Effect of vaccination with a *Mannheimia haemolytica* subunit vaccine on milk yield in lactating dairy cows

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Abstract

Vaccination of adult lactating dairy cattle can have a negative impact on milk production. Decreased milk production may occur from a combination of the cow's immune response, endotoxin level in the vaccine, and the impact of cattle handling. A randomized clinical trial utilized 3 treatment groups to examine changes in milk production following vaccination with a *Mannheimia haemolytica* subunit vaccine (MHSV; Nuplura PH, Elanco Animal Health) using 972 lactating dairy cows on a single Midwestern dairy: a vaccinated group (MHSV, n=315); a placebo-treated control (saline, n=342); and a negative control group (no injections, n=315). The decline in milk across a 3 d post-treatment period for the saline group was 0.5 lb (0.2 kg) greater than the negative control cows, but the difference was not significant (*P*=0.57). The decline in milk during the same time period for cows in the MHSV group was 1.5 lb (0.7 kg) more than the negative control, (*P*=0.02). The declines between the saline group (0.5 lb; 0.2 kg) and the MHSV group (1.5 lb; 0.7 kg) were not significantly different (*P*=0.17).

Key words: *Mannheimia haemolyticum* vaccine, dairy cattle, bovine respiratory disease

Résumé

La vaccination des bovins laitiers adultes en lactation peut avoir un impact négatif sur la production de lait. Une baisse de production laitière peut résulter de l'interaction entre la réponse immunitaire de la vache, le niveau d'endotoxine dans le vaccin et l'impact de la manipulation des bovins. Un essai clinique randomisé avec trois groupes de traitement a été mené pour examiner les changements dans la production de lait suivant la vaccination de 972 vaches laitières en lactation dans une même ferme du Midwest avec un vaccin à base de sous-unités de *Mannheimia haemolytica* (MHSV; Nuplura PH, Elanco Animal Health). Les trois groupes étaient : un groupe vacciné (MHSV, n=315), un groupe placébo (saline, n=342) et un groupe témoin négatif (sans injection, n=315). Par rapport au groupe témoin négatif, la baisse de production de lait dans le groupe saline sur une période de 3 jours suivant le traitement était de 0.5 lb (0.2 kg) mais cette différence n'était pas significative (P=0.57). La baisse de production de lait pendant la même période pour les vaches du groupe MHSV était de 1.5 lb (0.7 kg) de plus que dans le témoin négatif (P=0.02). Les baisses entre le groupe saline (0.5 lb; 0.2 kg) et le groupe MHSV (1.5 lb; 0.7 kg) n'étaient pas significativement différentes (P=0.17).

Introduction

Bovine respiratory disease (BRD) occurs in cattle of all ages. The incidence reported in the national adult dairy herd is 2.8%.[20] An Ohio survey of 16 herds found an annual pneumonia prevalence of 19 cases/100 cow-years,[11] while the 3-year average (2016-2018) individual herd incidence reported in a convenience sample of 172 herds in 26 different states ranged from 0.2% to 23.5% (average across herds of 3.7%), where herd size (milking cows) ranged from less than 200 to over 20,000, with an average of 3,660 cows.[a]

Bovine respiratory disease is caused by a variety of bacterial and viral pathogens, *Mannheimia haemolytica* being the most commonly isolated bacterial pathogen.[5,6,7] Dairy producers vaccinate cows against a variety of diseases in order to maximize health of their herds. Vaccination protocols typically include adult animals and young stock.[3,6,13] Pneumonia caused by *M. haemolytica* is 1 of the diseases dairy producers currently vaccinate against. It is reported that 3.5% of all dairy operations in the US vaccinate their cows with a *M. haemolytica* vaccine, and 8% of dairy operations with over 500 cows vaccinate their mature cows.[19]

Milk production losses associated with viral respiratory/reproductive vaccines, an *Escherichia coli* bacterin-toxoid, a *Coxiella burnetii* vaccine, and two 9-way killed vaccines has been reported.[1,12,16,17] Investigators report post-vaccination milk losses of 1.4 lb (0.6 kg) to 4.0 lb (1.8 kg)/day for the 3 d immediately following vaccination, depending on the vaccine used.[1,12,16,17] There are no published reports of milk production losses following the use of any of the *M. haemolytica* vaccines; but like any vaccine, there are potential negative consequences on milk production due to the cows' immune

response, the endotoxin load in the vaccine, and the handling, sorting, and restraint of the animals.[2,9,10,14,15] The contribution of each of these factors may be different in every situation.

Endotoxins produced by gram-negative infections or endotoxins present in vaccines can cause the release of pro-inflammatory cytokines leading to inappetence, pyrexia, and lethargy. These side effects are more pronounced as the level of endotoxin exposure increases.[14,15] Endotoxins have been shown to directly decrease milk production in lactating cows.[18] The method used to manufacture *M. haemolytica* vaccines has a significant impact on the amount of endotoxin in the final product. One report in the literature reported endotoxin levels in 2 *M. haemolytica* vaccines. The *M. haemolytica* subunit vaccine (MHSV[b]) used in that report contained 1,588 EU/mL, while the *M. haemolytica* toxoid[c] contained 56,120 EU/mL (*P*<0.01).[8]

Bovine respiratory disease can be a significant problem in adult dairy cows on some operations, therefore it is important to know the impact on milk production if cows are vaccinated against *M. haemolytica*. The objective of this clinical trial was to evaluate changes in milk production following vaccination with MHSV in accordance with label instructions.

Materials and Methods

This trial was done on a commercial Ohio dairy farm in the fall of 2019. It was approved by the Institutional Animal Care and Use Committee (IACUC), IACUC #1244. The only animal intervention on this farm was routine vaccination of adult dairy cows according to label instructions.

Sample size calculations and all statistical tests were performed using statistical analysis software.[d] Prior to the randomization procedure, daily milk data for the most recent 8 days were retrieved from the on-farm record system for cows where days-in-milk (DIM) = 31 to 400 and days pregnant <200. The daily milk results for the oldest 4 days were averaged. Next, the daily milk from the most recent 3 days were averaged, skipping 1 day to provide a slightly larger

level of difference across days for sample size estimation. The differences of earlier minus later daily milk averages were then used to estimate mean production, decline over time, and variation in milk weights amongst cows in order to test the proposed modeling approach and to estimate the level of variation in milk weight. Using the measured average standard deviation of 9.1 lb (4.1 kg), a type I error rate of 5% and a power of 80%, a total of 342 cows per group (1026 total) were deemed appropriate to detect a significant difference of 2 lb (0.9 kg) /day between groups, assuming a 5% loss to follow up.

Milk Production

Daily milk production was the key outcome variable for the study. The dairy had milk meters[e] mounted in the parlor, which were recently calibrated for improved accuracy. The herd milked all cows 3x daily, and following each milking the daily milk production results for each cow were uploaded into on-farm software.[f] The on-farm software stores daily milk results for the current day and the 7 previous days. Consequently, frequent retrieval of milk production data was necessary to capture the necessary data for the project. The primary study outcome, the change in milk production following vaccination, was calculated by comparing the 7-d average milk production prior to treatment (**7-d pre**) to a series of post-treatment milk production measures. First, the 3-d average milk production following treatment (**3-d post**) was subtracted from the 7-d pre, for each individual cow, to generate a 3-d post-milk difference. The 3-d post-measurement was the average milk produced on the day of treatment; d 0, and d 1 and 2. Additionally, the 7-d pre was compared to individual post-treatment d 0, 1, 2, and 3 to help further characterize the potential milk loss. The post-vaccination milk estimates were subtracted from the 7-d pre average and these differences were the outcomes of interest. A description of this timeline can be seen in Table 1. As defined, a positive milk difference indicates a decline in milk post-vaccination and a negative result indicates an increase in milk production.

Table 1. Timeline of study implementation and data collection during a study to evaluate milk production changes following vaccination with a *Mannheimia haemolytica* vaccines.

Study day	Event
-7	Begin collecting daily milk weights on all 3 experimental groups.
0	Treat Group 2 with a saline injection. Vaccinate Group 3 with MHSV.*
0-3	Collect daily milk weights.

Day relative to treatment	Procedure
-7	Daily milk yield recording for all study cows.
0	No treatment to Group 1, treat Group 2 with saline, vaccinate Group 3 with MHSV*. Treatment will be after the morning milking.
0 post-vaccination	Record individual cow milk weights for the 2:00 p.m. and 10.00 p.m. milkings separate from milking that occurs on day 0 before the cows are vaccinated.
Day 1, 2, 3	Continue recording daily milk weights on individual cows in all three groups.

*MHSV = *Mannheimia haemolytica* subunit vaccine (Nuplura PH, Elanco Animal Health, Greenfield, IN)

Since the majority of cows were post-peak across all 3 treatments and across all parity groups (lactation=1, lactation=2, and lactation>2), a positive difference between pre- and post-sampling was expected and considered normal.

Study Animals

The inclusion criteria required that cows be lactating and between 31 and 400 DIM, not in the hospital pen, not in the fresh pen, and have a current days pregnant <200 (to help ensure cows would be available for post-treatment milk recording prior to being moved to the dry pen). Data collection began 7 d prior to the day of vaccination. Subsequent to the beginning of data collection, cows were excluded from the analyses if 1 or more of the follow criteria were met: cow had a movement to the hospital pen or recorded health event during the week prior to vaccination; cow had a movement to the hospital pen or had a recorded health event during the week following vaccination; cow failed to have a full week of milk weights following vaccination (i.e., was dried early and moved out of the lactating herd or culled). The dairy herd software program has a proprietary method of interpolating any individual missing milk weights, and if a cow missed a single milk weight out of 3 within a day the estimated daily milk generated by the program was used. However, if more than 1 milk weight was missing for a single day, the cow was removed from the study.

A total of 1034 lactating dairy cows that met the inclusion criteria were randomized into 1 of 3 groups in the on-farm record system. Enrollment to the study was performed on the same day across the entire dairy.

On the morning of the treatments, in order to align cow numbers in the trial with the previously agreed contract, the owner decided to exclude 1 pen from the trial, resulting in only 991 lactating dairy cows being available for the study (318 in the MHSV group, 350 in the saline group, and 323 as negative controls). The removal of this pen caused the variation in cow numbers in the different groups. After removing 19 cows that changed pens during the study observation period or had missing milk weights, there were 315 cows that received MHSV, 342 treated with saline, and 315 negative control cows for a final total of 972. The loss of 19 cows was due to missing pre-treatment milk weights (7), missing post-treatment milk weights (3), or changes in housing pen during the observation period (9). Randomization to study group of MHSV (1), saline (2), or negative control (3) was performed in the dairy herd software program using a random number generator and a stratified randomization process by lactation group; first for lactation = 1, then lactation = 2, and finally for lactation >2.

Injections

MHSV was administered per label instructions: 2 mL subcutaneously in the neck for cows assigned to the MHSV group. For the saline cows, Sterile Saline[g] (2 mL) was administered subcutaneously in the neck. No injections were ad-ministered to the negative control cows. A 16-ga needle was used for both the MHSV and the saline treatments. Needles were changed after every 10 cows, or sooner if they became burred. MHSV and saline were administered at the end of the first milking of the day. By treating in the parlor, the negative control cows were also subjected to a minor disruption of their daily routine when people walked in front of them in the parlor to administer MHSV and saline to the other cows.

Statistical Analysis

Milk production and DIM were evaluated by parity group and by treatment group using one-way analysis of variance (ANOVA) to assess the randomization process prior to evaluating the results. The association between vaccination with MHSV and subsequent milk production was evaluated using ANOVA, and least square means were fit for the 5 different milk production outcome averages: cumulative milk for days 0 through 2, d 0, d 1, d 2, and d 3. Fixed effects of DIM, DIM^2, DIM^3, Lactation Group (1, 2, or >2), Initial Production Category (IPCat), Vaccination Group (Group) and 2-way interactions between Lactation Group, IPCat, DIM, and Group were offered in each model. The IPCat variable was created using pre-vaccination milk production quartiles (the lower 25th, 26th to 50th, 51st to 75th, and the top 25th) by parity group (1, 2, or >2). Group was a 3-level variable: MHSV, saline, and negative control. Pair-wise comparisons from the multivariable models were compared using Tukey's multiple comparison test. For all models, variables and their respective interaction terms were retained when $P \leq 0.20$. Significance was considered when $P \leq 0.05$.

Results

The stratified analysis of pre-treatment DIM by treatment within parity group (Table 2) and stratified analysis of pre-treatment milk by treatment within parity group (Table 3) revealed no significant differences across the groups. The least square means 7-d pre-milk production prior to treatment ranged from 92.6 lb (42.1 kg) to 93.2 lb (42.4 kg), but was not different across the 3 groups (Table 4). The primary study outcome, 3-d post-milk difference, was calculated using the average of daily milk weights from the herd software following vaccination, starting with d 0, which was the day of vaccination. Lactation Group x IPCat was retained (P=0.10), but all other interactions were removed due to each having a P>0.20. DIM^3 was not significant and was also removed leaving a final model with Lactation Group, DIM, DIM^2, IPCat and Group retained (all with P<0.05) and the interaction of Lactation Group x IPCat.

Table 4 shows the predicted least square means and overall P-value for the 7d pre vs average 3d post as well as the first 4 days post-vaccination individually. For describing the pair-wise results, the negative control cows served as the referent value. The decline in milk for the saline group was 0.5 lb (0.2 kg) greater than the negative control cows, but

Table 2. Days-in-milk comparison across treatment groups in lactating cows assigned to control, saline or vaccine groups, as stratified by parity at beginning of trial.

| | Treatment Group | | | | | | |
| | Negative control | | Saline | | MHSV* | | Group |
Parity	Mean	Std dev	Mean	Std dev	Mean	Std dev	P-value†
Lactation=1	164.3	(66.7)	151.4	(72.5)	137.9	(55.8)	0.20
Lactation=2	148.4	(64.2)	141.6	(77.6)	145.3	(83.3)	0.80
Lactation>2	148.3	(76.6)	144.1	(78.2)	149.6	(77.9)	0.79

*MHSV = *Mannheimia haemolytica* subunit vaccine (Nuplura PH, Elanco Animal Health, Greenfield, IN)
† *P*-value associated with differences in means across treatment groups.

Table 3. Pre-vaccination 7-day average milk production (lb) by treatment group within parity.

| | Treatment Group | | | | | | |
| | Negative control | | Saline | | MHSV* | | Group |
Parity	Mean	Std dev	Mean	Std dev	Mean	Std dev	P-value†
Lactation=1	71.9	(9.9)	71.3	(13.8)	72.6	(10.9)	0.86
Lactation=2	89.6	(17.5)	90.1	(18.9)	89.2	(20.0)	0.95
Lactation>2	99.2	(20.9)	98.3	(22.9)	98.3	(22.5)	0.91

*MHSV = *Mannheimia haemolytica* subunit vaccine (Nuplura PH, Elanco Animal Health, Greenfield, IN)
† *P*-value associated with differences in means across treatment groups.

Table 4. Summary of 7-d pre-vaccination milk production (lb) and milk production losses at day 0, 1, 2, and 3 post-vaccination for a *M. haemolytica* vaccine*, a saline placebo, and negative control (no injection) in lactating dairy cows (N=972).

| | Treatment Group | | | |
| | Negative control | Saline | MHSV* | Group |
Time period	LS Mean	LS Mean	LS Mean	P-value**
Pre-vac 7-d average†	93.2[a]	93.0[a]	92.6[a]	0.60
7-d pre minus 3-d post‡	3.5[a]	4.0[a,b]	5.0[b]	0.04
7-d pre minus d-0 post§	3.5[a]	3.6[a]	3.6[a]	0.99
7-d pre minus d-1 post‖	6.0[a]	6.3[a]	8.6[b]	0.00
7-d pre minus d-2 post¶	1.0[a]	2.1[a]	2.7[a]	0.14
7-d pre minus d-3 post#	3.9[a]	5.0[a]	4.6[a]	0.42

[a,b] Values with different letters within a row are different, alpha = 0.05
*MHSV = *Mannheimia haemolytica* subunit vaccine (Nuplura PH, Elanco Animal Health, Greenfield, IN)
** *P*-value for any differences across the 3 treatment groups
† Average milk production for 7-d prior to vaccination
‡ Average milk production for 7-d prior to vaccination minus average milk for first 3 d post-vaccination
§ Average milk production for 7-d prior to vaccination minus milk production on day of vaccination
‖ Average milk production for 7-d prior to vaccination minus milk production 1 d after vaccination
¶ Average milk production for 7-d prior to vaccination minus milk production 2 d after vaccination
# Average milk production for 7-d prior to vaccination minus milk production 2 d after vaccination

the difference was not significant (*P*=0.57). The decline in milk for the MHSV treatment was 1.5 lb (0.70 kg) more than the negative control (*P*=0.02), but the decline for the saline treatment (0.5 lb; 0.2 kg) and the MHSV treatment (1.5 lb; 0.7 kg) were not significantly different (*P*=0.17).

In order to better characterize when the production impact attributable to vaccination treatment occurred, subsequent models similar to the one described above were constructed to compare the 7-d pre-vaccination milk production to the daily milk production occurring on d 0, 1, 2, and 3. On the day of treatment (d 0), the least squares means differences relative to the 7-d pretreatment average were not different across groups (*P*=0.99). Milk production on the day after treatment differed by group (*P*=0.004). The decline for the saline treatment was 0.3 lb (0.1 kg), but was not significantly different from the negative control. The decline for the MHSV treatment was 2.6 lb (1.2 kg) more than the negative controls (*P*=0.005), and 2.3 lb (1.1 kg) more than the saline treatment (*P*=0.01). By d 2 and d 3 post-treatment, the differences were no longer significant across the groups (*P*=0.14 and *P*=0.42, respectively; Table 4).

Discussion

These results demonstrate a post-vaccinal milk loss per day that is at the low end of the range reported in the literature, which is 1.4 lb (0.6 kg) to 4.0 lb (1.8 kg).[1,12,16,17] Of interest is that there were no differences across the 3 groups on the day of vaccination. Day 1 milk production showed the largest decline, which is consistent with previous studies that have reported milk loss primarily between 12 and 48 h post-vaccination.[1,12,16,17]

The minimal milk loss may be due to the manufacturing process of a subunit vaccine. This process allows the antigens necessary for the animal to mount an immune response to be incorporated into the vaccine without the additional endotoxins associated with whole cell products.

A saline-injected group of cattle was included in the study to evaluate the impact handling and injecting cows has on milk production. This allowed a more accurate evaluation of milk loss due to the energy cost of an immune response, as well as the potential impact of endotoxin level in the vaccine. An earlier study that had both saline and negative control groups reported the saline cows lost 0.11 lb (0.05 kg) of milk per day, compared to the negative control, for the next 3 days following vaccination.[1]

Milk loss adds to the cost of vaccinating the lactating herd, and thus should be considered when developing vaccination programs. For example, if milk income over feed cost is $0.13/lb ($0.28/kg), then the 3-d milk loss of 12 lb (5.5 kg) would equate to decreased revenue from milk sales of $1.56 per cow. The comparable number from this study would be 1.5 lb x 3 days = 4.5 x $0.13 = $0.59.

Profitability on dairy farms, like most commodity businesses, is tight on average. The Center for Farm Financial Management analyzed financial records from dairy farms from 2015 thru 2018, and reported that herds with less than 200 cows made $160 profit per cow, those with 200 to 500 cows made profit of $84 per cow, and herds with more than 500 cows made about $275 per cow.[4] These are average profits, which means about half of the dairies would be making less profit per cow than the average. These low margins demand that dairy farmers look at every opportunity to minimize expenses while maximizing income. Vaccination programs on most dairy farms are critical to maintain animal health and well-being. While vaccinations on dairy farms represent a relatively small portion of the total cost on dairies, it is a cost that managers have control over. Managers should consider not only the cost of the vaccine, but milk losses associated with vaccine use, thus evaluating the full cost of the vaccine.

The authors of the current paper are not aware of any published reports that examined milk production changes associated with the use of *M. haemolytica* vaccines. The trial described here only looks at the impact 1 product has on milk production. It would be helpful to practicing bovine veterinarians if a comparison to other available *M. haemolytica* vaccines was studied.

On the morning the cows were to be vaccinated, the owner decided to eliminate 1 pen of cows from the study, even though they were included in the randomization performed earlier. This was unfortunate, but deleting 1 pen did bring the cow numbers into alignment with the study protocol, but made the number of cows in each treatment appear lopsided. This change did not impact the statistical significance of the results.

Conclusions

Based on the results of this study, veterinarians and producers might expect a modest decrease in milk production over the 3-day period following vaccination with the product used in this study. However, the production loss when using this vaccine may not be significantly more than handling cows and vaccinating with any other product.

Acknowledgements

Endnotes

[a] Personal communication, Kevin Dhuyvetter, PhD, Elanco Cattle Technical Consultant, April 01, 2020
[b] Nuplura PH, Elanco Animal Health, Greenfield, IN
[c] Presponse SQ, Boehringer Ingelheim Vetmedica, St. Joseph, MO
[d] JMP Pro 14.3.0, SAS Institute, Inc., Cary, NC
[e] GEA DermaTron 70, Düsseldorf, Germany
[f] DairyComp 305, Valley Agricultural Software, Tulare, CA
[g] Vedco, St. Joseph, MO

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