



PROFESSIONAL SERVICES

Boehringer Ingelheim Vetmedica, Inc.

## TECHNICAL BULLETIN

### Safety of Express® MLV vaccines in pregnant cows or calves nursing pregnant cows

#### INTRODUCTION

Similar to field strains of IBR and BVD virus, attenuated IBR and BVD in modified live virus (MLV) vaccines may cause abortions or fetal infections when administered to naïve, pregnant cows. As a result, modified live IBR and BVD vaccines have traditionally contained the statement “Do not use in pregnant cows or in calves nursing pregnant cows.” Based on guidelines in Veterinary Services Memorandum No. 800.110, USDA-APHIS may grant a modified live IBR and BVD vaccine an exemption to this statement provided the vaccine has been shown to be safe in cows vaccinated in any trimester of gestation. In general, the Memorandum states at least 1,200 cows must be vaccinated prior to breeding and then revaccinated in the first, second, or third trimester. The rate of abortion due to IBR and BVD virus must not exceed 0.5% and the rate of abortion, due to any cause, must not exceed 5.0% in any trimester of gestation. In addition, the vaccine must not result in IBR or BVD fetal infections when cows are revaccinated in the second or third trimester of pregnancy.

In an effort to remove the statement “Do not use in pregnant cows or in calves nursing pregnant cows” from Express® MLV vaccines, two studies were conducted to evaluate the safety of Express® FP in pregnant cows. One study measured abortions (fetal losses) and postpartum calf health following vaccination of pregnant cows with Express® FP 10. The purpose of the second study was to determine if vaccination of pregnant cows in the second or third trimester would result in BVD or IBR fetal infections.

#### KEY POINTS

- There were no abortions or fetal losses due to IBR or BVD viruses following vaccination of pregnant cows and heifers with Express® FP vaccines.
- Fetal losses due to all causes were 1.6% (13 of 810) in the Express® FP group and 1.9% (15 of 776) in the control group.
- Express® FP vaccine administered during pregnancy to animals previously vaccinated with Express® did not cause IBR or BVD fetal infections.
- Calves born to cows vaccinated with Express® FP during pregnancy were negative for pre-colostrum IBR, BVD 1 and BVD 2 antibodies.
- Express® MLV vaccines may be given to pregnant cows and heifers, or calves nursing pregnant cows, provided the females were vaccinated prior to breeding with any Express® FP vaccine.

# Evaluation of fetal losses and postpartum calf health in cows vaccinated with Express® FP vaccine during pregnancy

## OBJECTIVE

To investigate the calving outcome and postpartum health of calves born to cows and heifers that were vaccinated with Express® FP 10 prior to breeding and revaccinated with Express® FP 10 in the first, second or third trimester.

## STUDY DESIGN

This field safety study was conducted in three cow-calf herds and utilized 1,586 Angus or Angus-cross cows and heifers. Prior to breeding, all cows and heifers were confirmed BVD PI negative via immunohistochemistry and were vaccinated with Express® FP 10, a modified live virus vaccine containing IBR, BVD Types 1 and 2, PI<sub>3</sub>, and BRSV as well as *Leptospira canicola*, *grippotyphosa*, *hardjo*, *icterohaemorrhagiae*, *pomona* bacterins. Cows and heifers from two herds were bred via natural service. In the third herd, all heifers, and a majority of the cows, were synchronized, artificially inseminated and cleaned up with bulls. The semen from the bulls and the semen used for artificial insemination was confirmed negative for BVD virus by rt-PCR. In addition, all bulls used for breeding were ear notched and confirmed BVD PI negative.

Pregnancy status and eligibility for enrollment was determined with ultrasound during the first trimester. Pregnant cows and heifers were randomly assigned to one of three trimester groups: trimester 1 (T1), trimester 2 (T2), or trimester 3 (T3). Cows in each trimester group were then randomly assigned to receive a second dose of Express® FP 10 (vaccinates) or a dose of Lepto 5 (controls) during pregnancy. Cows in the T1 group received Express® FP 10 or Lepto 5 at pregnancy check on day 55 of gestation. Cows in the T2 and T3 groups were checked again by ultrasound and received Express® FP 10 or Lepto 5 on Days 140 and 210 of gestation, respectively (Table 1).

<b>Table 1: Trimester Groups</b>			
Group	Vaccinated and Pregnancy Checked (Day of Gestation)	# Vaccinated with Express FP10 (Vaccinates)	# Vaccinated with Lepto-5 (Controls)
T1	55	306	274
T2	140	237	335
T3	210	267	267

Serum samples were collected at the time of the trimester vaccination. Cows and heifers were followed to calving and the calving outcome recorded. Any animal confirmed pregnant at the trimester vaccination but open at the end of the trial was counted as a fetal loss. Cows and heifers diagnosed as open were bled at the time of diagnosis and 1 to 4 weeks later. Serum samples were tested for levels of serum neutralizing antibody to IBR, BVD 1 and BVD 2. A significant increase between the paired serum samples could indicate a potential fetal loss due to IBR or BVD virus.

All calves were observed daily for four weeks following birth. All calf losses and treatments were recorded. If possible, all dead calves and fetuses were necropsied and tissues (lung, thymus, cerebellum, liver, kidney, spleen, placenta, stomach contents, heart blood and pleural fluid) collected. Tests performed on the tissues included histology, IBR and BVD fluorescent antibody (FA), *Leptospira* FA, IBR and BVD virus isolation, aerobic culture, mycology culture and serum neutralization for IBR, BVD 1 and BVD 2. When obtained, fetal and post-calving ear notch samples were tested for BVD via IHC.

## RESULTS

Calving outcome was recorded as Open (diagnosed pregnant at trimester vaccination, but did not deliver a calf), Dead (dead calf at birth, not diagnosed as dystocia), or Live (live, normal calf at calving). Calves that died due to dystocia, exposure (frozen in blizzard) or other non-study related causes were not included in the final results. Open and dead cases were combined and recorded as fetal losses. Fetal losses were similar between vaccinates and controls. For vaccinates and controls in all three trimesters, there were **no fetal losses or abortions diagnosed due to IBR or BVD virus** and the fetal loss rate due to any cause was less than 5%. Table 2 shows number of fetal losses due to all causes.

<b>Table 2: Fetal Losses</b>						
	Vaccinates <sup>1</sup>			Controls <sup>2</sup>		
Trimester	Number Enrolled	Fetal Losses	95% CI	Number Enrolled	Fetal Losses	95% CI
1 <sup>st</sup>	306	7 (2.3%)	0.011, 0.046	274	6 (2.2%)	0.010, 0.047
2 <sup>nd</sup>	237	1 (0.42%)	0.000, 0.023	235	3 (1.3%)	0.004, 0.037
3 <sup>rd</sup>	267	5 (1.9%)	0.008, 0.043	267	6 (2.2%)	0.010, 0.048

<sup>1</sup>Vaccinated with Express FP 10 pre-breeding, re-vaccinated with Express FP 10 during respective trimester.

<sup>2</sup>Vaccinated with Express FP 10 pre-breeding, vaccinated with Lepto-5 during respective trimester.

Calf deaths in all trimester groups were low and treatments were primarily for minor cases of scours that cleared within 24 to 48 hours. Table 3 shows the postpartum calf deaths and treatments for each trimester group.

<b>Table 3: Postpartum Calf Deaths and Treatments</b>				
	Vaccinates <sup>1</sup>		Controls <sup>2</sup>	
Trimester	Postpartum Treatments/Total Calves	Postpartum Deaths/Total Calves	Postpartum Treatments/Total Calves	Postpartum Deaths/Total Calves
1 <sup>st</sup>	6/299	3/299	1/268	0/268
2 <sup>nd</sup>	6/236	0/236	2/232	1/232
3 <sup>rd</sup>	10/262	3/262	7/261	1/261

<sup>1</sup>Dams vaccinated with Express FP 10 pre-breeding, re-vaccinated with Express FP 10 during respective trimester.

<sup>2</sup>Dams vaccinated with Express FP 10 pre-breeding, vaccinated with Lepto-5 during respective trimester.

## SUMMARY

Vaccination with Express<sup>®</sup> FP 10 during pregnancy did not result in IBR or BVD virus abortions in cows vaccinated with Express<sup>®</sup> FP 10 prior to breeding. There were no deleterious effects on the health of calves born to cows vaccinated with Express<sup>®</sup> FP 10 during pregnancy.

# Evaluation of fetal infections due to IBR or BVD viruses following vaccination of pregnant cows with Express® FP vaccine

## OBJECTIVE

To evaluate the pre-suckling IBR and BVD virus antibody status of calves born to cows vaccinated with Express® FP 10 in the second or third trimester of pregnancy.

## STUDY DESIGN

This field safety study involved two groups of crossbred beef cows. Group 1 (n=120) cows were vaccinated prior to breeding with Express® 5 and Group 2 (n=141) cows were vaccinated prior to breeding with Express® FP 5. Cows were bred by natural service. After confirmation of pregnancy, Group 1 cows were vaccinated with Express FP 10 in trimester three and Group 2 cows were vaccinated with Express® FP 5 in trimester two. The third trimester cows also received an inactivated Coronavirus / Rotavirus / E. coli vaccine.

Following vaccination, cows were observed daily for visual signs of fetal loss or other health problems. As calving approached, cows were moved to a paddock for close observation. Shortly after birth, calves were bled to obtain a pre-colostrum sample. The blood was allowed to clot and serum separated. Serum was stored at -20° C until delivered to the Animal Health Laboratory, University of Guelph, Guelph, Ontario. Serum neutralization titers for IBR, BVD Type 1 (challenge virus, Singer) and BVD Type 2 (challenge virus, NVSL 125c) were determined on all serum samples. The level of gamma-glutamyl transpeptidase (GGT) was determined, rt-PCR assay for BVD virus, and virus isolation for IBR virus was completed on samples. A positive test for GGT indicates calves may have suckled. A direct relationship exists between the level of GGT and serum antibody level.

## RESULTS

Pre-colostrum serum samples were collected from 132 calves (65 third trimester and 67 second trimester). Of the 65 calves born to cows vaccinated in the third trimester, 6 were removed from the study. Four calves had suckled prior to collecting blood and had positive antibody titers and positive GGT. Two calves were suspected of having suckled, but were seronegative and had normal GGT results. Samples were collected from 67 calves born to cows vaccinated in the second trimester. Six of these samples were removed. Two samples were lost due to a centrifuge malfunction during processing of the serum. Four calves were noted as having suckled and had positive antibody titers and positive GGT. Two calves were noted by the investigator as suspected of suckling. One calf had negative antibody titers and normal GGT. The second calf suspected of suckling had positive antibody titers and normal GGT. The low level of antibody (IBR – 1:4; BVD 1 – 1:64; BVD 2 – 1:6) was consistent with it having absorbed a small amount of antibody from colostrum at the time the sample was drawn, but before sufficient GGT was absorbed to cause it to exceed the baseline level. This is consistent with the observations in this study and the published data.

**Pre-colostrum serum samples from the remaining 120 calves were all negative for antibody to IBR, BVD Type 1 and BVD Type 2.** In addition, all IBR virus isolation assays and BVD 1 and 2 rt-PCR assays were negative. There were no post-calving losses due to health problems.

## SUMMARY

Pre-colostrum serum samples from calves born to cows vaccinated with Express® FP during pregnancy showed the modified live IBR and BVD viruses did not result in IBR, BVD 1 or BVD 2 fetal infection.

<b>Express® 5:</b>	Modified live IBR, BVD 1, BVD 2, PI <sub>3</sub> , BRSV
<b>Express® 5 FP:</b>	Modified live IBR, BVD 1, BVD 2, PI <sub>3</sub> , BRSV Product contains more BVD 1 and 2 than Express® 5 Product has a Fetal Protection claim (prevention of BVD-PI calves)
<b>Express® FP 10:</b>	Modified live IBR, BVD 1, BVD 2, PI <sub>3</sub> , BRSV rehydrated with <i>Leptospira canicola</i> , <i>grippytyphosa</i> , <i>hardjo</i> , <i>icterohaemorrhagiae</i> , <i>pomona</i> bacterins Product has a Fetal Protection claim (prevention of BVD-PI calves)