Comparisons of Metaphylactic Treatments of Zactran® (gamithromycin) vs. Excede® (ceftiofur crystalline free acid) in High Risk, Stocker Calves

David Amrine[b]

Brad White[b]

Dan Goehl[b]

Shaun H. Sweiger[a]

Bruce Nosky[c]

Ronald K. Tessman[c]

[a]*Sweiger Enterprises, LLC, Oklahoma City, OK 73114*

[b]*Professional Beef Services, LLC, Canton, MO 63435*

[c]*Merial Limited, Duluth, GA 30096*

Corresponding author
Ronald K. Tessman (Ron.Tessman@Merial.com)

KEY WORDS: Bovine respiratory disease, cattle, metaphylactic

ABSTRACT

Bovine respiratory disease (BRD) complex is the most common disease occurring in backgrounding and feedlot cattle and is a significant source of losses from poor performance and death. Metaphylactic treatments are recognized as economically advantageous and have been associated with a 50% reduction in BRD associated morbidity. The multi-site study described here was conducted to compare health and performance parameters between newly received stocker calves treated metaphylactically with Zactran® (6 mg gamithromycin/kg subcutaneously) compared to Excede® (6.6 mg ceftiofur/kg subcutaneously).

Cattle (N = 1853) were beef or beef cross bulls, steers, and heifers approximately 4 to 11 months old of auction market origin. At a single study site in Oklahoma, calves (n = 1045) weighing between 115 to 258 kg (254-568 lb) were received over a period of two months. Five sites in northeast Missouri enrolled calves (n=808) weighing between 179 to 322 kg (395-710 lb) over a period of five months. Calves were randomized to treatment at each site and were penned according to treatment. Blinded personnel monitored calves daily for clinical signs of illness and up to three sequential administrations of BRD therapy with approved antimicrobials were given to animals with a clinical illness score (CIS) > 1 and a rectal temperature >40°C (104.0°F) or with a CIS > 2. Calves metaphylactically treated for BRD with Zactran® gained significantly more weight (28.51 ± 6.14 kg vs. 24.46 ± 6.14 kg; $p<0.05$) than calves treated with Excede®. Fewer first pulls were required for calves treated with Zactran® (probability:

Table 1. *Summary of enrollment dates, days on feed, and number of calves by treatment group for each site / replicate for each study region (Oklahoma and Missouri)*

Location	Site / turn¶	Date enrolled	DOF§	Calves enrolled (n)	
				Zactran®	Excede®
Oklahoma	1	9/17/13	44	95	95
	2	9/24/13	44	74	75
	3	10/1/13	44	114	116
	4	10/8/13	44	72	72
	5	10/22/13	43	69	70
	6	10/29/13	44	95	98
Missouri	A1	9/16/13	49	72	73
	A2	11/11/13	42	101	102
	B	10/7/13	49	40	40
	C	1/4/14	45	52	52
	D	11/13/13	48	109	109
	E	9/13/13	46	29	29

¶ - Oklahoma location was 1 site with multiple replicates. Missouri site A1 had multiple pens, all other sites were different geographic locations.
§ - Days on feed

0.32 ± 0.07 vs. 0.38 ± 0.08; $p<0.01$) compared to calves treated with Excede®.

INTRODUCTION

Bovine respiratory disease (BRD) is the most common disease occurring in backgrounding and feedlot cattle and is a significant source of losses from poor performance and deaths. This syndrome remains the most expensive disease of feedlot cattle in the United States, and financial losses due to increased labor, deaths, reduced feed efficiency, and annual treatment costs are estimated to run $500 million to as much as $4.28 billion.[1, 2] The National Animal Health Monitoring System (NAHMS) Feedlot 2011 study reported 16.2% of cattle placed in feedlots developed BRD.[3]

Some of the common stressors on calves are weaning, shipping, commingling of different herds, and weather, which can compromise the immune system, leaving the animals more susceptible to invasion by different infectious agents.[4] The most common viruses include bovine viral diarrhea, infectious bovine rhinotracheitis, bovine respiratory syncytial virus, and parainfluenza type-3 virus. Exposure to these viruses can cause severe damage to the respiratory tract and create opportunities for bacteria, such as Mannheimia haemolytica and Pasteurella multocida, to invade the lungs.[5]

Standard methods for prevention, control, and treatment of BRD include vaccination and antimicrobials, but other methods, including genetic selection, nutritional manipulation, and various management practices, also have been evaluated.[6,7] Diagnosis of BRD based on clinical signs of illness can be quite inaccurate; therefore, treatment of the entire pen or truckload can be economically preferable and is frequently implemented for those calves determined to be at high risk of developing BRD.[8, 9]

Gamithromycin is an azalide 15-membered semi-synthetic macrolide antibiotic that has been developed for treatment and prevention of BRD.[10, 11] Studies of the pharmacokinetic and pharmacodynamic properties of gamithromycin showed that a single subcutaneous dose at 6 mg/kg provides rapid therapeutic and persistent activity in the control and prevention of infections. Ceftiofur crystalline-free acid sterile suspen-

sion also has been approved for the treatment and control of BRD and studies have demonstrated a single dose in the posterior aspect of the ear at 6.6 mg/kg is effective for control and prevention of BRD.[12]

The objective of this study was to compare health and performance parameters of treatments with Zactran® (gamithromycin; Merial Limited, Duluth, Georgia, USA) to Excede® (ceftiofur crystalline free acid; Zoetis, Florham Park, New Jersey, USA) in a multi-site metaphylactic program for BRD in newly received stocker cattle.

MATERIALS AND METHODS

Animals

Beef or beef cross bulls, steers, and heifers (n=1045) approximately 4 to 11 months old, weighing 115 to 258 kg (254-568 lb), of sale barn origin were enrolled at a single site in Oklahoma. The site had six pairs of pens for the study and the enrollment schedule for each pair of pens (Zactran® and Excede®) is displayed in Table 1.

Five additional sites in northeast Missouri enrolled a total of (N=808) beef or beef cross bulls, steers, and heifers weighing 179 to 322 kg (395-710 lb) that were procured through conventional purchasing channels. One location had two pairs of replicate pens; the other four locations each had one pair of replicate pens, providing a total of six replicates for the study (Table 1).

At all sites, calves enrolled were in apparent good health in the opinion of the investigator, and any animals arriving with a pre-existing pathologic condition were ineligible for study enrollment. At each site, calves were received, identified and processed according to standard receiving protocols, including placement in a single pen until processing. Calves at all sites received Ivomec® Plus (Merial Limited) injectable according to labeled dosing instructions.

Randomization

Oklahoma site: Upon arrival at the research facility, animals were initially penned according to arrival truck (source). Calves in each shipment were paired by sex, and calves within each pair were randomly and sequentially allocated to pens within each of the six pairs of pens used for the study using a randomization table provided by the investigator. Pens within each pair were randomly assigned to treatment.

Missouri sites: At processing, calves at each location were randomly assigned to treatment using a randomization table developed in Microsoft® Excel®. At each location, calves were placed in pens within pen pairs according to treatment assignment.

Table 2. *Clinical illness score (CIS) system*

Clinical Illness Score	Description	Clinical Appearance
0	Normal	No abnormal clinical signs
1	Slightly Ill	Mildly abnormal character of respiration. Dyspnea may be combined with some depression, gauntness, nasal and/or ocular discharges. Hair coat may be rough.
2	Moderately Ill	Moderately abnormal character of respiration. Noticeable dyspnea, gauntness, depression, and nasal and/or ocular discharges. Hair coat may be rough.
3	Severely Ill	Severely abnormal character of respiration. Pronounced dyspnea, depression and gauntness. Nasal and/or ocular discharges. Hair coat may be rough.
4	Moribund	Down and at the point of death. Open-mouth breathing.

Table 3. *Definitions of calculated therapy response variables for calves receiving Zactran® or Excede® as metaphylaxis for BRD at multiple sites in northeast Missouri and a single site with multiple replicates in Oklahoma.*

Therapy Response Variable	Description
Treatment Success	An animal that is fully recovered following initial therapy 1 antibiotic period, no additional therapy required within 21 days of initial therapy.
1st pull for BRD	First time a calf was identified and treated for BRD following metaphylaxis (and post-metaphylaxis interval)
1st BRD pull rate	(# 1st Pull for BRD / n (head) at arrival)
1st Treatment success rate	1 – (# relapses / # 1st BRD pulls)
Relapse	An animal that meets treatment requirement for therapy 2 within 21 days of 1st pull for BRD
Second Relapse	An animal that meets treatment requirement for therapy three within 21 days of second therapy
1st treatment after 28 days	Calf received therapy 1 for BRD after 28 days on feed. This calf will also be included in 1st pull for BRD.
New Episode	An animal that meets treatment criteria > 21 days following the previous therapy.

Management

Receiving, growing, and finishing rations were fed according to standard practice of each site. Water was made available ad libitum at each study location. Total feed delivered to each pen was recorded daily.

Treatment and Dosing

At all sites, calves in each treatment group received either Zactran® at 6 mg gamithromycin/kg subcutaneously or Excede® at 6.6 mg ceftiofur/kg subcutaneously on the enrollment day (day 0). Day 0 was not the same calendar day for all animals (Table 1), but was the same day for all animals within a replicate. Zactran® was administered on the left side of the lateral neck, and Excede® was administered in the base (hinge) of the posterior aspect of the left ear. Individual doses were determined from a dosing chart using each animal's weight recorded on day 0 using a calibrated scale to calculate the correct dose. One Missouri site used the group average weight to determine a dose for the entire group as a scale at the working chute was not available.

Observations and BRD Therapy

Treatments for each pen were known by the sponsor and study director/investigator; however, personnel involved in daily observations were blinded to treatments in all studies. Animals were evaluated daily for signs of disease beginning the day after processing. A 6 day post treatment moratorium was observed following initial metaphylactic treatment and only animals exhibiting severe signs of BRD (Clinical Illness Score [CIS] > 3) (Table 2) were eligible for treatment during that time. Following the initial 6 day moratorium, all animals were assigned a CIS and those exhibiting clinical signs of illness (CIS > 0) were pulled for further evaluation. Calves with a CIS = 1 or 2 were

eligible for treatment only if their rectal temperature was > 40 °C (104 °F). Those calves assigned a CIS ≥ 3 had temperatures recorded; however, treatment was administered regardless of rectal temperature.

First-time BRD therapy at the Oklahoma site was Draxxin® (tulathromycin; Pfizer Animal Health, New York, New York, USA) and was administered at the labeled dose of 1.1 mL/100 lb subcutaneously. First-time BRD therapy for all Missouri sites was Baytril® (enrofloxacin; Bayer Healthcare AG, Leverkusen, Germany) administered at the labeled dose of 5.5 mL/100 lb subcutaneously. At all sites, animals not responding to therapy 1 were treated according to the therapy 2 regimen of Nuflor® (florfenicol; Merck Animal Health, Whitehouse Station, New Jersey, USA): 6.0 mL/100 lb subcutaneously. Animals not responding to therapy 2 were treated according to the therapy 3 regimen of 300 LA Pro® (oxytetracycline; Norbrook Inc., Lenexa, Kansas, USA): 4.5 mL/100 lb subcutaneously.

Study Evaluations

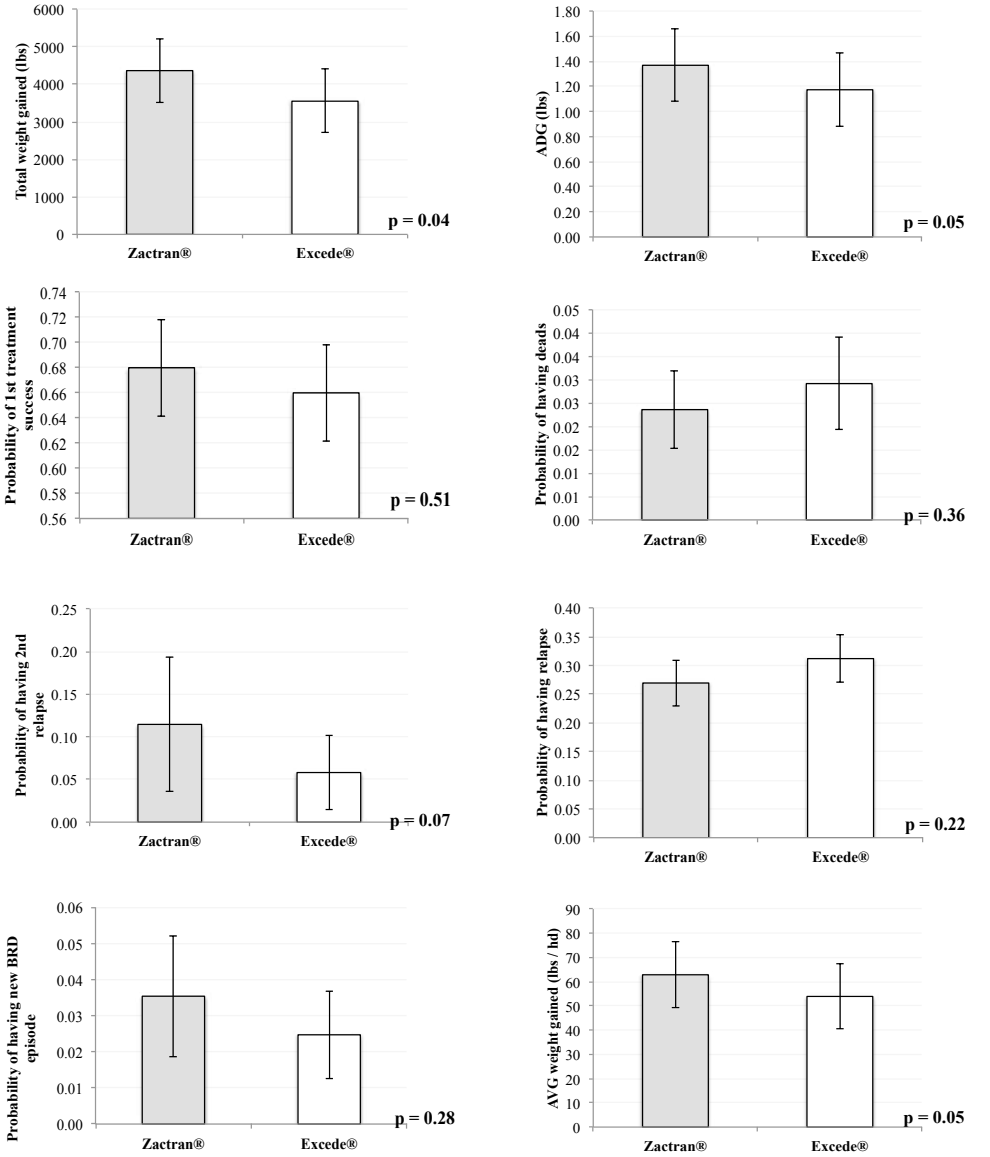
BRD morbidity data (animals with CIS>1 and rectal temperatures >40°C [104.0°F]) were recorded for two time intervals: days 0–28 and days 29–44/49. Clinical illness scores and rectal temperatures were recorded for all animals pulled from their treatment pens. All animals that died were necropsied by a veterinarian and classified as either BRD or non-BRD mortalities. Definitions and management of chronic and removed animals differed between the Oklahoma and Missouri sites; therefore, calculations of performance variables (total weight gained,

Table 4. *Statistical analysis of health and performance variables for calves receiving Zactran® or Excede® as metaphylaxis for BRD at multiple sites in northeast Missouri and a single site with multiple replicates in Oklahoma.*

	Treatment				
	Zactran®		Excede®		p - value
	LSM / prob(%)¶	SE	LSM / prob(%)¶	SE	Treatment
n (arrival)	--	--	--	--	--
Deads, chronics *	--	--	--	--	--
Average arrival weight (lbs)	450.90	22.90	450.20	22.90	0.83
Average end weight (lbs)	513.80	34.40	504.10	34.40	0.16
Total weight gained (lbs)	4366.58	848.34	3551.42	848.34	0.04
AVG weight gained (lbs / hd)	62.87	13.54	53.93	13.54	0.05
TOTAL weight gained (lbs) *	--	--	--	--	--
AVG weight gained (lbs / hd) *	--	--	--	--	--
Total feed given (lbs)	49554.17	9572.89	49255.75	9572.89	0.32
Total feed given on DM basis (lbs)	31198.58	4732.31	31070.08	4732.31	0.43
Feed:Gain §	11.18	2.36	15.94	2.36	0.14
Feed:Gain *	--	--	--	--	--
DM Feed:Gain §	7.34	1.94	11.05	1.94	0.16
ADG (lbs)	1.37	0.29	1.17	0.29	0.05
ADG (lbs) *	--	--	--	--	--
BRD 1st pulls (n)	0.32	0.07	0.38	0.08	0.01
BRD 1st pull %	--	--	--	--	--
1st Treatment Success rate	0.68	0.04	0.66	0.04	0.51
Deads (n)	0.024	0.01	0.029	0.01	0.36
Deads (%)	--	--	--	--	--
Treatment failures (n)	--	--	--	--	--
Relapse (n)	0.27	0.04	0.31	0.04	0.22
Second relapse (n)	0.11	0.08	0.06	0.04	0.07
New Episode (n)	0.04	0.02	0.02	0.01	0.28
1st treatment after 28 d	0.01	0.01	0.02	0.01	0.15
Chronics	--	--	--	--	--

¶ - Model estimated Least Square Means (LSM) were used for continuous variabls and probabilities (prob) for proportion count variables
* The definition of a chronic animal was different between investigators; therefore, could not be analyzed between investigator locations
§ Sites where Total weight gained was negative are not included in F:G calculations
-- Variables were not analyzed
All models included a random effect for investigator (PBS or Sweiger), site, and evaluated the fixed effect of treatment (Zactran®, Excede®)

Figure 1. Bar charts representing analysis of health and performance variables for calves receiving Zactran® or Excede® as metaphylaxis for BRD at multiple sites in northeast Missouri and a single site with multiple replicates in Oklahoma. All models include random effects to account for the hierarchical nature of the data (region - Oklahoma or Missouri) and multiple sites or replicates at a site.



average weight gained, feed:gain and ADG) was done on a deads-in basis. Individual weights were recorded at the beginning of the study before treatment on day 0 and at the end of the study (day 44–49). At one location in Missouri, a group weight was determined prior to processing and then pen (treatment) weights were determined at the end of the study period. Table 3 displays definitions of variables that were calculated and used in evaluation of therapy response.

Statistical Analyses

Data were imported into a software package (R: A Language and Environment for Statis-

tical Computing) for statistical analysis. The effect of treatment was analyzed for all continuous and count variables with site within region (Missouri or Oklahoma) included in all models as a random effect. Continuous variables (total weight gain, average weight gained, feed-to-gain ratios and average daily gain) were all analyzed with generalized linear mixed models. Potential associations of health outcome variables (count variables) for treatments were evaluated using logistic regression using a logit link function. Results of logistic regression models were converted to probabilities. These probabilities can be interpreted as the probability of variables by treatment. The level of significance was set at $p \leq 0.05$.

RESULTS

A total of 1853 calves were enrolled in the current study from September 2013 to January 2014. Average enrollment weights were 178 kg (392 lbs) and 180 kg (397 lbs) for Zactran® and Excede® treated calves at the Oklahoma site, respectively, and 231 kg (509 lbs) and 228 kg (503 lbs) for Zactran® and Excede® treated calves in Missouri, respectively. Average study days on feed were 44 and 47 for the Oklahoma and Missouri regions, respectively.

Total weight gain, average weight gain, and average daily gain were higher ($p \leq 0.05$) for Zactran® treated calves compared to those in the Excede® group (Figure 1 and Table 4). The probability of having first BRD pulls was lower ($p < 0.01$) for those calves treated with Zactran® compared to Excede® treated calves. No differences ($p > 0.10$) in feed to gain (F:G) on an as delivered or dry matter basis were observed between treatment groups.

DISCUSSION

This multi-site study evaluated health and performance parameters between stocker calves at high risk of developing BRD that received either Zactran® or Excede® as metaphylaxis at initial processing. Calves receiving Zactran® had higher ADG and a lower probability of being pulled for BRD, following metaphylaxis, compared to Excede® treated calves. In a multi-site study (n = 2), others[13] found no difference in ADG (days on feed = 120 d) in feedlot calves (n = 2529) at high risk of BRD receiving Zactran® or Draxxin® upon arrival; however, calves treated with Draxxin® had lower mean morbidity rate (22.9%) when compared to those calves receiving Zactran® (31.0%).

Beef cattle arriving at stocker and feedlot operations frequently have been transported for hundreds of miles, commingled and been exposed to many of the common pathogens associated with BRD.[9] Cattle considered at high-risk of developing BRD upon arrival to feedlot or stocker operations are frequently administered a metaphylactic antimicrobial to manage the risk of BRD within that population of cattle and this practice has shown to reduce morbidity by 50%. (Frank et al., 2002; Step et al., 2007). In a multi-site study, when compared with saline treated controls, calves metaphylactically treated with Zactran® upon arrival had higher ($p < 0.01$) percentage of BRD treatment successes (based on absence of clinical signs associated with BRD).[14]

Several antimicrobials are available for metaphylaxis in stocker and feedlot cattle at risk for BRD. Results of the study presented here indicate that a single dose of Zactran® dosed at 6 mg gamithromycin/kg is effective as a metaphylactic regimen in newly received stocker cattle. In these studies, stocker cattle treated with Zactran® on arrival gained significantly more weight and the probability of first pull for BRD therapy was lower compared to those calves treated with Excede®.

CONFLICTS OF INTEREST

Authors Amrine, White, Goehl and Sweiger, have no personal or financial relationship with other persons or organizations that could inappropriately influence or bias this study. Authors Nosky and Tessman are em-

ployees of Merial Limited, Duluth, GA.

ACKNOWLEDGMENTS

Funding for this study was provided by Merial Limited, Duluth, GA. The authors gratefully acknowledge Kathleen Newcomb, Blythewood Consulting, LLC for editorial assistance in the preparation of this manuscript.

REFERENCES

1. Smith RA: Impact of disease on feedlot performance: a review. *J Anim Sci* 1998, 76:272–4.
2. Griffin D: Economic impact associated with respiratory disease in beef cattle. *Vet Clin North Am Food Anim Pract* 1997, 13:367–377.
3. USDA: Types and Costs of Respiratory Disease Treatments in the U.S. Feedlots. Fort Collins, CO: National Animal Health Monitoring System; 2013. [USDA:APHIS:VS (Series editor)]
4. Duff GC, Galyean ML: BOARD-INVITED REVIEW: Recent advances in management of highly stressed, newly received feedlot cattle. *J Anim Sci* 2007:823–840.
5. Griffin D, Chengappa MM, Kuszak J, McVey DS: Bacterial pathogens of the bovine respiratory disease complex. *Vet Clin North Am Food Anim Pr* 2010, 26:381–94.
6. Cusack PM, McMeniman N, Lean IJ: The medicine and epidemiology of bovine respiratory disease in feedlots. *Aust Vet J* 2003, 81:480–7.
7. Taylor JD, Fulton R, Lehenbauer TW, Step DL: The epidemiology of bovine respiratory disease- What is the evidence for preventive measures. *Can Vet J* 2010, 51:1351–9.
8. White BJ, Renter DG: Bayesian estimation of the performance of using clinical observations and harvest lung lesions for diagnosing bovine respiratory disease in post-weaned beef calves. *J Vet Diagn Invest* 2009, 21:446–53.
9. Nickell JS, White BJ: Metaphylactic antimicrobial therapy for bovine respiratory disease in stocker and feedlot cattle. *Vet Clin North Am Food Anim Pr* 2010, 26:285–301.
10. Forbes AB, Ramage C, Sales J, Baggott D, Donachie W: Determination of the Duration of Antibacterial Efficacy following Administration of Gamithromycin Using a Bovine Mannheimia haemolytica Challenge Model. *Antimicrob Agents Chemother* 2011, 55:831–835.
11. Huang RA, Letendre LT, Banav N, Fischer J, Somerville B: Pharmacokinetics of gamithromycin in cattle with comparison of plasma and lung tissue concentrations and plasma antibacterial activity. *J Vet Pharmacol Ther* 2010, 33:227–237.
12. Hibbard B, Robb EJ, Chester ST Jr, Dame KJ, Moseley WW, Bryson WL: Dose determination and confirmation for ceftiofur crystalline-free acid administered in the posterior aspect of the ear for control and treatment of bovine respiratory disease. *Vet Ther* 2002, 3:22–30.
13. Torres S, Thomson DU, Bello NM, Nosky BJ, Reinhardt CD: Field study of the comparative efficacy of gamithromycin and tulathromycin for the control of undifferentiated bovine respiratory disease complex in beef feedlot calves at high risk of developing respiratory tract disease. *Am J Vet Res* 2013, 74:839–46.
14. Lechtenberg K, Daniels CS, Royer G, Bechtol D, Chester ST: Field Efficacy Study of Gamithromycin for the Control of Bovine Respiratory Disease in Cattle at High Risk of Developing the Disease. *J Appl Res Vet Med* 2011, 9:184–192.