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A randomized control trial investigating the effectiveness of a commercial pneumonia vaccine (Part II): Weaned lambs

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ABSTRACT

The objective of this randomized controlled vaccine field trial was to determine the effectiveness of a commercial respiratory bacterin, Ovipast™ Plus, administered to feedlot lambs at weaning, approximately 8 wk of age, to improve animal health, growth performance, and carcass traits. Lambs were weaned, weighed, and sorted into groups by sex and the previous Ovipast™ Plus vaccination status of their mother, because this is stage 2 of that ongoing trial (Gardner et al., 2023). Lambs born to vaccinated ewes were vaccinated with the Ovipast™ Plus bacterin and revaccinated 3–5 wk later. Lambs born to unvaccinated ewes were not vaccinated. During the growing and finishing phases of the trial, vaccination did not reduce pneumonia treatment rates, crude or pneumonia specific mortality rates, or improve growth rates. Vaccinated lambs had a lower carcass fat cover ($P < 0.001$) and a 1.33 times increased odds of yielding a Grade 1 carcass compared to unvaccinated lambs ($P = 0.01$). Vaccination reduced carcass fat cover and improved yield grades, but it had no beneficial effect on disease rates or growth performance, suggesting a limited economic benefit of vaccinating lambs post-weaning, which were borne from ewes vaccinated with Ovipast™ Plus during gestation.

1. Introduction

Pneumonia is a significant cause of death in weaned lambs, where the highest risk of disease is observed shortly after weaning (Navarro et al., 2019). Ovine respiratory complex (ORC) is a syndrome with many infectious causes, but *Mannheimia haemolytica* bacteria have been identified as the predominant pathogen (Australia Livestock Export Corporation Ltd, 2021; Van Donkersgoed et al., 2016). Ovine respiratory disease complex is often a silent disease because many fatal cases are acute and asymptomatic (Navarro et a., 2019). This finding suggests that clinically sick lambs only represent a small portion of the true occurrence of the disease in any given flock. Navarro et al. (2019) found that the peak incidence of ORC during the fattening period of lambs is 2–4 wk after feedlot arrival. The first peak in disease corresponded with the stress of transport, and the second peak corresponded with the onset of clinical coccidiosis. Navarro et al. (2019) observed that lambs with clinical coccidiosis had an increased risk of developing ORC within 2 wk (Navarro et al., 2019), most likely due to the immunosuppressive effects of the concurrent parasitic disease (Wright and Coop, 2007).

Factors that can influence the incidence of ORC in a flock include recent transport of stock, mixing stock of different immunological backgrounds, air quality, stocking density, and pen hygiene (Callan and Garry, 2002; Hilton, 2014; OMAFRA, 2021). Management of these factors is one way to reduce the risk of ORC cases in a flock. Vaccines are another tool that may reduce the number and severity of ORC cases in a flock.

Currently, there are no ovine respiratory vaccines licensed in Canada. Several vaccines are licensed in Canada against infectious agents in cattle that cause bovine respiratory disease (BRD). Vaccination against infectious viral and bacterial BRD pathogens is a widely adopted practice in beef cattle in North America, despite reports of variable vaccine effectiveness in the field (O'Connor et al., 2019a). Successful respiratory vaccine development for sheep has been slow, because of the many strains of *M. haemolytica* isolated from sheep (Alley, 2002). *Mannheimia haemolytica* has shown patterns of variation by pulsed field gel electrophoresis (PFGE) and phenotypic analysis (Villard et al., 2008). It is believed that a vaccine targeting this bacterium is unlikely to produce antibodies that cross-protect against other strains (Alley, 2002).

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Therefore, once immunity to 1 strain is established, there is a high probability that other strains of *M. haemolytica* or other opportunistic organisms, such as *Pasteurella multocida* (Black, 1997), would fill the void and cause disease. Although both cattle and sheep are susceptible to pneumonia caused by *M. haemolytica*, bovine pneumonia is typically caused by serotype A1, whereas ovine pneumonia is predominantly caused by serotype A2 (Frank, 1989; Gilmour and Gilmour, 1989). Additionally, the origin of the *M. haemolytica* strain used to create a vaccine, whether from cattle or sheep, is important because the outer membrane proteins (OMP) differ between species, and they may be protective vaccine antigens. Therefore, a vaccine generated from bovine strains most likely would not protect sheep, and vice versa (Hounsome et al., 2011). Respiratory vaccines need to be specifically developed and tested for use in sheep. Even if a vaccine containing the most prevalent pathogens were available, there are additional factors that influence vaccine effectiveness in the field, such as the timing of vaccination relative to disease challenge, a stressful event (e.g., transportation, weaning), pre-existing disease, the immune status of the animal, environmental factors such as housing and ventilation, and pathogen load (Callan and Garry, 2002).

Once an efficacious ovine vaccine has been developed and tested in experimental challenge studies, determining vaccine effectiveness in the field can be challenging. O'Connor et al. (2019a) conducted a meta-analysis reviewing the published literature on the effectiveness of bacterial and viral BRD vaccines administered to cattle at or shortly after feedlot arrival. They found that vaccines given close to the time of arrival did not reduce the occurrence of BRD in feedlot cattle. The authors discussed two main probable flaws in a portion of the studies included in the meta-analysis: 1) controls in some trials may have received a BRD vaccine upon arrival at the feedlot and were not true negative controls; and 2) vaccines are often licenced and approved for sale based on controlled laboratory experimental vaccine challenge studies, which may not represent natural disease challenge in the field. Stressors, such as transportation, comingling of sources, and administering multiple vaccines at processing, may reduce immune responses due to immune suppression and antigen overload; thus, influencing the effectiveness of another vaccine administered at that time (O'Connor et al., 2019a). The authors noted that it was not uncommon for cattle arriving at a feedlot to receive metaphylactic drugs, suggesting that some of the animals on arrival were unhealthy, which may affect vaccine effectiveness. Metaphylactic drugs, such as macrolides, have been shown to be effective in reducing BRD morbidity and mortality, and in improving growth performance in feedlot cattle (O'Connor et al., 2019b), but their use in a vaccine trial may reduce the ability to detect vaccine effects. O'Connor et al. (2019b) concluded that the best way to determine the effectiveness of a respiratory vaccine in the field and create informed vaccination guidelines, was a controlled field trial with a sufficient number of animals that represented the target population, under natural disease settings, where vaccines were randomly allocated to vaccinates and non-vaccinates; thus, controlling potential confounders that may bias trial results (Goodwin-Ray et al., 2008; O'Connor et al., 2019a).

A randomized control field trial using a commercial sheep pneumonia vaccine was conducted in New Zealand (Gilmour et al., 1991; Goodwin-Ray et al., 2008). The Ovipast™ Plus bacterin contains antigens for A1, A2, A6, A7, and A9 strains of *M. haemolytica,* and T3, T4, T10, and T15 strains of *Bibersteinia trehalosi*. Based on the continuous outcome of average daily gain (ADG) and the categorical outcome of pneumonic lung lesions, the authors concluded that the vaccinated group was not statistically different to the unvaccinated group. In that trial, vaccinated and unvaccinated lambs were housed together, which typically reduces the ability to see a vaccine effect due to herd immunity (O'Connor et al., 2019a). If the vaccine was effective, herd immunity from the vaccinated animals may have conferred some protection to the unvaccinated animals by reducing the spread of infectious agents amongst the group, potentially reducing the incidence and severity of disease in the unvaccinated animals; thus, making it more difficult to see a vaccine effect. This highlights the importance of trial design when determining the effectiveness of a vaccine in a commercial livestock operation. Goodwin-Ray et al.'s (2008) randomized control trial is the only published field trial on the effectiveness of the Ovipast™ Plus bacterin. Further investigation of this vaccine is warranted because New Zealand has an extensive lamb rearing system, which differs from Canadian, northern American, and European sheep operations, where most lambs are raised intensively.

The Ovipast™ Plus bacterin has a label claim to aid in the prevention of "pneumonic pasteurellosis in sheep of all ages, from a minimum of 3 wk of age, and in the control of systemic pasteurellosis in weaned fattening lambs and breeding sheep" (Intervet MSD). Based on these label indications, the current authors evaluated this vaccine in ewes during gestation to increase colostral immunity to reduce disease risks in pre-weaned lambs (Gardner et al., 2023). The objectives of the second phase of that same randomized controlled field trial, which is described here, were to determine the effectiveness of the Ovipast™ Plus bacterin, administered to lambs at weaning and post-weaning, in reducing morbidity and mortality rates from pneumonia, and improving growth performance and carcass traits in lambs under commercial feedlot conditions.

2. Materials and methods

This project received ethics approval for the animal utilization protocol (AUP#4625) from the Animal Care Committee at the University of Guelph.

2.1. Study design

This study is the second part of a larger, single, continuous controlled vaccine field trial, conducted at an Alberta, Canada sheep operation to evaluate the effectiveness of a commercial vaccine in both pre-weaned and weaned lambs. In brief, this farm consisted of approximately 10,000 Rideau Arcott breeding ewes that lambed year-round (Gardner et al., 2023). Upon weaning, at approximately 8 wk of age, lambs were moved from the breeding side of the farm to the feedlot side, where they were then housed in outdoor feedlot pens. Each pen had a covered structure to provide shelter. This trial included lambs from the initial first trial (Gardner et al., 2023) from weaning to slaughter, and was conducted from March 2nd, 2022, to November 23rd, 2022.

In the previous trial, pregnant ewes were randomly allocated to receive the Ovipast™ Plus bacterin (Intervet/Merck Animal Health, Milton Keynes, United Kingdom) twice during gestation, or remain as negative unvaccinated controls (Gardner et al., 2023). For this second phase of the trial, lambs born to vaccinated ewes were also vaccinated with the Ovipast™ Plus bacterin, subcutaneously at weaning, approximately 8 wk of age, and revaccinated 3–5 wk later. Lambs born to unvaccinated ewes remained as negative unvaccinated controls from weaning to slaughter.

The trial sample size for the pre-weaning phase of the study was 6000 lambs, 3000 lambs per group (Gardner et al., 2023), and the sample size for the post-weaning phase was the remaining live lambs at weaning. The inclusion criteria for lambs inducted into phase 2 of the controlled vaccine field trial were: 1) trial lambs that were part of the phase 1 study (Gardner 2023), 2) trial lambs that survived the pre-weaning phase, and 3) trial lambs that were not withdrawn from the trial pre-weaning (i.e., escaped from their feeding pen and could not be returned to it because of a missing identification ear tag). Vaccination status of the ewes in the previous trial was randomized and the lamb vaccine status in this trial was determined by the ewe's vaccine status, because the controlled vaccine field trial was evaluating the effect of vaccinating both the ewe and her lambs compared to unvaccinated ewes and their unvaccinated lambs.

2.2. Animal management and housing

Lambs were weaned abruptly at approximately 8 wk of age and then moved into the feedlot for the growing phase of their life, which lasted from 8 to 13 wk of age. They were then moved into the finishing phase of their life, until they reached approximately 50 kg of live weight, at which time they were sent to slaughter. Lambs remained in growing pens for an average of 5 wk, with some variation due to pooling of lamb ages within pens.

At the time of weaning, lambs were separated from the ewes, weighed to determine their weaning weight, and then sorted into separate feedlot pens according to sex and vaccine status: (1) unvaccinated ewe lambs, (2) unvaccinated ram lambs, (3) vaccinated ewe lambs, and (4) vaccinated ram lambs. To fill a growing pen to capacity and maximize pen usage on farm, 3 consecutive wk of lambs were weaned into the same growing pen, before a new pen was started. This age difference within a single growing pen resulted in a variation of 3–5 wk between the initial dose of the Ovipast™ Plus bacterin at weaning and the booster dose.

Lambs in the growing phase were fed a nutritionally balanced growing pellet, formulated for their stage in production by the operation's nutritionist, which was supplemented with straw as a source of forage. Lambs were weighed at weaning and at the end of the growing phase. At the beginning of the finishing phase of the study, lambs were sorted by individual body weight into feedlot pens, split by sex and vaccine status. Sorting of body weights was as follows: 1) < 40 kg, 2) 40–50 kg, and 3) >50 kg. Lambs > 50 kg were placed in a pen for immediate slaughter. Remaining lambs were moved into feedlot pens and not reweighed until approximately 50% of the lambs were estimated to be ready for slaughter at 50 kg. Estimations for when to reweigh a finishing pen were based on the entry weight of the lamb into the finishing pen and a predicted average daily gain (ADG) for that lamb. Once 50% of the pen was predicted to be over 50 kg, the entire pen was weighed. During this weight event, lambs > 50 kg were sorted out for immediate slaughter, and the remaining lambs were sent back to the same feedlot pen for further feeding. When the pen housed 100 head, it was not reweighed for slaughter until all animals were predicted to be over 50 kg. During the finishing phase, all trial lambs were fed the same finishing pellet designed to meet the nutritional requirement of that stage in production.

2.3. Outcomes

All lambs that died prior to slaughter were necropsied by the researchers or trained feedlot staff as per a standardized process to determine the cause of death based on gross morphologic lesions. Barn staff walked the feedlot pens every morning to collect any dead trial lambs, and necropsies were completed the same day.

The lungs of all trial lambs that died were evaluated and given a lung score based on presence of pneumonic lesions and pleurisy. Each lobe was allocated a point from 0 to 2 based on the percentage of lung lesions (0 = no lesions, 1 = individual lobe with < 50% affected by pneumonic lesions, and 2 = > 50% pneumonic lesions). An additional point was given for the presence of pleurisy (McRae et al., 2016; McRae et al., 2018). Lung tissue samples from lambs that died of pneumonia were frozen and formalin fixed. Frozen and formalin fixed tissues were sent to the Animal Health Laboratory, University of Guelph, Guelph, Ontario, Canada for culture and histopathology (Gardner et al., 2023).

A convenient subsample of lungs was scored at the slaughter plant using the pneumonic lung scoring system described by Bryant et al. (1999). Lungs were categorized based on the percentage of total lung consolidation: 0%, 1–15%, 15–50%, or >50%, with an additional yes/no category for the presence of fibrinous adhesions. Due to limited trial budget, all lungs from all trial lambs could not be assessed at slaughter.

2.4. Statistical analysis

All data on animal weights and death events were recorded in a computerized animal health management system (FeedIT, ITS Global, Okotoks, Canada). Trial data were pulled from the farm software system and put into Excel spreadsheets for statistical analyses. The weaning-to-slaughter phase of the Ovipast™ Plus trial was evaluated in two timeframes: (1) growing phase, and (2) finishing phase, due to rehousing of the trial lambs during the study. Master spreadsheets were created for each of the two timeframes. Any lamb that did not reach the end of the phase or died, was searched individually in FeedIT to confirm their outcome. They were considered removals if they met any of the removal criteria. Reasons for removals during the growing phase included a lamb that lost its identification ear tag or was placed into a non-trial pen.

For the growing phase, the variable, "DTG" (Days to Grow), was generated to sum the total time (days) each lamb spent in the growing phase. For the finishing phase, the variable "FTS" (Finish to Slaughter), was generated to sum the time in days each lamb was in the finishing phase. All variables were checked for min/max values and for missing data (NA = not available) to identify data entry errors and missing information. Both growing and finishing data were then evaluated separately. For descriptive production measures of weaning weight, growing phase end weight, and finishing phase end weight, days in each phase, and average daily gain (ADG) during the growing and finishing phases were generated by vaccine group and by sex. Additionally, descriptive statistics on slaughter parameters were also generated on yield grade (YG), fat cover of the carcass, and hot carcass weight (HCW), referring to the weight of the hung carcass prior to chilling once the skin, head, feet, and offal has been removed. The ADG parameter for the growing phase was determined by dividing changes in weight from weaning to the end of growing by DTG. The ADG parameter for the finishing phase was determined by dividing changes in weight from the end of growing to final weight before slaughter by FTS for the finishing phase. Lambs that were removed or died were not weighed at that time; thus, performance outcome variables do not include the weight of removals or dead lambs.

Descriptive statistics and regression models were generated in R/RStudio® (version "Prairie Trillium" Release (9f796939, 2022–02–16)). For continuous variables, normality and homoscedasticity were evaluated, and statistical significance was determined at a P-value of less than 0.05. To determine vaccine effectiveness, a univariate analysis was completed for each outcome variable, using logistic or linear regression, with pen included as a random effect, because animals were housed by vaccine group on a pen basis and infectious disease and feeding occurs on a pen basis. For the growing phase, the outcomes of pneumonia treatment rates, crude mortality rate, pneumonia mortality rate, and weight gain were investigated. For the finishing phase, pneumonia treatment rates, crude mortality rates, pneumonia mortality rates, days on feed, HCW, carcass fat cover, and the proportion of yield grade 1 (YG1) carcasses were investigated.

2.5. Model building

Five epidemiological models were developed for the growing phase data and 6 models were developed for the finishing phase data to look at other potential predictor variables of disease and growth. In all these models, vaccination status was forced into the model as it was known to differ in trial lambs, and other predictor variables of disease and growth were investigated. For brevity in this manuscript, only models with significant findings are included in Appendix 1. For both the growing and finishing phase data, the first model outcomes were the same. Model 1 was a logistic regression model with crude mortality as the outcome. Model 2 was a logistic regression model with case specific pneumonia mortalities. Model 3 was a logistic regression model only involving lambs that died, comparing case specific pneumonia mortalities to other causes of death. Model 4 was a logistic regression model with pneumonia treatments as the outcome. For the growing phase data, model 5

was a linear regression model with the outcome, weight gained from weaning to the end of the growing phase. Instead of ADG, weight gain was used, and DTG was introduced as a covariate, because the time component (denominator) varied among lambs. The fifth model for the finishing phase was the days spent in the finishing phase rather than the body weight gained in the finishing phase, because final live weight was artificially capped at approximately 50 kg of body weight by the feedlot, because this was their targeted slaughter weight. An additional 6th model was created for the finishing phase, and the outcome was the proportion of carcasses that scored YG1.

For the model 6, the continuous variable of final live weight was changed to a categorical variable, based on biologically relevant cut-points; <50 kg, 50–55 kg, 55–60 kg, and >60 kg, because the continuous variable did not allow the model to fit the data and a quadratic variable was not significant. For any categorical variable used in any model, the referent category was changed to the one with the largest number of individuals, to maximize the biological relevance of the resulting coefficients. The remainder of the model building process is described in greater detail in Gardner et al. (2023). The unit of measurement in this trial was the pen and it was accounted for as a random effect in each model as an interaction with vaccine status. In the growing phase this was referred to as "weaning group" because these groups were defined by the grouping and pen of animals that each lamb was weaned into. In the finishing phase this was referred to as the "finishing group", based on the grouping and pen that each animal entered in the finishing phase.

3. Results

3.1. Descriptive statistics and univariable regression: growing phase

Of the 2546 unvaccinated and 2511 vaccinated lambs initially enrolled in the trial, 2118 and 2096 lambs entered the growing phase, respectively (Table 1). Fourteen percent of the lambs during the growing phase were identified as sick in their feeding pen and individually treated with an antimicrobial (Table 1). Forty-two percent of these treated animals were treated for pneumonia. The treatment rate for pneumonia did not vary between vaccinated and unvaccinated lambs (Tables 1 and 3). Lambs were also treated during the growing phase for conjunctivitis (pinkeye), enteritis, abscess, arthritis, abortion, and listeriosis (circling disease).

During the growing phase, 100 lambs died (Table 2), and the mortality rate did not differ between vaccine groups (Tables 1 and 3). The top three causes of death were pneumonia (35%), diarrhea (14%), and septicemia (8%). Twenty-six lambs were removed from the trial during the growing phase, and this removal rate did not differ between vaccine groups (Table 1).

The average weaning weight and final growing phase body weight did not differ significantly between the vaccine groups (Tables 1 and 3). Based on simple descriptive statistics, average daily gain was statistically different between vaccine groups, with unvaccinated lambs gaining 346 g/day (95% CI: 341–350 g/day) and vaccinated lambs gaining 352 g/day (95% CI: 348–356 g/day) (P = 0.03) (Table 1). However, once overall weight gain was evaluated in the univariate analysis with days on feed accounted for, and pen included as a random effect, there was no significant difference in weight gain between the vaccine groups (Table 3). Based on the univariate analyses to evaluate vaccine effectiveness, there were no significant differences in any health or performance outcomes between vaccinated and unvaccinated lambs during the growing phase. There was no difference between vaccine groups in pathogenic respiratory bacteria cultured from pneumonic lungs throughout the post-weaning phase of production (Table 4).

3.2. Multivariate regression models: growing phase

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Table 1
Descriptive statistics from lambs in the growing and finishing phases of a controlled field trial in a Canadian sheep operation to determine the effectiveness of the Ovipast™ Plus bacterin.

Outcome	Unvaccinated	Ovipast™ Plus	P
Growing phase			
Number of weaned lambs	2118	2096	0.89
Entry weight (kg)	15.3	15.4	0.62
Removal rate (%)	0.6	0.7	0.82
Crude treatment rate (%)	13.6	13.5	0.93
Pneumonia treatment rate (%)	5.6	5.7	0.90
Crude mortality rate (%)	2.8	2.0	0.10
Pneumonia mortality rate (%)	1.1	0.6	0.10
Days on feed	34	35	0.05
Final weight (kg)	27.9	28.1	0.84
Average daily gain (kg/day)	0.35	0.35	0.03
Finishing phase			
Number of grower lambs	2046	2045	0.08
Entry weight (kg)	27.9	28.0	0.84
Removal rate (%)	0.3	0.5	0.45
Crude treatment rate (%)	2.9	2.8	0.57
Pneumonia treatment rate (%)	1.8	2.1	0.92
Crude mortality rate (%)	3.1	4.0	0.18
Pneumonia mortality rate (%)	1.0	1.5	0.26
Days on feed	98	97	0.80
Final live weight (kg)	55.7	55.7	0.91
Average daily gain (kg/day)	0.30	0.30	0.09
Lambs shipped to slaughter (%)	96.6	95.5	0.08
Carcass Data			
Number of carcasses	1976	1952	0.08
Hot Carcass Weight (kg)	26.6	26.5	0.14
Fat cover (mm)	15.7	15.1	<0.001
Yield Grade 1 (%)	36.1	42.3	<0.001
Yield Grade 2 (%)	38.1	34.1	0.01
Yield Grade 3 (%)	7.8	7.3	0.62
Yield Grade 4 (%)	17.9	16.0	0.13

Table 2
Causes of death by vaccine group and phase in production for lambs from a Canadian sheep operation participating in a controlled field trial to determine the effectiveness of the Ovipast™ Plus.

Cause of Death	Growing Phase		Finishing Phase	
	Unvaccinated	Ovipast™ Plus	Unvaccinated	Ovipast™ Plus
Total lambs	**2118**	**2096**	**2046**	**2045**
Pneumonia	23	12	21	30
Diarrhea	5	9	1	0
Autolysed	5	3	8	14
Other	0	1	8	8
Septicemia	6	2	5	9
Unknown	4	3	7	8
Starvation	1	4	0	1
Kidney Obstruction/ Abscess	0	0	3	2
Digestive Disease	0	0	4	0
Nervous signs	3	0	0	0
Trauma/injury	3	2	1	2
Arthritis	2	0	2	0
Listeria	3	0	0	0
Liver abscesses	1	1	1	2
Pulmonary edema	0	2	1	0
Exsanguination	0	1	0	0
Abscess	0	0	1	0
Laryngitis	1	0	0	4
Pericarditis	0	1	0	0
Peritonitis	1	0	0	0
Pleuritis	1	0	0	0
Rectal prolapse	0	0	0	1
Urolithiasis	0	0	1	0
Total	**59**	**41**	**64**	**81**

Table 3
Effectiveness of the Ovipast™ Plus bacterin administered to commercial lambs at weaning – Canadian controlled vaccine field trial: 2021–2022.

Outcome	Mean Value		OR or Coefficient[‡]	P	95% CI
Growing Phase	*Unvaccinated*	*Ovipast™ Plus*			
Pneumonia treatment rate (%)	5.6	5.7	1.01	0.93	0.78 – 1.32
Crude mortality rate (%)	3.1	4.0	0.70	0.08	0.47 – 1.04
Pneumonia mortality rate (%)	1.0	1.5	0.52	0.07	0.26 – 1.06
Pneumonia mortality versus other causes of death (%)	39.0	29.0	0.65	0.32	0.27 – 1.50
Weight gain during the growing phase (kg)	12.6	12.7	0.29[‡]	0.25	-0.20 – 0.78
Final weight (kg)	27.9	28.1	0.16	0.50	-0.31 – 0.62
Average daily gain (g/day)	0.35	0.35	0.01	0.28	-0.01 – 0.02
Finishing Phase					
Pneumonia treatment rate (%)	1.8	2.1	1.17	0.49	0.75 – 1.83
Crude mortality rate (%)	3.1	4.0	1.27	0.15	0.91 – 1.78
Pneumonia mortality rate (%)	1.0	1.5	1.43	0.26	0.77 – 2.65
Pneumonia mortality versus other causes of death (%)	32.8	37	1.20	0.60	0.61 – 2.42
Days on feed	98	97	-1.88[‡]	0.29	-5.38 – 1.61
Average daily gain (g/day)	0.30	0.30	0.00[‡]	0.67	-0.01 – 0.01
Final live weight (kg)	55.7	55.7	-0.15[‡]	0.44	-0.54 – 0.24
Hot carcass weight (kg)	26.6	26.5	-0.60[‡]	0.24	-0.94 – −0.27
Fat cover (mm)	15.7	15.1	-0.10[‡]	<0.001	-0.26 – 0.07
Yield grade 1 carcasses (%)	36.1	42.3	1.33	0.01	1.09 – 1.62

*The referent category for the odds ratios is unvaccinated animals
+pen was included as a random effect in all models

mortality, there were two significant predictor variables (Table 5). Weaning weight had a quadratic relationship with crude mortality (Fig. 1, 95% CI: 1.01–1.02, P < 0.001). Lambs with very low or high weaning weights had a higher probability of dying during the growing phase than lambs with average weaning weights. Litter size had a significant effect on crude mortality. Lambs born in a litter size of ≥ 4 lambs had 0.42 times lower odds of death, compared to lambs born as twins (95% CI: 0.20–0.88, P = 0.02). The R^2 value in this model is low; therefore, crude mortality is influenced by other unmeasured variables.

In the second generalized linear mixed model of pneumonia mortality, there was one significant independent variable (Table 6). Weaning weight significantly modified the odds of dying from pneumonia. The odds of dying from pneumonia dropped by 0.64 with every kilogram increase in weaning weight (95% CI: 0.57–0.72, P <0.001). For information on the relationship between weight gain during the growing phase and variables of interest, please refer to Appendix 1, Table 1 and Fig. 1.

3.3. Descriptive statistics and univariable regression: finishing phase

Of the 2046 unvaccinated and 2045 vaccinated lambs that entered the finishing phase, 1976 and 1952 went to slaughter, respectively. Three percent of the lambs were treated individually with antimicrobials, which did not differ between the vaccine groups (Tables 1 and 3). Of the 116 lambs that received antimicrobials, 67% were treated for pneumonia. The pneumonia treatment rate did not differ between vaccine groups (Tables 1 and 3). Other reasons for antimicrobial treatment included conjunctivitis, enteritis, abscess, arthritis, abortion, and listeriosis. Of the 38 lambs that were treated for these other diseases, 10 of them died prior to slaughter. The causes of death for these lambs were arthritis, laryngitis, and septicaemia, and undiagnosed due to autolysis.

Three and one-half percent of the lambs died, and there was no difference in the crude mortality rate between vaccinates and non-vaccinates (Tables 1 and 3). The top three causes of mortality were pneumonia (35%), unknown due to autolysis (15%), and other (11%) (Table 2). There was no difference in removals, average finished live weight, and average daily gain between the vaccine groups (Tables 1 and 3).

Average HCW was not different between the vaccine groups (Tables 1 and 3). More vaccinated lambs graded a YG1 carcass than unvaccinated lambs (P = 0.01) (Tables 1 and 3). Vaccinated lambs were 1.33 times more likely to have a YG1 carcass compared to unvaccinated lambs (P = 0.01, Table 3). Unvaccinated lambs had a higher fat cover than vaccinated lambs (P <0.001) (Tables 1 and 3). There was no difference in slaughter lung scores, fibrinous adhesions, and the proportion of lambs with any pneumonic lesion between the vaccine groups (Appendix 1, Table 3).

3.4. Multivariate regression models: finishing phase

In the multivariable linear regression model looking at the number of days spent in the finishing phase, there were three significant independent variables (Table 7). Ram lambs spent approximately 27 fewer days in the finishing phase than ewe lambs (95% CI: −40.67 to −12.60, P < 0.001). Weaning weight had a quadratic relationship with days in the finishing phase (95% CI: 0.08–0.15, P < 0.001). As weaning weight increased, the number of days spent in the finishing phase decreased in half, in a U-shaped curve, which started to plateau at a weaning weight around 30 kg, although this would be an above average weaning weight. Whether the lamb was treated for pneumonia affected the number of days in the finishing phase. Lambs treated for pneumonia spent approximately 19 d longer in the finishing phase than untreated lambs (95% CI: 12.14–25.89, P < 0.001). For information on the relationship between yield grade and vaccine status and sex, refer to Appendix 1, Table 2 and Fig. 2.

4. Discussion

Vaccination of feedlot lambs with the Ovipast™ Plus bacterin at weaning and revaccination a few wk later, which had been borne from vaccinated ewes, did not reduce pneumonia treatment rates, crude mortality rates, or pneumonia-specific mortality rates, or improve weight gain or HCW. The only beneficial effect of vaccination in this controlled vaccine field trial was a higher carcass yield grade and a lower fat cover.

Table 4
Comparison of culture results from lung samples of post-weaned lambs diagnosed with fatal pneumonia in a Canadian controlled vaccine field trial to determine the effectiveness of the Ovipast™ Plus bacterin: 2021–2022.

	Post-wean Confirmed Pneumonia		Post-wean %		
Culture Results	**Unvaccinated**	**Ovipast™ Plus**	**Unvaccinated**	**Ovipast™ Plus**	**P**
Number of samples cultured	35	33			
Mannheimia haemolytica (type I or II)	22	17	62.86%	51.52%	0.58
Bibersteinia trehalosi	1	0	2.86%	0.00%	1
Pasteurella multocida	12	11	34.29%	33.33%	1
Trueperella Pyogenes	14	7	40.00%	21.21%	0.16
Moraxella bovoculi	6	2	17.14%	6.06%	0.26
Mycoplasma Results	**Unvaccinated**	**Ovipast™ Plus**	**Unvaccinated**	**Ovipast™ Plus**	**P**
Number of samples cultured	15	11			
Mycoplasma ovipneumoniae	11	5	73.33%	45.45%	0.23
Mycoplasma arginini	15	8	100.00%	72.73%	**<0.001**

Table 5
A generalized linear mixed effects model of crude mortality in lambs in the growing phase from a Canadian sheep operation participating in a controlled field trial to determine the effectiveness of the Ovipast™ Plus bacterin.

Predictors	**Category**	**Odds Ratios**	**P**	**CI**
(Intercept)	-	16.19	<0.001	3.99 – 65.64
Vaccine Status	Unvaccinated	referent	-	-
	Ovipast™ Plus	0.72	0.12	0.47 – 1.09
Weaning Weight (kg)	-	0.49	<0.001	0.40 – 0.59
Weaning Weight^2 (kg)	-	1.02	<0.001	1.01 – 1.02
Litter Size	Twin	referent	-	-
	Single	1.49	0.30	0.70 – 3.19
	Triplet	1.04	0.87	0.66 – 1.64
	Quadruplet (or more)	0.42	0.02	0.20 – 0.88
Random Effects				
σ^2	3.29			
$\tau_{00\ \text{Vaccine status*Wean group}}$	0			
$\tau_{00\ \text{Weaning group}}$	0			
$N_{\text{Vaccine status}}$	2			
$N_{\text{Weaning group}}$	8			
Observations	4205			
Marginal R^2 / Conditional R^2	0.165 / NA			

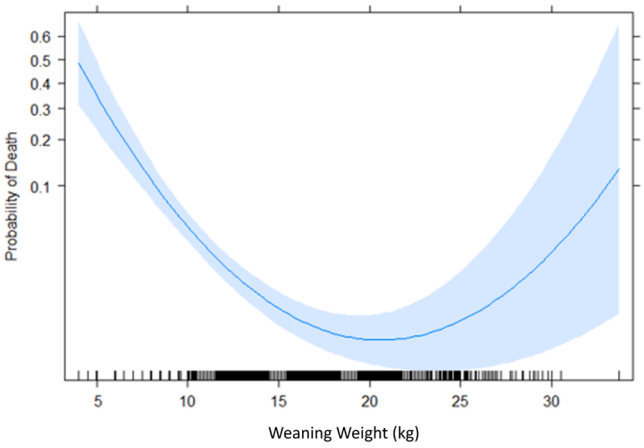

Fig. 1. Graph of the quadratic relationship between weaning weight and the probability of crude mortality from a generalized linear mixed model (Table 3) of lambs in the growing phase of trial to determine the effectiveness of the Ovipast™ Plus bacterin in a Canadian sheep operation.

Table 6
A generalized linear mixed effects model of pneumonia mortality in lambs in the growing phase from a Canadian sheep operation participating in a controlled field trial to determine the effectiveness of the Ovipast™ Plus bacterin.

Predictors	**Category**	**Odds Ratios**	**P**	**CI**
(Intercept)	-	2.87	0.09	0.84–9.79
Vaccine Status	Unvaccinated			
	Ovipast™ Plus	0.54	0.10	0.26–1.12
Weaning Weight (kg)	-	0.64	<0.001	0.57–0.72
Random Effects				
σ^2	3.29			
$\tau_{00\ \text{Vaccine status*Wean group}}$	0			
$\tau_{00\ \text{Weaning group}}$	0			
$N_{\text{Vaccine status}}$	2			
$N_{\text{Weaning group}}$	8			
Observations	4205			
Marginal R^2 / Conditional R^2	0.492 / NA			

Failure to see a vaccine effect may be due to several reasons: 1) vaccination was administered too late to generate a protective immune response prior to disease challenges; 2) vaccination at weaning did not generate a good immune response due to stressors at weaning, which may have compromised the immune response to vaccination; 3) the vaccine, a whole cell killed bacterin, may not have generated leukotoxin antibodies, which are important in disease protection from *M. haemolytica*, or 4) other infectious agents that caused pneumonia were not present in the vaccine.

Although the initial dose of the bacterin was given at weaning, it normally takes 2 doses of a killed bacterin, and 2–3 wk after vaccination, to induce a protective immune response. When respiratory vaccines are given at weaning, there may not be sufficient time for protective immunity to develop prior to disease challenge. In these trial lambs, 40% of pneumonia deaths occurred before revaccination. Weaning events also create stress, which may reduce an animal's response to vaccination (Karrow, 2006; Dartmouth Undergraduate Journal of Science, 2010, OMAFRA, 2021). While these lambs were not transported any distance, because they were on the same farm, there was weaning and mixing of different lambs in different pens at the start of the growing and finishing phases of the trial, along with ration changes, which can cause stress, and increase infectious agent spread amongst animals due to regrouping.

In both natural and experimental challenge studies of *M. haemolytica* vaccines, there have been varying results, with some studies demonstrating no effect, and others showing increased disease in the vaccinated group (Confer and Ayalew, 2018). Improved efficacy of *M. haemolytica* vaccines was seen when other antigens, such as the

Table 7
A linear mixed effects model of days on feed in the finishing phase in lambs from a Canadian sheep operation participating in a controlled field trail to determine the effectiveness of the Ovipast™ Plus bacterin.

Predictors	Category	Estimates	P	CI
(Intercept)	-	199.77	<0.001	185.89 – 213.65
Vaccine Status	Unvaccinated	referent	-	-
	Ovipast™ Plus	-1.35	0.46	-4.97 – 2.26
Sex	Ewe	referent	-	-
	Ram	-26.63	<0.001	-40.67 – −12.60
Weaning Weight (kg)	-	-7.52	<0.001	-8.72 – −6.32
Weaning Weight^2 (kg)	-	0.11	<0.001	0.08 – 0.15
Treatment for Pneumonia	No	referent	-	-
	Yes	19.01	<0.001	12.14 – 25.89
Random Effects				
σ^2	674.64			
$\tau_{00\ \text{Vaccine status*Finishing group}}$	10.73			
$\tau_{00\ \text{Finishing group}}$	95.66			
$N_{\text{Vaccine status}}$	2			
$N_{\text{Finishing group}}$	8			
Observations	3892			
Marginal R^2 / Conditional R^2	0.369 / 0.455			

leukotoxin, a type of exotoxin, were also included (Rice et al., 2007). Based on a recent experimental challenge trial, the Ovipast™ Plus bacterin did not increase leukotoxin ELISA antibodies after the initial and booster vaccination dose, which may explain in part, why it was not effective in reducing pneumonia in this trial (Van Donkersgoed et al., 2024). When including an exotoxin component in a vaccine to improve vaccine effectiveness, it is important that the exotoxin is attenuated to remove its toxic effects (Richeson et al., 2019). If this step is not taken, the active leukotoxin produced during the log-phase of bacterial growth, can be highly toxic to the animal. Similarly, endotoxins can also be released from a cell when the membrane is disrupted, and although not as toxic as exotoxins, endotoxins still have moderate toxicity (Woltmann et al., 1998). Ovipast™ Plus bacterin is a whole cell killed bacterin which may contain active endotoxins and exotoxins which could reduce a positive vaccine effect due to their toxicity, resulting in no difference or potentially higher disease in vaccinates compared to nonvaccinates. In a recent experimental *M. haemolytica* challenge study, the Ovipast™ Plus bacterin did not reduce clinical scores or mortality rates compared to a negative control (Van Donkersgoed, et al., 2024). The Ovipast™ Plus bacterin has been on the market in Europe for some time and there are no published reports suggesting increased disease rates in vaccinated animals compared to unvaccinated controls, other than that reported by Goodwin-Ray et al., 2008, who saw increased lung lesions at slaughter. Additional RCT are needed in commercial flocks to determine the effectiveness and safety of this commercial bacterin.

The only other known field trial conducted using the Ovipast™ Plus bacterin was in New Zealand (NZ), where it is currently approved for use. This study found that vaccination did not prevent the development of lung lesions and did not increase average daily gain. Upon further evaluation of the study results, the authors reported that the overall prevalence of lung lesions was higher in the vaccinated group of lambs (57.0% in the vaccinated, 53.8% in the unvaccinated group (P = 0.02)) (Goodwin-Ray et al., 2008). More lung lesions at slaughter suggests higher subclinical disease in the vaccinated lambs. Based on the lung scores performed at the slaughter plant in a convenience subsample of lambs from the present study (n = 1443), there were no significant difference in categories of percentages of lung consolidation between vaccinates and nonvaccinates. The number with fibrinous adhesions and the total sets of lungs with any pneumonic lesions did not differ between vaccinates and nonvaccinates. Although this does not mirror what Goodwin-Ray et al. (2008) found in the lungs of their slaughtered lambs, it also does not indicate a positive effect from the vaccine in reducing subclinical disease. It is important to note that the lung scoring at slaughter was a convenient sub-sample of lambs on trial and may not represent the true occurrence of lung lesions at slaughter and may be biased. The samples were only taken from the first 2 shipments of ram and ewe lambs sent for slaughter, which may have been the fastest growing lambs born earliest in the study, and this could underestimate overall disease. Goodwin-Ray et al. (2008) had withdrawals from their trial ewe lambs as some were kept as replacements in the flocks. This withdrawal may have removed the healthiest lambs from the trial and could have influenced the lung scoring results at slaughter, depending on how lambs were retained on farm. Whole cell bacterins against *M. haemolytica* in cattle were ineffective (Hamdy et al., 1965; Martin, 1983), or had detrimental effects (Schipper and Kelling, 1971; Friend et al., 1977; Wilkie et al., 1980); therefore, the results of this study evaluating a whole cell killed bacterin are not unexpected and agree with these findings. Newer leukotoxin vaccines against *M. haemolytica* are commonly used in fall placed calves in North American feedlots, with varying reports of vaccine effectiveness (Confer and Ayalew, 2018).

Goodwin-Ray et al. (2008) found that vaccinated lambs gained less than the unvaccinated lambs, although overall, there was no significant effect. In agreement with Goodwin-Ray et al., the present study found that overall, based on univariate and regression analyses, there was no difference in weight gain in the growing phase of the trial or in days spent in the finishing phase, despite simple descriptive statistics showing lambs vaccinated with the Ovipast™ Plus bacterin had increased ADG during the growing phase. This emphasizes the importance of using appropriate statistics before making final conclusions on vaccine effectiveness.

Lambs treated for pneumonia spent almost 20 d longer in the finishing phase of the trial, which supports the principle that increased respiratory disease negatively impacts daily weight gain. Disease load directly translates to weight gain, because the immune system requires a larger allocation of energy when being challenged, leaving less energy for production (Goodwin et al., 2004). Focusing more management efforts during the pre-weaning phase to prevent light lambs at birth and at weaning may reduce morbidity and mortality rates and improve growth rates.

There was a clear sex effect on health and performance outcomes that carried through from the pre-weaning phase. Ram lambs were 2.11 times more likely to be treated for pneumonia and 1.60 times more likely to die from any cause than ewe lambs. They grew faster in the finishing phase (fewer DOF), and they were more likely to have a YG1 carcass than ewe lambs. Ram lambs also had a significantly higher proportion of lungs at slaughter that were consolidated, with more fibrinous adhesions, and a higher overall proportion of pneumonic lesions at slaughter than ewe lambs. These findings suggest there are sex effects that could influence disease risks and vaccine effectiveness in the field, and this requires further investigation. In the present trial, the proportion of ram lambs per vaccine group was the same; thus, it was not a confounding factor affecting vaccine effectiveness. All rams in this study were intact males; therefore, they had testosterone, which may have played a role in the increased odds of morbidity and mortality observed compared to ewe lambs (Gardner et al. 2023). Further studies should focus on the effects of castration on animal health, growth rates, and vaccine effectiveness to determine if there are any significant negative financial and welfare effects from this surgical procedure.

Beyond the sex effect, weaning weight was significantly associated with various outcomes in the majority of the post-weaning models. Weaning was an event, set by lamb age, and not by lamb weight; thus, the weaning weight variable could be a proxy measure of lamb health

coming into the stressful event of weaning and going forward into the post-weaning phase of the lamb's life. The consistent significant association of weaning weight with health and performance outcomes of interest in both the growing and finishing models, indicates the importance of focusing on pre-weaning management of lambs to improve weaning weights. Ensuring lambs are healthy and growing well prior to weaning is important because it clearly has a long-lasting effect on the subsequent risk of respiratory disease, such as treatment and mortality rates.

The crude mortality rate in the post-weaning phase was 5.8% in this flock, which was higher than that reported by Fisher and Menzies (2000), who reported a 1.9% mortality rate post-weaning. The mortality rate reported by Fisher and Menzies was only measured from 51 to 100 d of age, which more accurately compares to the growing phase mortality rate observed here. Therefore, the results in the 2 studies are similar. The crude mortality rate seen in this flock during the post-weaning stage was not unexpected on this farm and was like previous years (Van Donkersgoed et al., 2016, 2024).

Pneumonia was the leading cause of death in both the growing phase and the finishing phase of this trial, like that previously reported (Van Donkersgoed et al., 2016, 2024). Other significant causes of death observed were diarrhea, septicemia, and digestive diseases, like that reported by Van Donkersgoed et al. (2016, 2024). There is little other published literature for this stage of lamb production in other areas of Canada to make comparisons to these mortality figures.

Based on the prevalence of pneumonia mortality seen in the post-weaning phase of this trial with a sample size of 2118 unvaccinated and 2096 vaccinated lambs, we had 80% power and 95% confidence to detect a vaccine effect of reducing pneumonia mortality from 2.1% to 1.0%, which was not observed here. To reliably state, with an 80% power and 95% confidence, a change of 0.1% in pneumonia mortality, which was the difference observed in this phase of the trial, the trial would have needed 318,000 lambs per vaccine group. Such a small difference in pneumonia mortality with vaccination would negate the economic value of vaccination.

There is a list of important factors to consider when designing and implementing a randomized control trial (RCT), which include testing vaccines in a natural disease setting (O-Connor et cal, 2019a). This study did test the vaccine under a natural disease setting and potentially this farm setting represented a slightly higher than average disease rate compared to more extensive Canadian lamb operations. O'Connor et al. (2019a) stated the importance of blinding in an RCT. In this trial, all staff at the barn were blinded to the vaccine groups, but the primary author was not. As the primary author conducted most necropsies, this lack of blinding could have led to some bias, but we are not aware of any directional bias. A systematic necropsy and lung sampling procedure was followed, and crude mortality is an objective outcome measure. Another potential limitation of this study was that blood samples were not collected to measure antibody levels prior to or following vaccination of the lambs to determine baseline antibody levels to *M. haemolytica* prior to vaccination and antibody responses after vaccination. This farm has a known history of pneumonia, including isolation of *M. haemolytica* and *B. trehalosi* from pneumonic lungs (Van Donkersgoed, 2016, 2024); thus, it is likely there was some baseline immunity to these infectious agents in the flock, which could have reduced the ability to see a positive vaccine effect. Given these infectious agents are common in many commercial sheep flocks, any commercial respiratory vaccine is expected to work under these situations.

Another reason for vaccine failure is that pneumonia in this flock may have been caused by other infectious agents which were not present in the vaccine. In this flock, *M. haemolytica* was the most common bacterial isolate from pneumonic lungs (Table 4); however, other bacteria such as *Pasteurella multocida*, *Mycoplasma ovipneumonia*, *M. argininia* were also isolated, indicating pneumonia was caused by mixed infectious agents. It is possible that a multi-agent vaccine is necessary to successfully reduce infectious pneumonia in commercial sheep flocks, because infectious agents can vary within and among flocks. Further research is warranted in this area.

Respiratory vaccines are "disease modifiers rather than absolute preventive agents" (Callan and Garry, 2002). Callan and Garry (2002) suggested that respiratory vaccines should reduce disease risk and severity in those that get sick, as well as improve flock immunity by reducing the spread of infectious pathogens within a population, rather than expecting to completely eradicate disease. Based on the results of this phase of the trial, the Ovipast™ Plus bacterin did not work as per the label claims, to aid in the prevention of "pneumonic pasteurellosis in sheep of all ages, from a minimum of 3 wk of age, and control systemic pasteurellosis in weaned fattening lambs and breeding sheep". Vaccinating lambs did not reduce disease risks or improve overall weight gain or reduce the days on feed in the finishing phase.

The vaccine did significantly improve the proportion of lambs that classified as a YG1 carcass and it reduced carcass fat cover, but this increased economic value needs to be balanced against the cost of vaccinating. There is an ovine leukotoxin vaccine licensed for use in Spain which exhibited significantly improved morbidity rates (12%) and mortality rates (50%) compared to another approved bacterin (HIPRA, 2023) in a small trial. Although this is a positive outcome, the small sample size, and the absence of a negative control group indicates that further RCT field trials in various commercial settings need to be completed to determine the effectiveness of this leukotoxin vaccine. Based on the results of our previous work (Gardner et al., 2023), there may be a benefit to vaccination in the first 1–2 wk of the lamb's life if there is no interference from maternal antibodies. The risk of pneumonia in lambs on this farm started to increase at 4 wk of age; therefore, vaccination with an effective vaccine two wk prior to this risk period should be investigated, assuming the vaccine is safe to administer to such young lambs. In beef cow-calf herds, intranasal viral vaccines are commonly used in Canada to reduce the interference of maternal immunity (personal communication), and this should be investigated as well as an option for ovine respiratory vaccines in neonatal lambs.

CRediT authorship contribution statement

M.D. Gardner: Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **J. Van Donkersgoed:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **C.A. Bauman:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **M.T. Spinato:** Writing – review & editing, Writing – original draft, Resources, Methodology.

Declaration of Competing Interest

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.smallrumres.2024.107269.

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