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Evidence based effectiveness of vaccination against *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* in feedlot cattle for mitigating the incidence and effect of bovine respiratory disease complex

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INTRODUCTION

Evidence-based medicine (EBM) was introduced to the medical literature in a 1992 article by the Evidence-based Working Group at McMaster University Health Sciences Centre in Canada to describe the clinical learning strategy they had been developing for over a decade.[1] The principles of EBM are being applied to the veterinary profession under the term evidence-based veterinary medicine (EBVM).[2-4] The underlying concepts of EBM and EBVM are rooted in clinical epidemiology and are not new, but are a formal and explicit effort to increase the occurrence of basing clinical decisions on a dispassionate review of published trials that adequately meet *a priori* standards of experimental design and experimental execution.

Although most clinical decisions in veterinary medicine are based on evidence of some type, some evidence is very strong (rigorously tested in the target species under natural conditions (e.g. cattle in commercial feedlots) in experiments designed to prove a theory to be false), some evidence is very weak (not tested), and some is intermediate.[5-7] The hierarchy of evidence is based on the strength of evidence for causation, the ability of the study to control bias, and the similarity between the study population and the population currently being considered in a clinical setting.

With respect to bacterial vaccination in feedlot cattle, sources regarded as the strongest evidence for the effectiveness of vaccination against *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* for mitigating the incidence and effect of bovine respiratory disease (BRD) complex are randomized controlled clinical trials in feedlot cattle under a typical husbandry environment with adequate blinding of investigators, a clear case-definition of BRD, and adequate intensity and length of follow-up; or systematic reviews of more than one trial that meet these criteria. In addition, other available evidence, including: studies testing the effects of

vaccination of cattle exposed to pathogen-challenged disease models, studies testing the effects of vaccination of cattle in dissimilar production settings (i.e. dairy calves), and studies utilizing *in vitro* methodologies to test vaccination effects can be used as indirect indicators in the clinical decision-making process, particularly when higher levels of evidence are lacking.

The 'body-of-evidence' for this clinical question is the sum of multiple studies investigating the effect of vaccines against *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* administered to cattle. Each individual research study contributes to that body of evidence and each publication can be ranked on a scale from weak evidence to very strong evidence; which for the veterinary practitioner, implies an increasing confidence in recommendations based on a particular study. And, although a simple ranking of experimental trial types is helpful to describe ascending levels of evidence, by its simplistic nature, it incorrectly depicts levels of evidence as a one dimensional and straightforward hierarchy. For example, veterinarians are often confronted with determinations such as, which is better evidence, a randomized trial in three month-old dairy calves (i.e. non-target animals, but a study design with high control of bias and confounding), or a pathogen-challenged disease model study in feedlot cattle (i.e. study with less external validity but in the target population)? In these situations, the clinical expertise, experience, and judgment of the veterinarian must be utilized to aid the ranking of evidence generated by these studies and to guide recommendations for use of bacterial respiratory pathogen vaccines into processing protocols in the field.

Veterinarians considering the strength of evidence must use several perspectives to determine the reliability of research for clinical use.

1) The first consideration is the internal validity of the research, which is determined by the study method and appropriate use of controls for bias. Research reports with good

internal validity provide assurance that the results represent an unbiased estimate of the true direction and magnitude of the treatment effect in the study population. For randomized controlled studies, accepted methods of random allocation and blinding of study investigators to the treatment for each experimental unit are key experimental design features to avoid bias and confounding.

2) The second consideration is the population used in the research and its appropriateness as a model for the population that generated the clinical question. Generally, the target species in similar housing and husbandry environments provides stronger evidence than the target species in significantly different housing and husbandry environments, related species, unrelated species, or *in-vitro* methods.
3) And thirdly the clinical relevance of the outcomes of the research should be considered with patient- or herd-oriented outcomes (such as morbidity risk, mortality risk, or average daily weight gain) providing more direct evidence of intervention effectiveness than disease-oriented outcome measurements such as behavior frequency, body temperature, or antibody response.

Using these considerations, the highest rating in all three dimensions would provide the highest level of evidence.

MATERIALS AND METHODS

A literature search was conducted to identify studies published in English that reported the effectiveness of *Mannheimia (Pasteurella) haemolytica*, *Pasteurella multocida*, and *Histophilus (Heamophilus) somnus* vaccination in cattle. A search strategy using (*Mannheimia haemolytica* OR *Pasteurella haemolytica* OR *Pasteurella multocida* OR *Haemophilus somnus*

OR *Histophilus somni)* AND (respiratory disease OR pneumonia OR pneumonic) AND (bovine OR cattle OR bos) AND (vaccine OR vaccinate) was used to query PubMed (164), CAB abstracts (379) and Biologic Abstracts (160) followed by a hand search through cited references (4). A published manuscript is considered a "study" while a "trial" is a direct comparison of a vaccine treatment to a control treatment within a study. A single study may include more than one trial. After reading the abstract from each unique publication, thirty-four studies were included in this review. Fifteen studies (twenty-two trials) were considered the highest level of evidence in that they were trials utilizing feedlot or stocker cattle in North American production settings appropriately allocated to treatment groups with naturally occurring disease.[8-22] One or more trials from five other studies were identified that utilized feedlot cattle in typical North American production settings, but they were weakened by lack of blinding, treatment being confounded by arrival group or other vaccine treatment, or significant loss-to-follow up and were discarded from the summary.[23-27] In addition, three terminal studies (five trials) investigated the use of commercially available vaccines in feedlot cattle with a pathogen-challenged disease model [14,28,29], three studies (five trials) utilized dairy or beef calves with naturally occurring disease to investigate effects of vaccination [27,30,31], and thirteen studies investigated the use of commercially available vaccines in dairy calves with an induced-disease model.[32-44] Studies were excluded from the review: if they did not report original data (primary study), if they did not include a non-vaccinated/placebo control group, if the outcome did not include an assessment of morbidity risk, mortality risk, or extent of lung involvement (e.g. only reported serologic titers), or if the same results were published in a more complete form elsewhere. Many studies did not report specific allocation schemes used or whether or not effective blinding occurred, and some studies utilized inappropriate statistical tests for the data collected. Studies

with obvious limitations due to experimental design were excluded, but studies with poorly described experimental designs were retained.

A meta-analysis was done and a Mantel–Haenszel risk ratio (RR) and 95% confidence interval (95% CI) were calculated for each trial reporting cumulative incidence of BRD morbidity or mortality (or crude morbidity or mortality).[45] Calculated RR less than 1.0 indicates that vaccinates had lower cumulative incidence compared to controls; while RR greater than 1.0 indicates that vaccinates had higher cumulative incidence compared to controls. In order to be considered to have a statistically significantly lower morbidity or mortality cumulative incidence in vaccinates compared to controls, the upper limit of the 95% confidence interval must be below 1.0; while in order to consider the cumulative incidence of morbidity or mortality to be statistically significantly higher in vaccinates compared to controls, the lower limit of the 95% confidence interval must be greater than 1.0. A Forest plot is provided to demonstrate graphically the relative strength of the treatment effects.

RESULTS

Studies utilizing feedlot cattle with naturally occurring disease (Appendix 1)

Data was extracted from the fifteen studies (twenty-two trials) that tested the effectiveness of vaccination against one or more of the bacterial pathogens: *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* in feedlot cattle for mitigating the incidence and effect of bovine respiratory disease complex using feedlot cattle with naturally occurring disease in order to calculate the risk ratio (RR) for each trial (Appendix 1). Using the criteria outlined in this manuscript, these studies are expected to provide the highest level of evidence from the available studies identified in the literature search. A brief account of the

studies, including a description of how the cattle were allocated to treatment, the timing of vaccine administration, and a characterization of the vaccines used, can be found in the appendices.

All twenty-two trials reported a cumulative incidence for morbidity. For some trials the case definition for being considered a case was not specified, other studies had clear case definitions for BRD morbidity. Some studies reported crude morbidity and mortality risk (morbidity or mortality due to any cause) while some studies reported BRD-specific morbidity and mortality risk.

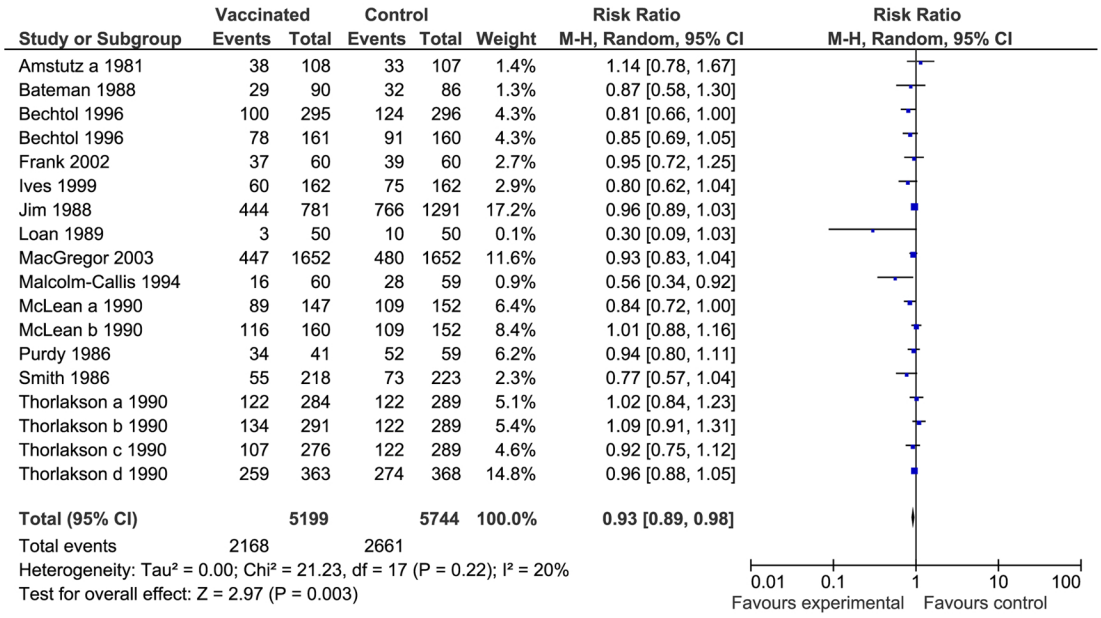
M. haemolytica and *M. haemolytica + P. multocida* vaccines

Studies investigating the effectiveness of several different commercially available vaccines against *M. haemolytica* (15 trials) and *M. haemolytica + P. multocida* (3 trials) were summarized, with three out of eighteen trials reporting a statistically significant reduction in BRD morbidity cumulative incidence in vaccinates compared to controls (e.g. upper 95% confidence interval was less than 1.00) [10,16,17], while four reported an increased risk of BRD morbidity [8,17,20] and eleven [9-15,18-20] reported a decreased risk of BRD morbidity cumulative incidence that was not different from control populations (Figure 1). The summary RR for these trials is 0.93 with a 95% confidence interval that does not cross 1.0 (0.89-0.98), indicating a statistically significant lower risk of morbidity in vaccinated feedlot cattle compared to controls.

The fifteen trials that investigated the effect of *M. haemolytica*-only vaccine accounted for 90% of the weighted summary RR; and two out of fifteen trials reported a statistically significant reduction in BRD morbidity cumulative incidence in vaccinates compared to controls

[16,17], while three reported an increased risk of BRD morbidity [17,20] and ten [9-15,18-20] reported a decreased risk of BRD morbidity cumulative incidence that was not different from controls. The three trials that investigated the effect of *M. haemolytica* + *P. multocida* vaccination accounted for 10% of the weighted summary RR. One of the three trials reported a statistically significant reduction in BRD morbidity cumulative incidence in vaccinates compared to controls [23], while one reported an increased risk of BRD morbidity [8] and one [23] reported a decreased risk of BRD morbidity cumulative incidence that was not different from control populations.

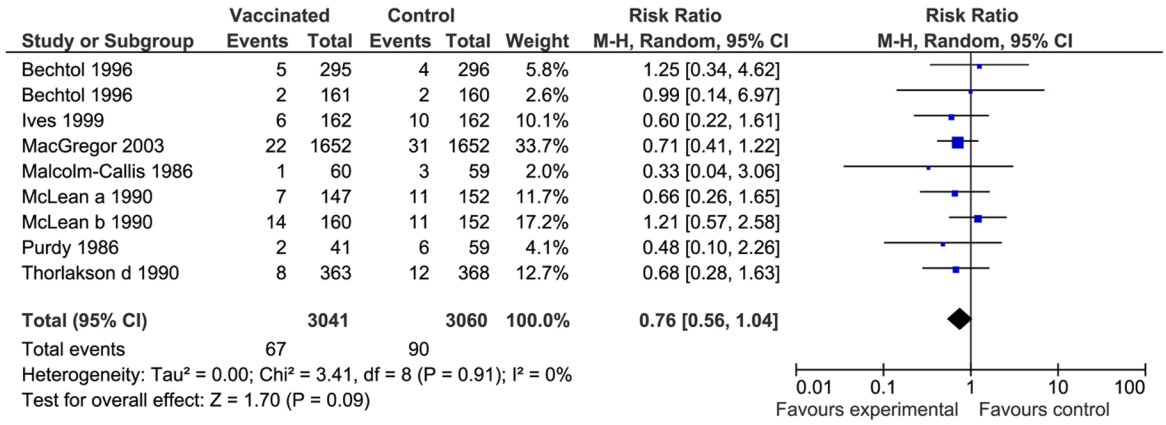
Figure 1. Forest plot of risk ratio (RR) for eighteen trials comparing cumulative morbidity incidence of feedlot cattle vaccinated against *Mannheimia haemolytica* (15 trials) or *M. haemolytica* + *Pasteurella multocida* (3 trials) compared to controls.



Evaluating mortality RR in nine studies that measured BRD-specific or crude mortality risk indicates that seven trials reported decreased cumulative mortality incidence that was not different in vaccinates relative to controls, while two reported an increased risk of mortality that

was not different from control populations.[10,12,15-18,20] An additional six trials reported cumulative mortality incidence, but the risk ratio could not be calculated because of non-events (zero for very low count cells) (Figure 2). The summary RR for these trials is 0.76 with a 95% confidence interval that crosses 1.0 (0.56-1.04), indicating mortality risk in vaccinated feedlot cattle is not statistically different than controls.

Figure 2. Forest plot of risk ratio (RR) for nine trials comparing cumulative mortality incidence of feedlot cattle vaccinated against *Mannheimia haemolytica* (7 trials) or *M. haemolytica* + *Pasteurella multocida* (2 trials) compared to controls.



<u>*M.. haemolytica* + *H. somni* vaccine studies</u>

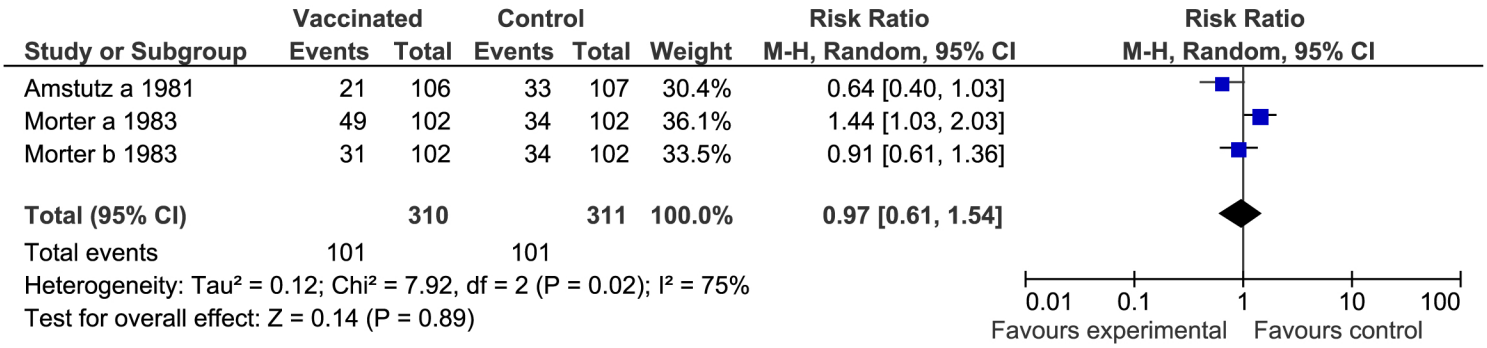
One study investigated the effectiveness of a commercially available vaccine against *M. haemolytica* +*H. somni* in feedlot cattle with natural disease challenge. [21] In this study, vaccinated cattle had statistically significantly lower morbidity compared to controls. There were no deaths in the vaccinates or controls (Appendix 1).

<u>*H. somni* vaccine studies</u>

Three trials were identified that investigated the effectiveness of *H. somni* vaccination of feedlot cattle to decrease the cumulative incidence of BRD due to natural challenge.[8,22] The

summary RR is 0.97 (95% CI 0.61, 1.54) indicating that BRD morbidity risk of vaccinated cattle was not statistically different than controls (Figure 3).

Figure 3. Forest plot of risk ratio (RR) for three trials comparing cumulative morbidity incidence of feedlot cattle vaccinated against *Histophilus somni* to controls.



As these studies provide the highest level of evidence for making the clinical decision about the effectiveness of vaccination against the pathogens *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* in feedlot cattle for mitigating the incidence and effect of bovine respiratory disease (BRD) complex, the weight of evidence from these twenty-two trials is particularly important. The summary RR indicates that these studies indicate that vaccination against *Mannheimia haemolytica* or *M. haemolytica* + *Pasteurella multocida* has the potential to decrease the incidence of bovine respiratory disease complex in feedlot cattle, but the numerical decrease in mortality risk was not statistically different from controls. Much less evidence is available to determine the effectiveness of vaccination against *Histophilus somni* in feedlot cattle, and although these studies using natural disease challenge indicate that the risk of BRD does not appear to be affected by vaccination against this pathogen, we have very little power to detect a true difference if it did exist.

Studies utilizing feedlot cattle with pathogen-challenged disease models **(Appendix 2)**

M. haemolytica vaccines

Three studies reporting five trials were identified that utilized feedlot cattle to evaluate the association between vaccination with commercially available *M. haemolytica* vaccines and mortality risk and lung lesion severity following induced disease with a transthoracic inoculation of *M. haemolytica*.[14,28,29] All five trials reported increased survival post-challenge and the four trials that reported lung severity, indicated decreased percentage of total lung volume being classified as pneumonic in vaccinates compared to controls.

Studies utilizing dairy or beef calves with naturally occurring disease (Appendix 3)

M. haemolytica and *M. haemolytica + P. multocida* vaccines

Studies utilizing dairy or beef calves during the first three to six months of life to test the efficacy of a vaccine against *M. haemolytica* or a combination vaccine against *M. haemolytica + P. multocida* are not considered to provide a high level of evidence for clinical questions arising from feedlot cattle health problems because of differences in age, housing, and management. Figure 4 depicts the Forest plots of the RR for BRD morbidity for three trials utilizing dairy calves vaccinated against *M. haemolytica* (2 trials) or *M. haemolytica + P. multocida* (1 trial).[27,30] Figure 5 depicts the Forest plot of the RR for crude mortality for two dairy calf trials evaluating *M. haemolytica* vaccine.[27] The trials that evaluated the effectiveness of *M. haemolytica* or *M. haemolytica + P. multocida* revealed summary RR indicating a statistically significant reduction in BRD morbidity (Figure 4), but not crude mortality (Figure 5) in vaccinated calves compared to controls.

Figure 4. Forest plot of risk ratio (RR) for three trials comparing cumulative morbidity incidence of dairy calves vaccinated against *Mannheimia haemolytica* or *M. haemolytica* + *Pasteurella multocida* compared to controls.

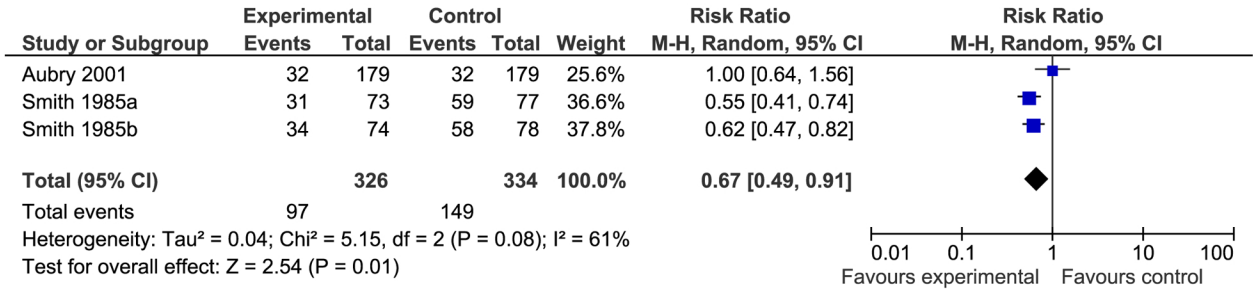
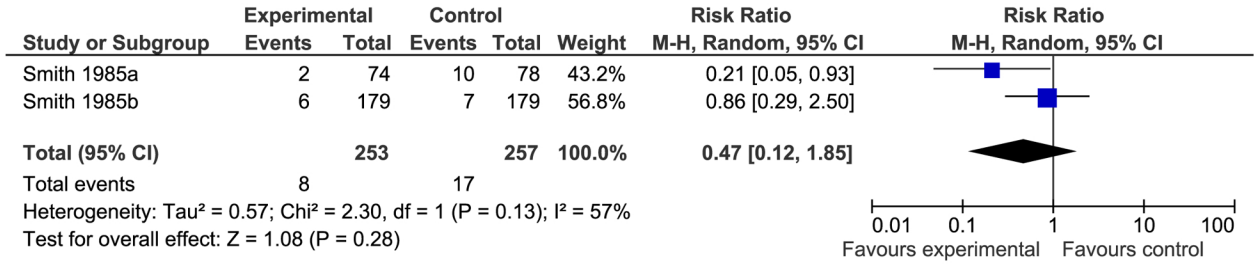


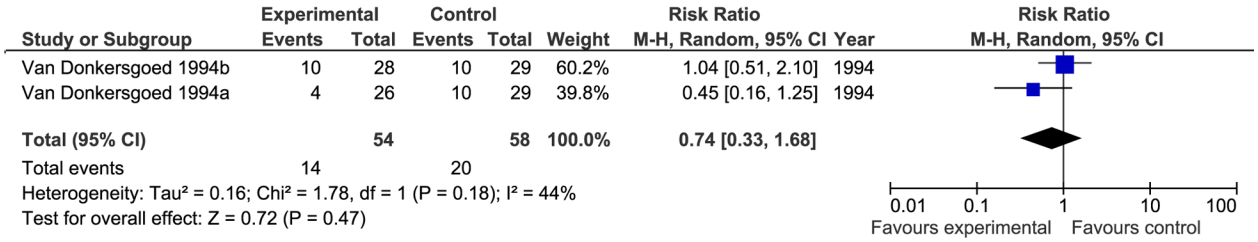
Figure 5. Forest plot of risk ratio (RR) for two trials comparing cumulative mortality incidence of dairy calves vaccinated against *Mannheimia haemolytica* compared to controls.



<u>*M. haemolytica* + *H. somni* vaccine studies</u>

Calves vaccinated with a genetically attenuated leukotoxin of *M. haemolytica* combined with bacterial extracts of *M. haemolytica* and *H. somni* did not have statistically significantly different risk of BRD morbidity compared to controls (Figure 6).[31]

Figure 6. Forest plot of risk ratio (RR) for two trials comparing cumulative morbidity incidence of dairy calves vaccinated against *Mannheimia haemolytica* + *Histophilus somni* compared to controls.



DISCUSSION

The clinical question of whether or not to utilize commercially available vaccines against bacterial pathogens associated with BRD in feedlot cattle is important to the veterinarians and producers making the decision, as well as to the health and well-being of feedlot cattle. Making an evidence-based clinical decision based primarily on published, scientifically accepted controlled trials utilizing feedlot cattle, with supportive information from published trials utilizing pathogen-challenged disease models or using dairy or beef calves housed and managed under different husbandry systems, requires not only the gathering and summarizing of the available information, but also considering the context of specific clinical questions. The summary data would indicate potential benefit for vaccination of feedlot cattle against *Mannheimia haemolytica* and *Pasteurella multocida* with no evidence of benefit for vaccination against *Histophilus somni* for mitigating the incidence and effect of bovine respiratory disease complex. Unfortunately, the published body of evidence does not provide a consistent estimate of the direction and magnitude of effectiveness in feedlot cattle vaccination against *Mannheimia haemolytica, Pasteurella multocida*, or *Histophilus somni*.

One limitation for the conclusions that can be drawn from this group of studies includes the fact that all the feedlot studies with natural disease challenge mixed vaccinated and unvaccinated calves in the same feedlot pens. This mixing may under-estimate the value of vaccination because of the phenomena of herd-immunity. In mixed pens, the vaccinated calves may reduce the disease challenge for unvaccinated controls and unvaccinated calves may increase the disease challenge for vaccinated calves compared to the exposure expected when entire pens are either vaccinated or not vaccinated. Another limitation is that some studies reported crude morbidity and mortality while other studies reported BRD-specific morbidity and mortality. Approximately 59% of the weighted summary RR for morbidity in the feedlot studies was derived from studies using a case definition for BRD as the criteria for being classified as a morbid animal, while 41% of the weighted summary RR came from studies reporting the effect of vaccination in all causes of morbidity. Similarly, approximately 57% of the weighted summary RR for mortality in the feedlot studies came from studies specifying mortalities associated with BRD, while 43% of the weighted summary RR was derived from studies reporting the effect of vaccination on all causes of mortality. If non-BRD mortalities were evenly distributed between vaccinates and controls in these studies, aggregating mortality of all causes to test the association with vaccination status will decrease the risk ratio between vaccinates and non-vaccinated controls.

A thorough search of the published literature and a structured meta-analysis to produce a summary Mantel–Haenszel risk ratio (RR) and 95% confidence interval (95% CI) are helpful tools for making an assessment of the evidence for the effectiveness of vaccination against *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* for mitigating the incidence and effect of bovine respiratory disease (BRD) complex in feedlot cattle. However,

because of the limitations of the studies used in the meta-analysis and the various specific clinical situations that feedlot veterinarians and producers confront, it is necessary to combine this summary with other sources of information and unpublished data, as well as continued monitoring of recommendations to arrive at the best advice for feedlot clients.

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Appendix 1. Articles reviewed for the evaluation of effectiveness of commercially available vaccines against *Mannheimia haemolytica, Pasteurella multocida* and/or *Histophilus somni* in feedlot cattle using natural disease challenge with cumulative morbidity risk and/or cumulative mortality risk reported as an outcome

Reference	Study Description	Vaccine	Risk Ratio (95% CI)
Mannheimia. haemolytica and *M. haemolytica* + *Pasteurella multocida* vaccine studies			
Amstutz et al. Bov Pract 1981	Random allocation of beef heifers vaccinated at feedlot arrival and 21 days later	*M. haemolytica* + *P multocida* bacterin / 2 IM doses	BRD Morbidity: **RR=1.14 (0.78-1.67)** Tx: 38/108 Control: 33/107 BRD Mortality: **RR=not calculated** Tx: 1/108 Control:2 /107
Bateman. Can Vet J 1988	Randomized control trial allocation using beef calves (avg. 255-268 kg) housed at two different locations vaccinated at feedlot arrival	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /1 IM dose	BRD Morbidity: **RR=0.89 (0.58-1.30)** Tx: 29/90 Control: 32/86 Crude Mortality: **RR=not calculated** Tx: 0/90 Control: 0/86
Bechtol and Jones. Vet Med 1996	Randomized block (paired sequentially by processing order) allocation using beef heifers (160-170 kg) vaccinated at spring arrival to 45-day backgrounding lot	Avirulent live culture of *M. haemolytica* and *P. multocida*/1 IM dose	Crude Morbidity: **RR=0.81 (0.66-1.00)** Tx: 100/295 Control: 124/296 Crude Mortality: **RR=1.25 (0.34-4.62)** Tx: 5/295 Control: 4/296 (some pens were mass medicated)
Bechtol and Jones. Vet Med 1996	Randomized block (paired sequentially by processing order) allocation using beef heifers (160-170 kg) vaccinated at July arrival to 45-day backgrounding lot	Avirulent live culture of *M. haemolytica* and *P. multocida*/1 IM dose	Crude Morbidity: **RR=0.85(0.69-1.05)** Tx: 78/161 Control: 91/160 Crude Mortality: **RR= 0.99 (0.14-6.97)** Tx: 2/161 Control: 2/160 (some pens were mass medicated
Frank et al. AJVR 2002	Systematic (every-other-steer) allocation using 170-230 kg steers vaccinated at order buyer premises prior to transit to a feedlot	Bacterin-Toxoid (chemically inactivated culture of multiple isolate of *M. haemolytica*)/ 1 IM dose	BRD Morbidity: **RR=0.95 (0.72-1.25)** Tx: 37/60 Control: 39/60

Ives et al. KSU Cattlemen's Day 1999	Systematic (every-other-heifer) allocation using beef heifers (avg. 227 kg) vaccinated at feedlot arrival	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /1 IM dose	BRD Morbidity: **RR=0.80 (0.62-1.04)** Tx: 60/162 Control: 75/162 BRD Mortality + Chronics **RR=0.60 (0.22-1.61)** Tx: 6/162 Control: 10/162
Jim et al. Vet Med 1988	Systematic allocation using cattle vaccinated at feedlot arrival and again 1 to 5 days later	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /2 IM doses	BRD Morbidity: **RR=0.95 (0.89-1.03)** Tx: 444/781 Control: 766/1291
Loan et al. Bov Pract 1989	Unknown allocation of cattle vaccinated at feedlot arrival and 28 days prior	Bacterin (tissue culture-derived *M. haemolytica* bacterin)/ 2 IM doses	BRD Morbidity: **RR=0.30 (0.09-1.03)** Tx: 3/50 Control: 10//50
MacGregor et al. Bov Pract 2003	Systematic (every-other-one) allocation using cattle vaccinated at feedlot arrival	Bacterin-toxoid (chemically inactivated culture of multiple isolate of *M. haemolytica*)/1 dose	BRD Morbidity: **RR=0.93 (0.83-1.04)** Tx: 447/1652 Control: 480/1652 Crude Mortality: **RR=0.69 (0.44-1.06)** Tx: 33/1652 Control: 48/1652 BRD Mortality: **RR=0.71 (0.41-1.22)** Tx: 22/1652 Control: 31/1652
Malcolm-Callis et al. Agri-Practice 1986	Unknown allocation of cattle vaccinated at feedlot arrival and 14 day later	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /2 IM doses	BRD Morbidity: **RR=0.56 (0.34-0.92)** Tx: 16/60 Control: 28/59 Crude Mortality: **RR=0.33 (0.04-3.06)** Tx: 1/60 Control: 3/59
McLean et al. Oklahoma State Univ Animal Science Research Report 1990	Random allocation of cattle vaccinated prior to transit to a feedlot and 7 days later	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /2 IM doses	BRD Morbidity: **RR=0.84 (0.72-1.00)** Tx: 89/147 Control: 109/152 Crude Mortality: **RR=0.66 (0.26-1.65)** Tx: 7/147 Control: 11/152
McLean et al. Oklahoma State Univ Animal Science Research Report 1990	Random allocation of cattle vaccinated at feedlot arrival and 7 days later	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /2 IM doses	BRD Morbidity: **RR=1.01 (0.88-1.16)** Tx: 116/160 Control: 109/152 Crude Mortality: **RR=1.21 (0.57-2.58)** Tx: 14/160 Control: 11/152

Purdy et al. JAVMA 1986	Unknown allocation of calves from a single ranch vaccinated 14 days prior to transit to an order-buyer where they remained for 6 days in contact with other cattle before being transported to a feedlot	Live culture of *M. haemolytica* /1 ID dose	BRD Morbidity: **RR=0.94 (0.80-1.11)** Tx: 34/41 Control: 52/59 Crude Mortality: **RR=0.48 (0.10-2.26)** Tx: 2/41 Control: 6/59
Smith et al. Vet Med 1986	Random allocation of steers and bulls vaccinated at feedlot arrival	Live culture of *M. haemolytica* /1 ID dose	Crude Morbidity: **RR=0.77 (0.57-1.04)** Tx: 55/218 Control: 73/223 Crude Mortality: **RR=not calculated** Tx: 0/218 Control: 1/223
Thorlakson et al. Can Vet J 1990	Systematic allocation of six to eight month old cattle vaccinated 21 days prior to transit at ranch of origin (not vaccinated at feedlot)	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens/1 IM dose	Crude Morbidity: **RR=1.02 (0.84-1.23)** Tx: 122/284 Control: 122/289 BRD Mortality: **RR= not calculated** Tx: 5/284 Control: 1/289
Thorlakson et al. Can Vet J 1990	Systematic allocation of six to eight month old ranch-fresh cattle vaccinated at feedlot arrival	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /1 IM dose	Crude Morbidity: **RR=1.09 (0.91-1.31)** Tx: 134/291 Control: 122/289 BRD Mortality: **RR= not calculated** Tx: 0/291 Control: 1/289
Thorlakson et al. Can Vet J 1990	Systematic allocation of six to eight month old cattle vaccinated at ranch of origin 21 days prior to transit and at feedlot arrival	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /2 IM doses (arrival and 21 d prior)	Crude Morbidity: **RR=0.92 (0.75-1.12)** Tx: 107/276 Control: 122/289 BRD Mortality: **RR= not calculated** Tx: 2/276 Control: 1/289
Thorlakson et al. Can Vet J 1990	Systematic allocation of auction derived cattle vaccinated at feedlot arrival	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /1 IM dose	Crude Morbidity: **RR=0.96 (0.88-1.05)** Tx: 259/363 Control: 274/368 BRD Mortality: **RR=0.68 (0.28-1.63)** Tx: 8/363 Control: 12/368
Mannheimia. haemolytica + *Histophilus somni* vaccine studies			
Van Donkersgoed et al. Can Vet J 1993	Random allocation of steers (avg. 237 kg) vaccinated at feedlot arrival or at arrival and 14 days later	Genetically attenuated leukotoxin of *M. haemolytica* combined with bacterial extracts of *M. haemolytica* + *H. somni*/1 or 2 SQ or IM doses	BRD Morbidity: **RR=0.37 (0.24-0.56)** Tx: 29/198 Control: 41/103 BRD Mortality: **RR=NA** Tx: 0/198 Control:2 /103

Histophilus somni vaccine studies			
Amstutz et al. Bov Pract 1981	Random allocation of beef heifers vaccinated at feedlot arrival and 21 days later	*H. somni* bacterin / 2 IM doses	BRD Morbidity: **RR=0.64 (0.40-1.03)** Tx: 21/106 Control: 33/107 BRD Mortality: **RR=NA** Tx: 3/106 Control:2 /107
Morter and Amstutz Bov Pract 1983	Random allocation of crossbred steers vaccinated at feedlot arrival	*H. somni* bacterin / 1 IM dose	BRD Morbidity: **RR=1.44 (1.03-2.03)** Tx: 49/102 Control: 34/102
Morter and Amstutz Bov Pract 1983	Random allocation of crossbred steers vaccinated at feedlot arrival and 21 days later	*H. somni* bacterin / 2 IM doses	BRD Morbidity: **RR=0.91 (0.61-1.36)** Tx: 31/102 Control: 34/102

Appendix 2. Articles reviewed for the evaluation of effectiveness of commercially available vaccines against *Mannheimia haemolytica, Pasteurella multocida* and/or *Histophilus somni* in feedlot cattle using an induced disease model with lung lesions or other measures of disease severity reported as an outcome.

Reference	Study Design	Vaccine	Outcome
Mannheimia. haemolytica vaccine studies			
Confer and Fulton Bovine Proceedings 1994	Unknown allocation of 136-205 kg beef calves vaccinated twice at 21 day interval prior to transthoracic *M. haemolytica* challenge 14 days after last vaccination	*M. haemolytica* bacterin-solubilized surface antigens	25% of control calves died and surviving cattle developed moderate to severe pneumonia while vaccinated cattle had transient clinical signs of BRD and no deaths. Pulmonary lesions for vaccinates were 64.5-71.4% less than for controls
Confer and Fulton Bovine Proceedings 1994	Unknown allocation of calves vaccinated once prior to transthoracic *M. haemolytica* challenge	*M. haemolytica* bacterin-toxoid (chemically inactivated culture of multiple isolate of *M. haemolytica*)	80% of control cattle and 10% of vaccinated cattle died following challenge. All control calves had severe pneumonia. The surviving vaccinated cattle had transient clinical signs of BRD. Pulmonary lesions for vaccinates were 52.5-53% less than for controls
Confer et al. Vaccine 2003	Unknown allocation of weaned beef steers vaccinated once prior to transthroacic challenge with 3.0×10^{9} CFU *M. haemolytica* 24 days later	Inactivated *M. haemolytica*, bacteria-free extract with leukotoxoid and bacterial surface subunit antigens /2 IM doses	At necropsy, mean lung lesion scores were 7.9 ± 3.6 for non-vaccinated controls and 3.0 ± 1.3 for vaccinates (62.0% reduction in lesion score)
Loan et al. Bov Pract 1989	Unknown allocation of 182-227 kg. cattle vaccinated twice at 28 day interval and challenged via transthoracic inoculation with *M. haemolytica* 7 days after last vaccination	Bacterin (tissue culture-derived *M. haemolytica* bacterin)/ 2 IM doses	More vaccinated calves survived 4 days post challenge than controls (14/18 vs. 0/18) and at necropsy 4 days post challenge, control calves had lung lesions that averaged 831 cm^3 while vaccinated calf lung lesions averaged 58 cm^3
Loan et al. Bov Pract 1989	Unknown allocation of calves vaccinated at 1 to 4 month of age and returned to their dams, vaccinated again 3 months later and challenged via transthoracic inoculation with *M. haemolytica* 7 days after last vaccination	Bacterin (tissue culture-derived *M. haemolytica* bacterin)/ 2 IM doses	More vaccinated calves survived 4 days post challenge than controls (8/8 vs. 1/8)

Appendix 3. Articles reviewed for the evaluation of effectiveness of commercially available vaccines against *Mannheimia haemolytica, Pasteurella multocida* and/or *Histophilus somni* in dairy or beef calves using natural disease challenge with cumulative morbidity risk and/or cumulative mortality risk reported as an outcome.

Reference	Study Description	Vaccine	Risk Ratio (95% CI)
Mannheimia. haemolytica and *M. haemolytica* + *Pasteurella multocida* vaccine studies			
Aubry et al. JAVMA 2001	Paired (sequentially by birth date) allocation of Holstein heifer calves first vaccinated at 14 and 20 days of age and again 14 days later	Avirulent live culture of *M. haemolytica* and *P. multocida*/2 IM doses	BRD Morbidity: **RR=1.00 (0.64-1.56)** Tx: 32/179 Control: 32/179 Crude Mortality: **RR=0.86 (0.29-2.50)** Tx:6/179 Control: 7/179
Smith et al. Vet Med 1985	Unknown allocation of dairy bull calves vaccinated once at two weeks of age (1984 vaccinates)	Live culture of *M. haemolytica* /1 ID dose	BRD Morbidity: **RR=0.55 (0.41-0.74)** Tx: 31/73 Control: 59/77
Smith et al. Vet Med 1985	Unknown allocation of dairy bull calves vaccinated once at two weeks of age (1985 vaccinates)	Live culture of *M. haemolytica* /1 ID dose	BRD Morbidity: **RR=0.62 (0.47-0.82)** Tx: 34/74 Control: 58/78 Crude Mortality: **RR=0.21 (0.05-0.93)** Tx: 2/74 Control: 10/78
Mannheimia. haemolytica + *Histophilus somni* vaccine studies			
Van Donkersgoed et al. Can Vet J 1994	Systematic allocation of beef calves vaccinated at 3 weeks and again at 5 weeks of age	Genetically attenuated leukotoxin of *M. haemolytica* combined with bacterial extracts of *M. haemolytica* + *H. somni*/1 or 2 SQ or IM doses	BRD Morbidity: **RR=1.04 (0.51-2.10)** Tx: 10/28 Control: 10/29
Van Donkersgoed et al. Can Vet J 1994	Systematic allocation of beef calves vaccinated at 3 weeks and again at 5 weeks of age	Genetically attenuated leukotoxin of *M. haemolytica* combined with bacterial extracts of *M. haemolytica* + *H. somni*/1 or 2 SQ or IM doses	BRD Morbidity: **RR=0.44 (0.16-1.25)** Tx: 4/26 Control: 10/29