ARTICLE

Five field trials on the efficacy of a bovine respiratory syncytial virus vaccine

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Abstract

Five field trials evaluated whether immunization of beef cattle prior to weaning, at weaning, or immediately upon arrival at the feedlot with a commercial bovine respiratory syncytial virus (BRSV) vaccine would reduce subsequent treatment for respiratory disease.

Bovine respiratory syncytial virus vaccination was associated with a significant ($p < 0.05$) reduction in treatment rate in one of three groups of calves immunized prior to weaning (−12%) and in calves immunized upon arrival at the feedlot (−4%).

There was no significant ($p > 0.05$) effect of the BRSV vaccine on treatment rate in calves immunized at weaning, in calves immunized upon arrival at the Saskatoon bull test station, or in yearlings immunized upon arrival at the feedlot.

Although the trend in these field trials was to a sparing effect of the BRSV vaccine, the small reduction in treatment rate may not justify the cost of the vaccination program.

Résumé

Cinq études cliniques évaluant l'efficacité d'un vaccin contre le virus respiratoire syncytial

Cinq études cliniques furent entreprises pour établir si l'immunisation avec un vaccin commercial contre le virus respiratoire syncytial du bovin (VRSB) avant le sevrage, au sevrage ou immédiatement à l'arrivée au parc d'engraissement réduirait la nécessité d'un traitement subséquent pour des maladies respiratoires.

La vaccination contre le VRSB fut associée avec une réduction significative ($p < 0,05$) de la thérapie chez un des trois groupes de veaux immunisés avant le sevrage (−12%) et chez les veaux immunisés à l'arrivée au parc d'engraissement (−4%).

Il n'y a pas eu d'effets significatifs ($p > 0,05$) de ce vaccin sur le taux de thérapie chez les veaux immunisés au sevrage, chez les veaux immunisés à l'arrivée de la station d'évaluation de Saskatoon ou bien chez les veaux d'un an immunisés à l'arrivée au parc d'engraissement.

Bien que la tendance de ces études cliniques indiquait une certaine protection attribuable à la vaccination contre le VRSB, la faible réduction des taux de traitements ne semble pas justifier le coût d'un programme de vaccination.

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Introduction

Bovine respiratory syncytial virus (BRSV), a virus prevalent in the cattle population, has been implicated as a predisposing agent of fibrinous pneumonia and a cause of interstitial pneumonia (1). Bovine respiratory syncytial virus-induced pneumonia is characterized by a degenerative, necrotizing bronchiolitis, syncytial cell formation, edema, and emphysema (2,3).

Bovine respiratory syncytial virus can damage ciliated tracheal epithelial cells (4) and reduce the bactericidal activity of pulmonary alveolar macrophages (5,6). These effects may increase the ability of *Pasteurella haemolytica* to invade the lung and cause fibrinous pneumonia (1). Kimman (3,7) has suggested that the lesions in BRSV-induced pneumonia are due to direct viral cytopathic mechanisms followed by activation of complement.

The protective roles of humoral immunity, cell-mediated immunity, and nonspecific immunity in BRSV-induced pneumonia are poorly understood. Two studies have noted an association between high BRSV serum antibody titers upon arrival at a feeding location and a reduced risk of subsequent treatment for respiratory disease (8,9). Further studies on the role of the humoral immune system in BRSV infection are currently in progress (10). The roles of cell-mediated immunity and nonspecific immunity in BRSV-induced pneumonia are presently not known. From the limited data available, it appears that active immunity from infection with BRSV will protect against the develop-

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ment of pneumonia but not from reinfection upon future exposure to BRSV (1).

Two commercial modified-live BRSV vaccines are available in North America (11,12). The few field trials that have examined the efficacy of these commercial BRSV vaccines report conflicting results (11–17).

The purpose of the field trials described in this report was to determine whether immunization with a commercial BRSV vaccine prior to weaning, at weaning, or immediately upon arrival at the feedlot would reduce the subsequent treatment rate for bovine respiratory disease (BRD) in beef cattle. In addition, the effects of vaccination upon average daily gain and BRSV serological titers were examined.

Materials and methods

Trial 1

The ranch

A beef cow herd in southern Alberta, comprised of four smaller cow-calf herds, was used in this field study. Serological data from the fall of 1986 and 1987 had associated BRSV with outbreaks of respiratory disease in weaned calves at this ranch. This particular ranch was well suited for a BRSV vaccine study because: 1) there was a history of respiratory disease and concurrent BRSV infection; 2) all calves were individually identified and records were maintained on each calf at each feeding location; and 3) the owners wanted to examine, objectively, the efficacy of the vaccine in reducing the incidence of BRD.

Processing and allocation of treatment

Six-hundred-and-twenty-five crossbred calves, born from March 8 to May 20, 1988, were immunized three weeks prior to weaning. They were given a home-made mixture of vitamins A and D and selenium, and immunized with a combined modified-live virus (MLV) infectious bovine rhinotracheitis (IBR) and parainfluenza-3 (PI3) virus vaccine and *Haemophilus somnus* bacterin (IBR-PI3/Somnugen, Boehringer Ingelheim Animal Health, Burlington, Ontario). Calf eartag numbers were randomized by computer within each herd to determine vaccination groups. Half the calves within each herd were vaccinated intramuscularly with 2 mL of a MLV BRSV vaccine (BRSV Vac, Pioneer Hi-bred Limited, Chatham, Ontario). Following immunization, calves were returned to their dams on pasture.

Three weeks later the calves were weaned. One-hundred-and-thirty-eight bull calves were sent to a neighboring bull test station. Upon arrival they were given ivermectin (Ivomec, MSD Agvet, Kirkland, Quebec) and immunized with a 7-way clostridial bacterin (Clostri-Bac 7, Haver-Lockhart, Bayvet, Shawnee, Kansas). Vaccinates received a second dose of the MLV BRSV vaccine (BRSV Vac).

Another 97 bull calves were sent to a custom feedlot in southern Alberta. Upon arrival all these calves were given implants of zeranol (Ralgro, I.M.C., Terre Haute, Indiana) and vaccinated with a combined MLV IBR-PI3 vaccine and *H. somnus* bacterin (IBR-PI3/Somnugen), with a 7-way clostridial bacterin (Clostri-Bac 7), and with a *Pasteurella haemolytica* cytotoxoid (Presponse, Langford Inc., Guelph, Ontario). Vaccinated calves received a second dose of the MLV BRSV vaccine (BRSV Vac). Rectal temperatures were determined for all calves and those with a temperature greater than 40.5°C were designated sick, treated with trimethoprim-sulfadoxine (Trivetrin, Coopers Agropharm Inc, Willowdale, Ontario) at a dose rate of 3 mL/45 kg, and sent to a sick pen. All other calves were treated prophylactically with long-acting oxytetracycline (Liquamycin LA, rogar/STB, Pointe Claire-Dorval, Quebec) at a dose rate of 7 mL/45 kg. On day 4 after arrival a rectal temperature was taken on all calves. Calves with a temperature greater than 40.5°C were treated with trimethoprim-sulfadoxine (Trivetrin) and long-acting oxytetracycline (Liquamycin LA); the remaining calves received only long-acting oxytetracycline.

Heifer calves (317) and bull calves (52) which remained at the ranch were immunized at weaning with a combined *H. somnus* and 7-way clostridial bacterin (Fermicon 7/Somnugen, Boehringer Ingelheim Animal Health, Burlington, Ontario) and given ivermectin (Ivomec). Vaccinated calves were given a second dose of the MLV BRSV vaccine (BRSV Vac). An outbreak of respiratory disease occurred in the ranch calves at weaning. Calves were given short-acting and long-acting oxytetracycline (Liquamycin LP, Liquamycin LA, rogar/STB, Pointe Claire-Dorval, Quebec) based solely on a rectal temperature greater than 39.5°C. Blood samples were collected from a random sample of clinically affected and unaffected ranch calves for serological analysis of BRSV titers.

Trial 2

The bull test station

The Central ROP Bull Test Station in Saskatoon evaluates the performance of bull calves owned by various purebred breeders within Saskatchewan. These bulls are of various breeds and are born from January 15 to April 15. In 1986, respiratory disease had been a problem in bulls at this test station and necropsy results had revealed a viral interstitial pneumonia, with histological lesions suggestive of BRSV infection.

Processing and allocation of treatment

Two-hundred-and-eighty-three bull calves arrived at the bull test station on October 27 and October 28, 1987. Immediately upon arrival, bulls were weighed, eartagged, given ivermectin (Ivomec), and immunized with a combined MLV IBR-PI3 vaccine and *H. somnus* bacterin (IBR-PI3/Somnugen) and with an 8-way clostridial bacterin (Tasvax 8, Coopers Agropharm Inc., Willowdale, Ontario). A rectal temperature was taken on all bulls and those with a temperature greater than 40.0°C were considered sick and treated by a standard treatment protocol.

The bulls were systematically randomized into the vaccinate and control groups. Vaccinated bulls were immunized with a MLV BRSV vaccine (BRSV Vac) once upon arrival and revaccinated two weeks later. Control bulls received a placebo of sterile water.

Blood samples were collected on days 0, 14, 30 and 70 for serological analysis of their BRSV titers. Bulls were weighed every month and were put on the per-

formance test after an adjustment feeding period of 28 days.

Trial 3

Processing and allocation of treatment

Two-hundred-and-fifty-three Charolais-cross calves, born in February and March at the research station in Melfort, Saskatchewan were weaned on October 20, 1987. At weaning the calves, which had previously been identified with eartags, were vaccinated with a combined MLV IBR-PI3 vaccine and *H. somnus* bacterin (IBR-PI3/Somnugen). Calves were systematically randomized into the vaccinate and control groups. Vaccinates were immunized with a MLV BRSV vaccine (BRSV Vac) at weaning and again three weeks later. Controls were given a placebo of sterile water. A rectal temperature was taken on all calves and those with a temperature greater than 40.0°C were considered sick and treated with short-acting oxytetracycline (Liquamycin LP) at a dose rate of 6 mL/45 kg.

Blood samples were collected on days 0, 21, 40 and 82 for serological analysis of BRSV titers. Calves were weighed every two weeks.

Trial 4

Processing and allocation of treatment

A total of 611 auction market-derived, yearling cattle entered a large, 10,000 head capacity commercial feedlot in central Saskatchewan between April 12 and April 20, 1988. Within 24 h of arrival at the feedlot all the cattle were processed. They were uniquely identified with eartags, branded, given injections of vitamins A and D (Poten AD, rogar/STB, Pointe Claire-Dorval, Quebec) and ivermectin (Ivomec), and immunized with a MLV IBR-PI3 vaccine (Coopers IBR-PI3, Coopers Agropharm Inc., Willowdale, Ontario) and with an 8-way clostridial bacterin (Tasvax 8). The heifers were given implants of testosterone-estradiol (Heifer-oid, Boehringer Ingelheim Animal Health, St. Joseph, Missouri) and the steers were given implants of progesterone-estradiol (Steer-oid, Boehringer Ingelheim Animal Health, St. Joseph, Missouri).

The cattle were systematically randomized into the vaccinate and the control groups, with the vaccinates receiving one dose of a MLV BRSV vaccine (BRSV Vac) at processing.

Trial 5

Processing and allocation of treatment

A total of 4913 yearlings and 1716 calves in a large, 10,000 head capacity commercial feedlot in central Saskatchewan were used in this field trial during the fall and winter of 1988–89. Processing was performed within 24 h of arrival at the feedlot. All cattle were uniquely identified with an eartag, branded, given injections of vitamins A and D (Poten AD) and ivermectin (Ivomec), and immunized with an 8-way clostridial bacterin (Tasvax 8) and with a MLV IBR-PI3 vaccine (Coopers IBR-PI3). Some calf-lots were also immunized with a *H. somnus* bacterin (Somnugen, Boehringer Ingelheim Animal Health, St. Joseph, Missouri) and with a *P. haemolytica* cytotoxoid (Presponse). A rectal temperature was taken on all calves and those with a temperature greater than 40.0°C were considered sick and treated by a standard treatment protocol. All other calves were treated prophylactically with long-acting oxytetracycline (Liquamycin LA).

An attempt was made to vaccinate one-half of each processing group so that a pen would contain approximately 50% BRSV-vaccinated cattle. However, for various reasons, such as a small number of animals, weekends, and the unavailability of vaccine, the final allocation of the BRSV vaccine was haphazard. This resulted in a variable proportion of vaccinates and controls per processing group and pen. Cattle were immunized with a MLV BRSV vaccine (BRSV Vac) once upon arrival.

Follow-up

In all of the trials, the vaccinated and unvaccinated cattle were housed together in the same feeding pens. Treatment personnel at each feeding location were unaware of the BRSV vaccination status of the cattle. The case definition of first time treatment for BRD was as follows: 1) a rectal temperature $\geq$40.0°C (fever); 2) an appearance that was subjectively different from penmates; and 3) the absence of clinical signs attributable to any organ system other than the respiratory system. The recurrence rate was defined as the second-time treatment for BRD. Sick cattle were identified and treated by a standard treatment protocol at each feeding location. Health records were maintained on all cattle. Cattle that died during the trials were necropsied at a local veterinary diagnostic laboratory.

In trial 1, calves were monitored daily for illness from September 19, 1988 to January 31, 1989. Twenty-one calves were removed from the trial because they were incorrectly vaccinated with the BRSV vaccine or they were not present at weaning. In trial 2, calves were monitored daily for illness from October 28, 1987 to March 15, 1988. Fifty bull calves were disqualified from the trial because: 1) they had received a BRSV vaccine prior to arrival; 2) they had a fever on arrival; or 3) the owners refused to participate in the study. In trial 3, calves were monitored daily for illness from October 20, 1987 to January 26, 1988. Calves with a fever at weaning were excluded from the trial. In trial 4, cattle were observed daily for illness from arrival until slaughter. In trial 5, cattle were observed daily for illness during the first 60 days after arrival. Cattle with a fever on arrival were excluded from the trial.

Serological procedures

The BRSV ELISA was carried out using procedures similar to those previously described (18). Viral antigen for the test was grown in Vero cells, sonicated, clarified by low speed centrifugation, and concentrated by ultracentrifugation. Similar procedures were used to prepare cell control antigen. Four percent polyethylene glycol (MW 8000) (BDH Chemicals, Toronto, Ontario) was used in the conjugate diluent to intensify the reaction, and 0.004 M orthophenylene diamine (Sigma, St. Louis, Missouri) was used as chromogen.

Table 1. Effect of BRSV vaccination on the treatment rate for bovine respiratory disease

	Treated/n (%) Controls	Vaccinates	Relative[a] risk	95%[b] CI
Trial 1				
— ranch	47/186 (25)	57/183 (31)	1.23	0.89–1.71
— feedlot	19/45 (42)	17/52 (33)	0.77	0.46–1.30
— station	13/76 (17)	3/62 (5)	0.28	0.09–0.85
Trial 2				
— wk 1–20	26/117 (22)	17/116 (15)	0.66	0.38–1.14
— wk 2–20	20/111 (18)	15/114 (13)	0.73	0.40–1.35
Trial 3	1/126 (0.8)	1/127 (0.8)	0.99	0.06–15.69
Trial 4				
— wk 1-kill	13/317 (4)	6/294 (2)	0.50	0.20–1.27
— wk 2-kill	11/315 (3)	5/293 (2)	0.49	0.18–1.36
Trial 5				
Yearlings				
— wk 1–8	323/2809 (11)	241/2104 (11)	1.00	0.85–1.17
— wk 2–8	110/2596 (4)	81/1944 (4)	0.98	0.74–1.30
Calves				
— wk 1–8	190/887 (21)	137/829 (17)	0.77	0.63–0.94
— wk 2–8	76/773 (10)	50/742 (7)	0.69	0.49–0.96

[a]A relative risk of 1 indicates equal treatment rate in controls and vaccinates; a relative risk greater than 1 indicates higher treatment rate in vaccinates than controls; a relative risk of less than 1 indicates lower treatment rate in vaccinates than controls

[b]Test-based 95% confidence intervals. If the CI contains the value 1, the difference in treatment rate between vaccinates and controls is not statistically significant

Table 2. Summary of the effect of BRSV vaccination on the treatment rate for bovine respiratory disease

Trial	Age	Vaccine program	Number of vaccinations	Treatment rate (%) Controls	Vaccinates
1	calves	prewean[a]	two		
			— ranch	25	31
			— feedlot	42	33
			— station	17	5
2	calves	arrival[b]	two	22	15
3	calves	weaning[c]	two	0.8	0.8
4	yearlings	arrival[d]	one	4	2
5	yearlings	arrival[d]	one	11	11
	calves	arrival[d]	one	21	17

[a]Vaccinated three weeks prior to weaning and again at weaning

[b]Vaccinated on arrival at bull test station and again two weeks later

[c]Vaccinated at weaning and again three weeks later

[d]Vaccinated once immediately upon arrival at feedlot

All ELISA results were calibrated against the standard positive control serum to give uniformity to the results. The RSV antibody-free fetal calf serum (FCS) was used as the negative control. The reactivity of the sera was assessed as the optical density (OD) of wells with viral antigen minus the OD of wells with cell control antigen. The final results were expressed in units as follows, values greater than 10 being considered positive:

$$\frac{\text{Mean net OD of test serum} - \text{Mean net OD of FCS}}{\text{Mean net OD of positive standard serum} - \text{Mean net OD of FCS}} \times 100$$

Statistical analysis

Case history, weight, treatment data, vaccine status, and BRSV serological titers were collected and entered into the Statistical Analysis System (SAS Institute Inc., Cary, North Carolina). Odds ratios, relative risks, and test-based 95% confidence intervals were calculated (19,20). The Mantel-Haenszel technique for calculating a summary odds ratio was used to test for the presence of confounding (19). The Breslow-Day test for homogeneity was used to test for statistical interaction (19).

In trial 1, treatment rate was stratified by feeding location so that interaction between vaccination status, treatment rate, and feeding location could be examined. In trial 5, data on calves was stratified by season of entry, and *H. somnus* and *P. haemolytica* vaccination, to determine if these factors were modifiers of vaccine effect. The "Student's" *t*-test (21) was used to analyze differences in average daily gain (ADG) between the controls and the vaccinates. Analysis of

Table 3. Average serological titer ± SD to BRSV classified by treatment for bovine respiratory disease and BRSV vaccination status

Trial	Sample date	Treatment Yes	Treatment No	Vaccination Yes	Vaccination No
1*	n	19	16	21	14
	Acute	36.7 ± 16.4	33.4 ± 15.6	41.0 ± 12.0[a]	26.4 ± 17.4[a]
	Convalescent	43.4 ± 19.6	49.2 ± 27.5	57.4 ± 21.7[b]	29.1 ± 13.7[b]
2	n	43	189	116	114
	day 0	5.5 ± 9.1	7.9 ± 14.0	7.4 ± 13.0	7.6 ± 13.7
	day 14	36.8 ± 20.7	41.9 ± 23.8	40.7 ± 22.5	41.3 ± 24.3
	day 30	80.3 ± 23.1	74.9 ± 35.6	71.9 ± 27.3	79.8 ± 38.7
	day 70	78.4 ± 26.0	71.4 ± 26.9	68.1 ± 26.3	77.2 ± 26.6
3	n	2	218	110	110
	day 0	8.5 ± 0.7	31.0 ± 25.3	31.3 ± 26.1	30.4 ± 24.5
	day 21	43.5 ± 26.2[c]	77.0 ± 24.1[c]	77.8 ± 24.6	77.3 ± 24.0
	day 40	134.0 ± 59.4[d]	97.2 ± 25.0[d]	102.6 ± 25.3[e]	92.8 ± 24.7[e]
	day 82	135.0 ± 80.6[f]	91.4 ± 23.8[f]	95.5 ± 24.7[g]	88.5 ± 24.3[g]

*Calves at the ranch during the outbreak of respiratory disease

[abcdefg]Superscripts with the same letter are significantly different from each other ($p < 0.05$)

variance, using repeated measures over time (19), was used to analyze BRSV serological titers.

Results

Trial 1

The overall treatment rate for the calves at the ranch was 28%; at the feedlot it was 37%; and at the bull test station it was 12%. At the ranch, 47 control calves (25%) and 57 vaccinated calves (31%) were treated for respiratory disease (Tables 1 and 2). One vaccinated heifer calf died from fibrinous pneumonia caused by *P. haemolytica*. At the feedlot, 19 control calves (42%) and 17 vaccinated calves (33%) were treated for BRD (Tables 1 and 2). At the bull test station, 13 control calves (17%) and 3 vaccinated calves (5%) were treated for BRD (Tables 1 and 2). The BRSV vaccine was associated with a significant ($p < 0.05$) reduction in the treatment rate of BRD in vaccinated calves at the bull test station.

A summary odds ratio or relative risk could not be calculated because of significant differences in the stratum specific odds ratios at each feeding location (20), indicating that the effect of the BRSV vaccine upon treatment rate was not the same at all locations.

There was a significant difference ($p < 0.05$) in acute and convalescent BRSV titers between vaccinated and control calves, but there was no association between BRSV serological titers and treatment for respiratory disease (Table 3). Titers significantly ($p < 0.05$) increased over time in vaccinated and control calves.

Trial 2

The overall treatment rate for bulls at the bull test station was 18%. Twenty-six control bulls (22%) and 17 vaccinated bulls (15%) were treated for respiratory disease (Tables 1 and 2). The treatment rate measured from week 2 to week 20 was 18% in the controls and 13% in the vaccinates (Table 2). There was no significant association between treatment rate and BRSV vaccination.

One control bull died from bloat and one vaccinated bull was slaughtered because of a fractured humerus. The average daily gain in the control bulls was 1.47 ± 0.20 kg/day, similar to ($p = 0.51$) the ADG in the vaccinated bulls, at 1.46 ± 0.21 kg/day.

Twenty-seven percent of the bulls had a positive (> 10 units, ELISA) serological titer to BRSV on arrival at the bull test station. There was no significant association between BRSV serological titers and vaccination for BRSV or treatment for BRD, but the titers increased significantly ($p < 0.05$) over time (Table 3).

Trial 3

The overall treatment rate in the calves was 0.8%. One control calf and one vaccinated calf were treated for BRD (Tables 1 and 2). The average daily gain in the control calves was 0.82 ± 0.21 kg/day, similar to ($p = 0.31$) the ADG in the vaccinated calves, at 0.84 ± 0.21 kg/day.

Eighty-five percent of the calves had a positive (> 10 units, ELISA) serological titer to BRSV at weaning. The BRSV titers were significantly ($p < 0.05$) associated with vaccination on days 40 and 82 and with treatment on days 21, 40 and 82 (Table 3). Titers increased significantly ($p < 0.05$) over time.

Trial 4

The overall treatment rate for yearling cattle was 3%. Thirteen control cattle (4%) and six vaccinated cattle (2%) were treated for BRD (Tables 1 and 2). The treatment rate from week 2 until slaughter was 3% in the controls and 2% in the vaccinates (Table 1). There was no significant association between treatment rate and BRSV vaccination. One vaccinated steer died three days after arrival at the feedlot from fibrinous pneumonia caused by *P. haemolytica*.

Trial 5

The overall treatment rate for yearlings was 11% and for calves was 19%. From week 1 to week 8, 323 of

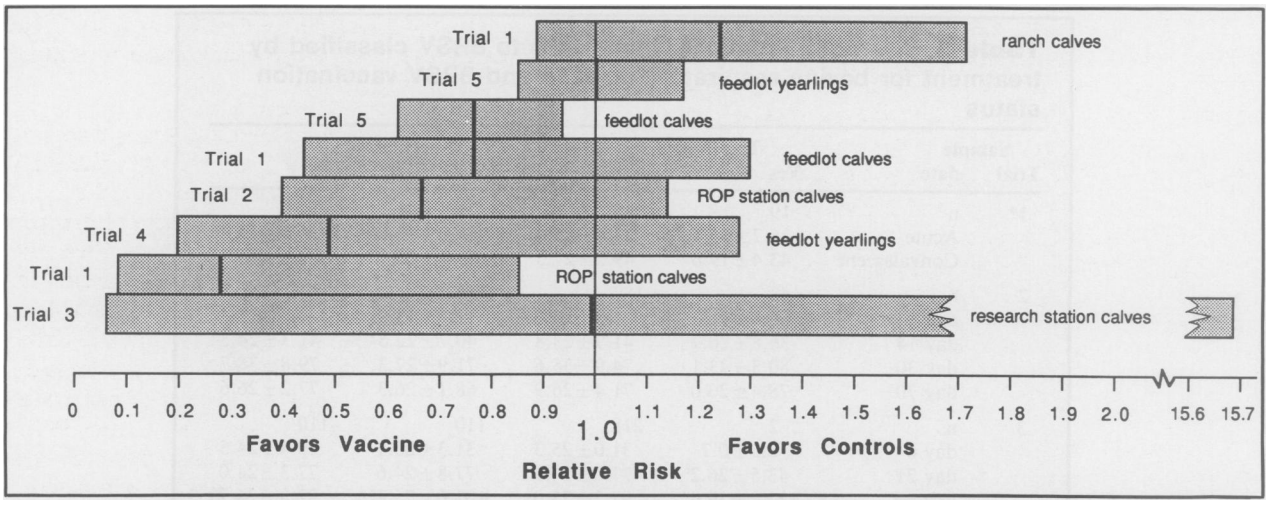

Figure 1. Ninety-five percent confidence intervals (95% CI) for the relative risk of respiratory disease (BRD) in five field trials on BRSV vaccine efficacy. 95% CI is represented by the horizontal bar and the relative risk is represented by the vertical line within the bar. See Table 1 for definition of relative risk and 95% CI. Example: In the case of the ranch calves in trial 1, the treatment rate of BRD in vaccinated calves was 1.23 times greater than the treatment rate of BRD in control calves. Since the 95% CI (0.89–1.71) contained the value 1, the difference in treatment rate between vaccinates and controls was not statistically significant.

the control yearlings (11%) and 241 of the vaccinated yearlings (11%) were treated for BRD. During the same period, 190 control calves (21%) and 137 vaccinated calves (17%) were treated for bovine respiratory disease (Tables 1 and 2). The treatment rate from week 2 to week 8 was 4% in yearlings and 8% in calves. The treatment rate from week 2 to week 8 in both control and vaccinated yearlings was 4%; in control calves it was 10% and in vaccinated calves it was 7% (Table 1). Bovine respiratory syncytial virus vaccination was associated with a significant reduction ($p<0.05$) in treatment rate in vaccinated calves, measured from week 1 or from week 2 to week 8. The recurrence rate of respiratory disease was 11% in control yearlings, 8% in vaccinated yearlings, 10% in control calves, and 7% in vaccinated calves. There was no significant association between recurrence rate and BRSV vaccination (data not shown).

Seven control yearlings (0.2%) and five vaccinated yearlings (0.2%) died from fibrinous pneumonia. One control calf (0.1%) and two vaccinated calves (0.2%) died from fibrinous pneumonia.

Vaccination with a *H. somnus* bacterin, a *P. haemolytica* bacterin, or season of entry into the feedlot were found not to be modifiers of the vaccine effect in calves.

Discussion

The results of all the trials could not be summarized to produce a single estimate of the effect of vaccination due to the variability in this effect in the different groups of cattle (Table 1). However, in all but one (ranch calves) of the eight distinct groups of cattle to which the vaccine was given, the trend was towards a beneficial effect (Figure 1), with a reduction in treatment rate in the vaccinates ranging from 0% to 12%. In two cases, this beneficial effect was statistically significant, with a reduction in treatment rate in the vaccinates of 4% and 12%. In one group of calves, the use of the vaccine tended to result in an increase in the treatment rate of 6%. Although this increase in the risk of treatment was not significant, we remain concerned that the use of the BRSV vaccine may not be safe in all instances. Further trials will be required to determine if the vaccine can, in some instances, result in an increased rate of BRD.

The failure to show a significant effect of the vaccine upon the treatment rate of BRD in the majority of the groups of cattle was not unexpected. The small effect of vaccination, the variability of this effect, the relatively crude case definition of disease, the low rate of disease in some groups, the relatively small numbers of animals in all but trial 5, and the nonrandom assignment of vaccination in trial 5 may all have combined to bias the relative risks of disease towards unity (22). Confining the vaccinates and the controls together in the same feeding pen may have resulted in herd immunity, which would also have reduced the perceived effectiveness of the vaccine (20).

In trials 4 and 5, cattle were not revaccinated two to three weeks after the first vaccination, as manufacturers recommend, which may have reduced the magnitude of the vaccine effect. Based upon the occurrence of morbidity and the high rate of natural seroconversion to BRSV shortly after arrival into the feedlot, revaccination of feedlot cattle may be of limited value.

In order for a vaccine to be most effective, it should be given at least two weeks prior to the period of greatest risk to allow time for the development of a protective immune response (23–25). The established structure of the North American beef feeding system often prevents vaccination of cattle prior to arrival at the feedlot. Epidemic curves of treatment rate for BRD in North American feedlots demonstrate that the greatest proportion of morbidity appears to occur within the first two weeks after arrival at the feedlot (26), before a vaccine given upon arrival could take effect. Analyzing the treatment rate from week 2 rather than from arrival is a more appropriate measure of vaccine effect when the vaccine is given upon

arrival. In these trials, measuring treatment rate from week 2 rather than from arrival resulted in a similar reduction in treatment rate in both the vaccinate and the control groups, thus not altering the relative risks.

A placebo was not used in the control groups in trials 1, 4 and 5. One reason a placebo may be used in a trial is to insure that the treatment personnel are unaware (blind) of the vaccination status of the cattle, reducing any potential information bias this knowledge may cause (22). In all of these trials, the treatment personnel were unaware of the vaccination status of the cattle. A second reason a placebo may be used in a trial is to determine if the protective effect of the vaccine is due to the antigen in the vaccine or to the excipients in the vaccine, such as the adjuvant. A placebo containing the excipients was not used in any of these trials. There is the possibility that the beneficial effect of the vaccine in the majority of these trials was due to the excipients, not the viral antigen in the vaccine. Use of the excipient as the placebo biases the results toward no difference. In this study, it was irrelevant whether the protective effect of the vaccine was due to the antigen or to the excipient because our interest, and that of the producer, is in the efficacy of the commercial product.

In trial 5, animals were assigned haphazardly to the vaccinate or to the control groups, not by a formal random procedure. This haphazard allocation may have resulted in selection bias, which could have reduced the similarity of the vaccinate and the control subjects, distorting vaccine effects (22). However, the large number of sources of auction market cattle that made up each processing group, and the large number of processing groups, probably reduced the likelihood of significant bias.

The interpretation of serological data from these trials was difficult. In trial 1, BRSV titers in calves wintered on the ranch were significantly higher in the vaccinate than the control groups, suggesting an antibody response to the BRSV vaccine. The constant low BRSV titers in the control group suggested an absence of BRSV infection during the outbreak of respiratory disease. In trial 2, serological BRSV titers were similar in the vaccinate and the control groups. Spread of the vaccine virus from the vaccinates to the in-contact controls may have resulted in the similar increase in titers over time, however this appears unlikely based on other studies which have suggested that the vaccine virus is not shed (11,12). The similar BRSV titers of the vaccinates and the controls most likely represents subclinical natural BRSV infection during the trial. Subclinical BRSV infection did not influence average daily gain. In trial 3, although BRSV serological titers were different between the vaccinates and the controls on days 40 and 82, the biological significance of this is unknown. Initial BRSV titers in the two treated calves were negatively associated with subsequent treatment for BRD.

In summary, immunization of cattle prior to weaning, at weaning, or upon arrival at the feedlot with the BRSV vaccine had a variable effect on the subsequent treatment rate for BRD. Although the trend in these field trials was to a sparing effect of the BRSV vaccine, the small reduction in treatment rate for BRD may not justify the cost of the vaccination program.

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