JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Vaccines and Vaccination

Research Article

Evaluation of Commercially Available Multivalent Modified-Live Viral Vaccines on Health and Performance in Feedlot Cattle

D.L. Step DVM, DACVIM[1], Clinton R. Krehbiel PhD[2], Cody Hixon MS[2], Mitchell R. Blanding DVM[3], Douglas R. Hilbig DVM[3], Victor S. Cortese DVM, PhD, DABVP[3*], Thomas H. Short PhD[3]

[1]*Department of Veterinary Clinical Sciences, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078, USA*

[2]*Department of Animal Science (Krehbiel, Hixon), Oklahoma State University, Stillwater, OK 74078, USA*

[3]*Zoetis Inc. (Blanding, Hilbig, Cortese, Short), 100 Campus Drive, Florham Park, NJ 07932*

**Corresponding author: Dr. Victor Cortese DVM, PhD, Dipl ABVP, Director Cattle- Equine Immunology, Zoetis Animal Health, 746 Veechdale Road, Simpsonville, KY 40067, 610-662-6505, Email: victor.cortese@zoetis.com*

Received: 09-03-2015

Accepted: 10-05-2015

Published: 11-17-2015

Abstract

Objective: To evaluate different processing protocols using commercially available multivalent vaccines in high-risk cattle.

Design: Randomized experimental study.

Animals: 1442 crossbred beef cattle.

Procedures: Upon arrival, calves were assigned to one of three treatments on arrival: Inforce 3[a], intranasal administration and OneShot BVD[b], subcutaneous adminsitration (INF) , Pyramid5/Presponse[d] , administered subcutaneously (PYR), or Vista/Once[f] administered subcutaneously (VIS) . On day 14, calves were revaccinated with a 5-way modified live viral (MLV) respiratory vaccine according to their respective treatments. Health and performance outcomes were measured.

Results: No differences were detected for body weight (BW), average daily gain (ADG),dry matter intake (DMI), or growth to feed ratio (G:F) from day 0 to 60 ($P > 0.05$). Calves in the INF treatment required fewer second and third treatments for clinical Bovine Respiratory Disease (BRD) than did calves receiving the VIS treatment and lower mortality rates were seen in the INF group. Actual sixty day costs were lower when an intranasal viral vaccine was a component of the arrival program.

Conclusions and Clinical Relevance: Results suggest that high-risk calves vaccinated with an intranasal modified live viral vaccine containing Bovine Herpesvirus 1, Parainfluenza 3 (temperature sensitive viruses) and Bovine Respiratory Syncytial Virus and a systemic modified live Bovine Viral Diarrhea Virus vaccine in combination with *M. haemolytica* bacterin/toxoid experienced a decreased number of cattle requiring second and third antimicrobial treatments for clinical BRD, and also reduced mortality. Vaccine programs that include intranasal and systemic virus vaccines in combination with *M. haemolytica* bacterin/toxoids in newly-received cattle in feedlots could improve cattle health with less mortality and thus decrease the use of therapeutic antimicrobials and overall costs.

Abbreviations

ADG: Average Daily Gain;

BHV-1: Bovine Herpesvirus 1;

BRD: Bovine Respiratory Disease;

BRSV: Bovine Respiratory Syncytial Virus;

BVDV: Bovine Viral Diarrhea Virus;

BW: Body Weight;

CP: Crude Protein;

DMI: Dry Matter Intake;

G:F: Gain-To-Feed Ratio;

IN: Intranasal;

MLV: Modified Live Viral;

NDF: Neutral Detergent Fiber;

PI3V: Parainfluenza Type 3 Virus;

SC: Subcutaneous;

WSBRC: Willard Sparks Beef Research Center

Introduction

Bovine respiratory disease complex (BRD) continues to be the single most costly loss associated with commercial beef production in the United States, accounting for 1,0555,000 animals lost in 2010 valued at $643 million [1]. Bovine respiratory disease is the result of a combination of pathogenic microorganisms infecting the host animal and stress. Generally, the most severe cases begin with stress and an initial viral respiratory infection leading to a compromised immune system that allows for bacterial colonization in the lower respiratory tract from pathogens such as *Mannheimia haemolytica* or *Pasturella multocida* [2]. Cattle that experience the greatest risk of developing BRD are light-weight calves (<250 kg, [<550 lb]) that have recently been weaned and are commingled with other calves from different origins before arrival at a feedlot. These cattle are classified as at "high risk" of developing disease after arrival at the feedlot. The weaning, assembly, marketing, and transportation process are stressful experiences in a calf's life, and the subsequent disruption of feed and water intake, coupled with increased vocalization due to the disturbance of known social order, leave the calf physiologically and immunologically susceptible to infection in the respiratory tract [3].

Vaccination against viral and bacterial respiratory pathogens is one of the most common management tools currently available to prevent losses associated with infectious diseases [4]. Vaccines are labelled for use in healthy cattle. Furthermore, it is well understood that in order to maximize the efficacy of any vaccine, it must be administered to an animal that is immunocompetent and prior to exposure with infectious agents [5]. However, because of unknown health histories of newly received cattle, vaccines are generally administered after arrival to feedlots when cattle may be immunocompromised due to the stress of assembly and transportation, and often times have already been exposed to pathogenic agents [6]. Increasing the understanding of how to effectively confer immunological protection to such high-risk cattle through vaccination procedures is imperative to decreasing losses associated with BRD.

Many vaccines are delivered parenterally, but the application through an alternative route via intranasal administration of vaccine to stimulate local protective mucosal immunity has received increasing amounts of attention and interest. Research has reported that mucosal vaccination of calves against BRSV was an effective method of conferring mucosal and some systemic antibody protection [7-10]. Calves vaccinated intranasally against BHV1 and PI3 have demonstrated both high levels of interferon and protection in vaccinated animals within 12 to 72 hours of vaccination [4,10-17].

Concern over antigen interference has also been expressed with commercially available multivalent MLV products, especially those containing toxoids for *M. haemolytica* (formerly known as *Pasturella haemolytica*). This effect was evaluated in a study focusing on vaccination of incoming calves (n=2,324) to a feedlot with a MLV BHV-1 product or a BHV-1 glycoprotein subunit (gIV) both in the presence or absence of a *P. haemolytica* vaccine.[18] The results demonstrated that administration of the MLV BHV-1 inhibited the efficacy of the *P. haemolytica* vaccination [18]. Reported outcomes from a 2011 study evaluating efficacy of concurrent administration of multivalent MLV respiratory vaccines in the presence of *M. haemolytica* bacterin/toxoid agree with the previous study using commercially available vaccines [19]. In contrast, intranasal administration of multivalent MLV respiratory vaccines in concurrence with subcutaneous delivery of *M. haemolytica* bacterin/toxoid has been reported to confer effective immunity to calves against all vaccinated pathogens [20]. These results would suggest that vaccination by different routes of administration has the potential to prevent antigen interference among common commercially available vaccines when administered concurrently.

The purpose of the present study was to evaluate these effects comparing two common parenterally (SC) administered pentavalent MLV respiratory vaccines containing a *M. haemolytica* bacterin/toxoid to concurrent administration of an intranasal (IN) trivalent MLV respiratory vaccine with a parenterally administered BVDV types 1 and 2 with *M. haemolytica* toxoid.

Materials and Methods

Animals:

Crossbred bull and steer calves (n = 1,442; average arrival BW = 216 ± 20 kg [475 ± 44 lbs]; 64.77% bulls and 35.23% steers) with unknown health histories were obtained from multiple auction markets from February to May 2014. Calves were obtained from auction markets in Oklahoma, Kentucky, Louisiana, Mississippi, and Florida. All cattle were shipped to the Willard Sparks Beef Research Center (WSBRC) in Stillwater, OK where the experiment was conducted (average shipping distance 600 km, [372 mi]). The experiment was completed in two separate time blocks with the first experimental group containing 724 bulls and steers (average arrival BW = 196 ± 8 kg [431 ± 18 lbs]), and the second group containing 718 bulls and steers (average arrival BW = 236 ± 16 kg [519 ± 35 lbs]). The blocks occurred successively with only a few days separating the completion of the first replicate and initiation of the second to minimize seasonal impacts. The study was approved by the Institutional Animal Care and Use Committee, Oklahoma State University.

Procedures

Upon arrival, calves were unloaded and allowed to rest for approximately one hour before being individually identified in the left ear with a unique identification numbered plastic bangle tag, weighed, and sex determined. After weighing and identifying, cattle were held in large receiving pens for 12 to 72 hours with ad libitum access to grass hay (CP = 9.3%; NDF = 71%) and fresh water. Any animals deemed clinically lame or morbid at this time were removed from the sample population, examined by the attending veterinarian, administered the appropriate treatment, and were not enrolled in the experiment. Within each arrival load, calves were weighed and sex determined (bulls vs steers) and sorted within sex from heaviest to lowest, then randomly assigned in groups of three to one of the three experimental treatments. This was done to ensure equal representation of bulls vs steers in each treatment group, as well as to distribute calf weights across treatments. Calves consisted of approximately 65% bulls and 35% steers and were evenly distributed across experimental groups.

Twenty four, 12.2 m x 30.5 m (40 ft x 100 ft) open air, dirt floor pens were used to house the cattle. Each pen contained 30.5 m (40 ft) of bunk space and shared an automatic water tank [h] with an adjacent pen. Pens were assigned to treatment in three blocks of eight pens per treatment, with a solid plywood barrier and an open pen separating pens assigned to differing vaccination groups. Pens containing different treatments did not share a water tank. In each time block of the experiment, there were 30 steers per pen and eight pens per treatment (n = 16 total pens per treatment for the experiment).

Calves were processed 12 to 72 hours after arrival and placed in their home study pen. Processing involved surgical castration of bull calves, tipping of horns, administration of a 7-way clostridial bacterin/toxoid injected subcutaneously in the neck per label directions [i], endectocide [j] injected subcutaneously based on truck load average weight, and assigned to one of three treatment groups. The treatments were as follows: INF were administered a 3-way intranasal vaccine [a] and combination *Mannheimia haemolytica* toxoid with MLV BVDV [b] subcutaneously on day 1 of processing followed by a 5-way MLV respiratory vaccine [c] on day 14; PYR were administered a combination 5-way MLV respiratory vaccine with *Mannheimia haemolytica* bacterin/toxoid [d] subcutaneously on day 1 of processing followed by a 5-way MLV respiratory vaccine [e] on day 14; VIS were administered a combination 5-way MLV respiratory vaccine with *Mannheimia haemolytica* bacterin/toxoid [f] subcutaneously on day 1 of processing followed by a 5-way MLV respiratory vaccine [g] on day 14 per label instructions. No metaphylaxis was administered to the cattle. On day 14, calves were weighed by pen and individual body weights were recorded on each animal. At the time of individual weighing, steers were revaccinated according to their respective experimental groups.

Nutrition:

The diet consisted of 10% dry-rolled corn, 54.8% sweet feed concentrate[k], 5.2% dry supplement (formulated to deliver 30 g/ton monensin and 8.25 g/ton tylosin phosphate to the final ration), and 30% chopped prairie hay. Bunks were managed so that no feed remained at 0530 when they were read. Feed was scheduled daily after bunks were read. Pens were fed twice daily at 0700 and 1300, and 50% of the days feed call was delivered at each feeding. A horizontal mixer and delivery wagon was used to feed all pens. Representative samples of the ration were taken once weekly and dry matter analysis was performed on each at that time. At trial termination, all dried feed samples were ground to 2 mm particle size, composited, and nutrient analysis performed [l]. On days that cattle were weighed, any remaining feed was collected from the bunk, weighed, and a dry matter analysis was performed to determine feed removed.

On day 60, cattle were weighed by pen, and individual body weights were recorded for every animal. Daily pen feed intake was recorded in a computer program [m] bunk management system. Individual morbidity, antimicrobial treatments, and mortality were recorded daily using spreadsheet software. [n]

Animal evaluation and treatment:

Cattle were evaluated once daily beginning at 0700 for clinical signs of respiratory disease by two evaluators who were blinded to treatments. Cattle were evaluated following standard WSBRC feedlot protocol for depression, appetite, respiratory signs, and temperature. The subjective evaluation was also assigned a severity score (1=mild, 2=moderate, 3=severe, 4=moribund) [21]. Cattle evaluated as having a clinical score of 1 or 2 were required to have a rectal temperature greater than or equal to 40°C (104°F)

to receive an antimicrobial treatment for clinical BRD. Cattle exhibiting a clinical score of 3 or 4 were administered antimicrobial treatment regardless of rectal temperature. All cattle were returned to their original pen unless it was determined by the attending veterinarian that their ability to thrive in their home pen had been compromised due to severe respiratory distress, lameness, or other medical condition.

Calves eligible for antimicrobial treatment were administered tulathromycin [o] at 1.1 mL/45.45 kg (1.1 mL/100 lb) of body weight with a post-treatment interval of 10 days. After the first post-treatment interval, calves which met the criteria for treatment were administered ceftiofur crystalline free acid [p] at 1.5 mL/45.45 kg (1.5 mL/100 lb) of body weight with a 7-day post-treatment interval. After the second post-treatment interval, if cattle were determined to be clinically ill danofloxacin [q] was given at 2.0 mL/45.45 kg (2.0 mL/100 lb) of body weight. After treatment with danofloxacin [q] , cattle were no longer eligible for antimicrobial treatment for clinical respiratory disease. For humane reasons, post-treatment interval was decreased by 50% if an animal received a clinical score of 3 or 4 (i.e., tulathromycin [o] ≥ 5 days or ceftiofur crystalline free acid [p] ≥ 4 days). All calves with non-respiratory health issues requiring antimicrobial treatment were treated according to standard disease treatment protocols for the WSBRC.

Cattle receiving three antimicrobial treatments for clinical BRD were weighed 14 days after their third treatment. If the animal lost weight from the recorded weight at the time of the third antimicrobial treatment, the animal met the WSBRC case definition of a chronic. For all animals that died during the study, a field necropsy was conducted by veterinarians from OSU to determine the cause of death.

Data were analyzed using mixed models in a commercial statistics package.[r] Categorical variables (e.g., mortality, morbidity) were analyzed with a general linear mixed models procedure[s], and continuous variables (e.g., average daily gain, daily feed intake) were analyzed with a mixed procedure.[t] The mixed model included a fixed effect of BRD treatment, and random effects of replication (1 or 2) and arrival lot within replicate. Pen was the experimental unit for all variables analyzed. Deads-in analysis was used to calculate ADG, DMI, and G:F. Head days were used as the denominator of calculation of daily dry matter intake (DMI). Deads-In ADG and G:F were calculated as follows:

DI_ADG = ((No. calves present at day 60 * 60-d pen gain)/No. calves on day 1)/60 DI_G:F = DI_ADG/ DMI.

Results

The criteria required for removing an animal from the data set in this experiment were as follows: severe respiratory distress, severe lameness, neurological abnormalities, or death. All cattle that were diagnosed as pneumonia on gross post mortem examination from d 0 to 60 were used in the calculation of mortality rate. A total of 103 animals died during the course of the study. There were 22 animals that met the case definition of chronic as previously described (15 from the first replicate and seven from the second replicate). Of the 22 chronic cases, nine subsequently died from severe respiratory disease or were euthanized following accepted methods (five from the first replicate and four from the second replicate). An animal was euthanized if an animal was classified as chronic, was showing no response to treatment and/or appeared to be suffering An additional ten animals were removed from study for severe respiratory distress that did not fit meet the case definition for chronic (six from the first replicate and four from the second replicate). One of those calves eventually died. A total of 16 animals were removed for severe lameness including one animal that required a claw amputation due to extensive septic arthritis of the distal interphalangeal joint (eight from the first replicate and eight from the second replicate; claw amputation from the first replicate; one died after removal from the second replicate). One animal was removed for neurological abnormalities (from the second replicate). The majority of mortality was due to respiratory disease. Only five animals died from non- respiratory causes (three digestive/bloats, one infected stifle and one from unknown causes).

Body weights, ADG, DMI, and feed conversion of calves in a 60-day receiving period are recorded in Table 1. There was no difference among treatment for initial shrunk BW (P = 0.84). No difference in d 60 BW was measured (P = 0.94). Average daily gain from d 0 to 60 did not differ among the three treatments (P = 0.69). Dry matter intake from d 0 to 60 was similar among all treatments (P = 0.83), and subsequently no differences in G:F was measured among treatments (P = 0.27). There were no differences among the three vaccine treatments for any performance variables measured.

Table 1. Body weights, ADG, DMI/hd, and feed conversion of calves in a 60 d receiving period when administered various commercially available multivalent MLV respiratory vaccines on arrival.

	INF	PYR	VIS	SEM	*P*-Value
BW (kg)					
d 0	216.80	216.80	215.50	20.45	0.84
d 60	280.50	279.50	279.50	18.20	0.94
ADG (kg/d)					
d 0-60[1]	1.00	0.95	0.95	0.05	0.69
DMI/hd (kg)					
d 0-60[1]	5.82	5.91	5.91	0.41	0.83

G:F					
d 0-60[1]	0.175	0.167	0.171	0.006	0.44
[1]Deads in analysis					

ment were similar (P = 0.56) for all vaccine treatments.

The number of animals that met the case definition for chronic in relation to the number of animals enrolled into a experimental group did not differ (P = 0.55) across all treatment groups. Mortality percentage for INF was 4.4 ± 1.9% which was numerically lower than PYR (6.4 ± 2.7%, p=.14)

Table 2. Morbidity, mortality, chronics and total costs observed in calves during a 60 d receiving period when administered various commercially available multivalent MLV viral respiratory vaccines program on arrival.

	INF	PYR	VIS	SEM	*P*-Value
Number of Heads	483	481	478	-	-
1st Treats, %	42.7	44.1	46.6	4.62	0.49
Days to 1st Treat	11.7	12.2	13.9	1.11	0.13
2nd Treats, %	8.0[a]	10.1[ab]	13.6[b]	4.32	0.01
Days to 2nd Treat	25.6	26.3	27.9	2.73	0.78
3rd Treats, %	3.7[a]	3.7[a]	6.7[b]	2.27	0.09
Days to 3rd Treat	31.1	31.5	35.0	2.54	0.56
Deads, %	4.4	6.4	7.6	3.10	0.09+
Chronics, %	1.7	0.9	1.5	0.77	0.55
Processing	$5,908.68	$5,364.74	$5,604.36		
1st Rx	$5,919.09	$5,909.47	$6,277.84		
2nd Rx	$873.79	$997.01	$1,358.78		
3rd Rx	$419.22	$386.71	$718.12		
Mortality	$22,061.25	$31,768.20	$36,829.80		
Chronics	$3,017.98	$1,676.66	$2,665.78		
DMI (tons)	178.55	177.88	176.02		
Feed Cost	$31,635.49	$31,516.78	$31,187.22		
Total Cost	$69,835.50	$77,619.56	$84,641.90		
Cost/Head++	$144.59	$161.37	$177.08		
Difference	-	-$16.78	-$32.49		
[a,b] Columns with differing superscripts differ by less than $P < 0.05$.					

+see results for more in depth discussion

++ Deads in calcualtions as described above.

Morbidity and mortality data are recorded in Table 2. There was no difference among vaccine groups for percentage of animals receiving one antimicrobial treatment (P = 0.49). Days from processing to first treatment did not differ among vaccination treatments (P = 0.13). INF group had 8.0 ± 2.8% receiving a second antimicrobial treatment as compared to 13.6 ± 4.3% second treats for VIS (P = 0.01). The PYR group had 2.1% more cattle receiving a second antimicrobial treatment (p value=.24). PYR vaccine group was not different (P > 0.05) from VIS for percentage of cattle receiving a second antimicrobial treatment. Days to second antimicrobial treatment from processing were not different (P = 0.78) across all vaccine treatment groups. INF (3.7 ± 1.4%) and PYR (3.7 ± 1.4%) had fewer (P = 0.03) cattle requiring a third antimicrobial treatment than VIS (6.7 ± 2.3%), INF and PYR were not different (P > 0.05) from each other. Days from processing to third antimicrobial treatand trended toward significantly lower mortality than VIS (7.6 ± 3.1%, p=.09).

Discussion

With the introduction of longer acting antibiotics for use on the control of BRD in arrival cattle, the use of arrival vaccination programs have been put under more scrutiny. In a recent study delaying vaccination of high risk cattle had no adverse impact on no impact on health parameters and increased intakes [22]. These studies have primarily involved systemically administered vaccines and led to the development of this study. Two of the commonly used systemic modified-live viral and *Mannheimia hemolytica* bacterins were chosen for inclusion in this study. The limited space precluded the comparison of all of the current systemic modified-live viral combination products. While this study

cannot definitely attribute all the differences to the arrival program a previous unpublished study compared administration of two doses BoviShield Gold5/OneShot with the same intranasal/MLV program used in this study[u]. While there were weight randomization issues in that trial, there was a significant improvement from the program used in this study over the double BoviShield vaccinated cattle. Those cattle were also in the same class(high risk) as the calves in the current study. In addition, a recent article showed that another commonly used five way viral combination product had similar results in comparison cattle to the PYR group [23]. Due to the relatively short duration of this study, any potential long-term performance differences resulting from the different vaccination protocols were not able to be measured. All treatment groups exhibited similar first pull morbidity rates; therefore, it was concluded that all cattle were exposed to pathogens before and early post-arrival and were equally likely to experience initial clinical signs associated with BRD. However, due to the decrease in subsequent need of antimicrobial treatment for clinical BRD signs in cattle receiving the INF treatment, these results suggest that cattle that were administered the combination intranasal vaccine [a] and parenteral BVDV/ *Mannheimia haemolytica* toxoid [b] experienced greater protection from BRD-causing pathogens [24].

Most vaccines are administered parenterally are designed to primarily elicit a systemic immune response commonly measured by increased serum antibody titers. Differences in interferon release between vaccines administered parenterally or intranasally have been previously demonstrated [2,10,15-17]. The ability of interferon to decrease viral replication is well known [25-31]. The higher level of interferon in the respiratory tract elicited by intranasal vaccination is possibly one of the mechanisms by which differences were seen in this study since over 90% of all infectious pathogens enter the body through mucosal surfaces [2]. In the case of BRD, these pathogens enter through a mucosal route (i.e. the respiratory tract) and colonize the respiratory epithelium where they can elicit their detrimental effects to the host's cells. Vaccination of mucosal surfaces presents a means to provide protective immunity at the source of infection, rather than relying on an systemic immune response to be mounted after pathogen colonization, reproduction, and entrance into vital body tissues has occurred [4, 7-16].

Furthermore, research has demonstrated MLV combination viral vaccines that contain a *Mannheimia haemolytica* bacterin/toxoid have the potential to result in antigen interference between BHV-1 and *M. haemolytica*. Researchers reported observing antigen interference in calves entering a feedlot (n=2,324; BW=250 to 350 kg) co-administered a MLV BHV-1/PI3 vaccine with a *Pasteurella haemolytica* bacterin [18]. This phenomenon of antigen interference between coadministered BHV-1 and *M. haemolytica* was also observed by others [19]. Scientists have proposed that if these two antigens were administered via different routes (i.e., subcutaneous and intranasal), this antigen interaction would be mitigated [19]. This proposed interaction has been observed in calves vaccinated intranasally with BHV-1 antigen and a *M. haemolytica* bacterin administered subcutaneously. The calves exhibited similar *M. haemolytica* titers post-vaccination when compared to calves that receiving only the *M. haemolytica* bacterin [20].

In the current study, cattle receiving the INF treatment had BHV-1 administered intranasally with the *M. haemolytica* bacterin administered subcutaneously; in contrast to the PYR and VIS treatment groups receiving all antigens at one subcutaneous injection site. This difference in site of administration could have led to the clinical observations and differences measured in the INF treatment group.

Although intakes throughout the study did not differ, feed intakes in the first 3-7 days post-arrival were not assessed. Studies have shown that early feed intake is important in minimizing BRD in high stressed cattle [22,32,33]. Research has shown that systemically administered viral vaccines may decrease feed intake when administered on arrival to cattle [34,35]. However, the intranasal vaccine used in this study has been shown to either have no adverse impact on intakes or actually stimulate appetite in arrival cattle [2,36-38]. This study could not determine if this was a factor.

Stimulation of mucosal immunity through vaccination procedures in cattle has the potential for great benefit; however, it is important to note that dosages administered into the respiratory tract must be given in concentrations capable of overcoming the innate clearance mechanisms present on mucosal surfaces [38,39]. Mucosal vaccination procedures have the potential ability to confer a more rapid and protective immune response in cattle, in-turn reducing the need for antimicrobial therapy and lowering costs associated with animal losses. Additional benefits would include improved animal performance and animal well-being, less labor investment, and a possible reduction in injection site reactions causing losses in carcasses. Further investigation needs to be conducted to identify more accurately our understanding of the complex nature of antigen interaction and the true long-term immunological protection conveyed by mucosal vaccination.

Conclusion

As shown in this study, the choice of arrival vaccination protocols that include concurrent administration of multivalent MLV respiratory vaccines in combination with *M. haemolytica* bacterin/toxoids in high stressed cattle could be have a significant impact on re-treatment and mortality rates in newly-received cattle in feedlots. Utilizing a program that includes intranasal viral vaccination as part of the program could result in improved animal health and well-being, decreased use of therapeutic antimicrobials, fewer losses associated with morbidity, mortality, and lowers cost due to better cattle performance.

Acknowledgements

This manuscript represents a portion of a thesis submitted by Cody Hixon to Oklahoma State University Department of Animal Science as partial fulfillment of the requirements for a Master of Science degree.

Supported in part by Zoetis Inc.

Footnotes

a. Inforce™ 3; Zoetis Inc; Florham Park, NJ

b. OneShot® BVD; Zoetis Inc; Florham Park, NJ

c. BoviShield® Gold 5; Zoetis Inc; Florham Park, NJ

d. Pyramid® 5 + Presponse; Boehringer-Ingleheim; St. Joseph, MO

e. Pyramid® 5, Boehringer-Ingleheim; St. Joseph, MO

f. Vista® Once SQ; Merck/Intervet; Omaha, NE

g. Vista® 5; Merck/Intervet; Omaha, NE

h. J360 continuous flow 20 gallon capacity; Johnson Concrete Products, Hastings, NE

i. UltraChoice™ 7; Zoetis Inc; Florham Park, NJ

j. Dectomax® injectable dewormer, Zoetis Inc; Florham Park, NJ

k. Cargill, Dalhart, TX

l. ServiTech Laboratories; Dodge City, KS

m. MicroBeef's Read-N-Feed, MWI/MicroBeef, Amarillo, TX

n. Excel 2013, Microsoft Corp., Redmond, WA

o. Draxxin® Zoetis Inc, Florham Park, NJ

p. Excede® Zoetis Inc, Florham Park, NJ

q. Advocin™ Zoetis Inc, Florham Park, NJ

r. SAS, version 9.3, SAS Institute, Cary, NC

s. GLIMMIX, SAS, version 9.3, SAS Institute, Cary, NC

t. Proc MIXED, SAS, version 9.3, SAS Institute, Cary, NC

u. data on file: study number 12PETINF01, Zoetis, INC.

References

1. NASS. 2010. Cattle death loss. 2014.

2. Griffin D. Etiology, pathogenesis, and clinical signs of bovine respiratory disease. Bovine Respiratory Disease: Sourcebook for the Veterinary Professional. Veterinary Learning Systems Co. 1996.

3. Loerch SC, Fluharty FL. Physiological changes and digestive capabilities of newly received feedlot cattle. J Am Sci 1999, 77: 1113-1119.

4. Bowersock TL, Martin S. Vaccine delivery to animals. Adv. Drug Delivery Rev. 1999, 38: 167-194.

5. Perino LJ. Immunology and prevention of bovine respiratory disease. Bovine Respiratory Disease: Sourcebook for the Veterinary Professional. Veterinary Learning Systems Co. 1996.

6. Mackenzie AM, Drennon M, Rowan TG. Effect of transportation and weaning on humoral immune response of calves. Res Vet Sci 1997, 63: 227-230.

7. Kimman TG, Westenbring F, Straver PJ. Priming for local and systemic antibody memory responses to bovine respiratory syncytial virus; effect of amount of virus, virus replication, route of administration and maternal antibodies. Vet Imm and Immunopath. 1989, 22: 145-160.

8. Ellis JA, Gow SP; Goji N. Response to experimentally induced infection with bovine respiratory syncytial virus following intranasal vaccination of seropositive and seronegative calves. *JAVMA* 2010, 236(9): 991-999.

9. Ellis JA, Gow S, Keith West. Response of calves to challenge exposure with virulent bovine respiratory syncytial virus following intranasal administration of vaccines formulated for parenteral administration. JAVMA. 2007, 230(2): 233-243.

10. Todd JD. Immune responses to parenteral and intranasal vaccinations. JAVMA. 1993, 163(7): 807-809.

11. Kucera, CJ, Beckenhauer WD. Time required to stimulate protection with intranasal administration of a temperate-sensitive , infectious bovine rhinotracheitis virus vaccine. Vet Med. 1976, 83-87.

12. Zygraich N Huygelen C Vascobioinic. Immunity studies in calves vaccinated with a multivalent live respiratory vaccine composed of IBR, parainfluenza 3 and bovine adenovirus 3. Proceedings international congress of IABS. 1976, 33: 379-383.

13. Zygraich N, Huygelen C, Vascobioinic E. Vaccination of calves against infectious bovine rhinotracheitis using a temperature sensitive mutant. Proceedings international congress of IABS. 1974, 26: 8-14.

14. Zygraich N, Lormann M, Vasccoboinic E. In vivo and in vitro properties of a temperature sensitive mutant of infectious bovine rhinotracheitis virus. Res Vet Sci. 1974, 16: 328-335.

15. Todd JD, Volenec FM, Paton IM. Intranasal vaccination against infectious bovine rhinotracheitis: studies on early onset of protection and use of the vaccine in pregnant cows. JAVMA. 1971, 159: 1370.

16. Gerber JD, Marron AE, Kucera CJ. Local and systemic cellular and antibody responses of cattle to infectious bovine rhinotraceitis virus vaccines administered intransally or intramuscularly. AJVR. 1978, 39(5): 745-760.

17. Kucera CJ, White RG, Beckenhauer WH. Evaluation of the safety and efficacy of an intranasal vaccine containing a temperataure-sensitive strain of infectious bovine rhinotracheitis virus. AJVR. 1978, 39: 60-699.

18. Harland RJ, Potter AA, Little van den Hurk SD. The effect of subunit or modified live bovine herpesvirus-1 vaccines on the efficacy of a recombinant Pasturella haemolytica vaccine for the prevention of respiratory disease in feedlot calves. Can Vet J. 1992, 33: 734-739.

19. Cortese VS, Seeger JT, Stokka GS. Serilogical response to *Mannheimia haemolytica* in calves concurrently inoculated with inactivated or modified-live preparations of *M. haemolytica* and viral combination vaccines containing modified-live bovine herpesvirus type 1. AJVR 2011, 72: 1541-1549.

20. Stoltenlow C, Cortese VS, Seeger JT. Immunologic response of beef calves to concurrent application of modified-live viral vaccine (intranasal and systemic administration) and systemically administered Mannheimia haemolytica bacterin-leukotoxoid. Bovine Prac. 2011, 45: 132-138.

21. Step DL, Krehbiel CR, Burciaga-Robles LO. Comparison of single vaccination ;versus revaccination with a modified-live virus vaccine containing bovine herpesvirus-1, bovine viral diarrhea virus (types 1a and 2a), parainfluenza type 3 virus, and bovine respiratory syncytial virus in the prevention of bovine respiratory disease in cattle. JAVMA. 2009, 235: 580-587.

22. Richeson JT, Beck PA, Poe KD. Effect of administration of a modified-live virus respiratory vaccine and timing of vaccine on health and perfromance of high-risk beef stocker calves. Bov Prac. 2015, 49(1): 37-42.

23. Rogers KC, Miles DG, Hughes HD. Effect of initial respiratory viral-bacterial combination vaccine on performance, health, and carcass traits of auction-market derived feedlot heifers. Bov Prac. 2015, 49(1): 43-47

24. Potter A, Gerdts V, Little-van den Hurk SD. Veterinary vaccines: alternatives to antibiotics? Am Health Res Rev. 2008, 9: 187-199.

25. Ank N, Iversen MB, Bortholdy C. An important role for type III interferon (IFN-lambda/ IL-28) in TLR-induced antiviral activity. J. Immuno. 2008, 180: 2474 –2485.

26. Diaz-San Segundo F, Weiss M, Perez-Martin E. Antiviral activity of bovine type III interferon against foot-and-mouth disease virus. J Virol. 2011, 413: 283–292.

27. Kotenko SV, Gallagher G, Baurin VV. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat. Immunol. 2003, 4: 69 –77.

28. Mordstein M, Neugebauer E, Ditt V. Lambda interferon renders epithelial cells of the respiratory and gastrointestinal tracts resistant to viral infections. J. Virol 2010, 84: 5670 –5677.

29. Okabayashi T, Kojima T, MasakiT. Type-III interferon, not type-I, is the predominant interferon induced by respiratory viruses in nasal epithelial cells. Virus Res. 2011, 160: 360 –366.

30. Semnani MJ, Kabbur MB, Jain NC. Activation of bovine neutrophil functions by Interferon-gamma, Tumor Necrosis Factor-alpha and Interleukin1-alpha. Comp Hematol Int. 1993, 381-388.

31. Nedergaard Grell S, Tjørnehøj T, Larsen LE. Marked induction of IL-6, haptoglobin and IFNγ following experimental BRSV infection in young calves. Vet Immun Immunopath. 2005, 103(3-4): 235-245.

32. Stokka G, Perino L. Modified-live vs. killed vaccines. Beef. 2000, 37: 8.

33. Karisch B. Considerations for Managing Stocker Cattle: Impacts on BRD. Cattle Business in Mississippi. 2015.

34. Cooper VL, Brodersen BW. Bovine Respiratory Disease. Veterinary Clinics: Food Animal Practice. 2010, 26(2).

35. Richeson JT, Beck PA, Gadberry MS. Effects of on-arrival versus delayed modified live virus vaccination on health, performance, and serum infectious bovine rhinotracheitis titers of newly received beef calves. JAmS 2014, 86(4): 999-1005.

36. Duff GC, Malcolm-Callis KJ, Walker DA. Effects of intranasal versus intramuscular modified live vaccines and vaccine timing on health and performance by newly received beef cattle. 2000, 20: 66.

37. Cummins J. Keeping cattle healthy. Feedlot management. 1983.

38. Caswell JL. Failure of respiratory defenses in the pathogenesis of bacterial pneumonia of cattle.Vet Path. 2014, 51(2): 393-409.

39. Lillie LE, Thomson RG. The Pulmonary Clearance of Bacteria by Calves and Mice. Can. J Comp Med. 1972, 36: 129-137.