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Abstract

Bovine respiratory disease (BRD) is the most prominent and costly ailment in the stocker cattle industry today, and its prevalence has not been diminished in the last thirty years. Therefore, the objective of this study was to investigate the effects of Zelnate, a DNA immunostimulant, administered upon arrival to calves (n = 261; initial body weight 253 ± 4.0 kg), on morbidity and mortality, growth performance, and producer costs. Crossbred male beef calves were acquired and transported to the University of Arkansas stocker unit for a 42-d backgrounding period. Calves were allocated into two treatment groups: 1) Zelnate, DNA immunostimulant administered or 2) Control, in which no immunostimulant was administered. Animals were checked daily for signs of morbidity and treated. Records for growth performance, morbidity, and mortality were kept. Data were analyzed using the GLIMMIX procedures of SAS. Significance was declared at $P < 0.05$ and tendencies between $0.05 \leq P < 0.10$. Zelnate treated calves tended ($P = 0.09$) to have a lower relapse rate compared to control calves. Average daily gain was similar ($P = 0.60$) between the two treatment groups. The treatment cost for the Zelnate group was more expensive than the cost to treat the control group ($P < 0.01$). Overall, our findings indicate that Zelnate administered upon arrival to high risk calves did not improve morbidity rates nor reduce the need for antibiotic treatment for respiratory disease, or affect performance, however it tended to decrease relapse rate and did increase costs by $9.24 per calf.

Based upon these results, Zelnate does not appear to be an effective metaphylactic therapy for BRD in newly received cattle.

Introduction and Literature Review

Physiological stress, commingling in sale barns, and numerous viral and bacterial pathogens are responsible for bovine respiratory disease (BRD), and it remains the leading cause of feedlot morbidity and mortality (Woolums et al., 2005). The economic losses the industry endures annually is upwards of $750 million (Griffin, 1997) and disease prevalence has remained unchanged for the last three decades (Miles, 2009). The portion of costs from BRD due to the combination of mortality and treatment costs is approximately 82% (Faber et al., 2000). Each individual treatment of this disease costs on average $23.60, for both small feedlot operations (1,000-7,999 head) and large feedlot operations (8,000 or more head) there was not a statistical difference in cost per case. This cost per case has nearly doubled since 1999 when it cost on average $12.59 to treat per case (USDA-APHIS, 2013). This is a troubling indication that BRD is trending upwards in cost quite rapidly. Part of this increase in cost isn't solely medical treatment but also due to loss of value of the livestock form poorer feed efficiency, less average gain, and lower meat grade (Griffin, 1997). In the beef industry the reduced daily live weight gains from BRD means a longer finishing time, leading to increased production costs (Potter, 2015).

Stocker-feedlot facilities are complex systems with small profit margins and cattle health affects every aspect of their day to day operation. The ability to effectively manage cattle health affects optimization of available pens and pastures, management of labor and facilities, performance of cattle, and ultimately profits (Sweiger, 2010). The direct costs of BRD alone highlight the reason why feedlot operator's management strategies are frequently directed at minimizing the occurrence of this disease in their cattle (USDA-APHIS, 2013). However, despite

advances in veterinary medicine, animal husbandry, and animal welfare, BRD continues to be a major problem for producers (Gorden, 2010). Stressors from handling, weaning, commingling, transporting, and changes in environment and diet contribute substantially to the probability of an animal contracting BRD by suppressing the animal's immune system.

BRD is of multifactorial origin, onset of this disease depends on complex interactions between viruses, bacteria, the environment and the host (Faber et al., 2000). Most animals with healthy immune systems can fight off the initial viral infections, thus avoiding severe disease. However, cattle with immune suppression due to stress factors are not able to combat the initial viral infection (Powell, 2010) The usual scenario leading to the development of the disease involves the combination of an immunocompromised calf (usually due to stress), exposed to an immunosuppressive viral agent such as bovine virus diarrhea virus or bovine herpesvirus-1 (infectious bovine rhinotracheitis virus). The establishment of a primary viral infection leads to the progressive development of BRD from the upper to the lower respiratory tract. This viral immunosuppression compromises the innate immune system and mucociliary escalator. This condition allows commensal bacterial pathogens to migrate and colonize the lower respiratory tract, leading to pulmonary compromise, inflammation, and gross pathology (Edwards, 2010). The main pathogenic bacteria responsible for colonization and replication inside the lower respiratory tract include *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (Potter, 2015).

The early clinical signs commonly associated with BRD are nasal discharge, decreased appetite, lethargy, separation form the herd, a gaunt appearance, an increased respiratory rate and coughing. Animals often also have a rectal temperature of greater than 40.0 degrees Celsius and occasionally sores on the mouth and/or nose (Powell, 2010). Once an animal is infected with BRD

the immune system's nutrient consumption increases dramatically. Rates of gluconeogenesis increase 150% to 200% during moderate infections, and the basal metabolic rate has been shown to increase 25% to 55% during periods of sepsis (Gorden & Plummer, 2010). If treatment of this disease is delayed, the number of deaths or chronically infected animals in the herd will likely increase. As it progresses, severe lung damage occurs from inflammation due to infection. Often, the lung damage caused by BRD is irreversible (Powell, 2010). Mortality rate of calves diagnosed and treated for BRD was 5.9% compared to .35% for those calves not diagnosed with BRD (Faber et al., 2000). Enteritis is the most common cause of death in BRD infected cattle, followed by pneumonia. Once an animal contracted enteritis or pneumonia the case fatality rate averaged 11.18% and 17.9% respectively (Silva et al., 1996).

A compounding difficulty in the process of successfully diagnosing BRD is it is quite difficult to accurately diagnose due to the nature of the disease and the nature of cattle themselves. Being a prey animal, cattle instinctively mask the clinical signs of sickness as a means of self-preservation. For this reason, subclinical disease is difficult, if not impossible, to identify. Based on the usual subjective methods of first identifying BRD, identifying sick cattle is sometimes considered a learned skill or an art (Edwards, 2010). The difficulty accurately identifying all animals that require treatment is the reason many clinicians put a greater emphasis on prevention of BRD instead of treating the disease post-infection (Griffin, 1997). In fact, treatment of BRD post-infection may be inadequate to prevent significant production loses. One study found that almost 70% of cattle never treated for BRD had pulmonary lesions at slaughter that were indicative of the disease, indicating many infected cattle were never identified. If this finding is representative of the general cattle population, then the use of clinical signs as indicators of disease could be resulting in a large misclassification bias (Wittum 1996). These cattle were likely infected with a

less obvious subclinical infection of BRD, which leads to performance effects that have a similar devastating economic impact as the more easily recognizable clinical infection. The imprecision of clinical diagnosis of BRD strengthens the argument for mass medications, particularly when significant morbidity in a group is anticipated (Sweiger & Nichols, 2010).

A way to avoid the current increasing resistance of BRD inducing bacteria while treating subclinical animals is by improving the active immune system of cattle by administering herd-wide vaccines. However, these vaccines often cause tissue injury and an inflammatory response at the injection site and reduced feed consumption upon successive vaccinations. These reactions lead to decreased carcass value due to having to remove inflamed or damaged tissue as waste and decreased gain to feed ratio that increases feed expenses for the producer. This issue of multiple vaccinations compounding these effects is profound in the stocker industry due to the lack of communication of specific vaccination schedules between locations, in fact some cattle may receive as many as six vaccinations during their life time, resulting in intense local reactions at the site of injection (Stokka et al., 1994). Nonetheless it must be acknowledged that this unknown history is not only a complicating and determining factor in cattle health but also an opportunity for the next owner of these calves to procure them at a discounted price relative to the market. These discounted prices are a major driver in profitability for producers in this segment of the industry (Sweiger & Nichols, 2010). Even when vaccines don’t damage carcass traits or feeding behavior, many pathogens and immune responses to these pathogens have been poorly characterized. As a result, it is difficult to develop effective vaccines to combat these pathogens (Babiuk, 2002).

Other anti-infectives such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been used as attempted treatments for BRD besides vaccines and antibiotics to

little avail. There is insufficient data to conclude a potential positive effect of NSAID use on the positive cost benefits of NSAIDs as treatments of BRD (Potter, 2015). The lack of effective treatments that do not cause rates of antibiotic resistance to increase has caused researchers to recommend future projects that examine the effectiveness of new types of vaccines that do not trigger similar immune responses as clostridial vaccines (Johnson, 2016).

One possible novel solution that falls in line with these recommendations is use of the recently released DNA immunostimulant Zelnate (Bayer HealthCare LLC, Shawnee Mission, KS) that has resulted in decreased lung lesion scores in cattle exposed to the Mannheimia haemolytica bacteria (Nickell et al., 2016) and a reduction of clinical signs of BRD in high-risk cattle upon feedlot entry (Rogers et al., 2016). This pharmaceutical is intended to counteract the immunosuppressant effects of stress on stocker calves by stimulating the subjects' innate immune system through exposing it to a liposome containing a non-specific DNA antigen that prepares the calf's body to fight off a Mannheimia haemolytica infection.

The principle upon which polynucleotide immunostimulants like Zelnate are based is that the liposome is taken up by a cell, and if the appropriate promoters/enhancers are present, the genes encoded in the liposome are expressed and are translated to produce the encoded protein. Since these proteins are foreign, they induce an immune response in the animal. The great advantage of this approach, especially for viral antigens, is that the antigen is expressed endogenously and, therefore, all the posttranslational modifications are similar to those present during infection. As a result, the antigens are authentic, with all the conformational epitopes required for protection being expressed. To assist in elevating the immune response, the liposome contains built-in adjuvants in the form of CpG sequences. These sequences are critical in not only creating the cytokine micro-environment required for induction of immunity, but also in providing the Th1±Th2 balance and

the long-term memory observed with DNA-based immunostimulants. A real advantage of DNA immunostimulants such as Zelnate is that they can induce immune responses in neonates even in the presence of passive antibody. This is a true advantage over conventional or genetically engineered vaccines. This observation is extremely encouraging since it will allow us to administer to animals at a very early age, a time when they are easy to handle, and this will ensure that they are fully protected at the time passive antibody decays (Babiuk, 2002). Also, the concern regarding typical vaccines negatively affecting growth performance or feeding behavior does not occur with Zelnate (Gaspers, 2016). This novel pharmaceutical has also been proven to be inactive on human and mouse toll-like receptor 9 in cell culture in both recombinant and natural cellular receptor settings despite the presence of numerous non-methylated CpG motifs in its plasmid DNA (Babiuk, 2002).

Zelnate is designed to reduce the clinical instances of BRD and reduce the use of antibiotics while improving performance in high-risk, newly received beef calves. The objective of the current study is to evaluate the effect of metaphylactic administration of Zelnate on morbidity, mortality, and growth performance in newly received high-risk calves during a 42-d receiving period. The majority of calves treated for BRD are treated within the first 27 d of the feeding period (Buhman et al., 2000).

Materials and Methods

Animals

Crossbred male beef calves (n = 261; bulls = 129; steers = 132, initial body weight (BW) = 253 ± 4.0 kg) acquired from multiple local auction markets were shipped to the University of

Arkansas, Division of Agriculture, Stocker and Receiving Cattle Unit located near Fayetteville, AR. Calves were received on 3 separate dates (blocks) with 98, 82, and 81 calves arriving each of these days, respectively. For each arrival date, 4 pens were assigned randomly per treatment. Treatment pens were separated such that cattle on different treatments were not housed with fence-line contact. Prior to study initiation, animal care and use procedures were approved by the University of Arkansas Care and Use Committee (approval #19018).

Allocation and Arrival Procedures

Upon arrival on d 0, calves were weighed, assigned a unique ear tag for identification, tested for the prevalence of persistent infection with bovine viral diarrhea virus (PI-BVDV), and arrival castrate status was determined. No calves tested positive for PI-BVDV. Calves were stratified chute side by arrival castrate status using random allotment sheets so that cattle that arrived as steers and bulls were evenly distributed within pen across both treatments (8 pens/block; 10 to 13 calves/pen) and pens were assigned randomly to 1 of 2 experimental treatments: 1) Zelnate, DNA immunostimulant metaphylactic administration (Zelnate, 2 mL intramuscularly (IM); Bayer HealthCare, Shawnee Mission, KS), 2) Control, in which calves received no immunostimulant.

On d 0, calves were administered the appropriate experimental treatment, and all calves received a pentavalent modified-live virus vaccine for respiratory pathogens Titanium 5, Elanco Animal Health, Greenfield, IN), a clostridial-tetanus toxoid (Covexin 8, Merck Animal Health, Madison, NJ), and an injectable anthelmintic (Cydectin Injectable, Bayer HealthCare LLC). Calves were branded on the right hip and intact males were castrated via banding (California Bander, InoSol Co. LLC, El Centro, CA). Blood was also drawn through jugular venipuncture into vacuum tubes with a clot activated gel. Blood was centrifuged and serum stored at -20° C until

analyzed. Serum analysis of haptoglobin concentrations from d 0 and 14 were conducted using ELISA panels (Immunology Consultants Laboratory, Inc.). Calves were revaccinated on d 14 with the same pentavalent modified-live virus respiratory vaccine and clostridial-vaccine.

Housing and Diets

Calves were moved to their assigned 0.4-ha pens and provided 0.45 kg/d (as-fed basis) of a receiving supplement which was increased to 1.8 kg/d and provided 160 mg monensin after diet adaptation. Supplement was offered daily at 0800 and calves had ad libitum access to bermudagrass hay and water.

Procedures

Body weights were measured on d 0, 14, 28, 41, and 42. Average daily gain was determined based on initial BW, two interim BW, and the average of the final 2 BW (d 41 and 42).

Assessment and Treatment of Morbid Calves

During feeding, a pen rider blinded to experimental treatments observed cattle daily for signs of morbidity and a Clinical Attitude Score (CAS; 0 [normal] to 5 [moribund]; Table 1) was recorded. Calves that scored a 1 or greater were pulled, weighed, and rectal temperatures were recorded via digital thermometer (Model No. M216, GLA Agricultural Electronics; San Luis Obispo, CA), if temperature exceeded 40.0° C calves were treated according to a preplanned protocol. Animals with a CAS > 2 were treated regardless of rectal temperature. All calves qualifying for first-line BRD therapy were given enrofloxacin (Baytril 100, 5.7 mL/45 kg BW subcutaneously (SQ); Bayer HealthCare, LLC). Enrofloxacin was followed by a 2 d post-treatment interval (PTI) and if criteria for BRD persisted including CAS score and/or rectal temperature, florfenicol (Nuflor, 6.0 mL/45 kg BW SQ; Merck Animal Health) was the second antibiotic

administered. Following a 2 d PTI for florfenicol, calves eligible for a third antibiotic per previously stated criteria were administered ceftiofur hydrochloride (Excenel, 2.0 mL/45.5 kg BW SQ; Zoetis, Parsippany, NJ).

Morbidity data recorded included treatment date, rectal temperature at time of treatment, incidence of first, second, or third clinical respiratory disease, treatment cost, and mortality. Calves that were treated were housed in designated pens until deemed healthy upon the 48 h recheck. Relapse was defined as: of those calves treated with the first antibiotic, the percentage of calves that were treated with a second antibiotic. No animals died during the study.

Statistical Analyses

Performance data, morbidity response variables, and cost analysis were analyzed using the GLIMMIX procedure of SAS (SAS Inst. Inc., Cary, NC). Pen served as the experimental unit for all variables while calf served as the observational unit. The lone fixed effect in the model was treatment and block (arrival date) was considered to be the lone random effect. Least squares means were separated via the PDIFF option. Statistical significance was declared at $P \leq 0.05$, and tendencies at $0.05 < P \leq 0.10$.

Results and Discussion

Growth Performance

Body weight was not affected by DNA immunostimulant inclusion at processing (Table 2; $P \geq 0.89$). Initial BW were similar between control (252.2 kg) and Zelnate (252.7 kg; $P = 0.93$) treated calves. Body weights on d 14 were not different regardless of treatment ($P = 0.89$). Day 28 BW were similar between treatment as control cattle were 278.6 kg and Zelnate cattle were 278.3 kg, respectively ($P = 0.95$). Final BW did not differ by treatment with control and Zelnate cattle

weighing 294.1 and 293.5 kg ($P = 0.91$), respectively. Results were similar to findings by Gasper et al. (2016) which investigated the differences in 1) saline, and 2) MLV vaccine in combination with *Mannheimia haemolytica*, 3) Zelnate, and 4) MLV in combination with *Mannheimia haemolytica* and Zelnate and concluded that there were no differences in final BW or ADG across treatments. The addition of Zelnate did not affect BW.

Similarly, to growth performance, average daily gain (ADG) for the 42-d backgrounding period was not affected by the inclusion of a DNA immunostimulant (Table 2; $P \geq 0.32$). From d 0 to 14, ADG was 0.88 and 0.79 for control and Zelnate cattle respectively ($P = 0.32$). Average daily gain from d 14 to 28 was unaffected by treatment ($P = 0.76$). Similar ADG between treatments was observed from d 28 to 42 ($P = 0.67$). Overall ADG over the 42 study was not different between control cattle (1.00 kg/d) and Zelnate cattle (0.97 kg/d; $P = 0.60$). Zelnate did not have an effect on growth performance in newly received, high risk calves. A study investigating the effects of Zelnate compared to a saline control over a 70-d backgrounding period (Woolums et el., 2019) also reported no advantage in ADG.

Morbidity

There were no chronically ill calves or mortalities in either treatment group. Percentage BRD morbidity for first treatment antibiotic (enrofloxacin) was similar between calves treated with the immunostimulant (56.5 %) and control calves (49.9 %; $P = 0.31$; Table 3) with days in which the first treatment was administered being similar ($P = 0.72$; Table 3). The percentages of calves treated with a second antibiotic (florfenicol) did not differ between treatments ($P = 0.37$) with days till second treatment occurring on day 13.2 and 12.9 for control and Zelnate calves, respectively ($P = 0.91$). Days until third treatment were similar ($P = 0.41$). Relapse percentage accounted for calves that were treated with a second antibiotic after being treated with the first treatment

antibiotic. The percentage of calves that relapsed tended to differ between treatments with 47.4 and 32.2% for control and Zelnate calves, respectively ($P = 0.09$).

Serum haptoglobin levels for both groups on d 0 ($P = 0.40$) and d 14 ($P = 0.99$) were similar. Rectal temperature was similar between control and Zelnate for calves treated for clinical BRD (Table 4; $P \geq 0.13$). Regardless of first ($P = 0.74$), second ($P = 0.13$), or third ($P = 0.71$) antibiotic use, the inclusion of a DNA immunostimulant did not impact rectal temperatures for calves treated for BRD. Treating high risk calves upon arrival with Zelnate did not have an effect on morbidity variables.

Economics

The cost of antibiotic treatments were analyzed. The cost of antibiotics including all 3 treatment antibiotics used to treat clinical BRD was similar between control ($13.12) and Zelnate cattle ($12.40) for the 42-d study (Table 4; $P = 0.72$). Overall costs including antibiotic costs and the cost to treat with Zelnate upon arrival were greater ($22.36) compared to the antibiotic costs to treat control calves ($13.12; $P < 0.01$).

Conclusions

The inclusion of Zelnate upon arrival had no impact on growth performance or the number of calves treated for BRD. During the 42-d backgrounding period, there were no differences in BW or ADG at any of the 14-d collection intervals. The percentage of calves treated for clinical signs of BRD with one or two antibiotics did not differ and calves on both treatments had similar days till antibiotic treatment. The cost to treat clinical signs of BRD were similar between control and Zelnate calves, however, when the cost Zelnate was incorporated, therapeutic costs became more expensive. In this study, the use of Zelnate as a metaphylactic treatment may have a limited

impact on performance and morbidity in high-risk, newly received calves for the 42-d period, at an increased cost to producers. There was a trend for a reduction in relapses and it is unknown whether there would be improved immunity when stocker calves are moved to the feedlot.

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Table 1. Clinical attitude score system used to diagnose bovine respiratory disease.

CAS	Diagnosis	Clinical signs
0	Normal	No BRD clinical signs; calf is bright, alert and responsive when approached.
1	Mild BRD	Calf looks ill with BRD until approached; calf brightens, moves readily, and appears normal when approached. Calf may be mildly depressed and small amount of nasal and/or ocular discharge may be present.
2	Moderate BRD	Calf is obviously ill with BRD; when approached calf does not brighten up and moves slowly. Calf is moderately depressed and may exhibit dyspnea, considerable nasal and/or ocular discharge and coughing.
3	Severe BRD	Calf is severely ill with BRD; when approached calf stumbles or moves only with extreme coercion. Calf is severely depressed and may be anorexic and coughing with copious nasal discharge.
4	Moribund	Calf is moribund; recumbent and not able or willing to rise or get feed and water.

Table 2: Effect of Zelnate on growth performance in high-risk, newly received beef calves.

	Treatment			
Item	Control	Zelnate	SEM	*P*- value
Body weight, kg				
Initial[1]	252.2	252.7	4.0	0.93
D 14	264.4	263.7	3.7	0.89
D 28	278.6	278.3	3.6	0.95
Final[2]	294.1	293.5	3.6	0.91
Average daily gain, kg				
D 0 to 14	0.88	0.79	0.07	0.32
D 14 to 28	1.02	1.04	0.06	0.76
D 28 to 42	1.10	1.14	0.08	0.67
Overall	1.00	0.97	0.03	0.60

[1]Body weight upon arrival
[2]Average of 2 consecutive day weights

Table 3: Effect of Zelnate on percentage morbidity in high-risk, newly received beef calves.

	Treatment			
Item	Control	Zelnate	SEM	*P*- value
Morbidity, %				
1st treatment[1]	49.9	56.5	0.04	0.31
2nd treatment[1]	23.6	18.3	0.04	0.37
3rd treatment[1]	6.0	1.5	0.2	0.12
Relapse[2]	47.4	32.2	0.6	0.09
Days till 1st treatment[1]	6.6	6.9	0.6	0.72
Days till 2nd treatment[1]	13.2	12.9	1.7	0.91
Days till 3rd treatment[1]	22.3	18.0	3.0	0.41
Serum haptoglobin levels d 0[3]	14.1	13.9	0.3	0.40
Serum haptoglobin levels d 14[3]	14.5	14.3	0.2	0.99

[1]1st treatment = Enrofloxacin, 2nd treatment = Florfenicol, 3rd treatment = Ceftiofur
[2]Relapse = number of calves retreated after 1st treatment
[3]Units = ng/mL

Table 4: Effect of Zelnate on rectal temperature and antibiotic usage cost in high-risk, newly received beef calves.

	Treatment			
Item[1]	Control	Zelnate	SEM	*P*- value
Rectal Temperature, °C				
1st treatment	40.6	40.6	0.1	0.74
2nd treatment	40.4	40.7	0.2	0.13
3rd treatment	40.5	40.3	0.3	0.71
Antibiotics				
Antibiotic cost, $/calf	13.12	12.40	1.5	0.74
Antibiotics plus Zelnate, $/calf	13.12	22.36	1.5	<0.01

[1]1st treatment = Enrofloxacin, 2nd treatment = Florfenicol, 3rd treatment = Ceftiofur, Antibiotic costs = cost to treat calves, Antibiotics plus Zelnate = cost to treat calves in addition to Zelnate cost upon arrival