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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[1]

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ABSTRACT: The goal of this study was to determine the clinical and economic impact of using tulathromycin as first line treatment for bovine respiratory disease (BRD) compared with other commonly used antimicrobials. Two decision trees were developed simulating the consequences of treating cattle at high risk of developing BRD [control model (CM)] or cattle with first clinical BRD episode [treatment model (TM)]. As comparators florfenicol and tilmicosin were considered in both models whereas enrofloxacin was included in the TM because it was only labeled for treatment of BRD at the time of development of the calculators. A total of 5 (CM) and 10 (TM) comparative clinical studies that reported efficacy data for the selected drugs and indications were identified as suitable for model population. The following outcomes were considered: first treatment success, number of subsequent BRD treatments, chronics, and mortalities. Cost parameters were considered from the perspective of the producer and included treatment costs (first treatment and retreatments) and costs of chronics and deaths derived from published sources for 2010 (default). The models allowed the estimation of clinical and economic consequences according to each individual trial outcomes. Treatment with tulathromycin resulted in more first treatment successes and fewer removals (chronics and deaths) in all comparisons. The average total number of antimicrobial treatments required for the management of BRD was also least with tulathromycin as first treatment option. Because of better efficacy, total costs over the entire study periods were always lowest with tulathromycin. Depending on the study selected as the basis for the efficacy evaluation, cost savings with tulathromycin were calculated in the CM between US$21.00 and $47.86 (vs. florfenicol) and $11.37 and $72.64 (vs. tilmicosin); cost savings in the TM ranged between $28.47 and $143.87 (vs. florfenicol) and $7.75 and $84.91 (vs. tilmicosin) as well as between $23.22 and $47.82 (vs. enrofloxacin), with the ranges reflecting a variety of settings in different trials. Thus, the higher drug costs of tulathromycin were more than offset by reduced BRD treatments, chronics, and mortalities in the herd. Fewer BRD episodes in cattle treated with tulathromycin not only contributes to overall savings in BRD management but also reduces the necessity of repeated antibiotic treatment, supporting prudent use of antimicrobials in livestock.

Key words: antimicrobials, bovine respiratory disease, economic outcomes, feedlot cattle, treatment success

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INTRODUCTION

Bovine respiratory disease (**BRD**) continues to be the most significant health problem in U.S. feedlots (Duff and Galyean, 2006). Bovine respiratory disease typically occurs shortly after arrival at a feedyard (Smith, 1998), when calves are stressed by transportation, mixing, and processing (Daniels et al., 2000). Early administration of an effective antimicrobial maximizes the chance of successful treatment of BRD-affected animals and mass treatment can decrease overall BRD morbidity in high risk cattle (USDA-APHIS, 2001).

Tulathromycin is the first member of a new macrolide class, which develops high and persistent levels of drug in the lung tissue (Nowakowski et al., 2004). The efficacy of tulathromycin has been well proven. A

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recent mixed-treatment comparison meta-analysis estimated the relative efficacy of 12 antibiotic treatments for BRD in beef cattle in the United States from 93 trials. For all treatments and an untreated control group (no active control), the authors estimated risk ratios for the incidence of retreatment as well as a mean ranking for being the worst treatment choice. Tulathromycin had the lowest risk of retreatment although superiority was not significant compared with enrofloxacin and danofloxacin. Probability of being ranked the worst treatment was zero with tulathromycin (O'Connor et al., 2013). An economic analysis revealed an advantage of treatment with tulathromycin over florfenicol of US$52.50 per animal, which was due to lower relapse and mortality rates with tulathromycin (Schunicht et al., 2007). A lower relapse rate not only reduces the costs and losses associated with these events, it also diminishes additional antibiotic treatments, thus enabling prudent use of antimicrobials in feedlots (Ribble et al., 2010).

The aim of this study was to develop 2 health economic models that estimate the clinical and economic consequences of using tulathromycin compared with florfenicol, tilmicosin, and enrofloxacin for control and treatment of BRD in U.S. feedlots.

METHODS

The study used a mathematical modeling approach to simulate outcomes with different treatment regimes for BRD. No experiments on animals were conducted to complete the study.

Model Approach

Two models were developed as decision trees in Microsoft Excel, version 2007 (Microsoft Corp., Redmond, Washington) and evaluated the clinical and economic benefits of initial treatment of cattle at high-risk of developing BRD [control model (**CM**)] and cattle with clinically apparent BRD infection [treatment model (**TM**)]. Florfenicol, tilmicosin, and enrofloxacin, belonging to those antimicrobials used most often in U.S. feedlots (USDA, 2000a), were selected as comparators to tulathromycin. In accordance with their label indications at the time of development of the calculators, florfenicol and tilmicosin were considered as comparators in both models (CM and TM) whereas enrofloxacin was included in the TM only.

The models simulated first treatment of cattle at high risks of BRD after arrival at the feedlot (CM) or treatment of cattle with first clinically apparent BRD infection at the feedlot (TM). Success of first treatment was defined as absence of any BRD infection in the CM and as cure and absence of any further BRD episode during the study periods in the TM. First treatment was considered as failure if the cattle developed any BRD (CM) or any further or persistent BRD (TM) or if a cattle died due to BRD (both models) or was classified as chronic (both models) over the observation periods. The following clinical consequences were considered in the 2 models: 1) success rate of first treatment, 2) number of subsequent BRD treatments after failure of first treatment, 3) number of chronics as defined in the respective trials, and 4) number of mortalities due to BRD.

Although the 2 models had to be highly flexible (i.e., easily adaptable to clinical variations as well as regional and timely changes in cost data), default values were defined allowing the estimation of results when using the predefined input data.

Efficacy Data Considered as Defaults in the Model

Two models were developed to allow simulations according to the clinical outcomes of the different individual trials rather than using 1 estimate for each clinical parameter as calculated by meta-analysis or pooling of data. Therefore, clinical studies evaluating the efficacy of tulathromycin vs. comparators in the relevant indications (control or treatment of BRD in U.S. feedlots) were identified by literature searches in MEDLINE (www.ncbi.nlm.nih.gov/pubmed) and other sources (e.g., reference lists) as well as by open Internet searches.

Different study sites reported in an article were included in the models as individual studies if results were stated separately for the different locations.

Comparative Clinical Studies Considered in the Control Model

The following 6 peer-reviewed articles (including 12 study sites) reported comparative clinical efficacy of tulathromycin for treating cattle at high risk of developing BRD (comparator or comparators and number of sites): Nickell et al. (2008) (tilmicosin at 1 site), Van Donkersgoed et al. (2008a) (tilmicosin at 1 site), Booker et al. (2007) (tilmicosin at 1 site), Step et al. (2007) (tilmicosin at 2 sites), Kilgore et al. (2005a) (tilmicosin at 4 sites), and Rooney et al. (2005) (florfenicol and tilmicosin at 3 sites). Three studies, published in 2 technical bulletins (Pfizer Animal Health, 2005a,b), were included in 1 of the peer-reviewed articles (Rooney et al., 2005); however, the technical reports were also considered for data extraction because they reported additional relevant information.

From the 6 articles identified, 3 papers reporting studies at 7 sites were excluded from the CM for the following reasons: Van Donkersgoed et al. (2008a) defined and interpreted probability of relapses differently to other studies, Kilgore et al. (2005a) reported short-term studies

over 14 d, which did not allow a final assessment of treatment success, and Step et al. (2007) compared a 2-drug regimen (ceftiofur + tulathromycin) with 1-course regimens (tilmicosin alone). Accordingly, the CM considered efficacy data from 3 peer-reviewed papers (supplemented by data from technical bulletins[Pfizer Animal Health 2005a,b] where appropriate) reporting 5 studies (2 studies vs. florfenicol and 3 studies vs. tilmicosin). The studies as well as type and origin of animals and study locations are listed in Table 1.

Comparative Clinical Studies Considered in the Treatment Model

Ten peer-reviewed articles were identified, including 2 systematic reviews (O'Connor et al., 2013; Wellman and O'Connor, 2007) and the following 8 articles (17 studies) reporting comparative efficacy of tulathromycin for treatment of clinically apparent BRD in feedlot cattle (comparator or comparators and number of sites): Van Donkersgoed et al. (2009) (florfenicol-flunixin meglumine at 1 site), Van Donkersgoed et al. (2008b) (florfenicol at 1 site), Perrett et al. (2008) (florfenicol at 1 site), Robb et al. (2007) (enrofloxacin at 2 sites), Schunicht et al. (2007) (florfenicol at 1 site), Kilgore et al. (2005b) (tilmicosin at 4 sites), Nutsch et al. (2005) (florfenicol and tilmicosin at 3 sites), and Skogerboe et al. (2005) (florfenicol and tilmicosin at 4 sites). Additionally, 4 technical bulletins (Pfizer Animal Health, 2007, 2005c,d,e) and a field trial report (Bayer Veterinary Services, 2006) were identified. Apart from 2 comparative studies vs. enrofloxacin (Pfizer Animal Health, 2007, 1 site; Bayer Veterinary Services, 2006), all other studies included in technical reports were published in peer-reviewed articles. However, these technical reports were also considered for data extraction if they reported additional information.

The 2 meta-analyses, 5 peer-reviewed articles (7 studies), and one technical report (Bayer Veterinary Services, 2006) were excluded from the TM for the following reasons: the meta-analyses did not provide additional data to the trials included, and the aim of the model was to consider efficacy data from various clinical studies rather than to use data combined by meta-analysis; the studies published by Kilgore et al. (2005b) were short-term studies over 14 d, which did not allow an overall assessment of treatment success because of the short time frame; 3 studies were excluded because they evaluated treatment efficacy of tulathromycin vs. florfenicol or enrofloxacin in cattle being pretreated with tilmicosin (Van Donkersgoed et al., 2008b; Bayer Veterinary Services, 2006) or tulathromycin (Perrett et al., 2008), and outcomes were influenced by prior antimicrobial treatments; and 1 study compared a combination product including florfenicol and the anti-inflammatory flunixin meglumine with tulathromycin alone (Van Donkersgoed et al., 2009). Accordingly, the TM considered efficacy data from 10 studies reported in 4 peer-reviewed papers (supplemented by data from technical reports where appropriate for model population) and 1 technical report (4 studies vs. florfenicol, 3 studies vs. tilmicosin, and 3 studies vs. enrofloxacin). The studies as well as type and origin of animals and study locations are listed in Table 2.

Economic Data Considered as Defaults in the Models

The models considered costs and losses associated with BRD and its treatments for the producers. Cost parameters included:

- Cost of first treatment with study drugs (CM and TM) and cost of first clinical BRD treatment in case of control failure (only CM): only the costs of the antimicrobials were considered as estimated from Internet pharmacies for 2010; for the calculation of treatment costs per animal, an average weight of 272.4 kg and dosages according to label were considered as default
- Cost of subsequent BRD treatments, that is, costs and losses associated with subsequent or persistent BRD episodes (including drug costs and lost income due to reduced average daily gain and lower carcass quality) as reported by McNeill et al. (2000)

Table 1. Overview of studies considered in the control model (CM) as basis for efficacy evaluation as well as type and origin of animals and study locations. References others than peer-reviewed articles were also considered, if they provided additional information relevant for model population

Comparator	Study no.	Peer-reviewed reference	Other sources of reference (name of the study)	Animals included	Origin of animals	Study location
Florfenicol (F)	CM-F1	Rooney et al., 2005 (Idaho)	Pfizer Animal Health, 2005b (223 d feedlot study)	Feeder steers	Washington and Oregon	Idaho
	CM-F2	Rooney et al., 2005 (Texas)	Pfizer Animal Health, 2005b (194/195 d feedlot study)	Feeder steers	Alabama, South Carolina, and Texas	Texas
Tilmicosin (T)	CM-T1	Rooney et al., 2005 (Colorado)	Pfizer Animal Health, 2005a (229 d feedlot study)	Steers	Colorado and Wyoming	Colorado
	CM-T2	Booker et al., 2007		Heifer calves	Western Canada	Alberta, Canada
	CM-T3	Nickell et al., 2008		Bulls and steers	Tennessee	Kansas State

- Cost of a chronic: loss compared with healthy cattle as reported by Waggoner et al. (2006)
- Cost of a dead: loss as reported by McNeill et al. (2000).

Although labor costs can be considered in the models, their default value was set at zero, being the most conservative approach.

Cost data were estimated at the time of model development (2010). Because cost data can vary substantially over time, all estimates were also adapted to 2012 to assess if cost changes would lead to changes of overall outcomes. Therefore, drug prices were newly defined from Internet pharmacies (valid as of 2012), and other cost data were inflation adjusted to 2012, using the "US Inflation Calculator" from the CoinNews Media Group LLC (www.usinflationcalculator.com/). All cost data included as defaults as well as the adapted values for 2012 are summarized in Table 3.

Outcomes Calculated by the Models

The 2 models presented clinical and economic outcomes as calculated for the specific study selected as the basis for efficacy evaluation.

Clinical outcomes included:

- First treatment success as reported in the clinical study, corresponding to no BRD episode (CM) or no further or persistent BRD episode (TM) during study period
- Percentage of chronics as reported or calculated from study data
- Percentage of mortalities as reported or calculated from study data
- Average number of subsequent BRD treatments as calculated from study data

The following economic outcomes were calculated:

- Medication cost of first treatment: cost of study drug per animal
- Costs of all subsequent BRD treatments (corresponding to all clinical BRD treatments in the CM and to all further BRD treatments after the first episode in the TM) as simulated according to clinical efficacy over the study period (including drug costs and lost income due to reduced average daily gain and lower carcass quality in cattle with 2 or more BRD episodes)
- Costs of removals: losses incurred with all chronics and deaths
- Total costs: sum of all costs calculated over the study period, that is, costs of first and subsequent treatments as well as removal costs as simulated according to clinical efficacy as reported in the different studies
- Incremental costs with tulathromycin: difference of calculated total cost with tulathromycin and total cost with comparator, with negative values referring to lower total costs (cost savings) with tulathromycin.

RESULTS

Results were calculated separately for each study included, and outcome variations reflect the differences in clinical efficacy as reported in the various studies (Tables 4 and 5).

Table 2. Overview of studies considered in the treatment model (TM) as basis for efficacy evaluation as well as type and origin of animals and study locations. References others than peer-reviewed articles were also considered, if they provided additional information relevant for model population

Comparator	Study no.	Peer-reviewed reference	Other sources of reference (name of the study)	Animals included	Origin of animals	Study location
Florfenicol (F)	TM-F1	Schunicht et al., 2007		Beef calves	Minnesota, North Dakota, and Kansas	Nebraska
	TM-F2	Skogerboe et al., 2005 (Nebraska)	Pfizer Animal Health, 2005e (study 1)	Feeder steers	Minnesota, North Dakota, and Kansas	Nebraska
	TM-F3	Skogerboe et al., 2005 (Greeley, CO)	Pfizer Animal Health, 2005e (study 2)	Feeder steers	Tennessee	Colorado
	TM-F4	Nutsch et al., 2005 (NE-2 and NE-3)	Pfizer Animal Health, 2005c (study 2 and study 3)	Feeder steers	Missouri, Kansas, Tennessee, Mississippi, South Carolina, and Kentucky	Nebraska
Tilmicosin (T)	TM-T1	Skogerboe et al., 2005 (Texas)	Pfizer Animal Health, 2005d (study 2)	Beef heifers	Oklahoma, and Arkansas	Texas
	TM-T2	Skogerboe et al., 2005 (Wellington, CO)	Pfizer Animal Health, 2005d (study 1)	Steers	Wyoming, and Colorado	Colorado
	TM-T3	Nutsch et al., 2005 (NE-1)	Pfizer Animal Health, 2005c (study 1 and study 3)	Feeder steers	Kentucky, South Carolina, Mississippi, and Tennessee	Nebraska
Enrofloxacin (E)	TM-E1	Robb et al., 2007	Pfizer Animal Health, 2007 (Colorado)	Feeder calves	Mississippi, and Texas	Colorado
	TM-E2	Robb et al., 2007	Pfizer Animal Health, 2007 (Texas I)	Feeder calves	Mississippi, and Texas	Texas
	TM-E3		Pfizer Animal Health, 2007 (Texas II)		Mississippi, and Texas	Texas

Clinical Outcomes

Clinical Outcomes in Control Studies. The 5 studies used as the basis for the efficacy evaluation included 4,109 animals in the tulathromycin groups and 4,081 animals in the comparator groups. Observation periods varied considerably between studies and ranged from 41 to 43 d in the shortest study to 227 to 229 d in the studies with longest duration.

In all studies of cattle at high risk for BRD, the success rate of tulathromycin was greater compared with that of florfenicol or tilmicosin, that is, cattle receiving tulathromycin had the lowest risk of developing clinical BRD. First treatment success ranged from 61.8 to 92.9% (tulathromycin), 32.2 to 72.0% (florfenicol), and 32.0 to 77.7% (tilmicosin). Where reported, the average number of clinical BRD treatments after initial treatment was lower with tulathromycin (range: 1.29 to 1.42) compared with florfenicol (range: 1.85 to 1.90) and tilmicosin (range: 1.37 to 1.67) (1 study did not report subsequent BRD cases). Cattle treated with tulathromycin required the fewest number of antimicrobial treatments of clinical BRD. In addition, the percentage of chronics and the mortality rates were lower in cattle treated with tulathromycin compared with florfenicol or tilmicosin, ranging from 1.0 to 1.7% (chronics) and 0.0 to 3.4% (mortalities), respectively. Respective results for florfenicol were 5.3 to7.0% (chronics) and 0.8 (mortalities) and 2.3 to 7.5% (chronics) and 1.2 to 13.6% (mortalities) for tilmicosin. Results from all studies are listed in Table 4.

Table 3. Cost data considered in the models from the perspective of the producer. Costs included in the models as defaults were estimated for 2010 from Internet pharmacies. Additionally, costs have been adapted to 2012 (drug costs from Internet pharmacies; costs of treatment failure inflation adjusted)

Cost data	Cost included as default,[1] US$	Cost adapted to 2012, US$
Cost of antimicrobial		
Tulathromycin	3.28/cwt	3.96/cwt
Florfenicol	2.85/cwt	3.24/cwt
Tilmicosin	1.47/cwt	2.10/cwt
Enrofloxacin	3.18/cwt	3.64/cwt
Cost of treatment failure		
Cost of first BRD[2] treatment in case of control failure (control model only), medication costs only	2.83/cwt	2.98/cwt
Cost of subsequent BRD treatment, that is, after failure of first BRD treatment	124.00/animal	165.49/animal
Cost of a death	609.00/animal	812.76/animal
Cost of a chronic	254.00/animal	309.02/animal

[1]cwt = 100 pounds (i.e., 45.4 kg).

[2]BRD = bovine respiratory disease

Clinical Outcomes in Treatment Studies. The 10 studies considered in the TM included a total of 1,495 animals in the tulathromycin groups and 1,273 animals in the comparator groups, and studies duration varied between 57 and 61 d and 317 to 319 d.

Table 4. Number of animals and study duration as well as clinical outcomes as reported or calculated from data reported in the studies. Assignments of studies (study no.) as defined in Tables 1 and 2

Comparator	Study no.	No. of animals (tula[1]/comp[2]) included for efficacy evaluation	Duration of study	Control or Treatment success (tula/comp)	Avg number of subsequent BRD[3] cases (tula/comp)	Percentage chronics (tula/comp)	Percentage mortalities (tula/comp)
Control model (CM)							
Florfenicol	CM-F1	238/242	223 d	61.8%/32.2%*	1.40/1.85	1.7%/7.0%	0.0%/0.8%
	CM-F2	248/246	194–195 d	81.9%/72.0%*	1.39/1.90	1.2%/5.3%	0.4%/0.8%
Tilmicosin	CM-T1	238/242	227 or 229 d	80.3%/62.8%*	1.42/1.67	1.3%/3.7%	0.8%/1.2%
	CM-T2	3,239/3,204	227–229 d	92.9%/77.7%*	1.29/1.37	1.0%/2.3%	0.3%/1.9%
	CM-T3	146/147	41 or 43 d	67.1%/32.0%*	Not reported	1.4%/7.5%	3.4%/13.6%
Treatment model (TM)							
Florfenicol	TM-F1	100/100	317–319 d	51.0%/25.0%*	2.14/2.32	18.0%/27.0%	6.0%/21.0%
	TM-F2	94/99	316–317 d	53.2%/23.2%*	2.86/3.17	19.1%/42.4%	1.1%/5.1%
	TM-F3	97/99	173–175 d	79.4%/63.6%*	1.74/2.06	3.1%/10.1%	1.0%/0.0%
	TM-F4	336/236	57–61 d	76.5%/53.0%*	1.30/1.53	3.9%/14.8%	0.9%/3.4%
Tilmicosin	TM-T1	100/100	257–259 d	73.0%/67.0%	1.33/1.91	2.0%/4.0%	0.0%/1.0%
	TM-T2	98/94	224–230 d	77.6%/60.6%*	1.32/1.56	0.0%/4.3%	0.0%/3.2%
	TM-T3	336/218	57–61 d	76.5%/43.1%*	1.30/1.53	3.9%/19.7%	0.9%/3.2%
Enrofloxacin	TM-E1	124/124	59 d	87.9%/70.2%*	1.27/1.25	0.0%/0.8%	0.0%/0.0%
	TM-E2	120/120	63 d	80.0%/62.5%*	1.43/1.41	5.8%/6.7%	2.5%/2.5%
	TM-E3	90/83	58 d	87.8%/74.7%*	1.00/1.08	0.0%/0.0%	5.6%/10.8%

[1]tula = tulathromycin.

[2]comp = comparator.

[3]BRD = bovine respiratory disease.

*$P < 0.05$.

In all treatment studies, success of first BRD treatment was greatest with tulathromycin, ranging from 51.0 to 87.9%. Corresponding ranges of success rates in the comparator groups were 23.2 to 63.6% (florfenicol), 43.1 to 67.0% (tilmicosin), and 62.5 to 74.7% (enrofloxacin). Over all studies, calculated numbers of subsequent treatments ranged from 1.00 to 2.86 for tulathromycin, 1.53 to 3.17 for florfenicol, 1.53 to 1.91 for tilmicosin, and 1.08 to 1.41 for enrofloxacin. Thereby, average numbers of subsequent BRD treatments were least with tulathromycin in most studies (8 out of the 10 studies) whereas in 2 comparative studies vs. enrofloxacin, average numbers of subsequent antibiotic administrations were slightly greater (1.27 vs. 1.25, and 1.43 vs. 1.41 for tulathromycin vs. enrofloxacin, respectively). Percentages of chronics were lower with tulathromycin in 9 out of 10 studies; in 1 study no chronics were reported for tulathromycin or comparator (enrofloxacin). Percentages of chronics ranged from 0.0 to 19.1% (tulathromycin), 10.1 to 42.4% (florfenicol), 4.0 to 19.7% (tilmicosin), and 0.0 to 6.7% (enrofloxacin). Mortality rates in the tulathromycin groups were lower in all 3 studies against tilmicosin and lower in 3 out of 4 studies against florfenicol whereas 1 study revealed a slightly but not statistically significant greater mortality rate with tulathromycin (1 vs. 0% with florfenicol). Compared with enrofloxacin, mortality rate was equal in 2 studies, and 1 study reported fewer deaths with tulathromycin. Depending on the selected study, mortality rates varied between 0.0 and 6.0% (tulathromycin), 0.0 and 21.0% (florfenicol), 1.0 and 3.2% (tilmicosin), and 0.0 and 10.8% (enrofloxacin). However, when considering all chronics and mortalities combined, corresponding rates were always lower with tulathromycin, regardless of the comparator or study selected. Results from all studies are listed in Table 4.

Economic Results in Control and Treatment Studies

Cost of medication was highest with tulathromycin. This applied to default data as of 2010 but was also confirmed for 2012. However, costs of subsequent treatments and costs of removals were lowest with tulathromycin in all control and treatment studies because of the lower probabilities of BRD occurrences or reoccurrences. Using the defaults as described, total costs per animal (considering cost of medication and all other BRD related costs) were lower with tulathromycin compared with florfenicol (CM and TM), tilmicosin (CM and TM), and enrofloxacin (TM). Depending on the study selected as basis for efficacy evaluation, overall costs per bovine varied in the CM between $27.89 and $49.60 (tulathromycin), $54.72 and $90.81 (florfenicol), and $40.72 and $122.25 (tilmicosin), and in the TM overall costs per animal associated with BRD were calculated be-

Table 5. Economic results as calculated per animal in the two models, considering cost data as defined as defaults and clinical data as reported in the respective study. Incremental costs were calculated as difference of total costs with tulathromycin and total costs of comparator; accordingly, negative incremental costs refer to overall costs savings with tulathromycin. Assignments of studies (study no.) as defined in Tables 1 and 2. All costs in US$ (as valid for the producer and defined for 2010)

Comparator	Study no.	Medication cost first treatment (tula[1]/comp[2]), $	Costs associated with subsequent treatments (tula/comp), $	Costs of chronics and mortalities (tula/comp), $	Total costs (tula/comp), $	Tula incremental costs (total costs tula– total costs comp), $
Control model (CM)						
Florfenicol	CM-F1	19.68/17.10	19.00/50.83	4.27/22.88	42.95/90.81	–47.86
	CM-F2	19.68/17.10	8.52/19.25	5.53/18.37	33.72/54.72	–21.00
Tilmicosin	CM-T1	19.68/8.82	9.46/23.02	8.32/17.00	37.47/48.84	–11.37
	CM-T2	19.68/8.82	3.81/14.17	4.39/17.73	27.89/40.72	–12.84
	CM-T3	19.68/8.82	5.59/11.56	24.34/101.86	49.60/122.25	–72.64
Treatment model (TM)						
Florfenicol	TM-F1	19.68/17.10	60.76/93.00	82.26/196.47	162.70/306.57	–143.87
	TM-F2	19.68/17.10	58.04/95.19	55.12/138.52	132.84/250.81	–117.97
	TM-F3	19.68/17.10	25.57/45.09	14.13/25.66	59.38/87.85	–28.47
	TM-F4	19.68/17.10	29.15/58.32	15.26/58.31	64.10/133.74	–69.64
Tilmicosin	TM-T1	19.68/8.82	33.48/40.92	5.08/16.25	58.24/65.99	–7.75
	TM-T2	19.68/8.82	27.84/48.81	0.00/30.24	47.52/87.87	–40.36
	TM-T3	19.68/8.82	29.15/70.53	15.26/69.66	64.10/149.01	–84.91
Enrofloxacin	TM-E1	19.68/19.08	15.00/37.00	0.00/2.05	34.68/58.13	–23.45
	TM-E2	19.68/19.08	24.80/46.50	30.04/32.16	74.52/97.74	–23.22
	TM-E3	19.68/19.08	15.16/31.37	33.83/66.04	68.67/116.49	–47.82

[1]tula = tulathromycin.

[2]comp = comparator.

tween $34.68 and $162.70 (tulathromycin), $87.85 and $306.57 (florfenicol), $65.99 and $149.01 (tilmicosin), and $58.13 and $116.49 (enrofloxacin). Cost data estimated for all studies included are listed in Table 5.

Accordingly, higher drug costs with tulathromycin were more than offset, resulting in cost savings for tulathromycin in all treatment and control studies. Incremental costs were calculated as difference of total costs with tulathromycin and total costs with comparator. Accordingly, negative incremental costs refer to lower costs, that is, costs savings, with tulathromycin, ranging from –$11.37 to –$72.64 per head in the CM and from –$7.75 to –$143.87 per animal in the TM, corresponding to the costs saved when tulathromycin was used for first treatment rather than a comparator drug.

When considering cost data as estimated for 2012, tulathromycin remained cost saving in all simulations, with incremental costs ranging from –$16.95 to –$96.76 (CM) and from –$13.08 to –$188.43 (TM) per bovine. Incremental values estimated for cost defaults and costs as of 2012 are graphically displayed in Fig. 1.

DISCUSSION

The purpose of this study was to estimate the clinical and economic consequences of treating feedlot cattle at high risk of BRD or cattle with clinically apparent BRD with tulathromycin or common comparators, licensed in the United States in the respective indication. For this reason a decision analytic modeling technique (decision tree) was chosen, which is especially suitable to define both clinical and economic consequences of medical actions (Nuijten, 1998). The studies considered in the models for efficacy evaluation represented very different feedlot conditions. Accordingly, it can be concluded that the outcomes simulated by the models can apply across a variety of settings.

First treatment success was greatest with tulathromycin in all control and treatment studies compared with florfenicol (CM and TM), tilmicosin (CM and TM), and enrofloxacin (TM), that is, in all studies the percentage of cattle that did not need any further antimicrobial treatment against BRD was highest with tulathromycin. Although ceftiofur crystalline free acid is another commonly used antimicrobial labeled for control and treatment of BRD (Robb et al., 2007), comparators in the calculators were restricted to the 3 aforementioned drugs. However, a recent mixed-treatment comparison meta-analysis, which included ceftiofur crystalline free acid (and other ceftiofur formulations), confirmed the superiority of tulathromycin regarding first treatment success (O'Connor et al., 2013).

Average numbers of subsequent BRD treatments were lower in all control studies and 8 out of 10 treatment studies. Although in 2 treatment studies the average numbers of subsequent treatments per nonresponder were slightly higher with tulathromycin compared with enrofloxacin, the total number of antimicrobial treatments over the entire study period was still lowest with tulathromycin when considering first treatment success rate (because the slightly higher numbers of subsequent treatments applied to fewer nonresponding cattle). Accordingly, when used as first choice for control or treatment of BRD, tulathromycin was associated with the lowest numbers of antimicrobial treatments necessary for the management of BRD in U.S. feedlots. Therefore, tulathromycin lowers the total absolute number of antibiotic treatments in feedlot cattle, contributing to a more prudent use of antimicrobials in livestock.

Removal (chronics and mortality) rates were also lowest with tulathromycin. However, the observation period varied substantially between studies: therefore, it cannot be ruled out that the number of subsequent BRD treatments as well as chronics or mortalities were underestimated. However, this should not be regarded as source of bias because all comparisons were made within studies and the overall trend of clinical efficacy was similar in all studies regardless of the duration. This also applied to the shortest study included (observation period: 41 to 43 d), which did not report subsequent BRD cases but presented otherwise similar trends in outcomes.

In all control and treatment studies, the higher drug costs of tulathromycin were more than offset by better efficacy, resulting in lower costs for subsequent treatments and chronics or mortalities. The economic advantages of tulathromycin were calculated between $7.75 and $143.87 per animal, depending on the study select-

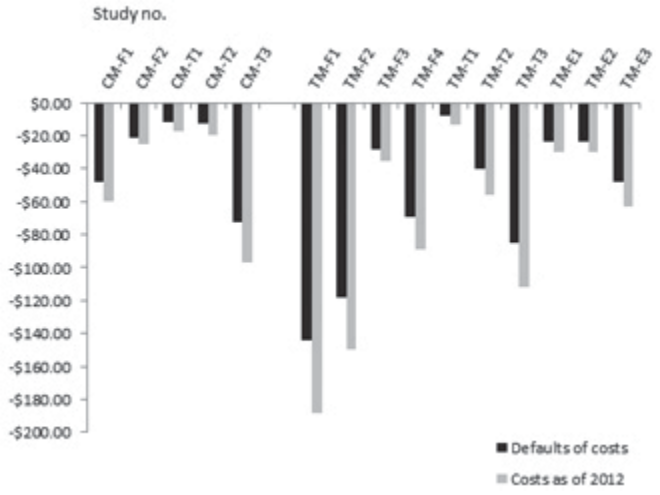

Figure 1. Incremental costs (US$) with tulathromycin (total costs over the entire observation period with tulathromycin minus total costs with comparator), as calculated for each clinical study included in the two models (CM = control model; TM = treatment model). Negative incremental costs correspond to cost savings with tulathromycin. Assignments of studies (Study no.) as defined in Tables 1 and 2. Default costs were estimated for 2010. Additionally costs have been adapted to 2012, to allow the assessment of currentness of outcomes calculated by the models.

ed as the basis for efficacy evaluation. These outcomes confirm previous results, which reported economic advantages of $52.50 per bovine with tulathromycin treatment (Schunicht et al., 2007). However, 2 studies, which included pretreated animals and therefore were not considered in our calculators, reported different economic outcomes. The authors calculated economic advantages of florfenicol over tulathromycin of CAD $17.70 (Van Donkersgoed et al., 2008b), and CAD $41.19 (Perrett et al., 2008) per treated animal, which were based on different costs of trial drug and mortality. Both studies included cattle that were pretreated with tulathromycin (Perrett et al., 2008) or tilmicosin, belonging to the same class of macrolides as tulathromycin (Van Donkersgoed et al., 2008b). In these studies, treatment success might be impaired as a result of acquired resistance to macrolides after first treatment failure as discussed by the authors of the first study (Van Donkersgoed et al., 2008b). To avoid such interactions, it is common practice in U.S. feedlots to change the choice of antimicrobial for treating an animal that failed to respond to the initial course of treatment (USDA, 2000b).

Cost defaults were estimated for 2010, corresponding to the time of model development. However, to determine if the results hold up over time, the cost data were adapted to 2012, and costs savings with tulathromycin have even increased in all studies, regardless of the comparator considered.

This study has limitations. First, it considered different studies for efficacy evaluation that were identified from literature review that was not systematic. However, the search was not restricted to scientific sources (PubMed; www.ncbi.nlm.nih.gov/pubmed) and reference lists but also included open-desk research, because scientific and nonscientific information on livestock has been made available on open Internet. Therefore, the search can be considered very comprehensive because no further studies comparing tulathromycin and the selected comparators in the chosen indications have been found. However, there is always a risk of bias with the selection or exclusion of studies. Therefore, first treatment success in the excluded studies was surveyed. In all but 1 study, first treatment success was greater with tulathromycin than with the comparator used in the respective study. Only 1 study excluded from TM reported no significant difference between tulathromycin and florfenicol in first relapse rate (Van Donkersgoed et al., 2008b). However, in this study all cattle had received tilmicosin on arrival at the feedlot. Because tilmicosin and tulathromycin both belong to the class of macrolides, study outcomes might be impaired as a result of acquired resistance to this class of antimicrobials after control failure (Van Donkersgoed et al., 2008b). Accordingly, the exclusion of studies did not lead to any bias regarding the overall statement of superior first treatment success with tulathromycin compared with florfenicol, tilmicosin, and enrofloxacin.

The models were constructed as cost calculators and did not consider income or productivity data. It has been reported that cattle with increasing numbers of BRD episodes and treatments have reduced quality grades compared with cattle never or only once being treated for BRD (Gardner et al., 1999). However, losses associated with 2 or more BRD episodes have already been considered in the costs for subsequent BRD treatments, as they included less return due to lower productivity and quality grades (McNeill et al., 2000). Losses of income in chronics or deaths were also considered in the costs defined for chronics and mortalities (Waggoner, 2006; McNeill et al., 2000). Accordingly, the restriction to cost models seemed to be a rational simplification, resulting in a greater transparency and traceability of results.

It is good modeling practice to include extensive sensitivity analyses of key parameters in health economic evaluations (Weinstein et al., 2003). Health economic analyses are usually based on a fixed input value for all variables, which can be the mean or median from the original data source such as a database. The range of each variable (over all data sources) is then used to determine the sensitivity of the outcome to the analysis, when input values are varied within its range (Nuijten and Hardens, 1997). However, the underlying models did not consider mean or median data as estimated from all studies included but used the actual values as measured in each study. Accordingly, the ranges as reported over all studies already correspond to sensitivity analyses on clinical efficacy. However, no sensitivity analyses were performed on cost data; but costs of treatment failures were considered extremely conservative, as no labor costs were included. Higher costs of treatment failures would be a disadvantage for the comparators, for which treatment failures were reported more often than for tulathromycin. Accordingly, the current approach is very conservative, that is, more advantageous for the comparators of tulathromycin, and it can be expected that differences in total costs over the entire observation period are even higher between tulathromycin and comparators in real life.

The 2 models allowed the calculation of clinical and economic consequences of treating BRD cattle at high risk or cattle with clinically apparent BRD infection in U.S. feedlots, considering efficacy data from all suitable clinical studies. Treatment with tulathromycin resulted in greater first treatment successes in all comparisons, that is, vs. florfenicol (CM and TM), vs. tilmicosin (CM and TM), and vs. enrofloxacin (TM only, according to label at the time of model development).

Higher drug costs with tulathromycin were more than offset by fewer BRD treatments and fewer removals (chronics and mortalities). The lowest number

of BRD episodes over the entire observation period as calculated for tulathromycin not only contributed to the overall savings with tulathromycin but also reduced the necessity of antibiotic treatment, thereby contributing to a more prudent use of antimicrobials in livestock.

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