

# The effect of respiratory vaccine components and route of delivery on weight gain and inflammatory response in suckling beef calves

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## Abstract

Two randomized studies of Angus beef calves (n = 110) from 2 Iowa locations were used to determine the effect of vaccine type and route of administration on weight gain and inflammatory response. The first vaccine contained avirulent-live *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3), and was administered intranasally (IN group). The second vaccine contained an adjuvanted *M. haemolytica* (type A1) toxoid and was administered subcutaneously (SC group). Control calves (CON) were given the same volume (2 mL) of sterile saline SC as other calves. At the time of vaccination (day 0), calf body weight (BW) and body temperature (BT) were recorded, and a blood sample was collected for serum haptoglobin analysis. Blood collection and BT measurement were repeated on days 1, 2, and 3 while BW was recorded on days 3 and 21 (location 1) or 24 (location 2) after vaccination. A final BW was taken at weaning at both locations. Changes in BW among calves during the first 3 days after vaccination were not significantly different across treatment groups. At location 1, calves given SC vaccine had a higher average BT compared to IN-vaccinated calves ( $P < 0.01$ ). Body temperature also tended to be higher in SC-vaccinated calves ( $P = 0.08$ ) compared to CON calves. At location 2, BT was not different between vaccinated groups, but vaccinated calves had higher BT compared to CON calves ( $P < 0.01$ ). Over the 21-day trial period at location 1, average daily gain (ADG) in calves given SC vaccine was lower compared to CON calves ( $P = 0.04$ ). At location 2, ADG was not significantly different among treatments, but IN calves had heavier final weights compared to other treatment groups ( $P < 0.01$ ). Serum haptoglobin levels were higher for SC calves compared to IN and CON calves on days 1, 2, and 3 following vaccination ( $P < 0.01$ ). Mean weight gain and ADG from vac-

ination through weaning tended to be greater ( $P = 0.06$ ) for IN calves at location 1, but were not different at location 2.

**Key words:** beef calves, vaccination, intranasal, haptoglobin, weight gain

## Résumé

Deux études randomisées sur des veaux d'engraissement Angus (n = 110) provenant de 2 sites dans l'Iowa ont été utilisées pour déterminer les effets du type de vaccin et de la route d'administration sur le gain de poids et la réponse inflammatoire. Le premier vaccin contenait *Mannheimia haemolytica* (type A1) avirulent-vivant et *Pasteurella multocida* (type A3), et a été administré par voie intranasale (groupe IN). Le second vaccin contenait une anatoxine *M. haemolytica* (type A1) avec adjuvant et a été administré par voie sous-cutanée (groupe SC). Le même volume (2 mL) de saline stérile a été administré SC aux veaux de contrôle (CON) comme aux autres veaux. Au moment de la vaccination (jour 0), le poids corporel (BW) et la température corporelle (BT) ont été enregistrés, et un échantillon de sang a été collecté pour l'analyse de l'haptoglobine sérique. La collection de sang et la mesure de BT ont été répétées aux jours 1, 2, et 3 tandis que le BW a été mesuré aux jours 3 et 21 (site 1) ou 24 (site 2) après la vaccination. Un BW final a été mesuré au sevrage sur les deux sites. Les changements de BW parmi les veaux pendant les 3 premiers jours suivant la vaccination n'ont pas été significativement différents entre les groupes de traitement. Au site 1, les veaux ayant reçu le vaccin par voie SC avaient une BT significativement plus élevée que celle des veaux vaccinés par voie IN ( $P < 0.01$ ). La température corporelle tendait également à être plus élevée chez les veaux vaccinés par voie SC ( $P = 0.08$ ) que chez les veaux CON. Au site 2, la

BT n'était pas différente entre les groupes vaccinés, mais les veaux vaccinés avaient une BT significativement plus élevée que celle des veaux CON ( $P < 0.01$ ). Durant la période d'essai de 21 jours au site 1, le gain moyen quotidien (GMQ) des veaux vaccinés par voie SC était plus faible que celui des veaux CON ( $P = 0.04$ ). Au site 2, le GMQ n'était pas significativement différent entre les traitements, mais les veaux vaccinés par voie IN ont eu des poids finaux significativement plus élevés en comparaison des autres groupes de traitement ( $P < 0.01$ ). Les niveaux d'haptoglobine sérique étaient significativement plus élevés chez les veaux vaccinés par voie SC vs IN et CON aux jours 1, 2, et 3 suivant la vaccination ( $P < 0.01$ ). Le gain de poids moyen et le GMQ à partir de la vaccination jusqu'au sevrage tendaient à être plus élevés ( $P = 0.06$ ) chez les veaux vaccinés par voie IN au site 1, mais n'ont pas été différents au site 2.

### Introduction

Bovine respiratory disease (BRD) has been referred to as a "syndrome" or "complex" due to the multifactorial relationships that exist between the infectious agents, the level of management applied to the calf, its preparation for weaning and immune status, and stress level in the environment.<sup>10</sup> Calf immune system management and the prevention of BRD is a life cycle process that begins at the cow-calf operation. Proper vaccine selection, safety, and timing of delivery are crucial to this effort. Because of this, vaccination of suckling beef calves against BRD is a relatively common management practice in the United States.<sup>17</sup>

Surveys of both cow-calf producers and veterinarians have provided insight into the incidence and risk factors associated with BRD in suckling beef calves.<sup>18,19</sup> This research indicates that approximately 20% of cow/calf producers saw evidence of preweaning BRD on their farm or ranch. Risk factors for the development of BRD included addition of new animals, a history of calf diarrhea on the operation, larger herd size, and management practices that increased animal contact or calf stress, such as estrus synchronization and creep feeding. The most commonly reported bacterial pathogens identified by practitioners included *Mannheimia haemolytica* (60%), *Pasteurella multocida* (53%), and *Mycoplasma bovis* (37%).<sup>19</sup> It should then come as no surprise that 87% of veterinarians in this survey recommended vaccination against BRD pathogens in suckling calves.

While vaccination can be a critical component in preventing BRD in young calves, the potential for undesirable side effects does exist. These effects may be due to the physical delivery of the vaccine causing injection site lesions,<sup>8</sup> a relatively high level of endotoxin contamination in gram-negative vaccines,<sup>5</sup> or an increase in acute phase protein levels following vaccination.<sup>15</sup> While injection-site lesions represent a permanent quality defect, the effects of endotoxin and acute phase proteins tend to occur rapidly and are relatively short-lived. Temporary changes in normal behavior, such

as decreased self-grooming, increased periods of inactivity, slowed rumination, and decreased intake of hay and feedlot rations have been described.<sup>5,15</sup> These effects may be especially problematic in the suckling calf due to its relatively young age and low body weight.

The objective of this trial was to compare the inflammatory response and weight gain of suckling beef calves following vaccination with 1 of 2 respiratory vaccines or sterile saline. Two studies were conducted at 2 different Iowa locations. The variables of interest included changes in calf body temperature, acute phase protein (haptoglobin) level, weight gain over a 21-day period, and weaning weight following vaccination.

### Materials and Methods

These studies were conducted between 18 November, 2013 and 9 January, 2014. All procedures performed within the scope of this project were reviewed and approved by the Iowa State University Institutional Animal Care and Use Committee (IACUC Log #11-13-7674-B). Fall-born calves were utilized for this project, and were located at the Iowa State University Beef Teaching Farm ( $n = 50$ ; location 1) near Ames and at the ISU McNay Research Unit ( $n = 60$ ; location 2) near Chariton, IA. The emphasis for genetic selection and calf production differed markedly at these units. The herd at the ISU Beef Teaching Farm selected animals with an emphasis on maternal traits for female production, while the McNay Unit emphasized carcass traits, such as marbling and ribeye area.

Calves at location 1 ranged in age from 46 to 103 days and weighed an average of 228 lb (103.7 kg), with a range of 114 to 348 lb (52 to 158.2 kg). Location 2 calves were 84 to 119 days of age at the beginning of the trial with an average weight of 281.3 lb (127.9 kg), and a range of 190 to 385 lb (86.4 to 175 kg). Of the 110 total calves used in this study, 105 were purebred Angus with the remainder Angus-Simmental cross. All calves were individually identified using a unique ear tag and tattoo.

At both locations, calves were assigned to a treatment group using a randomization table constructed in a commercially available spreadsheet program.<sup>a</sup> Calves were randomly assigned to treatment based on the order in which they entered the squeeze chute. Calves were divided so that each vaccine was represented equally, while approximately one-half the number of vaccinated calves remained as controls at each location. On the first day of the trial (day 0), calves assigned to the first treatment group received an intranasal (IN) avirulent live vaccine<sup>b</sup> containing *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3). The second treatment group was vaccinated subcutaneously (SC) with a vaccine<sup>c</sup> containing an adjuvanted leukotoxin from *Mannheimia haemolytica* (type A1). Both vaccines were rehydrated and administered according to label directions, using individual single-dose syringes, needles, or nasal cannulas. Control calves (CS) were given an equal volume (2 mL) of sterile saline<sup>d</sup> SC.

### Sample collection

In addition to being vaccinated on day 0, individual body weights (BW) and body temperatures (BT) were also recorded for all calves at both locations. A 10 mL jugular blood sample was collected from each calf using evacuated tubes<sup>e</sup> for serum haptoglobin (SH) analysis. Individual blood samples and BT were collected again on days 1 and 2 after vaccination. On day 3 after vaccination, individual blood sampling, BT, and BW were again repeated. On day 21, calves were again individually weighed to evaluate total BW changes from the time of treatment allocation on day 0. Calves were not separated from their dams prior to being sorted for weighing. After each handling for data collection, calves were reunited with their dam at both locations, and housed as a single group, regardless of vaccine treatment.

Following collection, blood samples were kept on ice in an insulated container while being transported back to Iowa State University for analysis of SH levels. Blood samples were centrifuged at 2,100 x g for 20 minutes at 68 °F (20 °C). Serum was then decanted and stored frozen at -4 °F (-20 °C) until all samples were collected and could be analyzed as 1 group. A commercial ELISA test kit<sup>f</sup> was utilized to determine individual SH levels for each time of collection. SH levels were reported out as µg/mL of serum for both locations.

Calves at location 1 had access to creep feed at approximately 3 to 4 months of age, continuing through weaning, while calves at location 2 did not receive preweaning creep feed. Due to the cold weather and relatively high cow maintenance costs during this time of year, calves at both locations were early weaned. This is an annual management practice at both locations, and is unrelated to the current study protocol. Calves were weaned on day 80 and 59 of the study at locations 1 and 2, respectively. Individual weaning weights were recorded as previously described on the day of weaning, and these weights were used to calculate total gain and average daily gain (ADG).

### Statistical analyses

Data were analyzed using the Glimmix procedure of SAS<sup>g</sup> and linear mixed models with vaccine group effects, or vaccine group effects over time, as the primary independent variables. Statistical significance was considered for a  $P$ -value of  $\leq 0.05$ ; however, because of the relatively low effective statistical power, pair-wise comparisons among treatments were evaluated when  $P$ -values for overall treatment effects were less than or equal to 0.1. Repeated measures analyses were used to evaluate the effects of vaccine treatment over time on calf weight change, BT, and SH levels. Means in BW at treatment allocation, change in BW by day 3 after vaccination, and ADG over the entire 21-day period were evaluated for differences by vaccine group. Due to differences in genetic selection, time of year the trial was conducted, and calf management differences (weaning date and use of creep feed), each location was evaluated independently and the data were not pooled for statistical analysis. Statistical sig-

nificance was set at  $P \leq 0.05$ , and a tendency was declared when  $P > 0.05 \leq 0.10$ .

## Results

Of the 50 calves enrolled on day 0 at location 1, 20 calves received IN vaccine, 20 calves were administered SC vaccine, and 10 control calves received sterile saline. At location 2, 60 calves were enrolled with 21 receiving IN vaccine, 23 receiving SC vaccine, and 16 were administered sterile saline. The uneven allotment between vaccinates at location 2 was due to an error in treatment assignment on day 0. Average cow age was not different across calf treatment at either location. At location 1, dams averaged 5.2 years, 5.7 years, and 7 years for IN, SC, and CS calves, respectively. At location 2, average cow age for IN, SC, and CS-vaccinated calves averaged 9.1, 7.9, and 8.1 years, respectively.

All calves at location 1 survived through day 21 after vaccination. Two calves at location 2 were removed from the study prior to the recording of BW; 1 calf was treated for infectious arthritis and the second calf died. Body weights were taken on day 21 at location 1, but due to inclement weather at location 2, weights were not recorded until day 24 after vaccination. No adverse reactions or injection site swellings were noted for any of the products.

There was no difference ( $P \geq 0.05$ ) in initial BW by treatment group on day 0 or body weight changes over the first 3 days following vaccination at either location (Tables 1 and 2). Due to the process of daily sorting the calves from the cows and collecting weight data, calves in all groups at both locations lost weight over the initial 3-day period; however, there were significant differences in BT at both locations during the same period. At location 1, SC-vaccinated calves had higher ( $P < 0.01$ ) average BT compared to IN-treated calves (Table 1). Calves in the SC group also tended ( $P = 0.08$ ) to have higher body temperature compared to CS calves over the same time period. Body temperature was not different between IN- and CS-treated calves at location 1. At location 2, BT differences between IN- and SC-treated calves were not significant (Table 2). However, calves in both treatment groups exhibited higher ( $P < 0.01$ ) average BT compared to controls.

Depending upon calf location, significant differences were noted in calf weight gain by day and ADG over the initial 3 weeks of the trial. At location 1, calves in the SC group had lower ( $P = 0.04$ ) ADG over the 21 day trial period compared to CS calves (2.25 vs 2.78 lb; 1.02 vs 1.26 kg) (Table 1). Although overall ADG was not different among treatments over the 24 days after vaccination at location 2, calves in the IN group were heavier ( $P < 0.01$ ) than calves in either the SC or CS groups at 24 days after vaccination (Table 2).

The acute phase response produced by the vaccines in this trial was evaluated using SH levels in the calves. On the day of vaccination, SH levels were similar and essentially 0 µg/mL across all treatment groups at both locations. However, for 3 days following vaccination, there was a significant

**Table 1.** Effect of vaccine type and route of delivery on suckling calf performance at location 1 (model adjusted means  $\pm$  SE).

Parameter	Treatment group			P-value for treatment effects
	IN	SC	CS	
Initial weight (lb)	225.3 ( $\pm$ 11.46)	237.1 ( $\pm$ 11.46)	225.4 ( $\pm$ 16.26)	0.73
Day 3 weight (lb)	224.4 ( $\pm$ 12.06)	233.5 ( $\pm$ 12.06)	222.8 ( $\pm$ 17.06)	0.15
Weight change, days 0 to 3 (lb)	- 0.90 ( $\pm$ 1.42)	- 3.65 ( $\pm$ 1.42)	- 2.60 ( $\pm$ 2.01)	0.39
Final weight (lb)	279.6 ( $\pm$ 12.06)	284.4 ( $\pm$ 12.06)	283.8 ( $\pm$ 17.06)	0.87
Average daily gain (lb)	2.58 <sup>ab</sup> ( $\pm$ 0.15)	2.25 <sup>b</sup> ( $\pm$ 0.15)	2.78 <sup>a</sup> ( $\pm$ 0.21)	0.04
Body temp, days 0 to 3 ( $^{\circ}$ F)	102.05 <sup>a</sup> ( $\pm$ 0.12)	102.51 <sup>b</sup> ( $\pm$ 0.12)	102.15 <sup>ab</sup> ( $\pm$ 0.17)	< 0.01

Vaccine treatment groups were: **IN** = intranasal avirulent-live *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3) (Once<sup>®</sup> PMH IN, Intervet/Merck Animal Health, Summit, NJ); **SC** = subcutaneous adjuvanted *Mannheimia haemolytica* (type A1) (One Shot<sup>®</sup>, Zoetis Animal Health, Kalamazoo, MI); **CS** = subcutaneous saline controls.

Calves were vaccinated on day 0 of the trial.

Final weights were taken 21 days after vaccination.

<sup>abc</sup>Least squares means without common superscript differ.

**Table 2.** Effect of vaccine type and route of delivery on suckling calf performance at location 2 (model adjusted means  $\pm$  SE).

Parameter	Treatment groups			P-value for treatment effects
	IN	SC	CS	
Initial weight (lb)	284.3 ( $\pm$ 9.33)	281.3 ( $\pm$ 8.70)	277.2 ( $\pm$ 10.43)	0.88
Day 3 weight (lb)	281.8 ( $\pm$ 9.99)	274.6 ( $\pm$ 9.32)	275.3 ( $\pm$ 11.18)	0.85
Weight change, days 0 to 3 (lb)	- 2.50 ( $\pm$ 2.40)	- 6.74 ( $\pm$ 2.24)	- 1.88 ( $\pm$ 2.68)	0.29
Final weight (lb)	304.9 <sup>b</sup> ( $\pm$ 10.02)	296.3 <sup>a</sup> ( $\pm$ 9.32)	294.9 <sup>a</sup> ( $\pm$ 11.21)	< 0.01
Average daily gain (lb)	0.87 ( $\pm$ 0.15)	0.63 ( $\pm$ 0.14)	0.72 ( $\pm$ 0.17)	0.51
Body temp, days 0 to 3 ( $^{\circ}$ F)	101.92 <sup>a</sup> ( $\pm$ 0.12)	102.08 <sup>a</sup> ( $\pm$ 0.11)	101.41 <sup>b</sup> ( $\pm$ 0.13)	< 0.01

Vaccine treatment groups were: **IN** = intranasal avirulent-live *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3) (Once<sup>®</sup> PMH IN, Intervet/Merck Animal Health, Summit, NJ); **SC** = subcutaneous adjuvanted *Mannheimia haemolytica* (type A1) (One Shot<sup>®</sup>, Zoetis Animal Health, Kalamazoo, MI); **CS** = subcutaneous saline controls.

Calves were vaccinated on day 0 of the trial.

Final weights were taken 24 days after vaccination.

<sup>abc</sup>Least squares means without common superscript differ.

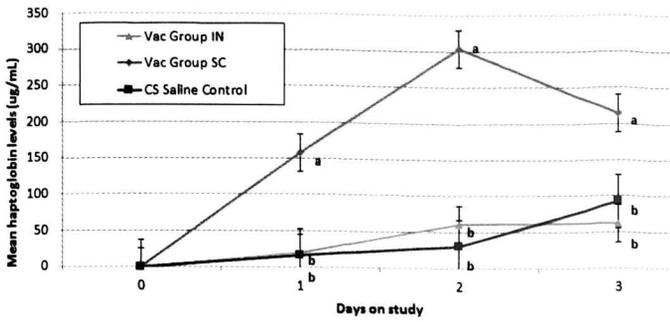
effect of treatment ( $P < 0.01$ ), time ( $P < 0.01$ ), and treatment-by-time interaction ( $P < 0.01$ ) at both locations (Figures 1 and 2). Calves vaccinated SC had significantly higher SH levels compared to IN-vaccinated and CS calves for 3 consecutive days after treatment. This increase in SH levels was consistent over this time period at both locations.

Total weight gain and average daily gain from the time of vaccination to weaning was determined at both locations. One calf at location 1 died from chronic bloat 8 days prior to weaning. Calf performance from the time of vaccination through weaning is shown for location 1 (Table 3). There was no significant difference in mean initial weight or in mean weaning weight on day 80 between treatment groups. However, IN-vaccinated calves tended to have higher ( $P = 0.06$ ) mean weight gain and ADG when compared to the other 2 treatment groups (deads excluded). When the dead calves were included in the analysis at location 1, ADG was similar

( $P \geq 0.41$ ) between treatment groups (Table 3). Likewise, performance parameters were similar ( $P \geq 0.38$ ) across treatments at location 2 (Table 4).

## Discussion

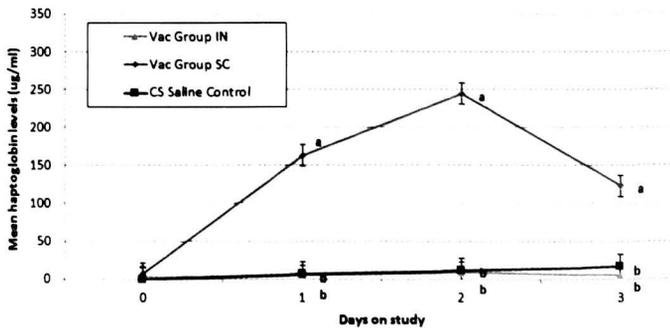
Vaccination against respiratory pathogens is one of the most common management procedures utilized to prevent losses associated with BRD. While complications due to vaccination are relatively rare, it is not totally without risk. This risk may take the form of injection-site reactions, increased body temperature, exaggerated acute phase protein response, and decreased weight gain. The negative effects demonstrated in this study may be transitory in nature, but performance (as determined by BW) was still affected as long as 80 days after vaccination at location 1, but weight gain through weaning did not differ at location 2.



**Figure 1.** Model-adjusted mean serum haptoglobin levels (µg/mL) and corresponding standard errors by study day for treatment groups (location 1). The effects of treatment, study day, and treatment by study day interaction were statistically significant.

Vaccine treatment groups were: IN = intranasal avirulent-live *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3) (Once® PMH IN, Intervet/Merck Animal Health, Summit, NJ); SC = subcutaneous adjuvanted *Mannheimia haemolytica* (type A1) (One Shot®, Zoetis Animal Health, Kalamazoo, MI); CS = subcutaneous saline controls. Calves were vaccinated on day 0 of the trial.

<sup>a,b</sup>Means without common superscripts within days differ ( $P < 0.01$ ).



**Figure 2.** Model-adjusted mean serum haptoglobin levels (µg/mL) and corresponding standard errors by study day for treatment groups (location 2). The effects of treatment, study day, and treatment by study day interaction were statistically significant.

Vaccine treatment groups were: IN = intranasal avirulent-live *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3) (Once® PMH IN, Intervet/Merck Animal Health, Summit, NJ); SC = subcutaneous adjuvanted *Mannheimia haemolytica* (type A1) (One Shot®, Zoetis Animal Health, Kalamazoo, MI); CS = subcutaneous saline controls. Calves were vaccinated on day 0 of the trial.

<sup>a,b</sup>Means without common superscripts within days differ ( $P < 0.01$ ).

Fever is usually initiated by the action of pyrogenic stimuli, including microorganisms, microbial production, antigen-antibody complexes, inflammatory processes, and tissue injury.<sup>2</sup> Regardless of the inciting cause, there is a metabolic “cost” to fever that results from inflammation. Elevations in body temperature are associated with an increase in metabolic heat production, reduced dietary energy intake,

and negative energy balance.<sup>2,5,16</sup> It has been estimated that there is a 10 to 13% increase in metabolic rate for every 1.8 °F (1 °C) increase in body temperature. While the fever response has evolved to enhance the survival of the animal in the long run, it can negatively impact growth and performance in the short-term.

Metabolic changes associated with inflammation and fever may also be accompanied by changes in behavior and growth. Young dairy calves of 2 different ages treated with intravenous endotoxin exhibited significantly higher rectal temperatures and frequency of respiration at 4 and 24 hours post-treatment compared to saline-treated controls.<sup>5</sup> Endotoxin-treated calves also exhibited decreased rumen activity, time eating hay, and increased the time calves spent lying inactive. These behavioral differences were seen more often in younger calves compared to their older counterparts (3 vs 20 weeks of age). It was interesting to note that there was not a difference in the amount of milk or concentrate consumed by the calves.

French researchers utilized reticulo-rumen temperature boluses to evaluate the incidence and duration of undiagnosed fever episodes in fattening bulls on weight gain.<sup>16</sup> Bulls at 3 locations were monitored over the first 40 days-on-feed, and 449 fever episodes were detected in 110 calves. Of these episodes, nearly 74% were not associated with clinical signs of disease. These undetected fever events were transitory in nature as 75% lasted less than 47 hours. However, the remaining 25% lasted 47 to 263 hours without obvious abnormal clinical signs. The duration of these undiagnosed fevers was associated ( $P = 0.002$ ) with a decrease of 33 g/day or 2.9 lb (1.3 kg) less gain over the 40-day monitoring period. Since individual feed intake was not recorded for each calf, it was not determined if the decrease in gain was due to a reduction in feed intake or an increase in catabolism or metabolic rate.

The potential for post-vaccination fever and decreased milk production was evaluated in a study involving lactating dairy cows.<sup>14</sup> Cows from 3 Canadian dairy herds were given 1 of 2 killed 9-way combination vaccines and compared to saline-injected controls. Cows were blocked by stage of lactation and level of production, and randomly assigned to a treatment group. Pretreatment milk production and body temperature were recorded prior to treatment. Cows in both vaccine-treated groups had significantly higher body temperatures compared to saline-treated controls over the first 24 hours. All groups exhibited a transient rise in body temperature that lasted approximately 48 hours before returning to normal. Depending upon the vaccine group and stage of production, there was a significant decrease in milk production. Cows in early lactation showed the largest decrease in milk production, but all groups returned to normal output by 5 days after vaccination. Therefore, when evaluating vaccine choices, the practitioner must weigh the disease risk against the current level of production in adults, the expected growth rate in young calves, and any negative impact on that performance associated with a particular vaccine.

**Table 3.** Effect of vaccine type and route of delivery on weaning performance in beef calves at location 1 (model adjusted means  $\pm$  SE).

	IN	SC	CS	P-value for treatment effects
Mean initial (day 0) weight (lb)	225.30 (11.46)	237.10 (11.46)	225.40 (16.21)	0.73
Mean weaning weight (day 80), deads excluded (lb)	451.16 (14.77)	442.53 (14.77)	414.33 (21.46)	0.37
Mean weight gain by weaning, deads excluded (lb)	222.11 <sup>a</sup> (6.80)	201.05 <sup>b</sup> (6.80)	200.33 <sup>b</sup> (9.88)	0.06
ADG calves weaned, deads excluded (lb)	2.78 <sup>a</sup> (0.08)	2.51 <sup>b</sup> (0.08)	2.50 <sup>b</sup> (0.12)	0.06
ADG for all calves, deads included (lb)	2.54 (0.30)	2.29 (0.30)	1.84 (0.43)	0.41

Vaccine treatment groups were: **IN** = intranasal avirulent-live *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3) (Once<sup>®</sup> PMH IN, Intervet/Merck Animal Health, Summit, NJ); **SC** = subcutaneous adjuvanted *Mannheimia haemolytica* (type A1) (One Shot<sup>®</sup>, Zoetis Animal Health, Kalamazoo, MI); **CS** = subcutaneous saline controls.

<sup>a</sup><sup>b</sup>Least squares means without common superscript differ.

**Table 4.** Effect of vaccine type and route of delivery on weaning performance in beef calves at location 2 (model adjusted means  $\pm$  SE).

	IN	SC	CS	P-value for treatment effects
Mean initial (day 0) weight (lb)	284.52 (9.03)	281.30 (8.62)	277.19 (10.43)	0.87
Mean weaning weight (day 59), deads excluded (lb)	346.05 (9.87)	335.87 (8.97)	349.64 (11.50)	0.59
Mean weight gain by weaning, deads excluded (lb)	63.42 (4.83)	54.57 (4.38)	61.07 (5.62)	0.38
ADG calves weaned, deads excluded (lb)	1.07 (0.08)	0.93 (0.07)	1.04 (0.10)	0.38
ADG for all calves, deads included (lb)	0.48 (0.30)	0.92 (0.30)	0.49 (0.35)	0.50

Vaccine treatment groups were: **IN** = intranasal avirulent-live *Mannheimia haemolytica* (type A1) and *Pasteurella multocida* (type A3) (Once<sup>®</sup> PMH IN, Intervet/Merck Animal Health, Summit, NJ); **SC** = subcutaneous adjuvanted *Mannheimia haemolytica* (type A1) (One Shot<sup>®</sup>, Zoetis Animal Health, Kalamazoo, MI); **CS** = subcutaneous saline controls.

The acute phase response is characterized by the rapid production of acute phase proteins by the liver in response to pro-inflammatory cytokines. Haptoglobin is an acute phase protein which functions to bind free hemoglobin in the plasma, and has been found to be a useful marker of inflammation in cattle.<sup>11</sup> The pro-inflammatory cytokines (e.g., interleukin-1, interleukin-6, and tumor necrosis factor) are produced as part of the non-specific innate immune response to microbial challenge, inflammation, or trauma.<sup>3,20</sup> They are also produced in response to vaccination and are an essential component for inducing the adaptive immune response (antibodies and T cell-mediated immunity) to vaccine antigens. Low levels of pro-inflammatory cytokines secreted locally in response to vaccine administration will cause only a local response in the draining lymph nodes. Moderate levels of pro-inflammatory cytokines produced in response to a vaccine can circulate systemically and produce a systemic response characterized by fever, lethargy, loss of appetite, and induction of acute phase protein secretion into the plasma.

Plasma haptoglobin concentrations in healthy cattle are typically negligible and below detectable levels.<sup>7</sup> Plasma

concentrations of haptoglobin increase rapidly following tissue damage associated with infection or inflammation.<sup>13,20</sup> Haptoglobin levels have been shown to be increased after challenge with BHV1 and *Mannheimia haemolytica* in 1 report. The concentration of haptoglobin in the plasma was significantly associated with measures of severity of disease.<sup>9</sup>

Increased concentrations of haptoglobin have also been negatively associated with performance of apparently healthy cattle.<sup>4,6,12</sup> In newly arrived feedlot calves haptoglobin was found to increase from the day of arrival through 7 days on feed, regardless of the BRD treatment status.<sup>4</sup> Calves treated for BRD did exhibit increasing levels of haptoglobin as the number of BRD treatments increased. The acute phase protein response has also been shown to be detrimental to reproductive performance in beef cows.<sup>6</sup> That study looked at differences in physiological responses of Brahman-crossbred cows that had been acclimated to human interaction vs control cows. Reproductive performance in that study was evaluated based on the probability of a cow becoming pregnant in a 90-day breeding season.

Post-vaccination elevations of acute phase proteins have been associated with calf feed intake and growth rate. Serum haptoglobin levels have been shown to be increased after clostridial vaccination; multiple doses of a 7-way clostridial vaccine resulted in significantly higher levels of SH when compared to calves receiving a *C. perfringens* type C and D toxoid and sterile saline.<sup>15</sup> This elevation in haptoglobin lasted for 6 days after vaccination and was associated with a 20% decrease in feed consumption compared to the other 2 groups. The SC vaccine used in the present trial has previously been shown to increase plasma haptoglobin concentration, peaking at 3 days after vaccination and returning to baseline levels by 7 days.<sup>7</sup> In a second trial using this same SC vaccine in recently weaned heifers, vaccinated calves also showed significantly higher SH levels compared to saline controls.<sup>1</sup> Haptoglobin did not return to baseline levels until 6 days after vaccination. There was no difference in feed intake over the following 2 weeks, but saline control heifers had significantly higher ADG (2.51 vs 1.92 lb/day; 1.14 vs 0.87 kg/d) and gain:feed (0.29 vs 0.22 lb; 0.13 vs 0.10 kg) compared to SC vaccinates.

Results in the present study support previous studies that highlighted the negative physiological effects of vaccine-induced inflammation. We found that the SC-vaccinated group that received a commercial product containing a killed adjuvanted leukotoxoid from *Mannheimia haemolytica* (type A1) showed a higher body temperature response and lower weight gain through weaning when compared to IN-vaccinated calves. Serum haptoglobin was markedly increased in calves in the SC group over the same time period at both locations as well. It is also interesting to note that the calves given IN vaccine at location 1 maintained a significantly higher ADG and weaning weight through 80 days post-vaccination compared to the other 2 groups. This occurred with no apparent clinical signs that would indicate a disease process occurring in these calves. The lack of significant differences in growth performance from vaccination through weaning at location 2 could be explained by a lower level of milk production in the cows, and the calves not receiving creep feed during the nursing phase. Combined with extremely cold weather, calves at location 2 may not have had enough dietary energy to grow at their genetic potential.

### Conclusions

Results of this study suggests that there was less inflammatory response to vaccination with the IN-administered vaccine compared to the SC vaccine. Average daily gain through 21 days post-vaccination in location 1 was lower in SC-vaccinated calves compared to calves vaccinated IN, but was similar between vaccine groups in location 2. Mean weight gain and ADG (deads excluded from the analysis) through weaning tended to be higher in the IN group in location 1, but ADG with deads included in the analysis were similar. Bodyweight and ADG at weaning did not differ between

treatment groups in location 2. Differences in performance outcomes between the 2 locations suggest the need for additional research to provide data for practitioners to make vaccine recommendations.

### Endnotes

- <sup>a</sup>Microsoft Excel 2010, Microsoft Corporation, Redmond, WA  
<sup>b</sup>Once® PMH IN, Intervet / Merck Animal Health, Summit, NJ  
<sup>c</sup>One Shot®, Zoetis Animal Health, Kalamazoo, MI  
<sup>d</sup>0.9% Sodium Chloride Injection, USP, Hospira Inc., Lake Forest, IL  
<sup>e</sup>BD Vacutainer®, Franklin Lakes, NJ  
<sup>f</sup>Life Diagnostics, Inc., West Chester, PA  
<sup>g</sup>Version 9, SAS Institute Inc., Cary, NC

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<sup>1</sup>Scours vaccine study. May 2007. Resear zons Inc., St. Louis, Mo. Interviews were conducted between April 30 and May 14, 2007.

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