Vaccine Field Efficacy: A Review of Field Efficacy Reported for Vaccine Antigens Used in Beef Cattle and Dairy Practice, 1996 to Present

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Abstract

An evidence-based approach to design and recommendation of vaccination programs requires a thorough review of the peer-reviewed veterinary literature. Criteria for inclusion in this review are: inclusion of a valid concurrent control group, blinding of evaluators of subjective outcomes, randomization of experimental treatments, appropriate statistical methods, sufficient statistical power and external validity. Also, only those peer-reviewed articles that report clinically relevant outcomes, e.g. morbidity, mortality, average daily gain, feed efficiency, milk production, lameness, etc, are included in this review. Furthermore, only reports of field studies done in North America were included.

CAB abstracts and PubMed databases were searched using the following search terms: bovine or cattle or cal? or bull or cow AND immun? or vaccin? or vaccine AND natural or field challenge. From these searches, 21 reports of well-designed studies done in North America to investigate field efficacy of vaccine antigens with relevance to beef cattle or dairy operations were found; 13 of these studies reported a benefit in clinically relevant outcomes.

Résumé

Une démarche factuelle en vue de la conception et de la recommandation de programmes de vaccination exige un examen approfondi de documentation vétérinaire évaluée par des pairs. Les critères d'inclusion dans cet analyse sont les suivants : inclusion d'un groupe de contrôle participant valide; travail à l'aveugle des évaluateurs de résultats subjectifs; caractère aléatoire des traitements expérimentaux; méthodes statistiques appropriées; efficacité statistique suffisante et validité externe. De plus, le présent examen ne s'intéresse qu'aux articles évalués par des pairs qui font état de résultats pertinents sur le plan clinique, par exemple la morbidité, la mortalité, le gain moyen quotidien de poids, la capacité de transformation des aliments, la production de lait, la boiterie et autres. En outre, on n'a retenu que les rapports des études sur le terrain réalisées en Amérique du Nord.

Des recherches ont été effectuées dans les bases de données CAB Abstracts et PubMed en utilisant entre autres les termes suivants : bovin ou bovins ou taureau ou vache ET immune? ou vaccin? ou vaccin ET infection naturelle ou expérimentale. Ces recherches ont fait ressortir 21 rapports portant sur des études bien conçues réalisées en Amérique du Nord en vue d'étudier l'efficacité réelle des antigènes des vaccins sur les bovins de boucherie ou les élevages laitiers; dans treize de ces études, les résultats pertinents positifs sur le plan clinique ont démontré un avantage.

Introduction

Numerous commercially available vaccines are available to bovine practitioners and their producer clients. These vaccines contain various antigens and antigen combinations. Therefore, bovine practitioners face many options in designing, recommending and implementing vaccination programs for their producer clients. An evidence-based approach to design and recommendation of vaccination programs requires a thorough review of the peer-reviewed veterinary literature. An effective evidence-based review of the literature will be systematic and rigorous, with specific criteria for inclusion that provides the practitioner an indication of field efficacy that is relevant and applicable in the production setting. A review that meets these criteria can guide the practitioner in making sound, or the most optimal recommendations available, to producer clients.

This review is designed to meet these objectives and is presented as an update and extension of the review published by Perino and Hunsaker in 1997.[17] The same principles of critical review of the literature used in the previous review have been applied to the articles included in this review. Specifically, criteria for inclusion in this review are: inclusion of a valid concurrent control group, blinding of evaluators of subjective outcomes, randomization of experimental treatments, appropriate statistical methods, sufficient statistical power

and external validity. Also, only those peer-reviewed articles that report clinically relevant outcomes, e.g. morbidity, mortality, average daily gain (ADG), feed efficiency, milk production, lameness, etc, are included in this review. Furthermore, only reports of field studies done in North America were included.

As stated in the previous review, the ultimate test of a vaccine must be under field conditions and is best obtained from well-designed, controlled studies of field use.[17] This statement serves as the premise for the current review.

Materials and Methods

CAB abstracts and PubMed databases were searched using the following search terms: bovine or cattle or cal? or bull or cow AND immun? or vaccin? or vaccine AND natural or field challenge. Reports of studies included in this review were required to meet the criteria of the review article published in 1997.[17] Specifically, these criteria are blinding, randomization, appropriate statistical methods, external validity, sufficient statistical power and an appropriate and concurrent control group.

To further reduce the likelihood of inadvertently omitting reports of studies that met the criteria of this review, names of individual agents were included in the search logic following the more general search. For example, a search for articles reporting IBRV vaccine efficacy, the search criteria were: infectious bovine rhinotracheitis virus or IBR AND bovine or cattle or cal? or bull or cow AND immun? or vaccin? or vaccine AND natural or field challenge. Also, search criteria were limited to studies done in North America and reported 1997 to the present.

As mentioned, only reports of studies done in North America under field challenge conditions were included in this review.

Results

Using the search terms described above, a search of the PubMed database resulted in 219 references and a search of the CAB abstracts database resulted in 139 references. We excluded 45 abstracts, proceedings and transcripts, since these are not typically peer-reviewed. From these searches, 21 articles met the critical review criteria outlined and are included in this review. Ten of the studies reported were done in beef cattle and 11 were done in commercial dairy settings. We have split this review into beef cattle and dairy sections to accommodate the interest and practice area of the reader. Also, management and conditions between dairy and beef cattle operations are markedly different and results may or may not be relevant to both.

Beef Cattle

Bovine Respiratory Syncytial Virus

MacGregor and Wray reported that yearling cattle vaccinated with a multivalent vaccine containing bovine respiratory syncytial virus (BRSV) antigen had reduced ($P<0.05$) respiratory morbidity, respiratory mortality, overall mortality, overall case-fatality and respiratory case-fatality compared to yearling cattle vaccinated with a multivalent vaccine not containing BRSV.[14] However, feeding performance outcomes such as dry matter intake, average daily gain and feed conversion were not found to be different between the two vaccine groups. Carcass characteristics measured were similar between the two vaccine groups, although there were less USDA Yield Grade 2 and more USDA Yield Grade 3 carcasses in the group administered the vaccine containing BRSV.

Clostridium spp bacterin-toxoid

One well-designed study reported that booster vaccination of cattle at re-implanting approximately 90 days prior to harvest resulted in no difference in incidence of crude, pen, or sudden death syndrome mortality proportions as compared to control cattle that were not boostered at re-implanting.[5]

Another report of a large feedlot study done in California appeared to meet the criteria of objectives of this review, although it was reported in 1985.[12] Since these are such widely used antigens by bovine practitioners and their clients, it is warranted that this report be included. Cattle vaccinated with a multivalent clostridial bacterin-toxoid on arrival to the feedyard and boostered approximately 30 days later had fewer deaths ($P<0.001$) than cohort cattle not vaccinated with a multivalent clostridial bacterin-toxoid. It can only be presumed that animals were randomly assigned to experimental treatment groups since the authors did not describe methods of randomization, but state that "half of the animals were given a bacterin-toxoid." Supportive of this statement is the fact that experimental treatment groups were very nearly equally balanced (varied ≤1 animal per treatment) for all lots enrolled. Blinding is not applicable in this case, since crude mortality was the outcome variable of interest.

Bovine Coronavirus

One group of investigators reported that intranasal vaccination of calves on arrival to the feedlot with a modified-live bovine enteric coronavirus (BCV) and rotavirus vaccine was associated with decreased risk ($P=0.008$) of treatment for BRD. Interestingly, the authors reported a significant positive association between isolation of BCV from nasal passages and a significant negative association between serum antibody titers to BCV and the risk of treatment for BRD.[18]

Fusobacterium necrophorum associated liver abscesses and footrot

Results of two studies that met the criteria of this review were reported. Both studies reported efficacy in reducing liver abscess incidence and/or severity following use of bacterins containing *Fusobacterium necrophorum*.

One group of investigators reported significantly reduced risk of developing liver abscess scores of A or A+ (OR=0.27; P=0.05) and of developing footrot (OR=0.18; P=0.03) in cattle vaccinated with a *Fusobacterium necrophorum* bacterin and fed a forage-based growing diet. No reduction in risk of developing liver abscesses or footrot was reported for vaccinated cattle fed a grain-based growing diet.[3]

Additionally, Jones *et al* reported that cattle vaccinated with a single dose of bivalent *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* bacterin-toxoid reduced the prevalence of liver abscesses in feedlot cattle at harvest from 31% to 16% in one study and from 48% to 30% in another study. Efficacy was reported for the high-antigen dose bacterin-toxoid when compared to a lower dose of antigen. No difference in liver abscess prevalence (P=0.108) was found between high-dose antigen vaccinated cattle and cattle fed tylosin-medicated feed. Additionally, a benefit in the proportion of USDA Yield Grade 1 and 2 carcasses was reported for cattle vaccinated with the high-antigen dose bacterin-toxoid in both cattle fed tylosin-medicated feed and cattle fed control ration not containing tylosin. However, no significant differences were reported in average daily gain or feed efficiency between vaccinated and unvaccinated cattle.[11]

Mannheimia (Pasteurella) haemolytica bacterins

Authors of one study reported that a single, 2 mL injection of *Mannheimia (Pasteurella) haemolytica* bacterin-toxoid reduced crude mortality. However, there were no significant differences detected in BRD-specific mortality, morbidity or ADG between vaccinated and unvaccinated groups.[15]

Moraxella bovis bacterins

Two studies are reported in the literature that evaluated the efficacy of *Moraxella bovis* bacterins to reduce pinkeye incidence or severity.

Davidson and Stokka reported no difference in the incidence of pinkeye between yearling cattle vaccinated with an autogenous *Moraxella bovis* bacterin and commingled unvaccinated cattle. Interestingly, a statistically lower incidence of pinkeye was reported in steers than in heifers.[4]

In another study, a recombinant *Moraxella bovis* cytotoxin subunit vaccine given as a primary immunization followed by a booster 21 days later, resulted in reduced cumulative proportion (P<0.05) of calves with ulcerative keratoconjunctivitis.[1]

Multivalent respiratory viral vaccines

One study done in Canada under commercial feedlot conditions resulted in improved (P<0.05) final weight, weight gain, and ADG, on both live and carcass weight basis, in the group vaccinated with a multivalent viral vaccine when compared to the group vaccinated with a monovalent vaccine. The multivalent vaccine contained modified-live infectious bovine rhinotracheitis virus, parainfluenza-3 virus, bovine viral diarrhea virus, and bovine respiratory syncytial virus antigens. The monovalent vaccine contained infectious bovine rhinotracheitis virus antigen. However, no significant differences were found in number of days on feed, daily dry matter intake, or feed efficiency (dry matter intake-to-gain ratio).[19]

Escherichia coli O157:H7 bacterin

Although fecal shedding of *E. coli* wouldn't typically be considered a clinically relevant outcome to a veterinary practitioner or a feedyard manager, it is included in this review since fecal shedding of *E. coli* is an economically important outcome relevant to beef packers and purveyors.

One report of a multiple-site field trial done to assess the efficacy of an *E. coli* O157:H7 bacterin to reduce fecal shedding of the organism in feedlot cattle resulted in no significant association between vaccination and pen prevalence of fecal *E. coli* O157:H7 following initial vaccination, at re-implanting, or prior to slaughter.[22]

Dairy

Coliform mastitis

Three studies are found in the peer-reviewed literature reporting efficacy of vaccination against coliform mastitis in lactating dairy cows. Two of those studies reported the efficacy of a mutant *E. coli* bacterin used three times prior to calving. The third study reported efficacy of a mutant *Salmonella typhimurium* bacterin.

A well-designed study by Gonzalez *et al* reported that dairy cows vaccinated strategically three times with a mutant *E. coli* vaccine were at 0.20 risk (P<0.005) of developing clinical coliform mastitis as unvaccinated cows.[8]

Hogan *et al* reported that dairy cows vaccinated strategically three times similar in timing to that reported by Gonzalez *et al* and using the same mutant *E. coli* strain antigen had reduced incidence (P<0.05) of coliform mastitis during early lactation as determined by bacterial culture of milk samples and the California Mastitis Test (CMT).[10] However, blinding was suspect

in this report, since cows were assigned by even- and odd-numbered ear tags and the herd manager assessed cows for signs of clinical mastitis, although the bacteriologic culture outcome was arguably objective.

A well-designed study reported by McClure *et al* resulted in reduction in clinical cases of coliform mastitis with positive coliform cultures, reduced culling proportion due to coliform mastitis and dramatically reduced mortality associated with coliform mastitis in cows vaccinated twice during the third trimester of pregnancy with a mutant *Salmonella typhimurium* bacterin-toxoid than unvaccinated cows.[16]

Intramammary Staphylococcus aureus *infection*

Smith *et al* reported a significantly higher (P=0.035) bacteriologic cure (40 vs 9%) in treated cows meeting the study definition for chronic intramammary *Staphylococcus aureus* infection. Experimental treatment was three vaccinations with a polyvalent *S. aureus* bacterin and five intramammary administrations of pirlimycin.[20] Although bacterial culture would generally be considered a substitution indicator for clinical mastitis, in the case of intramammary *Staphylococcus aureus* infection it seems bacterial culture may be the most clinically relevant and specific outcome of interest. Blinding was suspect in this study, although the primary outcome of interest, bacterial culture, is seemingly objective.

Luby and Middleton reported no significant differences in *S. aureus* intramammary infection cure rates between chronically infected cows randomly assigned to receive either extended pirlimycin intramammary therapy alone or extended pirlimycin therapy in conjunction with two doses of a polyvalent bacterin. However, cure rates in the vaccinated group, in conjunction with extended pirlimycin therapy, were approximately 17% greater than in the group treated with extended pirlimycin therapy alone. Also, no significant differences in somatic cell counts (SCC) were reported between experimental treatment groups. No statistical power was reported for any of the outcomes reported and blinding is not mentioned by the authors, presumably due to the objective nature of bacterial culture and SCC outcome variables.[13]

Bovine Respiratory Syncytial Virus

Ferguson *et al* reported that vaccination of cows with a quadrivalent viral vaccine containing BRSV resulted in higher (P= 0.03) milk production in first-parity cows during the first 21 weeks of lactation compared to cows receiving a trivalent vaccine not containing BRSV. Additionally, first service conception rates were higher in first- (P=0.03) and second-parity (P=0.06) cows vaccinated with the quadrivalent vaccine containing BRSV compared to cows vaccinated with trivalent vaccine.[7]

Bovine Viral Diarrhea Virus

No significant difference in morbidity (P=0.25) or mortality (P=0.32) after 15 days of age was reported between calves vaccinated with a killed BVDV vaccine at 15 days of age and a modified-live vaccine at 40 to 45 days of age compared to unvaccinated control calves. However, statistical power, i.e., the ability to detect differences that exist, was not reported for these two outcome variables.[21]

Mannheimia (Pasteurella) haemolytica

Aubry *et al* reported that Holstein dairy calves between 14 and 20 days of age were vaccinated twice with a modified-live *M. haemolytica* and *Pasteurella multocida* vaccine weighed three times at monthly intervals had no significant benefits in health or growth performance as compared to unvaccinated control calves.[2]

Cryptosporidium parvum

Harp *et al* reported no significant differences in incidence of clinical diarrhea coupled with isolation of *C. parvum* oocysts between calves vaccinated shortly after birth with an experimental *C. parvum* vaccine preparation, calves treated with a lactic acid-producing bacterial preparation, or untreated control calves. Also, no statistically significant differences were found in the mean number of days individual calves had clinical diarrhea.[9] Statistical power was not reported by the authors.

*Papillomatous Digital Dermatitis (*Treponema *spp)*

Authors of a large study designed to investigate efficacy of a Treponema bacterin to reduce incidence or severity of PDD reported no significant prophylactic (P>0.11) or therapeutic (P>0.12) effects of vaccination.[6] No estimates or calculations of statistical power were reported by the authors.

A list of commonly used vaccine antigens or agents that beef cattle veterinarians would potentially vaccinate against or recommend vaccination against are listed in Table 1. Also shown in this table is an indication of vaccine efficacy reported for the respective antigens. Table 2 contains agents that dairy veterinarians would vaccinate against or potentially vaccinate against and an indication of efficacy.

No reports of field efficacy meeting the criteria of this review were found in the peer-reviewed veterinary literature for *Campylobacter foetus*, *Leptospira* spp, *Neospora caninum,* or *Tritrichomonas foetus* bacterins. Also, no further reports in the peer-reviewed literature for IBR virus or *Haemophilus somnus* (*Histophilus somni*) were found since the previous review.

Blinding (masking) was mentioned in 14 of the 21 articles included in this review. For the remainder of

Table 1. Reported field efficacy of vaccine antigens commonly used or potentially used in beef cattle.

Antigen(s)	Reported Efficacy			
	Hunsaker & Tripp, 2007		Perino & Hunsaker, 1997	
	Author	Efficacy	No. articles	Efficacy
BRSV	MacGregor, 2004	Yes	14	4 Yes/ 10 No
Clostridium spp	DeGroot, 1997	No		
	Knott, 1985	Yes		
Coronavirus	Plummer, 2004	Yes		
E. coli O157:H7	Van Donkersgoed, 2005	No		
Fusobacterium necrophorum	Checkley, 2004	Yes		
	Jones, 2005	Yes		
Haemophilus somnus (Histophilus somni)			3	1 Yes / 2 No
IBRV			2	1 Yes / 2 No
Mannheimia (Pastuerella) haemolytica	MacGregor, 2003	Yes	10	4 Yes / 6 No
Moraxella bovis	Davidson, 2003	No		
	Angelos, 2004	Yes		

Table 2. Reported field efficacy of vaccine antigens commonly used or potentially used in dairy cattle.

Antigen(s)	Hunsaker & Tripp, 2007 Author	Efficacy
BVDV	Thurmond, 2001	No
BRSV	Ferguson, 1997	Yes
Cryptosporidium parvum	Harp, 1996	No
E. coli (coliform mastitis)	Gonzalez, 1989	Yes
	Hogan, 1992	Yes
Mannheimia (Pastuerella) haemolytica	Aubry, 2001	No
Pastuerella multocida	Aubry, 2001	No
Salmonella typhimurium	McClure, 2004	Yes
Staphylococcus aureus (mastitis)	Luby, 2005	No
	Smith, 2006	Yes
Treponema spp. (hairy footwart)	Ertze, 2006	No

studies included, five presumably didn't mention blinding since seemingly objective outcomes (i.e. death, bacterial culture, SCC) were the primary outcomes of interest. One report suggested blinding by referring to third party data collection services by name. Blinding was particularly suspect in one report since the randomization method was odd- or even-numbered eartags, which obviously violates blinding, and the outcome variables were subjective.[6]

Randomization methods were described in 12 of the 21 reports included in this review. Randomization or random allocation was at least mentioned in eight of the remaining reports. One report didn't specifically mention randomization; however, experimental treatment groups were nearly identically balanced (≤1 experimental unit), which is highly suggestive of a valid randomization scheme.

Sixteen of the 21 articles included in this review had author affiliation with the manufacturer of the vaccine, while 5 had no affiliation. Definition of affiliation did not include manufacture sponsorship or financial support of the study reported.

Discussion

It was again interesting to note the relatively few reports of studies that met the criteria for inclusion in this review, although the scope had been broadened to include essentially all antigens, both commercial and experimental, beef and dairy. However, it was encouraging from a practitioner's perspective that most antigens commonly used or recommended in bovine practice have at least one report of field efficacy that have met the criteria of this, or the previous, review. This is not to say that a vaccine or antigen is ineffective if it has not met the criteria of this review. However, as mentioned in the previous review, the ultimate test of a vaccine or antigen is under the conditions of field challenge.

As mentioned, this review was limited to reports of natural or field challenge studies done in North America. This is not to detract from or minimize the value of experimental challenge studies or studies that are done outside of North America. Within their scope, experimental challenge studies are enlightening in terms of pathogenesis and mechanisms of disease, and

studies done outside of North America may be extrapolated to some undeterminable extent to management practices in North America; however, they are outside the scope of this review.

Articles were included in this review if they met all other criteria and at least mentioned that randomization or random allocation of experimental units had been done. We believe it adds to the reliability and repeatability of a study if randomization methods are described. Twelve of the 21 articles included in this review described randomization methods, such as "computer-generated randomization schedule" or "coin flip." In one case[12], randomization was not indicated, but the nearly exact balance in subjects enrolled in each experimental treatment suggested that an effective randomization scheme was followed.

Blinding, or masking, is especially critical to the validity of a study, particularly for outcome variables that are subjective, such as morbidity or severity of lameness. It could be argued that blinding is also important for laboratory outcomes or seemingly objective outcomes, since knowledge of experimental treatment assignment could influence expected results and therefore, incubation times, necropsy diagnosis, efforts to detect the organism of interest, etc.—even inadvertently. Blinding in one article[6] was suspect since randomization was based on even- or odd-numbered eartags, which obviously violates blinding, or at least could bias suspicion of clinical observers towards one treatment group or another. In the case of the study in question, no difference between vaccinates and unvaccinated controls was reported; however, it would typically be expected in cases of violation of blinding that clinical observers would naturally favor the vaccinated group. We struggled with whether or not to include this article in the review based on the apparent violation of blinding. It was determined to include the article since violation of blinding may not have biased the reported neutral results, and we felt it was important for the reader to realize that an attempt to investigate efficacy of this antigen had been made. Therefore, interpretation and caution is left to the discretion of the reader.

Most of the included articles had no manufacturer affiliation with authorship; however, of the five articles with affiliation, four reported positive results for the vaccine antigen. Positive reporting bias may be slightly stronger for reports with manufacturer affiliation in the authorship since of the 16 articles without manufacturer affiliation in the authorship, 11 reported efficacy for the test antigen, while five neutral results of efficacy were reported. However, the association between positive result reporting and manufacturer affiliation in the authorship was not statistically significant ($P>0.05$).

Statistical power is important to estimate *a priori* to determine sample size requirements and predicted ability to detect clinically and/or economically important differences with available resources. A discussion of the power achieved in a study is important in the case of failure to find differences between experimental treatments. This gives the reader an appreciation of the ability of the experimental design to detect differences that truly exist. Power was estimated and discussed as a possibility for failure to find differences in four of the eight studies that reported neutral results.

Conclusions

A thorough review of the veterinary literature, using a systematic evidence-based approach, optimizes the use and recommendation of vaccine or bacterin antigens by bovine practitioners. An effective review will include critical review principles such as randomization of experimental units, blinding of clinical assessors to experimental treatment assignment, external validity, estimation of statistical power and a concurrent and valid control group. Of 21 reports of well-designed studies done in North America to investigate with relevance to beef cattle or dairy operations, 13 reported a benefit to vaccination with the respective vaccine or bacterin antigen in clinically relevant outcomes such as ADG, feeding efficiency, morbidity, mortality, lameness, milk production, etc.

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