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Evaluation of outcomes in beef cattle comparing preventive health protocols utilizing viral respiratory vaccines

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Abstract

Vaccination to reduce the occurrence of bovine respiratory disease is a commonly performed preventive health measure employed by veterinarians and beef cattle producers. Despite its widespread acceptance, evidence relating health and performance outcomes of receiving and feedlot cattle to vaccination for viral components of the bovine respiratory disease complex remains to be completely established. PubMed, CAB Abstracts, and *The Bovine Practitioner* were searched for peer-reviewed journal articles reporting field trials of viral respiratory vaccines utilizing naturally occurring disease models published in English between 1982 and 2012. Antigens of interest for this systematic review included bovine herpesvirus-1, parainfluenzavirus type 3, bovine viral diarrhea virus types 1 and 2, bovine respiratory syncytial virus, and bovine coronavirus. Search results were also reviewed for manuscripts reporting the effects of timing on viral respiratory vaccine efficacy in receiving and feedlot cattle. Studies were included in this review only if they reported clinically relevant outcomes, which were defined as morbidity, mortality, rates of chronic illness, lung lesions identified at necropsy or harvest, and performance parameters including average daily gain and feed-to-gain ratios.

Key words: bovine respiratory disease, virus, vaccines, vaccination

Résumé

L'utilisation de la vaccination afin de réduire l'ampleur des maladies respiratoires bovines est une mesure de santé préventive employée par les vétérinaires et les producteurs de bovins de boucherie. Malgré sa grande acceptation, il reste toujours difficile d'établir un lien entre la santé et la performance des bovins à leur entrée ou pendant leur séjour dans les parcs d'engraissement et la vaccination avec des composés viraux associés au complexe respiratoire bovin. Une revue de la littérature en langue anglaise a été menée en consultant *PubMed*, *Cab Abstracts* et *The Bovine Practitioner* pour trouver des publications avec comité de lecture parue entre 1982 et 2012 qui rapportaient des essais sur le terrain de vaccins viraux respiratoires avec des modèles de maladies qui surviennent naturellement. Les antigènes d'intérêt dans cette revue incluaient l'herpès-virus bovin 1, le virus parainfluenza 3 bovin, les virus de la diarrhée virale bovine de type 1 et 2, le virus respiratoire syncytial bovin et le coronavirus bovin. Les résultats de cette recherche ont aussi été retenus si les articles rapportaient l'effet du moment de la vaccination virale respiratoire sur son efficacité chez les bovins à leur entrée et pendant l'engraissement dans les parcs. Les études n'étaient incluses que si elles rapportaient des déterminants cliniques pertinents, telles que la morbidité, le taux de mortalité, le taux de maladies chroniques, les lésions pulmonaires identifiées à la nécropsie ou à

l'abattage, et des paramètres de performance comme le gain moyen quotidien et la conversion alimentaire.

Introduction

Bovine respiratory disease (BRD) involves complex interactions between viruses, bacteria, and stress. Veterinarians and producers recognize BRD as the most economically significant disease in the beef cattle industry from weaning through the finishing phase of production. Economic losses attributable to this disease include cost of medications to treat infections, reduced efficiency of facilities and usage of labor, death loss, and decreased performance on a live and carcass basis.[16] Additionally, consumers' concerns pertaining to animal welfare issues can be somewhat addressed by maximizing or improving the health of individual animals.

Recently, producers and veterinarians have placed more emphasis on programs of prevention rather than treatment of clinical disease. Veterinarians working with weaned calves, stocker, and feedlot cattle frequently recommend an initial processing protocol that includes a multivalent modified-live viral (MLV) respiratory vaccine.

A recent survey inquired about the health recommendations of 23 veterinarians responsible for the care of 11,295,000 fed cattle annually.[49] All respondents advised administering a viral respiratory vaccine containing bovine herpesvirus type 1 (BHV-1) and bovine viral diarrhea virus (BVDV) types 1 and 2 to cattle deemed at high-risk for developing BRD. In the survey, 15 of the 23 respondents recommended including a bovine respiratory syncytial virus (BRSV) component in the vaccine, while 14 recommended the inclusion of parainfluenzavirus type 3 (PI3V). The survey, however, did not discern whether the viral vaccines recommended were MLV or killed.[49]

In 1997, an extensive review was performed evaluating bacterial and viral respiratory vaccine field trials in feedlot cattle.[35] The authors reviewed published studies evaluating vaccines including BHV-1, PI3V, BVDV types 1 and 2, BRSV, and bovine coronavirus (BCoV) antigens. Studies were evaluated for scientific validity and clinically relevant outcomes; these included morbidity, mortality, and rates of chronic illness as well as growth performance measurements. Viral respiratory vaccine efficacy was found to be equivocal, ranging from mostly neutral to positive. The authors were unable to identify reliable field trials for PI3V, BVDV, and BCoV vaccines at the time of their review.[35]

More recently, an evidence-based review of bacterial vaccine efficacy in feedlot cattle was conducted.[24] This study did not rely on field trials alone, but rather on a hierarchy of evidence that included randomized controlled field trials, challenge model studies, and naturally occurring disease studies with dairy or beef calf subjects. Twenty-two trials utilizing a naturally occurring disease model in receiving or feedlot cattle were included in the review. Findings of 18 trials indicated a significant reduction of morbidity risk in cattle vaccinated for *Mannheimia haemolytica* or a combination of *M. haemolytica* and *Pasteurella multocida*, but no such reduction in mortality risk. In another study, cattle vaccinated with *M. haemolytica* and *Histophilus somni* antigens experienced a statistically significant ($P<0.05$) reduction in morbidity; no deaths occurred in the vaccinates or controls.[52] In the remaining 3 trials reviewed, cattle vaccinated with a *H. somni* antigen experienced no reduction in morbidity risk compared to unvaccinated controls.[1,29]

Considerations in the development of an effective evidence-based vaccination protocol include proper study design (randomized treatment assignment, a valid control group, blinding of health evaluators and treatment personnel, an externally relevant study population, controlling for confounding variables to the extent possible, power to detect differences should they exist, and proper application of statistical techniques),[19,24,35] the population to be vaccinated, previous vaccination history, specific pathogen characteristics, and projected cost-effectiveness. These criteria have been reviewed by others.[10,24,35,39,43]

In the absence of specific controlled field trials, practitioners must be able to assimilate the available information to develop a preventive health protocol for their clients that is medically sound and economically feasible.

Objective

The first objective of this study was to systematically review the published scientific literature for peer-reviewed journal articles concerning the use of vaccines against viral components of the BRD complex, specifically BHV-1, PI3V, BVDV types 1 and 2, BRSV, and BCoV. The second objective of this study was to review published data about the effects of timing of viral respiratory vaccine administration on clinical efficacy of the aforementioned viral antigens in receiving and/or feedlot cattle.

Materials and Methods

CAB Abstracts and PubMed were selected to search the peer-reviewed literature published between 1982 and 2012. This decision was informed by a recently published analysis of veterinary coverage in literature indexes and databases.[17] Additionally, because it is only selectively indexed by CAB Abstracts, the tables of contents of *The Bovine Practitioner* (1982-2012) were hand searched to assure inclusion of all pertinent articles.

Literature search. Bovine respiratory disease complex encompasses multiple disease etiologies, the descriptions of which vary in the literature. Search strategy, concepts, and synonyms were developed and adapted from

those used in previous systematic literature reviews of viral and/or bacterial vaccination of receiving and feedlot cattle.[24,35] Initial terms were modified after reviewing citations from test searches to identify the terminology, particularly synonyms, used in the peer-reviewed publications regarding this topic. Literature search criteria are outlined in Table 1. Terms that are obvious duplicative synonyms were included to facilitate running the same search in multiple databases on a variety of search platforms that use different proprietary search algorithms.

Transparent searches with replicable results using resources available to individuals not affiliated with institutions were important considerations. The investigators and veterinary librarian selected PubMed (1946-present)[38] and CAB Abstracts (via VetMed Resource, 1973-present)[9] for the electronic literature search. PubMed indexes the biomedical sciences broadly, includes the core peer-reviewed veterinary literature, and is freely accessible to the individual researcher. Additionally, PubMed includes, but is not limited to, the MEDLINE database.[32] CAB Abstracts is the most comprehensive index to the veterinary medical literature.[17] The VetMed Resource search platform has individual subscription options in addition to institutional subscriptions. Google Scholar was considered and dismissed because it changes frequently, searches are not transparent, and results are not replicable.

Searches were run initially in August 2012 and updated on January 23, 2013, to identify and include the most recently indexed articles with publication dates in 2012. No limits were placed on the searches or results. This is important, because there could be silent limits. For example, when searching PubMed any limits other than English Language will restrict results to MEDLINE records.

Inclusion and exclusion criteria. Search results from PubMed and CAB Abstracts were exported to a commercially available citation management software.[a] Duplicate citations were identified using the "Find Duplicates" command, hand verified, and duplicates removed. Records were sorted by date, and those falling outside the 1982 to 2012 publication date range were removed. CAB Abstracts records with reference type of Book, Book Section, Conference Proceeding, Report, and Thesis were removed, leaving only those designated Journal Article. All records from PubMed were retained. Records were sorted by author and hand searched for additional duplicates, which were removed. The citations were next sorted by the language field. Those identified with a language other than English were removed. Finally, citations were sorted by the journal/secondary title field. Those indexed in PubMed or included on the *Basic list of veterinary medical serials, third edition* were separated for further consideration in this study.[31,32,50] The remaining articles were evaluated by the main investigator as previously described and designated for inclusion or exclusion.[35]

Additional criteria. Titles and abstracts were reviewed by the main investigator for inclusion based on the following criteria: studies conducted outside the United States and Canada were considered for inclusion in this review if management reflected techniques similar to those used in North America and if they were published in English. Only studies using beef cattle at or near weaning through the finishing phase of production were included. Challenge studies, *in vitro* studies, and studies utilizing classes of cattle other than weaning-age, receiving, or feedlot beef cattle were excluded, so that only studies employing a naturally-occurring disease model in receiving and/or feedlot cattle remained. Studies in which treatment groups were administered different combinations of bacterin-toxoids in addition to different viral antigens were excluded. Finally, only manuscripts reporting clinically relevant outcomes were included.

Table 1. Literature search.

Search	Criteria
1	bos OR bovine OR cattle OR cow OR cows OR calf OR calves OR bull OR bulls OR steer OR steers OR heifer OR heifers
2	respiratory disease OR pneumonia OR pneumonic
3	vaccine OR vaccines OR vaccinate OR vaccinated OR vaccinates OR vaccination OR vaccinations
4	bovine viral diarrhea virus OR bovine viral diarrhea OR BVDV OR BVD OR bovine herpesvirus-1 OR bovine herpesvirus OR bovine herpes virus OR bovine herpesvirus type 1 OR bovine herpes virus type 1 OR BHV-1 OR BHV 1 OR BHV1 OR infectious bovine rhinotracheitis OR IBR OR bovine respiratory syncytial virus OR BRSV OR bovine parainfluenzavirus-3 OR bovine parainfluenza virus 3 OR bovine parainfluenza type 3 OR PI-3 OR PI3 OR PI3V OR bovine coronavirus OR BCV OR bovine respiratory coronavirus OR BRCV
5	Search 1 AND Search 2 AND Search 3 AND Search 4

For the purposes of this manuscript, clinically relevant outcomes were defined as morbidity, mortality, rates of chronic illness, lung lesions identified at necropsy or harvest, and performance parameters including average daily gain (ADG) and feed-to-gain (F:G) ratios.[34,35]

Search biases. Search biases include a lag between publication and indexing, meaning all articles published in 2012 may not have been indexed by January 2013 when the search was updated. Additionally, MEDLINE and CAB Abstracts are available through a variety of search platform interfaces. Proprietary search term mapping may result in different results when using a different search platform.

Variation in title and abstract terms and indexing may lead to relevant studies being excluded from literature searches. These need to be identified using other methods. In this case, the study authors are aware of 1 study[22] published within the last 5 years that search results did not include because nowhere in the PubMed or CAB Abstracts records and indexing was the required search string "respiratory disease OR pneumonia OR pneumonic" included. In the future, adding Science Citation Index or hand searching cited references of key papers could be helpful to negate this shortcoming.

The review that follows first reports studies that evaluated the role of the previously mentioned individual antigens of interest. Bovine herpesvirus-1 and PI3V combination vaccines and other multivalent vaccines are reviewed next. Finally, a review of manuscripts concerning the timing of administration of viral respiratory vaccines is reported. This review concludes with a discussion of the evidence related to comprehensive viral respiratory vaccination strategies for receiving and feedlot cattle.

Results

No published field trials using single-antigen PI3V vaccines in receiving or feedlot cattle were identified from the literature search. Vaccines containing multiple antigens, including PI3V, have been tested under field conditions and will be discussed in this review.[8,11,26,27,44]

Despite its widespread acceptance, no studies could be identified during the 30-year interval from January 1982 to August 2012 that specifically evaluated the effects of vaccination against BHV-1 alone. However, several multivalent vaccines containing BHV-1 antigens have been tested under field conditions.[7,8,11,26,27,44] One study compared a univalent vaccine for BHV-1 to a multivalent vaccine for BHV-1, PI3V, BVDV type 1, and BRSV.[44] Since the focus of the study was on the multivalent vaccine, it will be discussed in following paragraphs as outlined above with PI3V-containing vaccinations. Three additional studies evaluating the use of combined BHV-1/PI3V vaccines are also reviewed later.[11,26,27]

Results from BRSV vaccine field trials prior to 1997 did not yield conclusive evidence for incorporating this antigen in vaccination protocols.[35] One study consisting of 6,988 calves of multiple origins and management histories entering feedlots in the Pacific Northwest evaluated the effects of BRSV vaccination on BRD occurrence.[18] Cattle administered a vaccine containing BRSV had reduced rates of BRD occurrence, which varied based on calf origin. Auction market (multiple-origin, unknown health histories) derived calves receiving a BRSV antigen at feedlot arrival and again 14 days later experienced a BRD morbidity rate of 29.1% (174/597) compared to 45.2% (212/469) in those that did not receive a BRSV antigen ($P<0.00001$). BRD morbidity rates in freshly weaned and transported calves were 16.5% (228/1381) in non-vaccinates compared to 12.1% (161/1329) in vaccinates ($P<0.001$).[18] However, in the same study, administration of a vaccine containing a BRSV antigen made little or no difference in preconditioned and freshly weaned, non-transported calves (BRD morbidity rate: 3.4% [40/1171] in non-vaccinates compared to 2.2% [27/1201] in vaccinates, $P=0.11$). Researchers concluded that BRSV vaccination was associated with a reduction of treatment for clinical BRD from 13.9% (483/3486) in non-vaccinates to 10.5% (367/3502) in vaccinates ($P<0.00001$).[18]

More recently, a large field trial utilizing beef yearlings evaluated the effect of including a BRSV antigen in a multivalent viral respiratory vaccine. The study was conducted using 19,099 head with an average starting weight of 758 lb (344 kg) over a 2-year period in 3 Colorado feedlots.[25] Half of the cattle received a multivalent MLV respiratory vaccine containing BHV-1, PI3V, and BVDV (types not stated). The remaining study subjects were vaccinated with a MLV vaccine containing a BRSV component in addition to BHV-1, PI3V, and BVDV. The vaccine containing a BRSV antigen failed to produce a statistical reduction of either overall morbidity ($P=0.7969$) or respiratory morbidity ($P=0.5031$). However, total deaths and respiratory deaths were significantly lower in cattle that received the vaccine containing a BRSV antigen ($P=0.002$ and $P=0.006$, respectively). Cattle that served as test subjects in this study were primarily heavy yearlings procured from auction markets in the western and central United States.[25] Average daily gain (BRSV vaccinates: 3.37 lb [1.53 kg]; BRSV non-vaccinates: 3.36 lb [1.52 kg]) and F:G ratio (BRSV vaccinates: 6.23; BRSV non-vaccinates: 6.24) were similar ($P=0.8678$ and 0.8674, respectively).[25]

Another study also conducted in Colorado included a comparison of outcomes in auction market-derived feedlot cattle administered a pentavalent MLV vaccine containing BHV-1, PI3V, BVDV types 1 and 2, and BRSV, to cattle administered a trivalent vaccine containing BHV-1 and BVDV types 1 and 2.[8] Notably, the vaccines shared a common manufacturer and came from the same product line,

meaning they differed only in terms of antigen content. The addition of BRSV and PI3V antigens had no discernible effect on BRD morbidity (pentavalent vaccinates: 45.83%; trivalent vaccinates: 44.17%, P=0.09) or BRD mortality (pentavalent vaccinates: 3.95%; trivalent vaccinates: 4.31%, P=0.31). Average daily gain was similar between treatments whether calculated on a live-weight (pentavalent vaccinates: 2.76 lb [1.25 kg]; trivalent vaccinates: 2.74 lb [1.24 kg]) or carcass-weight (pentavalent vaccinates: 2.73 lb [1.24 kg]; trivalent vaccinates: 2.73 lb [1.24 kg]) basis (P=0.20 and 0.15, respectively). Feed-to-gain ratios for the two treatments were also equivocal on both a live-weight and carcass-weight basis (P=0.09 and 0.09, respectively).[8]

Researchers purchased 254 cattle from Ohio auction markets and transported them to a state-operated feedlot where all were vaccinated for BHV-1, PI3V, and BVDV in addition to *M. haemolytica*, *P. multocida*, and *H. somni*.[3] Test subjects were also randomly assigned to 3 treatment groups at the time of initial processing (day 0): vaccinated with a univalent killed BRSV vaccine on day 0 and again on day 14; vaccinated with a univalent MLV BRSV vaccine on days 0 and 14; or received no BRSV antigen (negative controls). Proportional numbers of cattle from each treatment group were commingled and penned together for a period of 40 to 60 days before being transported to 3 other feedlots and fed until harvest. Animals were monitored for clinical signs consistent with BRD and followed to harvest, at which time lungs were evaluated for pathology attributable to BRD. Mortality rate and the occurrence of lung lesions observed at harvest did not differ between treatments (P>0.05). Morbidity was reduced in cattle that received the MLV BRSV vaccine compared to negative controls (P value not reported). Finally, those animals receiving 2 doses of killed BRSV vaccine demonstrated a numerical advantage in ADG compared to negative controls (P=0.08).[3]

Another study was conducted to evaluate BRSV vaccination at pre-weaning, weaning or on arrival in both ranch and auction market calves entering feedlots and bull test stations in Alberta, Canada in the late 1980s.[51] Outcomes of interest for that study included BRD treatment rate and ADG. Measures of these criteria were equivocal for all classes and feeding situations except 2 groups. One group of calves vaccinated prior to weaning and subsequently shipped to a bull test station apparently benefited from vaccination (BRD treatment rate: 17.1% [13/76] in unvaccinated control calves compared to 4.8% [3/62] in BRSV-vaccinated calves, P<0.05). Additionally, a reduction in BRD treatment rate (from 21.4% [190/887] in unvaccinated control calves to 16.5% [137/829] in BRSV-vaccinated calves, P<0.05) was observed in a group of calves vaccinated at feedlot arrival. Results in other classes of cattle examined, including yearling cattle entering the feedlot, intact male calves entering a bull test station, and calves remaining at the research station where they were born, were equivocal.[51]

University researchers evaluated the effects of BRSV vaccination on morbidity, mortality, and ADG in calves purchased from a Kentucky buying agent and arriving at an Indiana feedlot over a 2-year period.[28] Calves receiving a BRSV vaccine at arrival had a numerically greater ADG of 2.03 lb (0.92 kg) (year 1) and 2.14 lb (0.97 kg) (year 2) compared to 1.81 lb (0.82 kg) (year 1) and 1.23 lb (0.56 kg) (year 2) in non-vaccinates, respectively (P value not reported). Feed-to-gain ratios in vaccinated steers were 4.48 (year 1) and 5.44 (year 2) compared to 4.75 (year 1) and 7.41 (year 2) in non-vaccinates, respectively, over the same 2-year period (P value not reported). In terms of BRD morbidity, treatment rates in non-vaccinated calves were 43.8% (21/48) (year 1) and 45.8% (22/48) (year 2) compared to 33.3% (16/48) (years 1 and 2) in BRSV-vaccinated calves. Mortality rate was not significantly different, with 1 vaccinated calf (1/48) dying in year 1 and 1 unvaccinated calf dying in year 2 (1/48) (P value not reported).[28]

A BRSV vaccine safety trial conducted in 1986 also reported morbidity, mortality, and ADG data for 422 steer calves (unspecified source and arrival weight) brought to a university research feedlot for a 28-day receiving period.[2] Outcomes of interest were equivocal for BRSV-vaccinated calves compared to negative controls (P>0.05) in terms of morbidity (29.1% [62/213], 32.5% [68/209], respectively), mortality (1.9% [4/213], 0.96% [2/209], respectively), and ADG (1.61 lb [0.73 kg], 1.52 lb [0.69 kg], respectively).[2]

Three additional BRSV vaccine studies were conducted during the 1980s. One reported a reduced morbidity rate in calves receiving a BRSV antigen (2.7% [26/961]) compared to negative controls (4.5% [42/935]) (P value not reported).[47] A second study evaluated the effects of vaccinating calves once or twice against BRSV, compared to negative controls.[23] Herds were monitored by serology to determine if they had been exposed to field strains of BRSV. In those herds determined to have encountered BRSV, morbidity rates were 26.9% (249/924), 20.5% (172/841), and 47.9% (559/1168) for calves vaccinated once, twice, and negative controls, respectively (P value not reported). Herds determined by serology to have remained unexposed to field strains of BRSV had less variable morbidity rates between treatments (once vaccinated: 4.5% [23/511], twice vaccinated: 1.9% [10/517], negative controls: 3.7% [20/539]; P value not reported).[23] Similarly, a Nebraska field trial of calves vaccinated at pre-weaning reported on the effects of administering a BRSV antigen once or twice, compared to negative controls.[4] Morbidity in calves vaccinated once (27.5% [230/837]) or twice (20.9% [169/810]) was less than negative controls (48.2% [397/823]) (P value not reported).[4]

Bovine coronavirus infection manifests as either respiratory (BRCoV) or enteric (BECoV) disease syndromes.

Whether these syndromes are attributable to a single disease etiology or to 2 closely related viruses remains an area of active research.[5,15] Although the focus of this review was on respiratory viral pathogens, our search revealed no field trials related specifically to vaccination for BRCoV. However, a field trial with an intranasal MLV vaccine containing BECoV and bovine rotavirus antigens administered at entry was associated with a reduction of BRD in 414 high-risk heifer calves purchased in small groups from multiple auction markets in the southeastern United States (P=0.008).[36] Replicates were randomized, assigned to treatment and control groups, and separated for 17 to 99 days following vaccination. Mortality during the separation period was not significantly affected by vaccination (0.96% [2/208] in vaccinates compared to 2.9% [6/206] in controls, P=0.17).[36]

Prior to 1997, no published field trials were available to evaluate the use of a single BVDV antigen vaccine to reduce BRD.[35] Since that time, the veterinary and research community has increased its attention on BVDV and its associated health and economic impacts, specifically its role in the BRD complex. Despite a vast increase in BVDV research, the literature remains essentially devoid of univalent BVDV vaccine field trials that measure clinically relevant outcomes. Rather, BVDV vaccine studies conducted to date have primarily been designed as experimental challenges[6,20,21,33,56] and have typically measured outcomes that include antibody titers,[13,14,55,56] identification of persistently infected (PI) cattle through immunohistochemistry,[14] leukopenia,[55,56] rectal temperature,[55,56] and viremia.[14,55] Vaccine field trials with outcomes including morbidity, mortality, ADG, and F:G ratio (with an acceptable case definition) are scarce.[19,34]

One study evaluated the effects of varying degrees of exposure of 3 groups of freshly weaned feedlot heifers to a known PI BVDV calf.[12] All heifers were procured through the same preconditioning sale. Eligibility for this preconditioning sale required 1 dose of multivalent MLV respiratory vaccine containing BHV-1, PI3V, BRSV, and either MLV or killed BVDV antigens. Additionally, all were administered metaphylactic antimicrobials and vaccinated with a pentavalent MLV respiratory vaccine containing BVDV antigens at initial feedlot processing and again at 28 days on feed (DOF) with a different pentavalent MLV vaccine. Following initial processing, the groups were either housed with a PI calf for 60 hours (at which time the PI calf was removed), remained housed with a PI calf for the entire study (215 days), or served as unexposed controls. Furthermore, spatial arrangement was evaluated to determine the effects of a PI animal on animals in adjacent pens. Exposure to a PI calf made no difference in ADG ($P \geq 0.36$), nor did direct exposure to a PI calf have an effect on F:G ratio ($P \geq 0.19$) when evaluated over the duration of the feeding period. Additionally, there was no observed difference ($P \geq 0.24$) in the number of cattle with active lung lesions at slaughter, regardless of whether they had been directly exposed or housed adjacent to a PI calf for any period of time. The authors suggested that prior vaccination against BVDV and metaphylaxis allowed PI-exposed cattle to perform at the same level as those that remained unexposed, with no change in their health status.[12]

Two BVDV vaccine field trials published in 2005 and 2006 utilized calves known to be PI with BVDV 1b noncytopathic (NCP) and BVDV 2a NCP, respectively, as a simulated natural source of infection.[13,14] Infection status was defined as detection by antigen-capture ELISA (ACE),[14] IHC,[14] viral isolation,[13,14] and changes in serologic titers as determined by virus neutralization.[13,14] Lung tissue from calves that died in the 2005 study was evaluated for histopathology and tested for both bacterial and viral pathogens;[13] however, no additional clinically relevant data was reported from either of these studies. The role of PI calves as potent sources of natural BVDV infections in feedlot cattle was supported by these studies.[13,14] A MLV vaccine that included BVDV1a and BVDV2a antigens administered 30 and 17 days prior to exposure to calves PI with BVDV2a was shown to be efficacious in preventing viremia;[14] however, calves vaccinated with BVDV1a and BVDV2a antigens 3 days prior to exposure to calves PI with BVDV1b were not protected against BVDV1b infection, as determined by changes in serologic titer by virus neutralization.[13]

Vaccines formulated for oral or intranasal (IN) administration are of interest due to their perceived ability to induce local IgA-mediated immunity at mucosal surfaces. One study conducted on 303 lightweight feedlot cattle compared the effects of oral and intramuscular (IM) administration of BVDV vaccine.[30] No difference was detected in morbidity (oral: 20.8% [20/96], IM: 27.1% [52/192]; P value not reported). Average daily gain was similar for the IM vaccinated (2.40 lb [1.09 kg]) and orally vaccinated (2.47 lb [1.12 kg]) groups (P value not reported). Although mortality rate was numerically greater in the group receiving the IM vaccine (2.1% [4/192]) compared to the group receiving the oral vaccine (0.0% [0/96]), no statistical analysis was reported.[30]

Commercially prepared vaccines containing BHV-1 and PI3V antigens have been examined under field conditions. Two studies with BHV-1 and PI3V antigens formulated for IN administration were conducted by Canadian researchers to evaluate vaccine efficacy.[26,27] Initial findings appeared to demonstrate a marginal benefit associated with a BHV-1/PI3V vaccine containing a temperature-sensitive (TS) strain of BHV-1, but not with a porcine tissue culture (PTC) origin BHV-1/PI3V vaccine.[26] Calves from 16 different farms were either vaccinated with 1 of the 2 intranasal vaccines or served as unvaccinated controls. Following transport and

placement in feedlots, 10.0% (3/30) of calves vaccinated with the TS vaccine were treated for respiratory disease, whereas 35.1% (27/77) of calves vaccinated with the PTC vaccine and 34.0% (17/50) of unvaccinated calves were treated for respiratory disease. Even though this difference was significant ($P<0.05$), after the researchers took into account the effect of source the conclusion was that the calves that apparently benefited from the TS vaccine originated from farms where the morbidity rate in unvaccinated controls was also lower. A follow-up study confirmed that negative controls, calves receiving the TS vaccine, and calves receiving the PTC vaccine experienced similar respiratory morbidity when source and feedlot were controlled for ($P>0.05$).[27]

More recently, research conducted in New Mexico over a 28-day receiving period evaluated the effects of an IN MLV BHV-1/PI3V or IM MLV BHV-1/PI3V vaccine compared to an unvaccinated control group.[11] Morbidity rates were not significantly different between the treatment groups (IN: 38.2%, IM: 41.8%, and Control: 40.8%; $P>0.10$). Calves receiving the IN vaccine had an ADG of 2.37 lb (1.08 kg), which was greater ($P<0.05$) than calves receiving the IM vaccine (2.00 lb [0.91 kg]), but did not differ ($P>0.10$) from the controls (2.20 lb [1.00 kg]). Additionally, cattle receiving the IM vaccine were less efficient (F:G 5.11) compared to those receiving the IN vaccine (4.60) ($P<0.05$).[11]

A number of field trials have been conducted to compare the effects of various combinations of viral antigens without the inclusion of a negative control group. This presents a significant challenge to the practitioner who wishes to compare results within and between studies. In theory, the absence of a negative control group renders this task virtually impossible. In practice, the question for most veterinarians is not whether they will vaccinate cattle against the common viral respiratory antigens associated with BRD, but which ones and in what combinations? On that basis, field trials falling in this category are reviewed.

Vaccination against BHV-1 is a long-standing and commonly performed preventive health measure.[34] One study evaluated the effects of vaccinating high-risk, auction market-derived calves arriving at a feedlot with a univalent vaccine (BHV-1) compared to a multivalent vaccine containing BHV-1, PI3V, BVDV type 1, and BRSV.[44] Each treatment group was revaccinated with its respective viral antigen(s) at approximately 70 DOF. The morbidity rate for the univalent treatment was 21.7% (561/2582) compared to 16.8% (433/2581) for the multivalent treatment ($P<0.05$). Average daily gain for the univalent treatment was 3.11 lb (1.41 kg) compared to 3.15 lb (1.43 kg) for the multivalent treatment ($P < 0.05$). However, F:G (5.77 for both treatments), BRD mortality rate (univalent: 2.1% [53/2582]; multivalent: 1.7% [44/2581]), and overall mortality rate (univalent: 3.3% [84/2582]; multivalent: 2.6% [68/2581]) were unaffected ($P=0.963$, 0.475, and 0.321, respectively).[44]

Timing and route of administration of MLV respiratory vaccines were evaluated in 1 New Mexico feedlot study.[11] Freshly received, high-risk steer and bull calves procured through a buying agent in southwestern Arkansas were assigned to 4 different vaccine groups and followed for a 28-day receiving period: 1) unvaccinated negative control (Control); 2) no vaccine on day 0 and BHV-1, PI3V, BVDV, and BRSV administered IM on day 7 (CON/IM); 3) BHV-1 and PI3V administered IN on day 0 and BHV-1, PI3V, BVDV, and BRSV administered IM on day 7 (IN/IM); and 4) BHV-1, PI3V, BVDV, and BRSV administered IM on days 0 and 7 (IM/IM). Morbidity rate and ADG did not differ ($P>0.10$). However, negative control cattle were less efficient (F:G ratio 5.23, $P=0.10$) compared to CON/IM (4.63), IN/IM (4.38), and IM/IM treatments (4.15).[11]

Another study conducted with steer calves procured from multiple auction markets in the central and western United States and sent to a Colorado feedlot evaluated 2 commercially available pentavalent vaccines containing BHV-1, PI3V, BVDV types 1 and 2, and BRSV, compared to a trivalent vaccine containing BHV-1 and BVDV types 1 and 2.[8] Overall and BRD mortality rates did not differ between treatments ($P=0.19$ and 0.31, respectively). Likewise, ADG did not differ between treatments ($P=0.20$). Cattle administered 1 of the pentavalent vaccines demonstrated a more efficient F:G ratio on a carcass-weight basis (5.56) compared to cattle receiving the other pentavalent vaccine (5.74) or the trivalent vaccine (5.79), but this difference was not statistically significant ($P=0.09$). The same pentavalent vaccine also had a numerical advantage in terms of BRD morbidity rate (40.8%), compared to the other pentavalent vaccine (45.8%; $P=0.09$).[8]

Two commercially manufactured pentavalent vaccines containing BHV-1, PI3V, BVDV types 1 and 2, and BRSV antigens were compared in a large pen study utilizing high-risk cattle in central Nebraska.[54] Study animals receiving 1 of the vaccines experienced reduced respiratory morbidity (5.5% [89/1632]) compared to animals receiving the other vaccine (7.8% [127/1632]) ($P=0.016$). The same group demonstrated an advantage in F:G ratio on a live-weight basis (5.93 compared to 5.97, $P=0.046$). Overall mortality, BRD mortality, and ADG did not differ between treatments ($P>0.05$).[54]

Colorado researchers conducted an additional study to compare 3 different commercially available trivalent vaccines, each containing BHV-1 and BVDV types 1 and 2.[7] Overall mortality, BRD mortality, and BRD morbidity did not differ between cattle receiving the different vaccines ($P=0.45$, 0.36, 0.15, respectively). Likewise, ADG and F:G were not different ($P=0.91$ and 0.79, respectively).[7]

Protective immunity requires time following administration of a vaccine and depends on the host's immune response. Stressors such as weaning, castration, dehorning, transport, auction market environments, weather, and dehydration can all compromise an animal's ability to develop immunity and mount a protective immune response.[48] The traditional marketing structure of the North American beef industry, which includes cow-calf, stocker, backgrounder, and finishing phases (often with 1 or more passages through an auction market or buying facility), presents a major challenge to veterinarians designing vaccination protocols for receiving and feedlot cattle. Owners and managers must be aware of these challenges and work with practitioners to implement an effective preventive health program. Over the last 5 years, academia and industry have invested significant amounts of time, effort, and money investigating the effects of viral respiratory vaccination timing, revaccination, and pre-weaning management on the health, performance, and well-being of receiving and feedlot cattle.

Administration of viral respiratory vaccines to young calves prior to weaning has been debated due to the perceived potential for maternal antibody interference with the development of adaptive immunity and to the potential shedding of the virus from a MLV vaccine to a pregnant dam, which might result in abortion.

To evaluate the effects of timing of pre-weaning viral vaccination on subsequent feedlot performance, researchers compared beef calves receiving a pentavalent MLV vaccine containing BHV-1, PI3V, BVDV types 1 and 2, and BRSV antigens at 3 different time points: vaccination at approximately 67 and 190 days of age (branding + weaning vaccinations), vaccination at approximately 167 and 190 days of age (pre-wean + weaning vaccinations), and unvaccinated negative controls.[22] Differences in feedlot morbidity rate were not detected between treatments (23.5% [28/119], 25.8% [31/120], and 24.6% [30/122], respectively). However, unvaccinated cattle experienced an increased ($P \leq 0.05$) mortality rate at the feedlot (3.3% [4/122]) compared to calves vaccinated at either 67 and 190 days (0% [0/119]), or 167 and 190 days (0.83% [1/120]). Mean ADG was not different ($P > 0.05$) between treatments (3.00 lb/day [1.36 kg/day], 2.96 lb/day [1.35 kg/day], and 2.92 lb/day [1.33 kg/day], respectively). Likewise, F:G ratio was unaffected ($P > 0.05$) by treatment (6.00, 6.01, 6.01, respectively).[22]

A similarly-designed study of 253 calves from university research herds in Arkansas compared the effects of administering a pentavalent MLV respiratory vaccine containing a *M. haemolytica* toxoid to calves at either 62 and 209 days of age or 188 and 209 days of age.[37] Observations extended 84 days past weaning for a total of 231 days, during which time ADG did not differ between vaccination treatments (1.44 lb/day [0.65 kg/day] for both groups, $P \geq 0.84$). Calves did not develop clinical signs consistent with BRD in either treatment group.[37]

One study evaluated the effects of MLV respiratory vaccination timing over a 42-day receiving period in auction market-derived cattle.[40] Each treatment received 2 doses of a commercially available pentavalent MLV respiratory vaccine 14 days apart; the only difference between the groups was whether vaccinations occurred at day 0 (the day after arrival) and day 14, or day 14 and day 28. Total mortality (2.3% in cattle first vaccinated the day after arrival compared to 0.8% in cattle receiving a delayed vaccination) and BRD morbidity (71.5% in cattle first vaccinated the day following arrival compared to 63.5% in cattle receiving a delayed vaccination) were unaffected by vaccination timing ($P=0.16$ and 0.12, respectively), while ADG over the 42-day period was improved in cattle receiving delayed MLV vaccination (1.65 lb [0.75 kg] compared to 1.43 lb [0.65 kg], $P=0.05$).[40]

A follow-up study was conducted to evaluate the timing of MLV respiratory vaccination and 7-way clostridial vaccination over a 56-day receiving period.[41] Mortality was unaffected by MLV vaccination timing ($P=0.70$), as was morbidity ($P=0.23$). Vaccination timing in this study did not have an effect on ADG ($P=0.34$).[41]

More recently, a backgrounding study evaluated the effect of exposing preconditioned ranch calves, which had been vaccinated twice prior to weaning with a pentavalent MLV respiratory vaccine, to BVDV-PI calves.[42] At the same time, auction market multiple-origin calves of a similar weight and class were purchased, brought to the backgrounding unit, and allowed a 1- to 3-day rest period before receiving the same vaccines the ranch calves had received on day 0 and day 14. Preconditioned calves experienced significantly less BRD morbidity than did auction market-origin calves ($P<0.001$). Exposure to PI calves, however, had no discernable effect on BRD morbidity ($P=0.50$). Similar results were observed with respect to ADG over the 42-day receiving period.[42]

An industry-conducted trial from 2008 found no reduction in overall mortality in cattle receiving 2 different preconditioning protocols that included viral respiratory vaccination, compared to unweaned calves with an unknown health history (0.30% [2/667] and 1.0% [2/292] in cattle with a history of viral respiratory vaccination and preconditioning compared to 1.2% [6/502] in unweaned calves with an unknown health history, $P>0.14$).[45] Pen F:G for calves with an unknown health history was 5.16, which was similar ($P=0.579$) to the F:G of preconditioned cattle (5.16 and 5.30). However, ADG of calves with an unknown health history (3.53 lb/day [1.60 kg/day]) was significantly ($P<0.05$) less than preconditioned calves (3.96 lb/day [1.80 kg] and 3.87 lb/day [1.76 kg/day]). Calves with no known vaccination history had significantly greater respiratory morbidity rates than either of the 2 preconditioned groups (42.6% [214/502]

respiratory morbidity in calves with an unknown health history compared to 15.4% [103/667] and 15.4% [45/292] in calves with a known viral respiratory vaccination and preconditioning history, P=0.0079).[45]

Traditional practice in many receiving and feedlot programs is to revaccinate cattle with viral antigens sometime after entry, with the intention of stimulating an anamnestic response in some animals and an initial immune response in those not capable of adequately responding at initial processing. There is, however, mounting evidence to support the adoption of single-vaccination programs administered at initial processing.

This management technique was evaluated in a 2009 study of high-risk, auction market-derived cattle that were subsequently followed through the finishing phase to harvest.[46] All cattle were vaccinated at the beginning of the preconditioning phase with a pentavalent MLV respiratory vaccine, with half of the calves being revaccinated 11 days later. BRD morbidity during the preconditioning phase was significantly reduced in once-vaccinated cattle (36.3%) compared to revaccinated cattle (44.5%) (P=0.04), but mortality and live performance measures remained unaffected. It should be noted that the average days to treatment for clinical BRD occurred before the second dose of MLV vaccine. At feedlot entry, each preconditioning treatment group was again divided in half to generate a 2x2 factorial study design in which half of the cattle from each preconditioning treatment were vaccinated at feedlot processing and half were not. Interestingly, cattle that were revaccinated during preconditioning demonstrated an improved F:G ratio during the finishing phase, regardless of vaccination treatment received at feedlot processing (P=0.02), which may have economic benefits for the owners.[46]

A 6-year retrospective study that included 1,354 preconditioned calves evaluated the health effects of timing of revaccination and timing of the last viral vaccination prior to arrival at a backgrounding facility.[53] Researchers determined that in preconditioned cattle, revaccination less than 14 days after initial vaccination was associated with increased BRD morbidity (29.8% [20/67]) compared to calves revaccinated either between 14 and 27 days following initial vaccination (10.6% [78/734]; P=0.03) or 28 days or more following initial vaccination (12.3% [41/331]; P=0.08). However, cattle that received the second vaccination 14 days or less prior to arrival at the backgrounding facility were at no greater risk of developing BRD (13.9% [17/121]) than were cattle that received a booster vaccine greater than 14 days prior to arrival (12.2% [125/1024]) (P>0.10).[53]

Discussion

Animal health protocols for modern beef production systems may focus on either preventing disease or treating disease once clinical signs manifest. Along with other management techniques, vaccination is accepted as an effective means of developing protective immunity to viral respiratory pathogens that predispose cattle to BRD. Effective vaccination protocols rely in part on evidence-based selection of antigens, proper timing of administration, and the immunocompetence of the animals to be vaccinated.

Antigens commonly included in viral respiratory vaccines include BHV-1, PI3V, BVDV types 1 and 2, and BRSV. Although BHV-1 is widely considered to be the most important viral respiratory antigen for receiving and feedlot cattle, the authors were unable to identify any randomized controlled field trial published between 1982 and 2012 comparing clinical outcomes of cattle receiving a univalent BHV-1 antigen vaccine with an unvaccinated control group. Likewise, no such studies could be located solely evaluating the efficacy of PI3V vaccines in receiving or feedlot cattle. Recently, increased emphasis has been placed on the role of BVDV in beef cattle production systems. At present, there is no published field trial data evaluating clinically relevant outcomes that lends definitive support to the use of BVDV vaccines in receiving or feedlot cattle in peer-reviewed literature. Studies employing known BVDV-PI calves to simulate natural exposure indicate that PI animals are potent shedders of the virus. While challenge studies would seem to indicate value associated with vaccination of receiving and/or feedlot cattle with BVDV antigens, additional randomized controlled and blinded field trials with negative control groups are warranted.

The benefit of BRSV vaccines in populations of interest for this review remains to be fully determined. The age of cattle may play a role, with calves appearing to derive a greater benefit compared to yearlings. Several large studies have utilized mostly yearling cattle; results in younger, high-risk calves may be different.

Still less is known regarding the potential role for BCoV vaccines in receiving and/or feedlot cattle. Ongoing research into the nature and pathogenesis of this virus may provide further understanding on the future use of BCoV vaccine, and how best to incorporate this antigen into a preventive health program. The only field trial conducted to date was able to demonstrate a reduction in BRD rates in a group of BECoV-vaccinated receiving-age heifers. The authors are unaware of any published randomized controlled field trials pertaining specifically to BCoV vaccination of feedlot cattle in the peer-reviewed literature.

Studies regarding the timing of viral respiratory vaccination are inherently difficult to compare. Frequently, these trials are part of a broader preconditioning study that introduces any number of confounding factors, including temporality, health and vaccination history on the farm of origin, method of marketing chosen, variable

BRD case definitions, and inconsistent starter rations after arrival at the backgrounding facility or feedyard. Furthermore, vaccination timing studies vary widely in terms of the length of observation. Indeed, this review includes studies ranging from 28 days post-arrival to the full duration of the finishing period.

Trials in which treatment groups are administered different combinations of bacterin-toxoids in addition to different viral antigens are difficult to interpret. One study included in the current review utilized a pentavalent MLV respiratory vaccine that also contained a *M. haemolytica* leukotoxoid. Because it focused on the effects of timing of viral respiratory vaccine administration rather than the viral antigens themselves, and because all calves received the same vaccine (only at different times), the *M. haemolytica* leukotoxoid was not considered an obstacle to interpretation. Vaccination timing studies included in this review generally indicate no significant difference in health outcomes, whether vaccinations are administered at arrival or delayed until a later date.

Conclusions

Although the veterinary profession's understanding of viral respiratory pathogens is growing and vaccine technology is improving, receiving and feedlot cattle continue to succumb to bovine respiratory disease. Increased efforts and resources must be directed to the investigation of viral respiratory antigens, vaccination timing, and management if the incidence of BRD in receiving and feedlot cattle is to be reduced while simultaneously meeting the demand of a growing world population for beef protein. Given the expense associated with purchasing and administering viral respiratory vaccines and the opportunity costs attributable to improperly designed or implemented vaccination protocols, further investigation of these antigens in large-scale randomized controlled field trials should be encouraged.

Endnote

[a]EndNote X6.0.1, Thomson Reuters, Carlsbad, CA

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