Vaccination: Is it Effective in Preventing Respiratory Disease or Influencing Weight Gains in Feedlot Calves?

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SUMMARY

Respiratory disease, both undifferentiated and etiologically defined, remains a major problem in feedlot cattle. Vaccination has been used in an attempt to reduce the frequency and/or severity of respiratory disease in the first few weeks after the cattle arrive at the feedlot.

The efficacy of vaccination has been studied both in controlled laboratory experiments and field trials as well as observational studies. (In this review, efficacy refers to the ability to reduce overall treatment rate and/or increase weight gains.) This review summarizes the data resulting from studies of vaccine efficacy.

In general, there is little published data to support the use of vaccines against respiratory disease under feedlot conditions. Treatment rates and weight gains usually did not differ between vaccinated and nonvaccinated groups. The use of live bovine virus diarrhea virus vaccines was associated with a significant subsequent increase in treatment rates. Criteria to be considered in future field trials are described.

RÉSUMÉ

La vaccination est-elle efficace pour prévenir les maladies respiratoires ou influencer le gain de poids, chez les bouvillons des parcs d'engraissement

Les maladies respiratoires, d'étiologie déterminée ou non, représentent toujours un problème majeur chez les bouvillons des parcs d'engraissement. On a utilisé la vaccination, dans un effort visant à réduire la fréquence et la gravité des maladies respiratoires, au cours des quelques semaines qui suivent l'arrivée des bouvillons dans les parcs d'engraissement.

On a aussi étudié l'efficacité de la vaccination, tant à l'aide d'expériences contrôlées en laboratoire qu'au moyen d'essais effectués dans les parcs d'engraissement ou d'études d'observation. Dans le présent article, le mot efficacité désigne la capacité de diminuer le nombre de traitements et/ou d'augmenter le gain de poids. Cette revue résume les données qui résultent d'études sur l'efficacité de la vaccination.

La littérature contient peu de données susceptibles de supporter l'utilisation des vaccins contre les maladies respiratoires, dans les conditions qui prévalent dans les parcs d'engraissement. Ordinairement, la fréquence des traitements et le gain de poids ne diffèrent pas entre les groupes des bouvillons vaccinés et ceux des témoins. L'utilisation de vaccins atténués contre la diarrhée à virus bovine s'est soldée par une hausse subséquente appréciable de la fréquence des traitements. L'auteur décrit les critères dont il faudrait tenir compte, lors d'expériences futures dans les parcs d'engraissement.

INTRODUCTION

Respiratory diseases are major causes of morbidity, mortality and economic losses in feedlot cattle and most cases of respiratory disease are observed in the first weeks after arrival in the feedlot. Although a number of pathologic entities are included in this manifestation; diseases of the lower respiratory tract, particularly fibrinous pneumonia, predominate in frequency and importance (22,34,35,48). The potential role of *Pasteurella haemolytica* and infectious bovine rhinotracheitis (IBR) or parainfluenza type 3 (PI_3) virus as causes of fibrinous pneumonia have been demonstrated experimentally (23,24,46,53,54). Other methods of inducing pneumonia have been reported (8,19,40) and an excellent review of work in this area has been published recently (67). Transportation stress apparently increases the susceptibility of calves to experimental infection (54) and a number of other factors; including ration, management and vaccination are related to mortality rates and treatment costs, at least in feedlots in Ontario (34,35).

From an epidemiological point of view, it is difficult to incriminate one specific organism as a sufficient cause (47) of most cases of respiratory disease. Rather, mixed infectious involving pasteurella together with one or more viruses, such as IBR, PI_3 or bovine virus diarrhea (BVD), are probably major components of the sufficient causes.

Various management techniques and practices have been suggested to reduce the occurrence of respiratory disease (2), although few of these suggestions have been submitted to formal evaluation to determine their efficacy. Much debate about one practice, vaccination, has occurred since reports of a significantly harmful effect on health, attributable to vaccination were published (34,35) by this author and coworkers. Many veterinarians and feedlot owners maintain that vaccination against respiratory disease is an essential component in their disease prevention programs, both to prevent specific conditions of the respiratory tract, such as clinical IBR, and to reduce losses due to respiratory disease in the first few weeks after arrival. Although personal experience, expert opinion and published reports may provide information on vaccine efficacy, only published reports are subject to formal scientific scrutiny. Methods for identifying and focusing expert opinion on a specific subject are available; but have not been used in veterinary medicine. An example of this method concerns

whether or not to vaccinate humans against swine-influenza (50).

In this review, field trials providing data on clinical outcome and/or weight gains have been selected. Field and laboratory studies with only serological titers or other immunological parameters as endpoints were, in general, not included in this review. The review concentrates on reports of the efficacy, against clinical respiratory disease and weight loss, of parainfluenza-3 virus, infectious bovine rhinotracheitis virus, *Pasteurella haemolytica* (Ph) or *multocida* (Pm) and bovine virus diarrhea virus vaccines.

The statistical technique used to summarize the differences in treatment rates across all studies is called the logarithm of odds ratios method (12). In comparing the rate of treatment in the vaccinated group to that in the control group, the rate in the control group is indexed to 'one'. The odds ratio is greater than one if the rate of treatment was higher in the vaccinates, equal to one if the rates were the same, and less than one if the vaccinated group had a lower treatment rate. Testing whether or not the calculated odds ratio should be considered different from one (statistically significant) is equivalent to using a chi-square test of association. That is, if the rates are significantly different as measured by the chi-square test, one concludes that the odds ratio does not equal one. The weight, or importance, given to the results of a particular study when calculating the summary odds ratio, is directly related to the number of animals in the study.

Parainfluenza- 3 Vaccines

In one of the first attempts at evaluating PI_3 vaccines, it was found that a single dose of formalin-killed PI_3 vaccine, with oil adjuvant, protected six vaccinated animals against experimental challenge (40). The period of time between vaccination and challenge was seven weeks. The challenge involved trucking the calves, during inclement weather, injecting PI_3 virus intranasally one day later and injecting Pm intratracheally forty-eight hours after virus challenge. All six unvaccinated calves developed respiratory illness, of varying severity, subsequent to challenge.

More recently, colostrum deprived isolation reared calves, six to 19 months old, were challenged with an aerosol of PI_3 virus four weeks after intramuscular vaccination with live PI_3 virus (13). The six vaccinated calves had a less severe disease than the eight unvaccinated calves (severity of illness scores of 9.5 and 27.1 respectively). However, in another study, when 48 three-month-old dairy calves, one-half colostrum-deprived, were challenged with PI_3 28 days after vaccination with live virus, there were no significant differences in the temperature responses among the intranasally vaccinated, intramuscularly vaccinated or control groups of calves (38). Also, in 1975 other workers (56) noted that intranasally vaccinated, intramuscularly vaccinated and control calves all got mild disease when challenged with PI_3 virus, 30 days after vaccination with live PI_3 virus. The latter calves were kept in a separate area of a feedlot to simulate natural conditions. The vaccinated, but not the control, calves received a bacterin (Phm) and some if not all the calves received an IBR-BVD intramuscular vaccine.

A summary of the data on morbidity rates in studies involving PI_3 viral vaccines is shown in Table I. Perusal of these data suggests little beneficial effect of vaccination, at least in terms of clinical cases and weight gains. Also, of the three papers reporting a beneficial effect of vaccination on weight gains, an incorrect test of signifi-

TABLE I
A SUMMARY OF RESULTS FROM FIELD TRIALS OF PARAINFLUENZA 3 (PI_3) VACCINES IN FEEDLOT CATTLE

Reference Number	Vaccine Status[a]	Number of Calves	Morbidity// Mortality[b]	Weight Gain kg/hd/d	Comments
66	PI_3	43	9(21%)	-	Inactivated PI_3 given just
	C	44	5(11%)	-	prior to shipment
64	PI_3 2X	16	0(0%)	-	Inactivated PI_3 given 30 days
	PI_3	41	5(12%)//1(2%)	-	before weaning. Sixteen
	C	163	14(9%)//5(3%)	-	calves given second injection at weaning
65	PI_3	43	3(7%)	-	Inactivated PI_3 given five days
	C	42	3(7%)	-	prior to shipment. All calves given a pasteurella bacterin
27	PI_3	50	6(12%)	-	Inactivated PI_3 given three
	C	83	8(10%)	-	weeks prior to shipment. Other trials performed but no calves developed "shipping fever"
60	PI_3	96	5(5%)	0.2	Inactivated PI_3 plus adjuvant
	C	180	5(3%)	0.3	given 30 days before weaning. Weights to 30 days postarrival
62	PI_3	93	4(4%)	-	Attenuated PI_3 given 30 days
	C	182	6(3%)	-	before weaning. Weight data appear incorrect
16	PI_3 (IM)	37	12(32%)	-	Attenuated PI_3 given 35 days
	PI_3 (IN)	32	0	-	before weaning. Calves not shipped. No control group
61	PI_3 2X	30	2(7%)	0.2	Nonshipped calves. Initial
	PI_3	30	7(23%)	0.8	vaccination was 30 days
	C	72	17(24%)	0.5	before weaning, repeat vaccination at weaning with killed PI_3 in adjuvant. Very large difference between different groups of calves in sickness rates. Weight data are 30 day gains

[a]IM-Intramuscular
IN-Intranasal
C-Control

[b]Number (percent). If // missing, only morbidity data presented

cance was used in two reports (60,62), the data appear to be incorrect in one paper (62) and in the third paper (61) the differences were claimed to be "significant" but no method of testing was stated. The only report presenting a valid "statistically significant difference" in treatment rates (16) compared intramuscular with intranasal vaccination, but did not include control calves.

For calves vaccinated once only, the average odds ratio was 1.41 with 95% confidence limits of 0.91 to 2.18. Thus, the rate of morbidity was 1.41 times higher in PI_3 vaccinated calves; but, since these limits include "one", there is no significant difference in morbidity rates between vaccinated and nonvaccinated groups of calves. The two groups of calves vaccinated twice (61,64) performed significantly better than calves vaccinated only once or not at all. The 95% confidence limits were 0.08 to 0.97 with an average odds ratio of 0.28. However, as will be mentioned subsequently, when PI_3 virus was combined with other agents the effectiveness of the two dose regime was not apparent and therefore the importance of these two studies is questionable.

Infectious Bovine Rhinotracheitis Vaccines

Most of the studies of vaccines containing only IBR virus have been conducted under laboratory conditions and challenge of resistance has been with IBR virus, rather than with agents capable of producing pneumonia. Nonetheless, since IBR virus may be an important cofactor (component of a sufficient cause) in causing pneumonia (24) these studies may provide some insight into the possible efficacy of IBR vaccines against respiratory disease, in general.

Initial studies of intranasal IBR vaccines concentrated on the time required, postvaccination, for protective immunity to develop. The first study (55) reported that calves six to nine months old required approximately three days for protection against IBR challenge. The calves were allowed to acclimate for at least one month prior to vaccination. Later, other workers (49) suggested that more than three days were required since all three calves challenged at three days postvaccination developed IBR. From three weeks to nine months after vaccination good protection was claimed, however no control calves were challenged at these time periods. The authors noted also that the vaccinated calves were somewhat dull and lethargic three days after vaccination. Significant levels of interferon were found in both studies by three days postvaccination; however, it is not possible to attribute resistance against IBR to the interferon based on these data (49).

An intranasal and intramuscular IBR vaccine were contrasted in one study. No vaccinated calves but six of seven control calves developed clinical IBR when challenged four weeks after vaccination. The authors reported that some vaccinated calves developed subclinical IBR and that it seemed more extensive and severe in the intramuscularly than in the intranasally vaccinated calves (37). In a recent study of intramuscular IBR vaccination, one of eight colostrum deprived calves developed clinical IBR following aerosol challenge with live IBR virus, 75 days after vaccination. Both control calves developed clinical IBR (14). Based on these laboratory studies, it appears that protection against IBR may develop within three to four weeks after vaccination.

The results of a field trial of intranasal IBR vaccination and an observational study based on an outbreak of IBR in a bull-test station are shown in Table II. The field trial results, although not significant statistically, tended to indicate that vaccination of feedlot cattle shortly after arrival may have been more harmful than beneficial under the circumstances of the trial (9). Subsequently, some debate occurred about the rationale of conducting field trials under these conditions (3,10). Nonetheless, recent studies (34,35) have verified that a large proportion of calves are vaccinated, on or shortly after arrival, although they have been subjected to long periods of transportation. The need for field trials conducted under "real-world" conditions has been stressed previously (33) and is a basic tenant of epidemiology (51).

In contrast, vaccination of bulls, prior to entry to a test station, appeared to be protective, because during an outbreak of IBR none of 57 vaccinates, but 34 of the 267 nonvaccinates, developed clinical disease (21). However, there was a large pen to pen variation in disease occurrence and the outbreak did not occur until approximately 100 days after entry (and thus more than 100 days after vaccination).

Thus, with respect to IBR vaccines,

TABLE II
A SUMMARY OF RESULTS OF INFECTIOUS BOVINE RHINOTRACHEITIS (IBR) VACCINE IN FEEDLOT CATTLE

Reference Number	Vaccine Status[a]	Number of Calves	Morbidity// Mortality[b]	Comments
9	IBR(IN)	169	30(18%)/ /10(6%)	Cattle purchased from salesbarns, held six to 24 hours then 2/3 were vaccinated — held 12-24 hours then placed in feedlot where IBR was present. Authors noted large variation among groups of calves but always in favour of nonvaccinates
	C	62	5(8%) / / 2(3%)	
21	IBR	57	0	Outbreak of IBR in bull-test station. Observations suggested "history of vaccination" was effective; but, large pen to pen variation. Affected bulls gain less (up to 0.3 lb/dy) than non-affected bulls
	C	267	34(13%)	
68	IBR(TS-IN)	193	27(14%)	No details provided in reference. First two groups not quarantined prior to natural exposure. Last two groups quarantined five days before natural exposure
	C	146	88(60%)	
	IBR(TS-IN)	138	0(0%)	
	C	19	19(100%)	

[a]TS-IN = Temperature sensitive intranasal vaccine
IN = Intranasal vaccine
C = Control

[b]Number (percent). If // missing, only morbidity data presented

it seems reasonable to conclude that such vaccines will protect some (an unknown proportion) calves against clinical IBR provided the calves have an opportunity to develop immunity prior to challenge-natural or otherwise. The extent of protection against respiratory disease and the safety of vaccination in recently shipped cattle remains unknown.

Combined Parainfluenza-3 and Infectious Bovine Rhinotracheitis Vaccines

Because both PI_3 and IBR viruses had been associated with field cases of respiratory disease it was natural that combination vaccines be developed. In an early laboratory study, healthy dairy calves were vaccinated intramuscularly with live IBR and killed PI_3 virus. Five weeks later the calves were challenged by temperature stress then PI_3 virus exposure and finally exposure to IBR virus. One of four vaccinated calves and both control calves developed respiratory disease (19). Later, the same workers performed a field trial, with similar vaccines administered three weeks before shipping and again on arrival at the feedlot (Table III) (17). The vaccinated calves had a higher morbidity rate and higher rate of gain than control calves but neither difference was significant, statistically.

In 1973, the results of a field trial suggested little difference with respect to morbidity among groups vaccinated before shipment, on arrival or two to three weeks postarrival, although the latter group was treated for a longer period of time. Some additional weight gain was observed in groups vaccinated on arrival or prior to shipment and the authors concluded this was the appropriate time to vaccinate. No unvaccinated calves were included in the study (29).

Other workers (31) reported a reduction in morbidity, but a slight reduction in weight gain in calves vaccinated intranasally on arrival. Reduced weight gains and elevated morbidity rates were noted when vaccination was conducted five to seven days after arrival, in the face of an outbreak of respiratory disease. None of the differences reported were statistically significant; however, the authors cautioned against using vaccines in the face of an outbreak.

In 1978 a method of reproducing pasteurellosis by aerosol challenge was reported (23). The method involved exposure to aerosols of IBR virus and then, four days later, exposure to an aerosol of Ph. This method produced fibrinous pneumonia in 11 of 20 calves and was used subsequently to evaluate selected vaccines. In the first studies of vaccination (54) none of the calves vaccinated intranasally with IBR virus only, or IBR and PI_3 viruses, developed pneumonia, whereas, four of the five control calves developed pneumonia and two of these died. The vaccination was performed three weeks prior to exposure and the calves were left with the cows until challenged. These findings were confirmed in subsequent trials using the same vaccination regime with IBR virus only. However, in another study, a regime of three vaccinations with IBR-PI_3 viruses did not provide good protection. In this study half the calves were stressed by transportation, prior to challenge and the transported calves appeared to be more susceptible than the calves that were not transported (53). Recently PI_3 virus was reported to be synergistic with Ph exposure producing an extensive purulent pneumonia (26). No vaccine protection studies have been reported using this model.

In 1980, I collaborated in a study to assess the efficacy of vaccination, three weeks prior to shipping, with intranasal IBR-PI_3 virus vaccines (Unpublished data). Although it was possible

TABLE III

A SUMMARY OF RESULTS FROM FIELD-TRIALS OF INFECTIOUS BOVINE RHINOTRACHEITIS (IBR) AND PARAINFLUENZA-3 VIRUS (PI_3) CONTAINING VACCINES IN FEEDLOT CATTLE

Reference Number	Vaccine Status[a]	Number of Calves	Morbidity // Mortality	Weight Gain kg/hd/d	Comments
17	IBR-PI_3 (IM)	20	4(20%)[b]	0.7	Calves vaccinated three weeks prior to shipping and again on arrival. IBR was attenuated and PI_3 killed
	C	95	15(16%)	0.6	
31	IBR-PI_3 (IN)	43	15(35%)//0	0.4	Calves vaccinated on arrival and placed in different pens in a feedlot
	C	40	22(55%)//1(2%)	0.5	
	IBR-PI_3 (IN)	49	36(68%)//1(2%)	0.2	Calves vaccinated five to seven days after arrival in face of respiratory disease. Weights are 47 day gains
	C	26	13(50%)//0	0.3	
Unpublished data (Author)	IBR-PI_3 (TS-IN)	30	3(10%)	-	Calves vaccinated three weeks before weaning. Other vaccines included but no significant effect. Calves shipped from western Canada to Ontario feedlots
	IBR-PI_3 (IN)	76	27(36%)	-	
	C	49	17(35%)	-	

[a] IM=Intramuscular
IN=Intranasal
TS-IN=Temperature sensitive intranasal
C=Control

[b] Number (percent). If // missing, only morbidity data presented

to follow only a small percentage of originally vaccinated calves to feedlots, the temperature sensitive IBR virus vaccine appeared to reduce morbidity rates in comparison to nonvaccinated controls (Table III). Data from more recent studies on preshipment vaccination failed to validate these findings and neither of the IBR-PI_3 vaccines tested produced a statistically significant, or practical, benefit. Other workers have reported a significant benefit from temperature sensitive intranasal IBR virus vaccines (Table II) (68).

Also in 1980, a preimmunized and preconditioned calf sale in Alberta, Canada provided an opportunity to study the effects of vaccination (5). Although this was not a controlled trial and the calves were vaccinated in groups (based on farms) the preconditioned calves (vaccinated, weaned and creep-fed) had fewer disease problems than the preimmunized calves (vaccinated only) in Ontario feedlots. Nonvaccinated calves from the same salesyard, three days later, shipped by the same method of transportation at the same time to the same feedlots in Ontario performed worse than either of the preimmunized or preconditioned calves, despite being three days 'fresher' on arrival. The preimmunized calves did not perform better than nonvaccinates among those calves remaining in western Canadian feedlots. The specific vaccines used were not stated although most were intramuscular IBR or IBR-PI_3 virus preparations.

An observational study of morbidity and mortality in about 300 groups of feedlot calves, in Ontario, found that most vaccines were combination IBR-PI_3 intramuscular vaccines (34,35). In general, vaccinated groups had significantly increased mortality rates and/or treatment costs relative to unvaccinated calf groups. Morbidity rates were also increased in vaccinated groups but not to a significant degree. The data, from 137 vaccinated groups of calves, were reanalyzed in an attempt to identify characteristics of groups of calves associated with low treatment costs and mortality rates. Only three factors were significantly associated with low mortality; namely, delaying silage feeding, for two weeks, continuing to feed dry hay and not treating calves for grubs. There was no significant difference in the effects of intranasal versus intramuscular vaccines. No factors were significantly related to treatment costs in vaccinated groups of cattle.

Thus, although evidence from laboratory experiments supports the use of IBR-PI_3 vaccines to prevent pasteurellosis, there is little data to substantiate their efficacy under feedlot conditions. The observation from laboratory experiments, that transportation increases susceptibility to pasteurellosis (53) raises questions about the safety, as well as the efficacy, of vaccines in stressed calves. The value of specific vaccines as part of preimmunization or preconditioning program remains to be elucidated.

Pasteurella Bacterins

In 1924 (4) it was reported that aggressin gave better protection than a pasteurella bacterin (Aggressin is the crude supernatant material obtained from cultures of bacteria). No methods or data were presented but the author stated that vaccinated cattle were more susceptible to disease than control animals for one to two days after vaccination. Another study, reported in 1927, indicated that aggressin was more beneficial than bacterin when given at the stockyards prior to sale (Table IV) (39). In the latter study, the numbers of cattle in the two groups were extremely different, the number in the bacterin control group were not specified and the treatment rates seem low, for stressed

TABLE IV
A SUMMARY OF RESULTS FROM FIELD STUDIES OF *PASTEURELLA* (P) BACTERINS IN FEEDLOT CATTLE

Reference Number	Vaccine Status[a]	Number of Calves	Morbidity// Mortality	Comments
39	B+	57,946	-//662(1%)[b]	Bacterin or aggressin given at stockyards
	C	Not reported	Same as above	
	A+	708	-//40(6%)	
	C	700	-//17(2%)	
11	B+(Yards) B+(Farm)	381	-//42(11%)	Results obtained from studying outbreaks of shipping fever on more than 100 farms
	B+(Yards) A+(Farm)	90	-//9(10%)	
	B+(Yards)	3754	-//108(3%)	
	B-(Yards) B+(Farm)	1306	-//50(4%)	
	B-(Yards) A+(Farm)	93	-//6(6%)	
	C	3530	-//46(1%)	
41,45	P(m)	2093	49(2.3%)//10(0.5%)	Bacterin given ten days to six weeks prior to shipping. No details on allocation of animals to treatment groups
	C	3255	177(5.4%)//30(0.9%)	
42	P(h&m)2x	111	12(11%)	Vaccination initially given approximately ten weeks prior to weaning; second injection, when given, was given approximately 30 days before weaning. Results varied widely depending on origin of calves and time of weaning
	P(h)	111	9(8%)	
	P(h&m)2x	111	9(8%)	
	P(h)-2x	110	13(11%)	
	C	111	24(22%)	
1	P(h&m)	108	38(35%)	All calves given IBR-PI_3 (IN) and BVD(IM). Bacterin given on arrival and 21 days later. Most sickness had occurred prior to second vaccination
	C	107	33(31%)	

[a]B+ -Unspecified bacterin
A+ -Unspecified aggressin
P -*Pasteurella* (h) *hemolytica* (m) *multocida*
C -Control
IN -Intranasal
IM -Intramuscular

[b]Number (percent). If // missing, only morbidity data presented

salesyard cattle, at least by today's standards.

In 1932 a report of a large observational study, based on investigations of respiratory disease outbreaks on over 100 farms, was published (11). Although morbidity rates were not presented, there was a dramatic increase in mortality rates when either bacterin or aggressin were given (Table IV). Very high death losses were found in groups receiving both bacterin and aggressin as well as in groups receiving two doses of either preparation. It is quite likely that a number of different bacterins and or aggressins were used; however, no details were provided.

In a more recent study, cattle were vaccinated ten days to six weeks before shipment (41,45). No details on allocation of animals were provided — it is likely that groups of animals were allocated to treatment groups — and the control groups were shipped at a different time than the vaccinated cattle, thus reducing the possible significance of the 50% reduction in morbidity and mortality in vaccinated groups. Other workers (42) noted a beneficial effect in a number of different cattle groups using various pasteurella antigens. The bacterin was given twice, initially about ten weeks before weaning and a second injection about 30 days before weaning. Although the level of disease varied widely, depending on origin of calves and time of weaning, this well designed study provided evidence of a beneficial effect; about a 50% reduction in morbidity rates, due to pasteurella bacterins.

Since the mid 1960s, three studies were reported contrasting Pasteurella-PI_3 vaccinated calves with controls (17,18,59). None of the results of these studies indicated a benefit to vaccination (Table V) and for some reason, interest in bacterins appeared to wane. Later, in 1977 and 1980, reports of more severe lesions in vaccinated than in nonvaccinated cattle were published (15,32).

Despite, or perhaps because of the above, renewed interest in different forms of pasteurella vaccines and routes of administration has emerged. In 1978, laboratory studies indicated that subcutaneous (twice) or aerosol vaccination with live Ph protected calves that were challenged two weeks after vaccination, with an injection of pasteurella into the diaphragmatic lobe. For best protection, aerosol exposure had to be approximately 15 minutes in duration. A major problem in these studies was that calves naturally infected with BVD virus tended to develop pneumonia subsequent to being vaccinated by aerosol (8). In 1982, it was reported that both single and multiple aerosol vaccinations with live Ph failed to protect calves when challenged with IBR virus and latter Ph (25). Other workers reported that a chemically altered Pm bacterin protected gnotobiotic calves against intratracheal challenge with pasteurella (28). The same authors also injected approximately 3000 feedlot animals for safety evaluation, but did

TABLE V

A SUMMARY OF RESULTS FROM FIELD TRIALS OF PARAINFLUENZA 3-PASTEURELLA PI_3-P VACCINE IN FEEDLOT CATTLE

Reference Number	Vaccine Status[a]	Number of Calves	Morbidity // Mortality[b]	Weight Gain kg/hd/d	Comments
18	PI_3-P(h&m)	48	8(17%)//1(2%)		Calves vaccinated three times; three weeks before shipping (weaning), at shipping (weaning) and one week after shipping (weaning) PI_3 was killed and included an adjuvant
	C	117	20(18%)//2(2%)		
	PI_3-P(h&m)	40	4(10%)//1(3%)		
	C	45	9(20%)//1(2%)		
	PI_3-P(h&m)	15	0		
	C	29	1(3%)		
17	PI_3-P(h&m)	30	5(17%)	0.6	Three injections of killed PI_3: three weeks before weaning, at shipping and at arrival. Two injections of PHM to group 1 and one of PM to group 2 were given. Weights are 30 day gains. Sick calves gained 26 lb/hd less than nontreated calves
	PI_3-P(h&m)	20	4(20%)	0.5	
	C	95	14(16%)	0.6	
	IBR-PI_3/P(h&m)	40	0(0%)	0.6	Calves given three injections of PI_3/PHM as above and one injection of IBR prior to shipment. The last two groups of calves were not shipped
	C	45	0(0%)	0.7	
	IBR-PI_3/P(h&m)	15	4(27%)	-0.4	
	C	35	12(34%)	-0.4	
59	PI_3/P(m)	39	0(0%)	0.3	Two injections of killed PI_3 and bacterin; 30 days before weaning and at weaning
	C	247	5(2%)	0.2	
	PI_3/P(m)	98	4(4%)	0.4	
	C	182	10(6%)	0.4	
	PI_3/P(h&m)	61	1(2%)	0.6	Weights for first four groups are 38 day gains, 90 days for last four groups
	C	134	2(2%)	0.5	
	PI_3/P(h&m)	49	10(20%)//1(2%)	0.5	
	C	110	0(0%)	0.6	

[a]All were killed intramuscular vaccines
P-*Pasteurella* (h) *haemolytica* (m) *multocida*
C-Control

[b]Number (percent). If // missing, only morbidity data presented

not include control animals. This was unfortunate because control animals would have been useful-necessary?-for safety evaluation and could have provided evidence of the efficacy of the vaccine under field conditions.

Thus, the efficacy of pasteurella bacterins appears to be unresolved. Bacterins are not widely used currently, in feedlot cattle; perhaps, in part because of: their lack of dramatic impact on morbidity rates, reports of allergic type reaction when revaccinated and their apparent harmful effects in experimentally exposed calves.

Infectious Bovine Rhinotracheitis and/or Parainfluenza-3 Virus with Pasteurella Bacterins

In 1964, laboratory trials of PI_3-Pm and PI_3-Phm vaccines were reported. Two of four PI_3-Pm calves, one of four PI_3-Phm calves and two of two control calves had pneumonic lesions at slaughter. Three injections of vaccine were given five, six and nine weeks prior to challenge, which comprised temperature stress, then PI_3 virus exposure, then exposure to pasteurella by intratracheal injection (19). That same year the authors (18) reported on three field trials of PI_3-Phm vaccines (Table V). The differences in morbidity and mortality among groups were not significant, statistically. Again, in 1965, these workers reported on further trials with PI_3-Pm, PI_3-Phm, and IBR-PI_3-Phm vaccines and no significant benefit from vaccination was observed (18).

In another study, 18 calves were vaccinated twice, three weeks apart, with PI_3-Phm beginning four weeks after arrival in a feedlot. One month after the second vaccination, these calves were challenged with an aerosol of IBR virus, and developed a significantly higher temperature response than calves vaccinated with IBR-PI_3-Phm or IBR-Phm. The 17 nonvaccinated calves responded similarly to the PI_3-Phm group and thus the authors concluded that the IBR component was necessary for protection (36). In 1974, other researchers (59) failed to demonstrate any significant benefit from vaccination, in fact, in one of the four groups the control calves appeared to do much better than the vaccinated calves.

The data on morbidity rates, from each of these trials, were combined and the average odds ratio, comparing the extent of morbidity in vaccinated to unvaccinated calves, was 1.00 with 95% confidence limits of 0.66 to 1.54. Thus, there is no indication of a statistically significant effect of these vaccines on morbidity rates.

A field trial at Kansas State University compared preweaning vaccination (IBR-Phm) to vaccination at weaning. None of the 299 prevaccinated calves developed respiratory disease or died, whereas five percent of 337 calves vaccinated at weaning were sick and one died. No nonvaccinated calves were included in the study (52).

Bovine Virus Diarrhea Containing Vaccines

Vaccinating against BVD to prevent respiratory disease is a relatively recent and controversial practice. Certainly, cattle with BVD appear to have more respiratory disease (34) and are more susceptible to experimental Ph infection (8), although the virus does not appear to act in the same way as IBR or PI_3 viruses (30). Three field studies were published in 1973 by one group of workers (Table VI) (57,58,63). In no case did BVD virus vaccines appear protective, in fact they appeared harmful with respect to morbidity rates. Weight gains were improved in one group but this was not significant statistically, nor was the weight gain advantage seen in the other vaccinated groups. When the data in Table VI were combined, the average odds ratio, contrasting morbidity rates in vaccinated to nonvaccinated calves was 1.68 with 95% confidence limits of 1.06 to 2.68. This is a significant ($\chi^2 = 4.79$) increase in morbidity rates in vaccinated groups.

Although the role of BVD virus infection in respiratory disease remains to be clarified, it seems extremely difficult to justify the use of current BVD vaccines in stressed feedlot cattle. In the first year of a three-year beef feedlot study, feedlot owners using live BVD virus containing vaccines had major health problems with both clinical BVD and respiratory disease. The use of this vaccine was discontinued in subsequent years and BVD problems, if not respiratory disease, were reduced (34,35). It was perhaps a twist of fate that the health study was underway and records were available to document the extent of health problems in the vaccinated calves.

TABLE VI
A Summary of Results From Field-trials of Bovine Virus Diarrhea (BVD) Containing Vaccines in Feedlot Cattle

Reference Number	Vaccine Status[a]	Number of Calves	Morbidity	Weight Gain kg/hd/d	Comments
63	IBR-PI_3-BVD	15	1(1%)	0.4	Vaccinated on arrival.
	C	16	0	0.5	Weights are 27 day gains
57	BVD(IM)-PI_3(IN) + Serum	49	14(29%)	1.1	Calves vaccinated at weaning. Not shipped but
	Serum only	47	3(6%)	0.7	placed on "medicated
	C	44	8(18%)	0.8	feed study"
58	BVD(IM)-PI_3(IN)	56	40(71%)	1.3	Six month old, nonshipped
	BVD(IM)-PI_3(IN)2x	53	27(51%)	1.3	calves, vaccinated 41 days
	C	55	27(49%)	1.3	before weaning and one-half (second group) revaccinated at weaning. Weights are 30 day gains

[a]IN-Intranasal
IM-Intramuscular
C-Control

DISCUSSION

If one accepts that published data should receive considerable weight in any decision about vaccination, then justifying the inclusion of past and current vaccines against respiratory disease in a preventive program would be quite difficult. However, before pursuing this particular theme farther, some general comments on the literature might be useful.

It is a basic tenant of epidemiology that field trials should be performed in the species of concern in its natural setting and this relates to assessing the efficacy of vaccination programs (51). A number of descriptions of the design of field trials are available (6,7,20,33, 43,44) and although two of these papers (43,44) are concerned primarily with evaluating cancer therapy, they are quite informative about clinical trials in general.

With respect to the literature on field-trials of vaccines against respiratory disease, this author was struck by the lack of detail provided in the reports concerning: the method of allocation to treatment, whether groups of animals or individuals were allocated, methods used to minimize noncompliance or bias during the study, specification of outcome (response) events and the lack of formal analysis of results. In some instances, analytic methods have been used incorrectly, yet, different journals over a number of years have accepted and published results based on these analyses (60,62, 63). The inferences drawn from these (false) statistically significant results may have mislead many readers as well as the author's of these studies. In other instances, differences are declared significant with no test specified (59,61). Eminent statisticians (20) have been cited (60) to justify analytic methods (the text cited does not support the use of the technique) and support for "significant" results, but, when the published data were reanalyzed, by this author, the differences were nonsignificant. (My guess is that the authors used the number of calves, rather than the number of groups of calves to calculate the standard error of the mean.) Until journals and their reviewers become more stringent with respect to the design and analysis of field studies, the reader must interpret published results with caution.

Finally although statisticians are of great assistance in analyzing the results of a trial, it is my opinion that they are even more helpful in the design phase of the trail. In any case, since the statistician needs to understand the design of the study to correctly choose the analytic method, early consultation would be beneficial to all parties. One specific comment in regard to design concerns the use (lack of) of factorial experimental designs. In order to understand the effect of a combined vaccine such as PI_3-Phm, it would appear useful to have PI_3-Phm, PI_3 only, Phm only and a nonvaccinated control group concomitantly in one study. Such a design could assess the main effects of PI_3 and Phm plus any additional effect (interaction) from their combination, without greatly increasing the number of animals required for the trial. This and other more complex trial designs can be formulated by any competent statistician and by close collaboration between veterinarians and statisticians much more powerful, efficient, and practical, trials can be conducted.

Given the lack of supportive data for vaccination against respiratory disease, this author wonders why so many practitioners and feedlot managers continue to use the available vaccines. If the vaccines are as effective as claimed it should not be difficult to document their effectiveness. If the data reviewed by this author are incorrect or incomplete the published record should be updated as soon as possible. Recently, the American Association of Bovine Practitioners produced guidelines for the control of bovine respiratory diseases (2). In that guideline two statements appear which on the surface are contradicted by the available data; namely, "Both intramuscular and intranasal vaccines (referring to IBR, PI_3 and BVD) provide adequate immunity" and "Bacterial infections can be controlled with bacterins". Although specific reports can be found to support these statements the majority of the available data do not. Consistent findings, in a number of field-trials, are probably more indicative of a vaccines' usefulness than highly significant (statistically) results from one study. This was a major rationale for summarizing the results of many studies in this review.

Readers may argue that it is unrealistic to expect vaccines against specific agents, such as IBR, PI_3, Ph, etc., to protect against general respiratory diseases under all conditions. While true, if these agents are important component causes of the respiratory disease complex and if the vaccines are effective, one would expect to obtain observable benefits in the majority of field trials and observational studies. That such evidence does not appear in the published record — which is biased towards publishing positive findings (43,44) — leads this reviewer to conclude that most vaccines are ineffective in preventing respiratory disease.

Well designed, large multicenter (involving private practitioners) field trials could provide extremely useful information about the types of vaccines that are, or are not, effective. Such trials have been performed for a number of drugs and vaccines used in human medicine and are not beyond the practical capabilities of veterinary medicine. Current evidence suggests that vaccines will continue to be used and that new forms of vaccines will be produced. It is the responsibility of the veterinary profession, to ascertain which of these vaccines, if any, are effective under field conditions.

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PRIX VÉTÉRINAIRE GAINES

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