INTRANASAL OR PARENTERAL RESPIRATORY VACCINATION UPON ARRIVAL OR DELAYED IN FEEDLOT HEIFERS

by

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Abstract

Modified-live virus (MLV) vaccines are used routinely to immunize cattle against bovine respiratory disease agents, but the route and timing of MLV administration may impact their safety and efficacy. The objective of this study was to evaluate the safety and efficacy of an intranasal or parenteral MLV administered on d 0 or 28. Three arrival blocks of heifers (initial BW = 208 kg; n = 600) were randomly assigned to treatments in a 2 × 2 factorial arrangement. The generalized complete block design consisted of 15 pens per treatment with pen as the experimental unit and 10 animals per pen. Treatments were: 1) Nasalgen 3 and Vista BVD on d 0 (NAS0); 2) Vista 5 SQ on d 0 (VIS0); 3) Nasalgen 3 and Vista BVD on d 28 (NAS28); 4) Vista 5 SQ on d 28 (VIS28). Performance, activity, and health data were analyzed using a mixed model in SAS and a subset of 3 cattle per pen were selected for antibody titer analyses with repeated measures. Body weight and blood samples were collected on d 0, 28, and 56. No differences existed for performance outcomes ($P \geq 0.19$). Activity (351.4 vs 354.3 min/d) and rumination (282.6 vs 285.4 min/d) time was less ($P < 0.01$) for delayed vs arrival vaccinated heifers. A timing × vaccine × day interaction existed ($P < 0.01$) for BRSV- and IBRV-specific antibody titers; VIS28 had the greatest ($P < 0.01$) BRSV antibody titer on d 56. For IBRV antibody titer on d 28, VIS0 was greatest, NAS0 was intermediate, and VIS28 and NAS28 were least ($P < 0.01$). Percentage of chronically ill cattle were reduced for arrival vs delayed (1.3 vs 4.7%; $P = 0.02$) and tended ($P = 0.06$) to be less for VIS vs. NAS (1.7 vs 4.3%). Arrival vaccinated heifers had a reduction in

antimicrobial treatment cost ($4.63 vs $7.31; $P = 0.02$). These data indicate improvement in some health outcomes for the parenteral route and arrival timing of MLV respiratory vaccination, but performance was not affected during the feedlot receiving period.

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Introduction

Bovine respiratory disease (BRD) is the most common morbidity and mortality event among feedlot cattle. Among U.S feedlots, 96.9% possessed cattle affected by BRD and 16.2% of cattle were affected by BRD following arrival to the feedlot (USDA-APHIS, 2011). The manner in which cattle are marketed in the U.S predisposes cattle to BRD (Ives and Richeson, 2015). Approximately 67% of cattle shipments arriving at U.S. feedlots originate from an auction facility (USDA-APHIS, 2011). Cattle derived from auction markets are typically commingled from a variety of sources. This high stress period in calves allows for pathogens associated with BRD to colonize the lower respiratory tract (Ives and Richeson, 2015) because immunity is impaired during chronic stress.

The role stress plays in BRD is part of the multifaceted nature of the disease; some important stressors are environmental factors, stress, viral and bacterial pathogens that result in bronchopneumonia (Guzman and Taylor, 2015). Cattle may experience physical or psychological stress, and both types of stress have a role in physiological stress which is involved in BRD (Grandin, 1997). Prevention is the best approach to reduce the prevalence and severity of BRD in the feedlot. The primary mechanism of prevention used today is vaccination in both the feedlot and cow calf sector. More than 90% of feedlots vaccinated cattle for some respiratory pathogen (USDA-APHIS, 2011).

Conversely only 68.9% of all cow-operations vaccinated cattle or calves in 2007 (USDA-APHIS, 2010). However, ideally vaccination should occur at the ranch origin to allow time for proper development of protective immunity. The effect of vaccination timing on the immune response and ultimately disease resistance is important. Vaccination at the feedlot may be administered in the face of significant stress which alters the animal's ability to mount a protective response and jeopardizes vaccine safety due to concurrent administration of a modified-live vaccine (MLV) with immunosuppression and acute infection (Richeson and Falkner, 2020). A MLV contains an attenuated virus that stimulates the immune response because it mimics natural infection. The stress-induced immunosuppression causes altered immune function in response to vaccines (Richeson et al., 2016). The route of respiratory vaccine administration should be considered for the prevention of BRD prior to arrival at the feedlot. Most respiratory vaccines are administered parenterally at either the ranch origin or at the feedlot (Waldner et al., 2018). However, in recent years the use of intranasal vaccination has increased due to increased availability and proposed benefits. Intranasal vaccines stimulate a local immune response that may act as a "barrier" to pathogen entry and prime the immune system (Greibel et al., 2009). The effect of route and timing of respiratory vaccinations requires further research to understand the safety and efficacy of intranasal vaccination versus parenteral vaccination for preventing BRD.

Bovine Respiratory Disease

While BRD is a highly complex and multi-faceted disease it can be prevented and managed successfully through an understanding of the pathogenesis. The causative factors of BRD are physiological stress, viral, and bacterial pathogens.

Viral pathogens associated with bovine respiratory disease

Bovine respiratory disease has 4 primary viruses associated with it; however, as new research and surveillance evolves additional viruses may be discovered; one such virus being studied as a potential respiratory pathogen is bovine coronavirus. However, the 4 viruses currently understood to be BRD causative are bovine viral diarrhea virus type 1 and 2 (BVDV), infectious bovine rhinotracheitis virus (IBRV), bovine respiratory syncytial virus (BRSV), and bovine parainfluenza-3 virus (PI3V).

Bovine Viral Diarrhea Virus is a pestivirus that contains a single strand of positive-sense RNA with a 5' untranslated region (UTR). Due to the highly conserved nature of the UTR this region of the RNA has been used to differentiate type 1 and type 2 (Ridpath et al., 1994). Clinically, there are several forms of BVDV with outcomes ranging in severity of subclinical, abortion, fatality associated with mucosal disease and general poor performance (Goyal and Ridpath, 2008). Host factors play a significant role in the outcome of clinical BVDV illness including but not limited to immunocompetence, immunotolerance, pregnancy status and/or gestational age and previous vaccination status (Baker, 1995). Bovine viral diarrhea virus is primarily acquired through aerosols that infect the nasal mucosa. Direct nose to nose contact is also considered an effective route through which transfer of BVDV occurs. If a fetus of a susceptible dam is exposed to BVDV between 90 and 120 days of gestation the immune system of the fetus will

become tolerant to the noncytopathic strain of the virus and become persistently infected (PI). A PI animal will then shed the BVDV virus for the duration of its life with a subclinical presentation unless it contracts mucosal disease which is typically fatal (Goyal and Ridpath, 2008; Kelling et al., 2002). Bovine viral diarrhea virus is also differentiated into biotypes which include non-cytopathic and cytopathic mechanisms. Cytopathic biotypes cause epithelial cell expiration. Noncytopathic biotypes of each genotype can cross the placenta membrane and create PI calves however there is some speculation if this is true because of the discovery of cytopathic biotypes being found in fetal calf serum (Bolin and Ridpath, 1998; Goyal and Ridpath, 2008). To create an effective control program for BVDV, genotypes have a more significant effect on management practices than biotypes.

Infectious bovine rhinotracheitis virus (IBRV) or bovine herpesvirus-1 (BHV-1) causes a febrile response upon initial infection and possesses the hallmark symptoms of red appearance of nasal mucosa, serous or mucopurulent discharge and heavy breathing or cough. Upon necropsy, affected animals will possess a red appearance of pharyngeal and tracheal mucosa epithelia due to severe hyperemia (Fulton, 2009). This virus has a role in BRD due to the significant epithelial damage that occurs, aiding in diminishing host ability to defend against further infection. A distinguishing characteristic of this virus is also the latent capability of IBRV. Following primary infection with IBRV the virus resides in the sensory neurons of the peripheral nervous system and is stored in the nervous ganglion. Cytotoxic (CD8+) T lymphocytes detect and eliminate IBRV infected cells; however, IBRV down-regulates class I major histocompatibility complex expression required for cytotoxic T lymphocyte activity (Muylkens et al., 2007). This is

accomplished via two mechanisms; UL49.5 blocking the transporter associated with antigen presentation and a protein encoded by UL41 acting together to cause inhibition (Muylkens et al., 2007). Also, IBRV encodes for two more unique proteins that inhibit specific immunity components in addition to UL49.5, which are glycoprotein G and bICP0. Glycoprotein G inhibits the activity of chemokines by blocking the cellular receptors that inhibit the transcription of IFN type 1 which is the innate antiviral signaling pathway (Henderson et al., 2005). This virus can remain latent for the life span of the animal and can reactivate by an external stimulus such as stress or immunosuppression (Jones, 2003).

Bovine respiratory syncytial virus is cytopathogenic and directly damages the cells of the respiratory tract (Hagglund et al., 2011). This virus is an enveloped, non-segmented, negative stranded, RNA virus that replicates in the nasal epithelium before traveling throughout the upper respiratory tract. A high infection rate is associated with BRSV at 60 to 80% of the population (Stott et al., 1980). Similar to previous viruses discussed, BRSV is transmitted through nose-to-nose contact with infected animals or aerosol. Transmission of viruses can occur through oral/oral, fecal/ oral and aerosol transmission. The incubation period for BRSV is between 2 and 5 days and infection can be asymptomatic, limited to the upper respiratory tract, or involve both the upper and lower respiratory tract in more severe infection. Clinical signs can range from slight depression and anorexia to a grunting expiration and open mouth breathing with severe infections (Valarcher and Taylor, 2007).

Parainfluenza-3virus is an RNA virus often subclinical during uncomplicated infection, but it can result in respiratory disease that is characterized by cough, fever, and

nasal discharge. Stress concomitant with PI3V can contribute to tissue damage and immunosuppressive characteristic of BRD (Haanes et al., 1997). There are 3 genotypes of PI3V: PI3Va, PI3Vb, and PI3Vc. Prior to a study conducted in 2015, it was thought that genotype PI3Va was the only genotype present in the U.S cattle herd. However, both PI3Vb and PI3Vc have since been found to be in circulation in the U.S. (Neill et al., 2015). Further research is required to evaluate the pathogenicity of the different genotypes. The inclusion of PI3V in BRD vaccines is questioned due to history of vaccination, pathogenesis, and typically mild effects. This virus is one of the "original" pathogens associated with BRD which has led some to question if routine vaccination and a relatively acute life cycle in the respiratory tract may lead to PI3V being innocuous in nature (Ellis, 2010).

Bacterial pathogens associated with bovine respiratory disease

Bovine respiratory disease not only involves a viral component but a bacterial component that plays a role in the pathogenesis of BRD. The primary bacterial agents in BRD are *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, *and Mycoplasma bovis*.

Mannheimia haemolytica (Mh) is an opportunistic pathogen that resides in the nasopharynx and tonsils of healthy cattle and sheep. This bacterium is a gram-negative, nonmotile, and non-spore forming bacteria. If an animal is stressed or immunocompromised this pathogen can invade the lungs and evade the hosts immune response. Once in the lungs, Mh can cause pulmonary inflammation with leukocyte

damage and apoptosis due to the production of leukotoxin (LKT) and increased free lipopolysaccharides (LPS) which can lead to death of the lung tissue (Clawson and Murray, 2014). This bacterium possesses additional virulence factors including an outer membrane that protects against the hosts immune response, along with the aforementioned increase in free LPS that results in edema, inflammation, and LKT production (Rice et al., 2007). The virulence factor that seems to have the largest impact on the pathogenesis of BRD is the production of the LKT. Leukotoxin can cause a range of effects like impairment of function to lysis of ruminant leukocytes (DeBey et al., 1996). In the lower respiratory tract, Mh produces LKT to cause major lung tissue injury and aids the bacteria in evading phagocytic cell destruction (Tatum et al., 1998). Viral infection also increases the susceptibility of the bovine leukocytes to LKT (Czunprynski et al., 2004). The LKT associated with Mh are pore-forming proteins that at high concentrations directly destroy cells and at low concentrations cause plasma membrane changes that initiate the apoptotic pathway (Naryanan et al., 2002). However, the full mechanism that is responsible for the lethal nature of LKT in ruminants in not fully understood. The change from commensal bacteria to pathogen is important in understanding the role Mh plays in the pathogenesis of BRD. Opportunistic pathogens like Mh become pathogenic when decreased reduction of bacterial clearance allows for the colonization of the respiratory tract, often following viral infection (Lima et al., 2016).

Pasteurella multocida (Pm) is a Gram-negative bacterium with 5 capsular serogroups and 16 serotypes and it is also a commensal bacterium found in bovine which becomes an opportunistic pathogen when the animal is under stress or other infection.

This bacterium has been isolated from the lungs of fatal cases in the feedlot by numerous investigators (Gagea et al., 2006; Watts et al., 1994; Welsh et al., 2004) and is increasing in prevalence according to Welsh et al. (2004). The virulence factors associated with Pm include adherence and colonization factors, iron-regulated and acquisition proteins, lipopolysaccharides, and extracellular enzymes. Lipopolysaccharide production associated with Pm exhibits classical signs of endotoxic shock and possesses very similar biological and chemical actions of various other Gram-negative bacteria (Harper et al., 2006). As a potent stimulator of inflammatory cytokines LPS is indicative of the significant lung inflammation associated with Pm (Dabo et al., 2008). It has been reported that Pm and *Mycoplasma bovis* have a synergistic relationship due to the increased isolation of both bacteria compared to individually (Hirose et al., 2003).

Histophilus somni (Hs) is a Gram-negative, commensal bacterium that resides in the nasopharynx and colonizes in the lower respiratory tract. These bacteria are non-encapsulated and have virulence factors that include outer membrane proteins, endotoxins and lipooliogsaccharides (LOS). The use of LOS allows this bacterium to evade the hosts immune response through antigenic phase variation and mediate endothelial cell apoptosis (Confer, 2009). Also, this bacterium can generate histamine that causes tissue inflammation and exopolysaccharides that cause the formation of biofilms or groups of bacteria. These mechanisms can result in symptoms not limited to abscessing laryngitis, incoordination, and fibrinopurulent bronchopneumonia (Corbeil, 2007). Research reveals a synergistic relationship between Hs and BRSV. In a study conducted by Gershwin et al (2005), it was found that concurrent infection with BRSV and Hs increased the duration of clinical illness and overall severity of clinical signs. It

was also discovered that severe lung pathology occurred even though this was not present with individual pathogens (Gershwin et al., 2005). Several studies conducted by Ruby (1999) found that administration of a MLV form of BRSV in conjunction with Hs bacterins led to adverse effects caused by the higher concentrations of eicosanoids which are associated with edema, chemotaxis, and late phase allergic reactions (Ruby, 1999). The prevalence of Hs is thought to be greater in Canada and the northwestern U.S. Additionally, Hs is more prevalent in areas throughout the fall and early winter where increased commingling, an abrupt change in temperature, and increased stress due to transportation are common (O'Toole and Sondgeroth, 2016). Recently, Hs has been detected frequently in diagnostic labs in the southern U.S. leading researchers to believe that Hs may be present in more than just the northern region of U.S. and Canada.

Mycoplasma bovis (Mb) is a commensal bacterium that inhabits the upper respiratory tract of healthy bovine and becomes an opportunistic pathogen similar to the previously discussed bacteria. This bacterium is associated with various diseases including pneumonia, mastitis, arthritis, otitis media, conjunctivitis, and reproductive disorders (Maunsell et al., 2011). The lack of a cell wall allows for natural resistance to β-Lactams as well as spontaneous resistance to other drugs (Poumarat et al., 2001). This bacterium also possesses exposed membrane proteins that facilitates the adherence to mucosal surfaces in combination with immunodominant variable surface lipoproteins that undergo high frequency phase and size variation which allow for immune evasion and persistence of Mb (Maunsell et al., 2011). The immune response of the host plays a major role in the pathogenicity of Mb. An excessive inflammatory response can be triggered through the inappropriate activation of alveolar macrophages which excessively produced

TNF-α (Jungi et al., 1996). The activation of macrophages by Mb also causes a recruitment of neutrophils to sites of inflammation and the extent of neutrophil recruitment is directly correlated with the severity of disease associated with Mb (Thomas et al., 1991). It is widely accepted that Mb causes inflammation, large accumulations of lymphocytes and production of proinflammatory cytokines; however, little is understood about the cytokines in the lungs following infection (Maunsell et al., 2011). Chronic BRD and Mb are also thought be associated due to the opportunistic qualities of Mb. This bacterium is frequently isolated in cattle with chronic BRD that suffer from immune dysfunction and it is questioned if Mb is a true BRD pathogen or just an opportunistic pathogen that uses other viruses and bacterium to take advantage of the host's immune function.

Pre-disposing factors of bovine respiratory disease

Predisposing factors are also important in the pathogenesis of BRD. Due to the multifaceted nature of this disease, it is essential to evaluate and understand the role that pre-disposing factors play in BRD. Pre-disposing factors are often various stressors and can include transportation, commingling, cold, sudden weather changes, dehydration, hypoxia, and acute metabolic changes (Taylor et al., 2010).

"Shipping fever" as BRD is sometimes referred to due to the widely accepted idea that transportation is one of the major non-infectious risk factors associated with BRD. In the United States cattle travel an average of 339 miles to the feedlot (USDA-APHIS, 2011). Transportation is considered a physiological stressor similar in nature to restraint, novel environment, and unfamiliar objects (Grandin, 1997). While there are various

studies evaluating the effects of transportation on feedlot cattle, there is conflicting research that correlates distance traveled with increased morbidity and mortality (Taylor et al., 2010). A study of feedlots throughout the U.S found that cattle arriving from an increased distance were at increased risk of initial BRD (Sanderson et al., 2008). However, other studies report no relationship between transportation distance and BRD incidence (Ribble et al., 1995). A study using 105 crossbred steers transported approximately 1,930 miles from Tennessee to a feedlot in Texas reported increased serum concentrations of oxidative stress biomarkers related to episodes of BRD and mortality in calves due to transportation stress (Chriase et al., 2004). It has been concluded that loading and sorting may be the most stressful components of transportation especially if not exposed to previously exposed with low stress handling (Grandin, 1997; Warriss et al.,1995).

Commingling is the mixing of cattle from different source ranches of origin exposing the animals to a variety of novel pathogens and stressors. The incidence of BRD greatly increases when cattle from multiple sources are commingled in the pen or on the truck (Sanderson et. al., 2008). This is common when purchasing from order buyers that purchase cattle from multiple auction barns and combine them to create a full truck load of similar cattle. In a study by Step et al (2008), researchers compared morbidity between ranch-direct calves, market calves and commingled calves. Treatments were ranch versus commingled versus market and weaning management was a factor where market served as the positive control. Researchers found that commingled steers (22.6%) ranked between ranch (11.1%) and market for morbidity rate, with market derived steers having the highest morbidity rate (41.9%). Total percent morbidity was greater for cattle

in the MARKET and WEAN treatments (41.9% and 35.1%, respectively) compared to animals in the WEAN45 and WEANVAC45 treatments (5.9% and 9.5%, respectively). It is important to note that cattle that were weaned and vaccinated at the ranch (WEANVAC45) did not differ from cattle that underwent only weaning at the ranch (WEAN45; Step et al., 2008). This suggests that weaning may have greater impact on the subsequent health of an animal than the vaccination status prior to arrival at the feedlot (Richeson and Falkner, 2020).

The origin of cattle may also play a major role in the incidence of BRD upon arrival to the feedlot. Various studies have exhibited that newly received cattle possess the greatest risk for BRD (Ribble et al., 1995; Sanderson et al., 2008, Alexander et al., 1989). Cattle marketed directly from the ranch origin are at a decreased risk of BRD incidence compared to those marketed through a sale barn (Step et al., 2008). Cattle marketed through the auction barn typically experience an increased number of predisposing factors like commingling and extensive transportation and handling which could play a major role in the BRD incidence rather than cattle bought from a single origin.

Cattle in the United States typically experience a variety of predisposing factors that additively may have a significant impact on the susceptibility of cattle to BRD. Other predisposing factors that may play a role in BRD such as weather (Ribble et al., 1995), castration especially if delayed until arrival at the feedlot (Zweiacher et al., 1979), gender due to bulls typically having received less management at the ranch origin than steers and from the castration procedure itself (Richeson et al., 2013), and dehorning which is a common practice if horns are present on arrival to the feedlot (Goonewardene and Hand,

1991). Predisposing factors increase stress of cattle allowing for increased susceptibility to BRD because stress can cause immunosuppression.

BRD Impact on Feedlot Production

BRD costs the beef finishing industry more than any other disease; direct economic losses occur with treatment costs and indirect impacts include performance and carcass losses (Duff and Gaylean, 2007). The average cost per BRD treatment is estimated to be $23.60 (USDA-APHIS, 2011). Calves treated once for BRD returned $40.64 less, those cattle being treated twice for BRD returned $58.35 less, and those cattle being treated a third time for BRD returned $291.93 less than their counterparts that were not treated for BRD (Fulton et al., 2002). The significant cost of BRD further illustrates the need for improved prevention and control. Control and management have been an area of focus due to the use of antimicrobial metaphylaxis and the high success rates associated with it. Metaphylaxis is the treatment of an entire group or population of cattle with a U.S Food and Drug administration (FDA) approved antimicrobials with the intent of controlling the incidence of acute onset disease in highly stressed, newly received calves (Urban-Chimel and Grooms, 2012). Munoz et al. (2020) evaluated metaphylaxis (META) with tulathromycin versus pentavalent MLV use in high-risk feedlot calves. There were 4 treatments in the study: 1) no META or MLV, 2) META on d 0, 3) MLV on d 0 and revaccination on d 14, 4) META and MLV. The META treatments had the greatest average daily gain (ADG), but there was no impact of MLV on overall ADG. This study concluded that high-risk cattle administered metaphylaxis, but not MLV, had improved health and performance (Munoz et al., 2020). The choice to use metaphylaxsis is based upon knowledge of the cattle history and the sources in which

they came from. However, that decision is made on an individual truck load basis. Highly stressed cattle typically receive a single injectable antimicrobial that has an extended duration of therapy for 3 days or more and cattle are typically ineligible for clinical treatment until the post-metaphylactic interval expires. The use of antimicrobial metaphylaxsis, and the repeatable benefit of it, has allowed buyers to manage high-risk cattle successfully with economic incentive. As consumer and societal pressure continues for decreased use of antimicrobials in food animals, a renewed focus on the prevention of BRD will be important.

BRD Vaccination Strategies

Strategies to prevent BRD are evolving due to innovative discoveries by veterinarians and the research community. The investigation of vaccination strategies in the feedlot is essential for creating an effective method of prevention of BRD. Respiratory vaccines used in U.S. feedlots may contain viral or bacterial components or a combination of both.

Viral vaccines that aid in the prevention of BRD contain antigens of the previously mentioned viruses in either MLV or killed virus (KV) versions. The less commonly used of the two versions is KV (USDA-APHIS, 2011). Killed vaccines possess viral components that are rendered non-infectious using chemical treatment like formaldehyde (Oirschot et al, 1999). These vaccines require the use of an adjuvant that is highly immunogenic and usually require the administration of a booster vaccination to stimulate a protective immune response. Requirement of a booster vaccine and the inferior immune response of KV compared to MLV is the reason that MLV vaccines are

much more popular in the feedlot (Griffin and Smith, 2007). However, KV are more common in the cow calf sector due to increased safety; they are not immunosuppressive or pathogenic to the fetus (Kelling, 2004). The delayed onset of protective antibody levels and the chance of viral challenge prior to this protection is another factor in the choice between KV or MLV vaccination (Newcomer et al., 2017). The advantage of KV is that they do not have potential to cause disease due to virulence or reversion and they are more stable in storage (Roth and Perino, 1998).

Modified-live virus vaccines produce greater serum concentration of antibodies and cell-mediated immunity compared to KV (Woolums et al. 2013). The MLV vaccines also have a more rapid onset of immunity. Partial protection from a BVDV challenge can occur in as few as 3 days following MLV vaccination with complete protection reported 5 days following administration (Brock et al., 2007). The MLV vaccines contain an attenuated version of the virus or viruses of interest. Attenuation occurs through the passage of multiple cell cultures with the goal of reducing virulence of the vaccine virus but still being able to stimulate immunity without causing clinical disease (Lobmann et al., 1984). Fulton et al (1995) compared 4 vaccine antigen types: 1) an inactivated, 2) MLV, 3) combination of chemically altered MLV and inactivated, and 4) a combination MLV and inactivated to understand differences in antibody responses. All 4 groups had increased IBRV antibodies at day 14 after initial injection but MLV and chemically altered had an increased duration of immunity compared to the inactivated and combination chemically altered and inactivated. The inactivated vaccine increased all antibody responses following day 140 revaccination (Fulton et al., 1995). All 4 types of

vaccines in this study exhibited an immune response to each type of antigens however, the duration and onset of immunity differed according to antigen type.

Bacterins like viral vaccinations also possess two classifications, inactivated or avirulent-live bacterium. These two types, along with leukotoxid fractions, aim to create a protective immune response. Approximately two out of every three feedlots are vaccinating with a bacterin containing *Hs* or *Pm* (USDA-APHIS, 2011). Previous research has indicated bacterins have no benefit or been detrimental to animal health (Wilkie et al., 1980; Martin, 1983). Following the discovery of leukotoxin, and the major role it has in the pathogenesis of Mh (Gentry et al., 1985), the efficacy of Mh bacterins improved from previous trials (Thorlakson et al., 1990). Subsequently, the use of combination viral and bacterin became common. The use of oil adjuvants enhanced resistance to bacterial challenge and better stimulated the production of antibodies against the bacteria (Confer and Ayalew, 2018). A significant decrease in lung lesion score was achieved using a Pm bacterin that develops antibodies to an iron chelator like iron-regulated outer membrane proteins (IROMP) or outer membrane (OMP; Dabo et al., 2008). Biological manufacturers have created a plethora of both MLV and KV vaccines that contain both viral pathogens like BHV-1, BVDV type 1 and 2, BRSV, and PI3 alone or in combination with Mh, Pm, and Hs bacterins (Richeson et al., 2019).

Timing of BRDVaccination

When a vaccine is administered can be as important as what the vaccine contains and the immune stimulation from it. Vaccination occurs at both the cow calf and feedlot sectors; however, vaccination at the cow calf sector is more effective. Preconditioned

cattle are those that have been properly weaned, received a series of vaccinations, dewormed, castrated, dehorned, and trained to eat from a bunk prior to leaving the ranch or farm of origin (Herrick, 1979). Roeber et al (2001) conducted a study evaluating differences between two preconditioning protocols versus a non-preconditioned control group prior to arrival at the feedlot. The three treatments included a traditionally preconditioned group (CPH), a group that received only vaccinations, dehorning, and castration (GT), and a control group that was obtained from auction markets (AM). Researchers found that cattle that received CPH had fewer hospital visits versus cattle that were not preconditioned, (0.55 vs 1.97 and 0.70, respectively). The ADG of preconditioned cattle increased compared to their counterparts that there was no history on or only received vaccination, dehorning, and castration (1.82 vs 1.67 and 1.63 respectively; Roeber et al, 2001). Many studies have demonstrated that preconditioned cattle possess increased performance and improved health (Richeson et al., 2012; Step et al., 2008; Lalman and Mourer, 2014). Vaccination at the cow-calf origin should occur due to the need of sufficient time for cattle to develop immunological protection against BRD pathogens prior to the marketing process (Richeson et al., 2019). This strategy is widely recommended by veterinarians; however, the majority (60.6%) of all cow-calf operations in the U.S do not vaccinate calves against BRD from birth to sale (USDA-APHIS, 2010).

Furthermore, only 34.7% of cattle have pre-arrival processing information when arriving at the feedlot (USDA-APHIS, 2011). This is due to the small size of operations that provide cattle for feedlot use and a disconnection between beef industry segments. The average U.S beef herd size is 43.5 cows per operation (USDA-APHIS, 2011). Due to

this very small operation size many small-scale cattle operations do not possess the adequate supplies, facilities, or incentive to precondition their cattle. The ability of vaccines to prevent BRD is plausible and demonstrated in the literature; however, administration of a vaccine at the appropriate time is essential to provide the animal with the appropriate immune response prior to natural disease challenge.

Vaccination in the feedlot

Vaccination administered during physiologic stress or a natural BRD outbreak may worsen BRD health outcomes (Richeson and Falkner, 2020). As previously mentioned, transport and arrival in a novel environment are highly stressful events in cattle. Most U.S feedlots desire for cattle be vaccinated for respiratory disease before entering the feedlot, and greater than 90% of feedlots vaccinate for respiratory disease of some kind (USDA-APHIS, 2011). Each vaccine administered should invoke a protective immune response; however, vaccine efficiency is questionable when administered on arrival at the feedlot. Vaccine efficiency is when vaccination clearly demonstrates improved clinical health and performance outcomes compared to nonvaccinated animals. Vaccine efficacy is defined as the ability of a particular vaccine to induce a significant immunologic response in the host (Richeson and Falkner, 2020). Vaccine efficiency of on arrival administration at the feedlot is questioned due to the time required to mount an immune response and the likelihood that most cattle have already been exposed to BRD pathogens prior to arrival at the feedlot, or very soon after arrival. In a study conducted by Hudson et al (2020), the effect of stress caused by normal industry practices, weaning and transportation, on performance, antibody, endocrine or hematological responses

following administration of a MLV or KV was evaluated. Researchers discovered that BRSV-titer response was delayed in the stressed treatment group and BVDV- specific antibody response was greater in the control treatment group (Hudson et al., 2020). Schumaher et al (2019) evaluated the health differences between three vaccination treatments: 1) vaccination at weaning and revaccination upon arrival at the feedlot (CON), 2) vaccination 15 d before weaning and revaccination 15 d before arrival at the feedlot (EARLY), and 3) vaccination 15 d after weaning and revaccination 15 d after arrival at the feedlot (DELAYED). Overall BRD incidence was less for EARLY cattle versus CON or DELAYED (16.9 vs 32.1% and 32.1%, respectively). However, there were no treatment differences in mortality between CON, DELAYED, and EARLY (5.5, 3.8, and 3.8%, respectively; Schumaher et al., 2019). This study further questions vaccine efficiency at the feedlot but health outcomes of cattle that received both doses of vaccine prior to transportation to the feedlot were improved slightly.

Delayed vaccination in high-risk stocker or feedlot cattle has been evaluated in recent research. Delayed vaccination is when cattle receive vaccines following a period of time after arrival at the stocker or feedlot facility to allow for decreased stress during the time of vaccination. In a study conducted by Richeson et al (2008), cattle were randomly allocated to two different treatment groups where a MLV vaccine was administered on arrival or on day 14. In that study, BRD morbidity rate was increased in arrival vaccinated cattle compared to those on day 14, 71.5% vs 63.5% respectively (Richeson et al., 2008). However, in a similar study, there was no effect on BRD morbidity due to timing of vaccination (Poe et al., 2013). In a large pen study conducted by Rogers et al (2016), compared an on-arrival vaccination, delayed vaccination, and the

inclusion of an immunostimulant to the arrival or delayed vaccination. It was found that delaying a MLV administration by 30 days significantly decreased the number of calves that received a second BRD treatment (8.36 vs 9.39 %, respectively; Rogers et al, 2016). One argument for delayed vaccination in the feedlot is due to the increased antigenicity of MLV vaccines in stressed cattle (Richeson and Falkner, 2020). When cortisol levels are increased due to the stressors experienced through the cattle marketing process, it causes an immunosuppressive state where enhanced replication of the MLV vaccine in the host cells could result in detrimental health outcomes (Richeson and Falkner, 2020).

In two experiments, Duff et al (2000) evaluated the effect of intranasal and intramuscular MLV vaccines and timing were evaluated. In the first experiment, control (no vaccine), intranasal IBR-PI3V, or intramuscular IBR-PI3V vaccines were compared and intranasal vaccinates had an increased ADG compared to intramuscular vaccinates (2.37 vs 2.00, respectively). However, there was no difference in the percentage of cattle treated for BRD. In the second experiment researchers evaluated control (no vaccine), no vaccine at processing and IM IBR-PI3V-BVD-BRSV on d 7 (CON/IM), intranasal IBR-PI3V at processing and IM IBR-PI3V-BVD-BRSV on d 7 (IN/IM), and IM IBR-PI3V-BVD-BRSV administered at processing and on d 7 (IM/IM). No differences for initial or final body weight, daily gain, dry matter intake (DMI), or morbidity were found in this experiment. Dry matter intake is the amount of feed an animal consumes per day on a moisture free- basis. However, feed to gain tended to be improved in vaccinated calves compared to control (Duff et al., 2000). This study suggested that intranasal vaccination might have advantages on performance when administered on arrival at the feedlot compared to intramuscular administration of MLV vaccines.

The debate on vaccination timing stems from the historical viewpoint that holds true today. Veterinarians and feedlot operators view vaccinations as an aid in the prevention of respiratory disease and in turn have adopted their use almost unanimously in the feedlot. However, the response to vaccines in highly stressed cattle requires further research to understand. The approval process for new vaccines is typically conducted in colostrum deprived dairy calves that are not highly stressed and do not provide an adequate representation of the entire population of cattle in the U.S. Ideally, animals should be vaccinated at the ranch origin prior to weaning, transportation and commingling, yet due to the lack of incentive and knowledge by the small operations the adoption rate remains less than desired.

Route of Vaccine Administration

There are two primary routes of administration of BRD vaccines that will be reviewed. Parenteral (injectable) is the most common method. In recent years, the increased availability of intranasal vaccines has led to adoption of intranasal vaccination at both the cow calf and feedlot sectors.

Parenteral vaccination

Most vaccines used in beef cattle are administered parenterally through either an intramuscular or a subcutaneous route (Waldner et al., 2018). When vaccines are administered subcutaneously, they can provide an adequate immune response to protect against BRD (Xue et al., 2010). However, there are concerns with administering parenteral vaccines to young calves when passive immunity might interfere with an active immune response (Prado et al., 2006; Ellis et al., 2014). Woolums et al (2013)

allocated calves to 1 of 5 groups comparing intranasal administration of a MLV for prevention of BRD compared to a subcutaneous administration at 2 or 70 days of age and a control group that obtained no MLV. It was reported that serum neutralizing titers were greater for the subcutaneous group at 70 days of age and overall nasal IgA concentrations and serum neutralizing titers against IBRV, BVDV, and BRSV increased. This study demonstrated that administering a subcutaneous injection to cattle at 70 days of age increased BVDV antibody titers prior to weaning (Woolums et al., 2013). Cortese et al (2020) concluded that administration of an intranasal vaccine concurrently with SQ administration of MLV respiratory vaccine can allow animals under certain stressors to produce an adequate immune response. This study provided data to further understand the relationship between local and systemic immunity; however, understanding the role of intranasal vaccination in conjunction with SQ MLV administration and the cattle immune response is complicated and requires further understanding.

Subcutaneous injection results in a depot of viral antigen into the fatty tissue under the skin where capillaries or lymphatic tissues can absorb the antigen into systemic circulation. Subcutaneous injection is the most common route of vaccine administration because of the adoption of Beef Quality Assurance guidelines becoming widely accepted. Also, it was found that the vaccinated calves compared to control calves had a short duration of nasal virus shedding (0.6 d and 3.3 d, respectively; Salt et al., 2007). The ability to administer multivalent vaccines is essential for increased vaccination in the cow-calf sector. In an analysis conducted by Newcomer et al (2015) found that parenteral vaccination is a proven method to decrease the incidence of PI animals that enter production. It was found that risk of fetal infection, origin of PI calves, was the lowest

when a polyvalent or MLV vaccine and in challenges 95.7% of unvaccinated animals resulted in fetal infection (Newcomer et al., 2015).

Parenteral vaccines when administer through the subcutaneous or intramuscular route induce a systemic proinflammatory response. This response promotes the production of humoral antibodies, particularly IgG, from antigen stimulated B cells. These B cells neutralize specific antigens by promoting the phagocytosis of bacteria or viruses and via antibody production. Parenteral vaccines initiate systemic immunity which is immunity that occurs within the body through antigen recognition in the lymph nodes and spleen after antigens enter the blood (Rayevskaya and Frankel, 2001).

Parenteral vaccination can be a safe and efficacious method of providing immunological protection against respiratory viruses in non-stressed cattle; however, cattle that are received at the stocker or feedlot operation experience varying levels of stress. Kolb et al (2020) found that administration of parenteral BRSV MLV to calves resulted in a 50% reduction in disease and produced a sufficient immune response when challenged 3 months following vaccination (Kolb et al., 2020). Long-term immunity of a quadrivalent parenteral vaccine against IBRV, PI3V, BVDV, and BRSV have been shown to be greater than or equal to 6 months (Peters et al., 2004).

Intranasal vaccination

Intranasal vaccines are a relatively new vaccine strategy that initiates a different form of immunity referred to as mucosal or local immunity. The physical barrier between the internal body and the external environment is the mucosal epithelium. The mucosal immune system is comprised of the mucosal epithelium of the esophagus and

gastrointestinal tract, the upper and lower respiratory tract, and the urogenital tract. These surfaces protect the animal from external pathogens; however, they also possess a plethora of bacteria that reside in the respiratory and gastrointestinal tracts referred to as commensal bacteria. The mucosal immune system has three main functions: 1) protection of the mucous membranes against colonization and invasion by dangerous microbes, 2) to prevent uptake of undegraded antigens including foreign proteins derives from ingested food, airborne matter, and commensal microorganisms and 3) to prevent the development of potentially harmful immune responses to these antigens if they do reach the body interiors (Holomgren and Czerkinsky, 2005). Mucosa-associated lymphoid tissue (MALT) uses epithelial cells to sample antigens through absorption and transfer them to antigen presenting cells (APC). These APCs can be dendritic cells (DC), B cells, or macrophages that present the antigen to CD4+ and CD8+ T cells (Holmgren and Czerkinsky, 2005). Intranasal vaccines prime the immune system so that the stimulation of a localized immune response occurs (Griebel, 2009). The primary antibody associated with mucosal immunity is secretory (s) IgA. Secretory IgA is the most prevalent immunoglobulin type at mucosal surfaces (Holmgren and Czerkinksy, 2005). The functions of sIgA include inhibiting bacterial adhesion to the mucosa, inhibiting the inflammatory effects of other Igs, neutralizing bacterial toxins and viruses, and enhancing innate defense mechanism (Holmgren and Czerkinksy, 2005). Immunoglobulin A is found in tears, nasal secretions, and saliva in the form of sIgA. The structure of sIgA is a dimer of immunoglobulin linked by a joining chain that during formation cleaves and creates a secretory component. The functions of sIgA include creation of a barrier at mucosal surfaces, eliminate pathogens within epithelial cells, and keep pathogenic

organisms from entering internal organisms (Corthesy, 2013). This antibody is activated through the switching of B-cell class in MALT (Brandtzaeg, 2010). Also, multiple cytokines modulate production of IgA including Interleukin- 4 (IL-4), transforming growth factor-β, IL-5, IL-6, and IL-10. Intranasal vaccines originally thought to increase IgA concentrations for a short amount of time having little effect on IgG concentrations (Kavanagh et al., 2013). However, the immunosuppression caused by dehydration and transport stress may allow intranasal vaccine antigens to penetrate mucosal membranes more readily and shift the antibody response from local (IgA) to systemic (IgG) (Kaufman et al., 2017).

Multiple studies have demonstrated that intranasal vaccines have been effective in calves in a controlled BRD challenge even in the presence of maternal antibodies (Vangeel et al., 2007; Ellis et al., 2013). In a study conducted by Midla et al (2021), 90 Holstein calves were used to compare the immune response of 2 commercially available intranasal vaccines and a control of colostrum fed calves. They evaluated the serum anti-BHV1 titers and nasal fluid samples for interferon (IFN)- α, IFN-γ and sIgA levels. It was reported that both vaccines induced innate and acquired immunity in calves even in the presence of colostrum antibodies (Midla et al., 2021). Mucosal immunity is an important mechanism of protection that can be used to aid in prevention of BRD.

Intranasal administration of vaccines has also reduced severity of BRD compared to non-vaccinated calves. The advantages of intranasal vaccines are that they tend to be effective even in the presence of maternal antibodies and can be administered earlier compared to parenteral vaccinations. Intranasal vaccines can contain BRSV, PI3V, and IBR as well as bacterial components like Mh and Pm. Intranasal administration of BVDV

has been shown to be efficacious in young calves (Xue et al., 2010); however, due to the immunosuppression that is associated with BVDV and safety concerns, there currently are no commercially available intranasal vaccines that contain BVDV.

Conclusions from the Literature

Bovine respiratory disease continues to have significant impacts on the beef cattle industry. Research demonstrates that cattle affected with BRD in the feedlot take longer time and more expense to reach suitable finish. Vaccination aids in the prevention of BRD; however, due to the lack of incentive to small operations the adoption of vaccination and preconditioning is limited in the cow calf sector. The use of MLV vaccines to prevent BRD can be effective; however, the timing of administration is important. Vaccines should be administered at the cow calf origin to allow enough time for development of protective immunity prior to natural disease challenge typical in the stocker and feedlot segments of beef production. The use of parenteral MLV vaccines in the feedlot is commonplace even though research indicates cattle that are vaccinated during periods of high stress results in increased antigenicity, replication, and nasal shedding of viral vaccine agents (Richeson et al., 2016). Intranasal administration of MLV is an alternative to traditional parenteral administration and may be advantageous due to the more rapid onset of local immune response.

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Chapter II

Effects of intranasal or parenteral respiratory vaccination administered on arrival or delayed in auction-derived feedlot heifers

Abstract

Modified-live virus (MLV) vaccines are used routinely to immunize cattle against bovine respiratory disease agents, but the route and timing of MLV administration may impact their safety and efficacy. The objective of this study was to evaluate the safety and efficacy of an intranasal or parenteral MLV administered on d 0 or 28. Three arrival blocks of heifers (initial BW = 208 kg; n = 600) were randomly assigned to treatments in a 2 × 2 factorial arrangement. The generalized complete block design consisted of 15 pens per treatment with pen as the experimental unit and 10 animals per pen. Treatments were: 1) Nasalgen 3 and Vista BVD on d 0 (NAS0); 2) Vista 5 SQ on d 0 (VIS0); 3) Nasalgen 3 and Vista BVD on d 28 (NAS28); 4) Vista 5 SQ on d 28 (VIS28). Performance, activity, and health data were analyzed using a mixed model in SAS and a subset of 3 cattle per pen were selected for antibody titer analyses with repeated measures. Body weight and blood samples were collected on d 0, 28, and 56. No differences existed for performance outcomes ($P \geq 0.19$). Activity (351.4 vs 354.3 min/d) and rumination (282.6 vs 285.4 min/d) time was less ($P < 0.01$) for delayed vs arrival vaccinated heifers. A timing × vaccine × day interaction existed ($P < 0.01$) for BRSV- and IBRV-specific antibody titers; VIS28 had the greatest ($P < 0.01$) BRSV antibody titer on d 56. For IBRV antibody titer on d 28, VIS0 was greatest, NAS0 was intermediate, and VIS28 and NAS28 were least ($P < 0.01$). Percentage of chronically ill cattle were reduced for arrival vs delayed (1.3 vs 4.7%; $P = 0.02$) and tended ($P = 0.06$) to be less for VIS vs NAS (1.7 vs 4.3%). Arrival vaccinated heifers had a reduction in

antimicrobial treatment cost ($4.63 vs $7.31; $P = 0.02$). These data indicate improvement in some health outcomes for the parenteral route and arrival timing of MLV respiratory vaccination, but performance was not affected during the feedlot receiving period.

INTRODUCTION

Bovine respiratory disease (BRD) is the most prevalent and expensive health challenge for U.S feedlots (Duff and Galyean, 2007; Woolums et al., 2005). Most viral and bacterial pathogens associated with BRD enter through the mucosal surfaces of the nose and mouth, and use of intranasal vaccines is increasing in both the cow calf and feedlot segments of the beef industry due to the ease of use and provision of mucosal immunity. Intranasal respiratory vaccines contain modified-live virus (MLV) antigens, or attenuated versions of infectious bovine rhinotracheitis (IBRV), bovine respiratory syncytial virus (BRSV), and parainfluenza-3 virus (PI3V). Due to the exclusion of bovine viral diarrhea virus (BVDV) antigens from commercial intranasal vaccines because of safety concerns, BVDV prevention also requires administration of a bivalent, parenteral vaccine containing BVDV type 1 and 2. Therefore, it may be more appealing to some producers to use a pentavalent parenteral vaccine and research is needed to understand differences in the safety, efficacy, and efficiency of the different vaccine types used in newly received feedlot cattle.

More than 90% of U.S feedlots vaccinate for respiratory disease (USDA-APHIS, 2011). The timing of respiratory vaccination may be as important as the vaccine itself. Most feedlots vaccinate on arrival; however, improved health and performance outcomes may exist for high-risk cattle that receive delayed vaccine administration (Richeson et al., 2008; Rogers et al., 2016). Delayed vaccination allows for the stress of transportation and

relocation to be resolved before vaccine antigen stimulation, which may improve vaccine safety (Richeson and Falkner, 2021). The objective of this study was to evaluate the safety and efficacy of a parenteral or intranasal MLV vaccine administered on d 0 or 28.

MATERIALS AND METHODS

This experiment was conducted from March 2020 to May 2020 at the Agri Research Center located 10.9 km northwest of Canyon, TX. Animal methods and procedures were approved by the IACUC committee at West Texas A&M University (protocol# 2020.04.001) before study initiation.

Arrival Procedures

A total of 600 crossbred beef heifers (initial BW= 208 kg ± 27 kg) obtained from auction markets in the southeastern U.S. were shipped to the Agri Research Center (Canyon, TX) on March 26, 2020 (Block 1), March 27, 2020 (Block 2), and April 2, 2020 (Block 3). Upon arrival, initial BW were recorded and each animal received duplicate color-coded ear tags and a 3-axis accelerometer ear-tag (Allflex Livestock Intelligence, Madison, WI). Heifers also received a multivalent clostridial vaccine (Vision 7, Merck Animal Health, Madison, NJ), oral fenbendazole suspension (Safe-Guard, Merck Animal Health), parenteral anthelmintic (Ivomec, Boehringer Ingelheim, Duluth, GA), metaphylactic administration of tildipirosin (Zuprevo, Merck Animal Health) and a growth promoting implant (Revalor-IH, Merck Animal Health). Randomization and allocation occurred according to chute order and a predetermined randomization table. Pens contained 10 head and there was a total of 60 pens (n = 15/treatment). Cattle were also tested for persistent infection with bovine viral diarrhea virus at arrival processing

and if positive were removed from the study (n = 1). Body weights were recorded on d 0, 28, and 56. Blood was collected from a randomly selected subset of 3 animals per pen for BRSV-, BVDV-, and IBRV-specific antibody titer analysis on d 0, 28, and 56.

Treatments

The generalized complete block design consisted of 15 pens per treatment with pen as the experimental unit and 10 animals per pen. Treatments were: 1) Nasalgen 3 (Merck Animal Health) and Vista BVD (Merck Animal Health) on d 0 (NAS0); 2) Vista 5 SQ (Merck Animal Health) on d 0 (VIS0); 3) Nasalgen 3 (Nasalgen 3, Merck Animal Health) and Vista BVD (Merck Animal Health) on d 28 (NAS28); 4) Vista 5 SQ (Merck Animal Health) on d 28 (VIS28). From this 2 x 2 factorial arrangement of treatments, main effects of vaccine type (Nasalgen 3 vs. Vista 5) and vaccine timing (day 0 vs. 28) were evaluated if an interaction was not evident for a dependent variable.

BRD Case Definition

Heifers were evaluated daily by a trained observer at approximately 1000 h. Animals received a clinical illness score (CIS, 0 to 3 severity scale). Morbidity investigators were blinded to experimental treatment and recorded identification numbers of heifers with a CIS of 1, 2 or 3. Heifers were pulled as a suspect clinical BRD case if they were assigned a CIS of 1, 2, or 3. Cattle with a CIS of 1 required a rectal temperature of 40º C to be classified as a BRD case and possessed mild depression including but not limited to isolation with head down, ears drooping but responsive to stimulation and or displaying mild dyspnea with gauntness and nasal or ocular

discharges. A CIS of 2 or 3 were treated for BRD regardless of rectal temperature. A CIS of 2 exhibited moderate depression including symptoms of recumbency or standing isolated with head down and obvious depression, may have stumbled if forced to trot, and noticeable dyspnea with gauntness and nasal/ocular discharges. A CIS of 3 was an animal that exhibited severe depression or moribund status. Animals with CIS 3 would have exhibited signs such as recumbency or when walking, ataxia, knuckling, or swaying, inability to stand, excess salivation/lacrimation, pronounced dyspnea and gauntness, and near death. Heifers that qualified for BRD retreatment were reweighed for calculation of antibiotic dose. Following a 7-day post metaphylactic interval (PMI) (Zuprevo, Merck Animal Health) and meeting the BRD case definition after expiration of the PMI, cattle were treated with a combination of florfenicol and flunixin meglumine (Resflor Gold, Merck Animal Health) and considered BRD1.

If a post-treatment interval (PTI) of 3 days expired and BRD was diagnosed for a second time then cattle received enrofloxacin (Baytril 100, Bayer Animal Health) and were classified as BRD2. The same PTI of 3 days was implemented prior to the third treatment. If cattle were treated a third time oxytetracycline (Biomycin 200, Boehringer Ingelheim) was administered and cattle were classified as BRD3. Cattle that received a CIS of 3 were eligible to be retreated prior to completion of PMI or PTI without meeting rectal temperature criteria at the investigator's discretion. If cattle required a fourth treatment the animal was removed to another pen and considered a chronic removal. Chronic removal, treatment, and euthanasia were determined according to the BRD case definition.

Housing and Management

Cattle were housed in soil surfaced pens that were approximately 13.94 m^2 with 22.86 cm of bunk space per animal. Throughout the study cattle had ad libitum access to water via automatic watering units and slick bunk feed management was used. Feed delivery and removals were recorded daily and recorded on a pen basis. Nutrient and dry matter analyses of the diet were conducted weekly and retained to ensure uniform feed quality and composition throughout the study.

Statistical Analysis

All data were analyzed in SAS version 9.4 (SAS Institute Inc., Cary, NC). This experiment was a generalized complete block design with a 2 × 2 factorial arrangement of treatments. Interactions were tested first, then main effects of vaccine (VAC) and timing of vaccination (TIME). Pen was defined as experimental unit with 15 pens per treatment and 10 animals per pen. Performance, activity, and health data were analyzed using the MIXED procedure and a subset of 3 cattle per pen were selected for antibody titers that were $\log_2$ transformed and analyzed as repeated measures. The error term of pen(ID*block) was considered as the random effect in the model. Activity and rumination data were averaged by pen and day prior to statistical analysis in PROC MIXED with repeated measures. For all dependent variables, statistical significance was declared at $P \leq 0.05$ and tendencies were noted at $0.05 < P \leq 0.10$.

RESULTS AND DISCUSSION

Performance Outcomes

Performance outcomes are displayed in Table 1. There were no significant interactions or main effects for performance variables ($P \geq 0.19$). The NAS0 and VIS0 treatments received a MLV on arrival containing antigens that stimulate an inflammatory response (Arthington et al. 2013). Cytokines associated with inflammation promote anorexia and tissue catabolism that can affect DMI and ADG (Hughes et al., 2013). Due to the inflammatory response from vaccination on d 0, a transient decrease in performance in the arrival group is plausible from d 0 to 28; whereas, delayed vaccinated groups were expected to have decreased performance following MLV administration on d 28 (Munoz et al., 2020). However, immunological protection afforded by vaccination would positively impact performance if health is improved. Nevertheless, neither scenario influenced performance outcomes in this study, as no statistical differences were detected. Richeson et al. (2015) reported that ADG was increased from day 14 to 28 for cattle administered a 14-d delayed MLV compared to those administered an arrival MLV (0.65 and 0.47 kg/day, respectively). In a similar study Richeson et al. (2008), compared on arrival MLV to a 14-d delayed MLV and reported that daily BW gains in the delayed cattle were greater for the duration of the study (0.75 vs 0.65 kg/d). However, Richeson et al (2009) reported that ADG was not affected throughout the duration of a 56-d receiving trial comparing on arrival vs delayed respiratory and clostridial vaccination. Similarly, Poe et al (2013) found no difference in ADG between arrival or delayed vaccination. The effect of MLV vaccination on animal performance is complicated by the

negative growth effects that MLV vaccination can cause, yet health improvement afforded by immunological protection can have a positive impact on growth.

Clinical Health Outcomes

Clinical health outcomes are reported in Table 2 and Figure 8. There were no interactions observed, but a main effect of vaccine timing existed for the percentage of cattle requiring a third BRD treatment (BRD3; $P = 0.03$). The arrival vaccinated cattle had less percentage of BRD3 treatments than delayed (3.67 vs. 8.00%). There was a tendency for arrival vaccinated treatments to have less BRD1 than delayed (17.67 vs. 25.00%; $P = 0.07$). Although not statistically significant ($P = 0.72$), VIS0 had numerically less BRD2 incidence compared to NAS0, VIS28, and NAS28 (6.0 vs 10.7, 11.3, and 14.0%, respectively). Percentage of chronically ill cattle was reduced for arrival vs. delayed (1.3 vs. 4.7%; $P = 0.02$) and tended to be less for VIS vs. NAS (1.7 vs. 4.3%; $P = 0.06$). Arrival vaccinated heifers had a reduction in antimicrobial treatment cost (4.63 vs. \$7.31; $P = 0.02$). Days to third treatment tended to have an interaction of VAC × TIME where VIS0 was the least compared to NAS0, VIS28, and NAS28 (24.0 vs 35.6, 35.5, and 34.8 d; $P = 0.06$). Most BRD outbreaks occur within the first 14 days feedlot arrival (Edwards, 1996; Babcock et al., 2010). In this population of heifers, the average time of initial BRD treatment occurred later than typical for most high-risk cattle populations with the average days to first treatment being d 21 across treatments (Figure 8). The timing of BRD outbreak is important when evaluating vaccine timing and morbidity findings attributed to vaccine timing in the current study may be explained 3-fold. First, the delayed groups (VIS28 and NAS28) had an average days to first treatment of 22 d, and they received the MLV on day 28 which may have contributed to their

clinical presentation and/or convalescence as MLV can cause inflammation, fever, and depression analogous to natural BRD (Tizard, 2021). Secondly, the arrival groups had an average days to first treatment of 19.2, and these cattle probably had adequate time to respond immunologically to the MLV administered on d 0 resulting in improved immunological protection against natural virus challenge compared to the delayed procedure. Thirdly, if natural virus and bacterial challenge peaked near d 28, the delayed MLV administration concurrent with peak wild-type virus infection could have altered the virulence of the naturally-acquired pathogens and overall clinical presentation (Richeson and Falkner, 2020). The morbidity results in the current study conflict with some of the previous research on vaccine timing in high-risk cattle. Rogers et al (2016) reported that when cattle were vaccinated parenterally with an MLV 30 days post-arrival at the feedlot, the percentage of calves that required a second BRD treatment was less than arrival vaccinated cattle. However other research resulted in no effect of vaccination timing on BRD morbidity (Richeson et al., 2009; Poe et al., 2013). The inconsistent findings of vaccine timing on health outcomes in the literature are attributable to differences in pathogen dynamics, stress-induced immunosuppression, and other factors between different study populations. Overall, the current data indicate improvement in some health outcomes for the parenteral route and arrival timing of MLV respiratory vaccination.

Serum Antibody Titers

Antibody titer results are displayed in Figures 3 to 7. A timing × vaccine × day interaction existed ($P < 0.01$) for BRSV- and IBRV-specific antibody titers. The VIS28 group had the greatest ($P < 0.01$) BRSV antibody titer on d 56. For IBRV antibody titer

on d 28, VIS0 was greatest, NAS0 was intermediate, and VIS28 and NAS28 were least ($P < 0.01$). This observation was expected because the delayed treatments, NAS28 and VIS28, did not receive MLV vaccination until d 28. The BVDV titers were analyzed as change in BVDV because baseline (d 0) treatment means differed. It is also important to note that a BVDV PI was present in block 3, which probably confounded the BVDV antibody response attributable to vaccination. A day × vaccine interaction was observed ($P = 0.03$) for change in BVDV-specific antibody titers on d 28, such that NAS tended to be greater than VIS (6.41 vs 5.30; $P = 0.08$), but the biological relevance of this finding is not clear. For BVDV- specific antibody titers, a main effect of time existed such that arrival was greater than delayed throughout the course of the 56-d study ($P = 0.006$).

Heifers received the same BVDV antigens and route of administration due to the lack of BVDV in the intranasal vaccine and the need for parenteral vaccination of BVDV in the NAS groups. Arrival treatment groups had greater percentage of cattle that were seropositive for BVDV at 74.1% vs. 43.3% of delayed vaccinated cattle at day 56. This may be due to the length of time the arrival treatment groups possessed for seroconversion. A previous study found that cattle have a continually increasing titer response for up to three months post vaccination for BVDV (Klimowicz-Bodys et al., 2021). The delayed treatment groups were inoculated for 28 days fewer than the arrival treatment groups which could be responsible for the difference in seroconversion. For IBRV titers there was a timing effect ($P = 0.002$) and a tendency for a timing × vaccine interaction ($P = 0.06$). The VIS0 treatment had the greatest percentage seropositive against IBRV, VIS28 was the least, and NAS0 and NAS28 were intermediate (60.7, 34.1, 37.0, and 43.7%, respectively). The ability of an animal to have a strong antibody

response can be affected by immunosuppression which the delayed treatment groups in this study could have experienced due to concurrent administration of MLV and BRD outbreak. Immunosuppression is a complicated concept when referring to how it effects the replication of MLV antigens. Immunosuppression causes an increase in the replication of the MLV antigen which leads to a higher antibody titer response however it also increases the risk of morbidity in the animal. In the present study, titer levels increased in both arrival and delayed vaccination groups exhibiting that all cattle invoked an immune response to both timing and vaccine type.

Activity and rumination behavior

Activity and rumination results are reported in Figures 1 and 2, respectively. There was a day × timing interaction ($P < 0.01$) observed for activity; delayed vaccinated heifers had less daily activity than arrival vaccinated heifers (351.4 vs. 354.3 min/d; $P < 0.01$). An interaction of day × timing on rumination minutes per day was observed, resulting in reduced rumination time for delayed vs. arrival heifers (282.6 vs. 285.4 min/d; $P < 0.01$). Previous research has demonstrated that animals clinically diagnosed with BRD spent more time lying down than healthy counterparts (Theurer et al., 2013). In a study by Pillen et al (2016), the number of steps taken by cattle diagnosed with BRD was decreased compared to healthy controls from d -6 to d-1 of BRD diagnosis (843 and 1,472 steps, respectively). The BRD cases also exhibited an overall decrease in motion index from d -6 to BRD diagnosis on d 0 (Pillen et al, 2016). These data support the idea that accelerometer tags that continuously monitor animal activity and rumination may aid in the early detection of BRD, but may also provide corroboration of clinical health findings between experimental treatments evaluated in research settings. The reduced

activity and rumination time observed for the delayed groups in the present study may be explained by the interaction of MLV vaccination during the late BRD outbreak in this study population, or lack of immune protection in delayed vaccinated and greater morbidity. Delayed heifers were beginning to break with BRD and then MLV was administered on d 28, increasing the chances of the MLV reverting to virulence (Roth, 1999) and decreasing overall activity. In the present study, delayed heifers exhibited decreased rumination and activity compared to arrival vaccinated heifers which corroborates the clinical health impacts observed from the late BRD outbreak and concurrent administration of a MLV in the delayed groups.

Conclusion

There was no difference between intranasal and parenteral vaccination, or the timing of vaccination, on performance outcomes evaluated in this study. The parenteral groups tended to have fewer chronic heifers compared to intranasal. The BRSV- and IBRV-specific antibody titer response was greater for the parenteral treatments, which supports the paradigm that IgG is more strongly stimulated by parenteral vaccination. Arrival MLV vaccination decreased the percentage of chronically ill cattle and antibiotic treatment cost compared to delayed vaccination. Cattle that were vaccinated on arrival had greater activity and rumination minutes compared to delayed cattle. The current data suggests that on arrival vaccination with a parenteral MLV was the most advantageous vaccination strategy in this population of auction-derived heifers. A negative control group is needed in future BRD vaccination studies to determine if differences between

arrival and delayed vaccination are attributable to improved vaccine safety, enhanced vaccine efficacy, or both.

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Table 1. Effects of parenteral or intranasal vaccination on day 0 or 28 on performance of heifers at high risk of developing BRD

Item	Arrival[1]		Delay[2]		SEM[4]	*P-value*		
	Vista 5	N3+V-BVD[3]	Vista 5	N3+V-BVD		VAC	Time	V x T
Body Weight, kg								
d 0	207	209	210	208	3.95	0.96	0.67	0.62
d 28	254	258	260	256	4.73	0.99	0.71	0.40
d 56	291	295	296	292	5.62	0.94	0.85	0.47
Average daily gain, kg/d								
d 0 to 28	1.70	1.77	1.78	1.70	0.07	0.96	0.95	0.26
d 28 to 56	1.31	1.30	1.29	1.27	0.06	0.76	0.66	0.98
d 0 to 56	1.50	1.54	1.50	1.49	0.05	0.84	0.98	0.39
Dry matter intake, kg/d								
d 0 to 28	5.10	5.09	5.29	5.27	0.14	0.92	0.19	0.97
d 28 to 56	7.88	7.79	7.62	7.60	0.21	0.80	0.30	0.87
d 0 to 56	6.48	6.42	6.44	6.33	0.18	0.64	0.70	0.88
Feed efficiency, F:G								
d 0 to 28	3.04	2.90	2.99	3.66	0.14	0.31	0.25	0.19
d 28 to 56	5.98	5.92	5.83	5.87	0.09	0.93	0.64	0.82
d 0 to 56	4.28	4.16	4.15	4.11	0.04	0.10	0.36	0.65

[1]Arrival treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 0
[2] Delayed treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 28
[3]BOVILIS Nasalgen 3 and BOVILIS Vista BVD CFP.
[4]Standard error of the mean.

Table 2. Effects of parenteral or intranasal vaccination on day 0 or 28 on morbidity, mortality, chronicity, and antibiotic treatment cost of heifers at high risk of developing BRD.

	Arrival[1]		Delay[2]			*P-value*		
Item	Vista 5	N3+V-BVD[3]	Vista 5	N3+V-BVD	SEM[4]	VAC	Time	V x T
BRD incidence[5], % of enrolled								
First, %	14.7	20.7	28.0	22.0	0.04	1.00	0.07	0.14
Second, %	6.0	10.7	11.3	14.0	0.03	0.20	0.13	0.72
Third, %	2.0	5.3	7.3	8.7	0.02	0.23	0.03	0.60
Days to treatment								
First	19.0	19.4	23.9	20.0	2.19	0.39	0.24	0.22
Second	28.6	30.1	31.4	32.1	3.43	0.55	0.19	0.99
Third	24.0	35.6	35.5	34.8	4.44	0.09	0.10	0.06
Chronically ill, %	0.0	2.7	3.3	6.0	0.01	0.06	0.02	1.00
Mortality, %	1.3	0.0	0.0	0.6	0.01	0.57	0.57	0.09
Antibiotic treatment cost, $/hd	3.61	5.65	7.63	7.00	1.13	0.54	0.02	0.24

[1]Arrival treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 0.
[2] Delayed treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 28.
[3]BOVILIS Nasalgen 3 and BOVILIS Vista BVD CFP.
[4]Standard error of the mean.
[5]Percentage of enrolled cattle treated for BRD.

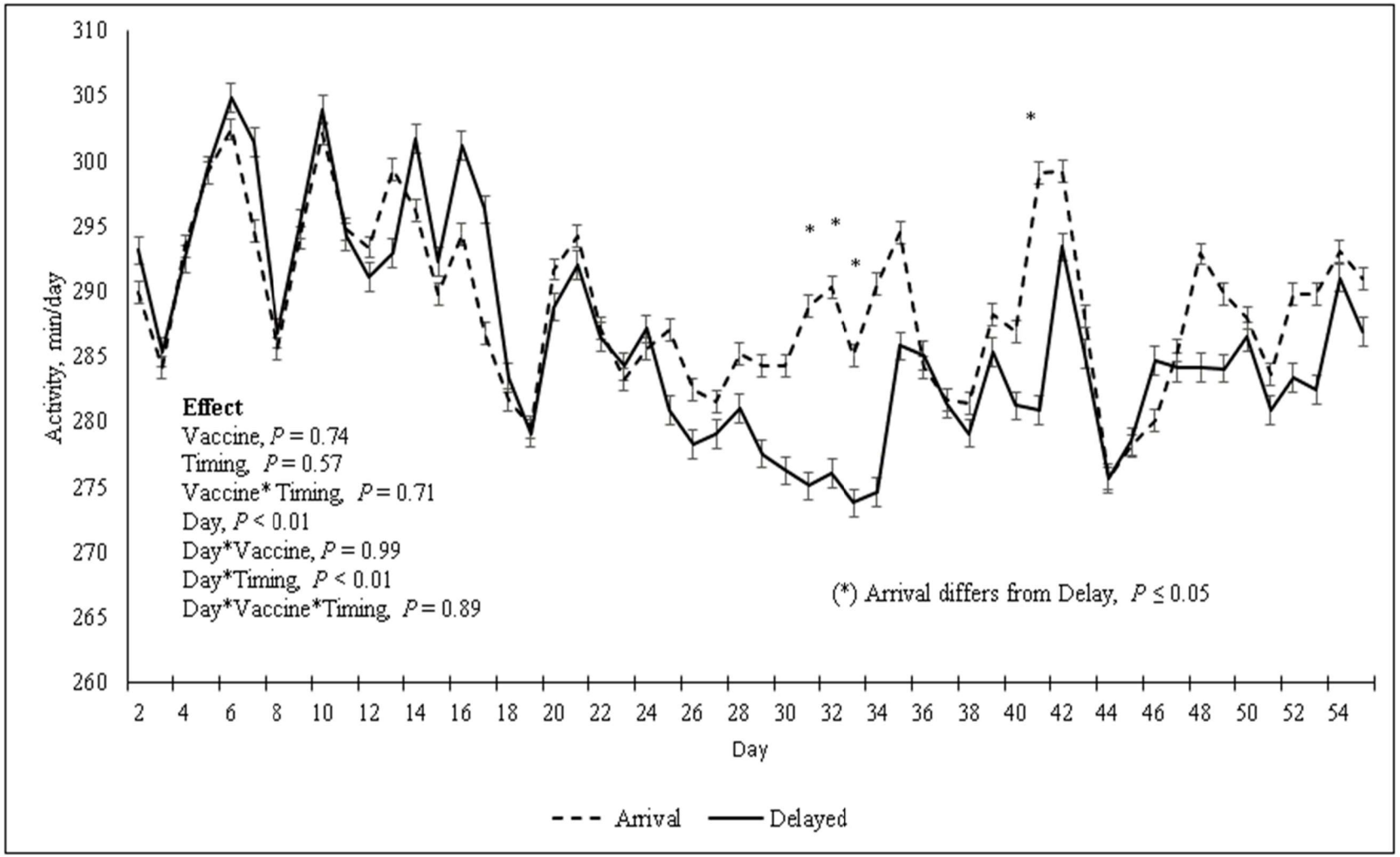

Figure 1. Effect of vaccination timing (d 0 or 28) on activity of heifers at high risk of developing BRD. Arrival treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 0. Delayed treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 28.

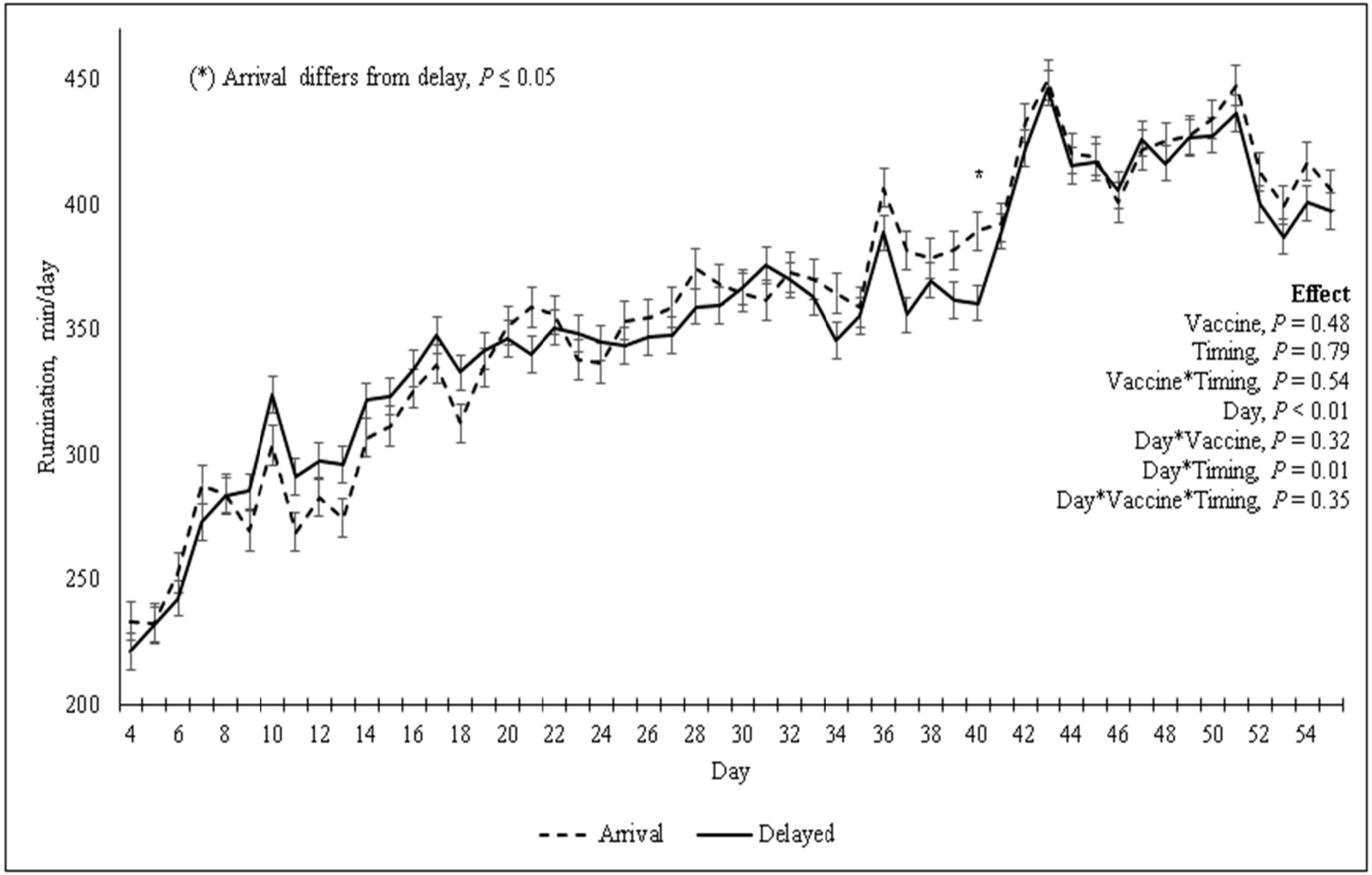

Figure 2. Effect of vaccination timing (d 0 or 28) on rumination of heifers at risk of developing BRD. Arrival treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 0. Delayed treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 28.

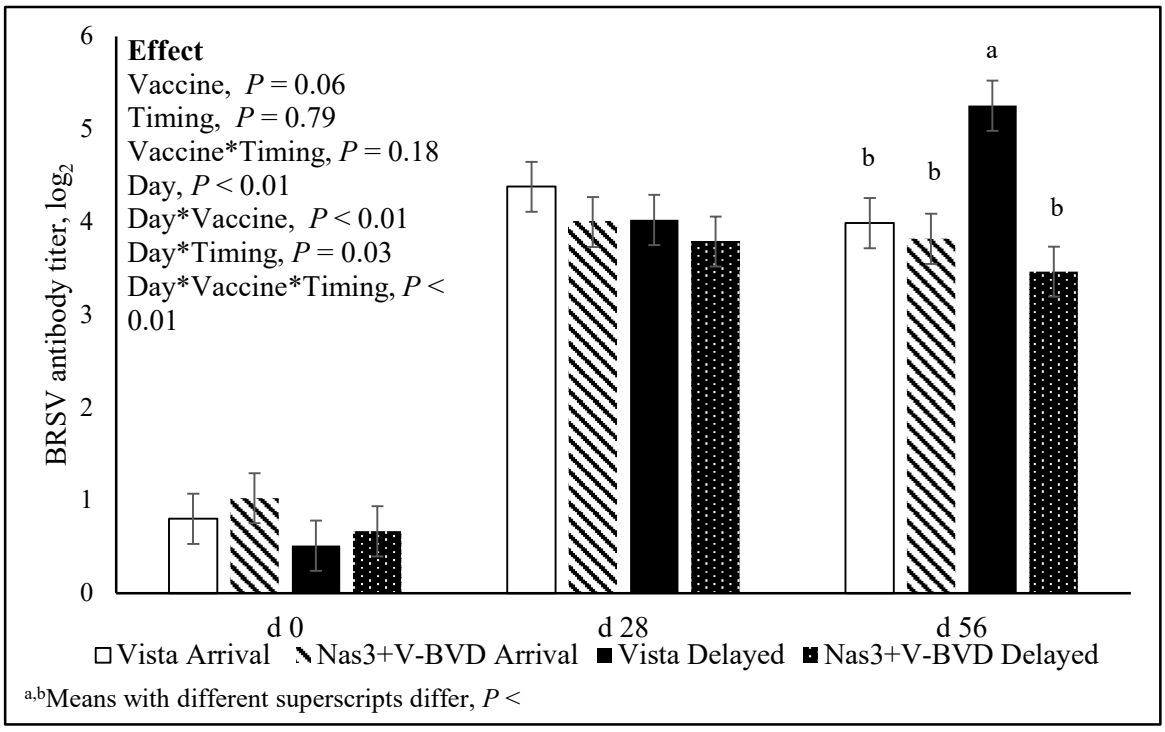

Figure 3. Effect of parenteral or intranasal vaccination on day 0 or 28 on BRSV-specific antibody titers of heifers at high risk of developing BRD.

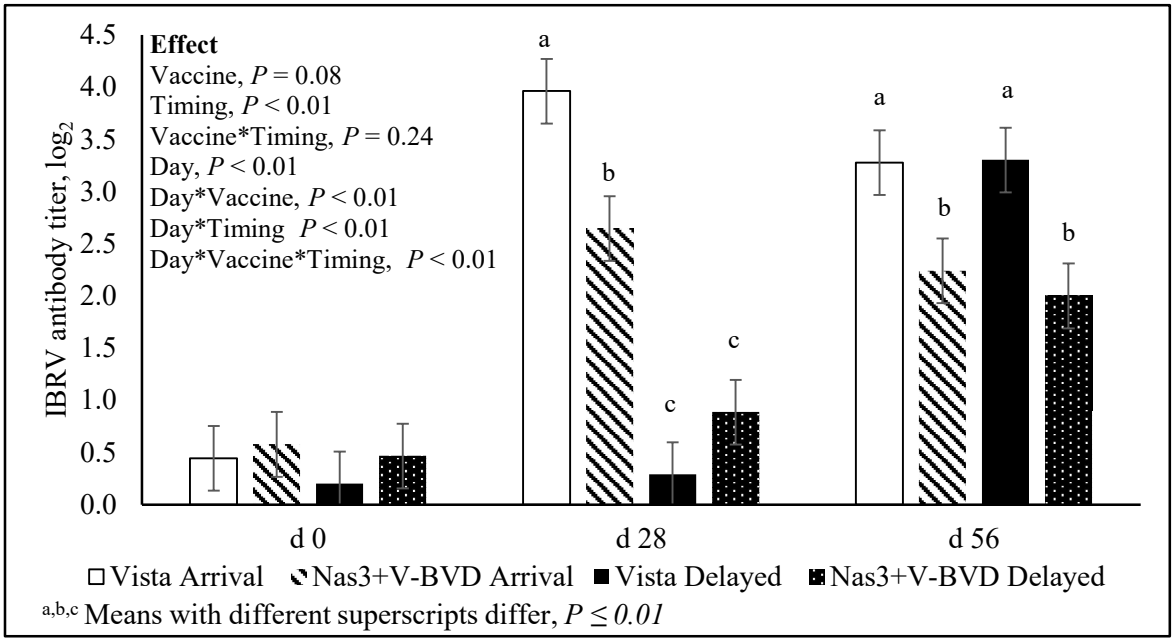

Figure 4. Effect of parenteral or intranasal vaccination on d 0 or 28 on IBRV-specific antibody titers of heifers at high risk of developing BRD.

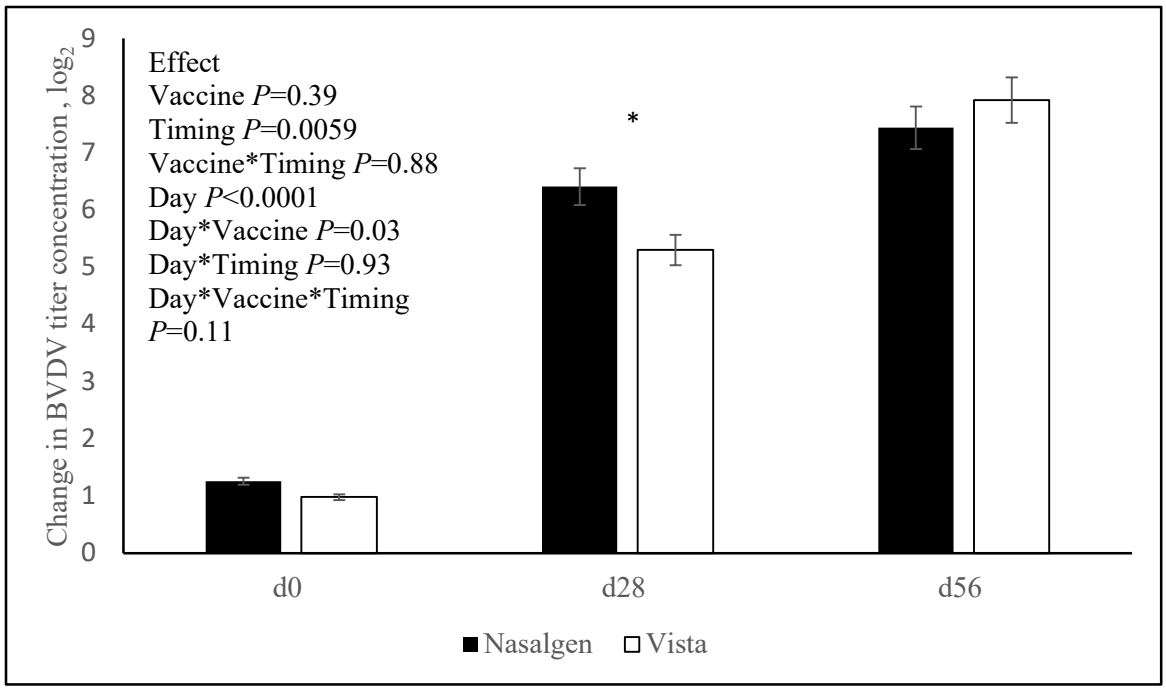

Figure 5. Effect of vaccination type (Nasalgen or Vista) on BVDV-specific antibody titer of heifers at high risk of developing BRD. Nasalgen treatments received Nasalgen 3 and Vista BVD CFP on d 0 or d28. Vista treatments received Vista 5 on d 0 or 28.

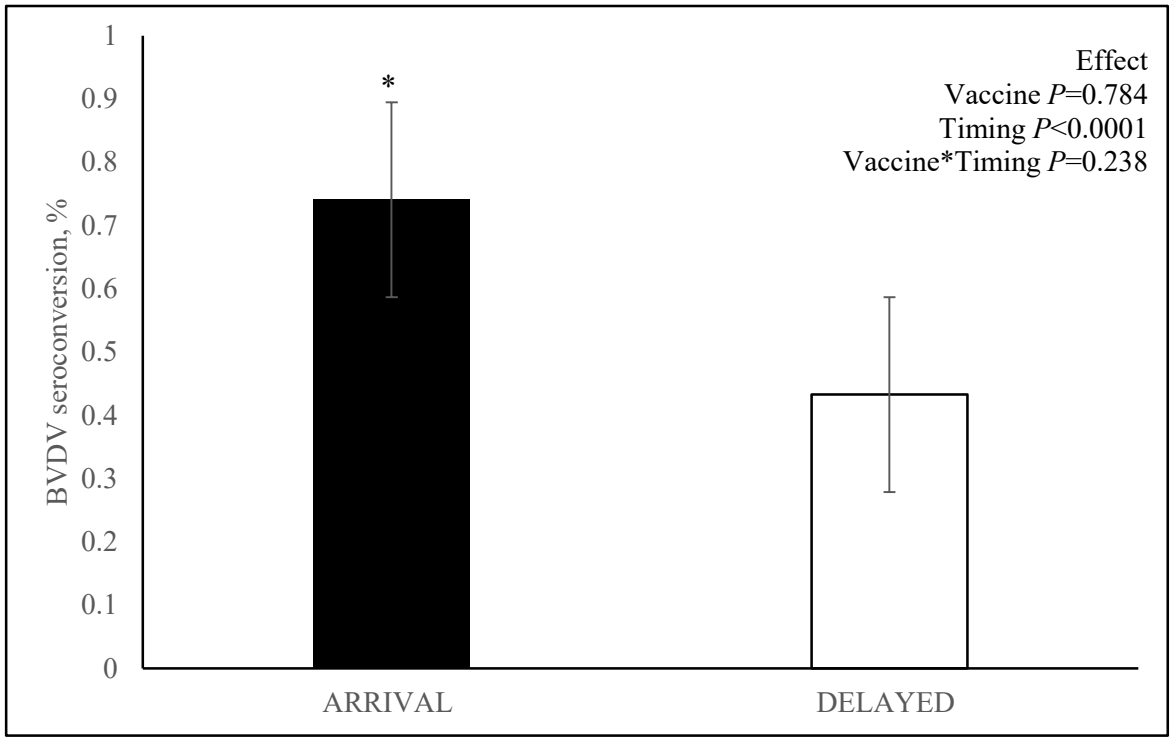

Figure 6. The effect of vaccination timing (d 0 or 28) on percentage BVDV seroconversion in sampled cattle. Arrival treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 0. Delayed treatment cattle received Nasalgen 3 and Vista BVD CFP or Vista 5 on d 28.

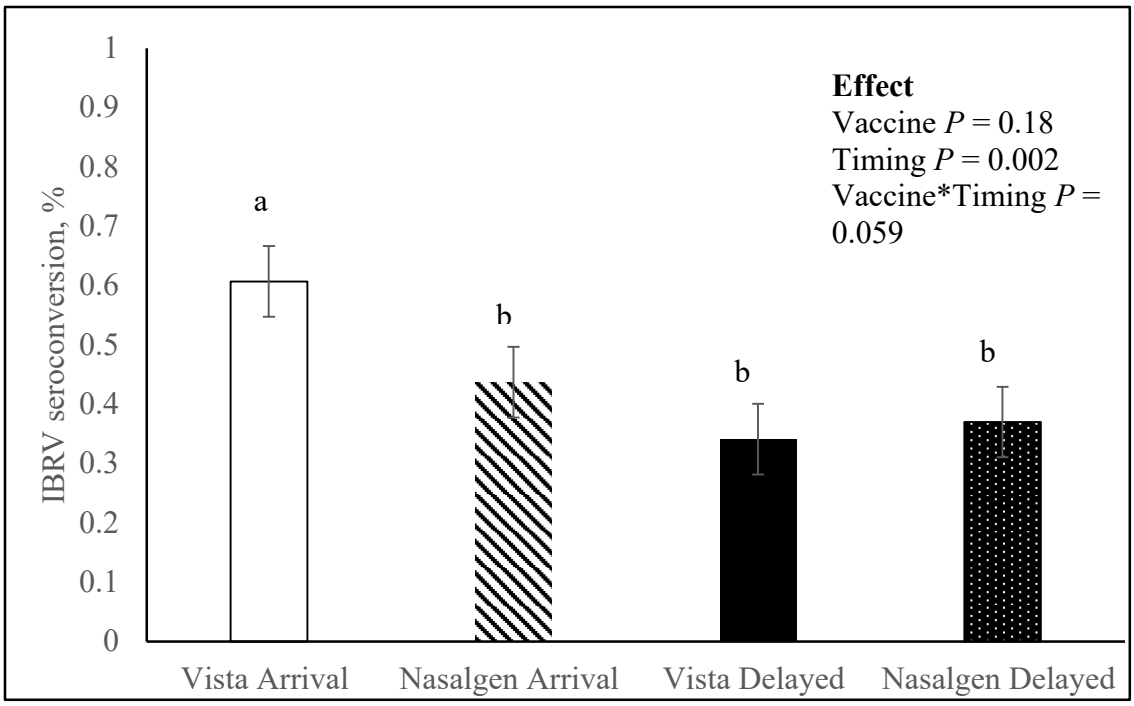

Figure 7. The effect of % IBR seroconversion in sampled cattle that received an intranasal or parenteral respiratory vaccination on arrival or delayed.

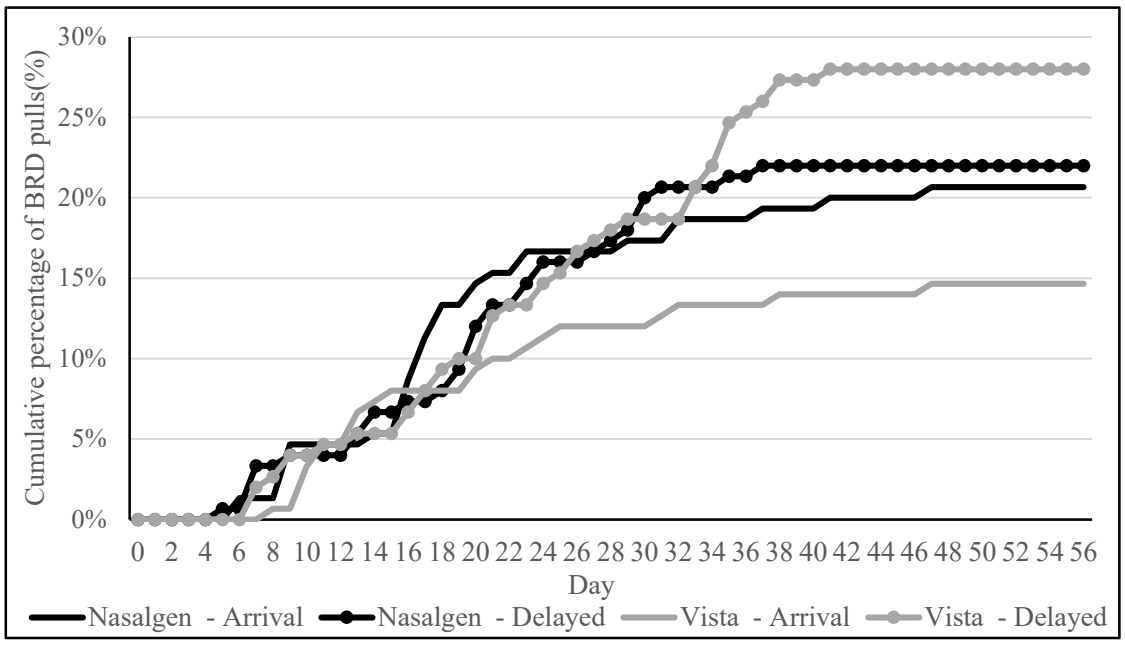

Figure 8. Cumulative number of BRD incidence of heifers receiving an on arrival or delayed intranasal or parenteral respiratory vaccine.