VACCINATION STRATEGIES FOR

PRECONDITIONING BEEF CALVES

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PRECONDITIONING BEEF CALVES

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Abstract: Cattle producers have adopted multiple strategies when administering vaccines to calves. Vaccine administration often occurs without the booster vaccination required by label directions. This practice may provide limited protection against bovine respiratory disease (BRD) for the calf. The study objective was to examine the effects of vaccine type and timing on animal performance and immune response in calves either pre-or-post weaned calves. Angus or Angus cross calves (n = 151) were assigned to one of three BRD vaccination protocols stratified by breed of sire, sex, and date of birth. Vaccination treatments included: 1) KV/MLV - a pentavalent killed viral (KV) vaccine at 2 to 3 months of age (day 0) or a pentavalent modified-live viral (MLV) vaccine at weaning (day 127); 2) MLV/MLV – MLV on day 0 (2 to 3 months of age) and at weaning on day 127; or 3) WEAN – MLV at weaning on day 127 and revaccinated with an MLV vaccine on day 140. Virus-specific antibody titer data was determined using serum-neutralization from serum collected on days 0, 127, 140, 154, 168, and 182. Antibody titers against bovine viral diarrhea virus type 1(BVDV-1) and bovine respiratory syncytial virus (BRSV), body weight (BW), and average daily gain (ADG) variables were evaluated following vaccination. Results indicated no treatment effect on BW but vaccination did affect ADG post-weaning. Serum neutralizing titers to BVDV-1 and BRSV displayed a treatment x day interaction. The MLV/MLV group provided the greatest response to vaccination from day 0 to day 154 over the other two treatments. There was no difference between the KV/MLV and the WEAN groups from day 0 to day 127. By day 168, the KV/MLV treatment had a greater immune response than the MLV/MLV and WEAN groups. Providing a KV at branding had minimal effect on BVDV-1 titers but responded well to revaccination with MLV. The WEAN group generated the lowest BVDV-1 serum antibody titers overall but provided an acceptable level of protection to BRD causative organisms by the end of preconditioning. Bovine respiratory syncytial virus titers were also examined but had a substantial decrease in titer levels (< 2) following baseline measurements, with limited response to revaccination.

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CHAPTER I

INTRODUCTION

Preconditioning practices among US beef cattle were first conceived in the mid-1960s by Dr. John Herrick of Iowa State University Extension veterinarian (Hilton, 2015) to minimize adverse effects associated with common stressors such as weaning and commingling of calves upon entry into the feedlot. During the early years, preconditioning protocols were highly varied. More recently, most programs have adopted a standardized set of protocols with minimum requirements of a 45-day weaning period, a record of vaccinations, castration, dehorning, and acclimation to a concentrate supplemented diet. The preconditioning period allows the calf time to overcome the physiological stress associated with weaning to develop a more robust immune system and ability to withstand marketing stressors before shipment. The biological cost of acute stress to the animal is generally minimal and may provide benefit by activating innate immune function (Anderson et al., 1999).

In contrast, chronic stress (> 24 h) poses a much more significant threat to allostasis and is metabolically costly (McEwen and Wingfield, 2010). A heightened hypothalamic-pituitary-adrenocortical (HPA) axis stimulates the release of glucocorticoids and catecholamines, which can negatively affect well-being (Korte et al., 2009). Weaning stress on calves can result in decreased feed intake and weight loss once separated from their dams. Weaning stress may also disrupt vaccine efficacy and subsequent titer production (Anglen et al., 2003), implying that the

timing of vaccination may be a vital component of the success of immunization during vulnerable periods.

Prolonged exposure to stress can suppress the immune system opening the possibility of pathogenic infection. A potential preventative measure used to control the spread of bovine respiratory disease in beef calves is a vaccination protocol. Stress can prevent animals from fully expressing immunity when vaccinated. There are many combinations of respiratory vaccines that are commercially available, with most protecting against bovine viral diarrhea virus type 1 & 2 (BVDV), infectious bovine rhinotracheitis (IBR), parainfluenza 3 virus (PI3), and bovine respiratory syncytial virus (BRSV).

Many available BRD vaccines vary in antigen and antigen type. Killed viral (KV) and modified-live viral (MLV) vaccines stimulate the immune system via different mechanisms. Killed viral vaccines use an inactivated form of the virus to initiate an immune response and are often combined with an adjuvant to increase the stimulation of immune function. Most KV vaccines, per manufacturer requirements, indicate the need for a booster dose administered following the initial vaccination for the vaccine to work to its full potential. In contrast, MLV can stimulate the immune system after a single dose. Timing strategies for administering vaccines should be optimized as maternal antibodies, poor nutrition, and stress may decrease vaccine efficacy (Chase et al., 2008; Chamorro et al., 2015; Cooke, 2019). In young calves, dependency on passive acquired colostral antibodies is vital to survival; however colostral antibodies can interfere with the calf's ability to develop and mount an immune response to vaccine antigens (Chase et al., 2008). Killed viral vaccines illicit a humoral immune response that is primarily antibody specific. Given the mechanism by which KV illicit an immune response, KV administered in the presence of high maternal antibody may form an antibody/antigen complex, neutralizing the vaccine antigen and preventing an antibody response (Endsley et al., 2003). Modified-live vaccines generate both a humoral and a cell-mediated immune response. Like KV,

maternal antibodies may also neutralize the humoral response to MLV. However, even in the presence of high levels of circulating maternal antibodies, a cell-mediated immune response to the MLV antigen can effectively establishes immunization in the young animal (Endsley et al., 2003).

'Branding' is the common term for working calves before turnout on summer grass pastures for spring born calves (2 to 4 months of age), it is a popular time amongst cattle producers to vaccinate calves, generally occurring during the late spring months. A recent survey of Oklahoma cattle producers identified that 66 percent of cowherds have no defined calving season (Oklahoma Beef Management Marketing Survey, 2018). One may speculate from the survey data that with no defined calving season, the reproductive status of the dams may also be unknown. The motive for using killed vaccines on suckling calves of dams with unknown reproductive status would be to avoid the potential for aborted fetuses. Aborting a fetus is a potential risk when using MLV vaccines on calves whose dams have no prior exposure to MLV vaccines. Viral shedding may occur from the MLV vaccinated calf to the dam void of previous MLV exposure. One common issue amongst calves receiving the primary dose of KV vaccine at branding is the failure to receive the booster dose in the time specified on the manufacturer's instructions. Vaccination failures are often due to management constraints (Richeson et al., 2009). Therefore, the objective of our study was to examine the effects of vaccination timing and vaccine type on BVDV and BRSV serum neutralizing antibody titers and body weight performance in pre-and post-weaned beef calves.

CHAPTER II

REVIEW OF LITERATURE

Beef Industry Segments

The U. S. beef cattle industry is a highly specialized system simplified into two distinct categories: cow-calf production and feedlot production. A third less distinct segment of the beef industry is the stocker/backgrounding phase, which is where calves are grown to larger frame, heavier bodyweights, and more advanced maturity before entering the feedlot. Cow-calf producers are responsible for producing and managing young calves until the market of weaned calves. Cow-calf operations vary when considering how producers manage the calves before marketing. Calf management practices in US cow-calf herds tend to vary based on the size of cattle operations. More extensive operations with 200 or more cows tend to incorporate more of the recommended husbandry practices in their calf management protocols. In 2020, the estimated calf crop was 35.1 million head, including beef and dairy breeds (NASS, 2021).

Calves are either weaned abruptly and shipped to the next production segment or placed in a preconditioning program, usually for a minimum of 45 days before shipping. Post-weaned calves leave the cow-calf sector and enter one of two feeding phases of the production system based on their weight at the time of marketing: the stocker/backgrounding phase or feedlot phase. According to recent reports, more than 60% of the US calf crop placement is in a stocker/backgrounding operation postweaning (Drouillard, 2018). During the stocker phase, calves are grown on pasture. In the Southern Plains region of the US, cattle are typically placed

on wheat pasture to graze during the winter months until their removal around March. The high plains region of the U.S. is dense with native range that provides grazing opportunities for stocker operators during the spring and early summer months. Backgrounding consists of feeding calves a mixed diet of harvested forage and concentrate in a dry lot similar to a feedlot setting. Placing calves in a stocker/backgrounding system provides the animal the opportunity to recover from weaning stress, build immunity, and add pounds prior to placement in a feedlot. Feedlots are an efficient way to finish cattle in confined pens with diets primarily consisting of cereal grains and grain byproducts harvested and produced regionally. Cattle entering the feedlot range in weight from 300 to 450 kg and are fed for 100 to 300 days (Drouillard, 2018) to a mature harvest weight averaging 540 to 640 kg depending on breed and sex.

Cattle Sourcing

There is extreme risk to such a segmented system. Due to the high susceptibility of cattle illness following physiological stressors associated with the movement and exposure throughout the system, cattle buyers often incur substantial economic losses as a result. Abrupt weaning, nutrition challenges during transportation to and from livestock markets, and comingling of cattle and calves with unknown health history are typical with auction sales. All are factors that can greatly impact the immune status of the animal. Despite the challenges market auctions present, nearly 64% of feedlots reported sourcing calves from livestock auction markets accounting for 67% of all cattle on feed (USDA-APHIS, 2011a). Age and weight of the calf at the time of marketing or feedlot entry are also considerations that can increase potential BRD occurrences as physiological stress on young or lightweight calves, those weighing less than 320 kg, can further suppress the immune system. In 2011, the USDA reported that 42% of cattle placed in feedlots were less than 320 kg (USDA-APHIS, 2011a). Given the number of cattle placed on feed sourced through auctions and weighing less than 320 kg, preconditioning and health management protocols are important tools to increase immune development that contribute to a feedlot ready

animal. Market conditions, cost of feed, and supply and demand all contribute to feedlot entry weights.

Economic Impact

Beef production in the U.S. is a multibillion-dollar industry. In 2018, commercial beef slaughter totaled 33 million head for 26.9 billion pounds of beef produced with cash receipts totaling 67.1 billion dollars (NASS, 2019). However, the feedlot industry faces a perpetual battle to minimize the costly effects of bovine respiratory disease (BRD), which affects about 2.3 million head annually (Johnson and Pendell, 2017). According to the USDA (2011a) National Animal Health Monitoring System (NAHMS) Feedlot survey, it concluded that 100% of feedlots with 8000 head or greater experienced BRD (NAHMS, 2011), and preventative measures, morbidity treatment, and decreased production costs between $800 and $900 million in lost revenue annually (Chirase and Greene, 2001). In addition to BRD-induced mortality, the effects of BRD are prevalent with decreased animal performance, lower quality carcass traits, and increased use of antimicrobial treatments (Holland et al., 2010).

Bovine Respiratory Disease

The bovine respiratory disease complex, more commonly known as shipping fever, is a multifaceted disease generally resulting from stress-induced immunosuppression, a primary viral pathogen and secondary bacterial pathogen (Grissett et al., 2015). The disease localizes in the upper and lower respiratory tract and develops into bronchopneumonia. The disease typically affects immunosuppressed calves of weaning age or older, complicated with immense stress common in beef management practices. Cattle with bovine respiratory disease (BRD) may lack clinical signs and require multiple procedures to determine a diagnosis and specific etiology (Fulton et al., 2016).

Viral Pathogens

Viral pathogens most commonly associated with BRD complex include bovine viral diarrhea virus (BVDV), infectious bovine rhinotracheitis virus (IBR), or bovine herpes virus 1 (BHV-1), parainfluenza-3 virus (PI3), and bovine respiratory syncytial virus (BRSV). The viruses may act alone or symbiotically as they are considered the primary cause of infection in BRD cases by compromising host immune function, thus increasing susceptibility to secondary bacterial infections (Grissett et al., 2015). Determining the contribution of each viral pathogen in BRD cases is varied based on age of animal, environment, and season.

Some viral respiratory infections may be age dependent as studies indicate BRSV to be more prevalent in young calves and older calves to be at greater risk of IBR or BVDV infections. A study examining the prevalence of respiratory viruses in calves three month of age or younger, detected one or more viruses in 34.6% of submissions with BRSV accounting for 11.6% followed by PI3 (7%), IBR (6.1%), and BVDV (5%) (O'Neill et al., 2014). Angen et al. (2009) found that 83% of dairy calves ≤ 4 months of age showing clinical signs of pneumonia contained BRSV-antigen. In feedlot calves, virus detection from either nasal swab or necropsy discovered the positive cases were BHV-1 (14.9%), BVDV (15.7%), BRSV (9.1%), and PI3 (8.3%) (Fulton et al., 2016). Interestingly, in all the virus detection studies mentioned, each found bovine corona virus present ranging from 29 to 62% of samples analyzed. Further research may be warranted to determine interaction among viruses.

Bovine Viral Diarrhea Virus

Bovine viral diarrhea virus is a group of single-stranded RNA viruses that includes two different genotypes, BVDV type I and BVDV type II, belonging to the *Flaviviridae* virus family and *Pestivirus* genus. It can be further divided into two biotypes: cytopathic (cp) and non-cytopathic (ncp) (Brodersen, 2014; Larson, 2015). The ncp type is predominant in nature and is

the most clinically severe form of acute BVDV infection. Non-cytopathic viruses offer a prolonged antigen expression (Plesa et al., 2006) and antiapoptotic mechanisms (Boya et al., 2004) to maintain replication. Cytopathic viruses are believed to result from a mutational event initiated by the ncp virus and are most often linked with mucosal disease and cellular degeneration (Ridpath, 2010) including cytoplasmic vacuolization and cell death by apoptosis (Darweesh et al., 2015). Nevertheless, infection from either biotype results in reduced circulating white blood cells (Bolin et al., 1985). Bovine viral diarrhea virus can infect calves of any age but is commonly seen in feedlot cattle contributing to BRD and is also responsible for infections impacting the reproductive and digestive systems (Antos et al., 2021). Acute BVDV infections are most commonly subclinical or may display mild clinical signs.

Bovine viral diarrhea virus induced lymphopenia (Brodersen, 2014) seems to serve as the primary factor responsible for respiratory infection by suppressing the immune system and creating an environment for secondary bacterial or viral infections. The innate immune system is the first line of defense in mitigating and eradicating foreign antigens. Infection caused by BVDV impacts a multitude of cells largely responsible for innate and acquired immune responses, which may result in altered function and a substantial reduction in immune cell numbers (Archambault et al., 2000; Glew et al., 2003), and the inhibition of normal cellular immune response to the viral infection varies based on the infecting strain (Chase et al., 2004). *In vivo,* the pathogenesis of BVDV infects T-lymphocytes and antigen-presenting cells (APC), causing a downregulation in maturation (Sopp et al., 1994). Dendritic cells (DC) are an essential APC in the innate immune response responsible for detecting and collecting foreign antigens in the periphery and antigen presentation to T-lymphocytes in the lymph node. Maturation of DC occurs upon arrival to the local lymph node for antigen presentation and is essential for proper functionality (Cardoso et al., 2016), bridging the innate and adaptive immune systems. The downregulation in maturation of dendritic cells effectively results in the immunosuppression of the host.

Bovine viral diarrhea virus infections are responsible for several diseases diagnosed in cattle including bovine viral diarrhea, mucosal disease, and fetal disease (McClurkin et al., 1979; Done et al., 1980). Fetal infections occurring from a non-cytopathic strain during intrauterine development before 180 days gestation may result in early embryonic death, abortion, congenital defects, and persistently infected (PI) calves. Persistently infected calves serve as the reservoir for the virus and are highly transmissible to a population. In PI calves, adolescent exposure to the cytopathic strain typically fails to mount an immune response as the viral antigen is recognized as self-origin, often resulting in mucosal disease (Larson et al., 2004).

Infectious Bovine Rhinotracheitis Virus

Bovine herpesvirus (BoHV-1), also known as infectious bovine rhinotracheitis (IBR), is another viral pathogen that makes up the BRDC. Some clinical manifestations of the disease include respiratory, reproductive, and neurological diseases and abortion in cattle (Biswas et al., 2013; Newcomer, 2021); however, the degree of disease severity is dictated by the route of entry and the subtype of the pathogen (Muylkens et al., 2007). Infectious bovine rhinotracheitis is highly virulent (Straub, 1978) and responsible for a large portion of BRD morbidity cases in feedlots (Church and Radostits, 1981). Post-infection, IBR establishes a latent infection in the nervous and sensory ganglia in a non-replicative state allowing the virus to go undetected (De Brun et al., 2021). Reactivation from the latent state can lead to viral shedding (Muylkens et al., 2007) and serve as a source of infection. Viral infection typically initiates in the epithelial cells of the upper respiratory tract and ultimately moving to the lower respiratory tract (Griffin et al., 2010b) where secondary bacterial infections occur.

Parainfluenza 3 Virus

Parainfluenza 3 (PI3), originally called myxovirus SF-4 (Reisinger and Heddleston), is commonly associated with the BRD complex, and in the genus *Respirovirus* within the

Paramyxoviridae family (Ellis, 2010). Common with respiratory viruses, transmission primarily occurs as large droplets are inhaled into the respiratory tract (Ellis, 2010) that first invade the mucosal surfaces of tracheal organs (Campbell et al., 1969; Griffin et al., 2010a). Associated lung lesions are the result of disease manifestation to bronchitis/bronchiolitis and alveolitis (Bryson et al., 1983). Clinical signs vary in severity and are wide ranging from asymptomatic to severe pneumonia, and given the multiple pathogens affiliated with BRD it is difficult to designate signs solely attributable (Fulton et al., 2000; Ellis, 2010), however, several have been identified such as pyrexia, coughing, mucopurulent nasal discharge, and inappetence.

Bovine Respiratory Syncytial Virus

The fourth virus identified in the BRDC, bovine respiratory syncytial virus (BRSV), belongs to the genus *Pneumovirus* within the *Paramyxoviridae* family (Valarcher and Taylor, 2007). The virus generally affects calves less than six months of age and approximately 60 to 80% of infections result in morbidity (Gershwin, 2007). The virus localizes and replicates in the lower respiratory tract inducing respiratory distress while reducing phagocytic activity of alveolar macrophages (Griffin et al., 2010b) resulting in bronchiolitis and alveolar lesions (Viuff et al., 1996).

Bacterial Pathogens

The most common bacterial pathogen associated with bovine respiratory disease included *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma bovis,* with *M. haemolytica* regarded as the leading contributor to BRD (Griffin et al., 2010b). *Mannheimia haemolytica* and *P. multocida* are known to contribute to the normal microflora found in the nasal passage. Calves stressed or challenged by viral pathogens contribute to creating a suitable environment in the respiratory tract where opportunistic bacteria rapidly reproduce and inflict disease upon the animal (Frank, 1984; Grissett et al., 2015) by suppressing the function of

mucosal surfaces and phagocytic activity (Babiuk and Tiloo, 2004) and even apoptosis to leukocytes (Czuprynski et al., 2004) of the innate immune system.

BVDV and Persistent Infection

Prenatal

The effects of BVDV infection on growth and development vary depending on the stage of pregnancy and an underdeveloped immune system. There are two main variables considered in fetal infections, (1) the age and viability of the oocyte or fetus at the time of infection, and (2) the strain of virus causing infection (Brownlie et al., 1998; Oguejiofor et al., 2019). Fetuses exposed to intrauterine BVDV infection between 42 and 175 days of gestation (McClurkin et al., 1984) are said to be immunotolerant; however, they are likely candidates for fetal death, abortion, and PI animals (Chase et al., 2008). Agammaglobulinemia is characteristic among bovine fetuses and neonates, which must rely on maternal antibodies for protection (Barrington and Parish, 2001). The fetus can develop antibodies to BVDV by 190 days (Banks and McGuire, 1989). Viruses infecting before breeding or conception may subsequently invade the ovaries and developing follicles (Fray et al., 1998). Evidence of oocyte necrosis was seen in the follicles of superovulated heifers infected with ncpBVDV. The infected heifers in this study also displayed fewer and smaller follicles than the control heifers (McGowan et al., 2003). Bovine viral diarrhea infections may also reduce the capacity of the sperm to attach and penetrate the oocyte's zona pellucida (ZP) at the time of fertilization, as was demonstrated during an *in vitro* study (Garoussi and Mehrzad, 2011). The oocyte's extracellular matrix provides a protective barrier and serves many crucial functions during fertilization and early embryonic development (Sinowatz et al., 2001). During *in vitro* fertilization, an intact ZP prevented the invading virus against both cp and ncp biotypes (Tsuboi and Imada, 1996; Stringfellow et al., 2000).

In contrast, hatched blastocysts and ZP-free embryos were susceptible to both biotypes of BVDV following *in vitro* inoculation (Vanroose et al., 1998). Following fertilization, a normal zygote undergoes cellular division and begins the cleavage process; however, cleavage was limited during the ovum phase in PI heifers (Altamiranda et al., 2013). Significant implications following implantation are seen during the first and second trimester, resulting in congenital defects, fetal death, abortion, and PI calves. Fetal viral infection and replication occur at the placenta along with infection of the allantoic and amnionic membranes. (Kelling and Topliff, 2013). Congenital defects are most often established between 100 and 150 days as this period involves the completion of organogenesis and the immune system. Congenital defects may make calves twice as likely to experience postnatal health issues (Munoz-Zanzi et al., 2004; Grooms, 2006).

Postnatal

Calves BVDV infected after 180 days of gestation are generally born as immunocompetent calves. By day 180 and after, the calf has a developed immune system capable of mounting an immune response to the invading virus. Subjects typically pass viral infections after two weeks (Fray et al., 2000). Immunotolerant calves that make it to parturition are likely born weak, and PI carriers of both the cp and ncp biotypes of the BVDV and are at significant risk for developing terminal mucosal disease (Taylor et al., 1994). Most PI calves cannot mount an immune response to the infection (Grooms, 2004), fail to survive until weaning, and an even greater proportion do not make it to slaughter (Taylor et al., 1994). Most PI calves are considered "poor-doers" as they struggle to perform as well as non-PI cattle, due to the constant immune stimulation they are facing. Tissue growth is severely retarded given the numerous targets of the virus, and quantifying outcomes is complex given many environmental and management conditions.

In a study examining 560 beef calves, 40 were identified as PI, with only four living past 12 mo. and making it to slaughter. On average, calves that survived until weaning were 43 kg lighter than non-PI calves. Persistently infected calves that reached slaughter were 118 kg and 15cm less than normal herd mates (Taylor et al., 1994). Another study examining performance variables of PI calves over 66 days resulted in a 25.9% death loss compared to 2.4% in death loss in non-PI cattle. Average daily gain (ADG) was also reduced in PI versus non-PI cattle at 0.55 kg and 0.74 kg and a cost of gain totaling $6.31 and $2.09 ($/kg), respectively (Hessman et al., 2009).

Further investigation into the shortcomings of these phenotypic measurements revealed the underlying factors. Taylor et al. (1994) provided a diagnosis of the PI population studied to display necrosis of the adrenal gland, sarcocystis of muscle tissue, and subepiphyseal primary spongiosa or "growth plate arrest." (Taylor et al., 1994). Long bone trabecular modeling impairment in PI calves may be due to a reduction in osteoblast and osteoclast activity (Webb et al., 2012). A non-functioning adrenal gland may severely alter the animals' ability to maintain and cope with several physiological processes such as stress, metabolism, and immune function. Immunosuppressed calves may also have enhanced severity of enteritis of the small intestine complicating proper nutrient absorption (Kelling and Topliff, 2013). In addition to decreased growth, females infected during the last half to one-third of gestation are also subject to reproductive consequences as they reach puberty which may result in failure to conceive (Munoz-Zanzi et al., 2003). Non-infected heifers were reported to display behavior of standing estrus 12 h prior to previously infected heifers at the time of breeding (McGowan et al., 2003), while other observations have recorded lag times to the onset of estrus to be as much as one-and-a-half-month (Munoz-Zanzi et al., 2004). Acutely infected young bulls may display disruption in testicular function and fertility as the virus can localize and replicate in the seminal vesicles of the testes (Kommisrud et al., 1996). Congenital infections with BVDV may result in poor motility and

deformation of sperm and an overall reduction in spermatogenesis in young bulls (Revell et al., 1988; Kommisrud et al., 1996). Conversely, other studies reported no impact on sperm quality in acute or PI animals (Kirkland et al., 1991; Kirkland et al., 1994). Caution should be used when deciding on replacement animals from potential BVDV infected sires or dams, and all animals should test PI-negative before breeding.

Respiratory Vaccines

Vaccines

One of the most economical methods of BRD prevention is vaccination. Vaccine products come in a multitude of combinations containing viral and/or bacterial antigens. Most commercially available respiratory vaccine products contain a modified-live (MLV) or inactivated killed viral (KV) component, or an inactivated bacterin toxoid developed to prevent a specific bacterium. Ideally, the vaccine should elicit an immune response with distinguishable difference between natural infection and inoculation (Tizard, 2017).

Vaccines are measured based on two main criteria: 1) vaccine efficacy and 2) vaccine efficiency. Vaccine efficacy is determined by proving to be biologically active through reducing disease incidence and safely activating an immune response to the vaccine antigen (Richeson, 2015). It is suggested that to decisively test vaccine efficacy, it should be done under field conditions from controlled studies (Perino and Hunsaker, 1997). Vaccine efficiency is achieved if a there is a significant reduction in clinical sickness, improved growth performance, and a definitive economic advantage in commercial operations (Richeson, 2015). Timely use of vaccines may increase animal welfare while reducing the need for costly antibiotic treatments (O'connor et al., 2019). It is often cheaper to prevent the incidence of disease than it is to treat sickness after considering the cost of antibiotic treatment, anti-inflammatory medications, loss of body weight, and increased days on feed. In 2022, the average cost of a multivalent MLV BRD

vaccine plus *M. haemolytica* costs between $4.30 and $4.50/dose. In a recent study examining pre-weaned dairy calves, the average cost/dose of MLV BRD vaccine was $4.64/hd (Dubrovsky et al., 2020). According to the USDA Feedlot report (2011), the average cost of BRD treatment was $23.60/head. It is suggested that the cost today may be substantially higher considering the average cost nearly doubled from 1999 to 2011 ($12.59 to $23.60) (Peel, 2020).

Modified Live versus Killed Virus Vaccines

Viral vaccines, whether live-attenuated or inactivated, stimulate the host immune system to elicit a humoral antibody mediated response, cell-mediated immune response or both (Woolums et al., 2013). Both have been developed to protect against IBR, BVDV type I and II, PI_3, and BRSV and are offered multiple routes of administration with most injected intramuscularly or subcutaneously, and orally or intranasally. Live-attenuated virus vaccines, such as MLV, are typically grown in unfavorable conditions that cause the virus to develop adaptations to a new host, thus reducing its virulence and ability to cause disease (Tizard, 2017). Live-attenuated viruses infect and replicate in the host cell amplifying the quantity of antigen to be presented endogenously (Burrell et al., 2017), and stimulate an immune response largely driven by a CD8+ cytotoxic T cell, type 1 response associated with cell-mediated immunity. However, MLV vaccines also stimulate the antibody driven humoral immune response. Activation of T and B cells will differentiate to a large number of memory cells providing long-lasting protection (Tizard, 2017). Strong and rapid immune responses are often achieved through a single MLV dose. Disease preventing protection was observed in as few as five days prior to experimental BVDV challenge in addition to a significant reduction in nasal shedding (Brock et al., 2007). Despite the record of benefit, MLV may also possess unfavorable consequences such as the potential to fully revert back to a virulent type if over replication occurs. Other areas of caution when using MLV is during pregnancy. Modified-live vaccines may impose a febrile reaction thereby increasing the risk of fetal defects or miscarriages (Burrell et al., 2017). It is

suggested that a safe time to administer MLV to dams is 30-60 d prior to the breeding season to avoid these risks to the fetus. There is also some concern surrounding the use of MLV on stressed or immunocompromised cattle as over replication may occur (Burrell et al., 2017). Vaccine manufacturer guidelines recommending avoiding vaccination of stressed cattle (Richeson et al., 2008).

Inactivated or killed virus (KV) vaccines are developed by destroying the infectivity of a virulent virus while maintaining immunogenicity. Typically, inactivation is by virus exposure to physical or chemical agent such as formalin. However, chemical alterations may reduce immunogenicity to antigen damaging levels specifically needed to elicit cell-mediated responses, resulting in a weaker immune response of short duration, and requiring larger amounts of antigen to stimulate the immune system and future maintenance boosters (Burrell et al., 2017). Inactivated organisms typically stimulate a type 2 response with the production of $CD4^+$ T cells and antibodies (Tizard, 2017). Compared to MLV vaccines, killed viral antigens are not capable of replication, but generally require the use of an adjuvant to increase immunogenicity. Adjuvants aid in prolonging the release of antigens and activation of the innate immune system (Burrell et al., 2017). The popularity of KV stem from the safety provided (Newcomer et al., 2017) and the ease of use. Safety is particularly true when used in the presence of a bovine fetus as KV have been demonstrated as neither immunosuppressive nor pathogenic (Kelling, 2004).

Studies examining vaccination of feedlot cattle using MLV or KV vaccines have mixed results (Schumaher et al., 2018). Most often the contradicting results are due to one or more variable in receiving cattle such as age, weight, breed, prior vaccination status, stressors, or timing of vaccination. In a study examining serum neutralizing (SN) antibody titers and cellular proliferation of six- to eight-month-old calves utilizing three different vaccination strategies (KV/KV, MLV/MLV, MLV/KV), results indicated the treatments consisting of at least one or two MLV vaccines has significantly higher SN titers than the KV/KV treatment which were non-

differing from the controls. Cellular proliferation was non-significant in the KV/KV treatment unlike the other treatments which included an MLV (Reber et al., 2006). Research indicates that vaccination protocols that contain at least one dose of MLV vaccine are successful in eliciting a strong antibody response. Protocols using a KV/MLV combination in a prime/boost application have proved effective at viral antibody stimulation and is a suggested protocol for calves nursing pregnant cows (Grooms and Coe, 2002; McNeff et al., 2021).

Pre- and Postweaning Vaccination

The debate over which vaccine type provides greater protection against BRD has been well documented (Reber et al., 2006; Chamorro and Palomares, 2020), however the answer isn't necessarily black and white. Variability in management practices and environmental conditions creates the inability to develop a 'one size fits all' protocol. A sound health protocol provides the right vaccine to the right animal at the right time.

Timing of vaccination may be the most important component to a successful vaccination program, but implementation may be based on management conveniences rather than what is best for the calf. Vaccination of neonates presents immunological challenges as maternal antibodies may interfere with establishing humoral immunity in the calf (Richeson, 2020). Live attenuated intranasal viral vaccines have been reported efficacious in neonate vaccinates (Vangeel et al., 2007; Chamorro and Palomares, 2020) and have been reported to induce innate immune pathways and Th1 cellular response (Nuijten et al., 2022). When vaccine induced humoral antibodies in the host become neutralized by maternal antibodies, innate and cellular pathways are of even greater importance in defending against viral invasion. Parenterally administered MLV vaccines also stimulate immune responses in neonates, but it is advised to avoid their use because BVDV strains have been linked to inhibiting bacterial killing cell of the innate immune system up to 14 days post-vaccination (Roth and Kaeberle, 1983).

In the late spring often before turnout on summer pastures, calves are worked at the time termed ‘branding’ (2 to 4 months of age), this is a popular time for vaccinating calves, however, maternal antibodies may still interfere with vaccine antigens at this age. For example, 2-month-old calves with maternal antibodies against BVDV vaccinated with a bivalent BVDV MLV or KV vaccine had no measurable SN antibody titers, although, the MLV vaccine did generate cell-mediated T-cell responses and both vaccine types did developed specific memory B-cells (Endsley et al., 2003). Another study examined the difference between vaccination at branding and preweaning using MLV (Powell et al., 2012). The results determined that calves vaccinated at ‘branding’ were capable of developing both a humoral and cell-mediated immune response and had greater antibody titers against BVDV than the prewean vaccinates.

Postweaning vaccination are part of many preconditioning programs which encompass a stronger development of the immune system but exposure to greater levels of stress that alter the potential effect of the vaccine. Livestock market sourced calves may benefit from postweaning vaccinations as antibody titers may reach peak levels at the time of market; whereas early vaccinates may have antibody titers that begin to wane (Grooms and Coe, 2002).

Stress and Vaccine Efficacy

Beef calves in U.S. production systems face many challenges throughout their lives, and many of them often result in adverse health consequences and economic impacts. Environmental exposures, nutrition changes, management strategies, and transportation induce stressors in these animals’ lives and subsequently impact animals’ ability to maintain physiological homeostasis. Stress is the most significant precursors to opportunistic pathogen-related disease (McEwen and Stellar, 1993), and two of the most stressful events in a calf’s life are weaning and transportation (Kelley, 1980; Kim et al., 2011). Stressed cattle may experience an inhibited inflammatory response and reduced immune response vaccination (Callan, 2001; Richeson, 2015) as a result.

Stress-induced glucocorticoids (GC) and adrenocorticotropic hormone (ACTH) have been linked to the suppression of antibody production (Kumar et al., 2012) and responses associated with disease expression of proinflammatory cytokines; interleukin (IL) 6, interferon gamma (INF-γ), and tumor necrosis factor alpha (TNF-α) and a subsequent reduction in immune system stimulus to vaccination (Grell et al., 2005).

Stress and Glucocorticoid Production

The association between stress and infectious disease has been the focus of many researchers. Adrenocorticotropin hormone is responsible for stimulating and secreting GC from the adrenal cortex. Secretion of GC is the body's normal response to stress and is a mechanism that provides negative feedback regulating the activity of the hypothalamic-pituitary-adrenal (HPA) axis. Though synthetic GC is used to treat many diseases in cattle, some research indicates that synthetic GCs such as dexamethasone have been shown to occasionally exasperate disease or increase adverse reactions in the host animal. Elevated levels of stress-induced GC can negatively impact the host immune system (Roth and Kaeberle, 1982). Research measuring cortisol levels in weaned calves has been highly documented and confirms that weaning stress increases cortisol concentrations in the blood regardless of age at the time of weaning, as was determined in five-day-old dairy calves and seven-month-old beef calves exposed to weaning and transportation (Kim et al., 2011; Hudson et al., 2020).

The mechanisms by which the stress axis suppresses the immune system is a complex interaction with many moving parts. One of the pathways involved in the suppressive function is the NF-κB pathway. The immune system's suppression by glucocorticoids occurs as the NF-kB pathway is blocked, limiting T cell function. The response results in an inability to activate IL-1 and IL-6 production, stimulating the hypothalamus and pituitary glands (Tizard, 2017). In such situations, alternate pathways stimulate the cytokines responsible for action on the hypothalamus

and pituitary and secretion of GC. Catecholamines may be responsible for stimulating IL-1 and IL-6 when alternate pathways are utilized. Supporting evidence of this was reported by Kim et al. (2011), who found an increase in proinflammatory cytokines IL-1 and IL-6 and decreased INF-γ when animals were subjected to weaning stress. In addition to GC's ability to block specific immune system pathways, GCs produced from weaning stress have also been reported to suppress antibody synthesis in calves (Crookshank et al., 1979; Kelley, 1980).

Glucocorticoids and Antibody Production

One of the fundamental mechanisms to fight pathogenic invasion is through the humoral immune function, which relies on producing specific antibodies by plasma cells to defend the host. When a foreign body, an antigen, enters the host, B-lymphocytes' recognize the antigen and responds by undergoing differentiation and proliferation. Through differentiation, some B-lymphocytes become plasma cells and produce antigen-specific antibodies. Research indicates that GCs may disrupt antibody proliferation through protein catabolism, thus reducing the ability to mount effective action to the antigen (Fauci, 1979), but disruptions in antibody production may be most dependent on the timing and duration of elevated glucocorticoids (Roth and Kaeberle, 1982). However, mixed results remain on the effects of GC and antibody production. Research conducted on female eider ducks implanted with corticosterone had twice the reduction of immunoglobulins than the controls (Bourgeon and Raclot, 2006). In a human study examining the antibody (IgG) response to keyhole limpet hemocyanin (KLH) in highly stressed individuals and minor stress events, individuals exposed to high-stress levels had lower antibody production. However, there were no differences between the two groups (Snyder et al., 1990). Gwazdauskas et al. (1978) demonstrated a negative correlation between antibody titer concentration and total plasma GC (Gwazdauskas et al., 1978). Antibody titers were higher when measured with lower stress exposure coinciding with a preweaning timeline versus postweaning. The study also concluded that the sex of the animal also played a role in antibody production, indicating that sex

steroids in circulation were likely responsible for the difference in antibody titers where steers had higher titer levels than the females. Other studies have also reported elevated cortisol concentrations in heifer versus steer calves (Henricks et al., 1984; Arthington et al., 2003). Antibody titers were not measured in this study, but there is evidence to suggest that sex does play some role in stress-induced cortisol concentrations and subsequent antibody production.

Conversely, Kim et al. (2011) reported that weaning stress in dairy calves did not affect serum antibodies. The age of animals used in this study when measurements were taken at 2 and 70 days may explain the results. Maternal antibody interference or a lack of immunocompetency may have limited any change in antibody levels when challenged with weaning stress. The stressor's type, duration, and frequency play a vital role in the outcome of the animals' immune status. The age and sex of the animal are also areas that should be considered when measuring GC's effects.

CHAPTER III

METHODOLOGY

Material and Methods

All animal work was conducted in strict accordance with Oklahoma State University's Institutional Animal Care and Use Committee (Protocol #20-34).

Treatment and Vaccination Procedures

On May 19, 2020 (d 0), 151 Angus, Angus x Hereford or Charolais x Angus calves (69 d ± 37. 5 days of age, n = 151 total calves with 67 heifers and 84 steers) were used to examine the effects of vaccine type and timing on animal performance, morbidity, and antibody response pre- and postweaning. Calves were assigned to one of three vaccination protocol stratified by breed of sire, sex, and date of birth. Vaccination treatments included: 1) KV/MLV – multivalent inactivated virus BRD vaccine (KV, ViraShield 6, Elanco US Inc., Greenfield, IN) administered on d0 followed by revaccination at weaning (d 127) with a pentavalent modified-live virus (MLV, Titanium 5, Elanco Animal Health, Greenfield, IN); 2) MLV/MLV – pentavalent modified-live virus (Titanium 5) administered on d 0 and 127; or 3) WEAN – pentavalent modified-live virus (Titanium 5) administered on d 127 and 140. There were 52 calves in KV/MLV, 49 in MLV/MLV, and 46 in WEAN treatments. Vaccines were administered subcutaneously using Beef Quality Assurance guidelines (BQA, 2019) at the recommended dose of 5 mL for KV and 2 mL for MLV. Both vaccines used are labeled as preventative

against diseases caused by infectious bovine rhinotracheitis (IBR), bovine viral diarrhea (BVD type 1 and type 2), parainfluenza type 3 (PI_3), and bovine respiratory syncytial virus (BRSV).

Animal Managements

Calves used in this experiment were born from February 12, 2020, to April 27, 2020, at Oklahoma State University's Range Cow Research Center – South Range Unit near Stillwater, Oklahoma (Latitude 36.1226, Longitude -97.2492, Elevation 965 ft.). Calf age at the start of the study (d0) averaged 69 d (± 37.5 d), and body weight (BW) averaged 110.53 (± 7.52 SD) kg and 107.79 (± 7.15 SD) kg for steers and heifer calves, respectively. The cow herd was grouped based on parity, where the first group consisted of first- and second-parity heifers and multiparous mature cows (> 6 years) at the range headquarters (HQ, n=89), and the second group consisted of three- to five-year-old multiparous cows (SEC, n=62). The two groups were housed on separate ranches approximately 3.2 km apart. All dams from each herd were vaccinated against BRD with a pentavalent MLV vaccine 30 to 45 d prior to spring breeding in the year prior to the birth of trial calves. Dams were not revaccinated during the course of our study. The stocking rate for HQ and SEC cows was approximately 1 cow/3.25 ha and 1cow/4 ha, respectively. Pasture forage resources comprised a range of warm season grasses, including bermudagrass *(Cynodon dactylon)*, dallisgrass *(Paspalum dilatatum)*, crabgrass *(Digitaria sanguinalis)*, and tallgrass prairie native species (primarily big bluestem [*Andropogon gerardii];* little bluestem [*Schizachyrium scoparium];* indiangrass [*Sorghastrum nutans)*.

On d 0, calves were separated from their dam at 0700, weighed without prior shrink, blood collected via jugular venipuncture, administered vaccine when appropriate, and then returned to their dams until weaning on d 127. On d 127, all calves were weighed, blood collected, vaccine treatment applied, and fence-line weaned (Price et al., 2003) for one week in a 0.61 ha pasture at their birth location. Fence-line weaning management was conducted as

described by Price et al. (2003) to reduce the stress from dam separation. Briefly, cows and calves were rotated into the weaning pasture, the next day cows and calves were separated, and calves returned to the weaning pasture with cows placed in the adjacent pasture separated by a steel pipe fence.

Following the one week of fence-line weaning, SEC calves were transported to the HQ weaning facilities and commingled in a 0.61 ha pen for one week, after which they were moved to a 15-ha paddock consisting of mostly dormant mixed grass (native and bermudagrass). Fourteen days postweaning (d 140), calves in the WEAN treatment were revaccinated with the same MLV vaccine type previously used. The weaned calves were fed a supplemental concentrate containing monensin (Rumensin, Elanco US Inc.) at an average of 0.5% of BW and top dressed with a corn-based coccidiostat (Deccox, Zoetis Animal Health) for the first 30 days from the onset of weaning. Ad libitum access to mixed grass hay and fresh water. Subsequent measurements of calf BW and blood collections occured on d 140, 154, 168, and 182.

On d 134, upon arrival at the HQ facility, all calves were treated for external parasites using a pour-on dewormer (Cydectin, Elanco Animal Health, Greenfield, IN) and internal parasites with an oral drench (Safeguard, Merck Animal Health), vaccinated with a multivalent clostridial bacterin-toxoid (Vision 7, Merck Animal Health). A coccidiosis preventative (Corid, Huvepharma Inc., Peachtree City, GA) was added to the drinking water for the first five days after arrival at HQ. On d140, all calves were vaccinated against *Mannheimia haemolytica* (Nuplura PH, Elanco Animal Health, Greenfield, IN).

Calves were observed each morning (0730) by experienced university personnel for clinical signs of respiratory illness. Evaluators were blinded to treatments assignments and cattle were not visually identifiable based on treatment during morbidity investigation. Calves were evaluated daily and scored using the DART system (Taylor et al., 2015) if clinical symptoms

were present. Calves receiving a score ≥ 3 were pulled and rectal temperatures measured. Animals displaying rectal temperature ≥ 40 °C were administered antibiotic treatment.

Blood Collection and Serology

One blood sample was collected from each calf at six-time points on d 0, 127, 140, 154, 168, and 182 via jugular venipuncture into a 10 mL evacuated tube without additive (Monoject, Covidien, Mansfield, MA.). Blood samples were stored in an insulated cooler with ice packs. The samples were allowed to clot and then centrifuged at 2100 x g for 20 minutes at 4 °C. Post centrifugation, serum was extracted and transferred to 2 mL microtubes and stored at -20 °C until serological analysis.

Serology was performed at the Oklahoma Animal Disease Diagnostic Laboratory (Stillwater, Oklahoma). Antibody titers against bovine viral diarrhea virus type 1 (BVDV-1) and BRSV were determined using a modification of the microtiter virus neutralization test (Rossiter and Jessett, 1982). Briefly, two-fold dilutions of each serum sample were made in Dulbecco's minimum essential medium (DMEM) in 96-well microtiter plates. An equal volume (25 µl) of virus diluted in DMEM to contain about 100 $TCID_{50}$/25 µl was added to all dilutions. After incubating the serum/virus mixtures for 1 hour, a cell suspension of MDBK cells containing about 10^4 cells in DMEM containing 10% fetal bovine serum was added to each well. Plates were incubated for 3 days at 37 °C, and wells were examined for the presence of virus-specific cytopathic effects (CPE). Titers were expressed as the reciprocal of the highest dilution of serum that completely neutralized the virus.

Statistical Analysis

Experimental data were analyzed as a randomized complete block design using PROC MIXED of SAS (SAS Institute, Cary, NC). Calf was identified as the experimental unit and the sampling unit. Blocks were the pastures (HQ and SEC). Calves were designated to a block based

on their birth pasture. Calves from HQ were assigned to block one and SEC calves assigned to block two. Birthdate, sex, and dam age were used as covariates in the body weight (BW) and average daily gain (ADG) analysis. Treatment, birthdate, dam age, sex and treatment x sex interaction were included in the model statement. The fixed effects for BW and ADG, and block was in the random statement. Blood constituent data were analyzed as repeated measures. Treatment, day, dam age, treatment x day, treatment x sex, and treatment x sex x day interactions were included in the model statement. Significance was observed at ($P < 0.05$). Virus-specific antibody titers against BRSV and BVDV-1 were tested for normality of distribution using PROC UNIVARIATE of SAS, and nonparametric data were $\log_2$ transformed and statistically analyzed as a repeated measure with day and treatment and their interaction as fixed effects and sampling date in the repeat statement.

CHAPTER IV

RESULTS

During the study, no mortality was reported. Seventeen calves were treated with antibiotics for infectious pododermatitis. Five calves were treated once with an antibiotic for respiratory illness determined by dullness, inappetence, nasal discharge, and rectal temperature ≥ 40 ℃. Four calves were from the KV/MLV treatment and one from the MLV/MLV treatment group. Four calves were removed from the study due to missing data or abnormal SN titer levels as deemed by diagnostic lab report. Choice of viral analysis was based on geographical disease potential and antibody response to vaccine.

Body Weight and Average Daily Gain

The analysis of BW indicated sex x treatment interaction ($P \leq 0.04$) on d 127, 140, and 154, while there was a sex x treatment interaction for ADG for the period between d 154 to 168. Effects of vaccine type and timing treatments on BW and ADG are presented in Table 1. Body weight was not affected by vaccination treatment at any point ($P \geq 0.4$) during the pre- or postweaning periods. The least square mean for average daily gains did show a difference between the KV/MLV and MLV/MLV between d 154 and 168 of 0.21 kg/d and 0.44 kg/d ($P = 0.02$), and again between d 168 and 182 of 0.79 kg/d and 0.55 kg/d ($P = 0.01$), respectively. The ADG observed between d 154 and 168 for all treatments were considerably less than ADG at any other measurement period during the study. We attributed the sharp decrease in ADG to an extreme weather event that occurred during the d 154 to 168 period consisting of freezing

temperatures and a four-day period of freezing precipitation. The sharp upturn in ADG observed during the following the period, d 168 to 182, was attributed to compensatory gain.

Effects of treatment by sex on BW and ADG performance are presented in Table 2. Differences measured on d 127 ($P = 0.04$) were due to sex effect within the KV/MLV treatment which can be expected as in general, steers are heavier than heifers. Heifers in the MLV/MLV group had greater BW as measured at d 140 and 154 when compared to the KV/MLV and WEAN treatments. There was no difference in BW among the steers. Treatment by sex effect for ADG occurred during d 154-168 with the steers in MLV/MLV treatment differing ($P = 0.04$) from both sexes across all treatments.

Bovine Respiratory Syncytial Virus SN Antibody Titers

The log-transformed SN antibodies to BRSV by day across sex are presented in Figure 1. Day 0 antibody titer concentrations are representative of maternal antibody circulation. No differences among treatment groups were identified at that time. Our result for neutralizing antibody titers against BRSV in calves vaccinated with either KV or MLV at d 0 suggests vaccine protection during the preweaning phase may have been minimal. Calves in both treatments were determined seronegative with SN < 2 (Peters et al., 2004) by d 127 which was similar to the result reported on the unvaccinated WEAN treatment group. Following revaccination of the KV/MLV and MLV/MLV groups on d 127, a treatment x day interaction on d 140 was determined. Antibody titers were greater in the KV/MLV ($P = 0.0002$) than in the MLV/MLV and WEAN treatment groups. Fourteen days post-revaccination of the WEAN group, a difference in antibody titers was observed, with the WEAN group having greater ($P = 0.03$) titer concentrations than the MLV/MLV treatment. No differences were observed at any of the other timepoints.

Least square mean BRSV antibody titers in heifers for treatment x sex x day interaction are presented in Figure 2. Differences among treatments on d 0 were due to passive immunity.

Day 140 data indicated a difference ($P<0.05$) in titers with the WEAN treatment heifers having the least reported titers compared to the other two treatments.

Least square mean BRSV antibody titers in steers for treatment x sex x day interaction are presented in Figure 3. Day 0 treatment differences were due to passive immunity. Day 140 data indicated a difference ($P < 0.02$) in titers among treatment steers with the KV/MLV treatment having the greatest antibody titers compared to the other two treatments.

Bovine Viral Diarrhea Virus SN Antibody Titers

The SN antibody response to BVDV type I and II vaccination are presented in Figure 4. Serum neutralizing (SN) antibody titers against BVDV-1 at d 0 were due to passive transfer from dams, and no difference was determined between treatment groups at that timepoint. However, analysis of measurements taken on d 127 indicated a difference among treatment groups for antibody titers. The MLV/MLV group had greater SN antibody titer response (3.48 ± 0.29, $P = <0.0001$) than both the KV/MLV (1.16 ± 0.28) and WEAN (1.11 ± 0.31) groups. Analysis of blood serum collected on d 140 found a difference ($P < 0.01$) in neutralizing antibodies among all three treatments. The MLV/MLV group again had the greatest SN antibody titer concentration following revaccination on d 127. A strong anamnestic response was present in the KV/MLV group following revaccination with a MLV vaccine on d 127 and subsequently had the greatest (5.6 ± 0.28, $P = 0.02$) titer concentration by d 168, differing from the MLV/MLV treatment. By the end of the 56-d preconditioning period, the mean across all treatment groups displayed sufficient SN antibody titers (>4, $\log_2$) to suggest protection against severe BVDV infection.

Treatment x sex interaction for BVDV-1 antibody titers is presented in Figure 5. The data analyzed indicated a treatment x sex interaction ($P < 0.0001$) within the MLV/MLV treatment with heifers having greater SN antibody titers over steers.

CHAPTER V

DISCUSSION

Bovine Respiratory Syncytial Virus

Serum neutralizing antibodies against BRSV had little immune response across all the treatments. By d 127 all treatments were seronegative (<2) (as defined by Peters et al., 2004) and remained seronegative for the remainder of the study despite revaccination on d 127. The greatest increase in titers was measured on d 140 in the KV/MLV group following revaccination on d 127 but steadily decreased to levels resembling that of the other two treatments to a mean titer level near zero by the end of the study. Previous research also observed increased antibody response after revaccination with both KV and MLV. The KV group in their study showed the greatest titers 14 days post-revaccination. This was similar to the KV/MLV in our study that also had the greatest vaccine-induced titers recorded 14 days post-revaccination. Fulton et al. (1995) performed sample collection for analysis every seven days over four weeks as compared to approximately 14 day intervals in our study, therefore we do not know if titers peaked at an earlier point following revaccination. (Fulton et al., 1995). Given the gap in time between our initial vaccination at branding, we are unable to determine which single dose of vaccine type produced the greatest antibody titers as there was no difference measured between treatments at d 127. The antibody response from the KV/MLV treatment may have resulted from stimulating the immune system by using a different antigen type.

Difference in BRSV titers were recorded from the treatment x sex x day interaction for both heifers and steers. On d 140, heifers in KV/MLV and MLV/MLV and steers in the KV/MLV treatments differed from the WEAN and MLV/MLV treatments, respectively. On d 140 the differences realized among treatments were the result of revaccinations of the KV/MLV MLV/MLV treatments on d 127. The WEAN treatment had only received their first vaccination on d 127 and was lagging in antibody production behind the other two treatments, with the exception of the MLV/MLV steers.

Despite vaccination and revaccination, host immune response to BRSV immunogen or timing of vaccination had little effect on antibody concentration during the preweaning and preconditioning period. Understanding why BRSV antibodies respond with low or rapidly declining levels is important as BRSV is problematic in calves less than six months of age with approximately 60 to 80% of infections resulting in morbidity (Gershwin, 2007). Bovine respiratory syncytial virus is generally problematic in calves less than six months of age and approximately 60 to 80% of infections result in morbidity. Grooms and Coe (2002) observed that two doses of MLV, 21 days apart, generated the strongest antibody response, but also observed rapidly waning titers against BRSV. It is not understood why the BRSV titer concentration decreases so rapidly post-revaccination. One theory suggests that failure to initiate an increase in BRSV antibodies is because pre-existing antibodies may have blocked production (Fulton et al., 1995; Downey-Slinker et al., 2016).

Bovine Viral Diarrhea Virus

The results of our study indicate that the SN antibody titer response to multivalent BRD vaccines varies based on the timing of vaccination and vaccine antigen used. The MLV vaccine used in the MLV/MLV group displayed the highest titers against BVDV-1 through pre-weaning

and sustained the highest measured antibody production approximately 27 days post-weaning. The longevity and level of antibody production that the initial dose of MLV vaccine provided was similar to others that also found that BVDV MLV vaccines elicited a more vigorous immune response and greater duration of viable antibodies (Fulton et al., 1995; Ridpath, 2013; Downey-Slinker et al., 2016) when compared with inactivated BVDV vaccines alluding to the greater efficacy of the MLV antigen. Serum antibody titers have long been used to measure immunity provided by vaccination or natural infection (Ridpath et al., 2003) in the host animal, although a definitive protective threshold has yet to be determined. Passively acquired antibody titers of ≥ 256 were demonstrated to provide adequate protection against the manifestation of BVDV disease but did not eliminate viral transmission (Bolin and Ridpath, 1995). Using SN antibody titers as a parameter alone may be misrepresentative of disease protection. Vaccine-induced serum antibodies are a measurable response to immunogens (Fulton et al., 1995) and vaccine efficacy but may not be precisely a measure of immunity; specifically among immunocompromised individuals which may have a reduced or even absent antibody response(Burrell et al., 2017). Studies have analyzed the relationship between antibody titer concentration and protective immunity, but the results are contradicting. Animals examined displaying low to moderate antibody titers had a greater level of protection post-challenge when comparing humoral and cell-mediated immune responses (Downey-Slinker et al., 2016). Conversely, another study showed the association between low neutralizing titers and severe clinical disease (Bolin and Ridpath, 1995).

In our study, no challenge was applied to determine the level of protection the vaccine treatments provided. The KV given at branding without a booster displayed low titer levels (< 2) by the time of weaning, similar to those observed in the WEAN treatment group that received no vaccine at branding. The low antibody titers at weaning were likely due to the protocol with which the KV was used. The manufacturer label suggests providing a booster dose 14-28 days

following the initial inoculation. It should not be assumed, despite seronegative results measured on d 127, that the calves vaccinated with KV were absent of protective immunity.

Despite decades of research surrounding BRD, limited progress has been made towards the advancement of controlling the spread of the disease, although years of research indicates the efficacy and efficiency of the vaccines to be significant, however, BRD continues to be the costliest diseases in feedlot cattle and breeding stock. Perhaps the answer to disease prevention is the timing of vaccine administration rather than the vaccine itself. Numerous studies examine the timing of vaccine administration in neonates, preconditioned and receiving cattle (Grooms and Coe, 2002; Richeson et al., 2008; Richeson et al., 2009). Here, our study followed vaccination protocols that most closely align with the Oklahoma Quality Beef Network, VAC45 preconditioning program (Robe et al., 2022) and also vaccination strategies commonly used by cow-calf producers. Our goal was to determine antibody response to BRD vaccination while focusing on vaccine type and timing under field conditions. In an extensive study examining the effect of vaccine type and timing on antibody titer response (Grooms and Coe, 2002). The Grooms and Coe (2002) study consisted of eight combinations of BRD vaccine types and utilized a prewean/wean (KV/KV, KV/MLV, MLV/MLV, MLV/KV) and wean/postwean (KV/KV, KV/MLV, MLV/MLV, MLV/KV) vaccination strategy and its effects on virus-neutralizing antibody titers. Results in their study showed neutralizing antibody titers against BVDV had the greatest antibody response utilizing a prewean/wean vaccination protocol. Within this protocol, the KV/MLV treatment group also had the highest titer level at the end of the study. Grooms and Coe (2002) results aligned with our findings which also resulted in the highest antibody titers by the end of study using KV and MLV at prewean and weaning, respectively. Also in line with our finding was the lack of immune response from a single dose of KV. Significant antibody production was not observed until collection dates post-revaccination with an MLV. The difference between our studies, however, was the timing of the initial vaccination. Ours study

administered vaccine at 2 to 4 mo. of age versus the Grooms and Coe (2002) study at 21 days before weaning. Results from these studies may suggest that inoculation during a low stress time prior to dam separation may be optimal for developing a robust antibody response. Our results would suggest that 'branding' vaccinations with MLV may provide disease protection during the preweaning and early weaning periods better preparing the calf for challenges associated with weaning. Vaccination at weaning may provide delayed protection that is more beneficial to the buyer rather than providing protection during the preconditioning period. Ultimately, vaccination timing depends on the goals of the operation. This information is of the utmost importance given a recent review and meta-analysis (O'Connor et al., 2019) that suggested that vaccines used at or near feedlot arrival did not reduce the incidence of BRD. Research is limited that ties the two industry segments together examining preweaning vaccination strategies and subsequent performance in feedlots. Such research would require a large expenditure in time and resources for a sample size large enough to produce significant results, but research that links the two segments of the industry is necessary.

Inactivated vaccines elicit an antibody-mediated humoral immune response as the primary mode of disease prevention. Our initial dose of BRD vaccines was administered to both the KV/MLV and the MLV/MLV groups at 69 days of age (±37 days), which is an age thought to have a high presence of passively acquired maternal antibodies (Endsley et al., 2003). Therefore, administering KV to a calf in the presence of high circulating maternal antibodies may result in the neutralization of the vaccine antigen (Kirkpatrick et al., 2001; Endsley et al., 2003; Woolums et al., 2013) and subsequently failing to establish an immune response in the calf. Conversely, MLV vaccines are not solely dependent on antibody production as the protection mechanism as they elicit both a humoral and cell-mediated response, with the latter considered more crucial in the generating optimal protection against invading viral pathogens (Chase, 2013; Downey-Slinker et al., 2016). However, similar to KV, circulating maternal antibodies have also been reported to

interfere with the humoral response generated by MLV (Kirkpatrick et al., 2001), thus stimulation of the cell-mediated response is likely the primary mechanism of disease protection by MLV at that age. Our initial dose of KV administered on d 0 may have elicited a priming effect despite potential maternal interference. The discussion for priming was evidenced by the robust secondary response to revaccination with MLV at weaning, which displayed the highest antibody titer level by d 168. The anamnestic response in the KV/MLV group is similar to recent findings in cattle vaccinated with either KV or MLV respiratory vaccine and subsequently challenged (Downey-Slinker et al., 2016). Downey-Slinker et al. (2016) suggested that the high titer response seen post-challenge in the KV treatment compared to those receiving MLV resulted from the MLV recipients being better equipped to control the viral replication. The treatment by sex interaction in the MLV/MLV treatment displayed greater antibody production in heifers compared to steers of the same treatment. There was no interaction among the other two treatments. The result of sex effect in our study aligns with reports from human studies. Human studies have found females have a greater capability of producing antibodies (Butterworth et al., 1967) and Th2 response (Taneja, 2018). Conversely, circulating sex steroids in heifers imposed immunosuppressive activity, resulting in lower antibody titers than steers (Gwazdauskas et al., 1978) and similar immunosuppressive activity in female mice (Hellig and Gerneke, 1975).

Body Weight and Average Daily Gain

The type and timing of respiratory vaccines in our study did not impact BW during pre- or post-weaning across treatments but did affect ADG in the final 28 days of the study. Overall BW does not seem to be affected by vaccination regimen (Duff et al., 2000; Powell et al., 2012). Sex x treatment interactions on BW were seen in the KV/MLV treatment with the steers having greater BW than the heifers which can be an expected outcome. There is conflicting research in regard to vaccine effect on ADG as multiple studies have reported no difference in ADG when receiving BRD vaccines during the preconditioning or receiving periods (Richeson et al., 2009;

Step et al., 2009; Bailey et al., 2016). These reports were similar to our observations with the exception of differences in the final 28 days of preconditioning. It is unclear whether the reduction and difference in ADG between treatments was a direct effect of vaccine treatment or rather that the reduction in animal gain was more so influenced by the weather event and subsequent compensatory gain.

Arthington et al. (2013) suggested that a reduction in ADG during the two weeks following vaccination may be a result of an acute-phase protein (APP) response which is often stimulated by local inflammation, endotoxin injections, or stressors (Baumann and Gauldie, 1994). Similarly, during a 28-d backgrounding study, results determined that both multivalent KV and MLV respiratory vaccines had negative ADG during the backgrounding phase in the two to three weeks following vaccination (Cusack et al., 2021). Six of the eight treatments in that study reported BW losses. The effect of vaccine on ADG observed by Richeson et al. (2008) may have been due to transportation stress which has been demonstrated to last up to 14 days following shipment (Richeson et al., 2008). Both of these studies demonstrated a reduction in ADG in the two weeks following vaccination. In our study, no ADG differences were reported for any treatment in the two weeks following vaccination or revaccination. Sex x treatment interactions were also noted during the final 28 days of preconditioning from d 154-168 with the steers in the MLV/MLV treatment differing from all other study calves but at no other time. Therefore, it would seem that the difference observed in ADG was a weather-related hardship.

CHAPTER VI

CONCLUSION

The data acquired from this experiment revealed variation in antibody production when vaccine antigen and timing of vaccination were considered. Analysis of SN antibody titers to BRSV antigen indicated no difference between treatments from d 0 (2 to 4 months of age) to 127 (weaning). However, KV/MLV had the greatest antibody response following revaccination at weaning on d 127. Antibody response to BVDV type 1 vaccine antigen had the longest sustained titers in the MLV/MLV group following initial vaccination on d 0 to 154. There was no difference in antibody response between the KV/MLV and WEAN groups from d 0 to 127, however, the KV vaccine given at branding may have had a priming effect as there was a strong anamnestic response following revaccination with MLV. All treatments had similar antibody titers by the conclusion of the study. Treatment did not affect BW but did differ in ADG, however, difference in results may have been due to weather challenge. Further field-based research investigating antibody production to vaccine type and timing with regard to the level of protection afforded, and the future immune status and performance through subsequent beef industry segments is needed to develop the most effective respiratory vaccination protocols.

Table 1. Effect of vaccination timing and type on growth performance of calves pre and post weaning

Item	KV/MLV	MLV/MLV	WEAN	SE	P-value
Body weight, kg					
Day 0	108	108	108	5.18	0.96
127	250	251	248	7.23	0.88
140	258	260	257	7.86	0.77
154	269	271	266	8.18	0.56
168	272	278	271	8.14	0.41
182	283	285	279	8.73	0.56
Average Daily Gain, kg					
D 0 - 127	1.11	1.14	1.13	0.035	0.62
127 - 140	0.58	0.70	0.62	0.144	0.56
140 - 154	0.77	0.79	0.65	0.123	0.29
154 - 168	0.21[a]	0.44[b]	0.35[ab]	0.071	0.02
168 - 182	0.79[b]	0.55[a]	0.65[ab]	0.081	0.01

[a – b] Least square means within rows with differing super scripts differ $P < 0.05$.
KV = killed vaccine (ViraShield 6, Elanco Animal Health, Greenfield, IN)
MLV = modified-live viral vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN)

Table 2. Effect of vaccination treatment by sex on growth performance

Item	Treatment							P value		
	KV/MLV		MLV/MLV		WEAN					
	H	S	H	S	H	S	SE	Sex	Trt	Sex x Trt
Body weight, kg										
Day 0	104	113	107	109	106	110	5.2	0.03	0.95	0.42
127	237[a]	263[c]	250[ab]	253[bc]	243[ab]	254[bc]	6.0	0.0005	0.85	0.04
140	245[a]	271[c]	259[bc]	263[bc]	252[ab]	262[bc]	5.3	0.0007	0.68	0.04
154	255[a]	283[c]	272[bc]	273[bc]	260[ab]	272[bc]	5.2	0.0006	0.48	0.02
168	258	286	274	281	265	277	5.5	0.0002	0.34	0.09
182	269	297	283	288	275	286	5.5	0.0005	0.56	0.06
Average Daily Gain, kg										
Day 0 - 127	1.06	1.16	1.13	1.14	1.09	1.16	0.04	0.02	0.64	0.27
127 - 140	0.57	0.59	0.66	0.72	0.66	0.58	0.17	0.99	0.62	0.82
140 - 154	0.72	0.81	0.90	0.70	0.58	0.70	0.15	0.96	0.23	0.18
154 - 168	0.20[a]	0.21[a]	0.19[a]	0.62[b]	0.35[a]	0.36[a]	0.11	0.05	0.08	0.04
168 - 182	0.80	0.79	0.63	0.49	0.68	0.61	0.12	0.37	0.06	0.79

KV = killed vaccine (ViraShield 6, Elanco Animal Health, Greenfield, IN) MLV = modified-live viral vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN). [a-c] Least square means within rows with differing superscripts differ $P < 0.05$

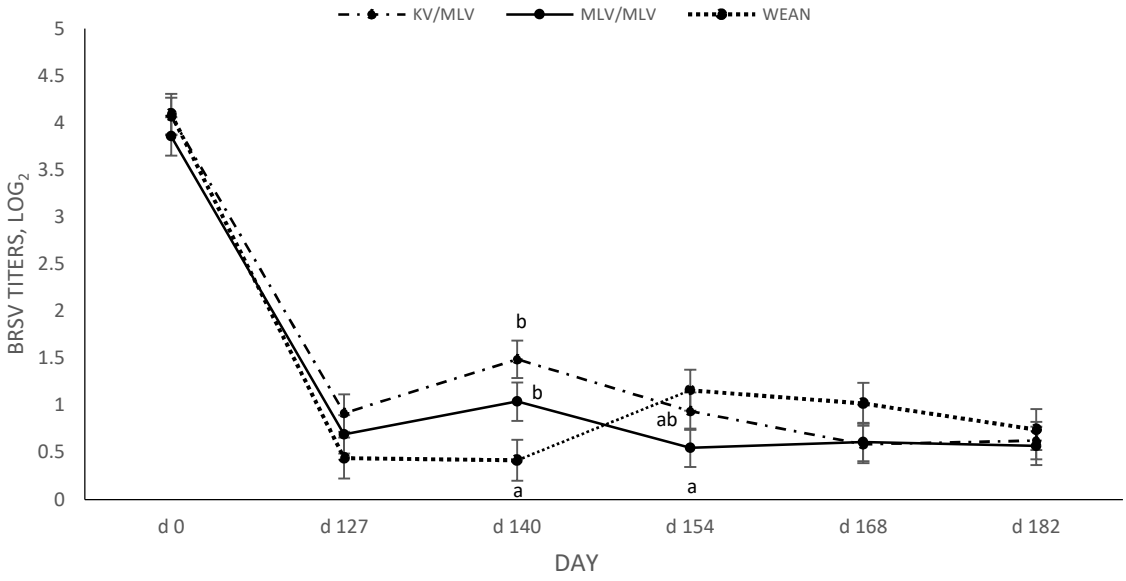

Figure 1. Least square mean log_2 BRSV antibody titers for treatment x day interaction in calves vaccinated with either an inactivated or modified-live viral BRD vaccine. Vaccines administered for KV/MLV at d 0 and 127, for MLV/MLV at d 0 and 127, and WEAN on d 127 and 140. D 0 represents colostral antibodies. D 140 KV/MLV and MLV/MLV differ from WEAN within d; d 154 MLV/MLV differs from WEAN within d, $P < 0.05$. KV = killed vaccine (ViraShield 6, Elanco Animal Health, Greenfield, IN). MLV = modified-live viral vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN). $^{a-b}$ Least square means with differing superscripts differ by $P < 0.05$.

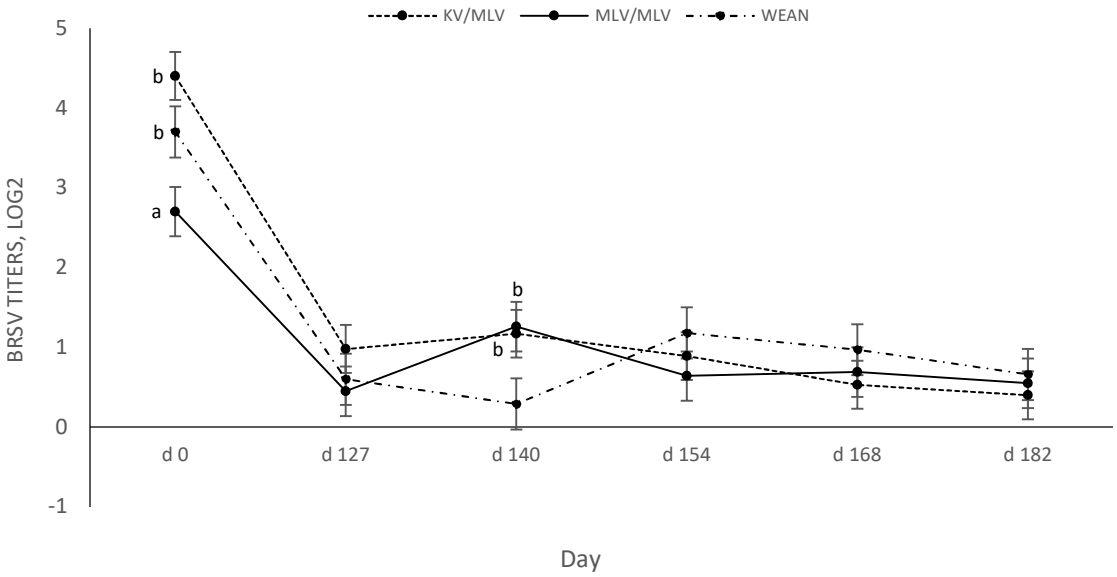

Figure 2. Least square mean $\log_2$ BRSV antibody titer in heifers for treatment x sex x day interaction in calves vaccinated with either an inactivated or modified-live viral BRD vaccine. Vaccines administered for KV/MLV on d 0 and 127, for MLV/MLV on d 0 and 127, and WEAN group on d 127 and 140. D 0 represents colostral antibodies. D 140, KV/MLV and MLV/MLV differ from WEAN within d. KV=killed vaccine (ViraShield 6, Elanco Animal Health, Greenfield, IN). MLV=modified-live viral vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN). $^{a\text{-}b}$ Least square means with differing superscripts differ by $P < 0.05$

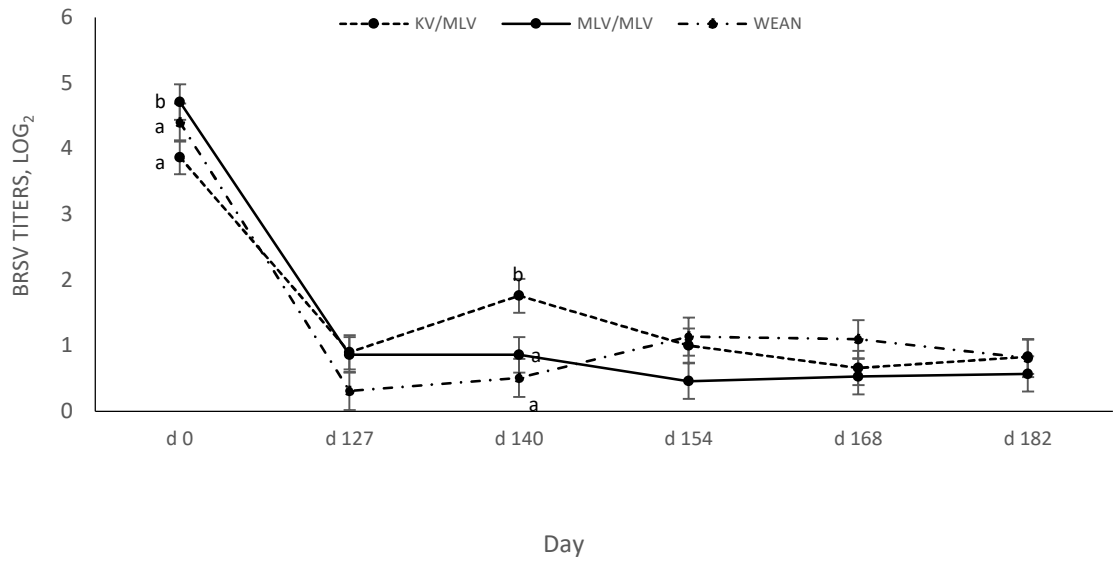

Figure 3. Least square mean, log_2 BRSV antibody titer in steers for treatment x sex x day interaction in calves vaccinated with either an inactivated or modified-live viral BRD vaccine. Vaccines administered for KV/MLV at d 0 and 127, for MLV/MLV at d 0 and 127, and WEAN on d 127 and 140. D 0 represents colostral antibodies. D 0 KV/MLV differed from MLV/MLV and WEAN groups within d. KV = killed vaccine (ViraShield 6, Elanco Animal Health, Greenfield, IN). MLV = modified-live viral vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN). [a-b] Least square means with differing superscripts differ by $P < 0.05$.

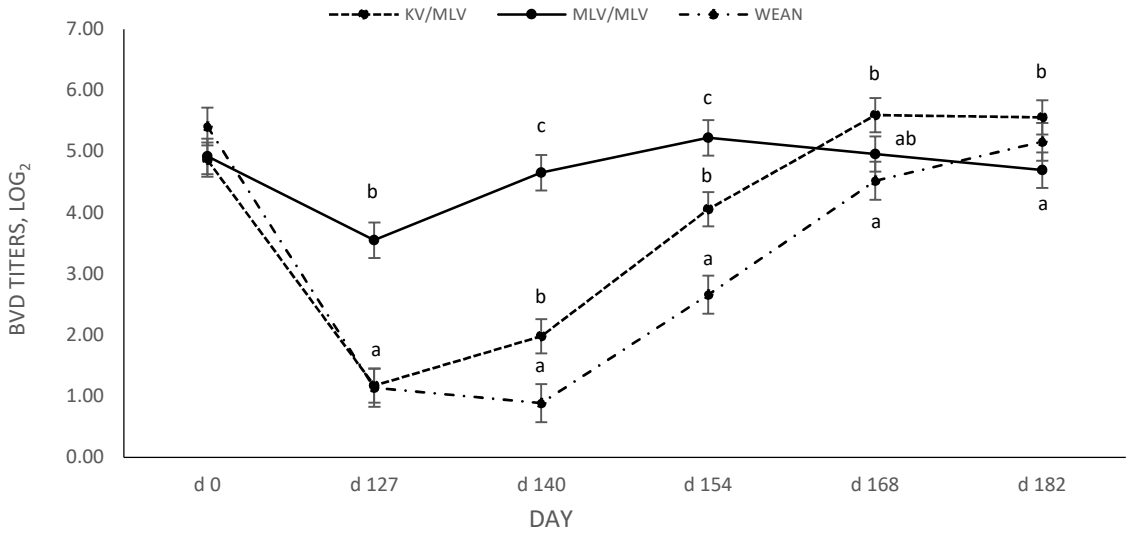

Figure 4. Least square mean Log_2 BVD antibody titers for treatment x day interaction in calves vaccinated with either an inactivated or modified-live viral BRD vaccine. Vaccines administered for KV/MLV at d 0 and 127, for MLV/MLV at d 0 and 127, and WEAN on d 127 and 140. KV = killed vaccine (ViraShield 6, Elanco Animal Health, Greenfield, IN). MLV = modified-live viral vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN). $^{a-c}$ Least square means with differing superscripts differ by $P < 0.05$.

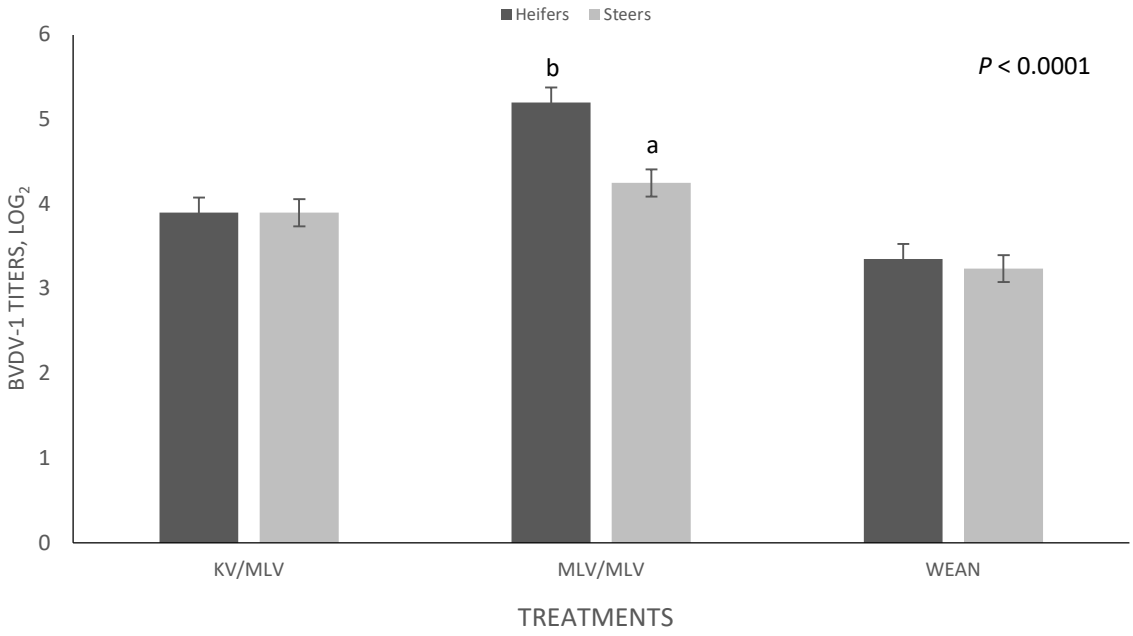

Figure 5. BVDV-1 antibody titers for treatment x sex interaction. The MLV/MLV treatment displayed a difference within treatment x sex ($P < 0.0001$) with the heifers having greater antibody titers. KV = killed vaccine (ViraShield 6, Elanco Animal Health, Greenfield, IN). MLV = modified-live viral vaccine (Titanium 5, Elanco Animal Health, Greenfield, IN). [a-b] Least square means with differing superscripts differ by $P < 0.05$.

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