Practical immunology and beef and dairy vx protocols: Starting from ground zero–what, when, and how

Chris Chase, DVM, PhD
Department of Veterinary and Biomedical Sciences, South Dakota State University, Brookings, SD 57007

Abstract

Vaccination is an important component for the prevention and control of disease in cattle. However, too often vaccines are viewed as a catch-all solution for management and nutrition errors; the "best" vaccine can never overcome these deficiencies. Proper vaccination in the young and developing heifer is the key to long-term development of that animal as a reproductive unit in the herd. Modified-live vaccines (MLV) have been used because of the good antibody response, longer duration of immunity, fewer doses needed per animal, and lower cost. However, non-adjuvanted MLV vaccines fail to booster well vaccinated animals, as active vaccine-induced immunity neutralizes vaccine virus preventing the MLV from replicating and preventing a booster immune response. Improved adjuvants have increased the scope and duration of both MLV and inactivated virus immunity. The periparturient period (the last 3 weeks prior to calving and the first 3 weeks following calving) are poor times to initiate an immune response—hormonal, dietary and metabolic factors limit immune responsiveness. Postpartum is also a difficult time to vaccinate as lactation energy demands supercedes immunity. Each vaccine program needs to be designed based on animal flow, actual "disease" threats, and labor on the farm.

Key words: immunology, vaccinology, mucosal immunity

Introduction–In the Beginning there was the Immune Response

The immune system consists of 3 lines of defense systems: mucosa epithelium, innate immunity, and adaptive or acquired immunity (Figure 1) that work together to give cattle protection from disease. The mucosa epithelium of the respiratory and gastrointestinal (GI) system is the largest immune organ of the body and provides the barrier, "the kill zone" that eliminates 99.9% of all infections (Figure 2).[19] The kill zone integrates all of the components of the immune system: 1) barrier components (mucous and mucins, tight junctions), 2) innate immunity (macrophages, defensins, neutrophils, interferon, cytokines, and 3) adaptive immunity (secretory IgA and IgG, and T and B lymphocytes). This system is very susceptible to dehydration and changes in microbial populations. In addition, the mucosa epithelium along with the lamina propria is the immune "fire wall" (Figure 3),[2] the immune regulatory system that provides "homeostasis" mechanisms that balance the immune system to provide a stable healthy internal environment to minimize inflammation (Figures 4A & B).[2] Once the mucosa epithelium is breached, the innate system is the first to be activated and responds almost immediately (Figure 5). The adaptive response follows up 10 to 14 days later in naïve animals. The immune system is regulated to prevent an over-response (too much of a good thing). The cumulative effect of this anti-inflammatory response is to regulate the immune system, maintain homeostasis and to direct the immune response away from the memory response to the short-term antibody immune response. At the same time, over expression of pro-inflammatory cytokines from infectious agents, feed intake issues (acidosis, ketosis), and stress can result in immune dysfunction and an over reactive immune system that can result in immunopathology and disease.[29]

What? Types of vaccines and pathogens/immunogens

MLV and Inactivated–Together is even better

Modified-live virus (MLV) vaccines have been used because of the good antibody response, longer duration of immunity, fewer doses needed per animal, and lower cost. To a lesser extent modified-live bacterial vaccines have also been used (*Brucella abortus, Mannheimia hemolytica, Pasteurella multicida, Salmonella dublin*). These ML vaccines are administered intramuscularly, intranasally or subcutaneously. As the basis for establishing a good immune response, they are the best. Although the return to virulence in MLV vaccines has been minimal, mutations will occur and there is some risk of new strains arising. Non-adjuvanted MLV vaccines also fail to booster well-vaccinated animals. Active vaccine immunity neutralizes vaccine virus, preventing the MLV from replicating and preventing a booster immune response.[10,25] Unlike maternal interference, this active immune interference **never goes away** in well vaccinated animals. The animal's immune system can't differentiate between a natural infection or vaccine virus. Another issue with MLV IBR (BHV-1) vaccines is that they result in latency and their continued use throughout the life of the animal will insure that BHV-1 will be present in the herd even though the rates of shed are between 0.13 and 2.6% of the animals shed.[7]

Inactivated vaccines contain chemically or physically treated bacteria, toxins and/or viruses. There is no danger of replication in the vaccinated animal of the pathogen or adventitious agents that maybe present in a MLV. Improved

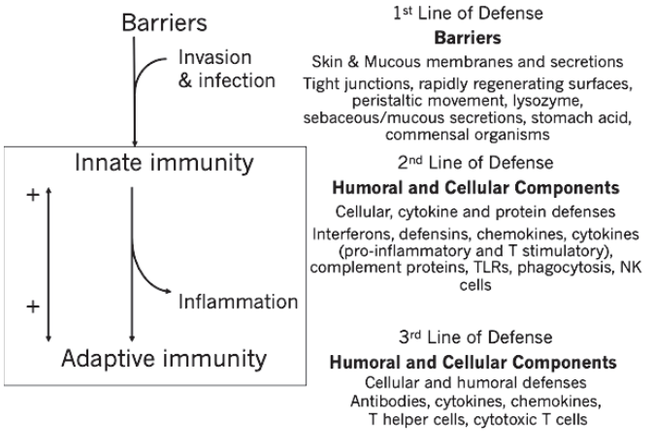

Figure 1. Immune responses.

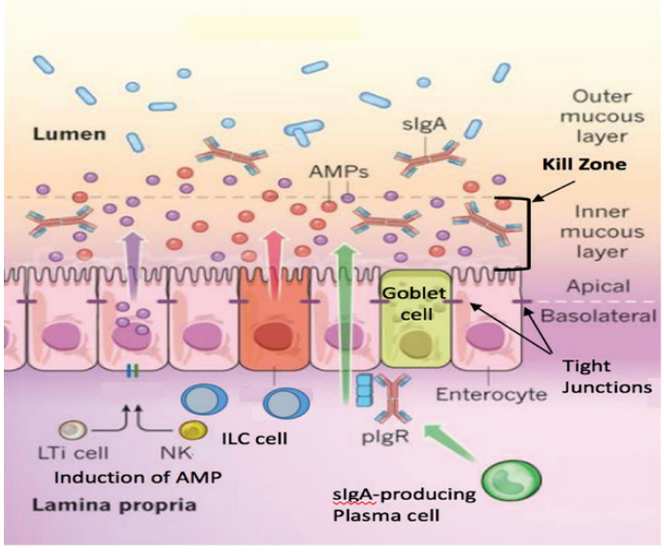

Figure 2. Mucosal epithelial cells (ME) are integrated into a continuous, single cell layer that is divided into apical and basolateral regions by tight junctions. ME sense the microbiota and their metabolites to induce the production of antimicrobial peptides (AMPs). Goblet cells produce mucin and mucous, that is organized into a dense, more highly cross-linked inner proteoglycan gel that forms an adherent inner mucous layer, and a less densely cross-linked outer mucous layer. The outer layer is highly colonized by constituents of the microbiota. The inner mucous layer is largely impervious to bacterial colonization or penetration due to its high concentration of bactericidal AMPs, as well as commensals specific secretory IgA (sIgA), which is moved from their basolateral surface, where it is bound by the receptor, to the inner mucous layer. Responding to the microbiotal components, innate lymphoid cells (ILC), lymphoid tissue inducer cells (LTi) and natural killer cells (NK), produce cytokines, which stimulate AMP production and maintain the epithelial barrier. Adapted from Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. *Nature* 2012;489:231-241. doi:10.1038/nature11551

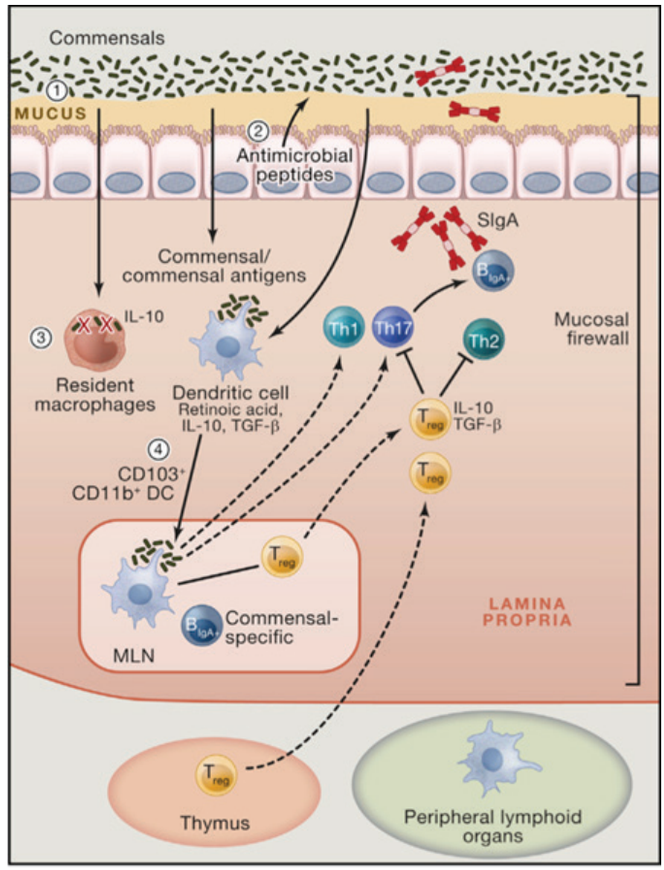

Figure 3. The mucus represents the primary barrier limiting contact between the microbiota and host tissue preventing microbial translocation. (2) Epithelial cells produce antimicrobial peptides that also play a significant role in limiting exposure to the commensal microbiota. (3) Translocating commensals are rapidly eliminated by tissue-resident macrophages. (4) Commensals or commensal antigens can also be captured by DCs that traffic to the mesenteric lymph node from the lamina propria but do not penetrate further. Presentation of commensal antigens by these DCs leads to the differentiation of commensal-specific regulatory cells (Treg), Th17 cells, and IgA-producing B cells. Commensal-specific lymphocytes traffic to the lamina propria and Peyer's patches. In the Peyer's patches, Treg can further promote class switching and IgA generation against commensals. The combination of the epithelial barrier, mucus layer, IgA, and DCs and T cells comprises the ''mucosal firewall,'' which limits the passage and exposure of commensals to the gut. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014;157:121-141. doi:10.1016/j.cell.2014.03.011

adjuvants have increased the scope and duration of inactivated virus immunity. They have several disadvantages including cost, and more doses required per animal. Inactivated vaccines generate cell-mediated responses.[27,30] Interestingly, there is ample evidence that inactivated vaccines can effectively boost MLV vaccines.[12,16,25,31,32] Inactivated vaccines have also been shown to decrease BHV-1 latency shed rates.[16]

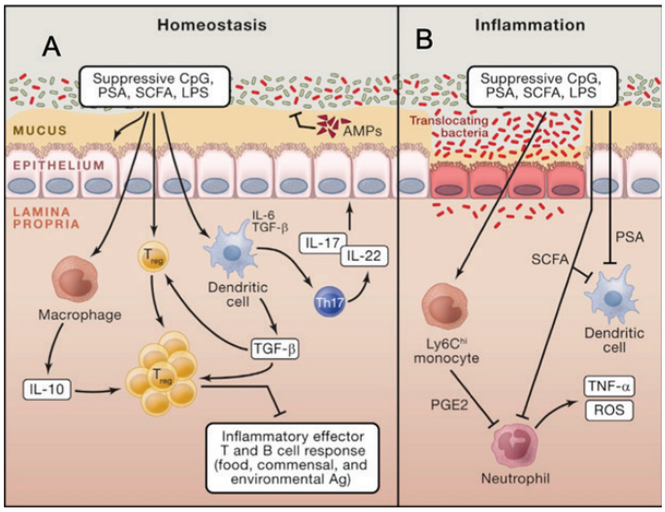

Figure 4. A) Commensals promote the induction of regulatory T cells via direct sensing of microbial products or metabolites by T cells or dendritic cells. Further commensals promote the induction of Th17 cells that can regulate the function and homeostasis of epithelial cells. In the context of inflammation, similar mechanisms may account for the regulatory role of the microbiota. (Right) Commensal-derived metabolites can also have a local and systemic effect on inflammatory cells. For example, SCFA can inhibit neutrophil activation. Upon entrance in the tissue, inflammatory monocytes can also respond to microbial-derived ligands by producing mediators such as PGE2 that limit neutrophil activation and tissue damage. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014;157:121-141. doi:10.1016/j.cell.2014.03.011

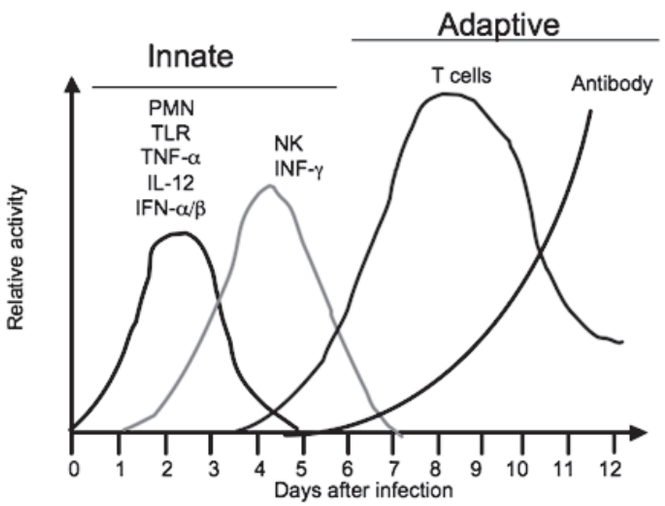

Figure 5. PMN-neutrophils, TLR-toll-like receptor, TNF-α-tumor necrosis factor alpha-proinflammatory, IL-12- interleukin 12-proinflammatory, IFN-α/β- interferon alpha/beta, NK-natural killer cell, IFN-γ-interferon gamma- proinflammatory

What to vaccinate for? What pathogens make sense?

Cattle vaccine programs are probably the most effective against viral pathogens (bovine herpesvirus 1 [BHV-1; IBR] bovine respiratory syncytial virus [BRSV] and bovine viral diarrhea virus [BVDV]). This is because many of the cattle bacterial pathogens (*Histophilus somni, Mannheimia hemolytica, Pasteurella multicida, Moraxella* spp, *Mycoplasma bovis, Salmonella typhimurium, Clostridium perfringens*) are normal inhabitants of the bovine microbiome and they are endemic in most herds.[18,20] Stressors discussed below play a major role in allowing these "normal" bugs to become pathogenic. When looking at a herd, it is essential to have a strong diagnostic program in place to get an accurate pathogen diagnosis. With next-generation sequencing, diagnostic PCR and good old-fashioned pathology and microbiology isolation, there has never been a better time to determine which pathogens are occurring and when. Being strategic in vaccination requires targeting those pathogens on that farm or ranch. Another term that we have learned from COVID19 is Replication Rate, called R naught (R_0).[7,11] Replication rate is the number of susceptible animals that 1 infected animal can infect (Figure 6). Probably one of the most infectious viruses is BRSV (Table 1). BRSV has been estimated to have a R_0 ~36. BRSV-susceptible animals (neonates) are highly susceptible to BRSV infection because of the high R_0. In a herd with BRSV disease history, BRSV vaccination would be at the top of the list. Once an animal is infected with BRSV and endemic, the immunity is not perfect, but R_0 is 1.1 so BRSV is barely circulating in the herd (Table 1). For IBR and BVDV transient infections, the rate is around ~3–meaning 1 infected animal shedding virus could potentially infect 3 susceptible animals (Table 1). By the time we get 70 to 80% of the animals either infected or protected from vaccination, the occurrence of infections to those viruses will be low and herd immunity has been achieved (Table 1). The BVDV PI

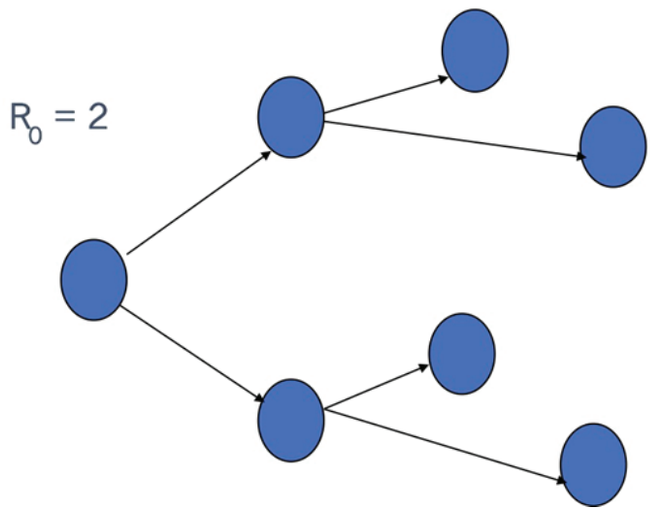

Figure 6. Basic reproduction number.

Table 1. Herd immunity thresholds for selected bovine vaccine-preventable diseases.

Disease	R_o	Herd immunity needed to prevent
BVDV PI	∞^	>95%
BRSV-naive	36.5*	>95%
BHV-1-naive	3.2#^^	75-86%
BVDV-Transient	0.25^-3.4##	70-80%
BRSV-endemic	1.14*	50-60%
BHV-1-latency	0.5^^	0%
COVID19	2-3	60-66%

*de Jong MCM, et al. *Am J Vet Res* 1996;57, 628-633.
#Bosch JC, et al. *Vaccine* 1998;16, 265-271.
##Moerman A, et al. *Vet Rec* 1993;132, 622-626.
^Sarrazin S, et al. *Vet J* 202, 244-249.

animal is the one case that totally destroys the concept of herd immunity. Since the BVDV PI animal continually sheds virus, any susceptible animal is at risk of infection. This makes the R_0 for a herd with BVDV PI of ∞ "infinity", indicating that a herd with a PI animal can never vaccinate their way out of the threat of BVDV. Endemic viral infections frequently include rotavirus and bovine coronavirus along with *C. perfringens*, representing a threat to the newborn susceptible animals. Environmental pathogens like *Bacillus anthracis* (anthrax), *Leptospira* spp, *E. coli,* and *Campylobacter* require considerations based on herd history and locality. Finally, *Brucella abortus* represents a "regulatory" vaccine.

When do we Vaccinate—Age and Stressors

Age

Neonatal Calves

The newborn calf is immunologically naïve at birth. It has had no chance to enhance adaptive immunity by "experience" because of the protective environment in the uterus. It is further handicapped by maternal factors and the hormonal influences of parturition, and by its lack of antibodies in circulation and in the tissues. The ingestion of colostrum is essential for providing the neonate with immunological protection during at least the first 2 to 4 weeks of life. While all the essential immune components are present in the neonate at birth, many of the components are not functional until the calf is at least 3 weeks of age, and may continue to develop until puberty.[6] This ongoing maturity of the immune system in the developing neonate, coupled with maternal antibody interference, makes vaccination strategy more complex. The mucosa epithelium provides immune function very early, making intranasal and oral vaccines effective in calves less than a week of age. Parenterally administered MLV vaccine responses begin at 7 to 10 days following birth, although BVDV MLV vaccines should be avoided particularly in dairy calves before at least 2 months of age as the major BVDV vaccine strains inhibit innate immune bacterial killing for 10 to 14 days following vaccination.[24] Bacterial parenteral vaccines typically don't have much response in animals less than 3 weeks of age, with the exception of *Clostridial perfringens* toxoids that have an immune response when administered at 3 days of age.[9]

Calves (<3 months)

Respiratory Diseases

- MLV intranasal vaccines (depends on maternal antibody levels-MANY MLV IM or SC are NOT EFFECTIVE BEFORE 30-45 days-ONLY adjuvanted MLV IM or SC)
- Branding time-beef- MLV IM or SC- adjuvanted; inactivated viral vaccines??- Well adjuvanted, not affected by maternal antibody?

Enteric Diseases

- Rota-coronavirus MLV-1 dose- within the first week of life- not recommended due to maternal interference and later onset of protection.
- *Clostridial perfringens* toxoid in the first 3 to 5 days after birth

Weaning-Puberty (Arrival)

Vaccination programs are a routine practice in beef and dairy operations to protect cattle against bovine respiratory diseases (BRD). Current vaccine protocols recommend that calves be vaccinated prior to weaning or commingling, to provide protection against BRD. Unfortunately, many calves are not vaccinated prior to weaning or commingling into backgrounding lots, feedlots or pasture operations. These animals are at increased risk of viral infection and are predisposed to secondary bacterial pneumonia. However, the highly-stressed calf presents a unique problem in that the vaccines may sometimes actually predispose the calves to more severe disease while on other occasions providing protection.

The time from vaccination to onset of protection can play an important role in subsequent management of newly arrived cattle against BRD viral agents, i.e., bovine herpesvirus 1 (BHV-1; IBR) bovine respiratory syncytial virus (BRSV), and bovine viral diarrhea virus (BVDV). Commercially available MLV vaccines administered to non-vaccinated, low-stress calves at weaning or at arrival to feed yards will provide increased weight gains and protection to animals as early as 48 hr prior to an IBR exposure, at 5 to 7 days prior to a BVDV, and 8 days prior to BRSV exposure.[4,8] This protection is due to the innate immune response, which is activated within hours after exposure to modified-live vaccines or infectious virus.

Frequency of vaccination

No more than 1 to 2 doses of MLV or 2 to 3 doses of inactivated vaccines should be administered in young calves less than 4 months of age to develop good herd immunity against respiratory diseases.

Interval between doses of vaccine

In all animals following vaccination, there is expansion in the populations of responding T- and B-cells. However, to have a complete and mature immune response, this T- and B-cell expansion must not only stop, but an active process of cell death (apoptosis) must also occur. This "waning process" allows "culling" T- or B-cells that may be poor responders or even cause autoimmunity to be removed by apoptosis. This whole process from vaccination to achieving mature immune response homeostasis takes at least 3 weeks (Figure 7). This fully developed mature primary response can then be boosted to get a true anamnestic secondary response. In many cases, cattle vaccine primary and booster doses are administered at 2-week intervals. In young calves, this is done to provide an opportunity to make sure that the calves develop a primary response in the face of maternal immunity. The adjuvants that are used with most commercial vaccines provide superior immune development over older generation adjuvants like alum. Therefore, in most instances if primary vaccination occurs after 3 weeks of age, booster vaccination beyond 3 weeks and even longer will be efficacious (Figure 7). The dogma that revaccination must occur within 2 weeks of the primary vaccination is not true, and the anamnestic response will be better if we wait longer.

Calves (>3 months)

Respiratory

- 2 to 3 weeks prior to weaning
  - MLV-1 dose
  - Inactivated-2 doses
  - Bacterial respiratory disease?
- At weaning
  - MLV-Immune dysfunction- delay–a few days to a month

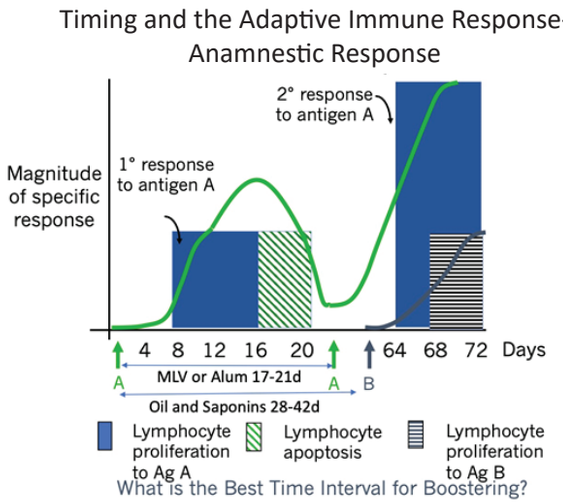

Figure 7. Vaccine A primary dose is administered and the booster dose is given ~21 days later.

- Inactivated-2 doses
- Bacterial respiratory disease?
- 2 to 3 weeks post weaning
  - MLV-1 dose
  - Inactivated-2 doses
  - Bacterial respiratory disease?

Heifer Development

Respiratory and Reproductive Diseases

Heifers (prebreeding) heifers need to receive at least 1 dose of MLV prior to addition to the breeding herd (1 dose should contain BVDV Singer Strain)

- MLV-2 doses-BVDV and BHV-1
  - >6 months and 2 months before breeding
- Inactivated viral-2 doses
  - 5 weeks and 2 weeks before breeding
- Leptospirosis-2 doses
  - 5 weeks and 2 weeks before breeding
- Brucellosis-1 dose

Prepartum Heifer & Cows–Colostrogenesis

The prepartum animal is an excellent animal to immunize- it is a "two-fer": respiratory and reproductive protection for the dam and colostral protection for respiratory and enteric disease for the calf. Beef cows, in contrast to dairy cows, will have better immune responses both in the prepartum and postpartum periods. Dairy cows are continuously managed to increase milk production. Some alterations in the host defense mechanisms that occur during the preparturient period are associated with changes in hormone profiles and the metabolic and physiological stress of parturition. The alteration of the immune system and the innate host resistance mechanism in dairy cows usually begins 3 weeks before parturition, and it is maximized 3 weeks after calving, when milk yield peaks and the energy balance begins to improve These changes can contribute to the high incidence of disease and the low immune response to vaccination experienced by the periparturient cow. Evidence of the changes in the immune system and the non-specific host defense mechanism occur in the periparturient dairy cow.[14,15]

Colostrogenesis

Colostrum synthesis in the mammary gland of the pregnant female is dependent on 2 factors: the presence of serum antibodies and a transport mechanism to move the antibody, primarily immunoglobulin G1 (IgG1), into the mammary gland.[1] Although the pregnant cow must be immunosuppressed to maintain the allogenic fetus (otherwise the bovine fetus would be rejected), this immunosuppression appears to occur most strongly in the uterus and the placenta. This fetal protective immunosuppression does not appear to cause a high level of generalized systemic immunosuppression that affects the cow's antibody response to vaccines or environmental antigens. However, some effect on the cell-mediated adaptive responses is observed in the pregnant animal. The

movement of antibody from the circulation to the mammary gland is hormonally regulated and begins 3 to 4 weeks prior to calving and has its highest transport in the last 1 to 2 weeks of pregnancy. This coincides with increases in estrogen, decreases in progesterone, and increase in the neonatal receptor (FcRn) in the mammary gland.[1] This small window of colostrogenesis makes timing of vaccine administration to the dry cow important. Non-adjuvanted vaccines would need to be given within 4 weeks of calving to get maximum circulating levels during colostrogenesis. Adjuvanted vaccines could be given earlier in the dry cow period, as they sustain higher antibody levels for longer periods of times. This ability to concentrate antibody ends rapidly after parturition. Colostrum from cows with premature calves will have lower levels of antibodies, so premature calves should be fed colostrum from cows that delivered full-term calves.

Respiratory and Reproductive Diseases -Cow and Respiratory Diseases-Calf

- MLV-1 dose
  - Vaccinating pregnant cows-lower efficacy demonstrated for preventing PI in subsequent pregnancy-problems with IBR abortion in poorly vaccinated animals
- Inactivated-1 dose-pregcheck time
  - Protection shown 1 year after vaccination

Enteric Diseases for Calf-Rotavirus, Coronavirus, *C. perfringens, K99 E. coli*

- MLV-2 doses- heifer- cows 1 dose
  - 5 weeks and 2 weeks before calving
- Inactivated-2 doses heifer- cows 1 dose
  - 10 to 12 weeks and 4-weeks before calving

Mastitis Dairy Heifer and Cow

First dose of J5 *E. coli* at 7 to 8 months of gestation in heifers and dry off in cows

Second dose of J5 *E. coli* 2 weeks following first dose

Third dose of J5 *E. coli* 2 to 3 weeks post calving

Postpartum heifer and cow

For the beef cow, the postpartum period is a good time for reproductive vaccination to attain the best protection for BVDV PI for the subsequent pregnancy. For the lactating dairy cow, this is a troublesome time. The common practice of vaccinating during the fresh period (15 to 45 days-in-milk) is an immunological challenge for the cows due to the negative energy balance associated with the high energy demands and the low dry matter intakes typically observed postpartum. The requirement of the immune system for energy becomes a secondary requirement compared to lactation. Since subclinical ketosis is present in nearly 30% of fresh dairy cows, suggesting vaccination during this period is probably not the best approach and vaccinating during the dry period might be a better alternative. In our research, we found that milk production, mastitis, and reproductive health were improved in dairy cows vaccinated in the prepartum period as compared to cows vaccinated in the postpartum period.

Reproductive Diseases-Cow

- MLV and Leptospirosis-1 dose
  - Vaccinate 45 to 60 days prior to breeding in beef cows to improve conception rate. In dairy cows vaccinate after 45 days-in-milk.
- Inactivated- Leptospirosis/(Campylobacter?-non-AI)- 1 dose
  - Do not use inactivated vaccine in the dairy cow-milk drop following vaccination. No effect of administering inactivated vaccines prior to breeding on conception rate.

Mastitis Dairy Heifer and Cow

- Third dose of J5 *E. coli* 2 to 3 weeks post-calving

Stressors and Vaccination

There is ample evidence that both physical and psychological distress can cause dysfunction of the immune function in animals, leading to an increased incidence of infectious disease.[20,25] Excess heat or cold, crowding, mixing, dehydration, weaning, calving, limit-feeding, shipping, noise, and restraint are stressors that are often associated with intensive animal production and have been shown to influence immune function in cattle (Figure 8).[13] Also, social status, genetics, age and the duration of stress (chronic vs acute) have been shown to be important in the animal's response to stress.[26] There is clear evidence that waiting to vaccinate at least 2 days and preferably as long as 2 weeks after the stress will result in better immunity and less sickness in that adjustment period after the stress.[22,23]

How do we vaccinate–Route and Good Nutritional Plane

Mucosal delivery vs parenteral delivery

Mucosal delivery of vaccine either orally or intranasally is a strategy that has been used for 3 reasons: 1) mucosal responses occur earlier in the neonatal calf than parenteral, 2) the presence of systemic maternal antibody has little effect on generating antigenic mass necessary for developing an immune response that occurs following immunizing with a mucosal vaccine (in the face of maternal antibody-IFOMA), and 3) mucosal vaccination results in the generation of secretory IgA that is produced locally and protects mucosal surfaces where most pathogens are colonized and/or infect the host (Figure 9). For all vaccines, mucosal or parenteral, the critical immune reactions occur in the draining lymph node (Figure 9 and Figure 10). With the right adjuvanted parenteral MLV vaccine, a protective mucosal IgA response can occur IFOMA.[17] The paradigm that only mucosal vaccines result in the immune response IFOMA and induce mucosal IgA is not true. However, the key ingredient for a parenteral MLV vaccine to induce mucosal immunity is the adjuvant.

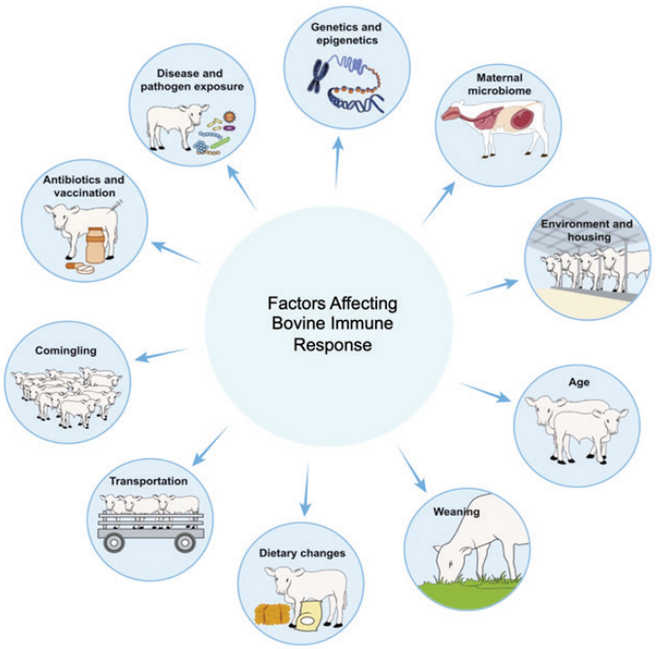

Figure 8. Immune responses are highly dynamic and are shaped by various host and environmental factors, including host genetics, mode of delivery, diet and the microbiota of the mother, environmental housing, weaning, feeding type, transportation, comingling, antibiotic treatment, vaccination, and pathogen exposure. Adapted from Zeineldin M, Lowe J, Aldridge B. Contribution of the mucosal microbiota to bovine respiratory health. *Trends Microbiol* 2019;27:753-770. doi:10.1016/j.tim.2019.04.005

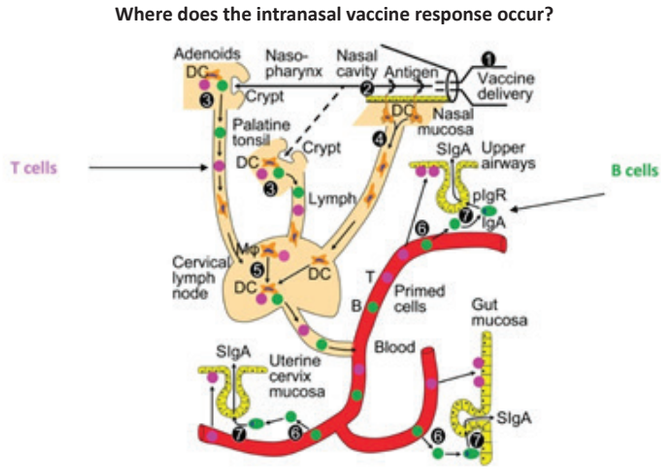

Figure 9. 1) Delivery of nasal vaccine; 2) Uptake of vaccine antigen through nasal mucosa; 3) Immune-induction in nasal associated lymphoid tissue (NALT) including tonsils; 4) Antigen targeting and migration of mucosal dendritic cells (DCs) to regional lymph node; 5) Immune induction and amplification in regional (cervical) lymph nodes by antigen-loaded DCs and macrophages (MΦ); 6) Compartmentalized homing and exit of NALT-induced T and B cells to secretory effector sites in airways, gut, and uterine cervix; and 7) Local production and polymeric Ig receptor (pIgR)-mediated external transport of dimeric IgA to generate secretory IgA (SigA). Brandtzaeg P. Potential of nasopharynx-associated lymphoid tissue for vaccine responses in the airways. *Am J Respir Crit Care Med* 2011;183:1595-1604.

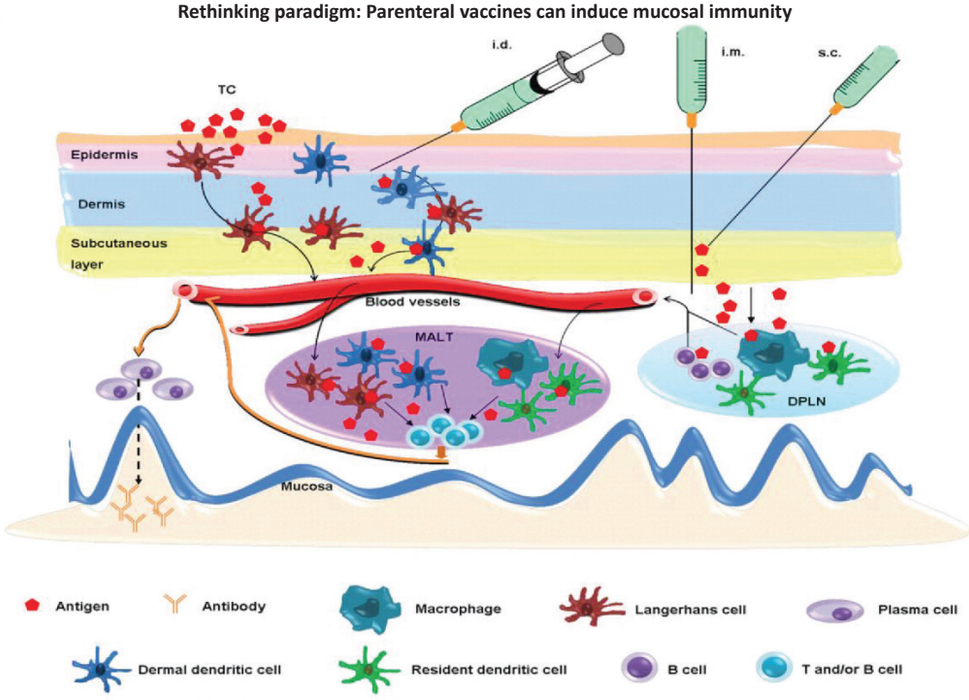

Figure 10. Properly adjuvanted parenteral vaccines can induce mucosal IgA responses via the draining lymph node. Su F, Patel GB, Hu S, et al. Induction of mucosal immunity through systemic immunization: Phantom or reality? *Hum Vaccin Immunother* 2016;12:1070-1079.

Most adjuvants can not overcome IFOMA and/or produce a mucosal IgA response (Figure 10). The more sophisticated oil-saponin adjuvants have this ability.[17]

Needleless Injections

Needle-free injection devices (NFID) result in a high-pressure stream that penetrates the epidermis, dermis with some subcutaneous penetration.[5] NFID-administered vaccines can use half to a tenth of the dose required for intramuscular vaccines because of the higher antigen dispersion and contact with the antigen-presenting cells found in skin. The use of NFID decreases the number of needle-stick injuries. Needle-free devices also have disadvantages, including start-up cost of the equipment, exhaustible gas-storage infrastructure (for those systems using a compressed or CO2 gas system), technical and operational expertise (training of the operators and maintenance of the units), and inability to completely replace needle-syringe devices. The cost of the equipment varies depending on the type of needle-free injector, and there are additional associated costs with maintenance and infrastructure, especially with compressed gas devices. Needle-free application requires a consistent application method. Needle-free devices are calibrated to deliver the vaccine when the needle-free device is perpendicular (90°) to the skin. Vaccinations made at more acute or oblique angles will affect the distribution of the vaccine in the tissue. In addition, because of the moving parts and gas system, regular maintenance is required. Finally, there is no "one-size-fits-all" needle-free device for all applications that require injections. Humidity, cattle breed, hide condition (haircoat, mud, snow, etc.), and age of the animal all effect the elasticity and thickness of the hide, greatly changing the force required for correct delivery. Different ages, breeds of cattle, treatment dose, and viscosity of injection substance require different injection volume, injection pressure, and even different NFIDs. Adoption of needle-free devices in the US cattle industry has been slow, although there has been better adoption in the swine industry driven by foreign markets that require the use of NFID. Reasons for this low industry implementation rate involve cost of the unit and associated maintenance and infrastructure costs, higher complexity than needle-syringe device, availability of devices (a smaller handheld injector that is used in Europe is not available in the US), uncertainty if the animal was vaccinated (i.e., no physical sensation that the animal was vaccinated and/or a "wet" appearance at the injection site) and requirement for training.

Hydration and Nutrition

One of the most critical issues in poor responses to vaccines are when animals have low water and feed intakes as a result of lack of supply, transportation, etc. The immune system requires hydration and energy for the barrier to be effective and for the immune system to actively respond and develop an effective immune response quickly, including duration of immunity and memory from vaccination. The immune system is a major consumer of energy and in times of negative energy, like seen in the newly weaned calf and the fresh dairy cow, can be difficult times for the immune system to respond.[29] The immune response requires energy, protein, vitamins, and trace minerals. Both malnutrition and overfeeding may result in impairment of immune function and increased susceptibility to disease due to a deficiency or excess of proteins or calories, or a relative imbalance in vitamin or trace mineral content. Animals under intensive production conditions typically have a completely controlled diet. Therefore, it is very important that the diet, especially the vitamin and trace mineral content, be optimally formulated. Key vitamins and minerals for optimal immune function include vitamins A, C, E, and the B complex vitamins, copper (Cu), zinc (Zn), magnesium (Mg), manganese (Mn), iron (Fe), and selenium (Se). Of these zinc, copper and selenium are the "immune microminerals". The balance of these constituents is especially important since excess or deficiency in one component may influence the availability or requirement for another. Zinc is involved in protein synthesis and antibody formation, cell differentiation, and enzyme formation and function. Zinc also plays a major role in skin and mucosa integrity, the first line of defense of the immune system. It is also essential for innate immune responses.[3] Copper and manganese are directly involved with cell-mediated immunity and protein matrix formation during the healing process. Copper has been linked with the ability of isolated neutrophils to kill yeast and bacterial infections. Selenium is an essential antioxidant.[28] Manganese plays a role in facilitating the "germ-killing" function of macrophages.[29]

Conclusions

Management of the cow's and calf's immune system is not a simple process. Stressors and nutrition often compromise immunity. It is important that vaccinations be given at optimal times and that vaccination is not overused. Vaccination can never overcome poor management.

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