PEER REVIEWED

Antimicrobial drug use for control and treatment of bovine respiratory disease in US feedlot cattle: A meta-analysis of comparative studies versus tulathromycin

Barbara Poulsen Nautrup[1], DVM, PhD; **Ilse Van Vlaenderen**[2], DVM, MSc; **M. Decker**[3], BS; **Ralph M. Cleale**[3], MS, PhD
[1]EAH-Consulting, Karlsgraben 12, 52064 Aachen, Germany
[2]CHESS, Zwarte Leeuwstraat 69, 2820 Bonheiden, Belgium
[3]Zoetis, 10 Sylvan Way, Parsippany, NJ 07932, USA
Corresponding author: Dr. Barbara Poulsen Nautrup; bpn@EAH-Consulting.de

Abstract

A meta-analysis of studies allowing the calculation of number of antimicrobial treatments needed for control or treatment of bovine respiratory disease (BRD) was conducted, comparing tulathromycin with other commonly used antimicrobials. Summary effect size (Hedges' g) was the standardized mean difference in number of treatments, with raw mean differences being calculated to estimate the clinical impact of results. Further analyses included subgroup meta-analyses, meta-regression, and meta-analysis of the relative risk (RR) of mortality. Tulathromycin as first-choice antibiotic was associated with fewer antimicrobial treatment courses than comparator products (Hedges' g = -0.374; $P < 0.0001$). Substantial heterogeneity (I^2 = 89.2%) was at least partly explained by subgroup analyses of comparator substance and study sponsor. The risk of mortality following tulathromycin treatment compared with comparator antimicrobials was reduced by half (RR = 0.512, $P < 0.0001$); accordingly, fewer treatment courses could not be attributed to higher mortality. Raw mean differences in number of antimicrobial treatment courses were -0.229 and -0.303 for control and treatment of BRD, respectively, translating to estimated reductions of between 0.8 and 1.8 million antibiotic courses per year in US feedlots when tulathromycin is used as first choice for metaphylaxis or treatment of BRD.

Key words: antimicrobials, bovine respiratory disease, meta-analysis, tulathromycin

Résumé

On a mené une méta-analyse d'études dont le but était de calculer le nombre de traitements antibiotiques requis pour le contrôle ou le traitement du complexe respiratoire bovin. Les études comparaient la tulathromycine avec d'autres antibiotiques couramment utilisés. Le descripteur de la grandeur de l'effet (la mesure g de Hedges) était la différence moyenne standardisée du nombre de traitements. On a utilisé la différence des moyennes brutes pour estimer l'impact clinique des résultats. D'autres analyses ont aussi été faites incluant des méta-analyses dans des sous-groupes, des méta-régressions et une méta-analyse du risque relatif de mortalité. Il y avait moins de traitements antibiotiques requis lorsque la tulathromycine était l'antibiotique de premier choix que lorsque d'autres antibiotiques étaient utilisés (g de Hedges = -0.374; $P < 0.0001$). Des analyses de sous-groupes ont montré que l'hétérogénéité substantielle (I^2 = 89.2%) s'expliquait en partie par le type de substances comparées et le commanditaire de l'étude. Le risque de mortalité était réduit de moitié (RR = 0.512, $P < 0.0001$) lorsqu'on utilisait la tulathromycine plutôt que d'autres antibiotiques pour le traitement. Par conséquent, le plus petit nombre de traitements requis ne pouvait pas s'expliquer par une plus grande mortalité. La différence moyenne brute du nombre de traitements antibiotiques requis était de -0.229 pour le contrôle du complexe respiratoire bovin et de -0.303 pour son traitement. L'utilisation de la tulathromycine comme antibiotique de premier choix pour la métaphylaxie ou le traitement du complexe respiratoire bovin permettrait une réduction estimée du nombre de traitements antibiotiques requis de l'ordre de 0.8 à 1.8 millions par année dans les parcs d'engraissement des États-Unis.

Introduction

Bovine respiratory disease (BRD) is the most common health problem in North American cattle feedlots, with injectable antibiotics being the treatment of choice. Antimicrobials used most frequently for control (metaphylaxis) or treatment of BRD in US feedlots include members of the macrolide, fluoroquinolone, and third-generation cephalosporin classes of antibiotics.[27] Because of their importance in human medicine, these classes also belong to the 'highest priority critically important antimicrobials'.[34] Development of bacterial resistance to critically important antimicrobials poses a serious

public health threat. Efforts have therefore been made to promote judicious use of antibiotics in both animal and human medicine.[5] The goals of judicious antimicrobial use are to maximize therapeutic efficacy and minimize development of resistant microorganisms.[25] Efficacy of antibiotic BRD treatments was assessed in a mixed-treatment meta-analysis, which showed that cattle given tulathromycin had the lowest BRD re-treatment rate.[14] Another study compared clinical and economic outcomes of using tulathromycin compared with florfenicol, tilmicosin, and enrofloxacin as first-line treatment for BRD, using decision analytic modeling technique. Based on the comparisons included in their analysis, the authors concluded that tulathromycin reduced the necessity for subsequent antimicrobial treatments, thereby contributing to more prudent use of antimicrobials in livestock.[17] The aim of the present study, using meta-analytic methods, was to test the hypothesis that tulathromycin reduces antimicrobial drug usage compared with other frequently used antimicrobials. Effectiveness was evaluated based on the number of antimicrobial treatment courses required for control or treatment of BRD in US feedlot cattle.

Methods

Literature search

Search methods, analysis, eligibility, and inclusion criteria were specified in advance. A literature search and screening process was conducted using Commonwealth Agricultural Bureaux (CAB) and Pubmed databases. Antibiotic substances used most often for control and treatment of BRD in US feedlots were defined from USDA data,[27] and amended by addition of 2 recently licensed antimicrobials (gamithromycin and tildipirosin). The following search terms were used: "(antimicrobial OR antibiotic OR tulathromycin OR gamithromycin OR florfenicol OR tilmicosin OR tildipirosin OR enrofloxacin OR danofloxacin OR ceftiofur OR oxytetracycline) AND feedlot". Bibliographies of relevant articles were hand-searched. In addition, websites of pharmaceutical companies distributing the defined antimicrobials were searched to identify relevant technical reports. Data search was limited to articles in English language published between 1991 and day of last search. Searches were conducted between October 06 and 23, 2015, and updated between March 02 and 03, 2016.

The following eligibility criteria were applied to identify studies for further evaluation: peer-reviewed articles or technical bulletins reporting efficacy of tulathromycin compared to other antimicrobials for treatment and/or control of naturally occurring BRD in feedlot cattle in North America. For inclusion in the data analysis, publications must have reported the outcome (success or failure) for study drug and at least 1 additional antimicrobial treatment. A template for data extraction, drafted before the start of the search, was used to compile the following information: report citation, study location and duration, animal breed, setting (control or treatment of BRD), initial antimicrobial treatment, BRD mortality rate, randomization, and blinding. A second template was developed which allowed the calculation of number of antimicrobial treatment courses.

Statistical analyses

Mean number of treatments. Average number of treatments was calculated from treatment success rates for first and subsequent antibiotic courses as reported in clinical studies. Cattle that did not develop BRD after metaphylactic treatment (control setting) or were cured after first BRD treatment (treatment setting) were classified as requiring 1 treatment course. Cattle that were cured after the second administration of antimicrobial drug were classified as requiring 2 treatment courses; additional treatments beyond 2 administrations were similarly summarized. Chronic cattle were assumed to have received the number of antibiotics required for classification as chronic in that trial. Average number of treatment courses was then calculated using the following formula:

$$\bar{x} = \frac{\sum_{i=1}^{n} w_i x_i}{\sum_{i=1}^{n} w_i}$$

where w_i is the number of cattle and x_i is the number of treatment courses. Standard deviation (SD) of the average number of treatments was calculated using standard statistics.[33]

Meta-analysis. A meta-analysis was conducted on the outcomes using the statistical software Comprehensive Meta-Analysis V. 2.2.[a] Primary analysis was meta-analysis of the difference between numbers of treatments required employing the standardized mean difference, which is the dominant method used for continuous data in meta-analysis.[9] The standardized mean difference corresponds to the mean treatment difference in each study divided by that study's SD.[2] We used Hedges' (adjusted) g, a modified version of Cohen's d, as the primary response criterion.[3] In case of substantial heterogeneity, reason for diversity between studies was evaluated using subgroup analyses for categorical parameters, and meta-regression for continuous parameters.[2] When possible, to account for variation across studies we used the random-effects model based on the assumption that the true effect size is not the same in all studies. In subgroup analyses, however, a fixed-effect model was used when subgroups with only 1 or 2 studies were included, because the random-effects model does not reveal accurate results if the number of studies is small.[2]

An additional analysis was conducted to assess whether an association exists between mortality and antibiotic treatment frequency. Stated differently, we questioned whether a reduced number of antibiotic treatment courses with 1 antibiotic compared to another was a function of death of animals that were therefore not eligible for further treatments, or whether it was a true treatment effect. For the

binary mortality data we used the risk ratio (RR) with the random-effects model. Studies with zero events (mortalities) in all groups were excluded, thus following standard practice in meta-analysis of risk ratios.[7] In a further analysis, the raw mean difference between number of treatments with tulathromycin and comparators was calculated for control and treatment of BRD (random-effects model), to allow for an estimation of the clinical relevance of results.

For each summary effect size, the Z statistic and corresponding P value was used to determine if differences between tulathromycin and comparator treatments were statistically significant.[2] Heterogeneity of results was quantified using Q and I^2 statistics. The Q statistic estimates heterogeneity between studies, and evaluates the null hypothesis that all studies reveal the same effect. While traditionally considered valid, others have argued that meta-analysis of data from studies that are both clinically and methodologically diverse should indeed result in heterogeneity reflected in the Q statistic, and thereby limit the meaningfulness of this measure of heterogeneity. Alternatively, the I^2 statistic was developed to describe the percentage of total variation across studies due to true heterogeneity rather than chance;[8] an I^2 value > 50% is considered to reflect substantial heterogeneity.[9] Statistical significance was declared based on two-tailed tests at $P < 0.05$.

Risk of bias. Potential publication or selection bias was examined with a funnel plot of the pooled effect size versus standard error for each comparison.[24] The trim and fill approach was used to provide the best estimate of unbiased outcome by recalculating the effect size until the tunnel plot was symmetric, then by imputing the adjusted point estimate.[4] Additionally, we estimated the Fail-Safe N,[20] which estimates the number of additional hypothetical studies with zero effect required to make the P value for the summary effect no longer significant. Further risks of bias were investigated by exclusion of studies from meta-analysis, thus estimating the impact of studies identified as potentially misleading.

Clinical significance of results

The clinical relevance of results from meta-analysis was estimated using the raw mean difference between treatments (tulathromycin versus comparators) for either control or treatment of BRD. We obtained the number of cattle treated annually for BRD, both metaphylactically or therapeutically, from USDA data.[27,28] Based on these data, we estimated the potential impact that tulathromycin could have on the total number of antimicrobial treatments in US feedlots compared to comparator products.

Results

Search results

A total of 707 references (408 from CAB and 299 from PubMed) were identified in initial database searches. After screening titles and abstracts, 23 articles were included for full assessment. Another 3 references were identified from bibliography searches, and 18 relevant technical reports were identified by screening websites of pharmaceutical companies marketing the defined antimicrobials. After removal of duplicates, 18 articles fulfilled inclusion criteria. A flow diagram of the study selection process is provided in Figure 1.

The 18 references represented a total of 26 studies, as 4 articles reported data from multiple studies conducted on different sites. Five articles included 3-arm studies (tulathromycin plus 2 comparators). Thus, 31 comparisons of tulathromycin to other antibiotics were considered in the meta-analysis, and comparators included ceftiofur, enrofloxacin, florfenicol, gamithromycin, oxytetracycline, tildipirosin, and tilmicosin. No data comparing danofloxacin to tulathromycin were located. With respect to florfenicol, 2 studies presented results involving a combination product that contains both florfenicol and flunixin meglumine.[6,30]

An overview of studies included in our analysis is provided in Table 1. Different randomization techniques were used for treatment allocation in all studies, and all but 1 study[29] reported blinding of the treatment response assessor to study drug allocation.

Statistical analysis

Mean number of treatments. Number of antimicrobial treatment courses was computed from treatment success rates reported for the different antimicrobials. The number of consecutive antibiotic courses for which outcomes were reported ranged from 2 (minimum required for inclusion) to 5. If an antibiotic treatment consisted of more than 1 application according to its posology (e.g., 2 doses 48 hours apart), it was considered as 1 course. Calculated mean numbers of treatment courses and associated SD are presented in Table 2.

Primary analyses. In the primary meta-analysis, the standardized mean difference in number of antimicrobial treatment courses with tulathromycin and comparators as the initial treatment choice for either control or treatment of BRD was assessed. Results are displayed graphically in the forest plot in Figure 2. The summary effect size was negative, which indicates a decreased number of antibiotic treatment courses was required when animals were treated with tulathromycin compared with other antibiotics (Hedges' g = -0.374; 95% CI: -0.447 to -0.301; $P < 0.0001$). The Q statistic revealed significant heterogeneity (Q = 278.4, df (Q) = 30, $P < 0.0001$). The I^2 statistic also indicated substantial heterogeneity in the response that could not be explained by random error (I^2 = 89.2%).

Subgroup analyses and meta-regression. Secondary analyses, investigated to explore potential causes of heterogeneity, included subgroup analyses and meta-regression. Parameters considered plausible moderators of study variance included comparator drug (substance), therapeutic setting (control or treatment of BRD), study sponsor, and study duration. Subgroup analysis was used to evaluate the impact of the categorical parameters (substance, therapeutic setting,

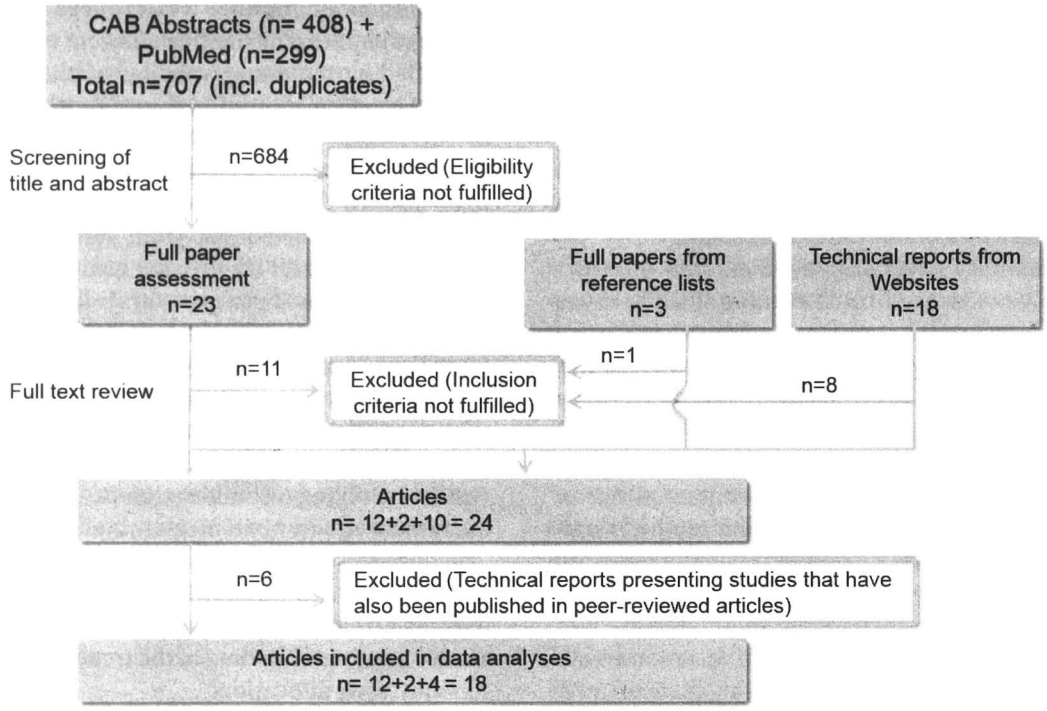


Figure 1. Flow diagram of study selection.

study sponsor) on effect size, whereas meta-regression was used to examine study duration, a continuous parameter. The first subgroup analysis assessed the effect of each substance compared to tulathromycin. A fixed-effect model was used because for 4 of the comparator antibiotics only 1 or 2 comparisons were included (Figure 3). Tulathromycin resulted in numerically fewer antimicrobial courses compared with all other antibiotics, and results were statistically significant for all comparisons except ceftiofur, for which only 1 comparison was found. Heterogeneity within and between subgroups was statistically significant ($P < 0.0001$); and diversity that could not be explained by random variation was substantial in 3 subgroups of comparators: florfenicol ($I^2 = 88.4\%$), tildipirosin ($I^2 = 89.2\%$), tilmicosin ($I^2 = 81.2\%$).

A second analysis evaluated the impact of treatment setting (control or treatment of BRD) on the outcome (Figure 4). Using the random effects model, Hedges' *g* was -0.357 (95% CI: -0.450 to -0.265; $P < 0.0001$) and -0.402 (95% CI: -0.548 to -0.255; $P < 0.001$) for control and treatment settings, respectively. Heterogeneity within treatment settings was significant ($P < 0.0001$), with a substantial proportion of the heterogeneity being explained as true rather than random variation ($I^2 = 93.3\%$ for control and $I^2 = 80.6\%$ for treatment setting). Heterogeneity between subgroups (control and treatment setting) was not statistically significant ($P = 0.616$), and the mean summary effect size was not significantly different between control or treatment of BRD.

A third subgroup analysis investigated the impact of study sponsor on outcomes. Studies were characterized as none (no pharmaceutical company sponsored the study; n = 2), yes – comparator (study was sponsored by manufacturer of the comparator; n = 8), yes – tulathromycin (study was sponsored by Zoetis; n = 21). Hedges' *g* for sponsor categories (Figure 5) was -0.206 for none (95% CI -0.280 to -0.132; $P < 0.0001$); -0.217 for yes – comparator (95% CI: -0.249 to -0.185; $P < 0.001$); and -0.372 for yes – tulathromycin (-0.402 to -0.342; $P < 0.0001$). Comparisons were evaluated with the fixed-effects model. Heterogeneity within and between subgroups was significant ($P < 0.0001$), with substantial diversity that could not be explained by random variation within the 3 groups ($I^2 = 96.3\%$, $I^2 = 93.2\%$, $I^2 = 79.1\%$, respectively, for none, yes - comparator, and yes - tulathromycin). Meta-regression was used to investigate the potential impact of study duration on number of antimicrobial treatments needed (Figure 6). For 3 comparisons, study duration was reported 'until harvest', but actual number of days was not specified or calculable. Therefore, these comparisons were not included in the meta-regression. No impact of study duration on effect size (Hedges' *g*) was found, with the computed slope being not statistically significant from zero ($P = 0.851$).

Additional analyses on mortality. Although not the primary aim of the study, a random-effects meta-analysis was conducted on relative risk (RR) of mortality to assess whether a lower number of treatments seen with tulathromycin was attributable to higher mortality, given that dead cattle are no longer eligible for treatment. The combined RR of mortality was 0.512 (95% CI: 0.364 to 0.719; $P < 0.0001$) for tulathromycin compared with all other antimicrobials included in analysis ($Q = 76.7$, df (Q) = 29, $P < 0.0001$, $I^2 = 62.2\%$). One study (Colorado site) was not included because mortality rate

Table 1. Summary of studies identified from literature search and considered in meta-analysis of number of antimicrobial treatment courses required for control or treatment of bovine respiratory disease in US feedlot cattle.

Study	Study site[a]	Source type[b]	Comparator(s)[c]	Setting[d]	Cattle description	Study duration, day
Booker et al (2007)[1]	Canada	Journal	Tilmicosin, oxytetracycline	C	Crossbred heifer calves	228-229
Hannon et al (2009)[6]	Canada	Journal	Florfenicol-FM, ceftiofur	T	Crossbred beef steer calves	254-263
Merck Animal Health (2012)[11]	Canada	CTB	Tildipirosin, tilmicosin	C	Crossbred calves	(harvest)
Nickel et al (2008)[12]	Kansas	Journal	Tilmicosin	C	Mixed-breed beef bulls and steers	43
Nutsch et al (2005)[13]	Nebraska 1	Journal	Tilmicosin	T	Crossbred feeder steers	60
Nutsch et al (2005)[13]	Nebraska 2	Journal	Florfenicol	T	Crossbred feeder steers	60
Nutsch et al (2005)[13]	Nebraska 3	Journal	Florfenicol, tilmicosin	T	Crossbred feeder steers	60
Perrett et al (2008)[15]	Nebraska	Journal	Florfenicol	T	Crossbred beef steer and bull calves	277
Pfizer Animal Health (2007)[16]	Texas II	CTB	Enrofloxacin	T	Mixed-breed heifers	58
Robb et al (2007)[18]	Colorado	Journal	Enrofloxacin	T	Feeder calves	59
Robb et al (2007)[18]	Texas	Journal	Enrofloxacin	T	Feeder calves	63
Rooney et al (2005)[19]	Idaho	Journal	Florfenicol	C	Crossbred feeder steers	223
Rooney et al (2005)[19]	Texas	Journal	Florfenicol	C	Crossbred feeder steers	195
Rooney et al (2005)[19]	Colorado	Journal	Tilmicosin	C	Crossbred steers	228
Schunicht et al (2007)[21]	Nebraska	Journal	Florfenicol	T	Crossbred beef calves	319
Skogerboe et al (2005)[22]	Nebraska	Journal	Florfenicol	T	Crossbred feeder steers	317
Skogerboe et al (2005)[22]	Colorado	Journal	Florfenicol	T	Feeder steers	174
Skogerboe et al (2005)[22]	Colorado	Journal	Tilmicosin	T	Crossbred steers	227
Skogerboe et al (2005)[22]	Texas	Journal	Tilmicosin	T	Crossbred beef heifers	258
Stegner et al (2013)[23]	Oklahoma	Journal	Tilmicosin	C	Heifers	208
Torres et al (2013)[26]	Kansas, Nebraska	Journal	Gamithromycin	C	Crossbred beef calves	120
Van Donkersgoed et al (2008)[29]	Canada	Journal	Florfenicol	T	Crossbred steer calves	(harvest)
Van Donkersgoed et al (2008)[31]	Canada	Journal	Tilmicosin	C	Crossbred heifer calves	218
Van Donkersgoed et al (2009)[30]	Canada	Journal	Florfenicol-FM	T	Beef steer and heifer calves	(harvest)
Zoetis (2016)[35]	Texas	CTB	Tildipirosin, tilmicosin	C	Crossbred beef steers	199
Zoetis (2013)[36]	Texas	CTB	Gamithromycin	C	Crossbred beef steers and heifers	217

[a]Study numbers provided if necessary for identification
[b]CTB = company technical bulletin
[c]FM = flunixin meglumine
[d]C = control, T = treatment

was zero in both groups.[18]

Risk of bias

Publication and selection bias. Funnel plots, with and without the "trim and fill" adjustment, are presented in Figure 7. Accounting for observed asymmetry, the "trim and fill" method resulted in an additional 6 studies to the left, leading to a greater standardized mean difference between treatments with tulathromycin versus other active ingredients. The number of hypothetical studies with zero-effect size required to make the tulathromycin effect non-significant (Fail-Safe N)[20] was calculated to be 5,115.

Other bias. One study did not specify whether the individual(s) responsible for clinical assessments was blinded to treatment allocation; it was therefore assumed that this study was not masked.[31] A further analysis evaluated the impact of excluding this study. With this study the Hedges' g was -0.374 (95% CI: -0.447 to -0.301; $P < 0.0001$), whereas excluding this study Hedges' g was -0.373 (95% CI: -0.449 to -0.296; $P < 0.0001$). An additional analysis investigated the impact of excluding non-peer-reviewed studies from the primary analysis; including only comparisons published in peer-reviewed journals did not have a relevant impact (Hedges' g = -0.408; 95% CI: -0.487 to -0.329; $P < 0.0001$).

Clinical relevance

To estimate the clinical relevance of our results, the raw mean difference in number of treatments between tulathromycin and comparators were calculated, and was -0.229 treatments/animal (95% CI: -0.288 to -0.171; $P < 0.0001$) and -0.303 treatments/animal (95% CI: -0.415 to -0.191; $P < 0.0001$) for control and treatment settings, respectively.

Table 2. Number of antimicrobial treatment courses required for control or treatment of BRD in US feedlot cattle as calculated from treatment success rates with tulathromycin and comparators. If a study included more than 1 comparator, evaluations were considered separately against each comparator.

Study (site)	Study site*	Comparator	Number of cattle† Tula / Comp‡	Tulathromycin No. treatments	SD	Comparator No. treatments	SD
Booker et al (2007)[1]	Canada	Tilmicosin	3,304/3,304	1.110	0.486	1.343	0.784
Booker et al (2007)[1]	Canada	Oxytetracycline	3,304/3,302	1.110	0.486	1.415	0.860
Hannon et al (2009)[6]	Canada	Florfenicol	50/50	1.080	0.444	1.180	0.482
Hannon et al (2009)[6]	Canada	Ceftiofur	50/50	1.080	0.444	1.320	0.683
Merck Animal Health (2012)[11]	Canada	Tildipirosin	3,359/3,358	1.149	0.457	1.163	0.484
Merck Animal Health (2012)[11]	Canada	Tilmicosin	3,359/3,356	1.149	0.457	1.298	0.630
Nickel et al (2008)[12]	Kansas	Tilmicosin	146/147	1.432	0.694	2.095	0.939
Nutsch et al (2005)[13]	Nebraska 1	Tilmicosin	98/97	1.296	0.629	2.062	0.876
Nutsch et al (2005)[13]	Nebraska 2	Florfenicol	118/116	1.271	0.580	1.759	0.841
Nutsch et al (2005)[13]	Nebraska 3	Florfenicol	117/112	1.325	0.570	1.625	0.829
Nutsch et al (2005)[13]	Nebraska 3	Tilmicosin	117/114	1.325	0.570	1.667	0.783
Perrett et al (2008)[15]	Nebraska	Florfenicol	274/281	2.226	1.213	2.292	1.242
Pfizer Animal Health (2007)[16]	Texas II	Enrofloxacin	85/74	1.071	0.258	1.176	0.417
Robb et al (2007)[18]	Colorado	Enrofloxacin	124/124	1.153	0.443	1.379	0.632
Robb et al (2007)[18]	Texas	Enrofloxacin	119/120	1.277	0.610	1.525	0.744
Rooney et al (2005)[19]	Idaho	Florfenicol	238/240	1.525	0.690	2.146	0.842
Rooney et al (2005)[19]	Texas	Florfenicol	247/244	1.231	0.514	1.439	0.743
Rooney et al (2005)[19]	Colorado	Tilmicosin	236/239	1.271	0.621	1.573	0.811
Schunicht et al (2007)[21]	Nebraska	Florfenicol	100/100	2.050	1.242	2.740	1.300
Skogerboe et al (2005)[22]	Nebraska	Florfenicol	93/94	2.215	1.524	3.862	1.703
Skogerboe et al (2005)[22]	Colorado	Florfenicol	96/99	1.281	0.627	1.566	0.859
Skogerboe et al (2005)[22]	Colorado	Tilmicosin	98/91	1.296	0.629	1.538	0.779
Skogerboe et al (2005)[22]	Texas	Tilmicosin	100/99	1.340	0.607	1.576	0.916
Stegner et al (2013)[23]	Oklahoma	Tilmicosin	617/614	1.156	0.454	1.342	0.629
Torres et al (2013)[26]	Kansas, Nebraska	Gamithromycin	1,266/1,263	1.329	0.638	1.424	0.702
Van Donkersgoed et al (2008)[29]	Canada	Florfenicol	254/258	1.083	0.276	1.070	0.284
Van Donkersgoed et al (2008)[31]	Canada	Tilmicosin	2,228/2,227	1.049	0.188	1.174	0.371
Van Donkersgoed et al (2009)[30]	Canada	Florfenicol	227/228	1.084	0.322	1.140	0.428
Zoetis (2016)[35]	Texas	Tildipirosin	427/403	1.300	0.568	1.501	0.710
Zoetis (2016)[35]	Texas	Tilmicosin	427/427	1.300	0.568	1.674	0.775
Zoetis (2013)[36]	Texas	Gamithromycin	1,146/1,124	1.232	0.522	1.322	0.611

*Study numbers provided if necessary for identification

†Number of cattle corresponds to the number included in the calculations of number of antimicrobial treatments. Depending on the outcomes reported for each study, number of cattle includes or excludes deaths, which deemed rational as mortalities occur at any time of study.[16] Accordingly number of cattle must not correspond to number of cattle enrolled in that trial.

‡Tula = tulathromycin, Comp = comparator

According to USDA data, a total of 30.2 million commercial cattle were harvested in 2014.[28] A survey of health and health management on US feedlots in 2011 revealed that 21.3% of feedlot cattle received metaphylactic treatment to prevent or minimize shipping fever (BRD). Additionally, 16.2% of all cattle became ill with shipping fever, and of these animals 87.5% were treated with antibiotics.[27] Using 95% CI on the raw mean differences in numbers of antibiotic treatments, between 1.1 and 1.8 million metaphylactic BRD antibiotic treatment courses, and between 0.8 and 1.8 million BRD treatment antibiotic courses could be avoided annually if tulathromycin is used as the first treatment instead of comparator products.

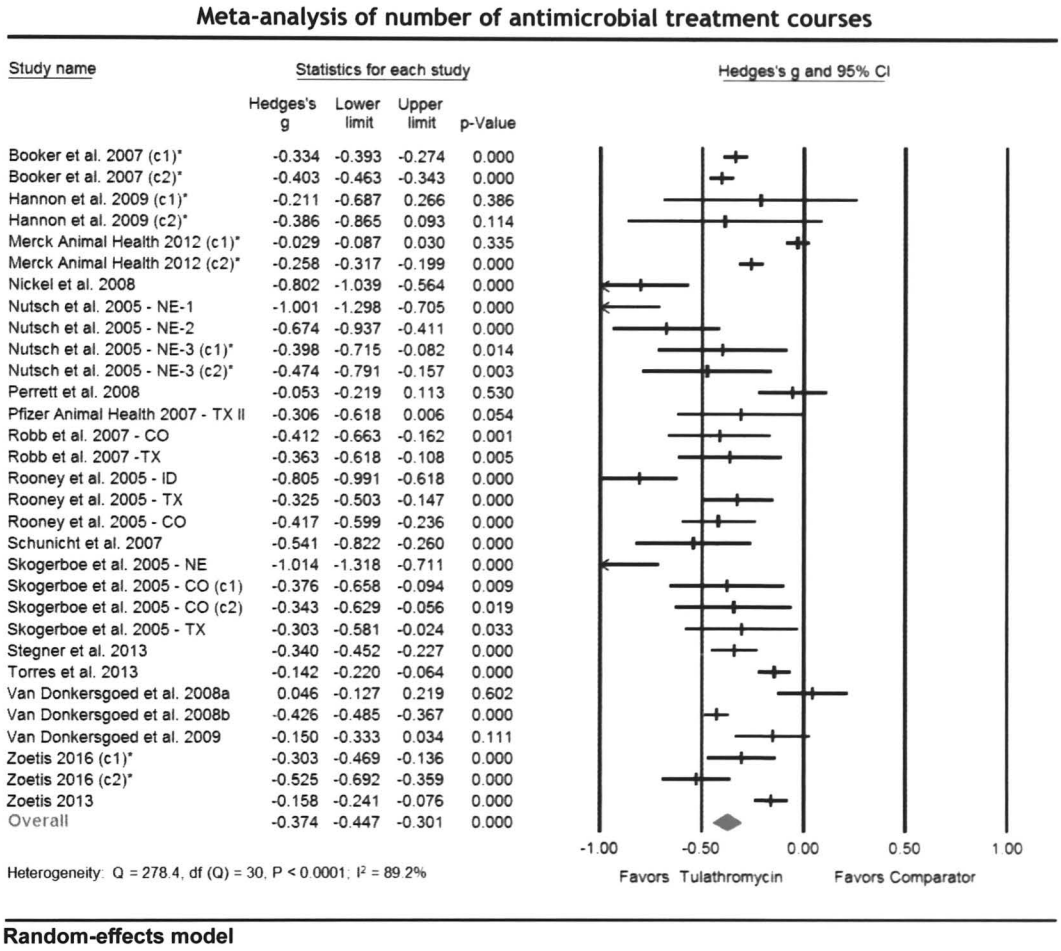


Figure 2. Forest plot of the standardized mean difference (Hedges' *g*) of number of antimicrobial treatment courses with tulathromycin and comparators using a random-effects model. Studies include different comparators (ceftiofur, enrofloxacin, florfenicol, gamithromycin, oxytetracycline, tildipirosin, tilmicosin) and different settings (control or treatment of bovine respiratory disease). Lower and upper limit refer to 95% CI, which are also graphically depicted by horizontal line. *P* values were calculated for *Z*-statistics (a *P* value of 0.000 corresponds to $P < 0.0001$). The diamond at the bottom represents the 95% CI for the overall point estimate. (c1 and c2 distinguish between different comparisons in the same reference; *signifies 3-arm studies.)

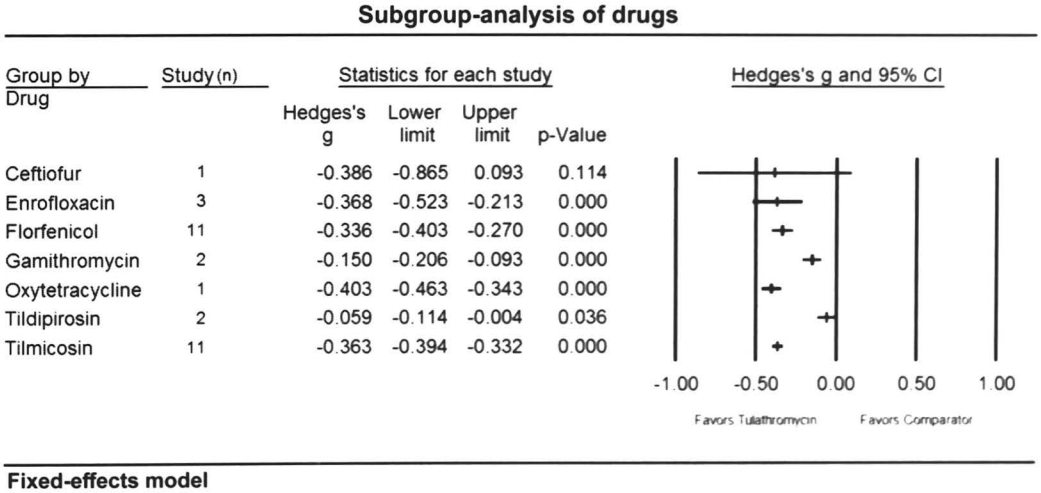


Figure 3. Subgroup analysis of therapeutic agents. Forest plot of the standardized mean difference (Hedges' *g*) in number of antimicrobial treatment courses with tulathromycin versus comparators, grouped by active ingredient. Because of the low number of studies included in 4 subgroups, the fixed-effect model was used. Lower and upper limit refer to the 95% CI, which are also graphically depicted by horizontal line. *P* values were calculated for *Z*-statistics.

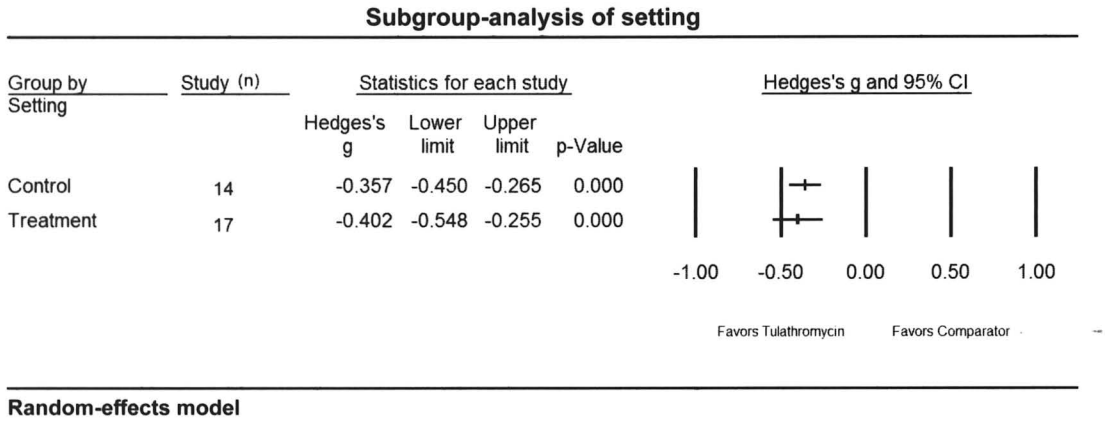


Figure 4. Subgroup analysis by setting. Forest plot of the standardized mean difference (Hedges' *g*) of number of antimicrobial treatment courses with tulathromycin and comparators grouped by setting (control or treatment of bovine respiratory disease), using a random-effects model. Subgroups include different comparators (ceftiofur, enrofloxacin, florfenicol, gamithromycin, oxytetracycline, tildipirosin, tilmicosin). Lower and upper limit refer to the 95% CI, which is also graphically depicted by horizontal line. *P* values were calculated for *Z*-statistics.

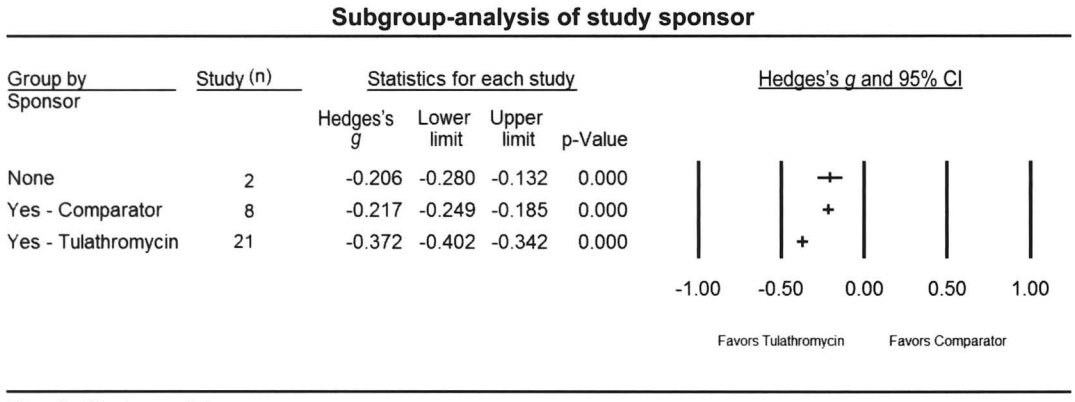


Figure 5. Subgroup analysis of study sponsor. Forest plot of the standardized mean difference (Hedges' *g*) of number of antimicrobial treatment courses between tulathromycin and comparators, grouped by study sponsor (None = no sponsoring from pharmaceutical company; Yes – comparator = comparator's manufacturer sponsored the study; Yes – tulathromycin = Zoetis sponsored the study). Because of the small number of studies in the subgroup "None", the fixed-effect model was used. Lower and upper limit refer to the 95% CI, which are also graphically depicted by horizontal line. *P* values were calculated for *Z*-statistics.

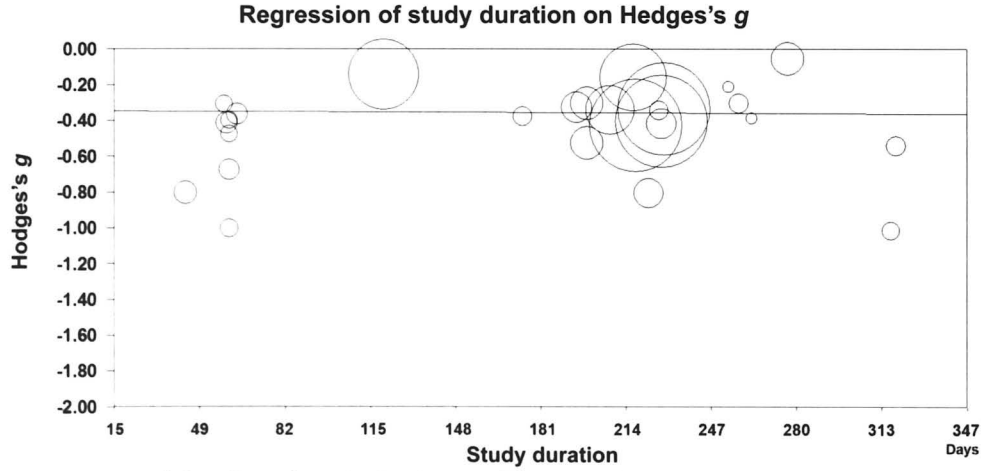
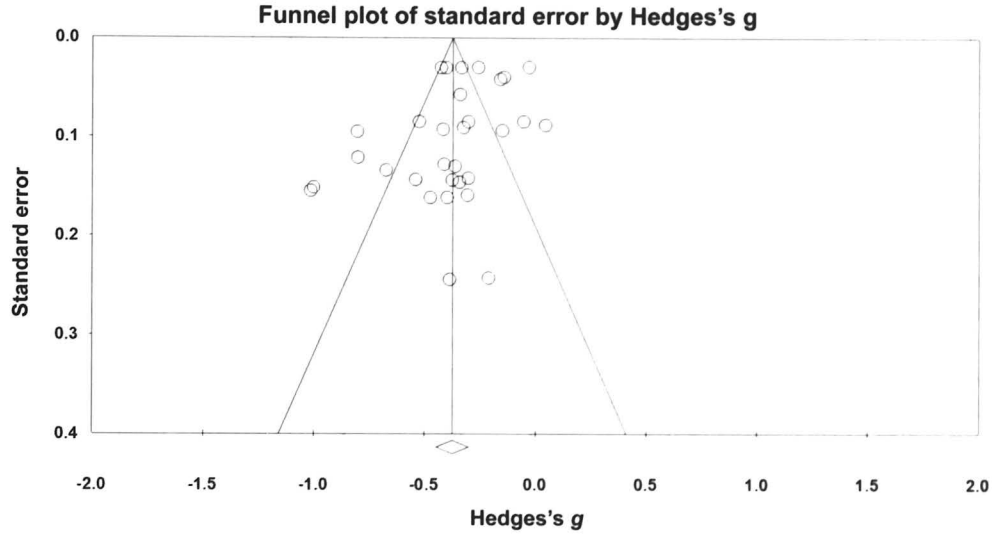
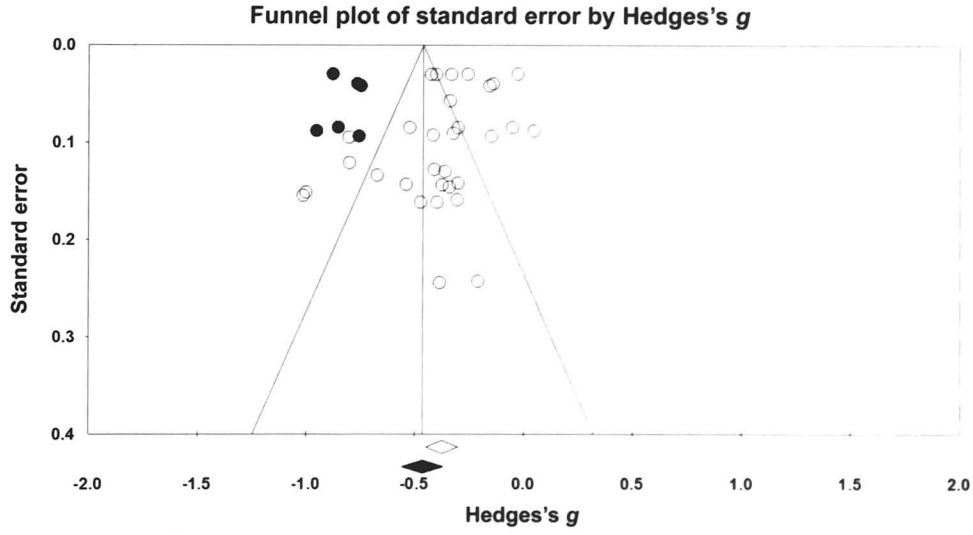


Figure 6. Results of meta-regression of the effects (standardized mean difference of number of antimicrobial treatment courses; Hedges' *g*) by study duration. The size of each circle indicates the relative weight of that study within meta-regression. The computed slope is not different from zero ($P = 0.851$); thus, study duration has no significant impact on the effect size.



A. Meta-analysis (observed values): Hedges' g = -0.374



B. "Trim and Fill" (adjusted values): Hedges' g = -0.463

Figure 7. Funnel plots for assessing publication bias, displaying the standardized mean difference of antimicrobial treatment courses with tulathromycin or comparator (x-axis) and standard error (y-axis). The vertical line represents the overall effect size estimate (Hedges' g; random-effects model). Without publication bias, number of studies is expected to be equal on both sides of the vertical line. A. Observed studies are shown as open circles, and the observed point estimate (Hedges' g = -0.374) as open diamond. B. "Trim and Fill" funnel plot with imputed studies to yield symmetry. Six studies were included on the left (filled circles) and the imputed point estimate is displayed as filled diamond (Hedges' g = -0.463). The 'adjusted' point estimate suggests a higher difference of antimicrobial treatment courses when accounting for an observed publication bias.

Discussion

Our purpose was to estimate magnitude of the difference in the number of antimicrobial treatment courses required with different antibiotics used as first treatment choice for control or treatment of BRD in US feedlot cattle compared to tulathromycin. In 2011, approximately 90% and 70% of antimicrobials used for metaphylaxis and treatment of BRD belonged to the class of 'high priority, critically important antimicrobials'.[27] Since 2011, 2 new macrolides (gamithromycin and tildipirosin) have been introduced to the market, and percentages that were estimated for 2011 are likely even higher today. With the majority of injectable feedlot antibiotics classified as belonging to the group of critically important antimicrobials, an evaluation of the number of antibiotic treatment courses that could be potentially avoided if one selected the most effective antibiotic as the first-line treatment was of interest.

We hypothesized that use of tulathromycin as the first-line drug would lead to the lowest number of antimicrobial

courses, either for control or treatment of BRD. Primary analysis confirmed this hypothesis. With 1 exception (danofloxacin), comparator antimicrobials included in clinical trials were antibiotics commonly used in US feedlots,[27] including 2 recently licensed substances, gamithromycin and tildipirosin. No clinical trials comparing efficacy of tulathromycin to danofloxacin were identified. Overall, terms for database searches were broadly defined, which minimized the risk that relevant studies were inadvertently overlooked.

Since heterogeneity was substantial, further analyses were conducted to define potential covariates that could explain diversity.[2] Comparator drug (substance) and study sponsor both contributed toward explaining the diversity within the study data pool, but variability not accounted for by these covariates remained substantial. Other potential sources of variability, including study setting or study duration, were shown to have no significant impact on heterogeneity within the data pool.

The finding that different comparator substances significantly contribute to the variation in response outcomes was not unexpected, as different antimicrobial products were previously shown to have vastly different efficacies.[14] In our study, tulathromycin resulted in statistically fewer treatment courses compared to all other antibiotics included, with the exception of ceftiofur. For the latter compound, only 1 comparative evaluation was located, and this limited the statistical power of the comparison. Although statistically significant differences existed between groups of substances, the direction of the effect relative to tulathromycin was identical with all drugs. This subgroup analysis, however, has limitations, as a fixed-effect model was used to calculate statistics within and between subgroups. The preferred model to evaluate treatment effects would have been a mixed-effect model, i.e. a random-effects model within study groups and a fixed-effect model between study groups. Because only 1 or 2 comparisons were identified for 4 substances, a random-effects model would result in incorrect point estimates and CI.[2] Thus, for purposes of subgroup meta-analysis of data comparing different antibiotics' active ingredients, the statistical approach involved use of a fixed-effect model. Although actual effect sizes computed with the fixed-effect model should be interpreted with caution, the effect direction comparing tulathromycin to other treatment options was similar over all comparisons, and confirmed that tulathromycin resulted in fewer antimicrobial treatment courses if used as the first-choice antibiotic rather than other comparators.

The impact of study sponsor on treatment response was a somewhat unexpected observation. In our analysis, studies not sponsored by a pharmaceutical company or sponsored by the manufacturer of a comparator product resulted in smaller differences in antimicrobial treatment responses than studies sponsored by Zoetis, the manufacturer of tulathromycin. Direction of the treatment effect, however, remained consistent in that fewer antimicrobial treatments were required with tulathromycin than if a comparator product was used as the first-line treatment. A potential explanation for the smaller difference in antimicrobial treatment effects compared to tulathromycin in studies sponsored by manufacturers of comparator products might be related to study design. Three of 8 comparisons sponsored by a comparator manufacturer included metaphylaxis during initial processing using tulathromycin, or tilmicosin, another antimicrobial from the macrolide classification of antibiotics.[15,29,30] Sequentially using the same or similar class of antimicrobial to treat the same clinical signs can potentially impair outcomes as a result of acquired resistance to a class of antimicrobial after control failure.[29] To avoid such interactions, it is common practice in US feedlots to change the class of antimicrobial use to treat an animal that failed to respond to the initial course of treatment.[27]

Of the studies included in the analysis, only 2 comparisons were not sponsored by a pharmaceutical company, which limits the explanatory power of the evaluation of the sponsor effect on study outcome. Due to the small sample size pertaining to trials not sponsored by an antibiotic manufacturer, we used a fixed-effect model to evaluate sponsor subgroups.

Study duration varied in clinical trials from 43 to 319 days. As shown in meta-regression, there was no correlation between study duration and effect size.

Although 2 covariates (comparator drug and study sponsor) explained some of the heterogeneity, studies still showed substantial diversity. This is likely a function of variation in feedlot conditions and management strategies, as well as choices of antimicrobials utilized for re-treatment of BRD infections when first-line treatments failed. We did not conduct further subgroup-analyses on antimicrobials used for re-treatments (any treatment after first antimicrobial course), as re-treatments differed substantially between studies, which prevented definition of plausible re-treatment groups. With the inclusion of different studies reflecting different feedlot conditions we can, however, expect our results to be valid over a broad range of feedlot conditions.

The funnel plot indicated a potential publication bias. However, this analysis suggested that the publication bias yielded an underestimation of the effect of tulathromycin relative to competitor products. Indeed, inclusion of apparently missing studies that resulted from the "trim and fill" procedure increased the magnitude of the difference in number of treatments between tulathromycin and comparators.

Results confirm previous findings that reported a lower number of antimicrobial courses following treatment with tulathromycin for control or treatment of BRD compared with enrofloxacin, florfenicol, and tilmicosin.[17] We are not aware of attempts of meta-analysis that compare the mean number of antimicrobial drug courses within the context of the antibiotic used as first choice. In 2 previous meta-analyses, tulathromycin was associated with higher first-treatment efficacy compared with tilmicosin or compared with other antimicrobials.[14,32] The more recent meta-analysis used a

mixed-treatment comparison, which included not only direct comparisons, but also indirect comparisons involving a total of 12 comparators.[14] Our analysis, however, was restricted to direct comparative clinical trials to tulathromycin, which resulted in data from fewer comparators (n = 8). In contrast to previous meta-analyses that focused on first-treatment efficacy, our study investigated the number of antimicrobial treatment courses that followed the initial treatment, which limited the available pool of studies to those which reported treatment outcomes to at least 2 antibiotic treatment courses.

Meta-analysis of mortality was included only as a secondary endpoint, and principally as a means to assess whether reduced antimicrobial treatments with tulathromycin was associated with higher mortalities. However, results were to the contrary; risk of mortality with tulathromycin was approximately half of the risk of mortality with comparator drugs. Because of its clinical and economic relevance, differences in mortality with different antibiotics used in feedlot calves should be addressed in further studies.

For purposes of statistically evaluating our hypothesis we utilized Hedges' *g* as the effect size because it is commonly used in meta-analyses, and also because it is recommended by the Cochrane collaboration.[3] To assess the clinical relevance of our findings we calculated the raw mean difference in number of treatment courses between tulathromycin and comparator antibiotics, and then estimated the clinical relevance based on the 95% CI of the raw mean difference. If we would use the mean-effect size rather than the 95% CI, we assumed that the percentage of cattle treated with the different comparative drugs in clinical studies reflected the percentage of use of the respective drug in daily practice, which most likely is not a realistic assumption. Thus, we calculated a range of antibiotic courses that could be avoided with use of tulathromycin based on the 95% CI around the raw mean difference between tulathromycin and comparator antibiotics. Based on the 95% CI, and with knowledge of the USDA-reported number of BRD-related metaphylactic and therapeutic antibiotic treatments in the US each year, we estimated that the number of antibiotic treatment courses that could be avoided if tulathromycin was the first-choice antibiotic, rather than a competitor product, is between 0.8 and 1.8 million courses for control of BRD, and between 1.0 and 1.8 million courses for treatment of BRD. Considering the large number of antimicrobial treatments given to US feedlot cattle, the potential reduction in antimicrobial treatment courses if tulathromycin was used as the first choice is substantial, even with small absolute differences relative to comparator antibiotics.

The total number of antibiotic treatments potentially avoided if tulathromycin is used for either control or treatment of BRD cannot be computed as the sum of estimates for control and treatment applications described above, because metaphylactic use of tulathromycin would already reduce the number of cattle affected by clinical BRD. Furthermore, using the same antibiotic (e.g., tulathromycin) for both control and treatment of BRD in the same population of cattle is not recommended; within a population of cattle, responsible antibiotic use dictates that tulathromycin be used for either treatment or control, but not for both applications. At a minimum, however, a conservative estimate is that use of tulathromycin as a first-line choice for control or treatment of BRD should reduce overall antibiotic treatments by up to 1.8 million courses/year in the US.

Procedures for conduct of the study largely met standard meta-analysis requirements, with some exceptions. The literature search and review were performed in a systematic manner with the exception that only 1 individual reviewed data in publications and made decisions regarding suitability for analysis; use of at least 2 independent individuals is customary to reduce the possibility of rejecting relevant reports.[10] However, Fail-Safe N computations revealed that 165 times the number of comparisons that are included in our meta-analysis would be required to nullify the relative tulathromycin effect noted. Given that bias is considered not a concern if the Fail-Safe N is ≥5 times the number of studies included in the meta-analysis,[20] we are confident that potential data selection bias is of little concern. The literature search was restricted to English language reports, an appropriate standard given that antimicrobial usage in North American feedlots was the subject of analysis. Calculation of the number of antimicrobial treatment courses administered/animal was computed based on either the total number of cattle enrolled into each study, or based on the number of cattle living at the end of study, and this depended on how results were reported. It was shown that mortalities (including BRD and non-BRD mortalities) occur at any time of study, i.e. before and after first treatment and re-treatments.[16] Therefore, we assumed the number of antimicrobial treatment course given to cattle that died was similar to the number of antimicrobial treatment courses given to cattle that lived. Finally, 2 studies evaluated the efficacy of the combination product florfenicol and flunixin meglumine versus tulathromycin.[6,30] In our analysis this combination product was not considered separately from the florfenicol-only group, but rather was included in the florfenicol comparator group to avoid a further class of drugs with low number of studies. This deemed an appropriate approach given that florfenicol is the only antibiotic moiety in the product and flunixin meglumine, a non-steroidal anti-inflammatory drug, has no antimicrobial properties.

Conclusion

This meta-analysis demonstrated that cattle treated with tulathromycin for control or treatment of BRD required fewer subsequent antimicrobial treatment courses compared with cattle treated with other commonly used antibiotics. Results of this study were very robust, and can be considered valid over a broad range of feedlot conditions. The mean absolute number of antibiotic courses that could be avoided was relatively low in clinical studies. When extrapolated across

US feedlots however, it translates to substantial reductions in antibiotic usage that could be achieved if tulathromycin is used as first choice for control or treatment of BRD rather than other antibiotic products. Hence, tulathromycin could be considered as a judicious first choice of antibiotic for use in US feedlot cattle. Of course, not only the choice of antibiotic contributes to a prudent use of antimicrobials; also other factors are essential in order to reduce antimicrobial consumption in livestock, such as avoiding the underlying reasons for needing an antibiotic at all.

Endnotes

[a]Comprehensive Meta-Analysis V. 2.2, Biostat, Englewood, NJ

Acknowledgements

This study was supported by an unrestricted grant from Zoetis. At the time the study was conducted, Barbara Poulsen Nautrup and Ilse Van Vlaenderen were paid external consultants to Zoetis. Melissa Decker and Ralph Cleale are employees of Zoetis.

References

1. Booker CW, Abutarbush SM, Schunicht OC, Jim GK, Perrett T, Wildman BK, Guichon PT, Pittman TJ, Jones C, Pollock CM. Evaluation of the efficacy of tulathromycin as a metaphylactic antimicrobial treatment in feedlot calves. *Vet Ther* 2007; 8:183-200.
2. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to meta-analysis*. West Sussex, UK: John Wiley & Sons, Ltd, 2009.
3. Deeks JJ, Higgins JPT. Statistical algorithms in Review manager 5, 2010. Available at: http://community.cochrane.org. Accessed 15 March 2016.
4. Duval S, Tweedy R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56:455-463.
5. FDA-CVM. Guidance for industry #209. The judicious use of medically important antimicrobial drugs in food-producing animals, 2012. Available at: http://www.fda.gov/AnimalVeterinary/ SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/. Accessed 01 October 2015.
6. Hannon SJ, Perrett T, Wildman BK, Schunicht OC, Vogstad AR, Fenton RK, Burciaga-Robles LO, Pollock CM, Jim GK, Berg J, Booker CW. Efficacy of a florfenicol-flunixin meglumine combination product versus tulathromycin or ceftiofur crystalline-free acid for the treatment of undifferentiated fever in feedlot calves. *Vet Ther* 2009; 10:E1-E18.
7. Higgins JPT, Deeks JJ, Altman DG. Special topics in statistics. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions*. West Sussex, England: John Wiley & Sons Ltd, 2008; 481-529.
8. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003; 327:557-560.
9. Lean IJ, Rabiee AR, Duffield TF, Dohoo IR. Invited review: Use of meta-analysis in animal health and reproduction: Methods and applications. *J Dairy Sci* 2009; 92:3545-3565.
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ionnidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Br Med J* 2009; 339:b2700.
11. Merck Animal Health. Canadian commercial feedlot study comparing Zuprevo® or Draxxin® and Micotil® when used on arrival in calves at high risk of developing BRD. Merck Tech. Bulletin ZUPCA-99-R. 2012. Available at: http://usa.zuprevo.com/cattle/research/. Accessed 19 October 2015.
12. Nickell JS, White BJ, Larson RL, Blasi DA, Renter DG. Comparison of short-term health and performance effects related to prophylactic administration of tulathromycin versus tilmicosin in long-hauled, highly stressed beef stocker calves. *Vet Ther* 2008; 9:147-156.
13. Nutsch RG, Skogerboe TL, Rooney KA, Weigel DJ, Gajewski K, Lechtenberg KF. Comparative efficacy of tulathromycin, tilmicosin, and florfenicol in the treatment of bovine respiratory disease in stocker cattle. *Vet Ther* 2005; 6:167-179.
14. O'Connor AM, Coetzee JF, da Silva N, Wang C. A mixed treatment comparison meta-analysis of antibiotic treatments for bovine respiratory disease. *Prev Vet Med* 2013; 110:77-87.
15. Perrett T, Abutarbush SM, Wildman BK, Fuchs MT, Schunicht OC, Pollock CM, Fenton RK, Jim GK, Guichon PT, Booker CW, Berg J, Roder J, Spire M. A comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in feedlot calves. *Vet Ther* 2008; 9:128-140.
16. Pfizer Animal Health. Efficacy of DRAXXIN or Baytril for treatment of naturally occurring bovine respiratory disease in calves at 3 feedlots. Pfizer Technical Bulletin DRX07033. 2007. Available at: https://www.zoetisus.com/products/pages/draxxinbeef/technical-information.aspx. Accessed 03 March 2016.
17. Poulsen Nautrup B, Van Vlaenderen I, Gasper SM, Holland RE. Estimating the comparative clinical and economic consequences of tulathromycin for treatment of present or anticipated outbreaks of bovine respiratory disease in feedlot cattle in the United States. *J Anim Sci* 2013; 91:5868-5877.
18. Robb EJ, Tucker CM, Corley L, Bryson WL, Rogers KC, Sturgess DJ, Brodersen B. Efficacy of tulathromycin versus enrofloxacin for initial treatment of naturally occurring bovine respiratory disease in feeder calves. *Vet Ther* 2007; 8:127-135.
19. Rooney KA, Nutsch RG, Skogerboe TL, Weigel DJ, Gajewski K, Kilgore WR. 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* 2005; 6:154-166.
20. Rosenthal R. The "file drawer problem" and tolerance for null results. *Psych Bull* 1979; 86:638-641.
21. Schunicht OC, Booker CW, Guichon PT, Jim GK, Wildman BK, Pittman TJ, Perrett T. An evaluation of the relative efficacy of tulathromycin for the treatment of undifferentiated fever in feedlot calves in Nebraska. *Can Vet J* 2007; 48:600-606.
22. Skogerboe TL, Rooney KA, Nutsch RG, Weigel DJ, Gajewski K, Kilgore WR. Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated bovine respiratory disease in feedlot cattle. *Vet Ther* 2005; 6:180-196.
23. Stegner JE, Lucas MJ, McLaughlin CL, Davis MS, Alaniz GR, Weigel DJ, Pollreisz JH, Tucker CM, Koers WC, Turgeon OA, Szasz JI. Comparative effects of therapeutic programs on bovine respiratory disease, performance, carcass, and profitability of high risk feedlot heifers. *Prof Anim Sci* 2013; 29:208-218.
24. Sterne JAC, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. *Br Med J* 2001; 323:101-105.
25. Teale CJ, Moulin G. Prudent use guidelines: a review of existing veterinary guidelines. *Rev Sci Tech Off Int Epiz* 2012; 31:343-354.
26. Torres S, Thomson DU, Bello NM, Nosky BJ, Reinhardt CD. Field study of the comparative efficacy of gamithromycin and tulathromycin for the control of undifferentiated bovine respiratory disease complex in beef feedlot calves at high risk of developing respiratory tract disease. *Am J Vet Res* 2013; 74:839-846.
27. USDA APHIS. Feedlot 2011. Part IV: Health and health management on U.S. feedlots with a capacity of 1,000 or more head. 2013. Available at: https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartIV.pdf. Accessed 01 October 2015.
28. USDA NASS. Livestock slaughter 2014 summary. 2015. Available at: http://www.usda.gov/nass/PUBS/TODAYRPT/lsan0415.pdf. Accessed 04 March 2016.
29. Van Donkersgoed J, Berg J, Hendrick S. Comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in Alberta feedlot calves. *Vet Ther* 2008; 9:275-281.
30. Van Donkersgoed J, Berg J, Hendrick S. A comparison of florfenicol-flunixin meglumine versus tulathromycin for the treatment of undifferentiated fever in fall-placed feedlot calves. *Vet Ther* 2009; 10:78-85.

31. Van Donkersgoed J, Merrill JK, Hendrick S. Comparative efficacy of tilmicosin versus tulathromycin as a metaphylactic antimicrobial in feedlot calves at moderate risk for respiratory disease. *Vet Ther* 2008; 9:291-297.
32. Wellman NG, O'Connor AM. Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. *J Vet Pharm Ther* 2007; 30:234-241.
33. Whitley E, Ball J. Statistics review 1: Presenting and summarizing data. *Crit Care* 2002; 6:66-71.
34. World Health Organization. Critically important antimicrobials for human medicine – 3rd rev. 2012. Available at: http://apps.who.int/iris/handle/10665/77376?locale=en&locale=en&locale=ru&null. Accessed 01 October 2015.
35. Zoetis. Comparative efficacy of Draxxin® vs Zuprevo® or Micotil® for control of BRD in high-risk feedlot cattle. Zoetis Technical Bulletin DRX-00027. 2016. Available at: https://www.zoetisus.com/products/pages/draxxinbeef/technical-information.aspx. Accessed 03 March 2016.
36. Zoetis. Metaphylactic efficacy of Draxxin® vs Zactran® for control of BRD in high-risk feedlot cattle. Zoetis Technical Bulletin DRX13035. 2013. Available at: https://www.zoetisus.com/products/pages/draxxinbeef/technical-information.aspx. Accessed 03 March 2016.

FUTURE MEETINGS

American Association of Bovine Practitioners

2017	Omaha, Nebraska	September 14 - 16
2018	Phoenix, Arizona	September 13 - 15
2019	St. Louis, Missouri	September 12-14
2020	Louisville, Kentucky	September 24-26

World Association for Buiatrics

2018	Sapporo, Japan	August 26 - 30

Vira Shield® Research Brief 1

Impact of Vaccination with an Inactivated or Modified-Live Viral Vaccine on Reproduction[1]

VIRA SHIELD®

Study overview

A study was conducted to determine how vaccination with an inactivated or modified-live viral (MLV) vaccine would impact reproductive parameters in beef cows.

Key study results

- Treatment of cows and heifers with Bovi-Shield® during pre-breeding decreased pregnancy success compared to treatment with Vira Shield®
- Treatment with Bovi-Shield tended to reduce the percentage of cows that calved in the first 21 days of the calving season compared to Vira Shield
  - This decrease in calving percent remained over the entire calving season
  - Delaying when the animal conceives/calves can have implications on the success of a cow/calf operation, including pounds of calf weaned, rebreeding and longevity in the herd

Background information

TRIAL DESIGN

- Total head — 1,304*
- Nine herds
  - Blocked by age and calving date in each herd
- Three treatments
  - Control
  - MLV (Bovi-Shield Gold FP 5 L5 HB)
  - Inactivated (Vira Shield 6 L5 HB)

STATISTICS

- Data were analyzed using the GLIMMIX procedure in SAS — treatment, day postpartum and the treatment by day postpartum interaction were analyzed
- No treatment by year interaction ($P > 0.66$)
  - Herd was included as a random variable to account for unknown differences between herd and years

Study results

Chart 1. Pregnancy success

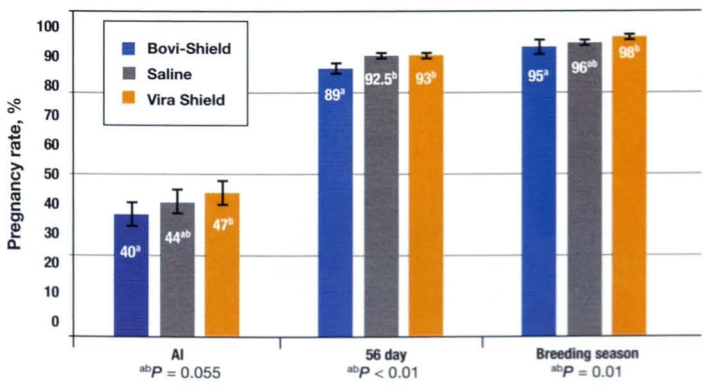


Chart 2. Calving by group

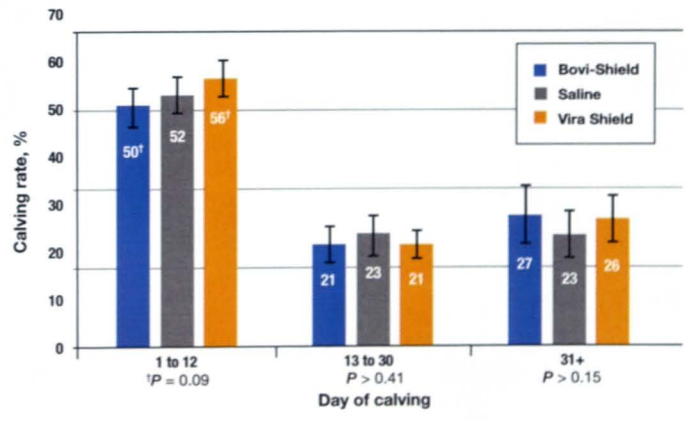
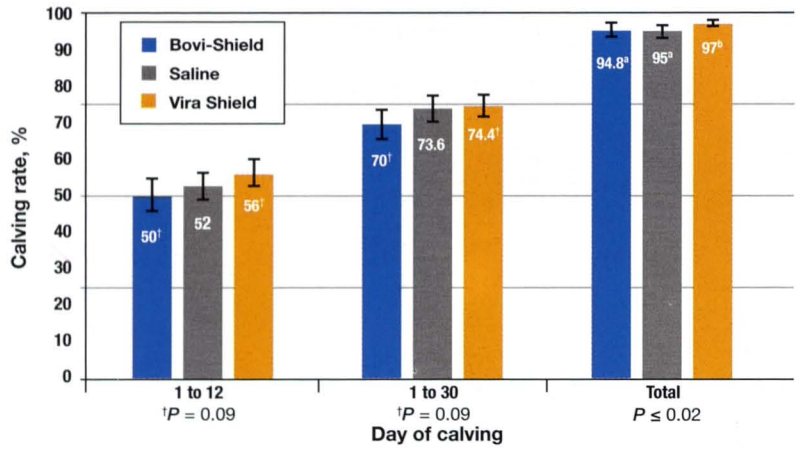


Chart 3. Cumulative calving data



Conclusions

- When evaluating reproductive vaccines, it's critical to consider the impact of decreased calving on the success of the cow/calf herd
- Your vaccine program may have impacts on estrus synchronization (ES) and timed artificial insemination (TAI), which in turn impact the economic efficiency of your operation
  - Potential impacts of ES and TAI include shortened calving season, increased calf uniformity, more calves born earlier in the season, enhanced preweaning growth and heavier calves at weaning[2]
  - There is a nearly $50/hd advantage for managing ES and TAI on your operation[2]
- Ensure that you're getting the most out of your breeding program by maximizing your reproductive vaccine program. To learn more about evaluating your vaccine program and how Vira Shield can help improve reproductive parameters, reach out to your veterinarian or Elanco sales representative

The label contains complete use information, including cautions and warnings. Always read, understand and follow the label and use directions.

*1,436 animals entered the initial study, but 132 were sold prior to calving for non-reproductive purposes.

[1]Perry, G., Larimore, E., et al. 2016. "Influence of vaccination with an inactivated or modified-live viral reproductive vaccine on reproductive parameters in beef cows." South Dakota State University.
[2]Rodgers, J.L., Bird, S.L., et al. 2012. "An economic evaluation of estrous synchronization and timed artificial insemination in suckled beef cows." J Anim Sci. Vol 90(11):4055-62.

nchlth 3554-1

Elanco™

USBBUVSH00014