REVIEW ARTICLE

ARTICLE DE REVUE

Meta-analysis of field trials of antimicrobial mass medication for prophylaxis of bovine respiratory disease in feedlot cattle

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Abstract

One hundred and seven field trials of prophylactic mass medication for bovine respiratory disease (BRD) in feedlot cattle were reviewed. Meta-analysis is the formal quantitative statistical review process that was used to synthesize the data from randomized field trials and draw conclusions concerning the efficacy of prophylactic mass medication in feedlot calves.

The results of the meta-analysis indicated that prophylactic parenteral mass medication of calves with long-acting oxytetracycline or tilmicosin on arrival at the feedlot would reduce BRD morbidity rates ($p < 0.001$). There were, however, unreliable data on the effects of mass medication on mortality rates and performance, insufficient data on the most effective treatment regimes, and no valid data on the efficacy of feed and water medication for prophylaxis of BRD.

This review highlights the gaps in our knowledge and points out the need for additional well-designed randomized controlled field trials of adequate size to assess the efficacy and socioeconomic impact of prophylactic mass medication for BRD in feedlot cattle.

Résumé

Analyse par la méthode "meta" d'essais cliniques de médicaments antimicrobiens administrés en prophylaxie de maladies respiratoires bovines à tous les sujets du troupeau gardés en parc d'engraissement

Cette étude porte sur le compte rendu de 107 essais cliniques, distribués de façon aléatoire, de médications prophylactiques, administrées contre les maladies respiratoires bovines, à tous les sujets du troupeau gardés en parc d'engraissement. L'analyse "meta" est l'étude statistique quantitative qui a été utilisée pour la synthèse des données dans le but de conclure de l'efficacité de la médication prophylactique.

Les résultats indiquent que l'administration d'une médication prophylactique à tous les sujets du troupeau dès leur arrivée au parc d'engraissement, soit de l'oxytétracycline à longue action ou du telmosin, réduit le taux de morbidité des infections respiratoires bovines ($p < 0,001$). Toutefois, les données n'étaient pas fiables concernant les effets de la médication sur le taux de mortalité ou sur la performance. De plus, les données étaient insuffisantes pour déterminer le traitement le plus efficace et non valide en ce qui a trait à l'efficacité de la médication prophylactique administrée dans la nourriture ou dans l'eau. Cette étude démontre les lacunes de nos connaissances et indique le besoin d'études complémentaires bien structurées, à partir d'essais cliniques, distribués de façon aléatoire, sur une population suffisante, afin d'évaluer l'efficacité et l'impact socio-économique d'une médication administrée, en prophylaxie contre les infections respiratoires bovines, à un troupeau en parc d'engraissement.

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Introduction

Bovine respiratory disease (BRD) is a major cause of economic loss in feedlot calves, with morbidity and mortality rates of 15–45% and 1.5%, respectively (1–4). Vaccination has resulted in equivocal changes in the incidence of BRD (4–8); therefore, various prophylactic mass medications have been used in attempts to reduce the level of disease. They include mass medication of the feed or water and individual medication of calves with sulfonamide boluses or injections of antimicrobials at various times before, during, or after arrival at the feedlot (2,9–56). It has been difficult to come to any conclusions regarding the safety and efficacy of mass medication because of the large number of studies reported with diverse treatment regimes and results (2,9–56). Therefore, veterinarians have been left with numerous questions regarding prophylactic mass medication in feedlot cattle. Is mass

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medication effective in reducing morbidity, mortality, and production losses from BRD? If mass medication is efficacious, then which cattle should be mass medicated? When should they be mass medicated? What antimicrobials are most efficacious and cost-effective? Which route of antimicrobial delivery is effective, convenient, and has the least negative side-effects? It is imperative that we try to answer these questions and avoid useless treatments because of increasing consumer concern for safe beef.

Meta-analysis (57–70) is the formal statistical process that I used to review the efficacy of prophylactic mass medication for BRD in feedlot cattle. The advantages of meta-analyses over traditional informal reviews (71,72) are: a) they are quantitative and try to avoid the reviewer's impressionistic views; b) they attempt to resolve uncertainty, when studies disagree, by combining results of all studies to gain power in detecting small differences and to estimate an overall treatment effect; c) they highlight gaps in the literature and help improve the design and reporting of trials; and d) they look at interactions or moderators of treatment effect to provide insights into new research (57–70). Major criticisms of meta-analyses include: a) they are biased because investigators tend to publish only positive findings; b) information is lost when data are summarized and an overall effect is calculated, thereby glossing over details; c) trials are included that have unreliable data or missing data; and d) results are pooled from different studies with different treatments and outcomes, thus overlooking moderator variables (57–70).

The purpose of the review reported herein is twofold. My first objective was to try to evaluate the effectiveness of mass medication in reducing morbidity, mortality, and production losses from BRD in feedlot cattle by critically analyzing all published fields trials and synthesizing the data using meta-analysis. My second objective was to introduce and discuss the strengths and weaknesses of meta-analysis as a technique to review the literature reported herein. It is hoped that this meta-analysis will not only highlight gaps in our knowledge, thus exposing needs for new research for the prevention and control of BRD in feedlot cattle, but also provide impetus to investigators to improve the design and reporting of future field trials.

Materials and methods

This review was restricted to field trials that tested the efficacy of oral or parenteral mass medication against naturally occurring respiratory disease in feedlot cattle. Studies were identified by computer-aided search using Medline, CAB Abstracts, and Procite from 1984–1991; by scanning the 1991 Current Contents inclusive to December 1991; and by examining the reference lists of papers that I had on file.

One hundred and seven field trials were reported in 49 studies which dated from 1952–1992 (2,9–56). Each field trial was carefully studied to assess the validity of its results based on criteria described by Gardner and Altman (64), Rothman (73), and Martin *et al* (74). A description of each study is given in Table 1 and includes: date of study, number of trials within each study, description of population, experimental unit, number of experimental units, allocation of experimental units to treatment, treatment regime, length of follow-up, major outcomes, and whether or not cases were defined and statistical analyses were reported.

The meta-analysis reported herein was restricted to randomized controlled field trials to guarantee the validity of both the statistical techniques used to pool data and the conclusions arising from treatment effects (58–60,67,73–75). The definition of a randomized controlled trial was a trial where mass medication was randomly allocated to the appropriate, independent, concurrent experimental units (73–75). The method of allocation was assumed to be nonrandom in those studies where it was not reported.

Statistical methods

Various meta-analytic procedures can be used to compare and summarize results of studies (63,65–70). In order to aggregate and synthesize the results of these mass medication studies, a common measure of statistical significance and treatment effect had to be calculated from the raw data or various summary statistics reported in each study. The common statistics calculated in the meta-analysis reported herein were the standard normal deviate Z with its one-tail p values and the Pearson's product moment correlation r (68,69). The formulas used for converting various test statistics to Z and r have been described previously (66,68,69). When studies only reported imprecise p values and insufficient data were available to calculate exact test statistics, conservative estimates of Z and r were made as described by Rosenthal (69), Mullen and Rosenthal (66), and Wolf (68). To reduce misclassification bias (73) in calculations of treatment effects, morbidity and mortality were restricted to BRD as defined by each separate trial.

Two methods were used to reduce problems with multiple (correlated) results (65,68,69). First, separate meta-analyses were performed for each different dependent variable, namely morbidity, mortality, average daily gain, and feed efficiency. Second, a mean level of significance and a mean effect size were calculated in studies with multiple treatments and similar outcomes.

The diffuse test was used to compare the heterogeneity of significance levels and effect sizes among studies (66). Stouffer's method was used to combine significance levels of studies to get an overall estimate of the probability of no effect of mass medication (69). Effect sizes were combined using a mean Fisher's Zr (69). Both unweighted and weighted combined tests were performed. Statistics were weighted by sample size to give greater weight to larger studies (66,69). Fishers's mean Zr was converted to r and 95% confidence intervals were calculated (73,76).

Separate meta-analyses were conducted by time of medication, type of medication, and antimicrobial to assess if they were moderator variables and sources of heterogeneity (68,69). The number (X) of new, filed, or unretrieved studies with null results required to overturn any overall significant p values was calculated from Rosenthal's formula (62).

Table 1. Description of field trials of prophylactic mass medication against BRD in feedlot cattle

Reference	Date	N Trials	Population	Exp[a] unit	N exp[b] units	Alloc[c]
Morck (56)	1992	1	300 kg calves	calf	1806	random
Harland (2)	1987	1	325 kg calves	calf	2112	random
Schumann (9)	1989	1	300 kg calves	pen	24	random
Schumann (10)	1988	1	300 kg calves	pen	24	random
Peters (11)	1985	1	6 mo old bulls	calf	262	random
Janzen (12)	1980	1	300 kg steers	calf	781	random
King (13)	1952	1	206 kg calves	calf	142	random
Bennett (14)	1983	1	159 kg calves	calf	608	random
Gill (50)	1986	2	214 kg calves	pen	67	random
Brown (55)	1989	1	180 kg calves	calf	400	nonrandom
Lofgreen (49)	1980	1	160 kg calves	pen	16	nonrandom
Lofgreen (15)	1983	4	200 kg calves	pen	96	nonrandom
Lofgreen (17)	1970	1	94 kg calves	pen	NA[d]	nonrandom
Schipper (54)	1971	1	125 kg calves	calf	275	nonrandom
Swafford (16)	1981	1	239 kg calves	pen	3[e]	nonrandom
Albak (48)	1985	1	227 kg calves	calf	1083	nonrandom
Schipper (51)	1962	1	136 kg calves	calf	9386	nonrandom
Schipper (52)	1974	1	136 kg calves	calf	1167	nonrandom
Boren (53)	1958	1	204 kg calves	pen	4[e]	nonrandom
Breeze (26)	1979	1	250 kg calves	pen	16	nonrandom
Perry (41)	1971	5	200 kg calves	pen	16	nonrandom
Woods (42)	1973	2	150 kg calves	pen	4[e]	nonrandom
Reynolds (43)	1954	3	calves	pen	6	nonrandom
Drain (44)	1966	4	feeder calves	pen	NA	nonrandom
Embry (45)	1962	3	186 kg calves	pen	8[e]	nonrandom
Hawley (46)	1957	21	280 kg feeders	pen	42	nonrandom
Cyanamid (22)	NA	6	159 kg calves	pen	24[e]	nonrandom
Beeson (28-30)	1968	4	219 kg calves	pen	14	nonrandom
Embry (33,34)	1966	4	180 kg calves	pen	8[e]	nonrandom
Furr (27)	1967	2	206 kg steers	pen	8	nonrandom
Vetter (35)	1967	2	302 kg steers	pen	4	nonrandom
Hale (23,25)	1967	4	276 kg steers	pen	10	nonrandom
Drake (31,32)	1967	3	174 kg calves	pen	8[e]	nonrandom
Phar (24)	1968	2	168 kg calves	pen	8[e]	nonrandom
Addis (36)	1976	3	136 kg calves	pen	419	nonrandom
Scheel (37)	1966	1	273 kg calves	calf	353	nonrandom
Swift (19)	1974	1	182 kg calves	pen	4[e]	nonrandom
Johnson (21)	1957	1	273 kg steers	pen	4	nonrandom
Addis (18)	1969	2	164 kg calves	pen	11[e]	nonrandom
Perry (20)	1986	2	197 kg calves	pen	70	nonrandom
Woods (38)	1970	2	184 kg calves	pen	4[e]	nonrandom
Theix (40)	NA	1	158 kg calves	pen	6[e]	nonrandom
Embry (39)	1969	3	199 kg calves	pen	12[e]	nonrandom
Smith (47)	1981	3	273 kg calves	pen	7[e]	nonrandom

[a]Experimental unit
[b]Number of experimental units
[c]Allocation
[d]Not available
[e]One experimental unit for a treatment group
[f]Long-acting
[g]Parenteral
[h]Trimethoprim-sulfadoxine
[i]Low pain
[j]Short-acting
[k]Dihydrostreptomycin
[l]Morbidity
[m]Mortality
[n]Average daily gain
[o]Feed conversion (efficiency)

Table 1. Description of field trials of prophylactic mass medication against BRD in feedlot cattle (cont'd)

Antimicrobial	Route	Time	Follow-up	Outcomes	Case def	Statistical analysis
oxytetracycline LA[f], tilmicosin	par[g]	arrival	90 days	BRD morb[l], BRD mort[m], adg[n]	yes	yes
oxytetracycline LA, TMP-sulfa[h]	par	arrival	5–6 mo	BRD morb, BRD mort	yes	yes
tilmicosin	par	day 0/3	30 days	BRD morb, mort, adg, fc[o]	yes	yes
tilmicosin	par	arrival	30 days	BRD morb, mort, adg, fc	yes	yes
oxytetracycline LA	par	day 7–10	90 days	BRD morb, mort, adg	yes	no
oxytetracycline LA	par	in-contact	32 days	BRD morb, mort, adg	yes	no
penicillin LA	par	preship	42 days	BRD morb, mort	yes	no
oxytetracycline LA	par	preship	28 days	BRD morb, mort, adg	no	yes
oxytetracycline LA, sulfa boluses	par/oral	arrival	28 days	BRD morb, adg	yes	no
oxytetracycline LA, sulfa boluses	par/oral	arrival	56 days	BRD morb, mort	yes	no
oxytetracycline LP[i]	par	arrival	28 days	morb, mort, adg, fc	no	yes
oxytetracycline LP/LA, sulfa boluses, tetracycline and sulfa (feed)	par/oral	arrival	46 days	BRD morb, mort, adg, fc	yes	yes
tetracycline (feed, water, par)	par/oral	arrival	28 days	morb, adg, fc	yes	no
penicillin LA, dihydrostreptomycin	par	arrival	NA	BRD morb, mort	yes	no
oxytetracycline LA, sulfa boluses	par/oral	preship	27 days	BRD morb, mort, adg	no	no
oxytetracycline LA	par	arrival	NA	morb, mort	yes	yes
penicillin LA/SA[j]	par	preship	NA	morb	no	no
penicillin LA/SA, DHSM[k]	par	arrival	NA	morb	no	no
penicillin, tetracycline, streptomycin	par	arrival	14	morb, adg	no	no
oxytetracycline LA	par	in-contact	30	morb, mort	yes	yes
tetracycline and sulfa (feed)	oral	arrival	28	morb, adg, fc	no	no
tetracycline and sulfa (feed)	oral	arrival	NA	morb, adg	no	no
tetracycline (feed)	oral	preship	NA	morb	no	no
tetracycline/sulfa (feed)	oral	arrival	4 wk	morb, adg, fc	no	no
tetracycline (feed)	oral	arrival	4 wk	morb, adg	no	no
tetracycline (feed)	oral	arrival	15 days	morb	no	no
tetracycline/sulfa (feed)	oral	arrival	28 days	morb, mort, adg	no	no
tetracycline/sulfa (feed)	oral	arrival	28 days	morb, adg, fc	no	no
tetracycline/sulfa (feed)	oral	arrival	29 days	morb, adg, fc	no	no
tetracycline/sulfa (feed)	oral	arrival	56 days	morb, adg, fc	no	no
tetracycline/sulfa (feed)	oral	arrival	28 days	morb, adg, fc	no	no
tetracycline/sulfa (feed)	oral	arrival	3 wk	morb, adg, fc	no	no
tetracycline/sulfa (feed)	oral	arrival	35 days	morb, adg, fc	no	no
tetracycline/sulfa (feed)	oral	arrival	28 days	morb, adg, fc	no	no
tetracycline (feed, water, par)	par/oral	arrival	28 days	morb, adg, fc	no	no
sulfa boluses	oral	arrival	NA	morb	no	no
tetracycline (feed)	oral	arrival	28 days	morb, adg	no	no
tetracycline (feed)	oral	arrival	90 days	morb, adg	no	no
tetracycline (feed, water)	oral	arrival	20 days	morb, adg	no	no
tetracycline (feed)	oral	arrival	56 days	morb, adg, fc	yes	yes
tetracycline/sulfa (feed)	oral	arrival	28 days	morb, adg, fc	no	no
tetracycline/sulfa (feed)	oral	arrival	98 days	morb, adg, fc	yes	no
tetracycline/sulfa (feed)	oral	arrival	34 days	morb, adg	no	no
tetracycline/sulfa (feed)	oral	arrival	56 days	morb, mort, adg	yes	no

Table 2. Summary of results of randomized controlled field trials evaluating the effect of mass medication for prophylaxis of bovine respiratory disease in feedlot calves

		Tests of homogeneity[a]		Unweighted combined tests		Weighted combined tests		
Outcome	K[b]	p	r	p[c]	r (95% CI)[d]	p[e]	r (95% CI)[f]	X[g]
Morbidity	9	0.002	0.31	<0.0001	0.22 (0.14,0.29)	<0.0001	0.18 (0.14,0.22)	204
Mortality	9	0.91	0.94	0.19	0.01 (−0.002,0.018)	0.05	0.02 (0.01,0.03)	NA[h]
ADG[i]	6	0.01	<0.001	<0.001	0.37 (0.06,0.62)	0.45	0.02 (−0.24,0.28)	21
FE[j]	2	0.65	0.38	<0.001	0.72 (0.53,0.91)	<0.0001	0.72 (0.27,0.91)	16

[a]p value corresponding to the diffuse test of homogeneity for significance levels p and effect sizes r
[b]K = number of studies
[c]One-tail p value of the unweighted Stouffer's combined test
[d]Unweighted mean effect size r (95% confidence interval)
[e]One-tail p values of the Stouffer's combined test weighted by sample size
[f]Mean effect size r (95% confidence interval) weighted by sample size
[g]X = number of new, filed, or unretrieved studies with null results required to overturn significant combined results
[h]Not applicable
[i]ADG = average daily gain
[j]FE = feed efficiency

Results

Mass medication was randomly assigned to the appropriate, independent, concomitant experimental units (73–75) in only ten field trials. All ten trials evaluated the efficacy of parenteral mass medication in feedlot calves; one trial also studied the efficacy of oral sulfonamide boluses. The treatment regimes, outcomes, case definitions of disease, and follow-up periods varied among the ten randomized trials.

The remaining 97 trials were nonrandom and included all trials testing the efficacy of feed and water mass medication. In addition to nonrandomization, other frequently observed defects in experimental design and analysis (73–75) of the mass medication trials reported herein included the use of only one experimental unit per treatment group (n = 34) and failure to report statistical analyses (n = 94) and case definitions of disease (n = 84).

Based on the unweighted meta-analysis of ten randomized field trials (Table 2), prophylactic mass medication significantly reduced BRD morbidity rates ($p < 0.0001$) and improved average daily gain ($p < 0.001$) and feed efficiency ($p < 0.001$) in feedlot calves. When the test statistics were weighted by sample size, mass medication significantly reduced mortality rates ($p = 0.05$), whereas increases in average daily gain were no longer significant ($p = 0.45$). There was significant heterogeneity ($p < 0.05$) among studies in the p levels for morbidity and average daily gain and in the effect sizes of average daily gain.

Mass medication before, during, and after arrival at the feedlot, and for in-contact prophylaxis during an outbreak, significantly ($p < 0.04$) reduced morbidity rates (Table 3). The largest and most reliable effect was observed in calves that were mass medicated on arrival; however, there was significant heterogeneity among studies in the p levels for morbidity. Mass medication on arrival reduced mortality rates ($p = 0.04$) when the data were weighted by sample size, and improved average daily gain (unweighted analysis) and feed efficiency ($p < 0.001$). There were no randomized trials that assessed the effect of preshipment mass medication on average daily gain and feed efficiency nor the effect of postarrival and in-contact mass medication on feed efficiency.

Parenteral mass medication was associated with a significant reduction in morbidity rates ($p < 0.001$) and an improvement in average daily gain ($p < 0.001$) and feed efficiency ($p < 0.001$) (Table 4). When the test statistics were weighted by sample size, the effect of parenteral mass medication on average daily gain was no longer significant, whereas its effect on mortality was significant ($p = 0.02$). Oral sulfonamide boluses, singly, or in addition to long-acting oxytetracycline, were not efficacious based on the results of one trial.

Long-acting oxytetracycline was associated with significant ($p < 0.05$) reductions in morbidity rates when given either prior to shipment, on arrival, postarrival, or for in-contact prophylaxis (Tables 3 and 5). Long-acting penicillin prior to arrival (data not shown) and tilmicosin on arrival (Table 5) or three days postarrival (data not shown) were also associated with significant ($p < 0.003$) reductions in morbidity rates. Trimethoprim-sulfadoxine, sulfonamide boluses, and long-acting oxytetracycline with sulfonamide boluses on arrival (Table 5) did not reduce morbidity rates ($p > 0.05$). Tilmicosin was the only antimicrobial which significantly ($p < 0.05$) reduced mortality rates and improved average daily gain and feed efficiency. When data were weighted by sample size, however, there were no antimicrobials which significantly increased average daily gain ($p > 0.40$). There were no studies that tested the effects of penicillins or sulfonamides on performance nor the effects of tetracyclines on feed efficiency.

Discussion

The most alarming finding of the review reported herein was the abundance of poorly designed field trials and the sparsity of randomized controlled field trials published on prophylactic mass medication for

Table 3. Efficacy of prophylactic mass medication for bovine respiratory disease in feedlot calves by time of medication

Outcome	Tests of homogeneity[a]			Unweighted combined tests		Weighted combined tests		
Time	K[b]	p	r	p[c]	r (95% CI)[d]	p[e]	r (95% CI)[f]	X[g]
Morbidity								
Preship	2	0.79	0.29	<0.001	0.18 (−0.08,0.41)	<0.001	0.15 (−0.07,0.35)	11
Arrival	5	<0.001	0.45	<0.001	0.26 (0.14,0.38)	<0.001	0.19 (0.01,0.27)	57
Postarrival	1	NA[h]	NA	0.04	0.11 (−0.01,0.23)	0.04	0.11 (−0.01,0.23)	1
In-contact	1	NA	NA	<0.001	0.13 (0.06,0.20)	<0.001	0.13 (0.06,0.20)	4
Mortality								
Preship	2	0.99	0.99	0.48	0 (0)	0.50	0 (0)	NA
Arrival	5	0.58	0.86	0.13	0.01 (−0.017,0.023)	0.04	0.04 (0.03,0.05)	NA
Postarrival	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
In-contact	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
Average daily gain								
Arrival	4	0.41	<0.01	<0.001	0.45 (0.04,0.73)	0.45	0.03 (−0.36,0.41)	18
Postarrival	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
In-contact	1	NA	NA	0.07	0.38 (0.32,0.44)	0.07	0.38 (0.32,0.44)	NA
Feed efficiency								
Arrival	2	0.65	0.38	<0.001	0.72 (0.53,0.91)	<0.001	0.72 (0.27,0.91)	16

[a]p value corresponding to the diffuse test of homogeneity for significance levels p and effect sizes r
[b]K = number of studies
[c]One-tail p value of the unweighted Stouffer's combined test
[d]Unweighted mean effect size r and associated 95% confidence interval
[e]One-tail p values of the Stouffer's combined test weighted by sample size
[f]Mean effect size r and associated 95% confidence intervals weighted by sample size
[g]X = number of new, filed, or unretrieved studies with null results needed to overturn significant combined results
[h]NA = not applicable

BRD in feedlot cattle. Of the 107 field trials reported, 91% were nonrandomized. I excluded the nonrandomized field trials from the meta-analysis despite the fact that such exclusion is a contentious issue among meta-analysts. Traditionally, meta-analysts have argued that all studies should be included in the meta-analysis, regardless of weaknesses, to avoid the reviewer's opinion and biased selection of available data (61,68,69). Meta-analysts have either combined all data, weighing each study by some *subjective* measure of internal validity and adjusting the statistical measures for bias, or they have performed separate meta-analyses on randomized and nonrandomized trials and compared the results (68–70). Recently, meta-analysts of clinical trials have insisted that only properly randomized trials should be pooled to minimize substantial bias in the meta-analysis; this guarantees the validity of both the statistical tests used to combine the data and the conclusions arising from the mean effect measures (57–60,67,73,74–75). I combined data from only randomized trials, in order to ensure the validity of the meta-analysis. This removed one of the major criticisms of meta-analysis, and such action may provide additional impetus for researchers to design randomized controlled field trials.

A major criticism of any review, including meta-analysis, is sampling bias (62,68,69,77). It is possible that I overlooked unpublished material and that only trials with positive treatment effects were published (77). This sampling bias could lead to a type 1 error, which is incorrectly concluding that mass medication is efficacious (77). To address this issue, I calculated the number of new, filed, or unretrieved studies with null results needed to overturn any significant conclusions arising from this meta-analysis (62). If the number of null studies (X) exceeded five times the number of positive studies, then most likely the results were not due to sampling bias (62).

Two additional criticisms of meta-analysis are that results from different studies with different treatment protocols are pooled together and that information is lost because data are summarized. To deal with these criticisms, I calculated the tests of homogeneity for p levels and effect sizes. When the tests of homogeneity were significant, indicating that studies yielded very different results from each other, I looked for explanations by subgrouping the data on potential moderators of treatment effect, namely time of medication, type of medication, and antimicrobial. By calculating both overall and subgrouped effects and presenting the results of all significance tests and effect sizes, I was able to glean considerable information about mass medication and make some general and specific comments about our knowledge of mass medication for prophylaxis of BRD in feedlot cattle.

Based on the meta-analysis of the ten randomized field trials, mass medication significantly ($p < 0.0001$) reduced morbidity rates. This result appeared to be fairly reliable because of the narrow 95% confidence limits of the effect size r and the large number of studies with null results ($X = 204$) required to overturn this conclusion. The test of homogeneity of p levels, however, was significant, suggesting caution in drawing any simple overall conclusion (69). The heterogeneity of p levels could have been due to heterogeneity of effect sizes and/or sample sizes (69). To uncover potential sources of heterogeneity, I looked for moderator variables by subgrouping the data by time

Table 4. Efficacy of prophylactic mass medication for the prevention of respiratory disease in feedlot calves by type of mass medication

Outcome		Tests of homogeneity[a]		Unweighted combined tests		Weighted combined tests		
Type	K[b]	p	r	p[c]	r (95% CI)[d]	p[e]	r (95% CI)[f]	X[g]
Morbidity								
Parenteral	9	0.001	0.36	<0.001	0.21 (0.12,0.29)	<0.001	0.18 (0.13,0.23)	195
Oral bolus	1	NA[h]	NA	0.500	(0)	0.50	0 (0)	NA
Par + bolus[i]	1	NA	NA	0.16	0.14 (−0.12,0.38)	0.16	0.14 (−0.12,0.38)	NA
Mortality								
Parenteral	9	0.91	0.94	0.19	0.01 (−0.002,0.018)	0.02	0.02 (0.017,0.023)	NA
Oral bolus	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
Par + bolus	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
Average daily gain								
Parenteral	6	0.008	<0.01	<0.001	0.36 (0.04,0.62)	0.46	0.02 (−0.27,0.30)	18
Oral bolus	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
Par + bolus	1	NA	NA	0.16	0.14 (−0.12,0.38)	0.16	0.14 (−0.12,0.38)	NA
Feed efficiency								
Parenteral	2	0.65	0.38	<0.001	0.72 (0.53,0.91)	<0.001	0.72 (0.27,0.91)	16

[a]p value corresponding to the diffuse test of homogeneity for significance levels p and effect sizes r
[b]K = number of studies
[c]One-tail p value of the unweighted Stouffer's combined test
[d]Unweighted mean effect size r and associated 95% confidence interval
[e]One-tail p values of the Stouffer's combined test weighted by sample size
[f]Mean effect size r and associated 95% confidence intervals weighted by sample size
[g]X = number of new, filed, or unretrieved studies with null results required to overturn significant combined results
[h]NA = not applicable
[i]Parenteral and oral sulfonamide boluses

of medication, type of medication, and antimicrobial.

When morbidity was grouped by time of medication, type of medication, and antimicrobial, the tests of homogeneity for p levels remained significant for long-acting oxytetracycline and tilmicosin mass medication on arrival. Since the tests of homogeneity for effect sizes were not significant, the heterogeneity of p levels was most likely due to differences in sample sizes among studies. Each different time of mass medication was associated with significant ($p < 0.05$) reductions in morbidity, but the only reliable effect was observed with mass medication on arrival. There were simply too few studies which tested the effect of mass medication prior to shipment, postarrival, and for in-contact prophylaxis of BRD. When morbidity was grouped by type of antimicrobial, only parenteral mass medication was significantly ($p < 0.001$) associated with reductions in morbidity. There was only one randomized study that tested the efficacy of oral sulfonamide boluses and there were no randomized trials that tested the efficacy of feed or water mass medication. Therefore, there were insufficient data to come to any conclusions regarding the efficacy of oral mass medication. The results from three observational studies by Martin *et al* (78–80) suggest that prophylactic antimicrobials in the water increase mortality whereas in the feed they decrease mortality. The validity and reliability of such observational data, however, remain uncertain.

Long-acting oxytetracycline and tilmicosin significantly ($p < 0.05$) reduced morbidity rates when given on arrival, whereas trimethoprim-sulfadoxine and sulfonamide boluses on arrival did not reduce morbidity rates. The largest and most reliable effect size was observed with tilmicosin. The large effect of tilmicosin may suggest that it is the most effective drug tested, or it may reflect differences in trial designs between studies testing tilmicosin and those testing other parenteral antimicrobials. Tilmicosin was evaluated in three trials and, in two of the trials, the pen was the unit of concern and all calves in the pen were either medicated or unmedicated. In the trials with other parenteral antimicrobials, the calf was the experimental unit and both medicated and unmedicated calves were housed together in the same feeding pens. As a result, herd immunity (74) may have reduced the magnitude of effect differences between medicated and unmedicated calves, thus explaining some of the differences in mean effect sizes between tilmicosin and other parenteral antimicrobials (2). To evaluate the relative efficacy of various antimicrobials, field trials should be designed that concurrently compare antimicrobials used in mass medication.

Mortality was reduced by mass medication in the weighted overall meta-analysis ($p = 0.05$); with mass medication on arrival ($p = 0.04$); with parenteral mass medication ($p = 0.02$); and, specifically, with tilmicosin mass medication on arrival ($p = 0.002$). This effect on mortality, however, was not robust (62) because it would take one unpublished, new, or unretrieved study with null results to overturn these conclusions. There were only two studies which showed a significant reduction in BRD mortality with prophylactic mass medication (2,56). The study of Morck *et al* (56) showed a significant reduction in BRD mortality with tilmicosin on arrival. The study of Harland *et al* (2) showed a significant reduction in BRD mortality during the second week after arrival when feedlot calves were mass medicated with long-acting oxytetracycline on arrival, but this effect was not significant when

Table 5. Efficacy of various parenterally administered antimicrobials used on arrival at the feedlot for prophylaxis of bovine respiratory disease in calves

Outcome	Tests of homogeneity[a]			Unweighted combined tests		Weighted combined tests		
Antimicrobial	K[b]	p	r	p[c]	r (95% CI)[d]	p[e]	r (95% CI)[f]	X[g]
Morbidity								
Tetracycline[h]	3	0.001	0.41	<0.001	0.08 (0.01,0.15)	<0.001	0.11 (0.06,0.16)	21
Tilmicosin	3	<0.001	0.46	<0.001	0.36 (0.27,0.45)	<0.001	0.26 (0.16,0.35)	50
TMP-sulfa[i]	1	NA[j]	NA	0.38	0.01 (−0.05,0.07)	0.38	0.01 (−0.05,0.07)	NA
Sulfa boluses	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
OTCLA + sulfa[k]	1	NA	NA	0.16	0.14 (−0.12,0.38)	0.16	0.14 (−0.12,0.38)	NA
Mortality								
Tetracycline	3	0.77	0.99	0.16	0.01 (−0.005,0.016)	0.12	0.03 (0.02,0.04)	NA
Tilmicosin	3	0.06	0.87	0.04	0.03 (−0.015,0.045)	0.002	0.08 (0.04,0.12)	1
TMP-sulfa	1	NA	NA	0.43	0.01 (−0.054,0.606)	0.43	0.01 (−0.05,0.61)	NA
Sulfa boluses	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
OTCLA + sulfa	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
Average daily gain								
Tetracycline	2	1.00	1.00	0.50	0 (0)	0.50	0 (0)	NA
Tilmicosin	3	0.01	<0.01	<0.01	0.21 (−0.28,0.61)	0.44	0.04 (−0.41,0.48)	16
Sulfa boluses	1	NA	NA	0.50	0 (0)	0.50	0 (0)	NA
OTCLA + sulfa	1	NA	NA	0.16	0.14 (−0.12,0.38)	0.16	0.14 (−0.12,0.38)	NA
Feed efficiency								
Tilmicosin	2	0.65	0.38	<0.001	0.72 (0.53,0.91)	<0.001	0.72 (0.53,0.91)	16

[a]p value corresponding to the diffuse test of homogeneity for significance levels p and effect sizes r
[b]K = number of studies
[c]One-tail p value of the unweighted Stouffer's combined test
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[g]X = number of new, filed, or unretrieved studies with null results required to overturn significant combined results
[h]Long-acting oxytetracycline
[i]Trimethroprim sulfadoxine
[j]NA = not applicable
[k]Long-acting oxytetracycline and oral sulfonamide boluses

measured over the entire length of the trial. Failure to reliably show significant effects of mass medication on mortality may a) reflect the true state of nature, i.e. mass medication does not reduce mortality rates reliably; b) be due to misclassification bias (2,73); or c) be due to type 2 errors (sample sizes were too small) within individual studies and the meta-analysis (70). For example, to be 80% certain of showing a significant reduction in mortality rates from 2% to 1% with mass medication, approximately 2300 experimental units need to be randomized to each treatment group (74). When mass medication causes larger reductions in mortality rates, then fewer experimental units are needed to show a significant difference. Except for the study of Morck *et al* (56), none of the randomized trials had large enough sample sizes to show significant overall reductions in mortality given their small treatment effect sizes. Since my meta-analysis was based on combined data from only ten trials, most with small sample sizes and low mortality rates, its power to detect reliable differences in mortality between mass medicated groups was also low. Additional randomized field trials of adequate size are needed to reliably determine the effect of various mass medication regimes on mortality.

Mass medication significantly improved average daily gain when the meta-analysis was based on unweighted combined tests. When the test statistics were weighted by sample size, however, this effect was insignificant. The tests of homogeneity of p levels and effect sizes were significant, also indicating heterogeneity in sample sizes and effect sizes among trials. When data were grouped by time of medication, mass medication on arrival improved average daily gain. However, this effect was heterogeneous among studies and insignificant when based on weighted test statistics, suggesting caution in accepting this conclusion. Parenteral mass medication did not improve average daily gain when results were weighted by sample size, and p levels and effect sizes were heterogeneous. The sources of heterogeneity appeared to be the antimicrobial used for mass medication and the trial design. When data were analyzed by antimicrobial agent, the results were homogeneous between long-acting oxytetracycline trials but still heterogeneous among tilmicosin trials. When tilmicosin trials were subgrouped by experimental unit (pen versus calf), the results were homogeneous within each group. Tilmicosin was the only drug that improved average daily gain and feed efficiency during the first 30 days on feed based on the results of two trials where the pen was the unit of concern (9,10). Additional trials are needed to substantiate this finding, to evaluate the effect of other antimicrobials and times of administration on performance, and to determine whether benefits in performance persist until slaughter or whether compensatory gain eliminates any short-term effects.

In summary, the results of this meta-analysis

indicated that parenteral mass medication with long-acting oxytetracycline or tilmicosin on arrival would reliably reduce BRD morbidity rates in feedlot calves. There were, however, a) unreliable data on the effects of mass medication on mortality rates and performance; b) insufficient data on the most effective treatment regimes; and c) no valid data on the efficacy of feed and water mass medication for prophylaxis of BRD. The review reported herein has highlighted large gaps in our knowledge and pointed out the need for additional well-designed, randomized field trials of adequate size to assess the efficacy and socioeconomic impact of prophylactic mass medication for BRD in feedlot cattle. Large-scaled randomized trials are expensive and logistically difficult to conduct, but they remain the best tool we have to evaluate the efficacy of therapeutic regimes and diagnostic methods (67). Government granting agencies, pharmaceutical companies, producer groups, and veterinarians must work together to support this applied research so that, as a united group, we can legitimize our preventive medicine practices to an increasingly perceptive and health conscious society. To avoid biasing our conclusions about the efficacy of treatments, researchers must publish negative trials as well as positive trials (77) and they must adequately describe the methodological characteristics of their studies and report exact test statistics (68,69). Meta-analysis can then be used to come to reliable, unbiased conclusions based on the weight of available scientific data which will be helpful in making management decisions (67).

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