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Effects of vaccination on the acute-phase protein response and measures of performance in growing beef calves[1]

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ABSRACT: Two experiments were conducted to evaluate the influence of vaccination on the acute-phase protein (APP) reaction (Exp. 1 and 2) and measures of performance (Exp. 2) in growing beef calves. In Exp. 1, the APP reaction was assessed in newly weaned steers administered 1 of 3 treatments (n = 8 steers/treatment), consisting of 1) *Mannheimia haemolytica* vaccine (One Shot; Pfizer Inc., New York, NY), 2) *Clostridium* vaccine (UltraBac 7; Pfizer, Inc.), or 3) saline-injected control. Blood samples for the evaluation of APP concentrations were collected on d 0, 1, 3, 5, 7, 10, and 14 and steer BW measured on d 0 and 21 relative to treatment administration. Plasma concentrations of haptoglobin (Hp) increased ($P < 0.05$) in vaccinated but not control calves and reached a peak on d 3 and 5 for steers receiving *Mannheimia haemolytica* and *Clostridium* vaccine, respectively. Plasma concentrations of ceruloplasmin (Cp) and fibrinogen (Fb) increased ($P < 0.05$) in all calves after treatment administration and Fb concentrations were greatest ($P < 0.01$) in calves receiving *Mannheimia haemolytica* vaccine on d 3 and 5 compared with the other treatments. There were no treatment effects (P = 0.44) on 21-d steer ADG (0.43 kg/d; SEM = 0.082). In Exp. 2, 23 heifers were randomly assigned to 2 treatments: 1) vaccinated (*Mannheimia haemolytica* vaccine (One Shot; n = 12) and 2) saline control (n = 11). After vaccination, blood samples were collected for determination of APP concentrations on d 0, 3, 6, 9, 12, and 15. During this period, individual heifer DMI was measured using an automated feed intake measuring system (Model 4000E; GrowSafe Systems Ltd., Airdrie, Alberta, Canada). Initial and final shrunk BW did not differ ($P > 0.36$) among treatments. On d 1, plasma Cp concentrations increased ($P < 0.01$) sharply in vaccinated heifers but not control heifers and were greater ($P < 0.05$) in vaccinated vs. control heifers on d 3, 6, 9, and 12 relative to injection. Daily DMI did not differ (P = 0.66) among treatments (average = 9.1 kg/d; SEM = 0.34); however, ADG and G:F were greater ($P \leq 0.05$) for control vs. vaccinated heifers (1.14 vs. 0.87 kg/d and 0.13 and 0.10 kg, respectively; SEM = 0.064 and 0.011). These data indicate that within a 2 wk period after vaccination, beef calves experience an acute-phase protein response, which may result in reduced ADG and feed efficiency.

Key words: acute-phase protein, calves, feed efficiency, vaccination

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INTRODUCTION

The acute-phase reaction is a component of the innate body defense mechanism and results in the production of a large and varied group of hepatic proteins (Baumann and Gauldie, 1994; Suffredini et al., 1999). These proteins, called acute-phase proteins (**APP**), are synthesized by the liver parenchymal cells and released in the bloodstream in response to several stressors, including local inflammation,

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bacterial infections, endotoxin injections, and physical injuries (Baumann and Gauldie, 1994; Suffredini et al., 1999). In addition, increased APP concentrations have been recognized as indicators of cattle morbidity (Godson et al., 1996; Carter et al., 2002; Petersen et al., 2004) and have been shown to be negatively correlated to BW gain (Qiu et al., 2007; Cooke et al., 2009; Araujo, et. al., 2010); therefore, attempts to better understand management procedures that stimulate the APP reaction may assist cattle managers in optimizing animal health and the efficiency of BW gain. Some management procedures have been shown to influence the APP reaction in beef calves, such as weaning and transportation (Arthington et al., 2003a, 2005), feed and water restriction (Cappellozza et al., 2011), changes in diet (Gozho et al., 2005), and vaccination (Stokka et al., 1994). Therefore, our hypothesis stated that vaccination would result in an APP reaction in beef calves and this reaction would be associated with reduced feed efficiency. To test this hypothesis, 2 experiments were performed with these objectives: 1) evaluate the effect of 2 commercially available cattle vaccines on the APP reaction and 2) investigate the effects of a vaccine-induced APP reaction on individual calf DMI, ADG, and feed efficiency.

MATERIALS AND METHODS

Calves were cared for in accordance with acceptable practices as outlined in the Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching (FASS, 2010). In addition the protocols were reviewed and approved by the University of Florida, Institute of Food and Agricultural Sciences, Animal Research Committee (number 008-08ANS).

Animals, Diets, and Sample Collection

In Exp. 1, 24 Brahman × Angus steers (approximately 8 mo of age) were randomly assigned to receive 1 of 3 vaccination treatments (8 steers/treatment), including 1) *Mannheimia haemolytica* vaccine (2 mL subcutaneous; One Shot; Pfizer Inc., New York, NY), 2) *Clostridium* vaccine (5 mL subcutaneous; UltraBac 7; Pfizer, Inc.), or 3) Control (5 mL subcutaneous; sterile 0.9% saline). Treatments were administered at the time of weaning (d 0), immediately after cow/calf separation. During the 21-d study period, steers were housed in a single, partially shaded, dry lot pen with free-choice access to water and long-stem grass hay (*Cynodon nlemfuensis*) hay. In addition, steers were group fed a pelleted calf starter feed (Lakeland Animal Nutrition, Lakeland, FL; 72% TDN and 14% CP, as-fed, per label specifications) in an amount not exceeding 4.5 kg/steer daily. Feed and hay DMI were not recorded; however, complete consumption of the offered calf starter was achieved by d 7 of the study. Full BW was recorded on d 0 and 21. To assess the effect of vaccination treatment on the APP reaction, blood samples were collected via jugular venipuncture into sodium heparin-containing blood collection tubes (Vacutainer, 10 mL; Becton Dickinson, Franklin Lakes, NJ) on d 0, 1, 2, 5, 7, 10, and 14 relative to vaccination. After collection, samples were immediately placed on ice and then transferred to 4°C and stored for 24 h before plasma was isolated by centrifugation at 2000 × *g* for 20 min at 4°C. Plasma was stored frozen at –20°C until later analysis for haptoglobin (**Hp**), ceruloplasmin (**Cp**), and fibrinogen (**Fb**) concentrations.

In Exp. 2, 23 weaned, Brahman × Angus heifers (approximately 12 mo of age and weaned >60 d) were placed into 1 of 2 fully covered, concrete floor pens and allowed to acclimate to an automated feed intake measuring system (GrowSafe; Model 4000E; Growsafe Systems Ltd., Airdrie, Alberta, Canada) for 21 d. After acclimation, heifers were randomly assigned within pen to receive 1 of 2 vaccination treatments (d 0), including 1) *Mannheimia haemolytica* vaccine (2 mL subcutaneous; One Shot; $n = 12$) or 2) Control (2 mL subcutaneous; sterile 0.9% saline; $n = 11$). To assess the effect of vaccination treatment on the APP reaction, blood samples were collected and processed as in Exp. 1 on d 0, 3, 6, 9, 12, and 15 relative to vaccination. Plasma was stored frozen at –20°C until later analysis for Hp and Cp concentrations. During both the acclimation and study period, heifers were provided free-choice access to a total mixed ration (Table 1) and individual DMI was recorded daily. Random samples of the mixed ration were collected at the beginning and end of the study, composited into a single sample, and analyzed in triplicate for nutrient content using wet chemistry procedures at a commercial laboratory (Dairy One Forage Laboratory, Ithaca, NY). Individual BW was determined after a 12 h feed and water withdrawal at the start (d 0) and end (d 16) of the study.

Acute-Phase Protein Analysis

Plasma Hp concentrations were determined in duplicate samples by measuring haptoglobin/hemoglobin complexing by the estimation of differences in peroxidase activity (Makimura and Suzuki, 1982). Results were expressed as arbitrary units resulting from the absorption reading × 100 at 450 nm with an inter- and intra-assay CV of 3.45 and 4.71% and 5.3 and 4.4% for Exp 1 and 2, respectively. In Exp. 2, the assay was expanded to include a standard curve generated from bovine samples with known Hp values confirmed via a commercial bovine ELISA assay (bovine haptoglobin

Table 1. Ingredients and chemical composition of the experimental diet[1]

Item, % of DM	Experimental diet
Ingredient composition	
Cracked corn	28.32
Cottonseed hulls	26.93
Ground grass hay[2]	22.84
Corn gluten feed	14.00
Pelleted supplement[3,4]	2.06
Liquid supplement[5]	1.88
Fat supplement[6]	1.22
Cottonseed meal	1.97
Sodium bicarbonate	0.57
Salt	0.21
Chemical composition[7]	
DM	90.5
CP	11.7
NDF	46.6
ADF	32.2
Ether extract	3.82
Ca	0.69
P	0.40
K	1.50

[1]Heifers were housed in 1 of 2 fully covered, concrete floor pens and allowed to acclimate to an automated feed intake measuring system (GrowSafe; Model 4000E; GrowSafe Systems Ltd., Airdrie, Alberta, Canada). Individual heifer DMI was measured daily.

[2]Coastal bermudagrass (*Cynodon dactylon*).

[3]Pelleted supplement contained (DM basis): 54.11% limestone; 29.85% monocalcium phosphate; 4.8% potassium chloride; 3.6% magnesium oxide; 2.3% dried distillers grains plus solubles; 1.74% C2MZ (chelated Zn, Cu, and Mn,; Albion Laboratories Inc., Clearfield, UT); 1.59% MgK base (chelated Mg and complexed K; Albion Laboratories Inc., Clearfield, UT); 0.62% Rumensin 80 (Elanco Animal Health, Indianapolis, IN); 0.47% copper sulfate; 0.31% zinc oxide; 0.26% manganous oxide; 0.13% selenium premix (1% Se); 0.10% vitamin E premix (50% vitamin E); 0.08% vitamin A (650,000 IU/g); 0.02% vitamin D3 (500,000 IU/g); 0.01% cobalt carbonate; and 0.01% ethylenediamine dihydroiodide.

[4]Supplied 28.6 mg of monensin/kg of diet DM (Elanco Animal Health, Indianapolis, IN).

[5]Mix30 (Agridyne LLC, Springfield, IL). Chemical composition of the supplement (DM basis): 43% DM, 38.26% CP, 2.16 Mcal NEg/kg of DM, 1.28% calcium, 0.81% phosphorous, 0.40% magnesium, 1.07% potassium, 0.81% sulfur, 0.046% iron, 0.0083% zinc, 0.0011% copper, 0.0030% manganese, 38.4 IU of vitamin A/g DM, 8.49 IU of vitamin D/g DM, and 0.11 IU of vitamin E/g DM.

[6]Chemical composition of the fat supplement (DM basis): 41.67% ether extract, 26.98% NDF, 22.92% CP, and 8.43% ash.

[7]Random samples of the mixed ration were collected at the beginning and end of the study, composited into a single sample, and analyzed in triplicate for nutrient content using wet chemistry procedures at a commercial laboratory (Dairy One Forage Laboratory, Ithaca, NY).

ELISA test kit; Life Diagnostics, Inc., West Chester, PA; Cooke and Arthington, 2012). The concentrations of Hp, based on the ELISA assay, ranged from 0.03 (low control) to 0.93 mg/mL (high control) with an intrassay CV of 1.27%. Plasma Fb concentrations were determined using a fibrinogen determination kit (Sigma procedure number 880; Sigma Diagnostics, St. Louis, MO) within a single run. Every 10th sample was assayed in duplicate for calculation of an intra-assay CV, which averaged 4.70%. Plasma Cp oxidase activity was measured in duplicate samples using colorimetric procedures described by Demetriou et al. (1974)and expressed as milligrams per deciliter as described by King (1965). Intra-assay variation among duplicate samples averaged 2.36% and inter-assay variation, determined from a single pooled sample included within each assay run, averaged 4.29%.

Statistical Analyses

Calf performance and APP data were analyzed within a completely randomized design using the mixed linear models with the MIXED procedure (SAS Inst. Inc., Cary, NC) with Satterthwaite approximation to determine the denominator degrees of freedom for the test of fixed effects. The model statement for analysis of BW, ADG, DMI, and G:F contained only the effects of treatment and were analyzed using calf(treatment) as the random variable. The model statement for APP analyses contained the effects of treatment, day, and the interaction. The specified term for the repeated statement was day, and the covariance structure used was compound symmetry. For all analyses, calf was considered the experimental unit. All results are reported as least squares means and were separated using PDIFF. Significance was set at $P \leq 0.05$ and tendencies if $P > 0.05$ and ≤ 0.14. Results are reported according to main effects when interactions were not significant.

RESULTS AND DISCUSSION

There were no differences ($P = 0.44$) in 21-d ADG among vaccination treatments in Exp. 1 (average = 0.43 kg/d; SEM = 0.082). The principle objective of the study, however, was aimed at assessing the APP reaction to vaccination. Additionally, the steers were weaned on the day of vaccination and thus little BW gain would be expected over this short evaluation period.

Among the 2 vaccines evaluated, the APP response was more profound for steers receiving *Mannheimia haemolytica* vs. the *Clostridium* vaccine. Plasma Hp concentrations were greater ($P < 0.01$) for steers receiving *Mannheimia haemolytica* vaccine vs. Control and the *Clostridium* vaccine on d 1 and 3 (Fig. 1). Peaking on d 3, plasma Hp concentrations were more than 2.5x greater ($P < 0.01$) in steers receiving *Mannheimia haemolytica* vaccine compared with the average of steers receiving *Clostridium* vaccine and Control (Fig. 1). Steers receiving *Clostridium* also experienced increased Hp concentrations but peaking later (d 5) than those receiving *Mannheimia haemolytica* vaccine (Fig. 1). Stokka et al. (1994) also reported increased

haptoglobin concentrations of steer calves vaccinated with the same 7-way *Clostridium* vaccine used in the current study. In that study, Hp concentrations peaked on d 3 and were greater ($P < 0.01$) than saline-injected control steers on d 3 and 6 but similar on d 9, 15, and 25 relative to vaccination. Sheep, vaccinated with a 7-way *Clostridium* vaccine, experienced similar increases in Hp concentrations, with a peak on d 1 followed by reductions to baseline concentrations by d 4 to 6 after vaccination (Eckersall et al., 2008).

Plasma Fb concentrations peaked on d 3 in steers receiving *Mannheimia haemolytica* vaccine and were greater than both Control steers and steers receiving *Clostridium* vaccine on d 3 and 5 (Fig. 1). Horses, which were provided 1 of 2 influenza and tetanus toxoid-combined vaccines, achieved similar increases in plasma Fb concentrations (Andersen et al., 2012). In that study, Fb concentrations remained elevated longer than in the current study, and with 1 of the vaccines, Fb concentrations were greater than prevaccination values at the final sampling period (96 h after vaccination).

There was no treatment × time interaction for plasma Cp concentrations; however, average Cp concentrations tended ($P \leq 0.14$) to be greatest for steers receiving *Mannheimia haemolytica* vaccine compared with Control steers or steers receiving *Clostridium* vaccine (28.6, 24.2, and 24.2 mg/mL, respectively; SEM = 1.95).

The vaccinations administered in this study were derived from commercial preparations (Pfizer Inc.) and contained proprietary adjuvant formulations. Commercial vaccine preparations typically contain adjuvants to elicit greater adaptive immune responses from the host as well as guiding specific forms of adaptive immunity that may assist in creating greater immune protection to the target antigen (Coffman et al., 2010). Although the critical importance of adjuvants for eliciting adaptive immune responses is widely accepted, their specific mode of action is highly varied and advancements in adjuvant technologies continue to be an important component of modern vaccine development (McKee et al., 2007). In general, adjuvants assist in recruiting antigen presenting leukocytes, predominantly macrophages, to the site of antigen (or vaccine) delivery. These phagocytic leukocytes engulf, process, and present the target antigen to T cell lymphocytes (i.e., adaptive immunity), which begins the cascade of inferring protective immunity to the host. In general, adjuvants are categorized as 1) depot adjuvants, which are intended to slow the degradation and elimination of antigen, thus prolonging the immunological stimulus, 2) particulate adjuvants, which serve to create a more readily phagocytosable antigen to antigen presenting cells, and 3) immunostimulatory adjuvants, which promote cytokine production and elicit helper T cell responses (Tizard, 2004). The inflammatory process can be witnessed in each of these 3 overlapping classification functions and therefore the APP reaction is an expected resultant of the action of adjuvants in vaccines. In fact, adjuvants have been widely used in research protocols to elicit immune responses from the host (Botrel et al., 1994; Arthington et al., 2003b), independent of the presence of the target antigen of a vaccine. The antigen fraction of the vaccines used in the current study could also stimulate antigen presenting cells and thus elicit the APP response. To our knowledge, however, the ability of vaccine antigen, without adjuvant, to elicit an inflammatory response has not been previously reported. Nonetheless, experimental challenges with viral pathogens that are common causative agents for respiratory disease in cattle have been shown to create a significant APP reaction (Arthington et al., 1996; Heegaard et al., 2000). However, the inactivated form of the *Mannheimia haemolytica* antigen presented in the commercial vaccine did not create the clinical signs of respiratory morbidity presented in these aforementioned studies; therefore, it is reasonable to conclude that the magnitude of the APP reaction in the current experiment

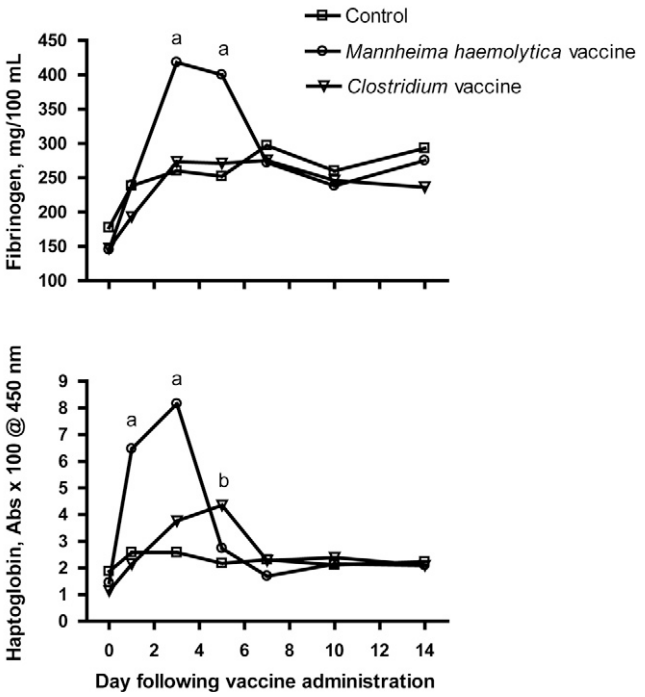

Figure 1. Plasma fibrinogen and haptoglobin concentrations (Exp. 1) of steers receiving *Mannheimia haemolytica* vaccine (2 mL subcutaneous; One Shot; Pfizer Inc., New York, NY), *Clostridium* vaccine (5 mL subcutaneous; UltraBac 7; Pfizer, Inc.), or Control (5 mL subcutaneous; sterile saline). Treatments were administered at the time of weaning (d 0; $n = 8$ steers/treatment). Samples were collected on d 0, 1, 3, 5, 7, 10, and 14 relative to vaccination. Values are least square means. Treatment × day: $P = 0.01$ and < 0.001 for fibrinogen and haptoglobin, respectively. Largest SEM = 51.6 and 0.56 for fibrinogen and haptoglobin, respectively. Superscripts: a = *Mannheimia haemolytica* vaccine greater than *Clostridium* vaccine and Control; $P < 0.05$, and b = *Clostridium* vaccine greater than *Mannheimia haemolytica* vaccine and Control; $P < 0.05$.

was enhanced by the adjuvant-induced inflammatory process. Because a greater APP reaction was achieved with the *Mannheimia haemolytica* vs. *Clostridium* vaccine, it was selected to be used in Exp. 2 to evaluate the effects of the vaccine-induced APP reaction on measures of beef calf performance.

In Exp. 2, plasma concentrations of Cp and Hp increased in vaccinated but not Control heifers, peaking on d 3 after vaccination for both APP ($P < 0.05$; Fig. 2). Plasma concentrations of Cp decreased gradually in vaccinated heifers but remained greater ($P < 0.05$) than Control heifers on d 6, 9, and 12 (Fig. 2). The vaccine-induced Cp response differed among the 2 experiments of the current study. These differences may be related to potential variations in Cu status among the calves in Exp. 1 vs. 2, because 90 to 95% of serum Cu is associated with Cp (Cousins, 1985). Similar to Exp. 1, plasma Hp concentrations declined sharply in vaccinated heifers after the peak on d 3 and were not different ($P \geq 0.40$) from Control heifers on each of the subsequent sampling days (Fig. 2).

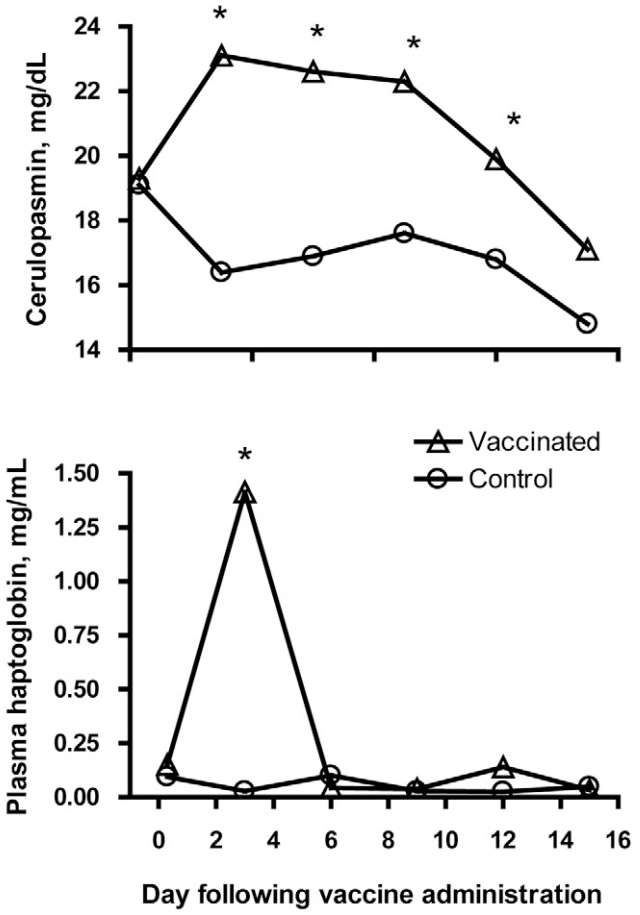

Figure 2. Plasma ceruloplasmin and haptoglobin concentrations (Exp. 2) of heifers vaccinated with *Mannheimia haemolytica* vaccine (2 mL subcutaneous; One Shot; Pfizer Inc., New York, NY; vaccinated), or Control (5 mL subcutaneous; sterile saline). Samples were collected on d 0, 1, 3, 6, 9, 12, and 15 relative to vaccination. Treatment × day: $P < 0.001$ for both ceruloplasmin and haptoglobin. Largest SEM = 0.88 and 0.042 for ceruloplasmin and haptoglobin, respectively. * = means differ within sampling day; $P < 0.05$.

There were no differences ($P \geq 0.37$) in initial (d 0) and final (d 16) heifer BW; however, ADG over the experimental period was 30% greater ($P < 0.01$) for Control vs. vaccinated heifers (Table 2). Individual heifer DMI did not differ ($P = 0.66$); therefore, Control heifers had a greater ($P = 0.05$) feed efficiency than vaccinated heifers during the 16-d evaluation period (Table 2). Similar to the current study, Stokka et al. (1994) reported no difference in mean feed consumption of steers receiving a primary *Clostridium* vaccination; however, feed consumption decreased by nearly 20% after a booster vaccination administered 34 d later.

The process of vaccination is an essential tool for optimizing health, welfare, and productivity of livestock. The APP reaction occurs as a normal result of vaccination in cattle (Stokka et al., 1994), horses (Andersen et al., 2012), and sheep (Eckersall et al., 2008). To our knowledge, the current study is the first to illustrate the influence of vaccination on decreased feed efficiency in cattle and link this production response to the APP reaction. The release of APP is predominantly stimulated by the pro-inflammatory cytokines, IL-1, IL-6, and tumor necrosis factor-α. Macrophages, phagocytic cells of the innate immune system, are the predominant source of these pro-inflammatory cytokines and are also an important first responder in the inflammatory process (Durum and Muegge, 1996). Therefore, macrophages are important to vaccine efficacy for both the presentation of antigen to T cells and the production of inflammatory mediators, such as the pro-inflammatory cytokines. In addition to stimulating APP release, these cytokines are also linked to fever, anorexia, and metabolic alterations such as muscle catabolism (Johnson, 1997). Although the anorectic response has been shown to represent over 70% of BW loss in cytokine-challenged chicks (Klasing

Table 2. Effects of vaccination on performance of growing beef heifers

Item	Control[1]	Vaccinated[1]	SEM	*P*-value
	kg			
BW, d 0,[2] kg	233	225	9.6	0.55
BW, d 16,[2] kg	251	238	9.8	0.37
ADG, kg	1.14	0.87	0.270	< 0.01
DMI,[3] kg/d	9.26	8.80	0.466	0.66
G:F, kg/kg	0.13	0.10	0.011	0.05

[1]Treatments were 1) Control (2 mL subcutaneous; sterile saline; $n = 11$) and 2) *Mannheimia haemolytica* vaccine (2 mL subcutaneous; One Shot; Pfizer Inc., New York, NY; $n = 12$) administered on d 0.

[2]Individual BW was determined after a 12 h feed and water withdrawal at the start (d 0) and end (d 16) of the study.

[3]Individual DMI measured using the GrowSafe (Model 4000E; GrowSafe Systems Ltd., Airdrie, Alberta, Canada) feed intake monitoring system. Heifers were allowed to acclimate for 21 d before the start of the study. Values are an average of d 1 to 15.

et al., 1987), depressed feed intake is not always represented in animals undergoing an APP reaction. In the present study, for example, no significant differences in DMI were observed among vaccinated vs. saline-injected Control heifers. In another study, calves reared under 2 management systems experienced marked differences in their APP reaction after transport and feedlot entry (Arthington et al., 2005). In that study, no differences in voluntary feed DMI were observed, but calves with a lesser APP reaction experienced nearly a twofold increase in feed efficiency during the initial 28-d receiving period. These results suggest that the APP reaction may be eliciting metabolic responses, which are impacting cattle performance beyond that which can be attributed to a reduction in DMI.

The results of the present study illustrate the APP reaction in overtly healthy cattle administered commercially available *Mannheimia haemolytica* and *Clostridium* vaccines. Furthermore, these data demonstrate a link between the vaccination-induced APP reaction and reduced cattle performance (ADG and feed efficiency). Further research is warranted to investigate potential nutrition and/or management interventions that seek to maximize vaccine-induced immune protection and optimize cattle performance.

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