Immune management and vaccination of the preweaning beef calf

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Abstract

Ensuring health of preweaning calves requires attention to colostrum intake and nutrition of the dam and calf, and targeted use of vaccination. Colostrum intake that leads to optimal, and not just adequate, passive immunity can improve calf health. The neonatal calf has a functional immune response, and calves can respond to vaccination in the first week of life. Maternal antibodies do not always suppress response to vaccination, but intranasal routes of vaccination may more effectively prime immunity in the first month or two of life, when maternal antibodies are at the highest concentration. Either intranasal or parenteral vaccines can be effective to prime immunity in calves at 90 to 120 days of age. In calves, booster doses are particularly important to ensure immunity, as not all calves will be prepared to respond optimally at the time of their first vaccination. Field trials indicate that preweaning vaccination can sometimes improve health postweaning, but few field trials have evaluated the effects of preweaning vaccination on preweaning disease. Challenge studies and research measuring immune function provide support for vaccination to prevent preweaning disease, but the evidence quality is not strong. More field trials testing vaccination of preweaning calves to prevent preweaning disease are needed.

Key words: colostrum, antibody, respiratory disease

Introduction

An effective immune response is the foundation for health and growth in calves. For beef calves, a program that supports cow health through preventive care and good nutrition is necessary to ensure calf health. For the calf, attention to colostrum intake, nutrition and timely use of vaccination also supports immunity. This presentation will review the information on factors that influence optimal transfer of passive immunity, the effects of nutrient supplementation to improve immunity, and the value of vaccination of preweaning calves to prevent disease in the preweaning and postweaning periods.

Immune responses in the newborn calf

The concept that calves are immunosuppressed at birth, or that they lack immune competence, is often discussed in the context of managing calves for health and growth. However, it is important to remember that this is relative, but not absolute. While immune responses in a calf that is immunologically naïve are generally slower or lower than the same responses in a naïve adult cow, multiple research studies have demonstrated that calves can mount an adaptive immune response to vaccination in the first week of life, and even on the first day of life. In fact, the fetal calf is immunocompetent in utero; this is demonstrated by the fact that a calf infected in utero may be born with antibodies to the infectious agent which can be measured in serum collected before the calf consumes colostrum. Vaccination of calves against Mycobacterium bovis on the first day of life induced protection against disease due to challenge 15 weeks later.[1] Colostrum-deprived Holstein calves exposed to live coronavirus orally and intranasally on the first day of life were protected from disease following challenge 21 days later.[12] When calves were vaccinated with ovalbumin (a model antigen for assessment of humoral immunity) at 2 days of age, antibody to ovalbumin was identified in serum of vaccinated calves 4 weeks later. Moreover, vaccination of calves at 2 days of age with bacille Calmette Guerin (BCG) led to skin test responses at 7 weeks of life.[19] This work demonstrated that both humoral and cell-mediated adaptive immune responses are functional in 2-day-old calves. However, calves with specific antibodies present in serum at the time of vaccination had depressed responses, indicating that serum passively derived antibodies could suppress the response to vaccination at 2 days of age. Taken together, these studies indicate that the calf's immune response is functional and can respond to vaccination in the first 2 days of life, but that the response can be depressed by the presence of specific antibodies.

Transfer of passive immunity via colostrum

While adaptive immune responses to vaccination as early as the first day of life have been demonstrated in calves, there is no question that calves lacking the protection of passively acquired maternal antibodies are more likely to become sick, and more likely to die, as compared to herdmates that obtain adequate passively acquired antibodies. This repeatedly demonstrated fact confirms that the functional immune response of the newborn calf is inadequate to provide optimal protection against infection in the first weeks of life. When failure of transfer of passive immunity (FTPI) is defined by a serum IgG concentration less than 800 or 1,000 mg/dl, studies have found that between 6% and 23% of beef calves have FTPI.[5,21,26] However, current recommendations are that optimal transfer of passive immunity is defined by a serum IgG concentration of 2,400 mg/dl or greater, and one large study found that 46% of 1,556 beef calves had suboptimal transfer of passive immunity. Beef calves with serum IgG concentrations of less than 2,400 mg/dl were 1.6 times as likely to become sick, and 2.7 times as likely to die, as calves with serum IgG concentrations of 2,400 mg/dl or greater.[5] These findings indicate that there is room for improvement in transfer of passive immunity in an important proportion of beef calves.

Recent research has clarified the factors that impact transfer of passive immunity in beef calves. In a crossbred cow-calf herd, calves that failed to nurse within 4 hours of birth had a 2.8 times greater odds of morbidity before weaning ($P = 0.03$), compared to calves that nursed within 4 hours of birth.[13] In this study, of the 77 cow-calf pairs studied, 3 calves died prior to weaning, and all failed to nurse by 4 hours of life. Of a variety of factors measured at 10 minutes after birth, a strong suckle reflex best predicted that a calf would nurse within 4 hours, and the combination of calving ease score (scored as unassisted, easy or difficult) and nursing within 4 hours best predicted whether a calf would have optimal transfer of passive immunity (defined by serum IgG of greater than 2,400 mg/dl). Importantly, there was no difference in the antibody concentrations of colostrum of cows with calves that failed to acquire optimal passive transfer and cows with calves that did, indicating that failure of transfer of optimal immunity was not due to inadequate quality colostrum, but was rather due to failure of the calf to ingest enough colostrum in time to absorb colostral antibodies.[13] In related work, this research group also showed that beef calves fed 1.4 L of colostrum with moderate concentrations of antibody (70 g/L) by esophageal feeder within 1 hour of birth went on to nurse from their dams at a statistically significantly earlier time, compared to calves that were fed 1 L of colostrum with 100 g/L IgG, or calves fed 2 L of colostrum with 100 g/L IgG. Regardless of treatment, all but 1 of the 39 calves included in the study achieved optimal transfer of passive immunity (serum IgG 2,400 mg/L or greater), with the remaining calf achieving adequate transfer of passive immunity (serum IgG greater than 1,000 mg/dl).[11] The interpretation of these investigators was that if calves are fed colostrum with an esophageal feeder, as long as the colostrum contains at least 70 g/L of IgG, the calf should achieve at least adequate transfer of passive immunity, and may stand and nurse on its own faster than calves fed a larger volume of colostrum, which could improve cow-calf bonding.

Nutritional supplements to improve immunity

The possible effects of nutritional supplementation on immune function is a subject of perennial interest among veterinarians and cattle producers. A comprehensive review of the subject is beyond the scope of this paper, and a simple summary of the state of knowledge regarding the effects of nutrient supplementation on immune responses in cattle is not easy to make. At least dozens, and perhaps hundreds, of research papers describe the effects of different feedstuffs, nutrients, and supplements of myriad types on immune responses in cattle and calves, with some studies demonstrating an effect, and some studies not demonstrating an effect. An older reference provided a thorough review of the literature at the time on nutrition and immunity in beef cattle and calves,[10] and a recent review summarized information related to nutrition and bovine respiratory disease.[17] The specific impact of nutraceuticals on the gastrointestinal microbiome, with potential relevance to health, has recently been reviewed in detail.[3]

Interpretation of the scientific evidence related to the impact of nutrients on immunity and health in cattle is complicated by the fact that different research studies measure different outcomes, making it difficult to compare studies to come to a consensus. Moreover, some studies measure immune responses but not resistance to disease, while others evaluate resistance to disease while not measuring immune responses. While measurement of immune responses in properly designed research studies can provide new information regarding the effects of nutrients on specific immune responses, the effects on practically important health outcomes are also critically important to measure. The mere presence of any measurable immune response may have no relationship to protection against disease or production loss in the field; therefore, any claims of efficacy of any nutrient, feedstuff, or supplement to impact immunity should be supported with evidence related to resistance against disease, preferably naturally-occurring disease in cattle in field settings.

Vaccination of preweaning calves: effects of maternal antibody

Historically veterinarians were taught that young calves cannot be effectively vaccinated because maternal antibodies would block vaccine responsiveness. However, many studies have shown that calves can, in fact, have a useful immune response to vaccines given in the face of maternal antibodies (IFOMA). Vaccination of calves IFOMA has been shown to induce an anamnestic (memory) response when they are boosted later in life;[18] vaccination IFOMA can prolong the persistence of antibodies,[9] and vaccination IFOMA can prime for T cell responses even when calves do not seroconvert.[6] Intranasal vaccination may be superior to parenteral vaccination in calves with high concentrations of circulating antibodies;[14] however, the duration of immunity provided by intranasal vaccination of calves with circulating maternal antibodies may not last for more than a few weeks. Calves vaccinated intranasally with a modified-live BRSV vaccine had decreased lung pathology after challenge at 9 weeks post vaccination, compared to controls; however, when calves were challenged at 14 weeks after vaccination, there was no difference between groups.[7] In general, reports describing positive outcomes to vaccination of calves IFOMA have most often used 2-dose (priming and later booster dose) regimens with modified-live virus vaccines. While more variable, some inactivated vaccines have been effective; the effect of both modified-live and also inactivated vaccines in calves with maternal antibody is influenced by the type of adjuvant contained in the vaccine, as has been recently reviewed.[4] Vaccination of calves in the first month of life, when maternal antibodies are highest and the calf's immune system is the most immature, is least likely to be reliable. For example, a large clinical trial showed that vaccination of dairy calves with maternal antibodies at 2 and/or 5 weeks of age did not decrease respiratory disease in the first 90 days of life. However, it should be noted that the majority of calves treated for respiratory disease in that study were treated before 5 weeks of age, before the vaccination regimen had been completed for all calves.[27] A thorough review on vaccination of calves IFOMA has recently been published.[28]

Effective use of vaccination in preweaning calves

All licensed vaccines have been shown to decrease disease post challenge, by some measure, in calves vaccinated prior to experimental challenge, as compared to unvaccinated control calves, as this is a requirement for licensure in the United States and other countries where the same or similar vaccines are used. However, most if not all licensing trials are completed in seronegative calves, which does not represent very well the way vaccines need to be used in the field. In practice, waiting to vaccinate calves until they are all seronegative is not necessary, as described above; moreover, it exposes calves to the possibility of disease when they become seronegative. Ideally the first priming doses of vaccine is administered while calves still have some level of passive immunity, which may at least be partially protective against disease, but not enough to completely suppress the response to vaccination. Such an approach has the potential to keep calves from ever becoming completely seronegative, improving their resistance to disease.

The fact that a population of preweaning calves will have a range of antibody titers at the time they are first vaccinated means that some calves will receive their first dose of vaccine when they are able to respond, while others will not be able to respond, due to very high concentrations of maternal antibody, or perhaps other factors. For example, a group of over 2000 Angus calves were vaccinated twice with a modified-live vaccine containing bovine herpesvirus-1 (BHV-1), bovine viral diarrhea virus 1 and 2 (BVDV1 and BVDV2), parainfluenza type 3 virus (PI3V) and bovine respiratory syncytial virus (BRSV). Calves were randomly assigned to be vaccinated either 3 weeks before weaning, and at weaning, or at weaning, and 3 weeks later. As measured by change in serum antibody titer, greater overall antibody response to BVDV1 and 2 was seen when calves received the first dose of vaccine at weaning, while greater overall antibody response to BHV-1 and BRSV was seen when calves received their first dose of vaccine 3 weeks before weaning.[16] The reason for this difference could not be determined by the study as designed. Importantly, although antibody titers were measured in all calves at four time points, of the over 2,000 calves evaluated, 107 calves had a BVDV1 titer of 0 at all time-points tested, and 227 calves had a BHV-1 titer of 0 at all time-points tested. This demonstrates that in a population of calves, there may be a small proportion of calves that never respond to vaccination. The variability in responsiveness of calves in a population to vaccination at any one time point is another justification for administration of booster vaccines, which give calves two opportunities to respond to vaccination.

The highest quality of evidence to support a clinical practice comes from meta-analyses and systematic reviews of multiple well-designed randomized controlled field trials. Unfortunately, few field trials have been completed that test the effect of vaccination of preweaning calves to prevent or decrease naturally-occurring disease. Preweaning, calf diarrhea and respiratory disease are the two syndromes most often addressed by vaccination; at the time of this writing there are apparently no published systematic reviews specifically focused on evaluating clinical trials testing the efficacy of vaccination to prevent diarrhea or respiratory disease in preweaning beef calves. Also, in trials that have been published, lack of a negative control group in some trials means that it is not possible to determine whether vaccination is better than no vaccination. A small field trial that included a negative control group found numerically, but not statistically, significantly decreased preweaning respiratory disease treatment risk in beef calves vaccinated at 3 and 5 weeks of age against Histophilus somni, Mannheimia haemolytica, and BRSV, compared to calves receiving no vaccination.[25] The small numbers of calves in each group (n = 26 - 29) may have decreased the power of this trial to identify significant differences. A clinical trial testing vaccination to prevent respiratory disease in preweaning beef calves showed evidence of benefit to decrease morbidity in the postweaning feedlot phase,15 while another trial by the same group did not show an effect of preweaning vaccination to decrease postweaning respiratory disease.[23] A small trial assessing the effect of vaccinating cows in late gestation on respiratory disease in their calves prior to weaning showed a tendency toward decreased disease in heifer calves born to vaccinated dams.[22]

While no systematic reviews have evaluated the effect of vaccination on preweaning disease in beef calves, two recent systematic reviews assessing vaccination to prevent bovine respiratory disease in feedlot cattle.[20,24] One of these reviews[24] concluded that the published trials were so variable that, while there was support for some viral vaccines to decrease bovine respiratory disease, the support was not strong; the second systematic review concluded that the variability in published clinical trials made it impossible to identify a positive effect of vaccination to prevent respiratory disease in feedlot cattle.[20] If veterinarians are to learn more about the true effects of vaccination to decrease disease in preweaning beef calves, more well-designed controlled field trials containing a nonvaccinated control group need to be completed. A helpful narrative review of evidence for various vaccination strategies used in cattle populations, including preweaning beef calves, was recently published.[2] In the absence of systematic reviews, challenge studies and assessments of immune response indicate that vaccination of preweaning calves may improve resistance to disease. Ranchers with perennial problems with preweaning beef calf pneumonia at 3 to 5 months have anecdotally reported decreased disease following institution of a program of intranasal modified-live viral vaccination in the first month or two of life, followed by a parenteral modified-live viral booster one to two months later, with the booster being given approximately one month before respiratory disease onset is expected. A recent challenge study indicated that an inactivated booster following intranasal priming of beef calves could improve protection against disease in calves challenged with BRSV.[8]

Conclusions

Opportunities exist for improving immunity in preweaning beef calves by ensuring optimal, and not just adequate, passive immunity through timely colostrum intake. Supplementation with nutrients or feed additives can improve immunity, but a large variety of possible treatments have been evaluated, and not all are effective; ask to see data showing evidence of protection against disease to support any claims. Vaccination of preweaning beef calves can decrease disease in the postweaning period; data supporting preweaning vaccination to decrease preweaning disease are limited. More field trials are needed to confirm the effect of preweaning vaccination on preweaning disease in beef calves. At this time, data from challenge studies and research evaluating immune responses post vaccination provides some support for vaccination to prevent preweaning disease. If the priming dose is given in the first month or two of life, the intranasal route may better circumvent suppressive effects of maternal antibody.

References

1. Buddle BM, Wedlock DN, Parlane NA, Corner LAL, DeLisle GW, Skinner MA. Revaccination of neonatal calves with Mycobacterium bovis BCG reduces the level of protection against bovine tuberculosis induced by a single vaccination. *Infect Immun* 2003; 71:6411-6419.

2. Chamorro MF, Palomares RA. Bovine respiratory disease vaccination against viral pathogens: modified-live versus inactivated antigen vaccines, intranasal versus parenteral, what is the evidence? *Vet Clin Food Anim* 2020; 36:461-472.

3. Chase CCL. What is all the fuss over the microbiome and immunity? It is more than bugs, guts and tears, in Proceedings, 53rd *Annu Conf Am Assoc Bov Pract* 2020; 224-229.

4. Chase C. Practical immunology and beef and dairy vx protocols: starting from ground zero–what, when and how, in Proceedings, A*m Assoc Bov Pract Recent Graduate Conference* 2021; 10-18.

5. Dewell RD, Hungerford LL, Keen JE, Laegreid WW, Griffin DD, Rupp GP, Grotelueschen DM. Association of neonatal serum immunoglobulin G1 concentration with health and performance in beef calves. *J Am Vet Med Assoc* 2006; 228:914-921.

6. Ellis JA, Hassard LE, Cortese VS, Morley PS. Effects of perinatal vaccination on humoral and cellular immune responses in cows and young calves. *J Am Vet Med Assoc* 1996; 208:393-400.

7. Ellis JA, Gow SP, Mahan S, Leyh R. Duration of immunity to experimental infection with bovine respiratory syncytial virus following intranasal vaccination of young passively immune calves. *J Am Vet Med Assoc* 2013; 243:1602-1608.

8. Ellis J, Gow S,Berenik A, Lacoste S, Erickson N. Comparative efficacy of modified-live and inactivated vaccines in boosting responses to bovine respiratory syncytial virus following neonatal mucosal priming of beef calves. *Can Vet J* 2018; 59:1311-1319.

9. Fulton RW, Briggs RE, Payton ME, Confer AW, Saliki JT, Ridpath JF, Burge LJ, Duff GC. Maternally derived humoral immunity to bovine viral diarrhea virus (BVDV) 1a, BVDV 1b, BVDV2, bovine herpesvirus-1, parainfluenza-3 virus, bovine respiratory syncytial virus, *Mannheimia haemolytica* and *Pasteurella multocida* in beef calves, antibody decline by half-life studies and effect on response to vaccination. *Vaccine* 2004; 22:643-649.

10. Galyean ML, Perino LJ, Duff GC. Interaction of cattle health/immunity and nutrition. *J Anim Sci* 1999;77:1120-1134.

11. Gamsjäger L, Haines DM, Pajor EA, Lévy M, Windeyer MC. Impact of volume, immunoglobulin G concentration, and feeding method of colostrum product on neonatal nursing behavior and transfer of passive immunity in beef calves. *Animal* 2021;100345.

12. Heckert RA, Saif LJ, Mengel JP, Myers GW. Isotype-specific antibody responses to bovine coronavirus structural proteins in serum, feces, and mucosal secretions from experimentally challenge-exposed colostrum-deprived calves. *Am J Vet Res* 1991; 52:692-699.

13. Homerosky ER, Timsit E, Pajor EA, Kastelic JP, Windeyer MC. Predictors and impacts of colostrum consumption by 4 h after birth in newborn beef calves. *Vet J* 228:1-6.

14. Kimman TG, Westenbrink F, Straver PJ. Priming for local and systemic antibody memory responses to bovine respiratory syncytial virus: effect of amount of virus, virus replication, route of administration and maternal antibodies. *Vet Immunol Immunopathol* 1989; 22:145-160.

15. Kirkpatrick JG, Step DL, Payton ME, Richiards JB, McTague LF, Saliki JT, Confer AW, Cook BJ, Ingram SH, Wright JC. Effect of age at the time of vaccination on antibody titers and feedlot performance in beef calves. *J Am Vet Med Assoc* 2008; 233:136-142.

16. Kramer LM, Mayes MS, Fritz-Waters E, Williams JL, Downey ED, Tait Jr RG, Woolums A, Chase C, Reecy JM. Evaluation of responses to vaccination of Angus cattle for four viruses that contribute to bovine respiratory disease complex. *J Anim Sci* 2017; 95:4820-4834.

17. Krehbiel CR. Bovine respiratory disease influences on nutrition and metabolism. *Vet Clin Food Anim* 2020; 36:361-373.

18. Menanteau-Horta AM, Ames TR, Johnson DW, Meiske JC. Effect of maternal antibody upon vaccination with infectious bovine rhinotracheitis and bovine virus diarrhea vaccines. Can *J Comp Med* 1985; 49:10-14.

19. Nonnecke BJ, Waters WR, Goff JP, Foote MR. Adaptive immunity in the colostrum-deprived calf: response to early vaccination with *Mycobacterium bovis* strain bacilli Calmette Guerin and ovalbumin. *J Dairy Sci* 2012; 95:221-239.

20. O'Connor AM, Hu D, Totton SC, Scott N, Winder CB, Wang B, Wang C, Glanville J, Wood H, White B, Larson R, Waldner C, Sargeant JM. A systematic review and network meta-analysis of bacterial and viral vaccines, administered at or near arrival at the feedlot, for control of bovine respiratory disease in beef cattle. *An Health Res Rev* 2020; 20:143-162.

21. Perino LJ, Wittum TE, Ross GS. Effects of various risk factors on plasma protein and serum immunoglobulin concentrations of calves at postpartum hours 10 and 24. *Am J Vet Res* 1995; 56:1144-1148.

22. Smith DR, Woolums AR, Grotelueschen DM, Thompson LE, Noffsinger T, Stokka GL, Maddux J, Hill H, Rowley L. Randomized longitudinal study to test the effect of pre-calving vaccination of range beef cows and other factors on the incidence of calf pneumonia, in Proceedings, 46th *Annu Conf Am Assoc Bov Pract* 2013; 179.

23. Step DL, Krehbiel CR, DePra HA, Cranston JJ, Fulton RW, Kirkpatrick JG, Gill R, Payton ME, Montelongo MA, Confer AW. Effects of commingling beef calves from different sources and weaning protocols during a forty-two-day receiving period on performance and bovine respiratory disease. *J Anim Sci* 2008;86:3146-3158.

24. Theurer ME, Larson RL, White BJ. Systematic review and meta-analysis of the effectiveness of commercially available vaccines against bovine herpesvirus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza type 3 virus for mitigation of bovine respiratrory disease complex in cattle. *J Am Vet Med Assoc* 2015; 24:126-142.

25. Van Donkersgoed J, Potter AA, Mollison B, Harland RJ. The effect of a combined *Pasteurella haemolytica* and *Haemophilus somnus* vaccine and a modified-live bovine respiratory syncytial virus vaccine against enzootic pneumonia in young beef calves. *Can Vet J* 35:239-241.

26. Waldner CL, Rosengren LB. Factors associated with serum immunoglobulin levels in beef calves from Alberta and Saskatchewan and association between passive transfer and health outcomes. *Can Vet J* 2009;50:275-281.

27. Windeyer MC, KE Leslie, SM Godden, DC Hodgins, KD Lissemore, SJ LeBlanc. The effects of viral vaccination of dairy heifer calves on the incidence of respiratory disease, mortality, and growth. *J Dairy Sci* 2012; 95:1-9.

28. Windeyer MC, Gamsjäger L. Vaccinating calves in the face of maternal antibodies challenges and opportunities. *Vet Clin North Am Food Anim Pract* 2019; 35:557-573.

