Systematic review of vaccine efficacy against *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in North American cattle

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Abstract

Bovine respiratory disease (BRD) continues to greatly affect beef, dairy, and veal production systems. Vaccination against the bacteria involved is common, yet questions remain regarding efficacy. The purpose of this review was to evaluate the evidence for effects of vaccinating United States or Canadian beef, dairy, or veal calves for *Mannheimia haemolytica*, *Pasteurella multocida*, or *Histophilus somni* on BRD-related morbidity, mortality, or postmortem lung lesions. Comprehensive searches were performed of MEDLINE, EMBASE, and CAB Abstracts via OVID. *The Bovine Practitioner* and references of relevant systematic reviews were searched by hand. Major commercial vaccine producers were queried for additional product information.

Peer-reviewed, published after 1979, full text available in English, performed in the US/Canada, control group included, sufficient evidence of randomization/blinding, and correct statistical methods were essential criteria for inclusion in the review. Five studies met the criteria. Of them, 1 investigated a *H. somni* and *M. haemolytica* vaccine in feeder calves, 1 studied *M. haemolytica* vaccination in feeder calves, 1 evaluated a different commercially available *M. haemolytica* vaccine and 1 experimental *M. haemolytica* vaccine in young Holstein calves, and 1 investigated multiple vaccines for *P. multocida* or *M. haemolytica* or combinations thereof in nursing beef calves. There are too few repeated studies on comparable populations to support further analysis of BRD bacterial vaccine efficacy in North American cattle.

Key words: bovine respiratory disease, vaccine, morbidity, mortality, lung lesions

Introduction

Important tools for minimizing incidence of bovine respiratory disease (BRD) include implementing low-stress weaning and handling strategies, limiting commingling, optimizing nutrition, and using effective vaccines. Which pathogens to vaccinate calves against, which product to use, and when or how frequently to do so are complex decisions that depend on many factors, including the population of cattle, the production system, and management practices in place.

Solid, repeatable research is required to make informed, evidence-based decisions from economic, disease mitigation, and animal welfare standpoints. Research has been carried out for decades focusing on vaccinating calves against the most common bacterial pathogens of BRD, *Mannheimia haemolytica*, *Pasteurella multocida,* and *Histophilus somni*. However, previous reviews[13,21] have found little evidence to support the use of vaccines against BRD bacteria in field settings and questions remain regarding the efficacy, utility, and importance of these vaccines in modern beef, dairy, and veal production systems.

One of the reviews exploring BRD-bacterial vaccine efficacy is nearly a decade old,[13] and 1 incorporated worldwide evidence, but only that pertaining to vaccinating beef calves at feedlot arrival.[21] A current systematic review of publicly available data is needed to critically evaluate and comprehensively summarize the recent literature for new evidence and to look for evidence in other populations of cattle. Therefore, we conducted a review of the current evidence for vaccination of US and Canadian beef, dairy, or veal calves for *M. haemolytica*, *P. multocida*, or *H. somni* on BRD-related morbidity, mortality, or lung lesions.

Methods

Information sources and methods

A comprehensive literature search was performed using 3 databases and hand searching. Initial searches were conducted on July 1, 2019. The searches were then peer-reviewed and updated several times during the project, most recently on November 24, 2020.

Searches were conducted in CAB Abstracts,[2] EMBASE,[7] and MEDLINE,[17] all via the OVID search platform. All indexes are available through a variety of search interfaces, for example MEDLINE is available through PubMed. OVID was chosen as the search interface for all searches because it allowed us to use adjacency. However, the searches were not conducted simultaneously on the OVID platform and no study registries were searched. Hand searches were also performed of the tables of contents of *The Bovine Practitioner*, 1980 to fall of 2020. Articles with titles that seemed relevant to bovine respiratory disease bacterial vaccines were saved for screening by title and abstract. Additionally, we searched the reference lists of 2 previously published review articles.[13,21] Major commercial vaccine manufacturers were contacted by RL to request any additional publicly available information beyond that published in the peer-reviewed literature.

Search strategies

The final search strategies used for each database are reported below and formatted to be copied, pasted, and run in each appropriate database per PRISMA-S guidelines.[27]

Searches were conducted with no limits specified in the databases. However, only articles published in 1980 or later were retained for further evaluation. No published search filters were used, and no search strategies from previously published literature reviews were adapted or reused. Each search was updated by rerunning in each database several times. Final searches were conducted in each database on November 24, 2020.

CAB Abstracts Search via the OVID search platform

((("bos".bt.) OR ("bovidae".bt.) OR ((cattle or cow or cows or bovine* or heifer* or bull*).ti,ab.) OR (cattle.od.) OR ((steer or steers or calf or calves).ti,ab.) OR (exp cattle/) OR (exp bovidae/) OR ((bos or bovidae).ti,ab.)) AND (((mannheimia adj1 haemolytica).mp.) OR ((pasteurella adj1 haemolytica).mp.) OR ((pasteurella adj1 multocida).mp.) OR ((histophilus adj1 somni).mp.) OR (exp mannheimia haemolytica/) OR (exp histophilus somni/) OR (exp pasteurella multocida/) OR ((mannheimia adj1 hemolytica).mp.) OR ((pasteurella adj1 hemolytica).mp.) OR ((pasturella adj1 haemolytica).mp.) OR ((pasturella adj1 hemolytica).mp.) OR ((pasturella adj1 multocida).mp.) OR ((hemophilus adj1 somnus).mp.)) AND (((pneumon* or (respiratory adj1 disease*)).ti,ab.) OR ("respiratory diseases".sh.) OR ((respiratory adj2 disease*).ti,ab.) OR (((shipping or undifferentiated) adj1 fever).ti,ab.) OR ((BRD or BRDC).ti,ab.) OR ((bovine adj1 respiratory adj1 disease*).ti,ab.) OR ((bovine adj1 respiratory adj1 disease* adj1 complex).ti,ab.) OR ((summer adj1 pneumon*).ti,ab.) OR ((enzootic adj1 pneumon*).ti,ab.) OR (pasteurellosis.mp.) OR (pasturellosis.mp.) OR (mannheimiosis.mp.) OR (pleuropneumon*.mp.) OR (bronchopneumon*.mp.) OR ((respiratory adj1 tract adj1 disease*).mp.)) AND ((vaccin*.ti,ab.) OR ("vaccination".sh.) OR ("vaccines".sh.) OR (immuni*.ti,ab.) OR (exp immunization/)))

EMBASE Search via the OVID search platform

(((exp domestic cattle/) OR ((cattle or cow or cows or bovine* or heifer* or bull*).ti,ab.) OR ((steer or steers or calf or calves).ti,ab.) OR ((bos or bovidae).ti,ab.) OR (exp cattle/)) AND (((exp mannheimia haemolytica/) OR (exp haemophilus somnus/) OR (exp pasteurella multocida/) OR ((mannheimia adj1 haemolytica).mp.) OR ((pasteurella adj1 haemolytica).mp.) OR ((pasteurella adj1 multocida).mp.) OR ((haemophilus adj1 somnus).mp.) OR ((histophilus adj1 somni).mp.)) OR ((mannheimia adj1 hemolytica).mp.) OR ((pasteurella adj1 hemolytica).mp.) OR ((pasturella adj1 hemolytica).mp.) OR ((pasturella adj1 haemolytica).mp.) OR ((hemophilus adj1 somnus).mp.))) AND ((exp respiratory tract disease/) OR ((pneumon* or (respiratory adj1 disease)).ti,ab.) OR ((respiratory adj2 disease*).ti,ab.) OR ((BRD or BRDC).ti,ab.) OR (((shipping or undifferentiated) adj1 fever).ti,ab.) OR ((summer adj1 pneumon*).ti,ab.) OR ((enzootic adj1 pneumon*).ti,ab.) OR (pasteurellosis.mp.) OR (pasturellosis.mp.) OR (mannheimiosis.mp.) OR (pleuropneumon*.mp.) OR (bronchopneumon*.mp.) OR ((respiratory adj1 tract adj1 disease).ti,ab.) OR ((bovine adj1 respiratory adj1 disease*).ti,ab.) OR ((bovine adj1 respiratory adj1 disease* adj1 complex).ti,ab.)) AND ((vaccin*.ti,ab.) OR (exp vaccines/) OR (immuni*.ti,ab.) OR (exp immunization/))

MEDLINE Search via the OVID search platform

(((exp cattle/) OR ((cattle or cow or cows or bovine* or heifer* or bull*).ti,ab.) OR ((steer or steers or calf or calves).ti,ab.) OR ((bos or bovidae).ti,ab.)) AND ((exp mannheimia haemolytica/) OR (exp haemophilus somnus/) OR (exp pasteurella multocida/) OR ((mannheimia adj1 haemolytica).mp.) OR ((pasteurella adj1 haemolytica).mp.) OR ((pasteurella adj1 multocida).mp.) OR ((haemophilus adj1 somnus).mp.) OR ((histophilus adj1 somni).mp.) OR ((mannheimia adj1 hemolytica).mp.) OR ((pasteurella adj1 hemolytica).mp.) OR ((pasturella adj1 hemolytica).mp.) OR ((pasturella adj1 haemolytica).mp.) OR ((hemophilus adj1 somnus).mp.)) AND ((exp bovine respiratory disease complex/) OR (exp respiratory tract disease/) OR ((pneumon* or (respiratory adj1 disease)).ti,ab.) OR ((respiratory adj2 disease*).ti,ab.) OR ((BRD or BRDC).ti,ab.) OR (((shipping or undifferentiated) adj1 fever).ti,ab.) OR ((summer adj1 pneumon*).ti,ab.) OR ((enzootic adj1 pneumon*).ti,ab.) OR (pasteurellosis.mp.) OR (pasturellosis.mp.) OR (mannheimiosis.mp.) OR (pleuropneumon*.mp.) OR (bronchopneumon*.mp.) OR ((respiratory adj1 tract adj1 disease).ti,ab.) OR ((bovine adj1

respiratory adj1 disease*).ti,ab.) OR ((bovine adj1 respiratory adj1 disease* adj1 complex).ti,ab.)) AND ((vaccin*.ti,ab.) OR (exp vaccines/) OR (immuni*.ti,ab.) OR (exp immunization/)))

Peer review

The original search strategy was written by Margaret Foster at Texas A&M University Libraries. The search was peer-reviewed by authors HM and SFC. Original search strategies were modified and finalized based on peer-review input.

Record management

Results for the final search were uploaded to Zotero[a] and duplicates removed. Items identified in the hand searches were compared with the search results, duplicates were removed, and the resulting unique articles were added to the screening process. Final results were exported for subsequent screening via titles and abstracts followed by full text review.

Eligibility criteria

To be eligible for inclusion in this review, studies had to meet the criteria present in Table 1. Studies were excluded if they did not meet the inclusion criteria. For example, if no randomization scheme or an allocation that was not completely or systematically random was described, the study was excluded. Additionally, if no mention was made regarding blinding of evaluators for subjective outcomes such as lung scores or BRD-related morbidity, then the paper was excluded. If the statistical methods included tests applied

Table 1. Inclusion criteria for systematic review of vaccine efficacy against important bacterial respiratory pathogens in North American cattle.

	Criteria
Type of literature	Peer-reviewed literature published 1980 to present representing original research
Language and format	English full text
Study location	United States or Canada
Study population	Calves in beef, dairy, or veal production systems
Intervention studied	Vaccination for *M. haemolytica*, *P. multocida*, *H. somni*, or any combination thereof
Outcomes evaluated	Lung lesions (any scoring methodology) BRD-related morbidity BRD-related mortality
Control group	Placebo or positive control
Methods requirements	Have an appropriate study design
	Show evidence of blinding related to subjective outcomes
	Show evidence of randomization (systematic or complete)
	Correctly apply and report statistical methods for the outcome, study design, and grouping of animals

to our outcomes of interest where the underlying assumptions were not met, then the paper was excluded. Conference proceedings were not considered eligible, as they did not provide sufficient details of methods in order to evaluate all of the inclusion criteria and were thus automatically excluded.

Study selection and data collection process

Articles first underwent a review of the titles and abstracts according to the aforementioned criteria. Two reviewers (SFC and RL) evaluated each article; articles were excluded if both agreed they did not meet 1 or more of the inclusion criteria; articles were retained if both agreed that there was insufficient information to exclude the article based on the title and/or abstract. Any disagreements in exclusion/inclusion were resolved via discussion until a consensus was reached. All articles that remained were then eligible for full-text review based on the same criteria. Any disagreements in exclusion/inclusion were resolved via discussion until a consensus was reached. Articles that passed full text review were further evaluated by each reviewer and pertinent details of each study were summarized in Tables 2, 3, and 4. Any disagreements in the extracted study data were resolved via discussion.

Risk of bias in individual studies

The risk of bias was evaluated on the study level. This evaluation consisted of each reviewer's evaluating studies for insufficient randomization and insufficient blinding of subjective outcomes. If the study did not adequately describe the blinding or randomization, then the assumption was made that it was not adequate.

Results

Study selection

Overall, 786 articles were presented for title/abstract screening. The full text of 183 articles were evaluated. Of these, 5 met our criteria (Figure 1).

Study characteristics

Four of the 5 studies provided information regarding commercially available vaccines.[6,15,16,31] Two of those 4 articles provided information about BRD-related morbidity (Table 2), and 3 of the 4 provided information on BRD-related mortality +/- postmortem lung lesions (Table 3). One of the 4 studies investigated a combination vaccine containing genetically attenuated *M. haemolytica* leukotoxin and bacterial extracts of *H. somni* and *M. haemolytica* given to feeder calves via different routes and in different doses;[31] 1 evaluated a vaccine for *M. haemolytica* in feeder calves vaccinated once on arrival;[16] 1 evaluated a different vaccine containing a bacterial extract of *M. haemolytica* A1 in 2- to 6-mo-old Holstein calves given either on d 0 and 21 or only d 21 of the study;[6] and 1 evaluated multiple vaccines containing either *P. multocida* or *M. haemolytica* or combinations thereof in nursing beef

Figure 1. Prisma flow diagram.*
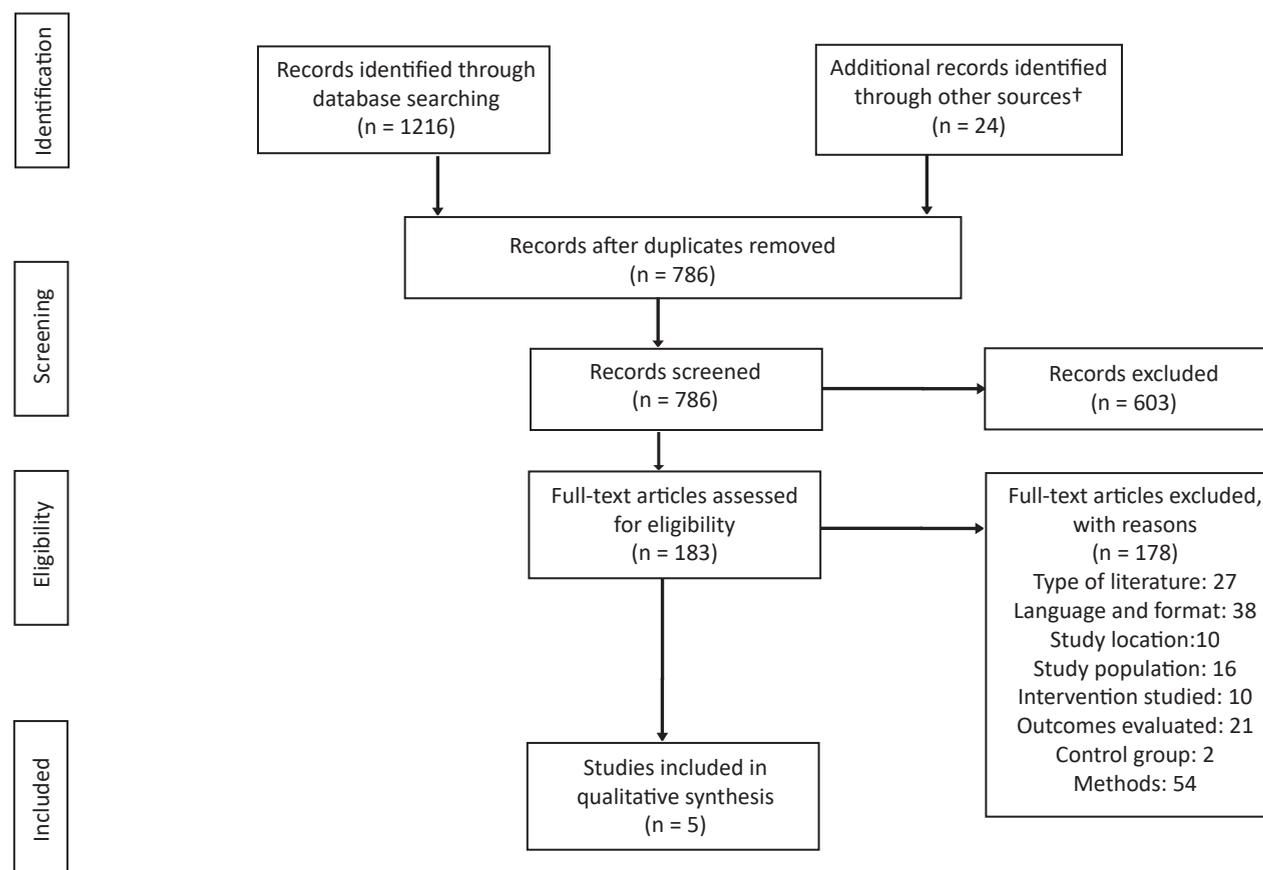
calves.[15] An additional study provided information regarding outcomes after vaccination of 14-d-old Holstein calves with an experimental intranasal *M. haemolytica* vaccine followed by a *M. haemolytica* challenge 70 d later.[20]

Risk of bias within studies

Because our inclusion criteria required that studies demonstrate blinding of any subjective outcome evaluators as well as randomization (either complete or systematic) of study subjects, the 5 studies included in our review were at low risk of bias. However, more than a third of the studies that advanced to full text did not provide adequate evidence of blinding, randomization, or both.

Results of individual studies

Two studies evaluated natural challenge models in feedlot calves, but each evaluated different commercial vaccines. One evaluated a commercial vaccine for *M. haemolytica* and found no significant difference in BRD-related morbidity or mortality between vaccinates and a negative control group (Tables 2 and 3).[16] Evaluation of a commercial vaccine including *M. haemolytica* leukotoxin and *M. haemolytica* and *H. somni* bacterial extracts in another study[31] found a numerical but not statistically significant reduction in BRD-related morbidity within the first 14 d of arrival in vaccinated vs unvaccinated feeder calves. However, a significant decrease in BRD-related morbidity (RR of 0.55; 95% CI of 0.31-0.96) in the first 77 d on feed was reported in calves that were vaccinated once SQ compared with the controls, but only a numerical decrease in the calves vaccinated twice SQ, once IM, or twice IM (Table 2). That study did not evaluate BRD-related mortality or lung lesions, so those outcomes could not be evaluated.[31]

Two studies used *M. haemolytica* A1 challenge models to evaluate commercial vaccine efficacy. One of the 2 explored multiple vaccines in small groups (n=5) of nursing beef calves challenged trans-thoracically on either d 83 or d 97 post-vaccination.[15] The researchers found that several vaccines were associated with significant differences in mortality and lung lesions compared with the controls (Table 3). The other study

Table 2. Characteristics and findings of the 2 studies evaluating vaccines for *Mannheimia haemolytica* (Mh), or a combination product containing genetically attenuated Mh leukotoxin combined with bacterial extracts of Mh and *Histophilus somni* (Hs) that reported a BRD-related morbidity outcome.

Study	Disease Challenge	Study Population			Vaccine Content	BRD Morbidity	
MacGregor et al*,[16]	Natural	452-752 lb (205-341 kg) feeder calves (n=3304, 15 lots)			Mh bacterin-toxoid‡	27.07%	
					Negative Control	29.04%	
Van Donkersgoed et al†,[31]	Natural	Steer calves (avg 522 lb [237 kg] on arrival) (n=301)		**n**		Day 0-14	Day 0-77
				51	Mh leukotoxin, Mh and Hs bacterial extracts§	25%	31%
				50	Mh leukotoxin, Mh and Hs bacterial extracts‖	20%	30%
				49	Mh leukotoxin, Mh and Hs bacterial extracts¶	20%	22%**
				48	Mh leukotoxin, Mh and Hs bacterial extracts#	25%	33%
				103	Negative Control	34%	41%

* Southern Idaho, USA

† Saskatchewan, Canada

‡ Pulmo-guard® PH-1 (BI) on feedlot arrival; no longer marketed at time of publication of this review; product data matching the vaccine name circa the time the study was done could not be found, but study lists as a Mh bacterin-toxoid.

§ Somnu-Star Ph, 1 dose IM

‖ Somnu-Star Ph, 2 dose IM

¶ Somnu-Star Ph, 1 dose SQ

Somnu-Star Ph, 2 dose SQ

** Significantly different than controls

evaluated Holstein calves given either 1 dose of a commercial *M. haemolytica* toxoid vaccine on d 21 or 1 dose of the same vaccine on d 0 and 21. Calves were challenged intratracheally on d 42 of the study and sacrificed on d 48. The researchers reported no significant difference in BRD-related mortality. Significant differences were reported in arcsine transformation of % pneumonic lung of both treatments compared to controls, but not between treatments (Table 3).[6]

One study evaluated the effects of an experimental intranasal vaccine against *M. haemolytica* administered to 14-week-old Holstein or Holstein-cross male calves on d 0, then challenged intratracheally with *M. haemolytica* on d 70, and euthanized 7 d later.[20] The investigators did not report BRD-related morbidity, but instead reported health results as a respiratory score, attitude score, and temperature score. As all calves were euthanized, no BRD-related mortality data were available, but postmortem lung lesion scores were reported (Table 4).

Synthesis of results

Because of a lack of replication of study populations and interventions studied, no quantitative synthesis of the results could be performed.

Discussion

At the time of publication, at least 2 other reviews asked somewhat similar questions to ours regarding BRD-related bacterial vaccine efficacy.[13,21] Larson and Step[13] explored the impact of vaccines for *M. haemolytica*, *P. multocida*, and *H. somni* on BRD-related morbidity, mortality, or associated postmortem lung lesions in feedlot cattle. To answer these questions and inform their meta-analysis, they evaluated studies involving natural disease and challenge models in either beef or dairy calves. Although their review included more articles than ours, they encountered many of the same issues, including relatively few articles for each type of vaccine and/or different vaccine combinations of antigens were identified. They also noted different studies used different populations and different definitions of outcomes (BRD-specific mortality vs cumulative mortality from all causes). Although their criteria regarding randomization, blinding, and methods did not strictly exclude studies based on potential biases or statistical methods, as ours did, they did note that evidence of bias and suboptimal statistical methods reduced the body of literature to relatively few studies. Ultimately, they concluded that some vaccines had potential benefit, but that the evidence available was not consistently in favor of vaccination having a positive impact.[13]

A systematic review by O'Connor et al in 2019 asked a slightly different and broader question regarding the effectiveness of on-arrival vaccination of beef feedlot calves (using any type of BRD-related vaccine) for reducing natural BRD incidence. Ultimately, the goal of that review was to obtain enough evidence to inform a network meta-analysis.[21] These authors incorporated evidence from any country

Table 3. Characteristics and findings of the 3 studies evaluating commercial vaccines for *Mannheimia haemolytica* (Mh), *Pasteurella multocida* (Pm), or combinations thereof and reporting BRD-related mortality +/- postmortem lung lesions as outcomes.

Study	Disease Challenge	Study Population	Vaccine Content		BRD Mortality		Lung Lesions	
MacGregor et al*,[16]	Natural	452-752 lb (205-341 kg) feeder calves (n=3304, 15 lots)	Mh[§]		1.33%		N/A	
			Negative Control		1.88%		N/A	
Loan et al[†],[15]	Transthoracic challenge on d 83 with MhA1 in TSB (avg 2.25 x 10^{10}) or d 97 with MhA1 in PBS (avg 2.43 x 10^{10})	Nursing mixed breed calves (n=139, 60 challenged)	n		Challenge day		Challenge day	
					d 83	d 97	d 83	d 97
			10	Mh bacterin-toxoid[‖]	4/5	2/5	1848[##]	474[##]
			10	Mh and Pm avirulent live culture[¶]	4/5	5/5	3584[##]	540[##]
			10	Mh toxoid, Pm bacterial extract[#]	1/5[§§]	4/5	460[§§,##]	911[##]
			10	Mh and Pm bacterin-toxoid[^]	1/5[§§]	1/5	455[§§,##]	332[##]
			10	Mh bacterin-toxoid[~]	1/5[§§]	1/5	819[§§,##]	458[##]
			10	Negative control	5/5	4/5	5202[##]	1436[##]
Conlon et al[‡],[6]	Intratracheal inoculation of MhA1 (2 X 10^{11} - 1 X 10^{2}) on d 42	2-6 month old male Holstein calves (n=50)	17	Mh toxoid**	d 48		d 48	
					2/17 (12%)		25.78[§§,¶¶]	
			15	Mh toxoid[††]	2/15 (13%)		25.18[¶¶]	
			18	Negative control[‡‡]	6/18 (33%)		45.30[¶¶]	

*Southern Idaho, USA; [†] East Texas, USA; [‡] Canada
[§] Pulmo-guard® PH-1 (BI) on feedlot arrival; no longer marketed at time of publication of this review; product data matching the vaccine name circa the time the study was done could not be found, but study lists as a Mh bacterin-toxoid.
[‖] One Shot® (Pfizer)[25]
[¶] Once PMH™ (Bayer)[24]
[#] Presponse™ HM, (American Home)[9]
[^] LeukoTox™ M (AAH)/ Pulmo-guard™ PH-M (BI) 2 doses, 2 weeks apart; same product, marketed under different companies[1]
[~] LeukoTox™ 1 (AAH)/Pulmo-guard™ PH-1 (BI); same product, marketed under different companies; no longer marketed at time of review publication; product data matching the vaccine name circa the time the study was done could not be found, but another study[16] lists it as a Mh bacterin-toxoid.
** PBS IM d 0, Presponse[8], 1 dose IM, d 21
[††] Presponse[8], 2 doses IM, d 0 and d 21
[‡‡] PBS Control, 2 doses IM, d 0 and d 21
[§§] Significantly different than controls
[¶¶] These are the arcsine transformation of % pneumonic tissue found at necropsy using the referenced scoring system[11]
[##] These lung lesions were calculated according to the scoring system reported by Panciera and Corstvet[23]

Table 4. Characteristics and findings of 1 study evaluating an experimental vaccine for *Mannheimia haemolytica* (Mh) and reporting several clinical criteria as well as postmortem lung lesions as outcomes.

Study	Disease Challenge	Study Population (n=84)	Vaccine Content and Route	Mean Lung Lesion Scores	Respiratory Scores	Attitude Scores	Rectal Temperature
Nordstrom et al*,[20]	Percutaneous transtracheal inoculation of 6.63 x 10^{8} CFU of *M. haemolytica* in 40 mL TSB 70 d after vaccination	14-d-old Holstein calves at time of study onset[†]	Mh[‡], intranasal	3.22%[§,‖]	NS	NS	NS
			Negative Control	11.24%[‖]	NS	NS	NS

* Kansas, USA
[†] Calves were split into 4 groups for a 2x2 factorial study evaluating tildipirosin treatment and the vaccine. No significant interactions were identified for tildipirosin x vaccine for any outcome. Thus, we report on the main effect of vaccination (n=42) vs negative control (n=42).
[‡] Seedstock of streptomycin-dependent *M. haemolytica* at the same titer (proprietary) licensed for commercial product(s) of Merck Animal Health circa the time the study was performed (undefined).
[§] Results were statistically significantly different at a cutoff of <0.05.
[‖] These lung scores are the average scores of two individual scorers who used the scoring system reported by Jericho et al.[11] A non-parametric rank analysis was performed.

and any commercial vaccine involving any BRD pathogen or combination of BRD pathogens. Because of disparities in study methods, only 14 of the 44 identified articles were summarized. Even with a broader question and a worldwide search, these authors concluded that there was "no evidence that vaccination of beef cattle upon feedlot arrival is effective in reducing BRD incidence".[21]

Despite the slightly different questions with different inclusion and exclusion criteria of these reviews compared to our current review, many of the same articles were identified with some notable differences in results. Given the similarity of the question, it was unsurprising that our review identified many of the same articles as did Larson and Step's.[13] However, there were several of these articles that we did not ultimately identify.[3,5,10,26,30] Two were from proceedings from a meeting,[5,10] and therefore were not eligible for inclusion in our review. Three of the references were not identified in either our initial or revised search, but would not have met our inclusion/exclusion criteria regardless. One would have been excluded for inadequate blinding and randomization,[3] 1 because of inadequate randomization, blinding, and statistics,[30] and 1 for lack of randomization, no blinding, and inappropriate statistics.[26]

The O'Connor et al review[21] yielded many of the same articles as ours, plus 2 that we did not find that would have been potentially pertinent to our question.[12,26] One would have been excluded for lack of randomization, no blinding, and inappropriate statistics,[26] while the other would have been excluded due to the intervention studied not matching our question.[12]

Although our search initially yielded nearly 200 studies for full-text review, several key issues with this body of literature ultimately resulted in exclusion of the vast majority of studies. Much of the older literature regarding BRD bacterial vaccine efficacy is reported in a way that makes it difficult or impossible to evaluate bias. This limitation led us to exclude many articles included in earlier reviews. Additionally, statistical methodology and reporting have improved greatly over the years we examined. Many statistical methods commonly used in older studies do not meet today's standards. Most notably, many articles lack adequate statistical control for issues such as clustering of calves within pens or incorrectly treat ordinal scoring systems as continuous variables. Such limitations resulted in exclusion of additional studies from our review. It is vitally important that future studies evaluating vaccine efficacy be adequately reported, with details on aspects such as randomization and blinding, so readers can estimate bias. The need for better reporting in the scientific literature has been widely noted, and documents detailing reporting standards for many types of studies are now available.[4,14,18,19,22,28,29]

Another problem we encountered is that for our topic, most research reported in the peer-reviewed literature has been performed on various vaccine component candidates or experimental vaccines that may never have made it to commercial production. We found it difficult (and often impossible) to relate any early, preliminary work to a final commercial product. The experimental vaccine product used in the 1 study we do report on[20] indicated it was prepared similarly to commercial vaccines produced by the same company, but did not explicitly state which intranasal product produced by that company it was meant to emulate and, in fact, that company does not currently have a commercially licensed intranasal vaccine with only the *M. haemolytica* antigen in it, which limits the utility of the data for producers. Additionally, we had difficulty finding sufficient information about even the commercially available products used in the studies. For example, several vaccines we reported on are not currently available, and their labels were not easily obtainable. Further complicating matters, nearly all manufacturers listed for these vaccines have changed at least once in the intervening years, and some manufacturers no longer exist at all. Therefore, understanding the vaccine components, label claims, and label recommendations relative to what was tested in these studies was extremely difficult. We suggest that the methods sections of future publications on vaccines include full label information for the products used, so as to aid future readers in better understanding these critical factors.

Much like previous authors, we found limited evidence available for BRD bacterial vaccine efficacy. The main challenge we encountered in fulfilling our objective was a lack of replication of similar interventions, in similar enough populations, and with similar enough outcomes that met our inclusion criteria. Therefore, although we would like to present a coherent summary of BRD bacterial vaccine efficacy, we are limited to summarizing the salient data already reported in the 5 studies we described.[6,15,16,20,31]

Although all 5 studies met our inclusion criteria, it is important to note that none were perfect and for some, only parts of the analysis or some of the outcomes could be reported herein. For example, in 1 study,[6] calves were assigned a clinical score post-challenge that was deemed to be statistically significant when comparing the vaccinates to controls. However, the statistical analysis performed was not valid given the way the clinical score was calculated and then analyzed. Because of the limited way data are often reported, it can be challenging and often impossible to modify the analysis to meet today's statistical standards. Thus, when we reported the results of that study, we only discussed the lung score results as evidence for or against vaccination (Table 3). This highlights how important it is that, when possible, study data be made freely available in public repositories and that authors and journal staff alike carefully consider how data are reported so that readers can gain the most from the peer-reviewed literature.

Our search results also highlight the heterogeneity in the peer-reviewed literature regarding how outcomes are measured and how case definitions for BRD vary widely. Each of the 5 studies we summarize used a different case definition and report a different way to measure what

should ultimately be the same outcome – BRD morbidity. Additionally, when lung scores were analyzed, different scoring systems and methodology for evaluating the lungs were used with 2 studies[6,20] using a system identified by Jericho et al[11] while another[15] used a system described by Panciera and Corstvet.[23] However, even within the 2 studies that used the same lung score system, the method of analysis was different, with 1 performing and reporting an arcsine transformed %[6] and the other actually had 2 scorers score each lung, and then averaged the 2 scores and performed a non-parametric rank analysis.[20] Thus, ultimately, the 3 studies that report lung scores are not very comparable even if they had been performed on similar populations with similar products, timing of administration, similar challenges, etc. This lack of a concise case definition for BRD combined with the differences in how BRD morbidity and lung scores are measured severely hampers the ability to compare studies, perform any sort of meta-analysis, and come to summary conclusions regarding the impact of mitigation or control measures such as vaccination. Further heterogeneity exists in how these mitigation or control measures are implemented, the timing of challenge relative to vaccination, and the method and type of challenge.

When exploring the limited statistically significant differences seen in the 5 studies, it is important to also take note of when differences were not observed. In 1 study with a small n of 5 calves per group, several vaccines seemed protective against both mortality and lung lesions when calves were challenged transthoracically 83 d later.[15] However, that protection did not hold true for any of the 3 vaccines when a second group of 5 calves was challenged transthoracically on d 97 post-vaccination with a slightly higher dose in a different carrier solution, even though that challenge appeared less severe given the lower lung lesions and mortality seen in the controls compared to the d 83 challenge (Table 3). Additionally, the results of challenge studies need to be interpreted cautiously as they do not exactly mirror natural pathogenesis or natural response of the animal to the pathogens. In another study that showed a statistically significant reduction in lung lesions in calves vaccinated only once with a product that is labeled for 2 doses given 2 to 4 weeks apart, compared to controls, there was no significant impact of the 2-dose regimen of that vaccine compared to controls.[6] Although the absolute values of the arcsine transformation of % pneumonic tissue measured in that study are quite similar between the 1-dose and 2-dose groups, the fact that they are not different is a curious result. In the 1 study that showed a reduction in morbidity, only 1 vaccine of the 4 studied showed a significant reduction compared to unvaccinated controls, and only when morbidity was evaluated over 77 d in the feedlot.[31] The limited and somewhat perplexing significant results point to the complexity of BRD management and control and indicate that if these vaccines are truly useful under field settings, they are only protective under a limited number of very specific conditions. This also points to the need for further

peer-reviewed BRD bacterial vaccine research to evaluate these products under other field conditions so that we may more fully understand the role they may or may not play in mitigating the impact of BRD in the real world.

Although we attempted to be thorough in our search, every systematic review has its limitations. Per our inclusion criteria, we did not explore conference proceedings or other non-peer-reviewed literature. Although proceedings might contain some novel information, they often lack the details needed to evaluate bias or to sufficiently judge outcomes. For example, details of the case definition or evaluation methods for BRD morbidity or the reference to the scoring system used when assigning lung scores is often absent from conference proceedings or lay articles. This information is vital when trying to compare studies regarding BRD-related outcomes. Our search also did not delve very far into the "grey literature." We queried current vaccine manufacturers regarding additional evidence, but did not rigorously explore patent literature, marketing materials, theses, or regulatory approval documents.

Another limitation of our search was that we considered only evidence produced in the USA or Canada and only articles published in 1980 or later. The goal of these criteria was to keep the production systems and interventions used within the studies as similar as possible. Undoubtedly, high quality research on BRD bacterial vaccine efficacy is taking place around the world. However, we felt that the resulting heterogeneity in products, study populations, and management practices would add complexity to any possible summary measures. Our reasoning for limiting the review to articles published after 1980 was similar. Beef and dairy production and management have changed quite substantially over the years, as have the commercially available vaccines. Therefore, we limited the age of evidence in our review to reduce that heterogeneity.

Conclusions

Of the 5 articles we summarized, sufficient similarities did not exist to create a summary recommendation regarding the evidence for BRD bacterial vaccine efficacy in beef or dairy calves. The paucity of peer-reviewed, field trial-based literature on BRD bacterial vaccine efficacy is not a novel finding. However, it is disappointing that such a large gap remains in our knowledge regarding such an important tool in our fight to manage and prevent BRD in beef and dairy cattle. Future research on BRD bacterial vaccines is needed, and it must be adequately reported in terms of methods and products used in order to aid future readers.

Endnote

[a] Zotero. Corporation for Digital Scholarship. https://www.zotero.org

Acknowledgements

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