A comparison of two multivalent modified live viral/bacterial combination vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease

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Abstract

Vaccine 1 (VAC1 group) and Vaccine 2 (VAC2 group) are commercially available vaccines labeled for the control of bovine respiratory disease (BRD) in beef cattle. There are limited data from large-scale commercial feedlot trials comparing Vaccine 1 and Vaccine 2 arrival processing vaccination programs. The objective of this study was to evaluate the relative effects of Vaccine 1 and Vaccine 2 arrival processing vaccination programs on animal health, feedlot performance and carcass characteristic outcomes in feedlot calves at ultra-high risk of developing undifferentiated fever/BRD under large-scale commercial production conditions. Animals were randomly allocated at feedlot arrival to 1 of 2 experimental groups: VAC1 or VAC2. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus-*Mannheimia haemolytica-Pasteurella multocida* vaccine at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus vaccine with a *Mannheimia haemolytica* toxoid at a dose of 2.0 mL per animal once at allocation. Vaccines differed regarding viral strains, bacterial protection, means for providing bacterial immunity, and adjuvant use. Animals were housed by experimental group in commercial feedlot pens and followed from allocation until slaughter. Although histophilosis mortality was higher in the VAC1 group compared to the VAC2 group ($P = 0.040$), no statistical differences were detected in overall mortality or any of the other outcome variables ($P \geq 0.050$). The relative cost effectiveness of each arrival processing vaccination program in the study population is therefore dependent on relative program cost.

Key words: shipping fever, beef, immunization

Introduction

Bovine respiratory disease (BRD), also commonly associated with undifferentiated fever (UF) and historically known as "shipping fever," continues to be one of the most common animal health concerns in commercial feedlot production.[1-7] This multifactorial disease complex typically involves a bacterial and/or viral infection of the respiratory tract alongside other predisposing factors that act to suppress immune function.[8,9] The primary etiological agents commonly associated with BRD include bacteria such as *Mannheimia haemolytica* (MH), *Pasteurella multocida* (PM), *Histophilus somni*, and *Mycoplasma bovis,* and viruses such as bovine herpes virus (also known as infectious bovine rhinotracheitis or IBR), bovine viral diarrhea virus types 1 and 2 (BVD), parainfluenza 3 virus (PI3), and bovine respiratory syncytial virus (BRSV).[10,11] Due to its multifactorial nature, diagnosing BRD in live cattle can be challenging, and confirmation of BRD typically occurs at postmortem examination.[10,12] A common clinical diagnosis associated with BRD in cattle is UF, which is characterized by an elevated rectal temperature and a lack of abnormal clinical signs referable to body systems other than the respiratory system.[1] Although we assume most UF cases are caused by BRD, some may be caused by other disease processes. Regardless, morbidity and mortality associated with BRD present a unique challenge to cattle producers.

Although beef feedlot operations have become more sophisticated in managing health problems, significant economic losses from BRD continue to be related to morbidity and mortality rates, reduced feedlot performance, and metaphylactic and therapeutic regimen costs.[13] The economic losses attributable to BRD are estimated to cost the North American cattle industry greater than $500 million US annually.[13] A more recent retrospective feedlot study involving 73,067,534 cattle in production lots that shipped from January 2005 to September 2014 showed a similar increasing trend in overall mortality, with BRD mortality comprising 47% of total mortality.[14] Therefore, it is important to seek the most efficacious, practical and cost-effective BRD prevention and treatment strategies based on high-quality field trial data.

Vaccination of beef cattle against viruses and bacteria is a widely accepted method for aiding in the control of BRD.[2,15] However, different vaccination strategies exist for different populations of cattle based on various factors, such as their perceived risk of developing BRD.[15,16] Predicting the risk of developing disease allows for differential management of animal health.[17] While there is no consensus best practice for predicting BRD risk, common factors such as age class (calf vs. yearling), body weight (often a proxy for age), procurement method (sale barn vs. ranch direct), amount of commingling before and after arrival at the feedlot, and previous vaccination and management history can be used to classify large

groups of cattle and build predictive models.[17-21] Often, cattle are classified as either low risk or high risk, although systems exist which incorporate more discerning levels such as ultra-high risk (UHR).[19,22] Despite the absence of an industry standard for classifying cattle as high risk or UHR, common risk factors may include calves being freshly weaned, being transported long distances, going through an auction market, and being highly stressed.[19]

Knowing the inherent risk profile of a cattle population is critical to selecting the most appropriate vaccination strategy, as there are numerous commercial vaccines in the market that offer different levels and modes of protection. A wide variety of proprietary virus strains are used throughout the industry, dependent on the vaccine manufacturer. However, most research is based on comparing whole vaccines and differences between individual strains are not well known or investigated. Protection against bacteria is usually accomplished through use of bacterins (attenuated live or killed bacterial cultures) and toxoids (inactivated bacterial virulence factors), although other modes of immunization exist.[23,24] There is no consensus on whether bacterins or toxoids provide greater acquired host immunity, with each having its own advantages and disadvantages.[23-26] Determining which bacteria to vaccinate against (if any) is also a matter of debate, and likely depends on the target cattle population and their respective respiratory microbial profiles. Similarly, the decision to include an adjuvant in a vaccine may impact its efficacy.[25,27-29] The mechanisms behind adjuvants are poorly understood though, further complicating assessment of their inclusion.[25,27-29]

Different vaccines may have increased efficacy in different populations of cattle based on vaccine composition and the inherent risk of the population for developing BRD. It is necessary to test different vaccines in commercial feedlot settings to determine relative efficacy. Unfortunately, although there are published data comparing many different types of bacterial and viral vaccines, there are limited data from large-scale commercial feedlot trials specifically comparing Vaccine 1[a] and Vaccine 2[b] arrival processing vaccination programs.[30,31] Therefore, the objective of this superiority study was to evaluate the relative effects of an IBR-BVD-PI3-BRSV-MH-PM vaccine (Vaccine 1) arrival processing vaccination program compared to an IBR-BVD-PI3-BRSV vaccine with an MH toxoid (Vaccine 2) arrival processing vaccination program on animal health, feedlot performance, and carcass characteristic outcomes in feedlot calves at UHR of developing UF/BRD under large-scale commercial production conditions.

Materials and methods

General overview

In this large-pen commercial field trial, auction market-derived, mixed beef-breed female calves at UHR of developing UF/BRD were randomly allocated at feedlot arrival to 1 of 2 experimental groups: VAC1 or VAC2. Study animals were housed by experimental group in commercial feedlot pens and followed from allocation until slaughter or death. There were 6 replicates allocated to the study, with each replicate comprised of 1 lot with multiple pens from VAC1 and 1 lot with multiple pens from VAC2. The experimental unit was the multi-pen lot. Outcome variables were measured from allocation to slaughter or death to evaluate the relative effects of each arrival processing vaccination program on animal health, feedlot performance and carcass characteristic outcomes. Statistical analyses were used to determine the probability of whether differences in outcome variables between the experimental groups were due to differences in the arrival processing vaccination programs or random chance.

Study facilities

The study was conducted at a commercial feedlot in Colorado, USA. The basic design of the feedlot is representative of standard designs used in the United States. Animals were housed in open-air, dirt-floor pens arranged side by side with central feed alleys. All individual animal events were recorded using onsite data collection and management software[c].

Study animals

All procedures involving live animals were approved by the Feedlot Health Management Services Ltd. (Feedlot Health) Animal Care Committee (a certified holder of a Certificate of Good Animal Practice) and in accordance with guidelines put forth by the Canadian Council on Animal Care (2009), with informed consent from the animal owners.

Candidate animals for the study were auction market-derived, mixed beef-breed female calves at a predicted UHR of developing UF/BRD that arrived between 04-Oct-2018 and 30-Oct-2018, inclusive. Risk of developing UF/BRD was predicted based on several factors, including age class (calf), body weight, procurement method (auction market), commingling before and after arrival at the feedlot, and unknown previous vaccination and management histories. Study animals were housed by experimental group in commercial feedlot pens. The experimental unit was the multi-pen lot, with 6 multi-pen lots allocated to each experimental group (average 501 animals/multi-pen lot, range 401 to 600 animals/multi-pen lot). The average initial individual animal weight of multi-pen lots allocated to the study was approximately 583 lb with a range of 564 to 598 lb (average 264 kg, range 256 to 271 kg).

At the time of study allocation, each animal received health and production products as per standard commercial feedlot practices. All animals had their temperature recorded on arrival. Those with a rectal temperature < 104.0 °F (< 40.0 °C) received a subcutaneous (SC) injection of metaphylactic tulathromycin[d] at a dosage of 1.1 mg/lb (2.5 mg/kg) body weight (BW) once at the time of allocation. Those with a rectal temperature ≥ 104.0 °F (≥ 40.0 °C) received a SC injection of florfenicol and flunixin meglumine[e] at a dosage of 18.1 mg florfenicol/lb (40 mg/kg) BW and 1.0 mg flunixin meglumine/lb (2.2 mg/kg) BW once at the time of allocation. In addition, study animals received the experimental vaccine specific for each study group, plus a SC multivalent clostridial and *Histophilus somni* bacterin-toxoid[f] at a dose of 5 mL/animal, a fenbendazole oral drench[g] at a dosage of 2.3 mg/lb (5 mg/kg) BW, and a pour-on parasiticide[h] at a dosage of 227 mcg/lb (500 mcg/kg) BW (all products given once at the time of allocation). Weight and hip height were recorded for each animal. With the exception of the experimental group-specific multivalent modified live viral (MLV) vaccine, all other post-arrival health and production products received throughout the study were standardized across experimental groups within a replicate. This included intramuscular dexamethasone[i] at a dose of 10 mL/animal (given at first revaccination), SC dinoprost tromethamine[j] at a dose of 5 mL/animal (given at first revaccination), a SC multivalent clostridial and *Histophilus somni* bacterin-toxoid[f] at a dose of 5 mL/animal (given at first revaccination), intramuscular

oxytetracycline[k] at a dosage of 4.5 mL/100 lb BW (given at first revaccination), and a SC MLV vaccine[l] at a dose of 2 mL/animal (given at first, second and third revaccination). Animals received 1 combination growth implant at each revaccination, which included either an estradiol/trenbolone acetate combination growth implant[m] in the middle one-third of the ear at a dose of 200 mg of trenbolone acetate and 20 mg of estradiol benzoate per animal (given at second revaccination) or an estradiol/trenbolone acetate combination growth implant[n] in the middle one-third of the ear at a dose of 100 mg of trenbolone acetate and 14 mg of estradiol benzoate per animal (given at first, second and third revaccination). First revaccination occurred at approximately 35 to 50 days on feed, with each subsequent revaccination occurring approximately every 90 days. The choice of which implant an animal received was based on marketing projections for each respective pen of animals.

Experimental design

An a priori sample size was calculated for this superiority study using variance estimates for overall mortality and initial post-metaphylactic BRD treatments (includes both UF and no fever [NF] treatments) from previous unpublished studies conducted by the investigators in the intended study population. Based on the historical baseline and variance estimates for overall mortality, an expected overall mortality difference between the experimental groups of 3.0%, an alpha level of 0.05, a power of 85%, and a 2-sided test, it was calculated that 6 replicates were required. Including 6 replicates was calculated to be sufficient to detect an 8.0% difference in initial post-metaphylactic BRD treatments (historical baseline initial post-metaphylactic BRD treatments, an alpha level of 0.05, a power of 80%, and a 2-sided test).

In this large-pen commercial field trial, animals were randomly allocated to 1 of 2 experimental groups at arrival processing using a proprietary computer-generated allocation table: VAC1 or VAC2. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a SC injection of Vaccine 1 at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a SC injection of Vaccine 2 at a dose of 2.0 mL per animal once at allocation. All injections were administered in the neck. Vaccine 1 and Vaccine 2 are widely used, clinically effective vaccines which have been licensed in Canada and the United States for the control of viruses and bacteria associated with BRD in beef cattle.[32] Vaccine 1 is a combination pentavalent MLV vaccine that contains MLV strains of IBR, BVD, PI3 and BRSV, and avirulent live cultures of MH and PM.[32] Vaccine 2 is a combination pentavalent vaccine containing MLV strains of IBR, BVD, PI3, and BRSV, plus an MH toxoid.[32] As these vaccines are manufactured by different pharmaceutical companies, the proprietary viral cultures utilized are different based on their respective manufacturer. Also, Vaccine 2 incorporates a MH toxoid and an adjuvant, whereas Vaccine 1 incorporates avirulent live bacterial cultures of both MH and PM but does not include an adjuvant.[32]

Animal health

Experienced animal health personnel, blinded to the experimental status of each pen, observed the study animals once or twice daily for evidence of disease. Using a standardized pen checking approach, the same animal health team checked all pens within a replicate on a given day. Animals deemed to be "sick" by animal health personnel (based on subjective criteria such as general appearance, attitude, gauntness, reluctance to move, etc.) were individually sorted from pen mates, moved to the hospital facility, and diagnosed and treated as per the standard feedlot protocols provided by the consulting veterinarian(s). Treatment events, including treatment date, presumptive diagnosis, drug(s) administered and dose(s) used, were recorded using a commercially available software program[c].

The case definition for initial UF was a lack of abnormal clinical signs referable to body systems other than the respiratory system, a rectal temperature ≥ 105.0 °F (> 40.5 °C), a period of at least 4 days had elapsed from allocation/arrival metaphylactic antimicrobial administration, and no previous treatment history for BRD. The case definition for initial no fever (NF) was a lack of abnormal clinical signs referable to body systems other than the respiratory system, a rectal temperature < 105.0 °F (≤ 40.5 °C), a period of at least 4 days had elapsed from allocation/arrival metaphylactic antimicrobial administration, and no previous treatment history for BRD. These clinical signs may have included, but were not limited to, nasal discharge, coughing and increased respiratory rate. If an animal presented clinical signs referable to body systems other than the respiratory system, the animal was not eligible for UF or NF treatment. All animals identified as "sick" by animal health personnel subsequent to initial therapy with clinical signs attributable to the same disease process were defined as relapses (i.e., cases that relapsed were defined as first, second or third relapses as appropriate). Animals could only be defined as a relapse after a period of at least 3 days had elapsed from initial therapy. Animals were deemed to be "chronic" if they underwent 3 or more treatment regimens for the same disease/condition. Chronic animals that did not die during the study were defined as wastage. All diseases were treated as per standard feedlot protocols developed by the consulting veterinarian(s) and therefore were standardized across experimental groups within replicates.

A gross post-mortem examination was performed on each animal that died when appropriate based on carcass condition (e.g., not autolyzed or frozen). In some instances, a Feedlot Health veterinarian conducted the post-mortem examination on site and determined the cause of death based on the findings of the clinical history and gross post-mortem examination. In instances where a veterinarian was not available, trained personnel prosected the dead animals using a standardized method to capture appropriate digital images as outlined in the written necropsy protocol provided by Feedlot Health.[33] Subsequently, all digital images were electronically transferred to Feedlot Health and the cause of death for each dead animal was determined based on the clinical history and findings of the gross post-mortem examination by a Feedlot Health veterinarian. The individual weights of all animals that died were collected by feedlot personnel. Bovine respiratory disease mortality included animals that died from or were euthanized due to bronchopneumonia, bronchointerstitial pneumonia, chronic pneumonia, chronic pleuritis, fibrinous pneumonia, lung abscess(es), or a combination of pneumonia and arthritis. Histophilosis mortality included animals that died from or were euthanized due to laryngitis, myocarditis, pericarditis, pleuritis, septicemia, or thromboembolic meningoencephalitis. Metabolic mortality included animals that died from or were euthanized due to atypical interstitial pneumonia, bloat, or caudal vena caval thrombosis. Arthritic mortality included animals that died or were euthanized due to arthritis without concurrent pneumonia.

Feeding program

Water and standard mixed complete feedlot diets, formulated to meet or exceed Nutrient Requirements of Beef Cattle,[34] were offered ad libitum throughout the feeding period. Feedlot diets were blended within the commercial mill batching system and delivered to the pens via delivery trucks equipped with electronic load cells. Diets were delivered to pens up to 3 times daily. Study animals were conditioned to a high-concentrate diet utilizing 4 transition diets. Animals remained on the high concentrate diet until shipment for slaughter. Diet formulations and diet changes were based on commercial feedlot protocols and were standardized across experimental groups within each replicate and production/marketing (P/M) cohort.

Marketing

The feedlot used standardized procedures to sort animals into P/M cohorts for optimization of production, marketing, and pen utilization. Within each replicate and P/M cohort, an equal number of animals from each experimental group were shipped and slaughtered on the same date at the same packing plant.

Data collection and management

Over the course of the trial, all individual animal feedlot data were collected using a commercially available software program[c]. At enrollment, allocation weight and allocation hip height were measured for each animal to assess the homogeneity of the animals in each experimental group. Daily feed data were captured electronically using the data collection systems in each feed truck and these data were electronically uploaded and stored in the feedlot's administrative software system. At slaughter, the United States Department of Agriculture (USDA) quality grade (QG), USDA yield grade (YG), and weight of each carcass were collected using the data capture system in place at each packing plant. All study data were entered or electronically imported into a spreadsheet program[o], collated, and verified.

Ancillary production variables were calculated for each multi-pen lot to describe the feedlot production system. Outcome variables describing animal health, feedlot performance (on both a live weight basis and carcass weight basis), and carcass characteristics were calculated for each multi-pen lot. The carcass characteristic variables included the proportions of QGs and YGs observed in each group. The USDA QGs included: USDA Prime, USDA Choice, USDA Select, Standard, Commercial, Dark Cutter, and Utility. The USDA YGs included: USDA 1, USDA 2, USDA 3, USDA 4, and USDA 5. Definitions and formulae used to calculate animal health, ancillary production and feedlot performance lot-level outcome variables are summarized in Table 1 and Table 2.

Statistical analyses

In this superiority study, data were analyzed using a commercially available analytical software program[p] (SAS) to compare the VAC1 and VAC2 groups. Baseline variables (allocation weight and allocation hip height) were tested as covariates of the feedlot performance variables and included in those final models if statistically significant ($P < 0.050$). Animal health data were analyzed using the GENMOD procedure in SAS with the Poisson distribution in a log-linear model for experimental group effects and adjusted for clustering of observations (lot nested within replicate) with generalized estimating equations.[35]The baseline, ancillary production, feedlot performance and carcass characteristic data were analyzed using the GLIMMIX procedure in SAS with the model containing the fixed effect of experimental group and the random effect of replicate.[35]

Results

The animal health data summary is presented in Table 3. The mortality rate due to histophilosis was higher in the VAC1 group compared to the VAC2 group (absolute difference 0.35%, $P = 0.040$). However, there was no difference in overall mortality between the groups (VAC1 group = 14.27% vs. VAC2 group = 14.36%, $P = 0.904$) and there were no differences detected in any of the other animal health variables between the experimental groups ($P \geq 0.050$). The cumulative distribution of initial UF and NF cases by experimental group and days on feed are presented in Figure 1 and Figure 2, respectively.

The baseline and ancillary production data summary is presented in Table 4. The experimental groups were considered homogenous ($P \geq 0.050$) with respect to the baseline variables average allocation weight and allocation hip height. There were no differences detected in any of the ancillary production variables between the experimental groups ($P \geq 0.050$). The daily dry matter intake by experimental group and week on feed is presented in Figure 3.

The feedlot performance data summary is presented in Table 5. There were no differences detected in any of the feedlot performance outcomes on a live weight basis or a carcass weight basis between the experimental groups ($P \geq 0.050$). However, there were numerical trends for poorer feed conversion on a live weight basis (difference 1.61%, $P = 0.071$) and a carcass weight basis (difference 1.78%, $P = 0.059$) in the VAC1 group compared to the VAC2 group.

The carcass characteristic data summary is presented in Table 6. There were no differences detected in any of the carcass characteristic variables between the experimental groups ($P \geq 0.050$).

Discussion

The objective of this superiority study was to evaluate the relative effects of an IBR-BVD-PI3-BRSV-MH-PM vaccine arrival processing vaccination program compared to an IBR-BVD-PI3-BRSV vaccine with an MH toxoid arrival processing vaccination program on animal health, feedlot performance and carcass characteristic outcomes in feedlot cattle at UHR of developing UF/BRD under large-scale commercial production conditions.

With respect to animal health outcomes, histophilosis mortality was higher in the VAC1 group compared to the VAC2 group. Although this difference was statistically significant ($P = 0.040$), it was not sufficient to drive a statistically significant difference in overall mortality between the experimental groups ($P = 0.904$). In addition, there were no differences detected in any morbidity variables between the experimental groups. This suggests that animal health outcomes are not significantly influenced by the choice between the arrival processing vaccination protocols compared in the study. Furthermore, there were no statistically significant ($P \geq 0.050$) differences detected between the experimental groups with respect to feedlot performance or carcass characteristic outcomes.

If including only statistically significant differences between the experimental groups in the economic model, the relative cost effectiveness of the VAC1 group compared to the VAC2 group would be dictated by program cost alone. However, there were numerical trends for poorer feed conversion on both a live weight basis ($P = 0.071$) and a carcass weight basis ($P = 0.059$) in the VAC1 group compared to the VAC2 group. If these trends represent real differences between the arrival processing vaccination programs, there would be an economic disadvantage in the VAC1 group compared to the VAC2 group that cannot be overcome with a lower relative program cost in the VAC1 group. Additional research which includes a larger sample size may be necessary to provide sufficient sensitivity to detect a statistical difference in feed conversion between experimental groups.

Table 1: Definitions and calculations for lot-level variables from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.

Animal health rates		
Initial UF treatment	=	# of animals treated for initial UF after metaphylaxis divided by the # of animals allocated
First UF relapse	=	# of animals treated for first UF relapse divided by the # of animals initially treated for UF
Initial NF treatment	=	# of animals treated for initial NF after metaphylaxis divided by the # of animals allocated
First NF relapse	=	# of animals treated for first NF relapse divided by the # of animals initially treated for NF
Chronicity	=	# of animals with chronic disease (all causes) divided by the # of animals allocated
Wastage	=	# of animals with chronic disease (all causes) that did not die divided by the # of animals allocated
Overall mortality	=	# of dead animals (all causes) divided by the # of animals allocated
BRD mortality	=	# of dead animals due to BRD divided by the # of animals allocated
Histophilosis mortality	=	# of dead animals due to histophilosis divided by the # of animals allocated
Metabolic mortality	=	# of dead animals due to metabolic disease divided by the # of animals allocated
Arthritis mortality	=	# of dead animals due to arthritis-associated disease divided by the # of animals allocated
Other mortality	=	# of dead animals (causes other than those previously listed) divided by the # of animals allocated
Ancillary production variables		
Slaughter weight	=	the total net* live weight prior to slaughter divided by the # of animals sold and represents the average net live weight of animals sold for slaughter
Weight gain	=	slaughter weight minus the average weight on arrival and represents the average weight gain of animals sold for slaughter
Carcass weight	=	total carcass weight at slaughter divided by the # of animals sold and represents the average carcass weight of animals sold for slaughter
Dressing percentage	=	total carcass weight at slaughter divided by the total weight at slaughter expressed as a percentage
DOF	=	average slaughter date minus the average allocation date and represents the average # of days on feed of animals sold for slaughter
DDMI	=	total quantity of feed consumed (100% dry matter basis) divided by the # of cattle days and represents the pounds of feed consumed per animal per day

* Corrected for gut fill as per standardized commercial production procedures used at the feedlot.

All animals were allocated on arrival at the feedlot.

= number, BRD = bovine respiratory disease, DDMI = daily dry matter intake, DOF = days on feed, NF = no fever, UF = undifferentiated fever.

Table 2: Definitions and calculations for lot-level variables from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.

Feedlot performance variables		
ADG–LWB	=	(total net live weight prior to slaughter plus total weight of animals shipped for salvage slaughter plus total weight of animals that died minus total allocation weight) divided by the # of animal days
ADG–CWB	=	(total carcass weight divided by a fixed dressing percentage (63.0%) plus total weight of animals shipped for salvage slaughter plus total weight of animals that died minus total allocation weight) divided by the # of animal days
DM:G–LWB	=	DDMI divided by ADG–LWB
DM:G–CWB	=	DDMI divided by ADG–CWB

All animals were allocated on arrival at the feedlot.

= number, ADG = average daily gain, CWB = carcass weight basis, DDMI = daily dry matter intake, DM:G = dry matter intake to gain ratio, LWB = live weight basis.

Table 3: Animal health data summary from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.

	Experimental Group		
Animal health variable	**VAC1**	**VAC2**	***P* - value**
Morbidity			
Initial UF treatment (%)	7.87	6.85	0.183
First UF relapse (%)	36.67	40.72	0.197
Initial NF treatment (%)	17.70	18.09	0.735
First NF relapse (%)	34.17	34.51	0.891
Chronicity (%)	5.70	5.54	0.890
Wastage (%)	2.66	2.77	0.727
Mortality			
Overall mortality (%)	14.27	14.36	0.904
BRD mortality (%)	9.31	9.05	0.860
Histophilosis mortality (%)	1.10[a]	0.75[b]	0.040
Metabolic mortality (%)	0.51	0.78	0.301
Arthritis mortality (%)	0.06	0.00	NA
Other mortality (%)	3.29	3.79	0.203

[ab] Means within a row lacking a common superscript differ at a $P < 0.050$ level.

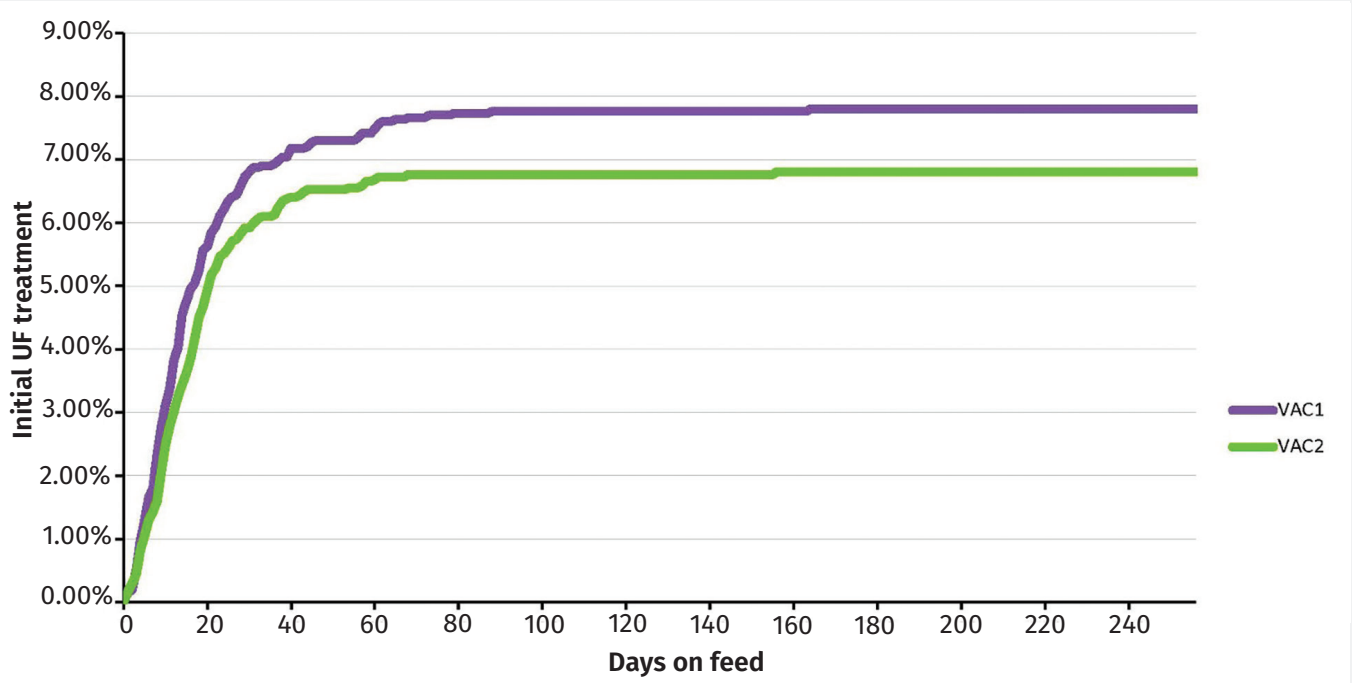
All animals were allocated on arrival at the feedlot. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus-*Mannheimia haemolytica-Pasteurella multocida* vaccine at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus vaccine with a *Mannheimia haemolytica* toxoid at a dose of 2.0 mL per animal once at allocation.

Data were analyzed using the GENMOD procedure of SAS® (Version 9.4, SAS Institute Inc, Cary, NC) with the Poisson distribution in a log-linear model for experimental group effects and adjusting for clustering of observations (lot nested within replicate) with generalized estimating equations.

BRD = bovine respiratory disease, NF = no fever, UF = undifferentiated fever.

NA = not available. Some models would not converge due to the small number of events.

Figure 1: Cumulative distribution of initial undifferentiated fever (UF) cases by days on feed from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.



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Conclusions

In summary, although histophilosis mortality was higher in the VAC1 group compared to the VAC2 group, no statistically significant differences were detected in overall mortality or any of the other animal health, feedlot performance, or carcass characteristic outcome variables when comparing an IBR-BVD-PI3-BRSV-MH-PM vaccine arrival processing vaccination program and an IBR-BVD-PI3-BRSV vaccine with an MH toxoid arrival processing vaccination program in feedlot cattle at UHR risk of developing UF/BRD under large-scale commercial production conditions. Given the lack of detectable statistical differences in overall mortality, morbidity, feedlot performance, and carcass characteristic outcomes, the relative cost effectiveness of each arrival processing vaccination program should be dependent on the relative cost of each program. Additional research, or allocation of additional replicates, is warranted to determine if the numerical trends for poorer feed conversion observed between the experimental groups represent a true statistical difference between the vaccine programs.

Endnotes

[a] Vista Once SQ, Merck Animal Health, Intervet Inc., Madison, New Jersey

[b] Pyramid® 5 + Presponse® SQ, Boehringer Ingelheim Animal Health USA Inc., Duluth, Georgia

[c] *i*FHMS, Feedlot Health Management Services Ltd., Okotoks, Alberta

[d] Draxxin®, Zoetis Inc., Kalamazoo, Michigan

[e] Resflor GOLD®, Merck Animal Health, Intervet Inc., Madison, New Jersey

[f] Bar-Vac® 7/Somnus, Boehringer Ingelheim Animal Health USA Inc., Duluth, Georgia

[g] Safe-Guard®, Merck Animal Health, Intervet Inc., Madison, New Jersey

[h] Ivermectin Pour-On for Cattle, Durvet, Inc., Blue Springs, Montana

[i] Dexamethasone 2, Vetoquinol N.-A. Inc., Commercial Division, Lavaltrie, Quebec

[j] Lutalyse® Injection, Zoetis Inc., Kalamazoo, Michigan

[k] Noromycin 300 LA, Norbrook Inc., Lenexa, Kansas

[l] Pyramid 5, Boehringer Ingelheim Animal Health USA Inc., Duluth, Georgia

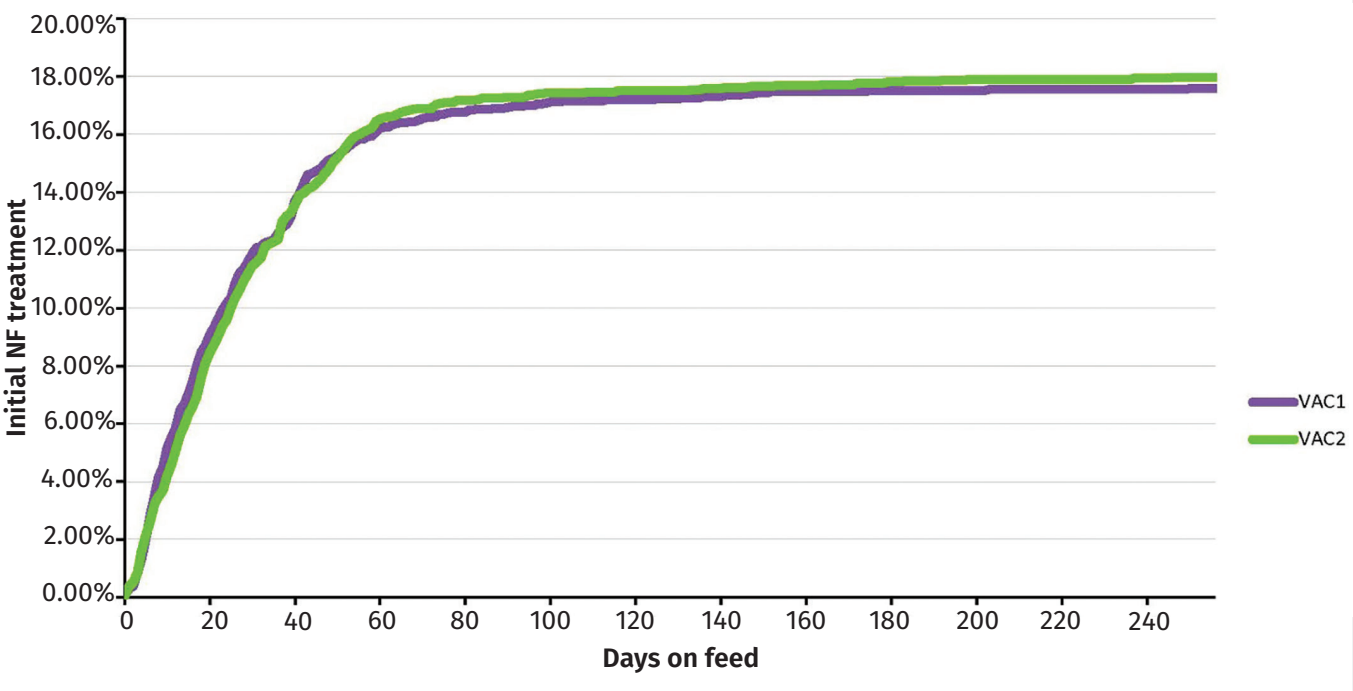
[m] Revalor®-200, Merck Animal Health, Intervet Inc., Madison, New Jersey

[n] Synovex Choice®, Zoetis Inc., Kalamazoo, Michigan

[o] Microsoft® Office Excel 365 ProPlus, Microsoft Corporation, Redmond, Washington

[p] SAS® for Windows, Release 9.4, SAS Institute Inc., Cary, North Carolina

Figure 2: Cumulative distribution of initial no fever (NF) cases by days on feed from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.



All animals were allocated on arrival at the feedlot. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus-*Mannheimia haemolytica-Pasteurella multocida* vaccine at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus vaccine with a *Mannheimia haemolytica* toxoid at a dose of 2.0 mL per animal once at allocation.

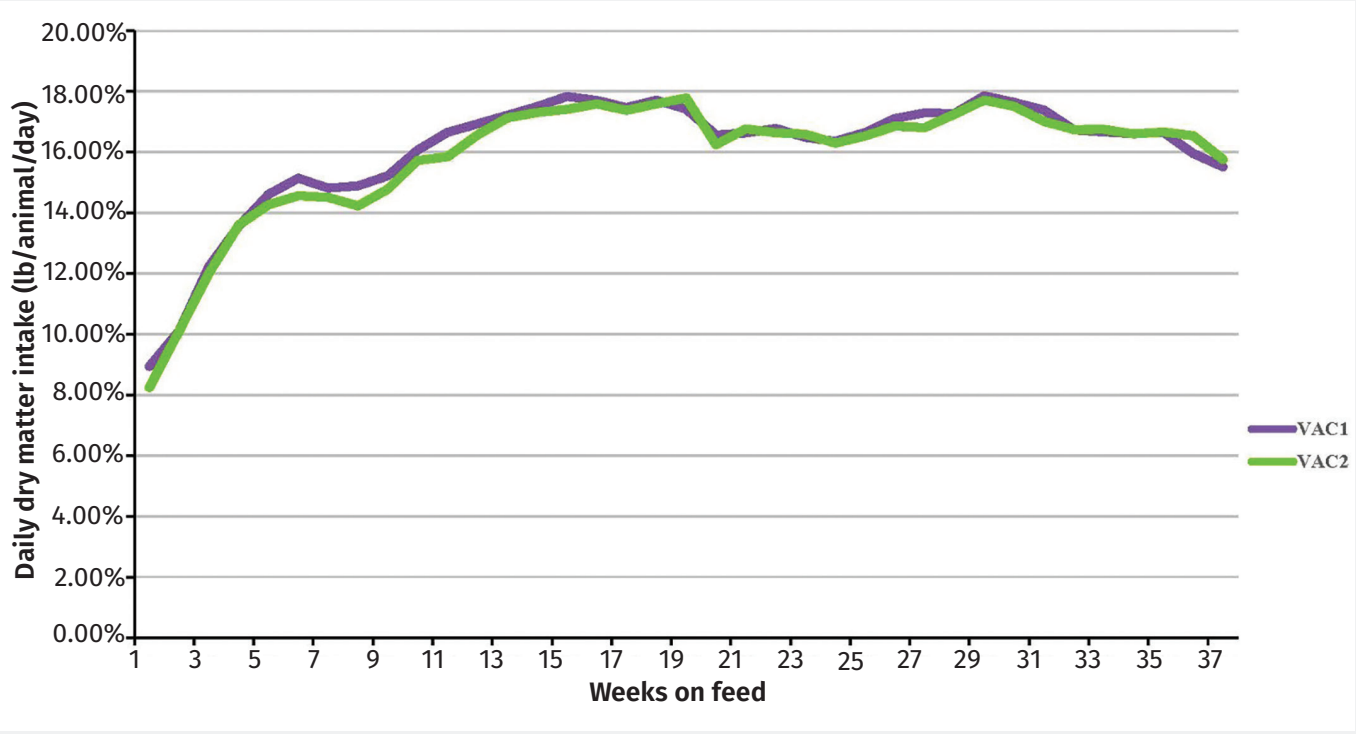
Table 4: Baseline and ancillary production data summary from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.

	Experimental group			
Production variable	**VAC1**	**VAC2**	**Standard error**	***P* - value**
Allocation weight (lb)	582.8	583.3	± 5.4	0.838
Allocation hip height (in)	50.4	50.4	± 0.3	0.679
Slaughter weight (lb)	1233.9	1234.8	± 7.7	0.915
Weight gain (lb)	651.0	651.4	± 6.9	0.954
Carcass weight (lb)	778.6	781.2	± 5.7	0.623
Dressing percentage (%)	63.20	63.26	± 0.14	0.660
Days on feed (day)	256.3	255.7	± 3.3	0.700
Daily dry matter Intake (lb/animal/day)	15.96	15.74	± 0.15	0.234

All animals were allocated on arrival at the feedlot. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus-*Mannheimia haemolytica-Pasteurella multocida* vaccine at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus vaccine with a *Mannheimia haemolytica* toxoid at a dose of 2.0 mL per animal once at allocation.

Data were analyzed using the GLIMMIX procedure of SAS® (Version 9.4, SAS Institute Inc, Cary, NC) with the model containing the fixed effect of experimental group and the random effect of replicate.

Figure 3: Daily dry matter intake by week on feed from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.



All animals were allocated on arrival at the feedlot. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus-*Mannheimia haemolytica-Pasteurella multocida* vaccine at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus vaccine with a *Mannheimia haemolytica* toxoid at a dose of 2.0 mL per animal once at allocation.

Table 5: Feedlot performance data summary from a study comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.

	Experimental group			
Feedlot performance variable	**VAC1**	**VAC2**	**Standard error**	***P* - value**
ADG (lb/day)				
LWB	2.52	2.53	± 0.02	0.693
CWB	2.54	2.55	± 0.02	0.510
DM:G				
LWB	6.32	6.22	± 0.05	0.071
CWB	6.29	6.18	± 0.05	0.059

All animals were allocated on arrival at the feedlot. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus-*Mannheimia haemolytica-Pasteurella multocida* vaccine at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus vaccine with a *Mannheimia haemolytica* toxoid at a dose of 2.0 mL per animal once at allocation.

Data were analyzed using the GLIMMIX procedure of SAS® (Version 9.4, SAS Institute Inc, Cary, NC) with the model containing the fixed effect of experimental group and the random effect of replicate. The models for average daily gain on a live weight and carcass weight basis included Allocation Weight as a covariate.

ADG = average daily gain, CWB = carcass weight basis, DM:G = dry matter intake to gain ratio, LWB = live weight basis.

Table 6: Carcass characteristic data summary from a comparing 2 multivalent modified live combination viral and bacterial vaccines in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease.

	Experimental group			
Carcass characteristic variable	**VAC1**	**VAC2**	**Standard error**	***P* - value**
Yield grades				
USDA 1 (%)	4.61	5.95	± 0.43	0.065
USDA 2 (%)	24.04	22.75	± 2.21	0.196
USDA 3 (%)	51.32	51.20	± 1.48	0.954
USDA 4 (%)	16.71	15.91	± 1.27	0.267
USDA 5 (%)	3.33	4.18	± 0.81	0.473
Quality grades				
USDA Prime (%)	10.03	9.97	± 0.93	0.967
USDA Choice (%)	70.43	69.43	± 1.17	0.561
USDA Select (%)	17.54	18.07	± 0.77	0.327
Standard (%)	0.32	0.54	± 0.16	0.337
Commercial (%)	0.54	0.89	± 0.36	0.385
Dark Cutter (%)	0.39	0.53	± 0.15	0.502
Utility (%)	0.76	0.56	± 0.27	0.203

All animals were allocated on arrival at the feedlot. Animals in the VAC1 group (6 multi-pen lots; 3,001 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus-*Mannheimia haemolytica-Pasteurella multocida* vaccine at a dose of 2.0 mL per animal once at allocation. Animals in the VAC2 group (6 multi-pen lots; 3,005 animals) received a subcutaneous injection of a bovine rhinotracheitis-virus diarrhea-parainfluenza 3-respiratory syncytial virus vaccine with a *Mannheimia haemolytica* toxoid at a dose of 2.0 mL per animal once at allocation.

Data were analyzed using the GLIMMIX procedure of SAS® (Version 9.4, SAS Institute Inc., Cary, NC) with the model containing the fixed effect of experimental group and the random effect of replicate.

Carcass data were unavailable for 1 shipment of animals from both experimental groups in replicate 6 (116 animals in the VAC1 group and 115 animals in the VAC2 group).

USDA = United States Department of Agriculture.

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Conflicts of interest

One of the co-authors is employed by Merck Animal Health, Intervet Inc., which provided funding for this study. The other co-authors declare no conflicts of interest.

Author contributions

BDH, TP, LKB and CWB were involved in the conception and design of the study. BDH, CGM, TP, SJH and CWB were involved acquisition of study data. BDH, CAM, CGM, TP, SJH and CWB were involved in analysis and interpretation of study data. All authors were involved in the manuscript drafting and/or revising process. All authors have approved the final version of this manuscript for publication.

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