FACTORS INFLUENCING THE PASSIVE, INNATE, AND ADAPTIVE IMMUNE SYSTEM AND THEIR EFFECTS IN BEEF CATTLE

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ABSTRACT

To investigate the factors influencing the passive, innate, and adaptive immune system and their effects in beef cattle, three experiments (exp.) were completed. Results from Exp. 1 indicate that there is some influence of birth weight and incidence of dystocia on the passive transfer of immunity from dam to offspring. Results from Exp. 2 indicated that supplemented dams had lower calving ease scores and tended to have greater colostrum production while their calves showed less evidence of mixed acidosis based on blood parameters of pCO_2, lactate, and base excess. In Exp. 3, vaccine treatments initiated an inflammatory response with subcutaneous MLV vaccine for IBR and BRSV having greater serum antibodies than the intranasal vaccine. Feed intake and ADG were unaffected by the use of vaccines compared to a sterile saline injection. In well-managed, properly-immunized herds, vaccination can stimulate antibody production without negative effects on feedlot performance.

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CHAPTER 1. LITERATURE REVIEW

Introduction

The immune system protects animals against microbial invasion and is essential for life. Fetal calves are able to respond early in gestation to foreign invaders; however, the dams' own immune system and the placenta provide additional protection to the fetal calf. The ruminant placenta is morphologically classified as cotyledonary and histologically classified as syndesmochorial (Lemley et al., 2015). The syndesmochorial placenta of the cow forms a syncytium between the maternal endometrium and the fetal trophectoderm; thus, separating the maternal and fetal blood supplies (Arthur, 1996). This separation of maternal and fetal blood supplies prevents the transmission immunoglobulins in utero (Weaver et al. 2000). Prevention of the transfer of immunoglobulins in utero means calves are born agammaglobulinemic; thus, the calves have very little to no immunoglobulins in circulation (Weaver et al. 2000), and are characterized as being immuno-naïve. (Barrington and Parish, 2001). Although immuno-naïve in utero, as the fetus develops so do the various innate and adaptive immune defenses (Barrington and Parish, 2001). By the time parturition takes place and the calf is born, it can respond to a variety of antigens, but still not as fully as when the calf is fully mature (Barrington and Parish, 2001). This is due to a lack of immunological memory that is achieved by the immune system responding to a threat and activating the immune system.

Intake and absorption of colostral components plays a critical role in passive immune transfer and ultimately survival rate of the neonatal calf (Stelwagen et al., 2009). Colostrogenesis occurs prepartum and results in the formation of secretory colostrum in the mammary gland (Stark et al., 2015). Colostrum contains a complex of cells and proteins that actively protect the neonate from pathogens and other extra-uterine challenges (Bendixen et al.,

2011). The bovine mammary gland plays an active role in regulating the concentration of various immunoglobulins in colostrum.

The passive transfer of colostral immune-proteins (PIT), specifically immunoglobulins, to the calf plays a critical role in short-term calf health (Smith and Little, 1922). Success of colostral transfer, reported by calf serum immunoglobulin concentrations, has been shown to be an important indicator of preweaning morbidity and mortality (Perino, 1997). Calves with inadequate serum IgG concentrations (<8 mg/ml) at 24 h are from 3.2 to 9.5 times more likely to become sick and 5.4 times more likely to die before weaning compared to calves with adequate concentrations of serum IgG (Perino et al., 1993).

The passive immune transfer is critical to immediate survival of the calf, while the continued health of the animal is paramount to long term productivity. In livestock, the major causes of death preceding slaughter are due to infectious diseases (Babiuk, 2002). Bovine respiratory disease complex (BRD) persists as the single most costly disease syndrome associated with commercial beef production in the United States. The appropriate use of vaccines can reduce the risk of BRD (Urban-Chmiel and Grooms, 2012). Disease control or elimination requires the stimulation of the immune system in a sufficient proportion of the population or herd (Siegrist, 2013). Immunization is achieved by inducing protection, through stimulation of the adaptive immune system (Siegrist, 2013). This immunity is achieved by the maintenance of antigen-specific immune effectors and/or by the induction of immune memory cells that can reactivate if re-exposure to the antigen occurs (Siegrist, 2013).

This literature review will discuss: 1) the in utero development of the calf and its immune system; 2) the formation of colostrum in the mammary gland; 3) the digestive physiology of the neonatal calf gut and the absorption of the immune components found in

colostrum; 4) factors that affect the efficiency of absorbing the immune components of colostrum; and 5) the immune response in relation to vaccination and its effect on prolonged calf health. When possible, examples from research performed on beef cattle will be used. However due to limited information and similarities observed in mammalian immune system, knowledge from across species will be included in this literature review. Following this literature review, the main experimental objectives of this thesis will be discussed in their own chapters, followed by a general discussion and considerations for future research.

In Utero Development

The cow is one of the "eutherian" species, i.e. those that have placentas (Schlafer et al. 2000). "Placenta" is taken from the Latin term meaning "flat cake" due to apparent similarity of the human discoid placenta to the round flat loaves of unleavened bread commonly made in ancient times (Schlafer et al. 2000). The ruminant placenta is morphologically classified as cotyledonary and histologically classified as syndesmochorial (Lemley et al., 2015). The syndesmochorial placenta of the cow forms a syncytium between the maternal endometrium and the fetal trophectoderm; thus, separating the maternal and fetal blood supplies (Arthur, 1996). This separation of maternal and fetal blood supplies prevents the transmission immunoglobulins in utero (Weaver et al. 2000). The bovine placenta contains a population of fetal macrophages (Schlafer et al. 2000), in human medicine these phagocytes are termed Hofbauer cells (Benirschke and Kaufmann, 1995). These cells play an important role in utero fetal defenses (Schlafer et al., 2000). Fetal placenta macrophages originate from the chorionic mesenchyme early in gestation or from fetal bone marrow-derived macrophages (Schlafer et al., 2000). Prevention of immunoglobulin transfer in utero means calves are born agammaglobulinemic; thus, the calf has very little to no immunoglobulins in circulation

(Weaver et al. 2000) and are characterized as being immuno-naïve (Barrington and Parish, 2001).

Although immuno-naïve in utero, as the fetus develops so do the various innate and adaptive immune defenses (Barrington and Parish, 2001). These mechanisms can be characterized into those dependent on antigen recognition by antibody and or lymphocytes, adaptive immunity, and those that occur independent of recognition events, innate immunity (Barrington and Parish, 2001). The innate immune defense mechanisms include effects such as secreted enzymes, acids in the stomach, epithelium, and normal flora that colonize the mucosal surfaces once the neonate is born (Barrington and Parish, 2001). The innate immune system also includes the complement system and phagocytic cells, both neutrophils and macrophages derived from pluripotent stem cells (Tizard, 2013). Neutrophils and macrophages contribute minimal protection in early fetal life since they remain in their derivation sites until being released into the fetal blood at approximately d 130 of gestation (Banks and McGuire, 1989). Complement activity has been reported at approximately d 90 of gestation (Osborn et al., 1974). Innate immunity defense mechanisms increase in their effectiveness throughout gestation and though they are functional by birth, they can be suppressed by stress, malnutrition, low level infections, or exposure to toxins (Barrington and Parish, 2001). The adaptive immune defense system consists of antibodies, memory lymphocytes, and effector cells (Tizard, 2000). Lymphocytes, also developed from pluripotent stem cells, are initially released into the circulation where they later migrate to specific locations to undergo further differentiation (Barrington and Parish, 2001). T-lymphocytes mature in the thymus and B-lymphocytes mature in the bone marrow and Peyer's patches (Barrington and Parish, 2001). During the first trimester of gestation, T and B-lymphocytes move from primary lymphoid organs to populate

the lymph nodes, spleen, and mucosal lymphoid tissues; this activity occurs independent of antigen exposure and stimulation (Barrington and Parish, 2001). By the time parturition takes place and the calf is born it can respond to a variety of antigens, but still not as fully as when the calf is fully mature due to a lack of immunological memory (Barrington and Parish, 2001).

In addition to growth and development of the fetal immune system, fetal growth overall is crucial and can be affected by nutritional status of the dam. In rats, Godfrey and Barker (2000) demonstrated that the maternal diet can have significant long- and short-term impacts on offspring health. Maternal nutrition is crucial to fetal and placental development, which ultimately influences lifetime performance of that animal (Funston et al., 2010). Despite improved management techniques and extensive research on mammalian nutrition, suboptimal nutrition during gestation continues to be problematic for many livestock species (Wu et al., 2004). Nutrition demand during the early phases of fetal development are critical to accommodate maximal placental growth, differentiation, and vascularization (Funston et al., 2010). Normal fetal development follows an exponential pattern, such that 75% of growth in the bovine fetus takes place in the last 2 mo (NRC 2000; Robinson et al., 1977). Nutrient demands of the fetus parallel the exponential growth of the fetal tissues (NRC, 2000). By d 250, uterine uptake from maternal nutrient supply is 46%, 72%, and 12% for glucose, amino acids, and acetate, respectively (Bell, 1995). In order to meet these requirements the dam may need to dramatically shift basal metabolism (Bell, 1995).

The protein requirement of the maternal diet will drastically increase with the increase in amino acid uptake in utero. Bull et al. (1979) reported that cows maintained on diets deficient in crude protein produced calves that exhibited symptoms classically seen of Weak Calf Syndrome. Calves born to heifers that received a protein-restricted diet had decreased heat

production of 11.4% compared to calves born to dams receiving adequate protein levels in the diet (Carstens et al. 1987). More recent research has shown positive results for cow weight and body condition in calves born from cows supplemented with a protein supplement (Larson et al., 2009), as well as improved performance and health of offspring (Martin et al., 2007; Stalker et al., 2006; Larson et al., 2009). Weaning weights, both actual and adjusted, were greater in calves from supplemented dams (Larson et al., 2009). Heifers from protein-supplemented dams were heavier at weaning, pre-breeding, first pregnancy, and had greater pregnancy rates than those from non-supplemented dams (Martin et al., 2007). Steers from protein-supplemented dams had increased weaning and carcass weights (Stalker et al., 2006; Larson et al., 2009). The carcasses from protein-supplemented dams also had greater intramuscular fat and increased percent choice quality grades (Larson et al., 2009). Earlier work by Martin et al. (2007) did not show a difference between protein- and non-supplemented dams, however, more recent research by Larson et al. (2009) indicates that protein-supplementation during late gestation did tend to affect calf birth weight.

Birth weight is commonly used as an initial reference point when regarding the development of an individual animal, and it represents the culmination of the most dynamic growth and development process in mammalian biology (Holland and Odde, 1992). At fertilization, the weight of the zygote is approximately 1.0 ng, by parturition, the fetal weight averages 38.5 kg, which equates to a 38 trillion fold increase in weight over an average 283 d period (Holland and Odde, 1992). Since gestation length is relatively constant, variations in birth weight (BW) are the result of differences in fetal growth rate (Holland and Odde, 1992). Offspring born at above-average BW have an increased chance of survival compared to those born at below-average BW (Funston, et al., 2010). However, above-average BW may increase

the incidence of dystocia (Laster et al., 1973), leading to increased birth asphyxia, metabolic and respiratory acidosis (Szenci, 1985), depressed immunoglobulin absorption (Odde, 1988), and an increased predisposition to disease (Roy, 1990). Offspring with below-average BW may lack vigor, tolerance to cold-stress (Carstens et al., 1987), resistance to infectious agents (Roy, 1990), or the ability to overcome stresses of parturition during adaptation to extra uterine life (Woodward and Clark, 1959; Herschler et al., 1962). Increased BW in livestock species can be advantageous or detrimental depending on production environment; thus, it is critical to recognize the demand environment places on the animal genetics (Jenkins and Ferrell, 2006).

Colostrogenesis

As previously mentioned, the syndesmochorial placenta of the cow separates the maternal and fetal blood supplies (Arthur, 1996); thus, preventing the transmission of immunoglobulins in utero and categorizing the neonatal calf as agammaglobulinemic (Weaver et al. 2000). Consequently, intake and absorption of colostral components plays a critical role in passive immune transfer and ultimately survival rate of the neonatal calf (Stelwagen et al., 2009). Colostrogenesis occurs prepartum and results in the formation of secretory colostrum in the mammary gland (Stark et al., 2015). The mammary gland begins concentrating colostral components during the final 4-5 wk of pregnancy (Stark et al., 2015). Colostrum is a combination of diverse components, such as fat, lactose, vitamins, and minerals that have a high quality nutritional composition (Ontsouka et al., 2003). In addition to and more important than the nutritional value, colostrum contains a complex of cells and proteins that actively protect the neonate from pathogens and other extra-uterine challenges (Bendixen et al., 2011). In colostrum the concentration of immunoglobulins is particularly high; in ruminants the major immunoglobulin class is IgG (Stelwagen et al., 2009). In addition to immunoglobulins,

colostrum contains viable cells such as neutrophils and macrophages, which secrete numerous immune-related components, as well as oligosaccharides, gangliosides, acute phase proteins, immunomodulatory factors, ribonucleases, and a range of peptide and proteins with antimicrobial activity (Stelwagen et al., 2009). These immune-related components secreted by neutrophils and macrophages include cytokines, antimicrobial proteins and peptides, and reactive oxygen species (Stelwagen et al., 2009). Mammary epithelial cells also contribute to the host defense by secreting innate immune effector molecules such as lactoferrin, β-defensin, and lipopolysaccharide-binding protein (LBP) (Stelwagen et al., 2009).

Research on the hormonal regulation of immunoglobulin transport into colostrum has been investigated but remains incomplete (Wheeler et al. 2007). Smith et al. (1971) suggested that changing serum concentrations of estrogen and progesterone in late pregnancy exerted a controlling influence on the transport of IgG. Other research suggests the IgG transfer is a consequence of mammary gland development, which is controlled by estrogen and progesterone. (Lascelles and McDowell, 1974).

The accumulation of immunological cells and proteins enter the bovine mammary gland in various ways. The bovine mammary gland plays an active in role in regulating the concentration of various immunoglobulins in colostrum, predominantly IgG and to a lesser extent IgA, however the mammary epithelium itself does not synthesize immunoglobulins (Stelwagen et al., 2009). A small amount of the immunoglobulins enter the colostrum from the blood serum through the paracellular route as a result of "leaky" intercellular tight junctions (Lacy-Hulbert et al., 1999). The vast majority of immunoglobulins enter through a selective receptor-mediated intracellular route (Stelwagen et al., 2009). These immunoglobulins may be blood-derived or produced in situ by intramammary plasma cells (Stelwagen et al., 2009).

Mayer et al. (2005) demonstrated the presence of a specific IgG receptor, neonatal Fc receptor (FcRN), in the mammary epithelial cell (MEC) that plays an active role in transporting IgG into the lactating bovine mammary gland. IgA found in bovine colostrum is produced by intramammary plasma cells (Stelwagen et al., 2009). These plasma cells move to the mammary gland through the blood, where their transport is mediated by chemokines (Wilson and Butcher, 2004). The movement of IgA across the MEC is facilitated by the polymeric immunoglobulin receptor (pIgR) expressed in the mucosal epithelium (Apodaca et al., 1994). On the apical side of the MEC, pIgR is cleaved and IgA is released into the alveolar lumen along with a secretory component of pIgR (Apodaca et al., 1994).

The movement of neutrophils and macrophages into the alveolar lumen is mediated in a separate fashion than that seen with IgG and IgA. Serum amyloid A3 (SAA-3), a variant of the serum amyloid A (SAA) family, is expressed by MEC in response to pathogens and is present in milk and colostrum (McDonald et al., 2001). The concentration of SAA-3 is increased 200 fold in colostrum than in later lactation milk (McDonald et al., 2001). The SAA protein has numerous proinflammatory actions including chemoattractant to neutrophils, monocytes, and T lymphocytes, causing adhesion to the MEC (Badolato et al., 1994; Xu et al., 1995; Su et al., 1999). These findings suggest a crucial function for SAA to establish and maintain inflammation (He et al., 2009). The inflammatory status produced by SAA allows a continued flow of neutrophils and macrophages into the alveolar lumen, which directly kill bacteria via phagocytosis, but also produce numerous cytokines, reactive oxygen species and antimicrobial peptides (Stelwagen et al., 2009). Cytokines are immunological regulatory proteins that affect a wide variety of cells and tissues (Tizard, 2000). Cytokines are redundant in their biological activities and many of them have similar effects. This has given rise to the concept of the

cytokine network (Hirako et al., 2005). Further explanation is beyond the scope of this review. Reactive oxygen species are highly reactive metabolites of oxygen, including superoxide anion, hydroxyl radicals, and hydrogen peroxide, that are produced by active phagocytes (Abbas et al., 2014). Reactive oxygen species are used by phagocytes, such as neutrophils and macrophages, to form oxyhalides that damage phagocytized bacteria and may also be released from the cells to promote an inflammatory response (Abbas et al., 2014).

The bovine MEC plays an active role in mammary gland defense and synthesis of lactoferrin, β-defensins, and LBP (Stelwagen et al., 2009). Lactoferrin is an iron binding molecule that transports iron ions; additionally, lactoferrin has a wide variety of biological functions (Brock, 2002). Lactoferrin provides antimicrobial activity, both bactericidal and fungicidal, to the mammary gland and to the neonate (Brock, 2002). The concentration of lactoferrin increases during most inflammatory reactions and some viral infections, and it is classified as an acute phase protein (APP) (Kanyshkova et al., 2001). B-defensins are a subset of antimicrobial peptides that interact with the adaptive immune system, and are produced in response to microbial products or pro-inflammatory cytokines (Ganz and Lehrer, 1998). Lipopolysaccharide binding protein (LBP) is one of the most produced immune system proteins during infections with gram-negative bacteria (Schumann et al., 1990). The main function of LBP is to bind bacteria lipopolysaccharides (LPS) expressed on the cell wall of bacteria, acting as a transporter for LPS and to help control LPS-dependent monocyte response (Stelwagen et al., 2009).

Bovine Neonatal Digestive Tract Physiology

Nursing by the calf on the dam will cause the closure of the esophageal groove (Dirr and Dirksen, 1989). Closure of the esophageal grooves allows colostrum and milk to bypass the

reticulo-rumen and enter the abomasum (Titchen, 1976). Fluid consumed by the neonatal calf must come into contact with the receptors located in the oropharyngeal area (Dirr and Dirksen, 1989). Nursing by the neonate and secretion of colostrum from the dam causes vagal stimulation of the afferent nerve located in the mouth and pharynx. This stimulation causes the lips of the esophageal groove extending from the cardia to the reticulo-omasal orifice to contract (Phillipson, 1970). A twisting movement of the lip draws the epithelium to the reticulum adjacent to it forming a tube for colostrum and milk to pass into the abomasum (Phillipson, 1970). Failure of the esophageal groove causes the colostrum or milk to flow into the reticulo-rumen (Dirr and Dirksen, 1989). If the colostrum or milk remains in the reticulo-rumen for a sufficient period of time, bacterial fermentation will take place, which can cause ruminal acidosis that can be fatal (Dirr and Dirksen, 1989).

The abomasum is similar to the monogastric stomach, and it is the only region in the gastrointestinal tract that contains secretory tissues, with fundic and pyloric regions that are histologically similar to the monogastric (Church, 1988). The fundic mucosa contains parietal cells, which secrete hydrogen chloride (HCL), peptic cells that secrete the proteolytic enzyme precursor pepsinogen, and mucous-secreting cells (Church, 1988). The secreted amounts of HCL are low at birth, although the plasma concentration of gastrin, which upregulates the secretion of HCL, is high (Guilloteau et al., 2009). The number of parietal cells, which release HCL are also very low at birth, but increases ten times during the first 72 h of life (Hill, 1956). The pH of the abomasum is approximately 5.8 at birth before the first nursing and decreases to approximately 3.0 after 42 h (Guilloteau et al., 1985). Chief cells in the abomasum, the only protease producing cells found in the abomasum, secrete an inactive proteolytic enzyme pepsinogen (Church, 1988; Johnson, 2013). Pepsinogen is converted to the active protease

pepsin at a pH of 2.1 (Church, 1988). The elevated pH seen in the abomasum at birth and for the first 24 h of life decreases proteolytic activation of pepsin (Guilloteau et al., 1983). This minimizes proteolytic and denaturing activity, which allows immunologic proteins and cells found in colostrum to move through the ruminant abomasum viably (Guilloteau et al., 1983).

Colostrum exits the abomasum via the pyloric valve and enters into the duodenal region of the small intestine. It is at the major duodenal papilla, very close to the pyloric valve in the small intestine, that the bile and pancreatic ducts enter (Church, 1988). At birth the pancreatic gland of the calf is well developed and ready to exert its exocrine function (Guilloteau et al., 2009). In the neonatal calf, secretions of the pancreatic juice are very low at birth (Guilloteau et al., 2009). The secretions respond to feeding from the first day of life. The secretions take place during the cephalic phase, during nursing, with the elevation of plasma concentrations of pancreatic polypeptide (Zabielski and Naruse, 1999). However, pancreatic secretions in the same study were not observed during the gastric and intestinal phases (Zabielski and Naruse, 1999). In the non-nursing neonatal calf, the exocrine pancreas secretes small amounts (about 1 μl/kg BW x min^{-1}) of pancreatic juice (Guilloteau et al., 2009). Pancreatic secretions steadily increase with age and reach 4.0 and 5.5 μL/kg BW/min^{-1} in 1 and 4 week old calves respectively (Zabielski and Naruse, 1999). Pancreatic proteases and trypsin secretions increase following the pancreatic juice volume patterns (Zabielski and Naruse, 1999). Bovine IgG, the most abundant immunoglobulin in colostrum, is most sensitive to degradation by trypsin (Pineiro, 1978). In order to combat trypsin degradation activity in the small intestine, colostrum contains trypsin inhibitors; colostrum has almost 100 times the level of trypsin inhibitors compared to conventional milk (Sandholm and Hankanen-Buzalski, 1979). The concentration of trypsin inhibitors in colostrum is positively related to the concentration of IgG

in the colostrum, which for poor quality colostrum can further reduce absorption due to a reduced defense against the proteolytic activity of trypsin (Quigley et al., 1995).

The amount of immunoglobulins transported across the epithelium of the small intestine increases from duodenum to ileum (Jochims et al., 1994). Absorption of colostral immunoglobulins occurs via transport through the enterocytes by pinocytosis (Jochims et al., 1994). The enterocytes of newborn calves seem to be non-discriminately permeable to all classes of immunoglobulins, as well as other proteins and macromolecules (Jochims et al., 1994; Tizard, 2000; Mayer et al., 2002). Immunoglobulins pass through the glycocalyx on the apical membrane of the enterocyte towards the basolateral membrane where they are exocytosed into the lacteals and intestinal capillaries and enter systemic circulation through the thoracic duct. (Tizard, 2000; Mayer et al., 2002; Weaver et al., 2000). The non-selectivity of this process has been substantiated by the fact that other protein macromolecule concentrations and enzyme activities such as γ-glutamyltransferase (GGT) are increased after ingestion of colostrum (Thompson and Pauli, 1981). However, Goldstein et al. (1951) identified clathrin molecules on the enterocytic microvilli in the jejunum and ileum of the calf near the IgG molecules, which may be evidence of a receptor mediated systems of transport. The presence of clathrin molecules implies the existence of the coated pits of vesicles (Stanley et al., 1972). Also, Mayer et al. (2002) determined the FcRN transporter protein in the neonatal ruminant enterocytes. In a similar fashion the specific IgG receptor FcRN in the MEC transports IgG into the lactating bovine mammary gland (Mayer et al., 2005). Reber et al. (2006) demonstrated the movement of whole leukocytes takes place from the intestinal lumen through the enterocyte and into circulation. They demonstrated that cytokines Cd43 and Cd11, necessary for leukocyte

transendothelial migration, are found in colostrum and assist in the migration through the enterocyte and into neonatal circulation.

The cessation of macromolecule absorption in the enterocyte is termed closure (Smith and Little, 1922). In the bovine neonate, closure of the enterocyte to colostral immune-proteins occurs with age at a progressively increased rate after 12 h postpartum (Stott et al., 1979a). Complete closure occurs at approximately 24 h postpartum when calves are not fed colostrum and even earlier on calves that receive colostrum shortly after birth (Stott et al., 1979b). Closure is caused by rapid neonatal enterocyte turn-over (Smeaton and Simpson-Morgan, 1985; Jochims et al., 1994). Lysosomes appear in new enterocytes at 24 h postpartum (Jochims et al., 1994). Lysosomes are membrane-enclosed organelles that contain enzymes capable of breaking down all types of biological polymers (Cooper, 2000). Immune-proteins that are absorbed by the enterocyte will come into contact with this organelle and be degraded (Jochims et al., 1994). Lysosomes first appear in the duodenum, followed by the cranial and middle regions of the jejunum (Jochims et al., 1994). The appearance of lysosomes first in the duodenum then in the upper and middle regions of the jejunum could be the reason that the lower section of the jejunum and the ileum were seen to absorb the largest amount of immunoglobulins (Jochims et al., 1994). Enterocytes will continue to absorb immune-proteins. However, the protein is destroyed proteolytically by the fusion of the lysosome with the vesicles containing the immune-proteins (Jochims et al., 1994).

Passive Immune Transfer and Factors Affecting its Efficiency

The PIT, specifically immunoglobulins, to the calf plays a critical role in short-term calf health (Smith and Little, 1922). Success of colostral transfer, reported by calf serum immunoglobulin concentrations, has been shown to be an important indicator of preweaning

morbidity and mortality (Perino, 1997). The primary immunoglobulin found in colostrum is IgG and it accounts for approximately 85% of the total immunoglobulins, with IgG_1 accounting for 80-90% of the total IgG (Larson et al., 1980). Calves with inadequate serum IgG concentrations (<8 mg/ml) at 24 h are from 3.2 to 9.5 times more likely to become sick and 5.4 times more likely to die before weaning compared to calves with adequate concentrations of serum IgG (>16 mg/ml) (Perino et al., 1993). When calves have inadequate serum IgG concentrations (<8 mg/ml) a failure of passive transfer of immunity (FPT) has occurred (Perino et al., 1993). In general, this is due to the inability of the dam to accumulate and secrete immunoglobulins and/or the neonatal calf's inability to nurse and absorb immunoglobulins in the bloodstream. Failure of the passive transfer of immunity itself is not a disease, it is a condition that predisposes the neonate to the development of infectious disease (Weaver et al., 2000). Numerous factors can cause FPT, the two most important are calf age at colostrum consumption and the mass of IgG consumed (Perino, 1997). Associated with these two factors are dystocia, twins, sex of calf, metabolic state of calf, dam disease and vaccination history, dam and calf genetics, dam age, dam body condition score, dam nutrition, and dam udder conformation and health (Perino, 1997; Weaver et al., 2000).

Immunoglobulin transfer across the enterocyte is optimized in the first 4 h postpartum and begins to decline rapidly after 12 h postpartum (Stott et al., 1979; Bush and Staley, 1980). Calves fed earlier will have a significantly higher serum IgG concentration than those fed later when similar concentrations are fed (Stott et al., 1979). In addition to the calf's ability to nurse and absorb is the dam's ability to accumulate and secrete immune-proteins. IgG comprises roughly 85% of the total immunoglobulins found in colostrum; thus, the concentration of IgG in colostrum has been considered the trademark for evaluating colostrum (Larson et al., 1980;

Godden, 2008). High quality colostrum has an IgG concentration greater than 50 mg/mL (McGuirk and Collins, 2004). The average concentration of IgG in dairy breeds (predominantly Holsteins) is 32 mg/mL in dams ranging in age from 2-5 plus years (Foley and Otterby, 1978) and in beef breeds (predominantly Hereford and Angus) is 57.65 mg/mL in dams ranging in age from 2-9 plus years (Odde, 1988). This difference is due to the inverse relationship of milk yield and colostral IgG production (Pritchett el al., 1991).

Incidence of dystocia has been reported to decrease PIT (Odde, 1988; Muggli et al., 1984). However, Stott and Reinhard (1978) did not find a dystocia effect on calf serum IgG concentrations when all calves were fed 1 L of colostrum. Prolonged parturition can cause the development of respiratory or metabolic acidosis, and calves with prolonged calving times are more likely to become acidotic than calves born from normal parturition (Szenci, 1983). Fetal asphyxia is characterized by mixed respiratory-metabolic acidosis (Bleul and Götz, 2013). The respiratory component of acidosis is caused by an accumulation of carbon dioxide in the fetus due to diminished removal by the placenta (Szenci, 1985). Metabolic acidosis in neonatal calves is caused by L-lactate (Bleul and Götz, 2013). L-lactate in blood plasma is the result of anaerobic glycolysis and is formed when pyruvate is converted by lactate dehydrogenase (Lagutchik et al., 1996). Carbon dioxide, a weak acid, and L-lactate, a strong acid, account for neonatal acidosis (Bleul and Götz, 2013). Studies have shown higher concentrations of lactate from calves delivered after calving assistance compared to unassisted calves (Diesch et al, 2004; Sorge et al., 2009; Bleul and Götz, 2013). Bleul and Götz (2013) determined duration of parturition had effects on pH and L-lactate but not on pCO_2. Serum IgG may be reduced in calves that have lower blood pH and elevated pCO_2 (Besser et al., 1990). Duration of metabolic acidosis exceeds that of respiratory acidosis, 48 and 4 h, respectively, in neonatal asphyxiated

calves (Bleul and Götz, 2013). Conversely, Boyd (1989) showed duration of metabolic acidosis did not exceed respiratory acidosis, 2 and >24 h, respectively. Most research on the effects of dystocia and PIT have focused on respiratory acidosis, measuring pH and pCO_2, and results have been confounding (Besser et al., 1990; Boyd, 1989; Drewry and Quigley, 1997). However, the potential relationships of dystocia, L-lactate, and the PIT have not been evaluated.

A thorough nutrition strategy can affect cow-calf productivity in many ways; however, there is little evidence of a direct link between gestational cow nutrition and PIT in calves (Perino, 1997). Concentrations of CP in gestational cow nutrition generally do not have significant effects on colostral IgG concentrations (Olson et al., 1981; Blecha et al., 1981; Hough et al., 1990). However, Odde (1988) did see an increase in both colostral IgG and serum IgG in protein restricted beef heifers. Odde (1988) noted that the effect seen in calf serum IgG was probably the result of all calves being fed 1 L of colostrum. Olson et al. (1981) did not see a significant effect of the concentrations of CP in gestational cow nutrition on serum IgG levels; however, similar effects were reported on colostral IgG levels and Burton et al. (1984) did see reduced serum IgG levels in calves from protein restricted dams. The control diet used by Burton et al. (1984) had dietary CP levels at 110% of NRC requirement. Most research investigating the relationships nutrition has on colostral IgG and serum IgG has focused on dietary restrictions. Further investigation is warranted on supplementation of CP and/ or specific amino acids. General cow nutritional status can be visually measured with the use of BCS (Perino, 1997). Odde (1988) reported that first calf heifers with increased BCS was associated with increased serum IgG concentrations in their offspring ($p = 0.03$); however, BCS in cows of all ages was not significantly ($p = 0.19$). Perino et al. (1995) did not see a relationship between BCS and serum IgG levels in the calf at 24 h.

Age of dam is an important factor to a successful PIT in beef breeds (Odde, 1988; Perino, 1995; Muggli et al., 1984) and dairy breeds (Morin et al., 2000; Pritchett et al., 1991). In all studies mentioned, first-calf heifers have calves with lower serum IgG concentrations. The data for both dairy and beef breeds shows an increase in calf serum IgG as cow's age increases, plateauing at 3 - 4 yr and beginning to drop off after 6 - 7 yr. The reduction in calf serum IgG was only noted in beef breeds (Odde, 1988; Muggli et al., 1984). Odde (1988) noted that colostral IgG concentration did not differ across age. First-calf heifers have a decreased total colostral volume compared to multiparous dams (Odde, 1988).

Udder and teat confirmation and health in beef cows are not often given consideration (Perino, 1997). Most research on udder and teat conformation have been conducted on dairy cows. In dairy cows, udders suspended closer to the floor led to increased time for calves seeking the teat and duration of first nursing event (Ventorp and Michanek, 1992). Similar to Ventorp and Michanek (1992), Edwards (1982) noted more pendulous udders did affect the success of their calves finding the teat and suckling. Wesselink et al. (1999) did not see significance of udder conformation on calves finding the teat and nursing. Ventorp and Michanek (1992) did not report colostral or 24 h serum IgG, thus PIT or FPT was not reported. Perino (1995) reported that calves born to dams with clinical mastitis any time during lactation had reduced serum IgG concentrations at 24 h; however it was not apparent if mastitis was a causative risk factor due to compromised colostrum quality and/or quantity or if was associated with poor udder confirmation.

The gender of the neonatal calf has been shown to affect colostrum production and later lactation milk production (Joaquin et al., 2015; Hinde et al., 2014). Additionally, Joaquin et al. (2015) found that both total immunoglobulin concentration and colostral volume were affected

by the sex of the neonate. Total immunoglobulin concentration was higher in dams carrying males than for those carrying females; however, total colostral volume was higher in dams with female offspring than dams with male offspring (Joaquin et al., 2015). The results of the previous study agree with research conducted by Hinde et al. (2014). They found that dams with female offspring produced 5% more milk during lactation than dams with male offspring. They suggested that hormones from the fetus and placenta may enter maternal circulation to bind to the dam's MEC and influence functional development and subsequent milk synthesis. The mechanism that influences milk production may also affect colostrogenesis (Joaquin et al., 2015). The results from the studies mentioned above were performed in dairy cattle. Further research in beef cattle is warranted. Odde (1988) reported a higher incidence of FPT in male beef calves. This could have been due to the higher incidence of dystocia noted in male beef calves (Odde, 1988). Perino et al. (1995) and Filteau et al. (2003) included dystocia in a multivariate analysis, and did not find any variation between male and female serum IgG levels.

Vaccines

Immunization of humans and animals against infectious diseases has been practiced for over 200 years (Babiuk, 2002). The experiences seen through the past two centuries have shown the benefits of immunization and that vaccinations are one of the most cost-effective methods to preventing economic losses and increasing the lifespan of livestock (Babiuk, 2002). In livestock, the major causes of death preceding slaughter are due to infectious diseases (Babiuk, 2002). Bovine respiratory disease complex persists as the single most costly disease syndrome associated with commercial beef production in the United States, accounting for losses in 2010 of 1,055,000 animals valued at $643 million (NASS, 2011). Increased morbidity and mortality, decreased weight gains, decreased feed utilization, and decreased carcass quality

account for the economic losses associated with BRD (Edwards, 2010). Bovine respiratory disease complex was originally termed “shipping fever” since signs often occur shortly after arrival into the feedlot (Urban-Chmiel and Grooms, 2012). The morbidity risk of BRD in feedlot cattle occurs in the first 45 d after arrival into the feedlot with the highest risk occuring in wk 1 to 3, after that morbidity declines (Buhman et al., 2000; Edwards, 1996). Vaccination for viruses and bacteria associated with BRD are widespread (Taylor et al., 2010). The viral vaccine components of BRD consist of bovine herpesvirus type 1, also known as infectious bovine rhinotracheitis (IBR), bovine viral diarrhea (BVD), parainfluenza virus type 3 (PI-3), and bovine respiratory syncytial virus (BRSV) (Urban-Chmiel and Grooms, 2012). The bacterial vaccine components of BRD consists of *Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni* (Urban-Chmiel and Grooms, 2012). Killed and modified live vaccines (MLV) are available in different combinations of viral pathogens (Urban-Chmiel and Grooms, 2012). The appropriate use of these vaccines can reduce the risk of BRD (Urban-Chmiel and Grooms, 2012).

The three most common types of vaccines used for cattle are MLV, killed, and genetically engineered (Tizard, 2013; Cortese, 2002). Modified live vaccines contain living bacterial or viral organisms that are typically collected from field disease cases and then grown and passed through host cells or media for virus and bacteria, respectively, to attenuate the pathogen (Cortese, 2002). Each growth cycle represents a passage, and the modified pathogen is then administered back into the animal to determine its virulence (Cortese, 2002). After several passages, the pathogen loses virulence and can no longer cause disease in the specific species, and is then tested to confer immunity (Cortese, 2002). The final vaccines are passed a number of times beyond virulence in order to reduce the risk of reverting back to a virulent state

(Cortese, 2002). Killed vaccines use a pathogen isolated from a disease outbreak, grown in a media, and then chemically or physically killed (Cortese, 2002). The inactivation of the pathogen is achieved using chemicals or ultraviolet rays (Cortese, 2002). A concern using this type of vaccine is that heat inactivation may degrade important epitopes needed for a proper immune response (Cortese, 2002). To improve efficacy and achieve an effective immune response in killed vaccines, adjuvant is added to heighten the immune response (Cortese, 2002). Genetically engineered vaccines have been altered through a mutation that results in a bacterium or virus with altered virulence or growth characteristics (Cortese, 2002). Genetically engineered vaccines have been engineered to delete a gene and cause an immune response deficient in specific antibody responses (Cortese, 2002).

The term adjuvant is defined as a substance that, when used in combination with an antigen, enhances the immune response beyond those elicited by the antigen alone (Iain et al., 1993). Iain et al. (1993) defined four general ways in which adjuvants promote an immune response. First, adjuvants maintain a depot of antigen at the site of injection. Second, adjuvants promote accumulation of immunoreactive cells at the site of injection and also into the draining lymph nodes. Third, adjuvants modify the activities of cells that generate, promote, and maintain the immune response. Fourth, adjuvants can modify the presentation of antigen to the immune system. The most common adjuvants used in veterinary medicine are aluminum hydroxide and oil and water micelles (Ian et al., 1993). The effects of an aluminum adjuvant depends on the adsorption of antigen on the surface of the precipitate (Hansen et al., 2007). The greater the adsorption the more effective the adjuvant, allowing more antigen in the same volume of solution (Hansen et al., 2007). This adsorption depends on the concentrations of the adjuvant and the pH of the solution (Seeber et al., 1991). At high concentrations of adjuvant

and lower pH more adsorption will take place; however, at pH below 6.0 and higher concentration of adjuvant, pain and tissue irritation are produced at the injection site (Makimura and Suzuki, 1982).

Vaccines used specifically against IBR are classified into five types: parental administered MLV vaccines, chemically altered live virus temperature sensitive vaccines, inactivated viral vaccines, combination and inactivated viral vaccines, and MLV intranasal vaccines (Fulton, 2002). MLV parental vaccines are attenuated by multiple passages in a cellular culture that retain the ability to replicate in a vaccinated animal, possibly causing viremia (Fulton, 2002). MLV vaccines stimulate a rapid immune response and generally one dose is needed to stimulate protective immunity (Sutton, 1980; Fulton, 2002). One dose will stimulate an adequate immune response, which varies in length depending on the form of disease challenge (Fulton, 2002). Long term immunity, shown by antibody and cell-mediated response is detectible after an MLV vaccine is administered (Fulton, 2002). MLV intranasal vaccines can be divided into two attenuation processes, those that are modified by cell culture and those modified by treatment so that they are temperature sensitive (Todd et al., 1972; Fulton 2002). MLV intranasal vaccines stimulate protection with one dose and induce an initial rapid onset of protection, possibly through interferon-γ found in nasal secretions (Todd et al., 1972).

Disease control or elimination requires the stimulation of the immune system in a sufficient proportion of the population or herd (Siegrist, 2013). Immunization is achieved by inducing protection, as a result of stimulating the adaptive immune system (Siegrist, 2013). This immunity is achieved by the maintenance of antigen-specific immune effectors and/or by the induction of immune memory cells that can reactivate if re-exposure to the antigen occurs

(Siegrist, 2013). Antigen-specific immune effectors are antibodies produced by B lymphocytes that are able to bind to a specific toxin or pathogen (Cooper and Newmerow, 1984). Other potential effectors are cytotoxic $CD8^+$ T lymphocytes (CTL) that may limit the spread of infectious antigens by recognizing and killing infected cells as well as secreting antiviral cytokines (Siegrist, 2013). The proliferation and maintenance of B lymphocyte and CTL response is supported by growth factors and signals from $CD4^+$ T Helper lymphocytes (Th) (Siegrist, 2013). All of these immune effector cells are controlled by regulatory T cells (Treg), involved in immune tolerance (Bacchetta et al., 2005). Most antigens and vaccines trigger a B and T cell response; however, killed vaccines mostly mediate protection through the stimulation of B lymphocytes secreting highly specific IgG serum antibodies (Siegrist, 2013). These antigen specific antibodies have been shown to confirm vaccine-induced protection against numerous diseases (Casadevall, 2004).

Innate and Adaptive Immune Response

The body is equipped with multiple levels of defenses; thus, an organism that breaks through the first line of defense is confronted with a second, higher barrier and so forth (Tizard, 2013). The first line of defense are physical barriers to invasion (Tizard, 2013). Intact skin provides an effective barrier to invasion; however, insults to the skin such as scratches, incisions, microscopic abrasions, burns, and even insect bites may allow microbes to invade (Tizard, 2013). Other body surfaces, such as the mucosal linings of the respiratory and gastrointestinal tracts can act as physical barriers as well (Tizard, 2013). Physical defenses include coughing, sneezing, and mucous flow of the respiratory tract and vomiting and diarrhea in the gastrointestinal tract (Tizard, 2013). In addition to physical defenses, there is a large

population of commensal bacteria on the skin and in the gastrointestinal tract that can outcompete poorly adapted pathogenic organisms (Tizard, 2013).

In order to elicit a vaccine response, a vaccine must provide enough danger signals from the antigen, typically paired with an adjuvant, to trigger the inflammatory reaction that is mediated by cells of the innate immune system (Hoebe et al., 2004). Upon injection of vaccine antigens, an acute phase inflammation develops within minutes (Tizard, 2013). Upon injection of an antigen, broken cells release molecules known as damage-associated molecular patterns (DAMPs) that trigger the release of cytokines, chemokines, and enzymes from sentinel cells (Tizard, 2013). The antigens also provide molecules pathogen-associated molecular patterns (PAMPs) that trigger sentinel cell response (Tizard, 2013). The swelling at the sight of injection causes sensory nerves to release bioactive peptides (Tizard, 2013). The complex mixture of molecules attracts defensive white blood cells and increases blood flow to the sight of injection. Sentinel cells, such as macrophages, neutrophils, and dendritic cells located near the site of injection are active when DAMPs and PAMPs bind to their pattern-recognition receptors (PRRs) located on the cell surface of the sentinel cells (Tizard, 2013). This causes the sentinel cells to synthesize and secrete a mixture of molecules that trigger inflammation and initiates the first steps of the adaptive immune system (Tizard, 2013). The three major cytokines secreted by sentinel cells include tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) (Tizard, 2013).

The release of TNF-α, IL-1, and IL-6 increases protein synthesis, specifically acute phase proteins (APP) (Tizard, 2013). APP are a group of blood proteins that change in concentration when an animal is subjected to external or internal challenges, such as infection, inflammation, and stress (Murata et al., 2004). One of the most prominent APP found in beef

cattle is haptoglobin (Hp) (Alsemgeest et al., 1994). Haptoglobin concentrations in healthy cattle are often undetected, but during an acute phase response bovine haptoglobin can increase 50-100 times (Conner et al., 1988). Hp binds to free hemoglobin (Hb) in the plasma and reduces the oxidative damage associated with hemolysis (Yang et al., 2003). The Hp-Hb complex is recognized by receptors on macrophages and phagocytized (Schear et al., 2002). This action prevents bacteria from utilizing iron and thus prevents bacteria from proliferating (Idoate et al., 2015). Haptoglobin also plays a key role in the recruitment of neutrophils in the early phase of inflammation (Riollet et al., 2000). Hp concentrations will increase with both bacterial and viral infections (Schroedl et al., 2001; Ganheim et al., 2003; Heegaard et al., 2000; Idoate et al., 2015), and Hp can be used as a tool to measure respiratory disease in feedlot conditions (Idoate et al., 2015).

The triggering of inflammation by cytokines, and the mobilization of phagocytic cells such as neutrophils and macrophages contributes to the rapid destruction of foreign microbes (Tizard, 2013). Inflammation and the actions of the innate immune system may be sufficient to protect the body, but it cannot be guaranteed to provide complete resistance to infection, or assist the body to learn from the experience (Tizard, 2013). This limitation of the innate immune response is the advantage of the adaptive immune response (Tizard, 2013). Dendritic cells are the link between the innate and adaptive immune system. Dendritic cells act as sentinel cells and activate the innate defenses when they first encounter foreign antigen, they can process antigen and initiate the adaptive immune system, and they regulate adaptive immunity by determining whether an antigen will trigger an antibody-mediated and or cell-mediated response (Tizard, 2013). Dendritic cells process and then present foreign protein antigen to T cells (Tizard, 2013). Immature dendritic cells patrol throughout the body as sentinel cells

(Siegrist, 2013). When exposed to an antigen, dendritic cells undergo a maturation process, modulating specific surface receptors and migrate towards the lymphatic system, in secondary lymph nodes (Siegrist, 2013). The central role of mature dendritic cells, in response to a vaccine, is to provide antigen-specific and costimulatory signals to activate naïve T cells (Palucka et al., 2005).

Dendritic cells and T cells that have been upregulated by antigen exposure migrate towards secondary lymphoid tissues, including lymph nodes, spleen, Peyer's patches and mucosal associated lymphoid tissue (MALT) (Siegrist, 2013). These cells up-regulate specific surface molecules that provide B cell activating signals (Siegrist, 2013). T cells help drive B cell differentiation into immunoglobulin secreting plasma cells that can produce low affinity germline antibodies (Maclennan et al., 2003). When exposed to an antigen, dendritic cells undergo a maturation process, modulating specific surface receptors and migrate towards the lymphatic system, in secondary lymph nodes (Siegrist, 2013). Phagocytosed antigen is loaded onto the MHC class II molecules and presented to T cells (Tizard, 2013). The central role of dendritic cells, in response to a vaccine, is to provide antigen-specific and costimulatory signals to activate naïve T cells (Palucka et al., 2005).

Dendritic cells and CD4+ helper T cells that have been upregulated by antigen exposure migrate towards secondary lymphoid tissues, including lymph nodes, spleen, Peyer's patches and mucosal associated lymphoid tissue (Siegrist, 2013). These cells up-regulate specific surface molecules that provide B cell activating signals (Siegrist, 2013). CD4+ T cell help drives B cell differentiation into immunoglobulin secreting plasma cells that can produce low affinity germline antibodies, termed the extrafollicular reaction. (Maclennan et al., 2003). During B cell differentiation, immunoglobulin class switching from IgM towards IgG, IgA, or

IgE occurs with the upregulation of activation-induced deaminase enzyme (Siegrist, 2014). CD4+ T cells exert helper functions during the extrafollicular pathway, and engagement on B cells skew class-switch recombination into particular immunoglobulin classes and subclasses (Siegrist, 2013). Antigen specific B cells that receive sufficient help from antigen specific T cells proliferate in structures known as germinal centers, where differentiation into plasma cells takes place (Siegrist, 2013). This stimulation of the germinal centers as a few B cells upregulate and migrate towards B cell follicles, due to the attraction follicular dendritic cells (Siegrist, 2013). Follicular dendritic cells play a key role in the B cell response, they attract antigen specific B and T cells as well as retain antigen for extended periods of time (Siegrist, 2013). This time allows for a massive proliferation of the antigen specific B cells, which results in the large production of antibodies with increased antigen binding affinity (Siegrist, 2013).

B cells process vaccine antigen into small peptides that are displayed on the MHC class II, in a similar fashion to dendritic cells (Siegrist, 2013). The MHC-peptide complex is displayed on their surface and binds to a subset of CD4+ T cells, follicular helper T cells (Siegrist, 2013). These follicular helper T cells have different sets of chemokine receptors, transcription factors, surface markers, and interleukins that are uniquely equipped to provide the most efficient B cell help through a series of coststimulatory molecules (Vinuesa et al., 2005). The interactions between antigen-specific germinal center B cells, antigen bearing follicular dendritic cells, and follicular helper T cells results in the production of B cells with the highest level of antigen-specific affinity (Siegrist, 2013). This combination provides signals necessary for the differentiation of germinal center B cells either towards plasma secreting specific antibodies or towards memory B cells (Siegrist, 2013). Antigen specific antibodies have been

formally demonstrated as conferring vaccine-induced protection against many disease, and the production of memory B cells allows for the long term disease protection (Casadevall, 2004).

The objectives of this thesis are to: 1) determine the effect of parameters such as birth weight, incidence of dystocia, maternal colostral immunoglobulins, and neonatal 24 h serum Ig's on the passive transfer of immunity in the neonatal beef calf; 2) determine the effects of DDGS supplementation on colostrum production, offspring birth weight, incidence of dystocia, respiratory acidosis, and the passive transfer of immunity; and 3) determine the response of vaccination protocols for the bovine respiratory complex on feeding behavior and feedlot performance in previously vaccinated, newly weaned, backgrounding steers.

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CHAPTER 2. RELATIONSHIP OF BIRTH WEIGHT AND CALVING EASE WITH PASSIVE TRANSFER OF IMMUNOGLOBULINS IN NEONATAL BEEF CALVES

Abstract

The absorption of immunoglobulins (Ig) found in colostrum is a passive transfer of immunity that neonatal calves receive from their dams. Calves that do not receive adequate levels of Ig from their dams can experience increased morbidity and mortality. Commercial crossbred beef heifers (n = 53) were used to determine the relationship of passive transfer of immunity and Ig absorption from colostrum on various neonatal traits. Heifers were fed, in a dry lot, a total mixed ration meeting 100% of NRC requirements through parturition and calved in March and April. Onset of the third stage of labor, time to birth, time to stand, and time of first nursing were recorded. Calving ease (CE), calf vigor (CV), birth weight, and 24 h blood samples for serum Ig were taken from each calf via jugular venipuncture. Mothering score, colostrum samples for colostral Ig, weight, body condition score, udder suspension, and teat size were recorded from the dams. All statistical analyses were conducted using the regression and correlation procedures in SAS (SAS Ins. Inc., Cary, N.C.). There was a negative correlation between serum IgG and CE ($P = 0.018$), positive correlations between birth weight and CE ($P < 0.001$), and udder suspension and teat size ($P = 0.002$). A negative correlation was found between serum IgG and birth weight ($P = 0.047$) and a tendency of a positive correlation between serum IgG and teat size ($P = 0.076$). After correlations were found, stepwise regression calculations were completed on all significant correlative variables. A linear regression was found between CE and serum IgG ($P = 0.01$) and quadratic regression between birth weight and serum IgG ($P = 0.04$). Difficulties during third stage labor increased as calf birth weight increased. The increases in CE scores were associated with decreased serum IgG

found in the calf after 24 h. This depression of serum IgG due to calving difficulty may impair the ability of calves to adequately defend against pathogen exposure and may influence subsequent growth and performance.

Introduction

Calf health is vital to North Dakota beef producers. Colostrum absorption is one of the most important factors in shaping calf health. Calves that fail to absorb enough Ig in colostrum have high pre-weaning mortality rates, up to 89% in the first week of life (McGuire et al., 1976), as well as other short-term and long-term losses related to animal health, welfare, and productivity (Godden, 2008). Adequate Ig absorption requires calves to receive a sufficient volume of their dam's colostrum within the first 24 h of birth. Colostrum is vital to the calf due to the bovine placental type that prevents transmission of protective Ig. The absorption of Ig helps protect the calf against diseases until its own immature immune system becomes functional.

The interaction of the dam and her offspring is also vital for the calf to absorb the necessary amounts of Ig needed to mount a defense against pathogens. Stresses during birth such as dystocia, environment, and individual handling of the animals can affect each animal differently. These stresses can impact both the dam and her offspring negatively and may lead to a decrease in Ig within colostrum secreted by the dam and absorbed by her calf. Understanding the stress that the animal is under during late pregnancy may be beneficial for North Dakota cattle producers.

The objectives of this study were to determine relations of parameters such as birth weight, incidence of dystocia, maternal colostral Ig's, and neonatal 24 h serum Ig's with the passive transfer of immunity in the neonatal beef calf. We hypothesize that parameters such as

birth weight and incidence of dystocia are associated with differences in IgG concentrations in either maternal colostrum or offspring serum.

Materials and Methods

All procedures were approved by the North Dakota State University Animal Care and Use Committee. Fifty three primiparous Angus cross beef heifers were synchronized, artificially inseminated on 20 June, 2012, and exposed to Angus bulls in pasture at the Central Grasslands Research and Extension Center. Heifers calved in March and April. When adequate forage was no longer available, heifers were kept in a dry lot and a total mixed ration was fed meeting 100 percent of their requirements for gestation, weight, and growth trajectory (NRC, 2000).

Onset of third stage labor, time to birth (min) and time to stand (min) were recorded. Third stage labor started when the amniotic sac appeared at the vulva and ended when the calf was expelled from the dam. Stop time was subtracted from start time to achieve a birthing time. A 1 to 5 calving ease score was assigned post labor (1 = no assistance; 5 = caesarian section). Time to stand started when calf made first movements and ended when calf could step without falling. This was observed while dam was in dry–lot unless calving difficulty was noticed. If 2 h passed from the onset of third stage labor without birth of the calf, the dam was brought into the calving barn and assistance was provided.

After time to stand was recorded, calf and dam were brought into the calving barn working facilities. The dam was weighed (kg) and given a 1 to 9 body condition scores (1 = emaciated; 9 = obese). A 1 to 9 udder suspension (1 = very pendulous with a broken floor; 9 = very tight) and teat size scores were assigned to the dam, (1 = very large, balloon–shaped; 9 = very small). A colostrum sample was taken from one of the front quarters. Ten strips of

colostrum were removed before a 5 mL sample was collected and frozen. The calf was weighed (kg) and tagged. Both dam and calf were then moved to a pen in the calving barn where the calf and dam were allowed to freely interact and the calf was allowed to nurse.

First nursing event was timed (min), starting when calf was actively nursing and obtaining colostrum and ending when calf showed little interest, moved away, and laid down. The calf was then brought back into the working room and weighed (kg) again. Throughout the calving process a mothering score (1 = the dam was up within ten minutes after delivery, is actively licking the calf to stimulate standing and is vocalizing to the calf encouraging it to nurse; 4 = cow shows aggression towards calf, will not let calf nurse, and does not vocalize) was assigned to the dam and a calf vigor score (1 = normal; 5 = stillborn) was assigned to the calf post first nursing event.

At 24 h after birth, a blood sample was taken via jugular venipuncture from each calf. The whole blood was centrifuged and a 5 mL sample of serum was frozen. Both colostrum and serum samples were shipped to The Saskatoon Colostrum Co. LTD where radial immunodiffussion RID (U.S. Veterinary Biological Permit No. 448A) was used to calculate total IgG concentration in the colostrum and serum samples. All data were analyzed using the correlation procedure of SAS (SAS Ins. Inc., Cary, N.C.). Correlations on all variables were calculated first. The mixed procedure of SAS was used with sex fitted as a fixed effect. No treatments were applied to these animals. Significance was determined with an alpha of $P \leq 0.05$.

Results

There was a positive correlation between the time it took the calf to stand and the labor time of the dam ($r = 0.53$, $P < 0.0001$) (Table 2.1). An increase in labor time may influence the

time it takes the calf to stand. Birth weight was positively correlated with the time it took the calves to stand (r = 0.36, P = .009) (Table 2.1). Larger calves took longer to stand up and nurse from their dams. Birth weight also had a positive correlation with third stage labor time (r = 0.55, P <.0001) (Table 2.1); thus, larger calves experienced prolonged labor times. The time to stand was negatively correlated with the serum IgG concentrations of the calf (r = -0.44, P = 0.001) (Table 2.1). Calves that took longer to stand up after birth tended to have lower serum IgG concentrations. (P = 0.07) (Table 2.1). A negative correlation was seen between serum IgG and birth weight of the calf (r = -0.28, P = .047) (Table 2.1).

Dams that needed birthing assistance either by manual assistance or caesarian section, due to increased calf weight, had increased labor times and calves took a longer time to stand and start nursing. Calving ease score had a positive regression plot with birth weight (P < .0001) (Figure 2.1). Calving ease score had a positive correlation with time of third stage labor (P <.0001) (Figure 2.2) and time to stand (P < .0001) (Figure 2.3). Calving ease score had a negative relationship with serum IgG concentrations in the calf at 24 hours (P = .0184). Increased time of labor and the increased difficulty of labor were associated with a decrease in serum IgG concentrations in the calf.

Mothering score had a positive relationship with calf vigor score (P = .007) (Table 2.1). Aggressive dams were more likely to have calves that were weak and needed assistance. Udder and teat characteristics were positively correlated with each other (P = .002) (Table 2.1); therefore, dams with larger more pendulous quarters also had large more bulbous teats. Udder suspension was related to BCS, dams that have higher body condition scores also were more likely to have larger more bulbous quarters (P = .027) (Table 2.1). However, teat score had a negative relationship with cow weight (P = .016) (Table 2.1).

When sex was analyzed as the independent variable, labor times for bull calves were 36 min longer (± 7.5 min) when compared to heifer calves ($P = 0.001$) (data not shown). Bull calves were also 4.45 kg larger than heifer calves at birth ($P = 0.0009$) (data not shown). There was a tendency of bull calves to have a decreased calving ease score compared to heifer calves ($P = 0.072$). This could be due to the differences seen in calf birth weight and labor time associated with bull calves. All other variables were not significantly different between male and female offspring.

Table 2.1. Pearson correlation coefficients (P – Value) for Serum IgG, Cow Weight, BCS, Udder Score, Teat Score, Calving Ease, Mothering Score, Labor Time, Calf Vigor Score, Calf Birth Weight, and Stand Time.

	Cow Weight	BCS	Udder Score	Teat Score	Calving Ease	Mothering Score	Labor Time	Calf Vigor Score	Calf Birth Weight	Stand Time	Nursing Time
Serum IgG	-0.04	-0.07	-0.02	-0.25	-0.33	-0.16	-0.25	-0.09	-0.28	-0.44	-0.06
	(0.80)	(0.61)	(0.87)	(0.08)	**(0.018)**	(0.31)	(0.07)	(0.54)	**(0.047)**	**(0.001)**	(0.68)
Cow Weight		0.25	-0.04	-0.34	0.03	0.2	-0.17	0.09	0.14	-0.07	0.12
		(0.08)	(0.76)	**(0.016)**	(0.84)	(0.20)	(0.25)	(0.51)	(0.31)	(0.65)	(0.40)
BCS			0.31	-0.04	-0.14	0.21	-0.18	0.23	-0.27	-0.19	0.04
			(0.026)	(0.80)	(0.33)	(0.18)	(0.20)	(0.10)	**(0.054)**	(0.19)	(0.79)
Udder Score				0.422	-0.05	0.07	0.04	0.27	-0.12	0.05	-0.04
				(0.002)	(0.73)	(0.64)	(0.08)	(0.056)	(0.41)	(0.71)	(0.76)
Teat Score					-0.1	-0.05	-0.04	-0.06	-0.09	0.04	-0.21
					(0.48)	(0.73)	(0.76)	(0.69)	(0.54)	(0.76)	(0.14)
Calving Ease						-0.08	0.65	0.24	0.62	0.64	0.14
						(0.61)	**(<.0001)**	(0.09)	**(<.0001)**	**(<.0001)**	(0.34)
Mothering Score							-0.18	0.41	-0.06	0.07	-0.21
							(0.24)	**(0.007)**	(0.69)	(0.62)	(0.19)
Labor Time								0.04	0.55	0.53	-0.03
								(0.79)	**(<.0001)**	**(<.0001)**	(0.83)
Calf Vigor Score									0.16	0.01	0.03
									(0.27)	(0.94)	(0.85)
Calf Birth Weight										0.36	-0.02
										(0.009)	(0.86)
Stand Time											0.07
											(0.62)

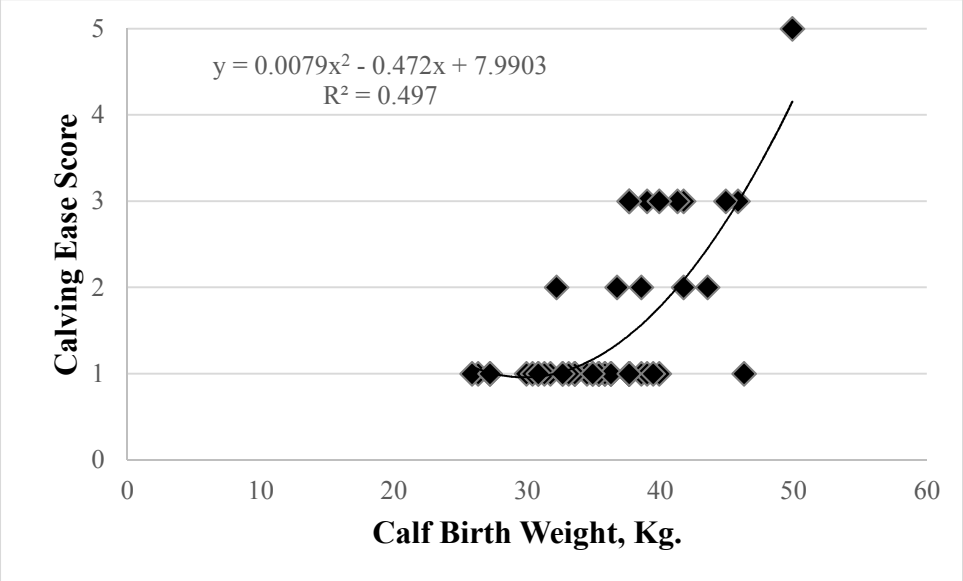

Figure 2.1. The relationship of calving ease and calf birth weight in commercial beef heifers

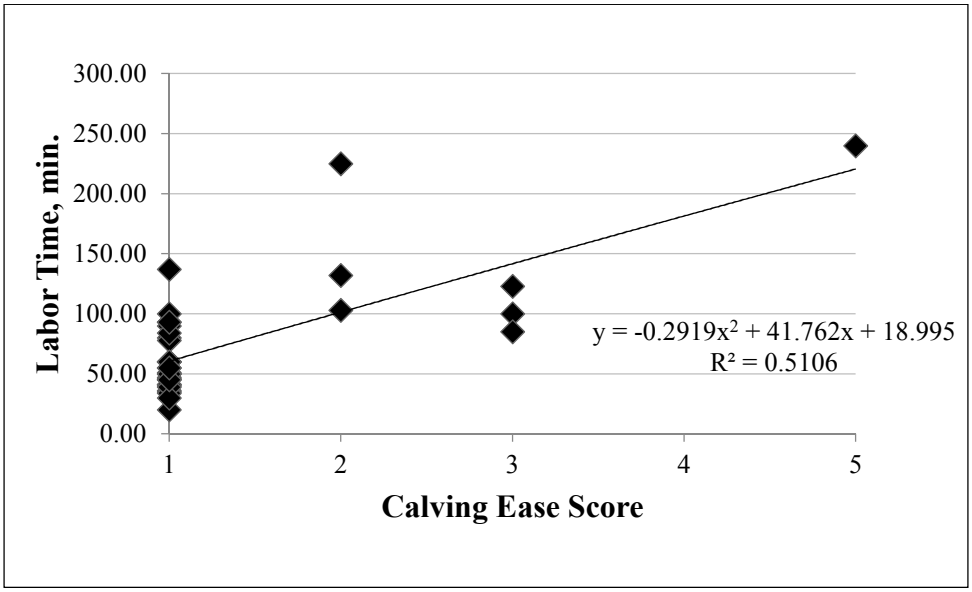

Figure 2.2. The relationship of labor time and calving ease score in commercial beef heifers

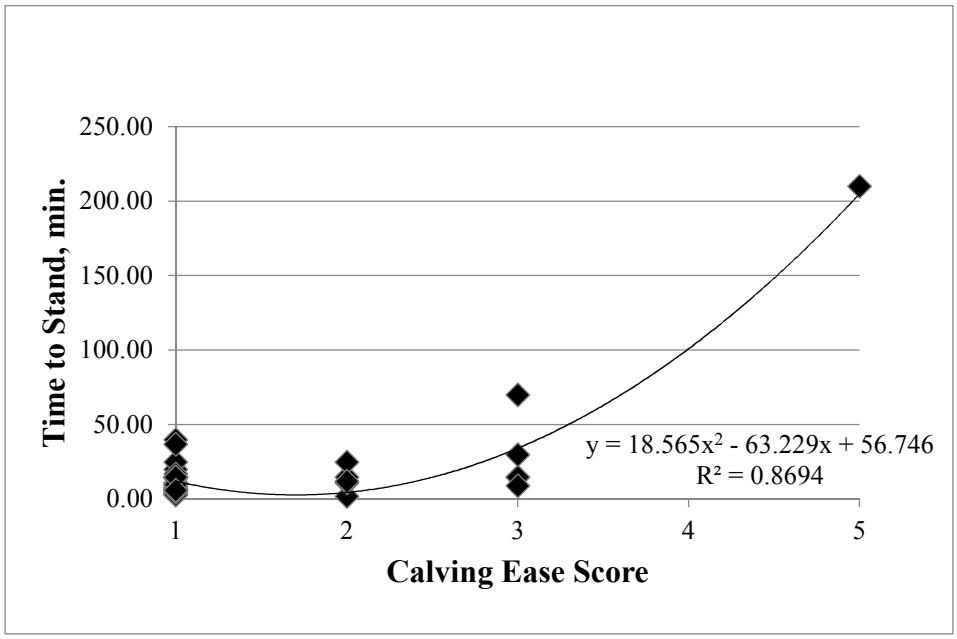

Figure 2.3. The relationship of time to stand and calving ease score in commercial beef heifers

Discussion

Our results indicate that there is some influence of birth weight and incidence of dystocia in beef cattle on the passive transfer of immunity from dam to offspring. Calves with increased birth weights and calves that have experienced difficulty during birth had decreased serum IgG concentrations. The passive transfer of colostral immune-proteins (PIT), specifically immunoglobulins, to the calf plays a critical role in short-term calf health (Smith and Little, 1922). An increase in third stage labor time may influence the time it takes a calf to stand. Larger calves experienced increased labor times and take longer to stand up and nurse from their dams. This coincides with Odde (1988) and Muggli et al. (1984) research which indicated as incidence of dystocia increased, a successful PIT decreased.

Calves that had increased time to stand up after birth had decreased serum IgG concentration at 24 h. Turnover of the enterocytes of the small intestine rapidly decrease the transfer of immune components from colostrum to serum (Stott et al., 1979), thus the increased

time need for the calf to take its first steps and begin nursing may restrict efficiency of absorption and total serum immune component levels. Larger calves may absorb less IgG than smaller calves within the first 24 h after birth due to increased standing and labor times. Dams that required birthing assistance either by manual assistance or caesarian section, due to increased calf weight, had increased labor times or had calves that took longer to stand and nurse. Prolonged parturition can cause the development of respiratory or metabolic acidosis, and calves with prolonged calving times are more likely to become acidotic than calves born from normal parturition (Szenci, 1983). This may have been a factor that contributed to the correlations observed with level and incidence of dystocia on labor and standing times, these calves may have been suffering from metabolic and or respiratory acidosis and thus may have been too weak to immediately stand and nurse. Increased labor time and increased stress due to prolonged labor showed a decrease in serum IgG concentrations in the calf.

Mothering score was positively related to calf vigor score. Dams that showed aggression or little interest in their calves had calves that were weaker and needed increased assistance. Dams with larger more pendulous quarters also had larger more bulbous teats. In primiparous dams as teat size score increased, calf serum IgG concentrations tended to decrease. Edwards (1982) noted more pendulous udders did effect the success of calves finding the teat and suckling. However, the author did not observe any relationship on teat conformation. Numerous other studies, performed on dairy cattle, also did not observe any significant difference on udder and teat conformation for calves finding the udder and nursing (Ventorp and Michanek, 1992; Wesselink et al., 1999). None of the trial listed above on udder conformation reported colostral or 24 h serum IgG levels, thus PIT and failure of passive transfer (FPT) were not reported.

It should be noted that the dams of this trial were all primiparous, and that age of the dam is an important factor to successful PIT in beef breeds (Odde, 1988; Perino et al., 1995; Muggli et al., 1984). Odde (1988), Perino et al. (1995), and Muggli et al. (1984) noted that primiparous dams have calves with lower serum IgG concentrations. First calf beef heifers have colostral IgG concentrations similar to older dams, however primiparous dams have decreased total volume compared to multiparous dams (Odde, 1988).

In conclusion, increased birth weight, incidence of dystocia, time required for a calf to stand, and teat size decreased serum IgG concentrations which may impair the ability of calves to develop an adequate immune response early in life. This research can contribute to new approaches on neonatal calf health and consequently beef cattle productivity as a whole. This work may inform producers of important factors associated with FPT and how to mitigate them.

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CHAPTER 3. EVALUATION OF RESPONSE TO SUPPLEMENTATION OF CORN DRIED DISTILLER'S GRAINS PLUS SOLUBLES TO LATE GESTATING BEEF COWS ON INCIDENCE OF DYSTOCIA, METABOLIC AND RESPIRATORY ACIDOSIS, AND THE PASSIVE TRANSFER OF IMMUNITY

Abstract

Intake and absorption of colostral components plays a critical role in passive immune transfer and ultimately survival rate of the neonatal calf. Maternal nutrition is crucial to fetal and placental development and can have significant long-and short-term impacts on offspring health. To test the effects of supplementation with corn dried distiller's grains plus solubles (DDGS) to late gestating beef cows on the incidence of dystocia, acidosis, and the passive transfer of immunity, multiparous beef cows were randomly divided into control (n = 15) and supplemented (n = 12) groups. Control diet consisted of an ad libitum diet containing 90% corn stover and 10% corn silage and supplemented group contained the same diet with the supplementation of DDGS (0.35% of BW). Corn silage inclusion was increased to 30% as gestation progressed to meet increasing requirements. At parturition, labor time, time to stand, and time to nurse were recorded. Calving ease, calf vigor, and mother scores, were assigned. The back right quarter of each dam was completely emptied of colostrum and a sample was collected. Udder and teat score were assigned. Blood samples were collected from calves at 0 and 24 h. Dams were weighed at 0 and 24 h and were assigned a BCS at 24 h. Supplemented dams weighed more postpartum then dams fed the control diet (695.3 vs. 609.9 ± 23.65 kg, P = 0.01). Colostrum production tended to be greater in supplemented dams than in control dams (836.9 vs. 614.0 ± 94.76 g, P = 0.098). Dams carrying female offspring produced more colostrum (890.5 vs. 560.5 ± 101.8 g, P = 0.02). Calves of supplemented dams were heavier at

birth and at 24 h (0 h, 43.2 vs. 39.8 ± 0.97, $P = 0.02$; 24 h, 44.0 vs 40.4 ± 1.12, $P = 0.02$). At birth, pCO_2 tended to be greater in calves born to supplemented dams (58.7 vs. 51.0 ± 2.93, $P = 0.059$). At 0 h, lactate levels were greater in calves born to control dams (4.68 vs. 3.53 ± 0.99, $P = 0.039$), but at 24 h lactate were greater in offspring from supplemented dams (3.77 vs. 2.61 ± 0.39, $P = 0.037$). At 24 h, base excess was greater in offspring born to control fed dams (7.79 vs. 4.18 ± 1.20, $P = 0.039$). Serum protein levels at 24 h tended to be greater in calves born to supplemented dams (6.42 vs. 5.85 ± 0.24, $P = 0.09$). Offspring from control fed dams experienced more difficulty at birth and weighed less, however there were no differences in 24 h serum IgG levels.

Introduction

The syndesmochorial placenta of the cow forms a syncytium between the maternal endometrium and the fetal trophectoderm, thus separating the maternal and fetal blood supplies (Arthur, 1996). This separation of maternal and fetal blood supplies prevents the transmission immunoglobulins in utero (Weaver et al. 2000). Prevention of immunoglobulin transfer in utero means calves are born agammaglobulinemic, thus the calf has very little to no immunoglobulins in circulation (Weaver et al. 2000), and are characterized as being immuno-naïve (Barrington and Parish, 2001). Although immuno-naïve in utero, as the fetus develops so do the various innate and adaptive immune defenses (Barrington and Parish, 2001). These mechanisms can be characterized into those dependent on antigen recognition by antibody and or lymphocytes, adaptive immunity, and those that occur independent of recognition events, innate immunity (Barrington and Parish, 2001).

In addition to growth and development of the fetal immune system, fetal growth overall is crucial and can be affected by nutritional status of the dam. In rats, Godfrey and Barker

(2000) demonstrated that the maternal diet can have significant long- and short-term impacts on offspring health. Maternal nutrition is crucial to fetal and placental development, which ultimately influences lifetime performance of that animal (Funston et al., 2010). Despite improved management techniques and extensive research on mammalian nutrition, suboptimal nutrition during gestation continues to be problematic for many livestock species (Wu et al., 2004). By d 250, uterine uptake from maternal nutrient supply is 46%, 72%, and 12% for glucose, amino acids, and acetate respectively (Bell, 1995). In order to meet these requirements the dam may need to dramatically shift basal metabolism (Bell, 1995).

The protein requirement of the maternal diet will drastically increase with the increase in amino acid uptake in utero. Bull et al. (1979) reported that cows maintained on diets deficient in crude protein produced calves that exhibited symptoms classically seen of Weak Calf Syndrome. More recent research has shown positive results for cow weight and body condition (Larson et al., 2009), as well as performance and health of offspring when dams are supplemented with protein (Martin et al., 2007; Stalker et al., 2006; Larson et al., 2009). Weaning weights, both actual and adjusted, were greater in calves from supplemented dams (Larson et al., 2009). Heifers from protein-supplemented dams were heavier at weaning, pre-breeding, first pregnancy, and had greater pregnancy rates than those from non-supplemented dams (Martin et al., 2007). Steers from protein-supplemented dams had increased weaning and carcass weights (Stalker et al., 2006; Larson et al., 2009). The carcasses from steers out of protein-supplemented dams also had greater intramuscular fat and increased percent choice quality grades (Larson et al., 2009). Earlier work by Martin et al. (2007) did not show a difference between protein- and non-supplemented dams, however, more recent research by

Larson et al. (2009) indicates that protein-supplementation during late gestation did tend to affect calf birth weight.

Birth weight is commonly used as an initial reference point when regarding the development of an individual animal, and it represents the culmination of the most dynamic growth and development process in mammalian biology (Holland and Odde, 1992). Offspring born at above-average BW have an increased chance of survival compared to those born at below-average BW (Funston, et al., 2010). However, above-average BW at birth may increase varying incidence of dystocia (Laster et al., 1973), leading to increased birth asphyxia, metabolic and respiratory acidosis (Szenci, 1985), depressed immunoglobulin absorption (Odde, 1988), and increased predisposition to disease (Roy, 1990). Offspring with below-average BW at birth may lack vigor, tolerance to cold-stress (Carstens et al., 1987), resistance to infectious agents (Roy, 1990), or the ability to overcome stresses of parturition during adaptation to extra uterine life (Woodward and Clark, 1959; Herschler et al., 1962). Increased BW at birth in livestock species can be advantageous or detrimental depending on production environment, thus it is critical to recognize the demand environment places on the animal genetics (Jenkins and Ferrell, 2006).

We hypothesize that dried distillers grains plus solubles (DDGS) supplementation to cows fed a low quality forage will alter colostrum production, offspring birth weight, incidence of dystocia, respiratory acidosis, and the passive transfer of immunity. The objectives were to investigate the effects of DDGS supplementation on colostrum production, offspring birth weight, incidence of dystocia, respiratory acidosis, and the passive transfer of immunity.

Materials and Methods

All procedures were approved by the North Dakota State University Animal Care and Use Committee. As previously described by Kennedy et al. (2015) 27 multiparous beef cows (Angus or Angus x Simmental) were divided randomly into a control group (n = 15) and a supplemented group (n = 12). Cows weighed 674 ± 17 kg and were 6 ± 5 yr old at the start of the study. Cows were housed at the NSDU Beef Cattle Research Complex in two adjacent pens, one for the control group and one for the supplemented group. After a 3-wk acclimation period, intake was monitored and controlled by the Insentec Roughage Feeders (Insentec, B. V., Markanesse Netherlands) beginning on d 201 of gestation for 10 wk. Cows were fitted with radio-frequency identification tags to monitor intake. A basal diet of 90% corn stover and 10% corn silage (5.0% CP on a DM basis, marginally deficient in NE and deficient in rumen degradable protein) was fed ad libitum to both groups, with the supplemented group receiving dried distiller's grains plus solubles (DDGS) at 0.35% of BW (DM basis). Inclusion of corn silage was increased to 20% on d 246 (gestation diet 2; 4.7 % CP on DM basis) and again increased to 30% on d 260 (gestation diet 3; 5.5% CP on a DM basis) to meet increased NE demands during pregnancy, supplementation administration remand the same throughout the trial. Each pen contained 8 Insentec feed bunks. In the control pen, all 8 feed bunks contained the basal diet, while in the supplemented pen 6 feed bunks contained the basal diet and 2 contained the DDGS supplement. Both pens had free access to water and trace mineralized salt blocks (95.5 to 98.5% NaCl, 3,500 mg of Zn/kg, 2,000 mg of Fe/kg, 1,800 mg of Mn/kg, 280 to 420 mg of Cu/kg, 100 mg of I/kg, 60 mg of Co/kg). On d 270 of gestation, close to parturition, all cows were fed the same diet (48% corn stover, 30% corn silage, 22% DDGS; DM basis, 10.8% CP) ad libitum for 10 wk, DDGS supplementation was concluded at the start of this diet.

During gestation cows were weighed mid-day (between feeding times at 0730 and 2630) every 2 wk from initiation of the project until d 242 of gestation. Cows were also weighed on d 180, 216, and 246 (± 5 d) of pregnancy and body condition scores were assigned by three technicians.

Feed samples of the total mixed diet and DDGS (both approximately 500 g) were collected and analyzed. All feed samples were analyzed for ash, CP, NDF, ADF, EE, Ca, and P. Forage samples were dried in a 55° C oven for 48 h and ground to pass through a 1-mm screen. Forage and DDGS samples were analyzed for DM, ash, N (Kjehldahl method), Ca, P, and EE by standard procedures (AOAC, 1990). Crude protein was calculated by multiplying N concentration x 6.25. NDF (using heat stable amylase and sodium sulfite and expressed inclusive of residual ash) and ADF (expressed inclusive of residual ash) concentration were analyzed sequentially by methods of Robertson and Van Soest (1981) using a fiber analyzer (Ankom Technology Corp., Fairport, NY).

During calving, cows were allowed to remain in their pens with the group until signs of labor were observed. If it was possible to move the cow inside the barn without causing undo stress, she was brought inside and put in an individual pen for calving, otherwise she was allowed to calve outside with the group and the cow-calf pair was immediately brought inside. Cows had access to hay and water ad libitum. Upon parturition third stage labor time was recorded, time started when amniotic sac appeared at the vulva and ended when calf was expelled from the dam. A calving ease score was assigned post labor (1 = no assistance; 5 = caesarian section). Time to stand was recorded, time started when calf showed first signs of movement and concluded when the calf could stand and take a step without falling. After time to stand was recorded the calf was removed from the pen, where a blood sample was taken via

jugular venipuncture. Excess amniotic fluid was removed and calf was weighed (kg). During this time the cow was removed and placed into the Silencer Hydraulic Squeeze Chute (Moly Manufacturing Inc., Lorraine KS.) For each cow, weight was determined, and the right rear quarter was milked completely to collect a colostrum sample. Total colostral weight was recorded (g). A subsample was placed in cryo-vials and frozen at -20° C until later analysis. An udder score (1 = very pendulous with a broken floor; 9 = very tight) and teat size scores (1 = very large, balloon–shaped; 9 = very small) was assigned to each dam. After completion the cow calf pair was placed back into the pen. Time of first nursing was recorded, starting when calf was actively nursing and obtaining colostrum and ending when calf showed little interest, moved away, and laid down. A calf vigor score (1 = normal; 5 = stillborn) was assigned to each calf and mothering score (1 = the dam was up within ten minutes after delivery, is actively licking the calf to stimulate standing and is vocalizing to the calf encouraging it to nurse; 4 = cow shows aggression towards calf, will not let calf nurse, and does not vocalize) was assigned to each dam. Each cow calf pair was monitored for signs of general health. At 24 h post calving calves were once more removed from the pen, a weight was recorded (kg) and a second blood sample was collected via jugular venipuncture. Cows were weighed and given a BCS.

All blood samples collected via BD Vacutainer sodium heparin 158 U.S.P. green top tubes (BD; I Becton Drive, Franklin Lakes, New Jersey 07417). Immediately following collection, 400 µL was pipetted from BD Vacutainer, approximately 80 - 200 µL was pipetted into a CG4+ i-STAT cartridge (measuring blood pH, pCO_2, pO_2, Base Excess, HCO_3, TCO_2, sO_2, and Lactate) and another 80 - 200 µL was pipetted into a E3+Cl i-STAT cartridge (measuring blood Na, K, Cl, hematocrit, and hemoglobin). Cartridges were placed into the Vetscan i-STAT 1 handheld analyzer (Abaxis North America, Union City, CA.). Remaining

blood samples were placed in a refrigerator 1° C for 30 min and centrifuged for 20 min at 1,380 x g to separate plasma, which was then pipetted into cryo-vials and frozen at -20° C until later analysis. All plasma and colostrum samples in cryo-vials were taken out of freezer and placed in sample tube holders at room temperature (21° C) until completely thawed. Subsamples were pipetted into new cryo-vials and placed in Styrofoam coolers with icepacks and shipped overnight to The Saskatoon Colostrum Co. LTD where radial immunodiffussion (U.S. Veterinary Biological Permit No. 448A) was used to calculate total IgG concentration in the colostrum and serum samples.

Data were analyzed using the mixed procedure of SAS (SAS Institute Inc., Cary N.C.). The model included fixed effects of maternal diet (supplement vs. control), sex of offspring, and their interaction. The interaction was tested and removed from the model (P value > 0.20).

Results

As previously reported by Kennedy et al. (2015), supplemented cows gained BW (P <0.01, 1.27 kg/d) and control cows tended to lose BW (P = 0.06, 0.23 kg/d). The BCS of control cows decreased (P < 0.01) and the BCS of supplemented cows did not change (P = 0.79) (Kennedy et al., 2015). Dam weight at 0 h was significantly greater in supplemented dams (695.3 vs. 609.9 kg ± 23.65, P = 0.01; Table 3.1) compared to control fed dams. Dam weight at 24 h remained greater in supplemented dams (694.2 vs. 597.2 kg ± 22.6, P = 0.004; Table 3.1) compared to control fed dams. Control fed dams lost 12 kg in 24 h while supplemented dams only lost 1.1 kg. Dam BCS was also greater in supplemented dams (5.81 vs. 4.96 ± 0.15, P = 0.001; Table 3.1) compared to control fed dams. Time of third stage labor did not differ between treatment groups (P = 0.67; Table 3.1). Udder and teat scores did not differ by treatment. Colostrum weight tended to be greater in supplemented dams (836.9 vs. 614.0 ±

94.8, $P = 0.098$; Table 3.1) compared to control fed dams. There was an effect of sex on colostrum production where dams with female offspring produce more colostrum (890.5 vs. 560.5 ± 101.8, $P = 0.02$) than dams that had male offspring (Kennedy et al., 2015). Colostral IgG concentrations were not significantly different between treatment groups ($P = 0.23$; Table3.1).

Table 3.1. Influence of treatment on dam parturition parameters

	Treatment			
Item	Control	Supplement	SEM[a]	*P* Value
labor Time (min)	48.08	57.31	15.1	0.66
0 Hour				
Dam weight, kg[b]	609.9	695.3	23.6	0.01
Colostrum weight, g[b]	614.0	836.9	94.8	0.098
Colostrum IgG, mg/mL	119.1	130.2	6.57	0.23
Udder Score	4.59	5.37	0.49	0.25
Teat Score	5.67	5.74	0.55	0.93
24 Hour				
Dam weight, kg[b]	597.15	694.2	22.6	0.004
Dam BCS[b]	4.96	5.81	0.15	0.001

[a]Standard error of the mean (n = supplement 12; contol 15).

[b]Kennedy et al., 2015

At 0 h, pCO_2 from whole blood tended to be greater in offspring from supplemented dam (58.7 vs. 51.0 mmHg, $P = 0.059$; Table 3.2) compared to the offspring of control fed dams. However, 0 h lactate from whole blood was greater in offspring from control dams (4.68 vs. 3.53 mmol/L, $P = 0.04$; Table 3.2) compared to offspring from supplemented dams. Zero h whole blood parameters for pH, pO_2, hemoglobin, and base excess were not significantly different between treatment groups. At 24 h, lactate from whole blood switched and was greater in offspring from supplemented dams (3.77 vs. 2.61 mmol/L; $P = 0.04$ Table 3.2) compared to offspring from control dams. Base excess from whole blood was greater in offspring of control

fed dams (7.69 vs. 4.1 mmol/L, $P = 0.04$; Table 3.2) compared to offspring of supplemented dams. Twenty-four h blood parameters for pH, pCO_2, pO_2, and hemoglobin were not significantly different between treatment groups. The difference (24 h – 0 h) in lactate was significantly decreased in offspring from control fed dams (-2.10 vs. 0.34 ± 0.90 mmol/L, $P = 0.05$; Table 3.2), while the levels in offspring of supplemented dams slightly increased. The difference (24 h – 0 h) in base excess was significantly increased in offspring from control fed dams (3.59 vs. -1.07 ± 1.40, $P = 0.02$; Table 3.2). There was an effect for change (24 h – 0 h) in hemoglobin by sex, where male offspring had a greater decrease (-1.45 vs. -0.83 ± 0.21 d/dL, $P = 0.04$). The difference (24 h – 0 h) in all other blood parameters pH, pCO_2, and pO_2 was not significant.

Table 3.2. Influence of treatment on blood parameters in offspring

	Treatment			
Item	Control	Supplement	SEM[a]	*P* Value
0 Hour				
pH	7.38	7.34	0.04	0.40
pCO_2, mmHg	50.99	58.73	2.93	0.059
pO_2, mmHg	23.27	25.04	5.45	0.14
Lactate, mmol/L	4.68	3.53	0.99	0.04
Hemoglobin, g/dL	12.53	13.19	0.46	0.30
Base Excess, mmol/L	4.10	5.25	1.61	0.59
24 Hour				
pH	7.52	7.44	0.04	0.19
pCO_2, mmHg	38.52	42.42	3.05	0.35
pO_2, mmHg	44.43	41.73	11.21	0.86
Lactate, mmol/L	2.61	3.77	0.39	0.04
Hemoglobin, g/dL	11.25	12.19	0.48	0.16
Base Excess, mmol/L	7.69	4.18	1.20	0.04
Change (24 h - 0 h)				
pH	0.14	0.11	0.04	0.53
pCO_2, mmHg	-12.47	-16.31	3.05	0.35
pO_2, mmHg	8.55	15.33	10.03	0.61
Lactate, mmol/L	-2.10	0.34	0.90	0.05
Hemoglobin, g/dL	-1.28	-1.00	0.20	0.33
Base Excess, mmol/L	3.59	-1.07	1.40	0.02

[a]Standard error of the mean (n = supplement 12; contol 15).

Serum IgG and total serum protein did not differ between treatment groups at 0 h. At 24 h total serum protein tended to be greater in offspring of supplemented dams (6.42 vs. 5.85 ± 0.24, $P = 0.091$; Table 3.3) compared to offspring of control fed dams. Twenty-four h serum IgG concentrations did not differ between treatment groups. The change (24 h – 0 h) in serum IgG and total serum protein was not different between treatment groups. The time that it took to stand and nursing times were not different between treatment groups. Calving ease and calf vigor scores were different between treatment groups. Calf weights at 0 h were greater in offspring from supplemented dams (43.2 vs. 39.8 ± 0.97, $P = 0.02$; Table 3.4) compared to

offspring of control fed dams, the same was noted at 24 h (44.0 vs. 40.4 ± 1.12, *P* = 0.02; Table 3.4) (Kennedy et al., 2015).

Table 3.3. Influence of treatment on serum protein and IgG in offspring

	Treatment			
Item	Control	Supplement	SEM[a]	*P* Value
0 Hour				
Serum IgG, mg/mL	0.33	0.29	0.07	0.63
Serum protein, g/dL	4.16	4.23	0.06	0.33
24 Hour				
Serum IgG, mg/mL	31.41	37.60	3.74	0.23
Serum protein, g/dL	5.85	6.42	0.24	0.091
Change (24 h - 0 h)				
Serum IgG, mg/mL	31.05	38.27	3.90	0.18
Serum protein, g/dL	1.69	2.23	0.25	0.11

[a]Standard error of the mean (n = supplement 12; contol 15).

Table 3.4. Influence of treatment on incidence of dystocia and vitality offspring

	Treatment			
Item	Control	Supplement	SEM[a]	P - Value
0 Hour				
Time to stand, min	38.9	50.8	8.16	0.30
Time to nurse, min	34.0	23.4	6.50	0.23
Calving Ease Score	1.87	1.44	0.36	0.39
Calf Vigor Score	1.00	1.15	0.12	0.36
Calf weight, kg[b]	39.8	43.2	0.97	0.02
24 Hour				
Calf weight, kg[b]	40.4	44.0	1.12	0.02

[a]Standard error of the mean (n = supplement 12; contol 15).

[b]Kennedy et al., 2015

As reported by Kennedy et al. (2015) on d 44 of lactation, supplemented dams took longer to finish milking (12.9 vs 10.7 ± 0.8 min, *P* = 0.05). Supplemented dams tended to produce heavier milk samples (2.8 vs. 2.1 ± 0.3 kg, *P* = 0.07) compared to control fed dams,

this resulted in a tendency for a greater milk production rate in supplemented dams (562.7 vs. 425.6 ± 50.7 g/hr, $P = 0.07$).

As reported by Kennedy et al. (2015), calves gained weight ($P < 0.01$) from birth to d 56 of lactation however there were no differences in weight gain across treatment ($P = 0.68$). Offspring from the supplemented dams were heavier at weaning (309.7 vs. 292.0 ± 6.0 kg, $P = 0.05$). Adjusted 205 d weaning weights tended to be greater in offspring of supplemented dams (288.4 vs. 274.0 ± 5.4 kg, $P = 0.06$) compared to the control fed dams.

Discussion

We accept our hypothesis that dried distiller's grains plus solubles (DDGS) supplementation to cows fed a low quality forage will result in altered colostrum production, offspring birth weight, incidence of dystocia, and respiratory acidosis. However, we did not see an effect of DDGS supplementation to cows fed a low quality forage on the passive transfer of immunity.

As previously discussed by Kennedy et al. (2015) a diet was created deficient in rumen degradable protein (RDP) and distinction between treatment groups was confirmed. Cows on the supplemented diet had increased RDP (estimated at 430 vs. 866 g/d, respectively) and metabolizable protein (MP) (estimated at 654 vs. 1245 g/d, respectively) supply due to DDGS supplementation. The control diet was also deficient in NE throughout the treatment period but was sufficient by the supplementation of DDGS (14 Mcal/d, compared to 22 Mcal/d when supplemented). Feeding the control diet resulted in decreased BCS and a tendency for weight loss, while feeding the supplemented diet resulted in maintained BCS and weight gain. Normal fetal development follows an exponential pattern, such that 75% of growth in the bovine fetus takes place in the last 2 mo (NRC 2000; Robinson et al., 1977). Nutrient demands of the fetus

parallel the exponential growth of the fetal tissues (NRC, 2000). By d 250, uterine uptake from maternal nutrient supply is 46%, 72%, and 12% for glucose, amino acids, and acetate respectively (Bell, 1995). In order to meet these requirements, the dam may need to dramatically shift basal metabolism (Bell, 1995). Also worth noting is the influence of sex on colostrum production where dams with female offspring produce more colostrum (890.5 vs. 560.5 ± 101.8, $P = 0.02$) then dams that had male offspring (Kennedy et al., 2015). This phenomenon has been reported in dairy cows (Joaquin et al., 2015; Hinde et al., 2014). Joaquin et al. (2015) found that both total immunoglobulin concentration and colostral volume were affected by the sex of the neonate. Total immunoglobulin concentration was higher in males than for females (Joaquin et al., 2015). However, total colostral volume was higher in dams with female offspring than dams with male offspring (Joaquin et al., 2015). The results of the previous study agree with research that was conducted by Hinde et al. (2014). Hinde et al., (2014) found that dams with female offspring produced 5% more milk during lactation than dams with male offspring.

There is little evidence of a direct link between gestational cow nutrition and PIT in calves (Perino, 1997). The tendency seen on protein supplemented dams (836.9 vs. 614.0 ± 94.8, $P = 0.098$) having greater colostrum production has been reported in ewes (O'Doherty and Crosby, 1996). There were no differences between supplemented and control dams on IgG concentration in the present study ($P = 0.23$). Olson et al. (1981), Blecha et al. (1981), and Hough et al. (1990) also reported seeing no differences on CP supplementation to gestational cows having significant effects on colostral IgG concentrations. Olson et al. (1981) did not see a significant effect of the concentrations of CP in gestational cow nutrition on serum IgG levels

as well. However, similar effects were reported on colostral IgG levels, Burton et al. (1984) did see reduced serum IgG levels in calves from protein restricted dams.

Though some of our indices of dystocia; time of third stage labor, time to stand, time of first nursing event, calving ease score, and calf vigor score did not show any significant differences, there were differences in blood parameters typical of respiratory and metabolic acidosis and associated with dystocia. Szenci (1983) noted prolonged parturition can cause the development of respiratory or metabolic acidosis, and calves with prolonged calving times are more likely to become acidotic than calves born from normal parturition. Studies have shown higher concentrations of lactate from calves delivered after calving assistance compared to unassisted calves (Diesch et al, 2004; Sorge et al., 2009; Bleul and Götz, 2013). Fetal asphyxia is characterized by mixed respiratory-metabolic acidosis (Bleul and Götz, 2013). The respiratory component of acidosis is caused by an accumulation of carbon dioxide in the fetus due to diminished removal by the placenta (Szenci, 1985). Metabolic acidosis in neonatal calves is caused by L-lactate (Bleul and Götz, 2013). Carbon dioxide, a weak acid, and L-lactate, a strong acid, account for neonatal acidosis (Bleul and Götz, 2013). A tendency was shown for elevated pCO_2 levels at 0 h (P = 0.059) and lactate levels were at 24 h ($P = 0.04$) in offspring of supplemented dams. The aspects that make up fetal asphyxia were most notably seen in the offspring of control fed dams. Zero h lactate from whole blood was greater in offspring from control dams ($P = 0.04$), base excess from whole blood was greater in offspring of control fed dams ($P = 0.04$), as well as the changes associated over the first 24 h of life seen in lactate in offspring from control fed dams ($P = 0.05$).

Though there were no significant differences in 24 h serum IgG and total serum protein with the supplementation of DDGS supplementation to cows fed a low quality forage, there

were differences in BW seen at birth as well as the difference in blood parameters seen in the first 24 h of life may have impacted the growth trajectory of the offspring at weaning. These findings warrant further investigation as they imply influences and may be strengthened by a larger number of cows in future experiments. Further investigation on late gestational diet and its impact on calf health and performance are warranted.

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CHAPTER 4. EVALUATION OF RESPONSE TO VACCINATION ON THE FEEDLOT PERFORMANCE OF WEANED CALVES

Abstract

The bovine respiratory disease complex (BRDC) is one of the costliest diseases for beef production in the U.S. Vaccination protocols to prevent BRDC are commonly used in beef herds. Unfortunately, some vaccines upon administration may negatively impact feed intakes, and feeding behavior. Previously vaccinated beef steers (356.21 ± 35.85kg, n = 76) were blocked by weight and randomly assigned to one of four treatments (n = 19 per treatment), treatment one was a 2 mL sterile saline injected subcutaneously in the left side of the neck, treatment two was a MLV vaccine (IBR, PI3, BRSV, BVDV type 1 and 2) in combination with a *Mannheimia haemolytica toxoid*, treatment three was an intranasal MLV vaccine (IBR, PI3, BRSV) along with a MLV vaccine (type 1 and 2 BVDV) in combination with a *Mannheimia haemolytica toxoid*, and treatment four was a MLV vaccine (IBR, PI3, BRSV, BVDV type 1 and 2) in combination with a *Mannheimia haemolytica toxoid* plus an intransal MLV vaccine (IBR, PI3, BRSV). The objective was to determine the effects of vaccination protocols on the acute phase inflammatory response, adaptive antibody response, feeding performance and feeding behavior of weaned calves. All treatments were administered as per label. Individual feed intake and feeding behavior was monitored using the Insentec roughage intake control system (Insentec, B. V., Marknesse, the Netherlands). Calves were vaccinated on day 0 of the trial, and weights and blood samples were collected on d 0, 1, 3, 6 and 28 of the trial. Haptoglobin, an acute phase protein, as well as antibody titers for bovine respiratory syncytial virus (BRSV) and infectious bovine rhinotracheitis (IBR), were used as a proxy to measure vaccine response. All vaccines initiated an inflammatory response ($P < 0.001$). Treatments two

and four induced an increase in serum antibodies by d 28. Feed intake and behavior were unaffected by the use of vaccines. ADG tended to be higher in treatment two ($P = 0.06$). In well-managed, properly-immunized herds, vaccination against BRD pathogens can stimulate antibody production without negative effects of the acute phase inflammatory response on feed intake, feeding behavior and performance.

Introduction

The experiences observed through the past two centuries has shown the benefits of immunization and that vaccinations are one of the most cost-effective methods to preventing economic losses and increasing the lifespan of livestock (Babiuk, 2002). In livestock, the major causes of death preceding slaughter are due to infectious diseases (Babiuk, 2002). Bovine respiratory disease complex (BRD) is one of the costliest diseases for beef production in the United States, accounting for losses in 2010 of 1,055,000 animals valued at $643 million dollars (NASS, 2011). Increased morbidity and mortality, decreased weight gains, decreased feed utilization, and decreased carcass quality account for the economic losses associated with BRD (Edwards, 2010). The morbidity risk of BRD cases in feedlot cattle occur in the first 45 d after arrival into the feedlot with the highest risk occuring in wk 1 to 3, after that morbidity declines (Buhman et al., 2000; Edwards, 1996).

To help combat this costly inefficiency, cattle producers have implemented vaccination protocols for their beef herds. The viral vaccine components of BRD consist of bovine herpesvirus type 1, also known as infectious bovine rhinotracheitis (IBR), bovine viral diarrhea (BVD), parainfluenza virus type 3 (PI-3), and bovine respiratory syncytial virus (BRSV) (Urban-Chmiel and Grooms, 2012). The bacterial vaccine components of BRD consist of *Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni* (Urban-Chmiel and

Grooms, 2012). Disease control or elimination requires the stimulation of the immune system in a sufficient proportion of the population or herd (Siegrist, 2013). Immunization is achieved by inducing protection, as a result of stimulating the adaptive immune system (Siegrist, 2013). This immunity is achieved by the maintenance of antigen-specific immune effectors and/or by the induction of immune memory cells that can reactivate if re-exposure to the antigen occurs (Siegrist, 2013). The appropriate use of these vaccines can reduce the risk of BRD (Urban-Chmiel and Grooms, 2012). However, exposing an animal to an antigen can negatively affect their performance in the feedlot (Stokka et al., 1994).

To elicit a vaccine response, the vaccine must provide enough signals from the antigen, or with an adjuvant, to trigger the inflammatory reaction that is mediated by cells of the innate immune system (Hoebe et al., 2004). Injection of a vaccine antigen initiates an acute phase inflammation response, which develops within minutes (Tizard, 2013). Upon injection of an antigen, broken cells release molecules known as damage-associated molecular patterns (DAMPs) that trigger the release of cytokines, chemokines, and enzymes from sentinel cells (Tizard, 2013). The three major cytokines secreted by sentinel cells include tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) (Tizard, 2013). Acute phase proteins (APP) are a group of blood proteins that change in concentration when an animal is subjected to external or internal challenges, such as infection, inflammation, and stress (Murata et al., 2004). One of the most prominent APP found in beef cattle is haptoglobin (Hp) (Alsemgeest et al., 1994). Haptoglobin is one of a number of a number of acute phase proteins synthesized and secreted during the initial inflammatory response. Haptoglobin concentrations in healthy cattle are often undetected, but during the inflammatory reaction to a vaccine, can increase 50-100 times (Conner et al., 1988). Haptoglobin concentrations will increase with both

bacterial and viral infections (Schroedl et al., 2001; Ganheim et al., 2003; Heegaard et al., 2000; Idoate et al., 2015). Hp can be used as a tool to measuring respiratory disease in feedlot conditions (Idoate et al., 2015).

The triggering of inflammation by cytokines, and the mobilization of phagocytic cells such as neutrophils, macrophages and dendritic cells contributes to the rapid destruction of foreign microbes (Tizard, 2013). Additionally dendritic cells act as sentinel cells and activate the innate defenses when they first encounter foreign antigen, they can process antigen and initiate the adaptive immune system, and they regulate adaptive immunity by determining whether an antigen will trigger an antibody-mediated or cell-mediated response (Tizard, 2013). When exposed to an antigen, dendritic cells undergo a maturation process, modulating specific surface receptors and migrate towards the lymphatic system, in secondary lymph nodes (Siegrist, 2013). The central role of mature dendritic cells, in response to a vaccine, is to provide antigen-specific and costimulatory signals to activate naïve T cells (Palucka et al., 2005). These cells up-regulate specific surface molecules that provide B cell activating signals (Siegrist, 2013). T cells help drive B cell differentiation into immunoglobulin secreting plasma cell that can produce low affinity germline antibodies (MacLennan et al., 2003). During B cell differentiation, immunoglobulin class switching from IgM towards IgG, IgA, or IgE occurs with the upregulation of activation-induced deaminase enzyme (Siegrist, 2013). The interactions between antigen-specific germinal center B cells, antigen bearing follicular dendritic cells, and follicular helper T cells results in the production of B cells with the highest level of antigen-specific affinity (Siegrist, 2013). This combination provides signals necessary for the differentiation of germinal center B cells either towards plasma secreting specific antibodies or towards memory B cells (Siegrist, 2013). Antigen specific antibodies have been

formally demonstrated as conferring vaccine-induced protection against many disease, and the production of memory B cells allows for the long term disease protection (Casadevall, 2004).

The objective of this study was to evaluate the response of vaccination protocols for the bovine respiratory complex on feeding behavior and feedlot performance in previously vaccinated, newly weaned, backgrounding steers. We hypothesized that the vaccination protocols for the bovine respiratory disease complex of previously vaccinated, newly weaned, backgrounding steers will not have an effect on feeding behavior and feedlot performance.

Materials and Methods

All procedures were approved by the North Dakota State University Animal Care and Use Committee. This study utilized 76 weaned Angus, Simmental, Angus X Simmental, and Shorthorn beef calves born (1 January 2014 to 31 March 2014) at the North Dakota State University beef barns. At birth, calves were vaccinated with Inforce 3 (Zoetis; 100 Campus Drive, Florham Park, New Jersey 07932) administered via the intranasal route and Ultrabac C & D (Zoetis; 100 Campus Drive, Florham Park, New Jersey 07932) administered via the subcutaneous route. On 2 April 2014, calves were vaccinated with Bovishield Gold 5 and Ultrabac 7 subcutaneously and received Dectomax pour on. On 3 September 2014, calves received Bovishield Gold VL5 and One Shot Ultra 7 subcutaneously and received Dectomax pour on. Calves were weaned for 30 d and then shipped to the NDSU's Beef Cattle Research Complex. Upon arrival on 21 October 2014, calves (n = 76, body weight [BW] = 741 ± 69.7) were trained for 21 d to the Insentec Roughage Feeders (Insentec; Insentec B. V. Repelweg 10, 8316 PV Marknesse, The Netherlands).

Insentec Roughage Feeders measure dry matter intake (DMI) kg, time spent at feeder measured in minutes and number of visits, and the number of meals can be calculated. Body

weight kg was determined on d -21, 0, 1, 3, 6, 28, and 29 and average daily gain (ADG), feed conversion ratio (FCR), and gain-to-feed (G:F) were calculated. Time spent at feeder, number of visits, and meals were calculated on a 24-h cycle. A meal is defined as a distinct, separate eating period and visit not separated by intervals longer than seven minutes.

Calves were allowed ad libitum access to total mixed ration in the Insentec Roughage Feeders, water, and trace mineralized salt blocks (95.5 to 98.5% NaCl, 3,500 mg of Zn/kg, 2,000 mg of Fe/kg, 1,800 mg of Mn/kg, 280 to 420 mg of Cu/kg, 100 mg of I/kg, 60 mg of Co/kg). Diet composition included corn, corn silage, hay, and dried distillers grains (DDGS). Samples of the total mixed diet were collected (approximately 500g) and analyzed weekly. All feed samples were analyzed for ash, crude protein, nitrogen, NDF, ADF, ether extract (EE), available starch, calcium, and phosphorus (Table 4.1). Samples were dried for 48 h at 60˚ C in a forced air Grieve SB-350 oven (The Grieve Corporation, Round Lake, IL) and ground to pass a 2-mm screen using a Wiley mill (Model #3; Arthur H. Thomas, Philadelphia, PA). Samples were analyzed for ash, EE, calcium and phosphorus (AOAC, 2010), N (Kjeldahl method) as well as NDF and ADF (Goering and Van Soest 1970). Starch was analyzed using the methods of Herrera-Saldana and Huber (1989) on a microplate spectrophotometer (Synergy, H1 Microplate reader, BioTek Instruments, Winooski, VT). Crude protein was calculated by multiplying N concentration ^{X} 6.25.

Table 4.1 Analyzed composition of calf diets derived from corn, corn silage, hay, dried distillers grains (DDGS), and premix

Diet	% of DM								
	Ash	N	CP	NDF	ADF	EE	Starch	Ca	P
d 0	7.37	1.89	11.79	50.32	26.19	3.03	17.95	0.45	0.37
d 7	8.24	7.88	11.77	52.30	27.39	30.40	17.91	0.52	0.36
d 14	7.96	1.90	11.85	50.38	27.08	3.20	18.78	0.53	0.29
d 21	8.93	1.98	12.37	52.56	28.37	2.86	13.83	0.64	0.35
d 28	8.40	1.92	12.02	52.08	27.37	2.84	14.97	0.73	0.43
Average (d 0 - 28)	8.18	3.11	11.96	51.53	27.28	8.47	16.69	0.58	0.36

On d 0, calves were blocked by weight, randomly assigned to one of four possible treatments. Treatment one was a 2 cc sterile saline negative control subcutaneously injected in the neck, treatment two was Bovishield Gold with One Shot (Zoetis; 100 Campus Drive, Florham Park, New Jersey 07932), treatment three was Inforce 3 and Bovishield BVD with One Shot, and treatment four was Bovishield Gold with One Shot and Inforce 3. Both Bovishield Gold with One Shot and Bovishield BVD with One Shot were subcutaneously injected in the neck. Treatments two, three, and four were administered as a 2 cc dose subcutaneously on the left side of the neck. Inforce 3 was administered as a 2 cc dose administered in one nostril via the intranasal route. Blood samples were collected via jugular venipuncture in the morning on days 0, 1, 3, 6, and 28 post vaccination in BD Vacutainer sodium heparin 158 U.S.P. green top tubes (BD; I Becton Drive, Franklin Lakes, New Jersey 07417). Samples were placed on ice for 30 min and centrifuged for 20 min at 1,380 x g to separate plasma, which was then pipetted into cryo-vials and frozen at -20° C until later analysis. All plasma samples in cryo-vials were taken out of freezer and placed in sample tube holders at room temperature (21° C) until completed thawed. Subsamples were pipetted into new cryo-vials placed in Styrofoam coolers with icepacks and shipped overnight to University of Guelph and Oklahoma State University for hb

and antibody titers, respectively. Plasma samples from d 0, 1, 3, 6, and 28 were sent to the University of Guelph diagnostic lab for hp concentrations analysis using a Roche Cobas 6000 c501 biochemistry analyzer. Plasma samples from d 0, 3, 6, and 28 were sent to Oklahoma State University diagnostic lab for BRSV and IBR antibody titers using the serum neutralization test method (Mahy and Kangro, 1996).

Data was analyzed using the mixed procedure of SAS (SAS Ins. Inc., Cary, N. C.) The model included fixed effects of treatment, day and their interactions with a repeated measure statement for hp, BRSV antibody titers, and IBR antibody titers. Antibody titers were converted using the natural log to normalize data. Significance was determined with an alpha of $P \leq 0.05$.

Results

The inflammatory response upon injection was observed for all injections with the exception of sterile saline ($P < 0.001$; Figure 4.1). Hp levels increased beginning at the 1 d post injection ($P < 0.001$) and peak response occurred 3 d post injection ($P < 0.001$). By d 6, Hp levels declined and returned to levels observed on 0 d. At d 6 the inflammatory response of the innate immune system returned to homeostatic levels observed on d 0. However, d 6 shows the start of antibody production of the adaptive immune system. Both treatment two (Bovishield Gold with One Shot) and treatment four (Bovishield Gold with One Shot and Inforce 3) had higher serum antibody levels for BRSV and IBR compared to treatment one (sterile saline) and treatment three (Bovishield Gold BVD with One Shot and Inforce 3; $P < 0.001$; Figures 4.2 and 4.3). Though treatment three (Bovishield BVD with One Shot and Inforce 3) did initiate an inflammatory response ($P < 0.001$; Figure 4.1), it did not show an increase in IBR and BRSV antibody titer levels by d 28. Feeding behavior and growth performance were not affected by the injection of a modified live vaccine and adjuvant (See tables 4.2 and 4.3). On the contrary,

treatment two tended to have an increased average daily gain over the other three treatment groups ($P = 0.06$).

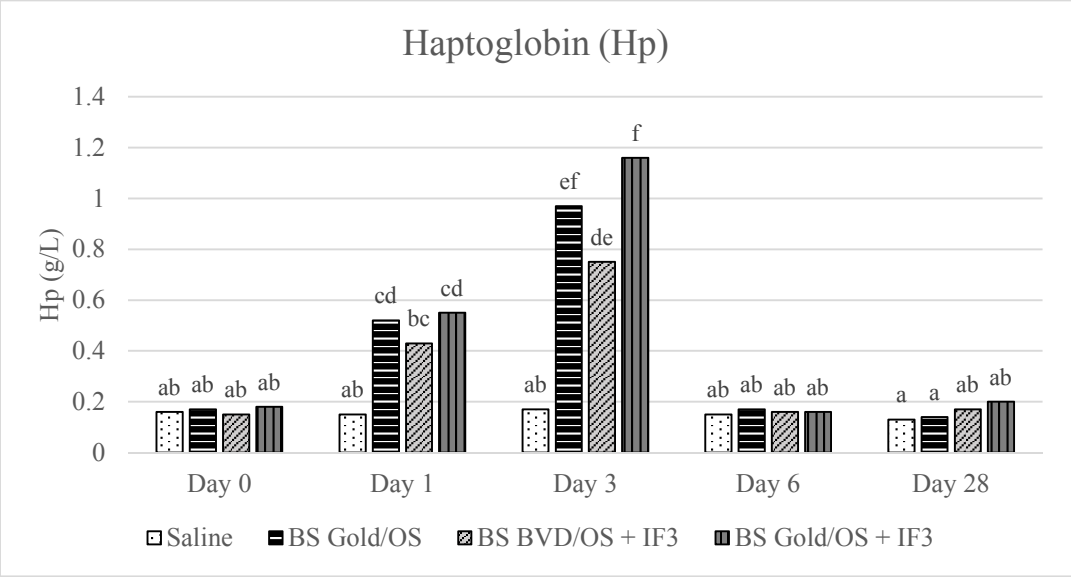

Figure 4.1. Haptoglobin levels (g/L) by vaccination treatment across time. *P*-values for treatment, day, and treatment by day effects were less than 0.0001. [a,b,c] Bars with different letters differ by $P < 0.05$.

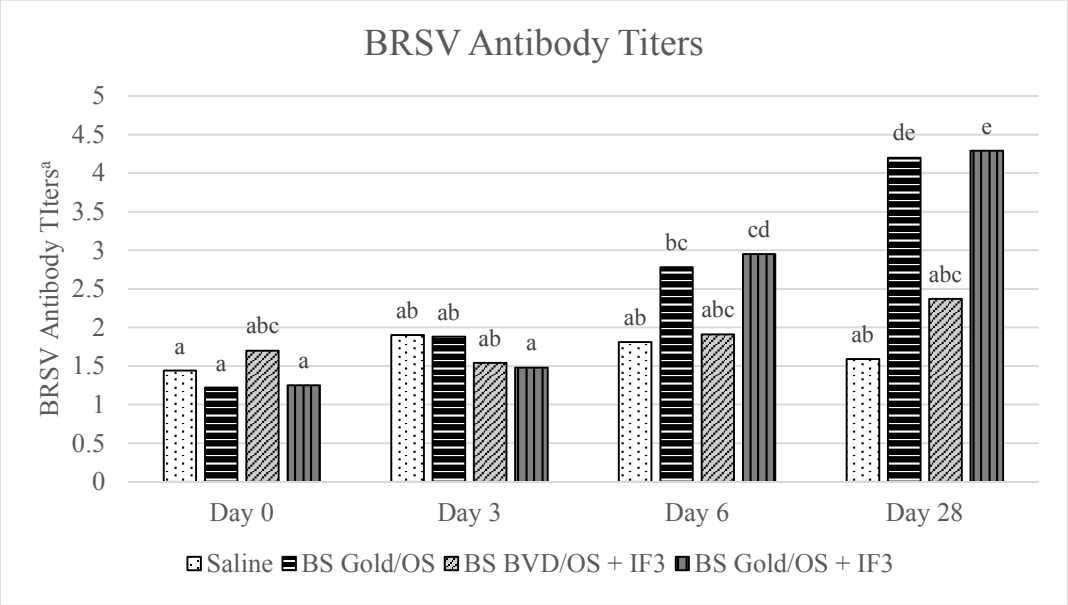

Figure 4.2. BRSV antibody titers by vaccination treatment across time. SN titer values were normalized using the Natural Log. *P*-values for treatment, day, and treatment by day effects were less than 0.0001.
[a,b,c] Bars with different letters differ by $P < 0.05$.

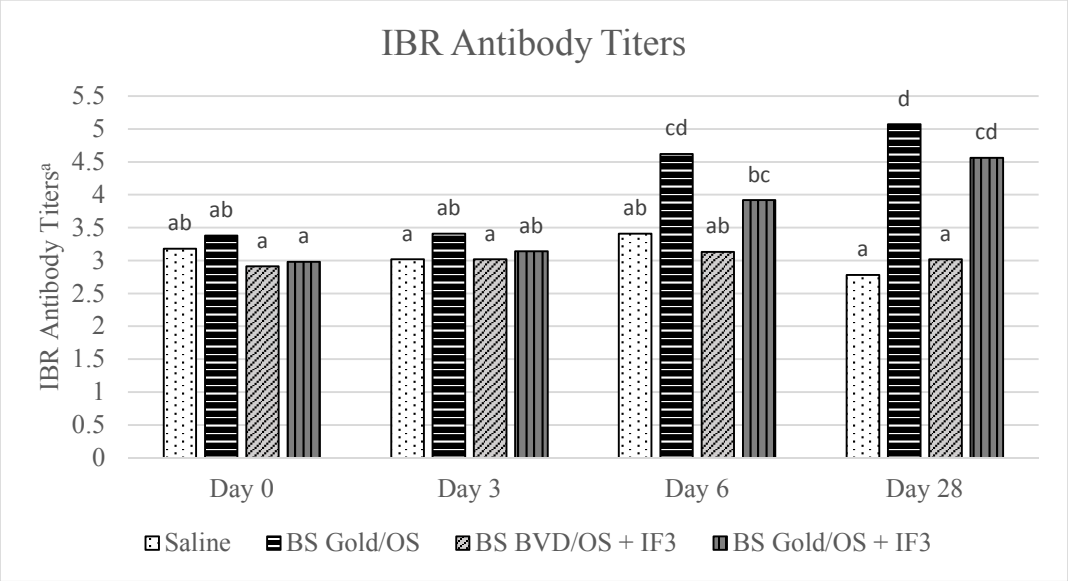

Figure 4.3. IBR antibody titers by vaccination treatment across time. SN titer values were normalized using the Natural Log. *P*-values for treatment, day, and treatment by day effects were less than 0.0001.
[a,b,c] Bars with different letters differ by $P < 0.05$.

Table 4.2. Influence of vaccination on feeding behavior in backgrounding steers.

	Treatment					
Item	1	2	3	4	SEM[a]	*P* Value
DMI	8.85	9.15	9.04	8.80	0.17	0.41
Eating events, no./d						
Visits	42.6	42.2	41.5	36	2.97	0.36
Meals/d	12.0	12.1	11.8	11.2	0.42	0.43
Eating time, min						
Per visit	4.54	4.51	4.70	5.31	0.37	0.39
Per meal	14.8	14.9	15.3	16.4	0.83	0.49
Per day	172	175	176	178	5.06	0.85
Feed DMI, kg						
Per visit	0.23	0.24	0.24	0.26	0.02	0.70
Per meal	0.75	0.78	0.78	0.81	0.03	0.70
Per min	0.05	0.05	0.0.5	0.05	0.002	0.44

[a]Standard error of the mean (n = 19).

Table 4.3. Influence of vaccination on growth performance in backgrounding steers.

	Treatment					
Item	1	2	3	4	Sem[a]	*P* Value
Initial BW, kg	360	355	356	355	5.41	0.85
Final BW, kg	384	386	383	381	5.89	0.95
Gain, kg	23.7	30.8	26.4	26.1	1.94	0.06
Weight change						
3 day	2.75	3.62	4.30	4.19	1.80	0.92
6 day	2.56	5.96	4.60	4.66	1.63	0.50
ADG[b]	0.84	1.10	0.94	0.93	0.07	0.06
G:F	0.10	0.12	0.10	0.10	0.01	0.11

[a]Standard error of the mean (n = 19).
[b]Calculated by dividing the total gain calculated from the average initial and final weights by 28 days

Discussion

We accept our hypothesis that the vaccination protocols for the BRD complex of previously vaccinated, newly weaned, backgrounding steers will not have an effect on feeding behavior and feedlot performance. Throughout the trial there were no negative effects on feeding behavior or feedlot performance. Also, after completion of the trial and the backgrounding phase, we did not observe any signs of respiratory disease leading up to finishing weights and slaughter.

Modified live vaccines (MLV) containing living bacteria or viral organisms are collected from field disease cases and then and passaged in host cells or media for viruses and bacteria respectively to attenuate the pathogen (Cortese, 2002). Each growth cycle represents a passage, after several passages the pathogen loses virulence and can no longer cause disease to the specific species (Cortese, 2002). The two most common MLV vaccines administered are parenteral administered vaccines and intranasaly administered vaccines (Fulton, 2002). Both types were used in the present study. Bovisheild Gold and Bovishield BVD are parenteral vaccines and Inforce 3 is an intranasal vaccine. Parentally administered vaccines stimulate a rapid immune response and generally one dose is needed to stimulate protective immunity (Sutton, 1980; Fulton, 2002). One dose will stimulate an adequate immune response, which varies in length depending on the form of disease challenge (Fulton, 2002). Long term immunity, shown by antibody and cell-mediated response is detectible after MLV vaccine is administered (Fulton, 2002). Intranasal vaccines stimulate protection with one dose and induce an initial rapid onset of protection, possibly through interferon found in nasal secretions (Todd et al., 1972).

The inflammatory response upon injection was observed for all injections with the exception of sterile saline. Hp levels increased beginning 1 d post injection and peak response occurred 2 d post injection. By d 6 Hp levels declined and returned to levels observed on 0 h. This reaction across time is consistent with the innate immune response observed during exposure to an antigen. However, the acute phase response, in the form of hp (g/L), was only 5 to 7-fold increase from 0 h to 72 h. This study did not show the 50 to 100-fold increase as mentioned by Conner et al. (1988). At d 6 the inflammatory response of the innate immune system returned to homeostatic levels observed on d 0.

Day 6 shows the start of antibody production of the adaptive immune system. Both treatment two, Bovishield Gold with One Shot, and treatment four, Bovishield Gold with One Shot and Inforce 3, had significantly higher serum antibody levels for BRSV and IBR compared to treatment one, sterile saline, and treatment three, Bovishield Gold BVD with One Shot and Inforce 3. Though treatment three, Bovishield BVD with One Shot and Inforce 3 did initiate an inflammatory response, it did not show an increase in IBR and BRSV antibody titer levels by d 28. The treatments two and four have Bovishield Gold which contains modified live IBR, PI3, BRSV, and BVD, type 1 and 2 viral antigens whereas treatment three, Bovishield BVD only contains modified live BVD type 1 and 2 viral antigens, with the IBR, PI3, and BRSV antigens administered via the intranasal route as Inforce 3. Treatments two, three and four contain One shot, a *Mannheimia haemolytica* toxoid which includes an adjuvant. The lack of an antibody response to treatment three is likely due to the route of administration of these specific antigens, IBR, PI3, and BRSV. Because this entire group of calves had previously received three doses of vaccine containing the IBR, PI3, and BRSV antigens, it is logical to assume that the defense mechanisms present at the natural route of infection, the nasal passages,

were able to resist these live vaccine viral particles administered via the intranasal route. Treatment two and four received the same antigens but via the subcutaneous route of administration, thus bypassing the natural route of infection and the natural defense mechanisms that exist in the previously immunized animals.

During an immune response to a pathogen, upregulated signal molecules can have adverse effects on temperature regulation, appetite, energy metabolism, and endocrine functions (Klasing, 1988). This could be induced by vaccines with enough antigenic load or adjuvant to elicit a significant immune response. However, in this study feeding behavior and growth performance was not negatively affected by the injection of a modified live vaccine and adjuvant. On the contrary, treatment two tended to have an increased average daily gain over the other three treatment groups. This group did receive a subcutaneous shot of Bovishield Gold, however did not receive Inforce 3. This group had the second largest Hp and BRSV response at 3 and 28 d respectively, as well as having the largest IBR response at 28d. At low doses, signals used to upregulate Hp can also increase feed intake and growth (Klasing, 1988). This could be the reason for the numerical increase in average daily gain observed in treatment two.

The calves used in this study were exposed to vaccine antigens three times prior the study, from the same heard, and were allowed to acclimate to their new environment for 21 d before the start of this study. Results on high stress animals that are weaned, vaccinated and comingled with calves from different herds may have much different results. Further research is needed to evaluate unvaccinated, immune-naïve, calves that are weaned and brought together in a backgrounding feedlot environment.

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CHAPTER 5. GENERAL DISCUSSION AND FUTURE DIRECTIONS

The passive immune transfer is critical to immediate survival of the calf. Colostrum absorption is one of the most important factors in shaping calf health. Calves that fail to absorb enough Ig in colostrum have high pre-weaning mortality rates, up to 89 % in the first week of life (McGuire et al., 1976), as well as other short-term and long-term losses related to animal health, welfare, and productivity (Godden 2008). The continued health of the animal is paramount to long term productivity. In livestock, the major causes of death preceding slaughter are due to infectious diseases (Babiuk, 2002). Bovine respiratory disease complex (BRD) persists as the single costliest disease syndrome associated with commercial beef production in the United States, accounting for losses in 2010 of 1,055,000 animals valued at $643 million dollars (NASS, 2011). Increased morbidity and mortality, decreased weight gains, decreased feed utilization, and decreased carcass quality account for the economic losses associated with BRD (Edwards, 2010). It is apparent that health in beef calves from birth to weaning is critical to a more efficiently industry. The beef industry is under constant pressure to produce a product that is cost effective, nutritious, and humane. It is our job as researchers and stewards of these livestock species to promote health and productivity.

Chapter two discussed the relationship between birth weight and calving ease with passive transfer of immunoglobulins in neonatal beef calves. Briefly, increases in labor time may influence the time it takes the calf to stand. Larger calves have prolonged calving times and took longer to stand up and nurse from their dams. Larger calves may absorb less IgG than smaller calves within the first 24 hours after birth. Dams that needed birthing assistance either by manual assistance or caesarian section, due to increased calf weight, had increased labor times and calves that look a longer time to stand and start nursing. Aggressive dams were more

likely to have calves that were weak and needed assistance. The outcomes observed have been observed and sited before. This allowed a baseline of preliminary data and set a focus on a new physiologic measure to help determine the incidence of dystocia.

Chapter three discussed impacts of supplementation of corn dried distiller's grains plus solubles to late gestating beef cows on incidence of dystocia, mix acidosis, and the passive transfer of immunity. Research and results from chapter two carried over to this project. Categorical variables that were significant in the preliminary trial were utilized as well as physiologic variables to help determine fetal asphyxia and the incidence of dystocia were incorporated. Also, the supplementation of a protein source to look at potential fetal, colostral, and neonatal programing was incorporated. Briefly, supplemented dams weighed more postpartum then dams fed control diet. Colostrum production tended to be greater in supplemented dams than in control dams. Dams carrying female offspring produced more colostrum. Calves of supplemented dams were heavier at birth and at 24 h. At birth, 0 h pCO_2 tended to be greater in calves born to supplemented dams. At 0 h, lactate levels were greater in calves born to control dams, but at 24 h lactate levels were greater in offspring from supplemented dams. At 24 h, base excess was greater in offspring born to control fed dams. Serum protein levels at 24 h tended to be greater in calves born to supplemented dams. Offspring from control fed dams experienced more difficulty at birth and weighed less, however there were no differences in 24 h serum IgG levels. Offspring from the supplemented dams were heavier at weaning, and adjusted 205 d weaning weights tended to be greater in offspring of supplemented dams. The findings of this research the positive effects that protein supplementation can have on the health of the neonatal calf, which can improve its growth trajectory at weaning.

Finally, chapter four discussed the response to vaccination on feedlot performance of weaned calves. The passive immune transfer is critical to immediate survival of the calf, continued health of the animal is paramount to long term productivity. Briefly, previously vaccinated beef steers were assigned to one of three vaccination protocols or a sterile saline control. Haptoglobin, an acute phase protein, as well as antibody titers for bovine respiratory syncytial virus (BRSV) and infectious bovine rhinotracheitis (IBR), were used as a proxy to measure vaccine response. All vaccines initiated an inflammatory response. Treatments two (Bovishield Gold with One Shot) and four (Bovishield Gold with One Shot and Inforce 3) induced an increase in serum antibodies by d 28. Feed intake and behavior were unaffected by the use of vaccines. ADG tended to be higher in treatment two. In well managed, properly immunized herds, vaccination against BRD pathogens can stimulate antibody production without negative effects of the acute phase inflammatory response on feed intake, feeding behavior and performance.

No animal study is without limitations and short comings, and there is certainly room for improvement if these trials were to be repeated. A solution to obtaining more accurate results in trials from chapters two and three would be to increase the number of animals as well as observations – this would certainly aid in better understanding the passive transfer of immunity and factors that influence it. In chapter two there were no treatments applied and the only statistics used were correlation and stepwise regression. These statistics can be helpful, but there must be biological rational, to avoid correlation without any physiologic causation. In chapter three there were even less females used. With the large number of *P* values between 0.20 and 0.10, a larger number of females may have cleared up the results. The continued use of physiologic marks in addition to categorical variables is very important. The use of lactate, base

excess, pH, pCO_2, and pO_2 assisted in monitoring and quantifying fetal asphyxia and incidence of dystocia. The next step for chapter three would be to examine a wider array of immune factor as well. The research in chapter four had a large enough number of animals to effectively look at the vaccination response. That trial does have its limitations as well. The steers used in that trial were all previously vaccinated and all from the same herd. A similar trial on immune-naïve calves from multiple herds may not respond in the same manner. The stresses of weaning and comingling may depress their immune systems and being exposed to a vaccine antigen may negatively affect feeding behavior and feedlot performance. A sex affect was also not determined on this vaccine trial. Heifers in a similar trial may not react in the same manner.

These projects have prospective uses both for future research as well as a benefit to the livestock industry, particularly for those in cow-calf and backgrounding operations. With the potential to design feeding programs during late gestation to help the calf transition healthily into extra-uterine life as well as assist in vaccination regimes that will keep calves immunologically sound to moving into the next phases of life.