper tier" treatment arms included tulathromycin, the "middle tier" include tildipirosin, gamithromycin, ceftiofur, tilmicosin, and oxytetracycline, and the "lesser tier" included TMS. Mean OR for all comparisons between antimicrobials with 95% CrIs for each event outcome are shown in Table 2.

For BRD mortality cumulative incidence d 1 to closeout and BRD retreatment morbidity d 1 to closeout, classifying the treatment arms into tiers was not possible due to overlapping 95% CrIs. However, there were some differences between individual antimicorbials. In Fig. 2(c), the 95% CrIs for tulathromycin did not overlap with the 95% CrIs of tilmicosin and oxytetracycline. Overall, tulathromycin and tilmicosin has a lesser odds than the controls, and oxytetracycline is similar to the controls. The OR and 95% CrIs of the comparison of tulathromy-

Figure 2. Forest plots of the odds ratio comparison between individual antimicrobials and control in the mixed treatment comparison with a 95% CrIs for BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period (a)[1], BRD morbidity cumulative incidence d 1 to close out of the feeding period (b)[2], BRD mortality cumulative incidence d 1 to closeout (c)[2], and BRD retreatment morbidity cumulative incidence d 1 to closeout (d)[2]. [1]Binomial likelihood, complimentary log-log link, random-effects model. [2]Binomial likelihood, logit link, random-effects model.

cin vs. tilmicosin is 0.26 (0.13 to 0.49) and tulathromycin vs. oxytetracycline is 0.20 [0.08 to 0.41; Table 2(c)]. OR for tulathromycin is different from tilmicosin and oxytetracycline, and the odds of mortality cumulative incidence d 1 to closeout of the feeding period is 4 times greater for tilmicosin than tulathromycin, and 5 times greater for oxytetracycline than tulathromycin.

DISCUSSION

The results of the MTC meta-analysis were able to accurately identify differences between metaphylactic antimicrobials related to BRD morbidity, retreatment, and mortality. A wide variety of trials conducted between different antimicrobials were identified in the published literature. This MTC meta-analysis allows for simultaneous inference between treatment arms based on the model estimates (Lu and Ades, 2004). The data included in the MTC meta-analysis performs comparisons between the direct and indirect treatments and allows precision to increase with the assumption of consistency between these antimicrobials (Salanti et al., 2008).

Veterinarians and producers establish a metaphylactic treatment protocol based on prior knowledge of the incoming group of calves risk factors, season, weight, geographic origin, prior experience, and published literature

(Ribble et al., 1995; Snowder et al., 2006; Sanderson et al., 2008; USDA, 2011). The overall goal of a metaphylactic antimicrobial is to decrease the risk and negative effect of BRD in feedlot cattle. The results from this MTC meta-analysis provide veterinarians and producers guidance to more accurately predict the expected outcomes when choosing among antimicrobials to use on incoming high-risk cattle in a feedlot or stocker operation. For example, tulathromycin has the least OR compared to all other treatment arms in BRD morbidity cumulative incidence d 1 to ≤ 60 d, BRD morbidity cumulative incidence d 1 to closeout, BRD mortality cumulative incidence d 1 to closeout, and BRD retreatment morbidity cumulative incidence d 1 to closeout outcomes when compared to controls (Fig. 2). Tulathromycin is also comparable to other antimicrobials for BRD morbidity cumulative incidence d 1 to ≤ 60, because the 95% CrIs of tulathromycin overlaps with gamithromycin and tilmicosin (Fig. 2(a)). These 3 "upper tier" treatment arms appear comparable in the effect differences between controls for the odds of disease. Results from a MTC meta-analysis can be applied to a group of incoming cattle, if this group has a predicted BRD morbidity of 30% within the first 60 d of the feeding period. If all cattle are administered at arrival an "upper tier" treatment with an OR 0.1 to 0.2, then the expected BRD morbidity would be about 4% to 8%, or a 80 to 90%

Table 2. The mean odds ratio with 95% credibility intervals for BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period (a)[1], BRD morbidity cumulative incidence d 1 to close out of the feeding period (b)[2], BRD mortality cumulative incidence d 1 to closeout (c)[2], and BRD retreatment cumulative incidence d 1 to closeout (d)[2] of the mixed treatment comparison meta-analysis. The metaphylactic antimicrobial on the left for all odds ratio comparisons is the reference category

Event outcome	Comparison[3]	OR	95% CrIs		
	tilmicosin vs. TMS	3.59	1.19	–	9.30
	tilmicosin vs. oxytetracycline	2.16	1.11	–	3.92
	tilmicosin vs. florfenicol	3.15	1.26	–	6.68
	tilmicosin vs. tulathromycin	0.59	0.27	–	1.14
	tilmicosin vs. ceftiofur	1.10	0.43	–	2.43
	tilmicosin vs. gamithromycin	0.69	0.39	–	1.15
	TMS vs. oxytetracycline	0.74	0.24	–	1.74
	TMS vs. florfenicol	1.11	0.26	–	3.03
	TMS vs. tulathromycin	0.21	0.05	–	0.57
(a) BRD morbidity d 1 to ≤ 60	TMS vs. ceftiofur	0.39	0.09	–	1.14
	TMS vs. gamithromycin	0.24	0.07	–	0.58
	oxytetracycline vs. florfenicol	1.57	0.54	–	3.56
	oxytetracycline vs. tulathromycin	0.30	0.11	–	0.63
	oxytetracycline vs. ceftiofur	0.55	0.18	–	1.26
	oxytetracycline vs. gamithromycin	0.34	0.16	–	0.62
	florfenicol vs. tulathromycin	0.22	0.07	–	0.53
	florfenicol vs. ceftiofur	0.41	0.11	–	1.12
	florfenicol vs. gamithromycin	0.25	0.09	–	0.55
	tulathromycin vs. ceftiofur	2.05	0.65	–	5.07
	tulathromycin vs. gamithromycin	1.26	0.64	–	2.27
	ceftiofur vs. gamithromycin	0.73	0.29	–	1.55
	tilmicosin vs. TMS	2.07	1.11	–	3.56
	tilmicosin vs. oxytetracycline	1.29	0.94	–	1.77
	tilmicosin vs. tulathromycin	0.23	0.16	–	0.32
	tilmicosin vs. ceftiofur	0.97	0.54	–	1.62
	tilmicosin vs. gamithromycin	0.64	0.35	–	1.08
	tilmicosin vs. tildipirosin	0.50	0.27	–	0.83
	TMS vs. oxytetracycline	0.67	0.37	–	1.14
	TMS vs. tulathromycin	0.12	0.06	–	0.22
	TMS vs. ceftiofur	0.51	0.21	–	1.04
(b) BRD morbidity d 1 to closeout	TMS vs. gamithromycin	0.34	0.14	–	0.69
	TMS vs. tildipirosin	0.26	0.11	–	0.53
	oxytetracycline vs. tulathromycin	0.18	0.12	–	0.27
	oxytetracycline vs. ceftiofur	0.77	0.39	–	1.36
	oxytetracycline vs. gamithromycin	0.51	0.25	–	0.92
	oxytetracycline vs. tildipirosin	0.39	0.20	–	0.70
	tulathromycin vs. ceftiofur	4.43	2.17	–	7.88
	tulathromycin vs. gamithromycin	2.94	1.41	–	5.28
	tulathromycin vs. tildipirosin	2.27	1.10	–	4.06
	ceftiofur vs. gamithromycin	0.71	0.30	–	1.43
	ceftiofur vs. tildipirosin	0.55	0.23	–	1.12
	gamithromycin vs. tildipirosin	0.84	0.35	–	1.70

Continued

Continued

Event Outcome	Comparison[3]	OR	95% CrIs		
	tilmicosin vs. TMS	1.35	0.28	–	3.84
	tilmicosin vs. oxytetracycline	1.44	0.74	–	2.70
	tilmicosin vs. tulathromycin	0.26	0.13	–	0.49
	tilmicosin vs. ceftiofur	0.88	0.25	–	2.02
	tilmicosin vs. gamithromycin	1.96	0.44	–	5.43
	tilmicosin vs. tildipirosin	1.21	0.32	–	3.17
	TMS vs. oxytetracycline	1.64	0.37	–	4.82
	TMS vs. tulathromycin	0.31	0.06	–	1.00
	TMS vs. ceftiofur	1.07	0.14	–	3.56
(c) BRD mortality d 1 to closeout	TMS vs. gamithromycin	2.86	0.25	–	8.95
	TMS vs. tildipirosin	1.52	0.17	–	5.41
	oxytetracycline vs. tulathromycin	0.20	0.08	–	0.41
	oxytetracycline vs. ceftiofur	0.74	0.15	–	1.75
	oxytetracycline vs. gamithromycin	1.52	0.27	–	4.60
	oxytetracycline vs. tildipirosin	1.02	0.19	–	2.70
	tulathromycin vs. ceftiofur	3.81	0.83	–	9.42
	tulathromycin vs. gamithromycin	8.41	1.45	–	25.26
	tulathromycin vs. tildipirosin	5.39	1.03	–	14.73
	ceftiofur vs. gamithromycin	3.38	0.42	–	10.70
	ceftiofur vs. tildipirosin	2.01	0.30	–	6.41
	gamithromycin vs. tildipirosin	1.15	0.12	–	3.58
	tilmicosin vs. oxytetracycline	1.00	0.59	–	1.60
	tilmicosin vs. tulathromycin	0.50	0.22	–	0.98
	tilmicosin vs. ceftiofur	0.82	0.39	–	1.52
	tilmicosin vs. gamithromycin	0.86	0.37	–	1.70
	tilmicosin vs. tildipirosin	1.38	0.60	–	2.69
(d) BRD retreatment morbidity d 1 to closeout	oxytetracycline vs. tulathromycin	0.52	0.22	–	1.01
	oxytetracycline vs. ceftiofur	0.90	0.34	–	1.85
	oxytetracycline vs. gamithromycin	0.93	0.33	–	2.05
	oxytetracycline vs. tildipirosin	1.67	0.54	–	3.24
	tulathromycin vs. ceftiofur	2.04	0.62	–	4.65
	tulathromycin vs. gamithromycin	2.06	0.59	–	5.13
	tulathromycin vs. tildipirosin	3.39	0.97	–	8.09
	ceftiofur vs. gamithromycin	1.30	0.37	–	2.88
	ceftiofur vs. tildipirosin	1.94	0.61	–	4.53
	gamithromycin vs. tildipirosin	2.01	0.55	–	4.77

[1]Binomial likelihood, complimentary log-log link, random-effects model.
[2]Binomial likelihood, logit link, random-effects model.
[3]The antimicrobial on the left of each comparison is the denominator in the ratio, and the antimicrobial on the right is the numerator. If the OR are equal to 1, odds of the event occurrence are the same for each antimicrobial; if odds are less than 1, the odds for the event occurrence are greater for the antimicrobial on the left; if odds are greater than 1, the odds for the event occurrence are greater for the antimicrobial on the right.

reduction in odds of being diagnosed with BRD compared to controls. Overall, this type of analysis has the potential to efficiently estimate the odds of disease which can be used to assess comparative health, performance, and economic outcomes of feedlot and stocker cattle.

Previous meta-analyses have indicated metaphylaxis can reduce BRD morbidity, and that reduction can be from 55% to 29% comparing control cattle to treated (Van Donkersgoed, 1992; Wileman et al., 2009). Mortality

due to BRD has also been reported to be reduced from 3.8% to 1.8% for cattle not receiving metaphylaxis compared to those that do receive metaphylaxis (Wileman et al., 2009). The results from this MTC meta-analysis presented similar results; cattle treated with an antimicrobial have a reduced OR compared to controls for morbidity (Fig. 2) and allows producers and veterinarians to compare efficacy between antimicrobials, to determine antimicrobials that are similar (i.e., no difference), and antimicrobials that may be superior to other antimicrobials (i.e., a difference exists).

Event outcome for BRD mortality in Fig. 2(c) had overlapping 95% CrIs for all the treatment arms making full interpretation of these antimicrobial comparisons challenging. The lack of identified differences between multiple treatments arms may be due to the low incidence of mortality in feedlots (Snowder et al., 2006), and the incidence was low in the studies included in the analysis which most likely contributes to the overlapping CrIs. The lack of differences does not imply observed differences would not be higher in populations at a higher risk for BRD mortality.

In the US, 59% of all feedlot cattle are treated with a metaphylactic antimicrobial at arrival (USDA, 2011). Analyzing retreatment of cattle diagnosed with BRD after metaphylactic administration is beneficial in determining the overall affect the metaphylactic antimicrobial has on BRD morbidity, treatment success, and mortality. Retreatment for the present study refers to animals initially diagnosed with BRD and treated with an antimicrobial that required an additional antimicrobial for BRD. The results from this MTC meta-analysis for the BRD retreatment morbidity cumulative incidence were challenging to interpret, event outcome for BRD retreatment morbidity in Fig. 2(d) had overlapping 95% CrIs for all the antimicrobial arms. An analysis to compare retreatment protocols after initial metaphylactic administration was attempted, but was unsuccessful due to few trials with similar BRD retreatment morbidity protocols that could be compared.

The prevalence of BRD morbidity differs among days following feedlot arrival (Babcock et al., 2010). The reported trial days in the treatment period d 1 to ≤ 60 were variable in the total days at risk for calves. Accounting for variability days at risk for treatment periods is necessary when analyzing the odds of disease for a MTC meta-analysis which we accomplished using the binomial likelihood, complimentary log-log link, random-effects model for combining direct and indirect evidence in mixed treatment comparisons using a Bayesian approach. While this model accounts for days at risk, it cannot account for a skewed distribution of morbidity case occurrence in the first 60 d.

When a study is published, reporting all aspects of the design, such as blinding, randomization, and allocation to treatment units, is crucial to perform a MTC meta-analysis. Because of incomplete reporting, making decisions based on published literature can be hampered due to limited data and subjective prediction (Pollreisz et al., 1991; Jackson, 2006). Previous publications have reported lack of reporting of crucial aspects of trials and the influence the inclusion or exclusion of specific trials have on the final analysis of a systematic review or meta-analysis (Van Donkersgoed, 1992; O'Connor et al., 2013; Theurer et al., 2015). A limitation of this project included the limited published literature for many of the metaphylactic treatments. Inconsistency may increase when later publications are combined with earlier publications due to changes in cattle, pathogens, or management over time, and careful consideration should be made when interpreting results from a MTC meta-analysis if the data between trials appears to be inconsistent (Mills et al., 2012).

Conclusion

The results from this MTC meta-analysis identified differences between parenteral metaphylactic antimicrobial options currently available. Metaphylactic antimicrobial options appear to offer different effects on BRD morbidity and mortality odds in feedlot and stocker cattle. Further research is needed to determine the effects of different metaphylactic antimicrobials on the BRD mortality, retreatment morbidity, performance, and economics of feedlot cattle.

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