PEER REVIEWED

An Evaluation of the Effectiveness of a Commercial *Mannheimia (Pasteurella) haemolytica* Vaccine in a Commercial Feedlot

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Abstract

A single, 2-ml injection of a *Mannheimia (Pasteurella) haemolytica* bacterin-toxoid was administered subcutaneously to calves on arrival at the feedlot. Calves receiving the bacterin-toxoid had reduced crude mortality. There were no differences in BRD-specific mortality, morbidity or average daily gains (mean days on feed = 179).

Résumé

Une simple injection sous-cutanée de 2 ml d'une bactérine-anatoxine contre *Mannheimia (Pasteurella) haemolytica* a été administrée à des veaux dès leur arrivée dans l'élevage semi-intensif. Les veaux qui reçurent l'injection de la bactérine-anatoxine montraient un taux brut de mortalité plus faible. Il n'y avait pas de différence au niveau de la mortalité, de la morbidité et du gain moyen quotidien (jours moyens en élevage = 179) reliés spécifiquement aux maladies respiratoires bovines.

Introduction

The bovine respiratory disease (BRD) complex has been extensively investigated and numerous vaccines have been developed for its control. Despite these efforts, BRD continues to be the most common cause of morbidity and mortality in feedlot settings. Respiratory disease is particularly prevalent during the first 45 days after calves have been weaned, transported and placed in a feedlot.[9]

The clinical signs, lesions and death loss associated with BRD, or shipping fever, usually can be attributed to bacterial pneumonia caused by *Mannheimia (Pasteurella) haemolytica*, *Pasteurella multocida*, or *Haemophilus somnus*. These bacteria are commonly found in the nasopharyngeal area of healthy animals.[5,6] Under normal conditions the bacteria are unable to move into the lower respiratory tract and cause pneumonia.[19] However, if the animal is stressed, has a viral respiratory infection, or is otherwise immunosuppressed, severe pneumonia can be established by a relatively small number of bacteria.[5,6,19] This has led to the concept that BRD has a multifactorial etiology involving a complex interaction among stressors, viruses and perhaps other immunosuppressive factors that act separately or together to suppress the defense mechanisms in the lung and predispose the animal to bacterial pneumonia.[6,19]

Findings reported in the literature are equivocal on the use of more recently available *Mannheimia* spp vaccines before, and at feedlot arrival. Three studies have shown reduction in morbidity and/or mortality in calves administered a *P. haemolytica* toxoid at arrival.[2,10,13] However, two clinical trials showed no significant effects when the same vaccine was given at arrival[14] or three weeks before shipment and/or arrival.[18] Negative health performance in vaccinates has not been reported.

There are reports on various other commercial or experimental *Mannheimia* spp vaccines. Field studies of a streptomycin-dependent live *Pasteurella* spp vaccine[11] and an intradermally-administered live *P. haemolytica* vaccine demonstrate efficacy.[17] Alternatively, a field study of a *P. haemolytica* capsular antigen vaccine failed to show significant health effects,[8] as did a study using a tissue-culture-derived *P. haemolytica* bacterin.[7] There are reports of lack of field efficacy with earlier *Mannheimia* spp bacterins.[1,15] There is also a

report of increased health problems following vaccination with earlier *Pasteurella* spp bacterins.[3] However, this study did not mention whether treatment assignment was random and the experimental unit is unclear. For some currently available *Pasteurella* spp vaccines there are no peer-reviewed reports of field trials examining clinical effects in North American beef cattle.

Because of dosage and timing requirements for optimal immunity (7 to 10 days following a 14- to 21-day booster dose), the theoretical efficacy of *Mannheimia* spp vaccines should be compromised when used only in a feedlot arrival program. Current consensus is that it is best to administer at least the priming dose and sometimes the booster dose before weaning. However, paradoxically, the literature cited above supports the use of *M. haemolytica* toxoid at the time of arrival to the feedyard.

The purpose of this study was to evaluate the effectiveness of a commercial bacterin-toxoid whole cell product[a] derived from chemically inactivated cultures of multiple isolates of *M. haemolytica* in a triple adjuvant when administered once, on arrival, in a commercial feedlot setting. Immunogenicity studies have resulted in serum antibody titers to leukotoxin and cell wall components that met USDA requirements for licensure (data not shown). Additionally, this bacterin-toxoid has been reported effective in stimulating anti-leukotoxin and *M. haemolytica* surface antigen serum antibodies.[4] These data suggest that protection against natural challenge may be expected. However, the authors of the previously cited study cautioned that, although stimulation of anti-leukotoxin and *M. haemolytica* surface antigen serum antibodies has enhanced resistance to experimental challenge, antibody data alone is not a reliable indicator of field efficacy of a vaccine.[4]

Materials and Methods

Location and animals

Beginning September 15, 1997, 3304 calves were received into a 50,000-head commercial feedlot in southern Idaho. Calves originated from Washington, Idaho, Oregon and Utah auction facilities and weighed from 450 to 750 lb (205 to 341 kg). Calves were in 15 lots that ranged in size from 92 to 267 head (mean 220 head). Each lot was assembled over a period of 5 days or less. Two or more lots were often assembled within the same week.

Cattle enrolled in the trial were fed according to the standard feedlot program for an average of 179 days (range 162 to 207). The diet consisted of alfalfa hay, corn, small grain silage, whey, a liquid protein supplement and tallow. NEg for the ration was 66.7 kcal/kg and NEm was 100 kcal/kg. A standard 4-step acclimation program was used, with the final ration consisting of 87.93% concentrate.

Treatments and randomization

On arrival at the feedlot, lots of cattle were systematically sorted into two groups using a one-by-one gate cut. Following sorting, all cattle were processed using the standard feedlot program which consisted of an individually numbered ear tag, 2-ml of a commercial modified-live multivalent viral respiratory vaccine[b] administered subcutaneously, treatment with an avermectin[c] (1 ml/110 lb [1 ml/50 kg] body weight), and a growth promotant implant[d] administered subcutaneously in the ear. Additionally, one group in each lot was given a commercial *Mannheimia haemolytica* bacterin-toxoid[a] while the other group in the lot served as unvaccinated controls. Treatment and control groups were assigned randomly with a coin toss. Treated and control groups in a lot were fed in the same pen. The number scheme used to identify treated and control cattle was changed for each lot of calves, blinding observers to treatment assignment. All dead calves were examined postmortem (DSM or trained feedyard personnel) to determine the cause of death.

Outcomes

Outcomes assessed included average daily gain, morbidity, relapse morbidity, non-responders, crude mortality and BRD mortality. Crude mortality was defined as all mortality over the period of the study, regardless of diagnosis.

Calves were observed daily for signs of respiratory disease (depression, lack of rumen fill, and ocular or nasal discharge). Calves classified as morbid had at least one of these signs and a rectal temperature ≥103.5°F. Calves identified as sick were treated according to the standard feedlot treatment protocol independent of experimental treatment group assignment. Personnel responsible for assessment of cattle for morbidity were blinded to experimental treatment assignment. Specifically, the treatment protocol for cattle identified as being sick was tilmicosin[e] (4.54 mg/lb; 10 mg/kg body weight, subcutaneously), oxytetracycline injection[f] (9 mg/lb; 19.80 mg/kg body weight, subcutaneously), and sulfadimethoxine[g] (25 mg/lb [55 mg/kg] BW intravenously on day 1 and 12.5 mg/lb [27.5 mg/kg] BW intravenously on days 2 and 3 of treatment). Cattle that required subsequent treatment were also treated as above.

Statistical analysis

Treatment or control group within a lot was the experimental unit. The paired t-test was used to analyze differences between experimental treatment groups for statistical significance with a pair consisting of the

group within each of the 15 lots. Normality of distribution for each outcome was assessed using the Shapiro-Wilk normality test. If the data met the assumption of normality, the data were subjected to the paired t-test, testing the null hypothesis that the average difference between pairs of treatments and controls is zero (no treatment effect). If the data failed to meet the assumption of normality of distribution, the data were subjected to the nonparametric equivalent of a paired t-test (Wilcoxon signed rank test). This also tests the null hypothesis that the average difference between pairs of treatments and controls is zero (i.e., no treatment effect). If no statistically significant differences were found, the power was evaluated by calculating the maximum detectable difference using the study sample size and standard deviations observed. Alpha was set at 0.05 and beta at 0.20 *a priori*.[h]

Results and Discussion

All outcomes measured, with the exception of BRD mortality, were normally distributed. There was a statistically significant reduction in crude mortality in the vaccinated compared to the control cattle (1.99% versus 2.91%, P = 0.01; Table 1). This is compatible with findings reported by others.[2,10,17] Bechtol *et al*[2] reported that ranch calves given a commercially available *P. haemolytica* vaccine at the ranch of origin at spring branding and boostered on arrival at the feedlot, or calves that were vaccinated with this vaccine at feedlot arrival and boostered 7 to 10 days later, had significantly lower mortality than unvaccinated control calves. Jim *et al*[10] reported that vaccination with a commercially available leukotoxin-rich, cell-free *P. haemolytica* vaccine reduced overall mortality and mortality due to fibrinous pneumonia. Smith *et al*[17] reported that intradermal administration of a live *Pasteurella haemolytica* vaccine resulted in reduced morbidity and mortality. However, the experimental unit is not clearly defined and an experimental antibiotic was used for BRD treatment, which may have impacted response to treatment.

Conversely, other investigators have reported no detectable effect of *M. haemolytica* vaccination on mortality.[3,13,14,18] Inability to find differences in mortality is common in field trials reported in the literature, since there are generally low to marginal numbers of experimental units and the incidence of mortality is too low to detect differences between experimentally treated cattle and control animals. This was the case for the reports cited which did not find detectable differences in mortality between vaccinated and control groups. The current study used an experimental design that was intended to reduce the variability between experimental units, and therefore enhance statistical power. It is interesting that although calves were vaccinated and boostered in the reports cited, booster vacination did not seem to affect mortality as compared to cattle that were vaccinated only on arrival to the feedyard, as was done in our study. The particular vaccine used has not been a predictable indicator of mortality, since similar types of vaccines were used in two reports where differences were found in crude mortality in one study but not in the other.[2,18]

The Shapiro-Wilk normality test suggested that the distribution of the differences in BRD mortality might not be normal (P = 0.07). The Wilcoxon Signed Rank test suggested a trend (P = 0.08) towards reduction in BRD-attributable mortality in the vaccinated group. Only two of the studies cited distinguished between crude (or total) mortality and BRD-specific mortality. Thorlakson *et al*[18] reported differences between experimental treatments in BRD-specific mortality; calves vaccinated at feedyard arrival only had significantly lower BRD-specific mortality than calves that were vaccinated at the ranch of origin, but not vaccinated on arrival at the feedyard. Jim *et al*[10] reported significant reduction of overall mortality and fibrinous pneumonia mortality in calves vaccinated on arrival to the feedyard and re-vaccinated 1 to 5 days post-arrival. This is compatible with the trend reported in the current study, although we were unable to detect statistically significant differences in BRD-specific mortality (P=0.08). This is paradoxical in that it would be ex-

Table 1. Health and growth performance of cattle vaccinated once on arrival with commercially available *Pasteurella haemolytica* vaccine.

Treatment	Crude mortality	BRD mortality	Morbidity	Relapse morbidity	Non-responders	ADG (lb)
Vaccinates	1.99%[a]	1.33%	27.07%	18.08%	17.28%	3.16
Controls	2.91%[b]	1.88%	29.04%	19.42%	26.88%	3.13
Mean delta	1.00%	0.57%	1.03%	3.77%	2.32%	0.034
Std deviation	1.34	1.37	7.78	12.50	5.61	0.15
P =	0.01	0.08	0.61	0.26	0.13	0.40

[a,b]Superscipts that differ within an outcome (column) are significantly different, P<0.05.

pected that calves vaccinated prior to a substantial challenge would be more effectively protected than cattle that were vaccinated at the time of stressful events associated with arrival at the feedyard.

In this study, there were no statistically significant differences found between vaccinate and control groups in primary morbidity, relapse morbidity, non-responders or average daily gain (Table 1). Others have also failed to detect differences in morbidity or average daily gain in *Mannheimia haemolytica*-vaccinated calves.[1,7,8,15] Amstutz *et al*[1] reported that average daily gain tended to be reduced in calves vaccinated with a *Pasteurella* spp bivalent bacterin or a *Haemophilus somnus* bacterin as compared to unvaccinated control calves during the first 34 days post-vaccination.[1] However, gains were nearly identical by 133 days post-vaccination. Therefore, studies which report differences early in the feeding period may not be indicative of closeout growth performance. In the current study, only closeout average daily gain was calculated.

Improved gain in calves vaccinated with a *M. haemolytica* vaccine has also been reported.[11] These authors report that preconditioned calves had significantly greater gain than cattle vaccinated only once on arrival at the feedyard or unvaccinated control calves. As mentioned, in the study reported here, cattle were only vaccinated once on arrival to the feedyard. Further investigation would be required to determine the potential effects on growth performance of preconditioning or revaccination with the vaccine used in this study.

In cases where vaccine effect on morbidity is not detected, such as in the current study, it is possible that case definition for BRD is relatively non-specific. In other words, cattle identified as being morbid, removed from the pen and treated with antimicrobials may have infectious or inflammatory processes involving organ systems other than, or concurrently with, the respiratory tract. Generally, these cattle are identified by feedyard personnel based on non-specific clinical signs rather than respiratory-specific clinical signs. This is especially true under the conditions of large-scale commercial cattle feeding operations. This could have substantial impact on the ability to detect experimental treatment effects, since outcomes could be diluted with responses that are potentially unrelated to treatment effect.

Conversely, some investigators have reported reduced morbidity in vaccinated calves.[12] In contrast to the current study, Loan *et al*[12] had only 50 experimental units per treatment group. Additionally, calves in this report were vaccinated 28 days prior to weaning and revaccinated at weaning prior to shipping from Tennessee to Texas. The case definition is not clearly described by the authors. However, observation of much fewer numbers of cattle by research personnel in contrast to feedyard personnel in a commercial feedlot setting may explain the difference in ability to detect treatment effects as compared to the current study.

Interestingly, one investigator reported increased incidence of respiratory disease in *P. haemolytica*-vaccinated calves.[3] However, the description of the experimental unit and statistical methods are unclear.

Whenever a study fails to detect a statistically significant difference between treatments, as is the case in this study for primary morbidity, relapse morbidity, non-responders and average daily gain, it is important to consider the statistical power of the study. The experimental design in this study provided adequate power to detect a 1.35% difference in crude mortality, an 8% difference in primary morbidity, a 13% difference in relapse morbidity, a 6% difference in non-responders and a 0.1 lb/head/day difference in average daily gain.

Conclusions

A single injection of a *Mannheimia haemolytica* bacterin-toxoid[a] on arrival at the feedyard significantly reduced crude mortality. There were no differences in BRD-specific mortality, primary morbidity, relapse morbidity, non-responders or average daily gains.

Footnotes

[a] Pulmo-guard® PH-1, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO 64506
[b] Pyramid® MLV 4, Fort Dodge Animal Health, Fort Dodge, IA 50501
[c] Ivomec® 1% injection, Merial, Iselin, NJ 08830
[d] Ralgro® Implants, Schering-Plough Animal Health Corporation, Union, NJ 07083
[e] Micotil® 300 Injection, Elanco Animal Health, Indianapolis, IN 46240
[f] Bio-mycin® 200, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO 64506
[g] Albon®, Pfizer Animal Health, Exton, PA 19341
[h] Samples.exe in Computer Programs for Epidemiologic Analysis (PEPI) Version 2.07a.

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