Environmental and management factors influencing BVDV antibody levels and response to vaccination in weanling calves

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Summary

Vaccination has many benefits for disease prevention and overall health status of animals. Not all animals respond equally to vaccinations. A number of factors can be shown to influence a young animal's response to vaccination. Calves with more maternal antibodies at the time of vaccination have poorer immune response. The level of maternal antibodies at the time of vaccination is influenced by the amount of passive immunity transfer obtained via colostrum in the first 24 hours and the subsequent loss of maternal antibodies over the period up until vaccination. Younger dams appear to supply fewer passive antibodies to their calves and these maternal antibodies from younger dams appear to degrade at a faster rate than those from older dams. The level of response achieved in vaccinated calves varies by calving season. Vaccination during periods of high stress, such as weaning, has shown negative impacts on response. Further, calf age impacted the ability of a calf to mount an antibody response. Calves needed to be at least 130 days of age to elicit a positive response to vaccination. Collectively, these data suggest ranchers may be able to improve the value of vaccination by avoiding this activity at weaning and by consideration of the age of the dams, and the age of the calves at vaccination.

Introduction

Bovine Respiratory Disease: Bovine respiratory disease (BRD) has the greatest incidence among feedlot diseases and has the largest negative economic impact, with an estimated cost of $750 million annually, to the feedlot industry (Holland et al., 2010). It has been characterized as a complex disease that involves environment, stress, and infectious pathogens (Step et al., 2009). The viral agents most often associated with BRD are bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), bovine infectious rhinotrachetious (BIR), and parainfluenza 3 (PI_3) (Salt et al., 2007). BRD is seldom caused solely by a viral pathogen, but most often is the result of a secondary bacterial infection, which resulted due to a weakened immune system as a consequence of the viral pathogen infection (Salt et al., 2007).

Vaccination: Vaccination is currently used as a primary method for prevention of respiratory disease. Vaccination has been shown to improve animal health and productivity by reducing disease incidence as animals move through production phases. Optimization of vaccination protocols to decrease disease prevalence provides an opportunity to reduce these losses. It has been shown that vaccination of weaned cattle prior to arrival into the feedlot can prevent infectious diseases that may lead to the onset of BRD (Kirkpatrick et al., 2008). While the practice of vaccination has been adopted in many production systems, a protective response from the vaccines is still necessary for disease prevention.

Maternal Antibodies: Newborn calves passively acquire antibodies from their dams via consumption of colostrum immediately after birth. However, factors such as dam age, quality and quantity of colostrum, and timeliness of colostrum consumption may influence the amount of maternally derived antibodies present in the circulatory system of a calf. As a calf's immune system is not fully developed at birth, maternal antibodies are important for prevention of disease, such as infection of BVDV shortly after birth. However, passively acquired antibodies have been shown to block the ability of the calves' immune system to mount an antibody response to vaccination, and therefore may need to have decreased to a sufficiently low level in order for calves to respond to vaccines (Menanteau-Horta et al., 1985). There is a period of vulnerability, during the period that maternal antibodies have regressed up until the time vaccination has induced a sufficient level of protection. This vulnerability period impacts a manager's decision about when to vaccinate calves to elicit a protective response (Endsley et al., 2003). Therefore, the age of dam, total passive immunity transferred, and the maternal antibody decline rate may be important factors to consider when developing a vaccination protocol.

Stress: There have been a number of studies that have shown that stress has deleterious effects on antibody development, growth performance, and carcass quality in calves (Niekamp et al., 2007; Richeson et al., 2008; Salak-Johnson, 2007; Step et al., 2008). Some high stress periods have been identified as weaning, transportation, de-horning, castration, bunk breaking, and commingling (Elenkov, 2002). Weaning has often been incorporated with vaccination to reduce labor needs. However, this may have detrimental effects on an animal's ability to respond to vaccinations. Therefore, minimizing stress at the time of vaccination may likely give the best return on vaccine use. However, this may not always be a viable management option.

Vaccination of cattle has been considered a standard management procedure for disease prevention, and remains one of the most effective methods for disease prevention. There are environmental and genetic factors that contribute to an animal's ability to respond; both are of interest for improved immune response (O'Neill et al., 2006; Richeson et al., 2008). There are management factors that can be controlled by producers such as, but not limited to, induced stress, calf age at vaccination, and animal nutrition, which can enhance or impede the vaccine response of calves (Bagley, 2001). While vaccination is a disease prevention method, animals must develop a protective response from the vaccine in order to actively protect against pathogens. The goal of this project was to develop vaccination management recommendations, which increase the effectiveness of vaccinations. In this study, weanling calves were evaluated to identify factors that effect maternal antibody transfer and persistence in the calf along with environmental factors that impact an animal's ability to respond to vaccination.

Materials and Methods

Sample Collection: To evaluate response to BVDV type II vaccination, data and serum samples were collected from 1,012 purebred American Angus calves from the Iowa State University breeding project at the ISU McNay Research and Demonstration farm. Calves were born in 2007, 2008, and 2009 with 334, 354, and 324 calves born in each year, respectively. The cow herd was managed in two calving seasons with 380 calves born in the fall season and 632 calves in the spring season. Animals were vaccinated using a standard two-shot protocol, with shots administered approximately three weeks apart, as suggested by the vaccine manufacturer. All calves in this study were vaccinated with the recommended 2cc dose of Pfizer Bovisheild Gold-5®. In addition to response to BVDV II vaccination evaluation, the effect of wean stress on the ability of calves to respond to vaccination was incorporated. Approximately half of the calves in each year/season were weaned at initial vaccination and the other half of the calves were weaned at booster vaccination, with 512 and 500 animals being weaned in each group, respectively (**Figure 1**). To evaluate antibody levels and response measurements, serum samples were collected at four time points. The first sample was collected three weeks prior to the initial vaccination (**pre-vaccination**) to quantify the level of maternal antibodies present in the calves and enable assessment of maternal antibody loss over a period of time prior to vaccination. Three other samples were collected: just prior to the initial vaccination (**initial**); at booster vaccination (**booster**); and three weeks post booster vaccination (**final**) (**Figure 1**). Serum was analyzed using a viral neutralization assay to quantify BVDV II neutralizing antibodies. These neutralizing antibodies were the BVDV II specific antibodies that were present in the serum that were capable of attaching to the virus and preventing infection, this was done using a serial dilution of individual calf's serum. The highest dilution of serum that carried enough antibodies to protect against the virus was reported as a titer score. The higher the titer score the higher the level of antibodies present in the serum of a calf, which should equate to an increased protection against viral infection.

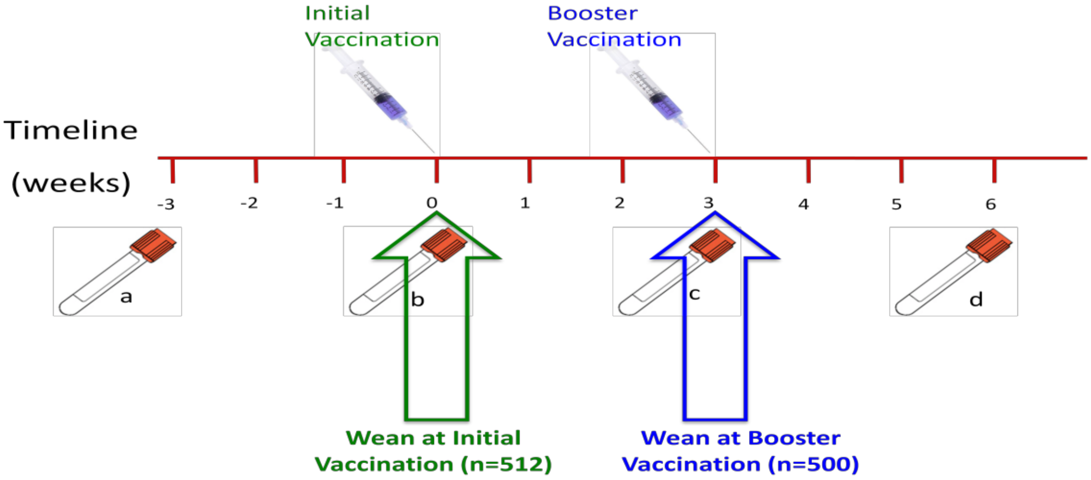

Figure 1. Diagram of serum sample collection, vaccination timing, and weaning timing. The syringes at week 0 and 3 indicate time when vaccine was administered to calves. The collection tubes indicate the four serum collection time points. **a**) Pre-vaccination antibody level (n=615). **b**) Antibody level at initiation of the vaccination protocol (n=1,012). **c**) Antibody level in calves 3 weeks after the initial vaccination (n=1,012), i.e., response to initial vaccination and at booster. **d**) Final antibody level achieved following the 2-shot protocol (n=1,012). The green arrow indicates that half (n=512) of the calves were weaned at initial vaccination. The blue arrow indicates the time of weaning for the second half (n=500) of the calves.

Variable Calculations: Pre-vaccination and initial titer levels were used to evaluate maternal antibody transfer and rate of maternal antibody regression. Initial titer was used with pre-vaccination titer to determine the **rate of maternal antibody decline** (**Figure 2**). Maternal antibody decline was calculated as the difference between initial and pre-vaccination titers divided by the number of days between the two samples.

Final titer was used to evaluate total antibody development of the animal three weeks post booster vaccination (end of the vaccination protocol). Three response variables were also evaluated: **response to initial vaccination**, **response to booster vaccination**, and **overall response**. Response to initial vaccination was calculated as the difference between the booster and initial titers. Response to booster vaccination was calculated as the difference between final and booster titers. Overall response was calculated as the difference between initial and final titers (**Figure 2**).

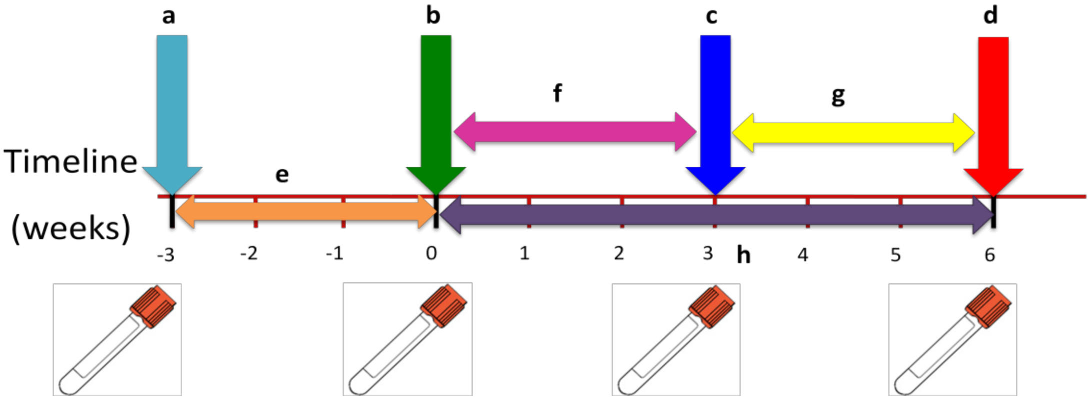

Figure 2. Collection tubes represent the times of serum collections and therefore the titers at these points. The arrows indicate the evaluated variables, a) pre-vaccination titer level, b) initial titer, c) booster titer, d) final titer, e) decline of maternal antibodies, f) response to initial vaccination, g) response to booster vaccination, h) overall response.

Results

Environmental Factors: Effects of: dam age, calf age, circulation of maternal antibodies, year by season, time of wean stress, and gender were evaluated for their influence on antibody levels and response to vaccination variables. Calf gender was not found to influence antibody levels or affect overall response to vaccination. However, there was a significant difference seen in year by season groups.

Means and Correlations: Pre-vaccination and initial serum antibody levels were evaluated for age of dam effects, specifically for differences in maternal antibody transfer. Additionally, rate of decline of maternal antibody decline was evaluated on dams of different ages. **Table 1** has the observed means with standard deviations for titer score (base 2 log), calf age (days), and weight (lbs) for the four collection time points (pre-vaccination, initial, booster, and final). These means are then broken down by season, as seasonal differences have been observed.

Table 1. Means for titer level, calf age, and calf weight at four serum collection time points, which were collected ~21 days apart. Data are also reported by calving season, spring or fall.

Collection Time	N	Titer Score (base 2 log)	SD	Age (days)	SD	Weight (lbs)	SD
Pre-vaccination	615	4.36	±2.24	99.1	±26.6	276	±67.5
Initial	1,012	3.05	±2.25	133	±30.4	327	±84.6
Booster	1,012	2.56	±1.86	154	±30.7	376	±92.9
Final	1,012	4.01	±1.84	176	±29.5	426	±96.1
Spring-born							
Pre-vaccination	303	2.86	±1.57	115	±21.7	292	±72.6
Initial	632	2.03	±1.83	149	±24.5	359	±80.9
Booster	632	1.81	±1.50	170	±25.4	406	±95.6
Final	632	4.28	±2.06	191	±25.5	456	±98.5
Fall-born							
Pre-vaccination	312	5.82	±1.78	83.7	±21.4	261	±58.0
Initial	380	4.74	±1.82	107	±19.5	272	±58.1
Booster	380	3.80	±1.73	128	±17.9	327	±62.8
Final	380	3.56	±1.30	152	±17.1	377	±67.6

Calf age (days), age of dam (years), and weight (lbs) were correlated with pre-vaccination, initial and final antibody levels to evaluate their relationships. Calf age had a higher correlation with pre-vaccination and initial antibody level than did calf weight (**Table 2**). Thus, calf age may be the more informative indicator of maternal antibody levels in the calf's circulatory system. Additionally, age of dam was also highly correlated with both pre-vaccination and initial antibody levels. Therefore, there may be differences in maternal contributions depending on the age of the dam.

Table 2. Correlations for pre-vaccination, initial, and final antibody (titer) levels with calf age, dam age, or calf weight.

Collection Titer	Pre-vaccination	Initial	Final
Calf Age	-0.626	-0.621	0.315
Age of Dam	0.602	0.531	-0.063
Weight	-0.230	-0.363	0.266

Maternal Antibody Acquisition and Decline: Pre-vaccination and initial antibody levels were representative of the amount of passive antibodies that were acquired by calves. It is expected that this passively acquired immunity will erode over time. By including calf age as a covariate for pre-vaccination or initial titers, a generalized rate of maternal antibody decline was estimated and the level of maternal antibody transferred at birth was then estimated. The general maternal antibody decline can be seen in **Figure 3**, as there is a decline between pre-vaccination and initial antibody levels.

Pre-vaccination and initial antibody levels, after correction for calf age, were significantly influenced by dam age (**Figure 3**). There was a significant difference in the transfer of passive immunity for each dam age group for two to five year old dams, but once cows reach five years of age there were no further differences in the amount of maternal antibodies transferred to the calf (see **Figure 3**). The improvement in passive antibody transfer seen across dam age could be due to differences in colostrum quality and quantity that was available to calves and timeliness of colostrum intake by calves (i.e. how quickly the dam mothered up the calf to nurse).

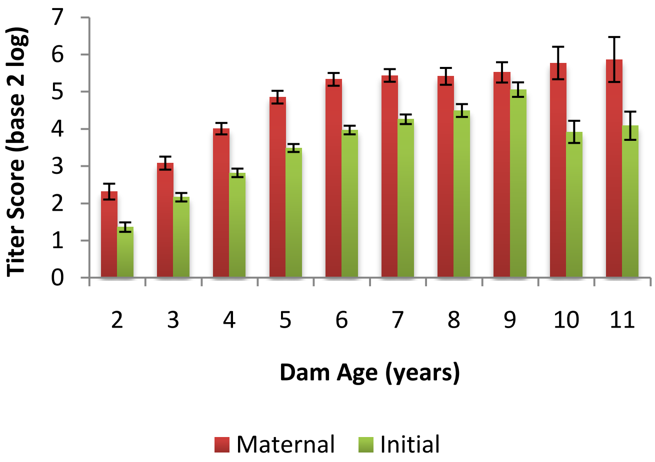

Figure 3. LSMean titer scores for dam age for pre-vaccination and initial antibody levels.

Differences in animal specific maternal antibody decline rate were evaluated by age of dams in this population. The rate of maternal antibody decline in calves from younger cows was faster than the rate of decline observed in calves from older dams when year by season, age of dam, calf age, and pre-vaccination titers were accounted for (**Table 3**).

Recognizing that two-year old dams have transferred fewer maternal antibodies to their offspring, their calves would potentially reach negligible levels of maternal antibody at a younger age and therefore be vulnerable to a natural infection at a younger age than calves from older dams. Thus, calves from younger dams may need to be vaccinated at a younger age to provide them with adequate protection against viral infection.

Maternal Antibody Interference: Maternal antibodies serve protective roles in young calves with immature immune systems, but high levels of maternal antibodies at the time of vaccination can impede the development of the specific immune system in calves.

Table 3. LSMean for rate of decline of maternal antibodies by age of dam. Estimates with different superscript (a,b,c) are significantly different at P<0.05.

Dam Age (years)	**Titer Decline Rate (Titer/day)**
2	-0.061 (±0.006)^{bc}
3	-0.051 (±0.005)^{bc}
4	-0.045 (±0.004)^{ab}
5	-0.046 (±0.005)^{bc}
6	-0.033 (±0.005)^{ab}
7	-0.023 (±0.005)^{a}
8	-0.022 (±0.006)^{a}
9	-0.036 (±0.008)^{ab}
10	-0.045 (±0.012)^{ab}
11	-0.023 (±0.017)^{ab}

Figure 4 displays mean antibody level (titers) by age of dam across the four collection time points (pre-vaccination, initial, booster, and final antibody levels). Calves from younger dams had lower maternal antibody levels at pre-vaccination. High maternal antibody levels can block/inhibit the immune systems ability to respond to vaccination. Maternal antibodies present at the time of vaccination were shown to inhibit overall response to vaccination by -1.2 titer scores for every 1-point titer increase in circulating maternal antibodies at initial vaccination. Therefore, at day 0, when calves were administered the initial vaccine, those calves that were

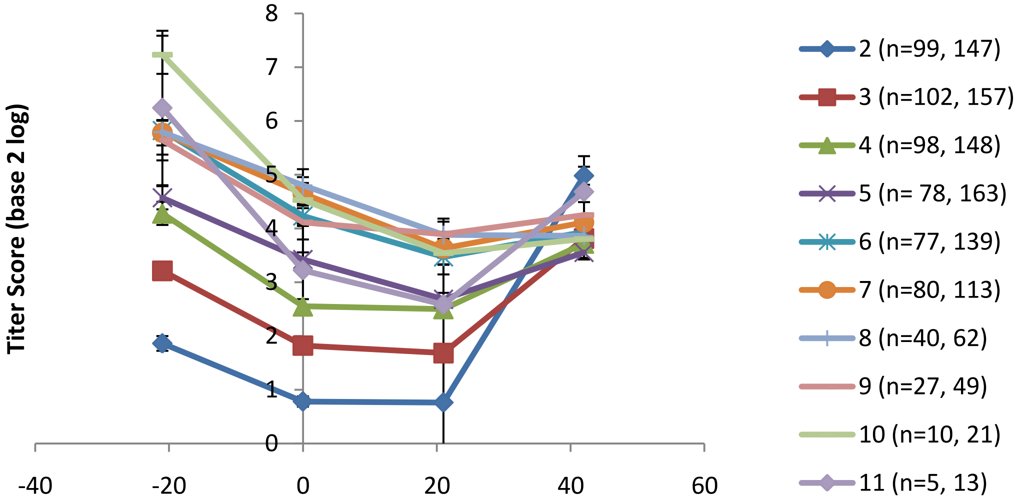

Figure 4. Average antibody level (titer scores) for the four collection time points (-21, 0, 21, and 42 days) by dam age (2 through 11 year old dams). Number of calves for each dam age is listed in parentheses following the dam age label, with sample number at pre-vaccination followed by the number of calves for the three subsequent collection time points.

from younger dams had lower initial titer scores and were more likely to develop and antibody response to vaccination; thus, enabling those calves to show a greater overall response to vaccination.

Calf Age: Beyond age of dam, calf age also significantly affected pre-vaccination and initial antibody levels. To look at the age affects on antibody level over time, calves were grouped by age in 21-day intervals (**Figure 5**). Not surprisingly, younger calves tended to have higher initial antibody levels compared to older calves, while older calves had a higher antibody level at the final response and had a greater overall response to vaccination (see **Figure 5**). The ability of older calves to mount a high overall response may be explained by the removal of more maternal antibodies that could inhibit a response to vaccines. These results indicate that vaccinating calves at an older age will allow them to mount a larger positive response to vaccination.

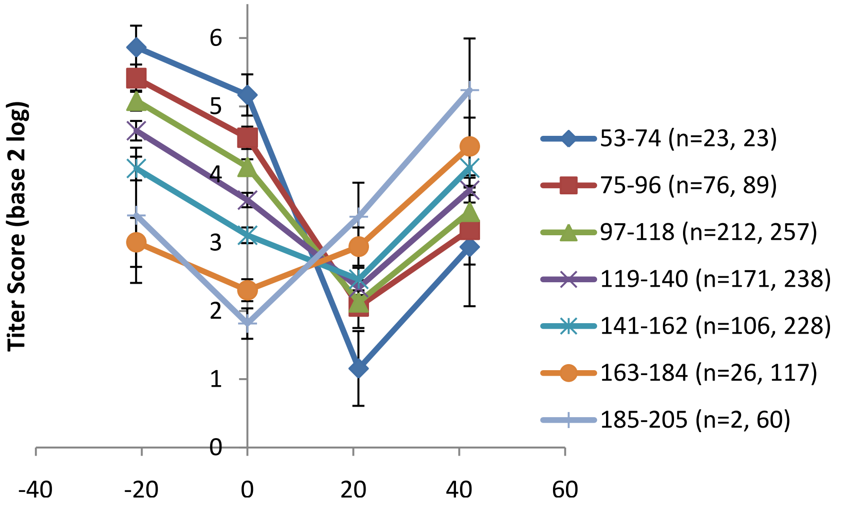

Figure 5. LSMean for calves grouped by 21-day intervals by age for maternal, initial, booster, and final antibody titer comparison, with the sample number listed by maternal titer, initial titer. The older calves show less circulating maternal antibodies at the beginning of the vaccination protocol and higher final response to vaccinations.

As another method to evaluate the effect of calf age on time vaccination, calves were separated into non-responders, low responders, and high responders. The LSMeans for age at initial vaccination for these response groups were then estimated (**Table 4**). Non-responder calves had a negative or zero overall response, with titers less than zero. Low responder calves had overall

Table 4. LSMean for age at vaccination by response to vaccination group: non-responders, low responders, and high responders. Superscripts indicate significant differences in ages at P<0.05. Year by season has been accounted for in the age at vaccination mean.

Response Group	Age at Vaccination (days)	Mean Overall Response (base 2 log)
Non-Responders	123.1 (±0.856)[a]	-1.776 (±0.987)
Low Responders	129.5 (±1.089)[b]	1.680 (±1.217)
High Responders	135.5 (±1.445)[c]	5.981 (±1.217)

response titers from zero to five; and high responders were calves that had overall response titers (antibody levels) of five or more. Forty-nine percent of the calves were classified as non-responders, 28% were classified as at low responders, and 23% were classified as high responders. There were significant differences by response group in their ages at vaccination. In this study, the calves that achieved a response to the vaccination were approximately 130 days old at the time of the initial vaccination vs. 123 days old for.

Weaning Stress Interference: Periods of high stress are known to suppress the immune system and thereby increase the risk of disease during these elevated stress periods (Salak-Johnson, 2007). Weaning has been identified as a high stress period in cattle that could affect the immune response (Niekamp et al., 2007). This immune suppression, caused from weaned calves, affects antibody response in vaccinated cattle. Therefore, vaccination of calves in a stress free environment would be the ideal management practice. However, in many commercial operations, this is not a practical management option and weaning and vaccination occur simultaneously. Therefore, it has been shown that timing of weaning can have significant effects on an animal's ability to respond (**Figure 6**; Niekamp et al., 2007). This effect of wean-stress timing was evaluated for the three response variables. Two wean-stress times were identified, weaning at the initial vaccination and weaning at the booster vaccination, as these may be typical management practices applied in production settings. **Figure 6** illustrates the effects of these two wean-stress periods. Once year and season differences are accounted for, animals weaned at the initial vaccination elicited a higher overall response than calves weaned at the booster vaccination. Therefore, if a high stress activity, such as weaning, was implemented at time of vaccination, there is a greater overall response from those calves that experienced the stress at the initial vaccination.

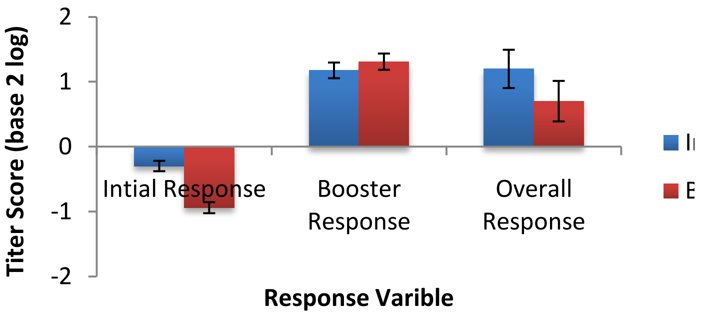

Figure 6. LSMean titer scores for the two weanstress periods for initial response, booster response and overall response. Animals weaned at initial vaccination elicit a greater response to vaccination than animals weaned at booster vaccinations.

Conclusion

Timing of vaccination is very important in order to induce a protective antibody response in weanling calves. Optimal timing of vaccination is influenced by both age of dam and calf age. Increases were seen in the amount of antibody transfer for each dam age group from two to five year olds, once cows reached five years of age no significant differences in maternal antibody transfer were seen. The rate of maternal antibody decline is also dam age dependent, with younger cows having a faster antibody decline rate. The amount of maternal antibodies transferred and the rate of decline will both influence the optimum calf age for vaccination to enable a positive response. Before a vaccination can have a positive response, maternal antibodies must have declined to a level low enough not to immediately neutralize antigens from vaccines. Therefore, calves from younger dams would be eligible to be vaccinated at a younger age than calves from older cows to avoid periods of infection vulnerability. This age at which to vaccinate calves was also influenced by passively acquired immunity. As maternal antibody level needs to decline to a sufficiently low level so that an immune response can be elicited response. However, calves need to be vaccinated before they enter into a vulnerable period for infection. Stress can negatively impact immune response to vaccination, however if weaning stress and vaccination occur simultaneously, calves that were weaned at the initial vaccination saw an increased overall response.

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