# EFFECTS OF PROPHYLACTIC ADMINISTRATION OF A NONSPECIFIC IMMUNOTHERAPEUTIC ON THE PERFORMANCE OF HUTCH-REARED CALVES

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## INTRODUCTION

Mycobacterium Cell Wall Fraction (MCWF) is a nonspecific immunotherapeutic that aids in protection from multiple infectious organisms by activation of the cell mediated immune response. Mycobacterium Cell Wall Fraction Immunostimulant, trade name Immunoboost®, is an immunotherapeutic, licensed by the United States Department of Agriculture (USDA), that enhances the immune system to reduce death loss and clinical signs associated with *E. coli* K99 diarrhea in calves.[1] This host animal trial investigates additional aspects MCWF has on the production, performance and health when given prophylactically to calves less than 24 hours of age.

A newborn calf's treatment in the first few hours and days of its life can have a significant impact on its performance and health as it matures and enters different segments of a beef or dairy production cycle.[2] A calf is born with a sterile gut and respiratory system. As soon as it is born, it is exposed to both pathogenic and nonpathogenic organisms through the nose and mouth. In intense management operations these pathogens are ubiquitous. Undifferentiated Respiratory and Enteric Diseases (URED) are prevalent infections in most commercial operations. Increasingly, these organisms are resistant to most therapeutic antibiotics and are a major concern to herd health.

There are many factors with potential to have negative impact on neonatal health. Bad weather can increase stress, and poor calving conditions can provide increased environmental pathogen levels. Herd immunization, cow condition and dystocia can also have a negative effect. Critical to insuring good early health is adequate quality colostrum intake within the first 12 hours. The passive antibodies derived from colostrum are a calf's major defense against early disease. Unfortunately, the amount and quality of colostrum a newborn calf ingests is usually unknown and often inadequate. The calf must develop its own cell-mediated protection through active immune stimulation.

Dairy calves are routinely removed from the cow immediately after birth and separated into pens or placed in a trailer for transport. These calves offer a unique husbandry and health situation to veal producers, heifer replacement raisers, and Holstein calf ranch operators. Traditionally, these operations struggle to get neonatal calves' immature immune systems functioning properly to fight off URED and other specific diseases. Morbidity and mortality can be quite high under intense commercial management. Routine diagnostics on sick or dead calves reveal mixed infection etiologies in both enteric and respiratory disease complexes. Bacterial isolates are often highly resistant to antibiotic treatments.[3]

Immunotherapeutics, like Mycobacterium Cell Wall Fraction, can play an important role in turning-on the immune system to help fight disease. Precocious immune maturation as a result of MCWF therapy in calves less than 24-hours old has been demonstrated.[4] This could lead to increased production and an overall decrease in the need for antibiotic therapies as demonstrated in this study.

## OBJECTIVES

1. To evaluate health parameters of calves receiving Mycobacterium Cell Wall Fraction (MCWF) treatment compared to control calves.
2. To evaluate production parameters of calves receiving MCWF treatment compared to control calves.
3. To evaluate the economic advantages of calves receiving MCWF treatment compared to control calves.
4. To compare intravenous, intramuscular and subcutaneous routes of administration of MCWF relative to objectives 1 to 3.

## ANIMALS

Holstein and Holstein-cross bull and heifer neonates, less than 24 hours old, were collected daily and block randomized into four (4) groups. Over a three-week period, a total of 400 calves from multiple dairies had entered the trial at a large commercial calf ranch in southern California, USA. Individual calf history was unknown to investigators. All calves received their assigned study treatment at less than 24 hours of age.

## STUDY PROTOCOL

On arrival, each calf was randomly assigned to one of four treatment groups. All calves received routine calf ranch processing. Calves in Groups A, B, and C received a single 1 mL injection of Immunoboost by the designated route of administration (A - intravenous, B - intramuscular, C- subcutaneous). The controls, Group D, received no MCWF. Administration route and dose for each group is listed in Table 1.

*Table 1*

| Group | # of calves | Age | MCWF | Dose Administration Route |
|---|---|---|---|---|
| A | 100 | < 24 hours | 1 mL | Intravenous (IV) |
| B | 100 | < 24 hours | 1 mL | Intramuscular (IM) |
| C | 100 | < 24 hours | 1 mL | Subcutaneous (SC) |
| D | 100 | < 24 hours | 0 | None (Controls) |

Throughout the 75-day study, calves were individually housed in hutches and all groups were fed and handled the same. Grain and water were always available and milk replacer was fed twice a day by nipple-bottle. Experienced farm staff evaluated the calves twice daily for any signs of sickness and administered therapeutic treatments as directed by calf ranch management and veterinary consultation.

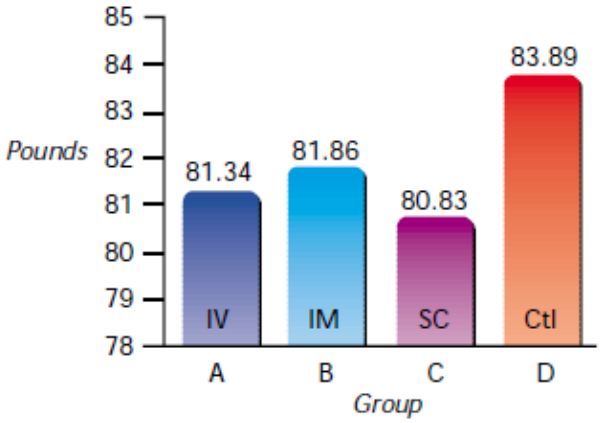
Individual weights were taken on day one of the trial and again on day 75, at the end of the hutch phase. All treatment of sick calves was recorded. Medications administered and dates of treatment were noted. Calculations were performed to determine average weights, average daily weight gain (ADG), average treatment costs, and economic advantage. Weights are in pounds (lbs) and costs are in $US.

## RESULTS

Individual calf birth weights ranged from 55 to 115 pounds. Average "In Weights" are represented in Graph 1 and "Out Weights" (trial end weights) in Graph 2. Although calves in the subcutaneous group (Group C) began with the lowest average body weight (80.83 lbs), they finished with one of the heaviest average body weights (162.34 lbs). The average "Out Weight" of control calves (Group D) was 153.28 lbs.

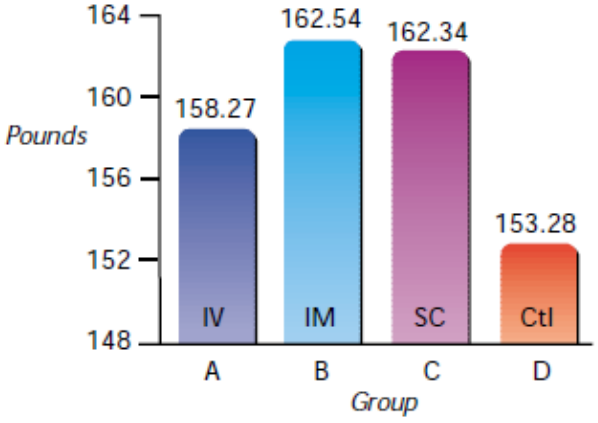
*Graph 1*

***Average Calf In Weight (lbs) (Day 0)***




*Graph 2*

***Average Calf Out Weight (lbs) (Day 75)***

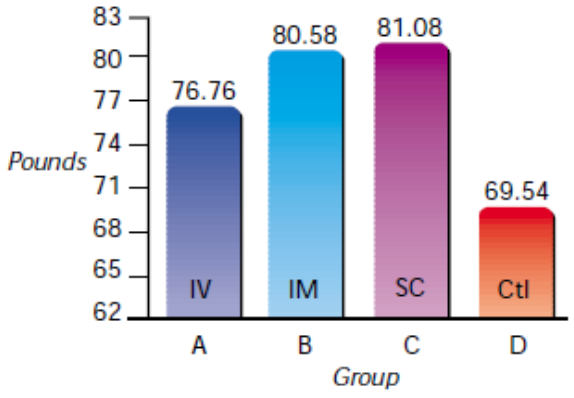



The average weight gain per calf over the 75-day feeding period is represented in Graph 3. The MCWF calves gained an average of 76.76 pounds (Group A), 80.85 pounds (Group B), and 81.08 pounds (Group C). Control calves gained an average of 69.54 pounds (Group D).

Average daily weight gain for control group calves was 0.92 pounds. Calves receiving MCWF by intramuscular and subcutaneous routes of administration (Groups B and C) showed an ADG of 1.07 pounds. ADG is represented in Graph 4. MCWF treated calves gained an average of 0.14 pounds per day more than control calves.

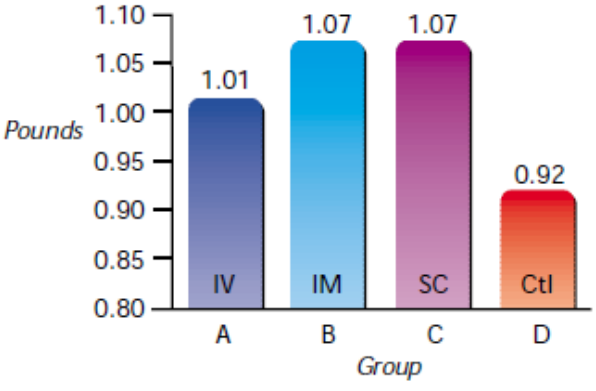
*Graph 3*

***Average Gain per Calf (lbs) (Day 75)***




*Graph 4*

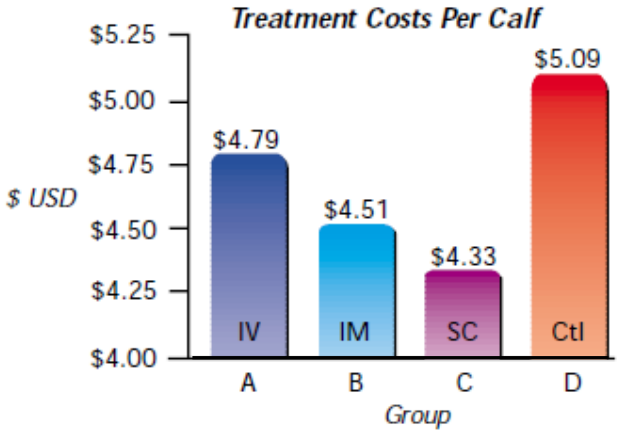
***Average Daily Weight Gain (lbs)***



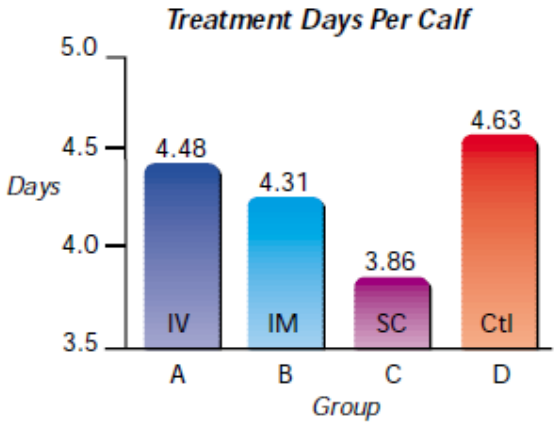
Treatment costs reflect the direct cost of medications to treat URED. Time and labor were not factored into the costs. Average treatment costs per calf in Group A are $4.79, Group B - $4.51, Group C - $4.33, and Group D - $5.09. Treatment costs are shown in Graph 5.

Treatment days per calf are shown in Graph 6. The total number of treatment days in a group divided by the total number of calves in the group calculates these values. Group C calves had 3.86 treatment days per calf compared to 4.63 days for control calves.

*Graph 5*




*Graph 6*




Death loss was less than 5% overall and demonstrated no significant differences between groups (Chi-square $P > 0.05$).

## STATISTICAL ANALYSIS

When given to calves at less than 24 hours of age, Mycobacterium Cell Wall showed a statistically significant positive effect on both weight gain and health. ANOVA and Dunett's methods were used for analysis.

Since there is no evidence of a difference in mean average daily gain among treatment Groups A, B and C (MCWF groups), they can be combined together and compared to Group D (controls). The difference in average daily gain is 0.124 pounds per day ($P < 0.0001$).

A comparison of Group C (subcutaneous administration) to Group D (controls) is also highly significant. MCWF calves gained 0.143 pounds per day more than control calves ($P < 0.0002$). A 95% confidence interval for the difference is 0.077 to 0.220 pounds per day. [5]

## DISCUSSION

This study demonstrates that Immunoboost®, a commercially available Mycobacterium Cell Wall Fraction Immunotherapeutic, has a highly significant positive effect on weight gain, health and economics when administered to calves less than 24 hours of age. Additionally, administration by the subcutaneous route seemed to show production advantages over intravenous or intramuscular routes. Although these differences were not statistically significant, the ease of administering a subcutaneous injection is labor saving compared to intravenous administration.

**Calves receiving MCWF by subcutaneous administration required less treatment days and less antibiotic use compared to control calves, resulting in an 18% decrease in treatment costs. In a 75-day feeding period, they gained an average of 11.5 pounds more than control calves, representing a 15% increase in average daily weight gain.**

The explanation for the profound effect MCWF has on health and performance when administered to a neonatal calf involves consideration of several factors: a calf's immature immune system, the immunological effect MCWF has on the cellular level, clinical and subclinical Undifferentiated Respiratory and Enteric Disease (URED) and energy utilization.

Calves are born with a complete, but immature, immune system. There are very few activated leukocytes present in the blood of newborn calves. A single subcutaneous injection of MCWF significantly increases the frequency of activated T-lymphocytes in the blood of newborn calves. Specifically, it increases the number of MHC Class II CD4 T-lymphocytes. It has also been shown that MCWF increases interferon (IFNγ) production, which is critical in immune defenses against intracellular pathogens such as viruses and some bacteria[4], increases phagocytosis ability of neutrophils[6], and stimulates interleukin-1 (IL-1)[6].

Commercial cattle feeding operations raise calves under intensive management conditions. There is continual exposure to organisms, both pathogenic and nonpathogenic. Experienced calf caretakers can easily identify and treat clinically sick animals; however, calves that are incubating a subclinical disease go unnoticed and untreated. Early stimulation with MCWF sets up the calf's immune system to more effectively fight pathogen insult. As a result, there are fewer subclinical infections that progress to clinical disease. Additionally, calves that do become clinically sick require shorter treatment time because their immune system is more efficient.

All species, require an incredible amount of energy to maintain the immune system. When cattle are sick and highly stressed, they gain less or lose weight. A major reason for the weight loss is that energy that would normally go towards growth is now needed by the immune system to fight disease. If we can optimize immune function early in a calf's life, it is more likely to remain healthy and maximize its production potential. More energy can be directed to growth when it is not required for disease fighting activity.

## CONCLUSIONS

**The use of MCWF (Immunoboost®) in these commercially raised calves resulted in:** [A]

- **Increased Performance -** Calves receiving MCWF by intravenous, intramuscular and subcutaneous administration demonstrated significantly better overall performance than control calves.
- **Less Antibiotic Usage -** Calves receiving MCWF by subcutaneous administration were treated an average of 3.86 days while controls were treated 4.63 days. MCWF calves required 17% less antibiotic treatment.
- **Increased Average Daily Weight Gain -** Calves receiving subcutaneous MCWF gained an average of 11.5 pounds more than control calves over the 75-day feeding period. This represents a 15% increase in ADG.
- **Decreased Treatment Costs -** Calves receiving subcutaneous MCWF had an average treatment cost of $4.33. Control treatment costs were $5.09. This represents an 18% decrease in medicine costs.

## SUMMARY

The effects of prophylactic administration of a single dose of a nonspecific Mycobacterium Cell Wall Fraction (MCWF) Immunotherapeutic (Immunoboost®, Vetrepharm, Inc.) to Holstein and Holstein-cross neonates was evaluated in a clinical field study. Intravenous (IV), intramuscular (IM) and subcutaneous (SC) routes of MCWF administration were compared, both individually and as a MCWF group, to control calves receiving no MCWF. The specific effect of MCWF on Undifferentiated Respiratory and Enteric Disease (URED) and overall production and performance were investigated.

**Calves that received MCWF showed a 15% increase in average daily weight gain (ADG) compared to controls. Overall health and effect on URED findings revealed a decrease in treatment days per calf and a resulting decrease in antibiotic use of 17% in calves administered MCWF.**

Differences between MCWF treatment calves and control calves are statistically significant (ANOVA $P < 0.01$) when comparing each route of administration separately or when comparing all routes collectively. Within the MCWF groups, there was no statistical difference between routes of administration, although calves receiving subcutaneous MCWF did show production advantages over intramuscular and intravenous routes.

Previous studies have demonstrated the immunostimulatory effect of MCWF in bovine, canine and equine species. A precocious immune maturation effect on neonatal calves has also been demonstrated. Expanded commercial use and ongoing clinical studies in various segments of the cattle industry continue to define the value of immunotherapeutics like Mycobacterium Cell Wall Fraction.

[A] See ADDENDUM (next page) for updated Canadian Information

## REFERENCES


1. Immunoboost®, Vetrepharm, Inc., Athens, GA, USA.
2. Losinger, W. and J. Heinrichs (1996). Management Variables Associated with High Mortality in Calves Prior to Weaning. Journal American Veterinary Medical Association, Vol. 209, No. 10, 1756-1759.
3. California Veterinary Diagnostic Laboratory System, San Bernardino, CA, USA.
4. Griebel P., Evaluation of the Ability of Mycobacterium Cell Wall Fraction (MCW) Immunostimulant to Alter Blood Leukocyte Populations in Newborn Calves, Veterinary Infectious Disease Organization, Saskatoon, Saskatchewan, Canada.
5. Dixon, P., Ames, Iowa, USA.
6. Dekaban, G, *et al*. (1993) John P. Robarts Research Centre, London, Ontario, Canada.


## ADDENDUM

NovaVive
An immunobiology company

USDA registered, intravenous administered product: **Immunoboost®**

CFIA submitted, intravenous and subcutaneous administered product: **Amplimune™**

**CONCLUSIONS (updated to CA$, kg and 2015 values)**

- **Increased Performance** - Calves receiving MCWF by intravenous, intramuscular and subcutaneous administration demonstrated significantly better overall performance than control calves.
- **Less Antibiotic Usage** - Calves receiving MCWF by subcutaneous administration were treated an average of 3.86 days while controls were treated 4.63 days. MCWF calves required 17% less antibiotic treatment.
- **Increased Average Daily Weight Gain** - Calves receiving subcutaneous MCWF gained an average of **5.22 kg** (11.5 lbs) more than control calves over the 75-day feeding period. This represents a 15% increase in ADG.
- Decreased Treatment Costs - Calves receiving subcutaneous MCWF had an average treatment cost of **CA$ 7.01**[A]. Control treatment costs were **CA$ 8.22**[A]. This represents an 18% decrease in medicine costs.

When this study was conducted, the average price of a 1 to 7 day old, 50 kg male calf, was approximately **CA$ 112.10**[B]

The average price of the same 50 kg male calf in Canada today is more than **CA$ 500.00**[C]

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[A] http://www.bankofcanada.ca/rates/exchange/cad-usd-rate-lookup/ *Average USD-CAD exchange rate for April, 2000*

[B] http://futures.tradingcharts.com/historical/FC/2000/4/linewchart.html *USD prices per 100 lb calf converted to CAD*

[C] Quebec male bob calf prices in Canadian dollars on 2015, April 14 *Average 50 kg male calf price: CA$ 518.10*