A Review of Bovine Respiratory Disease Vaccine Field Efficacy[a]

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Introduction

The ultimate test of a vaccine must be under field conditions and is best obtained from controlled studies of field use.[1,2,3] Our objective is to review field efficacy of bovine respiratory disease (BRD) vaccines in North American beef cattle, based on research that uses scientifically valid methods with clinically relevant outcomes reported in peer-reviewed publications.

Methods

We conducted a literature search of CAB Abstracts using KnowledgeIndex in CompuServe (Table 1). It included articles from January 1972 to January 1996. We reviewed the 521 citations, deemed 183 relevant to the objective and reviewed them more closely. Additional potentially relevant articles, especially those published before 1972, were identified by less formal means, such as review of bibliographies. There is a debate concerning rigor of the review process between different publications. We did not attempt to differentiate between these. We included all sources that used any review process. We excluded 30 proceedings, transcripts, and abstracts of presentations since they are not routinely peer-reviewed.

Table 1. Literature search strategy.

Search	Criteria[a]	Citations found
1	bovine or cattle or cow?[b] or calf or calves or bull? or steer? or heifer?	334,972
2	find vaccine? or vaccinat?	31,130
3	find pulmon? or respirat? or pneumon?	58,974
4	(search 1 or search 2) and search 3	521

[a]Only English language articles included.
[b]"?" is an wildcard character allowing extensions of the word to be found in the search.

The materials and methods were reviewed to ensure that the methods were sound, to the degree discernible. Key issues were inclusion of a valid control group, randomization of treatments, blinding of evaluators of subjective outcomes, and adequate statistical power. Methods were also reviewed to ensure that they included clinically relevant outcomes such as morbidity rates, chronic rates, mortality rates, and/or growth performance. Substitution indicators of efficacy, alone, were insufficient to warrant inclusion of the paper in the review. Examples include antibody titer, lymphoproliferation, cytokine levels, and/or safety.

Statistical methods were reviewed to determine appropriateness. When sufficient information was provided, the statistical results were confirmed. If the study met other inclusion criteria but statistical analysis was not done, we attempted to analyze the data.

We were interested in field efficacy, so studies using natural or simulated natural exposure in a field setting were included; studies using experimental challenge models were not. Additionally, reports were excluded when the class of calf, production setting, or vaccine regime used, limited the external validity of the study to beef cattle production in North America.

Results

Based on these criteria, 22 articles remained. One-hundred thirty-seven articles were excluded for one or more of the reasons listed in the methods section. Some difficulties were encountered during the reviews. Optimally, the method of treatment assignment should be clearly and explicitly explained in the materials and methods. This was done in 12 of the 22 reports. This can include formal randomization schemes or systematic schemes that control for important confounding biases, both of which allow for fair evaluation of the treatments. The remainder of the articles (10 of 22) presented statements such as "treatments were assigned randomly". While this suggests that random methods were used, it does not allow the reader to evaluate the validity of the method of randomization. Articles that mentioned randomization were included in the review.

[a]Adapted from a paper that appeared in *Optimal Health Management for Enhanced Calf Value.* Proceedings of a Symposium at the 1997 TNAVC, Orlando, FL, 1997. © 1997 Veterinary Learning Systems, Inc.

In some of the unused articles the method of treatment assignment was not mentioned. In this case, it must be assumed that the methods used were, at best, haphazard, and, at worst, biased. For example, some of these articles have severely unbalanced treatment group size, suggesting that a valid treatment assignment scheme was not followed. This results in unreliable conclusions, whether positive or negative, so these articles were excluded.

Determining if evaluators were blinded to treatment assignment was another difficult issue. In many papers, morbidity is the outcome, making unbiased assessment critical to the validity of the results. In 7 of 22 reports, blinding was done and the methods were described in detail. Blinding was not mentioned in 15 of 22 articles. In some designs, it could be inferred that the evaluators would be unlikely to know or be able to determine treatment assignment. In some articles, it was obvious that blinding was not done; in others it was impossible to determine. Articles that did not mention blinding, but met other criteria, were included in the review and footnoted.

Along with blinding of evaluators, a complete and consistently applied case definition is critical to validity of subjective outcomes, such as morbidity. In 5 of 22 papers case definition was not mentioned; however, papers were not excluded on this alone.

Statistics were presented in 18 of 22 reports and statistical methods were discussed in detail in 13 of these. All or some of the authors of 7 of 22 (32%) of the papers were affiliated with the manufacturer or developer of the vaccine reported (Table 2). Nine articles reported positive vaccine effect while 13 reported neutral or negative effects on clinically relevant outcomes.

Table 2. Outcomes of articles and affiliation of authors.

Outcome of trial*	No author affiliation	Author affiliation**
Positive	3	6
Neutral	11	1
Negative	1	0

*Articles were broadly classified based on the overall results of the study. Neutral or negative results were 2.8-times more likely to be reported in articles with no author affiliation (2-tailed Fishers exact p-value=0.007)
**One or all authors worked for or were the manufacturer or developer of the vaccine under study.

Infectious Bovine Rhinotracheitis Virus (IBRV) / Bovine Herpesvirus 1

The IBRV vaccine efficacy studies that met the criteria of this review are equivocal in that results were positive or neutral; however, none were negative. The studies date back to 1958 and 1974 and may not apply to current cattle feeding management practices in North America. In a field trial using modified-live IBRV vaccine at arrival, the incidence of upper respiratory disease was reduced from 17.2% in 3,371 unvaccinated calves to 1% in 3,345 vaccinates (RR=16; p<0.0000).[4] A well-designed trial using modified-live IBRV5 given at arrival failed to show benefits in health performance. Another report that failed to show IBRV vaccine efficacy involves additional antigens and is presented in the "multiple antigens" section.

Bovine Virus Diarrhea Virus (BVDV)

There are no reliable reports of field trials examining clinical effects of BVDV vaccines in North American beef cattle, based on research that uses scientifically valid methods with clinically relevant outcomes reported in peer-reviewed publications.

Parainfluenzavirus type 3 (PI3V)

Seven field trials which investigated efficacy of vaccination against PI-3 virus infection were done in the 1960's; however, all of these trials had significant design flaws and were excluded from this review.

Bovine Respiratory Syncytial Virus (BRSV)

Mixed results are reported from studies investigating efficacy of BRSV vaccination of calves upon arrival. Statistically significant benefit of BRSV vaccination was shown in auction-market purchased and transported calves with vaccinated calves 2-times less likely to be treated for BRD (OR=2.0, p<0.00001). Freshly weaned and transported calves were 1.4-times less likely to be treated for BRD (OR=1.4; p<.001). Statistically significant benefit of BRSV vaccination was not shown in the two classes of calves with low morbidity rates. These included preconditioned calves (p= 0.11) and freshly weaned calves that were not transported (p=0.75).[6]

In a Canadian study (Table 3), results of five separate trials designed to assess BRSV vaccine efficacy were equivocal for calves vaccinated prior to weaning; however, reduction of treatment rate was reported in calves vaccinated once upon arrival. No benefit was found for vaccination upon arrival of yearling cattle.[7]

Two additional trials involving calves[8,9] and one trial involving stocker cattle[10] all failed to demonstrate benefit of BRSV vaccination at arrival (Table 3).

Pasteurella sp.

Findings reported in the literature are equivocal on the use of more recently available *Pasteurella* sp. vaccines before and at feedlot arrival (Table 4). However, there is a tendency to report only positive results

Table 3. Summary of BRSV vaccine field trials.

Vaccine Used & Reference	Calf Type	Vaccination Regime	General Outcome	Specific Outcomes
BRSV-Killed[6]	Auction-Market purchased and transported	Arrival	Positive	Reduced 60 day treatment rate from 45% to 29% (OR=2.0; p=0.00001)
BRSV-Killed[6]	Freshly weaned and transported	Arrival	Positive	Reduced 60 day morbidity from 16.5% to 12% (OR=1.4; p=0.001)
BRSV-Killed[6]	Preconditioned	30 days prior to shipment	Neutral	3.4% vx vs. 2.2% ctrl treatment rate (p=0.11)
BRSV-Killed[6]	Freshly weaned and non-transported	Arrival	Neutral	1.3% vx vs. 0.5% ctrl treatment rate (p=0.75)
BRSV-MLV[7]	138 bull calves sent to bull test station at weaning	3 weeks prior to weaning & boostered at weaning	Positive	120 day morbidity rate reduced from 17% to 5%. (p<.0.05)
BRSV-MLV[7]	97 bull calves sent to custom feedlot in southern Alberta	3 weeks prior to weaning & boostered at weaning	Neutral	
BRSV-MLV[7]	317 heifer calves and 52 bull calves remaining at ranch	3 weeks prior to weaning & boostered at weaning	Neutral	
BRSV-MLV[7]	283 bull calves arriving at bull test station	Arrival	Neutral	
BRSV-MLV[7]	253 Charolais-cross calves at research station	Weaning and boostered 3 weeks later	Neutral (adg)	
BRSV-MLV[7]	611 market-derived yearlings sent to commercial feedlot	Arrival	Neutral	
BRSV-MLV[7]	4913 yearlings & 1716 calves in large commercial feedlot	Arrival	Positive for calves; Neutral for yearlings	21% treatment rate in ctrl vs. 17% treatment rate in vx's; 8 wk observation period (p<0.05)
BRSV-MLV[8]	422 calves of undefined wt, age, breed	Arrival	Neutral	
BRSV-undefined[9]	192 calves; 96 in 1984 & 96 in 1985	Arrival	Neutral	
BRSV-undefined[10]	754 stocker cattle	Arrival	Neutral	

Table 4. Summary of *Pasteurella* vaccine field trials.

Vaccine Used & Reference	Calf Type	Vaccination Regime	General Outcome	Specific Outcomes
P. haemolytica toxoid[11]	560 to 827 lb. calves received in Oct. to Dec. in Canada	Arrival	Positive	Reduced 64-124 day mortality from 4.2% to 2.2%
P. haemolytica toxoid[12]	Spring-born, Hereford-cross ranch calves in southwest TX	Branding & arrival or arrival only	Positive	Reduced 60 day morbidity from 31% to approx. 20% & mortality from 2.5% to approx. 0.2%
P. haemolytica toxoid[13]	300 lb. calves hauled from KY to NM	Arrival & 14 days post-arrival	Positive	Reduced 28 day morbidity from 50% to 13% and mortality from 6.7% to 0%
P. haemolytica toxoid[14]	Auction market calves hauled from southeast US to OK	Preshipment or postshipment (arrival)	Neutral	
P. haemolytica toxoid[15]	500 to 600 lb., 6 to 8 mo. Old ranch calves in Canada	3 weeks before shipment &/or shipment	Neutral	
Streptomycin-dependent *P. multocida* & *haemolytica*[16]	300 to 600 lb. Preconditioned calves	14 days before shipment &/or arrival	Positive	Increase gain from 0.83 kg/day to approx. 1.1 kg/day
Streptomycin-dependent *P. multocida* & *haemolytica*[16]	410 to 600 lb. Auction market calves	Arrival	Neutral	
Live intradermal *P. haemolytica*[17]	534 lb. Auction market calves from southeast US	Arrival	Positive	Reduced 28 day morbidity from 40% to 33% and mortality from 1.2% to 0%.
Tissue-culture derived *P. haemolytica* bacterin[19]	Weaned calves hauled from TN to order-buyer barn, then to TX	98 to 95 days before weaning and arrival (8 days after weaning)	Neutral	
P. haemolytica capsular antigen[18]	290 lb. calves hauled from FL to OK	Arrival	Neutral	

in the scientific literature; thus, negative or neutral findings remain unpublished. This bias, along with the fact that there are reports that fail to show a positive effect, raises doubt concerning efficacy of *Pasteurella* sp. vaccines when used in the field.

The largest body of *Pasteurella* vaccine data exists for *P. haemolytica* toxoid. Three studies have shown statistically significant reduction in morbidity and/or mortality in calves administered a *P. haemolytica* toxoid at arrival.[11,12,13] However, two clinical trials showed no significant effects when the same vaccine was given at arrival[14] or three weeks before shipment and/or arrival.[15] In no reports was health performance in vaccinates negatively affected.

There are individual reports on various other commercial or experimental *Pasteurella* sp. vaccines. These include reports of significant efficacy in field studies of a streptomycin-dependent live *Pasteurella* sp. vaccine[16] and an intradermally-administered live *P. haemolytica* vaccine.[17] Alternatively, a field study of a *P. haemolytica* capsular antigen vaccine failed to show significant health effects,[18] as did a study using a tissue-culture-derived *P. haemolytica* bacterin.[19]

For some currently available *Pasteurella* sp. vaccines there are no reports meeting the objectives and criteria of this review. There are reports of lack of field efficacy with earlier *Pasteurella* sp. bacterins.[20,21] There is also a report of increased health problems following vaccination with earlier *Pasteurella* sp. bacterins.[22] However, this study did not mention if treatment assignment was randomly done and the experimental unit is unclear, making the validity of the data analysis suspect.

Haemophilus somnus

As with other vaccine antigens of bovine respiratory disease prophylaxis, results of field trials evaluating efficacy of *H. somnus* bacterins have been conflicting (Table 5). A 1984 review of this subject concluded that this is the case.[1] One group of investigators has reported negative effects of vaccination once with a commercial *H. somnus* bacterin in that significantly more animals in groups of calves vaccinated once were treated for respiratory disease as compared to groups of unvaccinated control calves or groups of calves vaccinated twice at a 21 day interval.[23] However, these findings conflicted with earlier reports by these authors that no significant difference in the number of animals treated was found between groups of calves immunized once with a commercial *H. somnus* bacterin and groups of unimmunized control calves.[21] Conversely, these investigators had reported earlier that morbidity (number of animals treated for respiratory disease) was significantly reduced in groups of calves vaccinated with a commercial *H. somnus* bacterin upon arrival at the feedlot and re-vaccinated 21 days later as compared to groups vaccinated twice with a bivalent *P. haemolytica*, *P. multocida* bacterin or unvaccinated controls.[20]

Table 5. Summary of *Haemophilus somnus* vaccine field trials.

Vaccine Used & Reference	Calf Type	Vaccination Regime	General Outcome	Specific Outcomes
H. somnus bacterin[23]	20 crossbred steers	3 groups: 1. unvaccinated 2. vaccinated at arrival 3. vaccinated at arrival & boostered 21 days later	Neutral to negative	grp 2 had significantly higher treatment rate than grps 1 & 3
H. somnus bacterin[21]	306 crossbred steers	Arrival	Neutral	
H. somnus bacterin[20]	340 crossbred heifers	Arrival & boostered	Positive 21 days later	reduced treatment rate from 21/106 vx vs. 33/107 ctrl

Mycoplasma sp.

While there are some reports on *Mycoplasma* sp. vaccines, there are no reliable reports of field trials evaluating efficacy of vaccines in North American beef cattle, based on research that examines clinically relevant outcomes with scientifically valid methods in peer-reviewed publications.

Coronavirus, Chlamydia, Adenovirus, Calicivirus

There are no reports of vaccine field trials for these pathogens, germane to North American beef-cattle production in peer-reviewed publications.

Multiple antigens

Field trials were carried out with vaccinates receiving multiple antigens, making it impossible to determine the effects of individual antigens. These can be subdivided into two broad groups: vaccine administered at or near the time of feedlot arrival and vaccine administered several weeks before feedlot arrival.

Assuming valid design, execution, and analysis, interpretation of the first group is fairly straightforward. Some studies of arrival vaccination suggest it does not affect or may even decrease health performance. A well designed study using modified-live IBRV and PI3V vaccine along with a *Pasteurella haemolytica* toxoid failed to show health performance benefits.[24] This is supported by findings in a multi-year observational study in Ontario, Canada, which reported that administration of respiratory vaccines (IBRV or IBRV-PI3V or IBRV-PI3V-*Pasteurella*) to calves vaccinated within two weeks of arrival was associated with increased risk of mortality (relative risk = 2.4).[25] In contrast, subcutaneous vaccination with a *P. haemolytica* and *H. somnus* vaccine at arrival reduced BRD morbidity from 41% to 29%.[26]

The second type of mixed-antigen study is when vaccines are administered several weeks before feedlot arrival. These are often part of a preconditioning or preweaning study. Since an unvaccinated, but similarly managed group, is rarely included in these studies, the effects of management interventions such as preweaning and bunk acclimation are totally confounded with vaccine effect. It is impossible to know which accounts for improvements in health performance.

Controlled studies of these systems have routinely shown improved health performance. When control groups of calves experience low morbidity rates, no preconditioning effect can be demonstrated. Because it is not possible to separate the effects of vaccination from other management interventions, these papers were not included in this review; however, review papers of preconditioning have been published.[27]

Conclusion

We are impressed with the small number of useful reports of clinical efficacy in field settings for BRD vaccines. While there are hundreds of reports in the literature, most suffer from one or more design flaws or limitations. Many of these are referenced in support of vaccination. In particular, published data supporting BRD vaccination at arrival in North American feedlots is equivocal, at best.

Since licensing of BRD vaccines is based, in part, on demonstration of efficacy and these vaccines are used widely in North American beef cattle production, it appears that this is largely based on biologically logical extrapolation from challenge studies, rather than field efficacy data. Controlled laboratory evaluations are an important and necessary step in vaccine development. They not only provide evidence supporting efficacy, but also frequently give invaluable insight into mechanisms of protective immunity. Studies of immune mechanisms are critical to our understanding of host-pathogen interactions and how to induce protective immunity. This insight is the basis for much of the progress in vaccine improvement. However, demonstration of activation of these immune mechanisms is not *de facto* proof of clinical efficacy in a field setting. Laboratory experiments are not substitutes for field trials and extrapolation of findings from the laboratory to the field is fraught with pitfalls.

As mentioned at the outset, the ultimate test of a vaccine must be under field conditions and is best obtained from controlled studies of field use. Economic justification for vaccination is based on this information, compared to vaccination costs. Each producer will place a different value on vaccine attributable benefits, such as improved health and/or growth performance. These values will also change with fluctuating market values of cattle and feed. This makes determining the cost:benefit ratio of vaccination a moving target. However, addressing this issue requires the clinically relevant, statistically significant differences we tried to identify in this review. Without sound field trial design and execution, which ensures the information is reliable, and statistical significance, which ensures the differences are real, clinical outcomes cannot be extrapolated to economic justification.

It seems prudent to mention that we do not believe that this review suggests that we should abandon vaccination of cattle for BRD before or at arrival. Rather, it suggests that we may be making less than optimal recommendations on vaccine use because of a lack of clinically relevant information. We believe this creates an opportunity.

It is time to critically evaluate vaccination as a management tool. Since it has not been done by the government, universities, or manufacturers yet, it

seems unlikely that it will be done very soon unless we take the initiative. There already exists a number of unusable studies, we suggest that those interested in undertaking this challenge be uncompromising in their experimental design. To be reliable, studies must:

- include a valid control group,
- use an externally relevant population,
- use a clinically reasonable treatment regime,
- use random treatment assignment,
- blind assessors to treatment assignment,
- use a field challenge in an externally relevant production setting,
- ensure adequate follow-up,
- have adequate statistical power to detect treatment effects,
- control for confounding variables,
- use appropriate statistical evaluation to determine if differences are real,
- measure clinically relevant outcomes to determine if differences are important.

All the above should be described in detail in the methods and, along with the results, be published in a peer-reviewed source. Reviewers should include these items in criteria used to evaluate submissions. Reports published in peer-reviewed journals are subject to formal scientific scrutiny and are available to the entire veterinary medical community. Access to reliable, clinically relevant information will enhance practical decision making.

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a. Blinding of assessors to treatment groups not mentioned.
b. Method of assignment of experimental units to treatment groups not mentioned.
c. No statistical analysis of data and insufficient information provided in paper to allow analysis.
d. Inappropriate statistical test used to analyze data; appropriate test used incorrectly; P-values reported are incorrect.
e. No control group or invalid control group.
f. Inappropriate definition of experimental unit and pseudoreplication.
g. Production setting and/or calf type and/or vaccine regime not practical or applicable to North American beef cattle production (external validity).
h. Used experimental challenge model instead of field or simulated field exposure.
i. Only reported outcomes such as antibody levels, seroconversion rates, immune function indicators, or product safety instead of clinically relevant outcomes, such as morbidity and mortality.
j. Inadequate statistical power to detect significant differences if they existed.
k. No data presented, editorial, or review.
l. Inadequate follow up of all animals that entered the field trial.
m. Statistical methods not discussed or explained in materials and methods.