Current concepts in dairy cattle vaccinology

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Abstract

Vaccination is an important component for the prevention and control of disease in the dairy 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. 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 inactivated virus immunity. Prepartum vaccination aimed at colostrum development is critical. Inactivated viral vaccines aimed at reproductive disease have greatly improved and should be considered to be given in the dry period to provide maximum conception rate during the fresh period. The peri-parturient 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. Post-partum is also a difficult time to vaccinate, as lactation energy demand supersedes immunity. Each vaccine program needs to be designed based on animal flow, actual "disease" threats, and labor on the farm.

Key words: dairy, vaccine, health

Résumé

La vaccination est une composante importante de la prévention et du contrôle des maladies dans les troupeaux laitiers. Les vaccins vivants modifiés (VVM) sont utilisés en raison de leur bonne production d'anticorps, de la longue durée de l'immunité, du faible nombre de doses requises et du moindre coût. Les VVM sans adjuvant ne causent pas d'amplification chez les animaux bien vaccinés parce que l'immunité active induite par le vaccin neutralise les virus du vaccin ce qui nuit à la réplication du VVM et empêche l'amplification de la réponse immunitaire. De meilleurs adjuvants augmentent la portée et la durée de l'immunité induite par des virus inactivés. La vaccination en prépartum ciblant le développement du colostrum est primordiale. Les vaccins viraux inactivés visant les maladies reproductives se sont très améliorés et devraient être considérés durant la période de tarissement pour maximiser le taux de conception durant la période fertile. La période autour du vêlage (les trois dernières semaines avant le vêlage et les trois premières semaines suivants le vêlage) n'est pas bien indiquée pour initier une réponse immunitaire car des facteurs hormonaux, alimentaires et métaboliques limitent l'immunocompétence. Il est aussi difficile de vacciner après le vêlage car la demande énergétique de la lactation supplante l'immunité. Chaque programme de vaccination doit s'ajuster aux mouvements des animaux, aux réelles menaces de santé et à la main d'œuvre de la ferme.

Immune Response

The immune system consists of 3 lines of defense systems: barriers, innate immunity, and adaptive or acquired immunity (Figure 1) that work together to give cattle protection from disease. The barrier system is probably the most overlooked, but it eliminates 99.9% of all infections. This system is very susceptible to dehydration and changes in microbial populations. The innate system is the first to be activated and responds almost immediately (Figure 2). The adaptive response follows up 10 to 14 days later in naïve animals. The immune system is regulated by anti-inflammatory response to prevent over-response. The cumulative effect of this anti-inflammatory response is to suppress the immune system 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.[37]

Active Immune Interference—Maternal Interference that Never Goes Away

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. These 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 viruses 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.[9,32] The animal's immune system can't differentiate between a natural infection or vaccine virus.

Inactivated vaccines contain chemically or physically treated bacteria, toxins, and/or viruses so there is no danger of replication in the vaccinated animal of the pathogen or

adventitious agents that may be present in a MLV. Improved adjuvants have increased the scope and duration of inactivated virus immunity. They have several disadvantages including cost, and more doses are required per animal. Inactivated vaccines generate cell-mediated responses.[34,38] Interestingly, there is ample evidence that inactivated vaccines can effectively boost MLV vaccines.[11,19,32]

Stress, Immunosuppression, Nutrition, and Immunity

There is ample evidence that both physical and psychological distress can cause immune dysfunction in animals, leading to an increased incidence of infectious disease (Figure 3).[28,33] 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.[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 (Figure 4).[33] There is clear evidence that waiting at least 2 days, and preferably as long as 2 weeks, before vaccination will result in better immunity and less sickness in that adjustment period after the stress.[29,30]
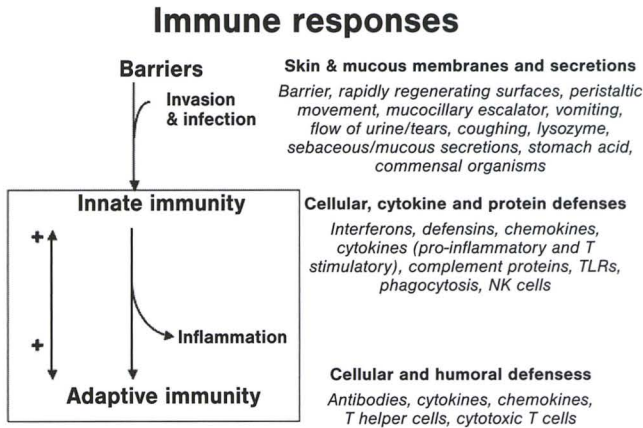
Immune responses

Barriers

Invasion & infection

Skin & mucous membranes and secretions

Barrier, rapidly regenerating surfaces, peristaltic movement, mucocillary escalator, vomiting, flow of urine/tears, coughing, lysozyme, sebaceous/mucous secretions, stomach acid, commensal organisms

Innate immunity

Cellular, cytokine and protein defenses

Interferons, defensins, chemokines, cytokines (pro-inflammatory and T stimulatory), complement proteins, TLRs, phagocytosis, NK cells

Inflammation

Adaptive immunity

Cellular and humoral defensess

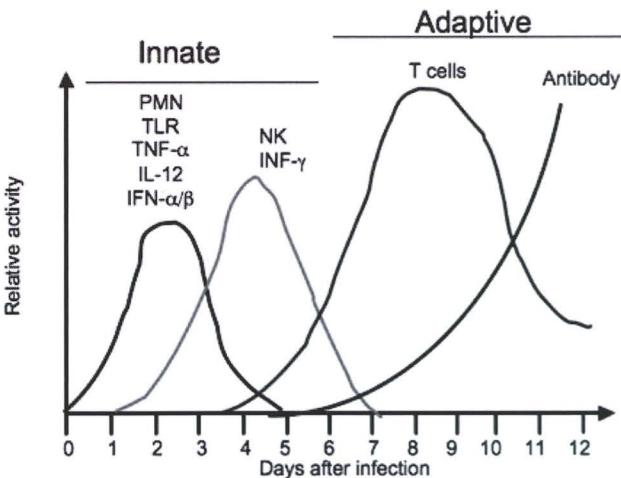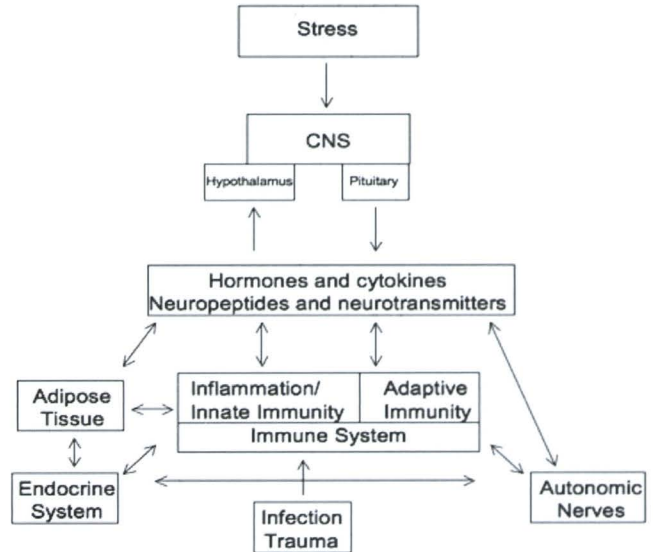*Antibodies, cytokines, chemokines, T helper cells, cytotoxic T cells*

Figure 1.

Figure 3.

Reiche EMV, Nunes SOV, Morimoto HK. Stress, depression, the immune system, and cancer. *The Lancet Oncology* 2004; 5:617-625. http://doi.org/10.1016/S1470-2045(04)01597-9.
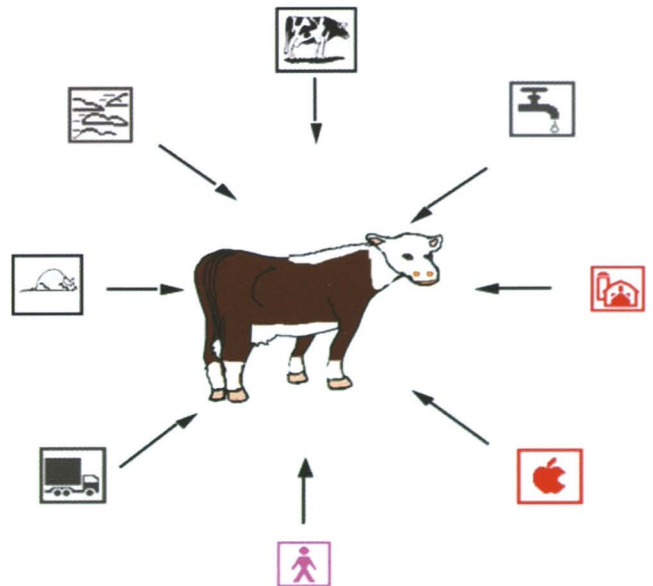
Figure 2.

Figure 4.

Nutritional Influences on Immunity

The immune system does not get a free ride when it comes to nutrition.[37] The immune system 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 anti-oxidant.[36] Manganese plays a role in facilitating the "germ-killing" function of macrophages.[37]

Immunity, negative energy balance, microflora, and cytokine storm

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 it can be difficult for the immune system to respond.[37] In addition, the mobilization of energy from adipose tissue (fat) results in infiltration of macrophages as activity of adipocytes (fat cells) results in inflammation. These macrophages are particularly sensitive to signals from gut bacteria, including endotoxin from gram-negative bacteria.[42] With diet changes that occur at weaning or at parturition for the dairy cow, the microflora populations are changing considerably. This combination of adipose remodeling, macrophage activation, and microflora can result in a cytokine storm (Figure 5).[4,40] A cytokine storm (hypercytokinemia) is the systemic expression of a healthy and vigorous immune system resulting in the release of more than 150 known inflammatory mediators (cytokines, oxygen free radicals, and coagulation factors).[40] It is an overreaction of the immune system. Both pro-inflammatory cytokines (such as tumor necrosis factor-alpha (TNF-alpha), Interleukin-1, and Interleukin-6) and anti-inflammatory cytokines (such as Interleukin 10 and Interleukin 1 receptor antagonist) are elevated in the serum of people or animals experiencing
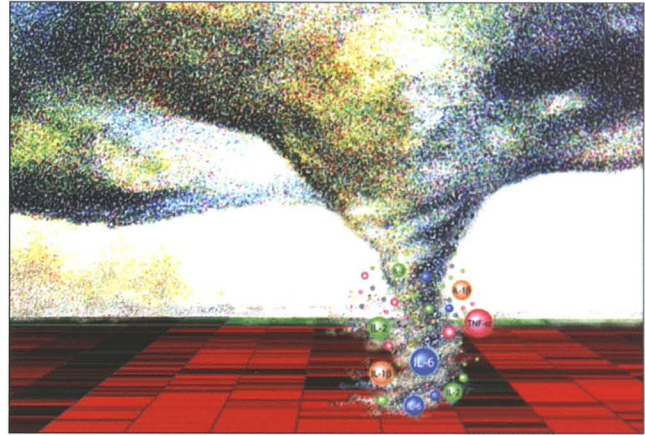

Figure 5.

Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiology and Molecular Biology Reviews* 2012; 76:16-32. http://doi.org/10.1128/MMBR.05015-11.

a cytokine storm. It is believed that cytokine storms were responsible for many of the human deaths during the 1918 influenza pandemic, which killed a disproportionate number of young adults. In this case, a healthy immune system may have been a liability rather than an asset. Preliminary research results also indicated this as the probable reason for many deaths during the severe acute respiratory syndrome (SARS) epidemic in 2003.[40] Human deaths from the bird flu H5N1 usually involve cytokine storms as well. Recent reports of high mortality among healthy young adults in the 2009 swine flu outbreak has led to speculation that cytokine storms could be responsible for these deaths, since the swine flu results from the same influenza strain as the Spanish flu of 1918.

What is the Best Time to Vaccinate Cows and Calves?

Immunity during the prepartum period

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. Evidences of the changes in the immune system and the non-specific host defense mechanism occur in the periparturient dairy cow.[17,18]

Hormonal changes in the endocrine system of cows later in pregnancy are well known and are characterized by

higher circulating levels of estrogen and progesterone. These hormones can depress the immune system function. High estrogen concentrations, for example, can reduce neutrophil function, and high levels of progesterone can suppress lymphocyte function. Cortisol produced in the fetal adrenal glands can affect the cellular mediated response in the cow, such as the production of interleukin-2 and interferon gamma.[5] Among these changes at calving time are high cortisol levels, which produce immunosuppression and an increment in estrogen that can also suppress lymphocyte function.

Prepartum Vaccination: Colostrum Formation—a Key Component of Dairy Vaccine Strategy

The lack of antibody transfer in the developing fetal calf makes the importance of colostrum ingestion paramount. Colostrum with high immunological activity is a product of proper vaccination and nutrition in the dam.

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.[2] 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.[2] 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 deliver a full-term calf.

Colostrum components

Colostrum's immunological component is composed primarily of antibodies, cytokines, and cells. Antibody is an extremely critical component of colostrum and provides an immediate source of antibody for the agammaglobulinemic calf. Colostrum contains 32 to 212 mg/ml of total IgG (20 to 200 mg/ml IgG1 and 3 to 12 mg/mL IgG2) and 1 to 6 mg/ml IgA.[14,23] Calves that ingest colostrum shortly after birth have significant concentrations of immunoglobulin in serum, while colostrum-deprived calves have only trace amounts of immunoglobulin during the first 3 days of life. Production of IgM in colostrum-deprived calves does not begin to appear in the circulation until 4 days after birth, and doesn't reach functional levels (1 mg/mL) until 8 days of age. Levels of circulating IgA, IgG$_1$, and IgG$_2$ do not reach appreciable levels in these calves until 16 to 32 days after birth.[21] The levels of these antibodies do not approach adult levels until about 4 months after birth, at which time IgG$_2$ is only half of adult levels, indicating a strong TH2 bias.

It has been well demonstrated that preparturient vaccination of the cow for enteric diseases such as colibacillosis, *Clostridium perfringens*, coronavirus, and rotaviruses results in production of pathogen-specific antibodies that provide protection for the neonate against severe disease.[15] Similar protection is also seen against respiratory pathogens including infectious bovine rhinotracheitis (IBR-bovine herpesvirus 1), bovine respiratory syncytial virus (BRSV), and bovine viral diarrhea virus (BVDV).[35] The quantity and the overall quality (i.e., not contaminated with bacteria and/or spoiled, having a relatively high concentration of total protein and sufficient fat) are important. Keeping colostrum free of microbial contaminants makes good collection and storage imperative, particularly in operations that pool and feed "normalized" colostrum, a practice that has favor in dairy operations.

The second family of components of colostrum includes cytokines.[12] These immunological hormones help in the development of the fetal immune response. It is not clear if these cytokines are secreted in the mammary gland or produced by the leukocytes found in colostrum, or both. Interleukin 1-beta (IL-1beta), IL-6, tumor necrosis factor beta (TNF-beta), transforming growth factor beta (TGF-beta), and interferon-gamma (INF-gamma) are present in bovine colostrum and are associated with a pro-inflammatory response, and may help in the recruitment of neonatal lymphocytes into the gut to aid in normal immune development. Colostrum rapidly improves the ability of neutrophils to phagocytize bacteria, which is primarily accomplished by absorption of small molecules like cytokines.[31] Work in pigs has demonstrated that colostral cytokines are absorbed and can be detected in the blood. The level of these cytokines (IL-4>IL-6>INF-gamma>IL-10) peaked at 1 to 2 days post-partum.[25] The high levels of 2 anti-inflammatory cytokines, IL-4 and transforming growth factor beta-1 (TGF-beta1), would suppress local secretion of pro-inflammatory cytokines in the intestine, allowing gut microbial colonization.

The third family of components of colostrum are cells. Colostrum contains between 1x10^6 and 3x10^6 cells/ml; almost exclusively leukocytes.[21] These viable leukocytes are present in percentages similar to peripheral blood, but with a larger fraction of macrophages (40 to 50%) and a smaller

fraction of lymphocytes (22 to 25%) and neutrophils (25 to 37%).[22,26] The vast majority of lymphocytes are T-lymphocytes, with less than 5% being B-lymphocytes. Some of these maternal cells enter the circulation and reach peak levels 24 hrs after birth.[27] Animals that receive colostrum-containing maternal leukocytes develop antigen presenting cells (APC) faster, which is important since APCs are the keystone cell for the development of an acquired immune response to pathogens or vaccines. Additionally, pathogen-specific maternal T lymphocytes from vaccinated cows have been isolated from the neonatal calf with maximum inducible proliferation at 1 day following birth.[7] The exact role of these cells in the long-term development of pathogen-specific acquired immunity is not clear, as they are no longer detectable in the circulation at 7 days of age.

Immunity in the post-partum period

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 post-partum. The requirement of the immune system for energy becomes a secondary requirement compared to lactation.

Depression in post-partum leukocyte function has been correlated to shifts in leukocyte trafficking patterns at this time.[18,19,20,24] The alteration in the proportions of the peripheral blood lymphocyte subset has been monitored in dairy cows during the pre-partum and post-partum periods. The variation of T cells was significant during the peri-partum period, particularly around parturition. B cell and MHC II + populations remained constant until after calving and then decreased, returning to the initial subset proportion by week 16. A decrease in the total number of T lymphocytes and changes in the T subpopulation have been reported in peripheral blood. In our research, we found that production, mastitis and reproductive health were improved in cows vaccinated in the prepartum period as compared to cows vaccinated in the post-partum period.[1]

Approximately 30% of dairy cows suffer subclinical ketosis during the fresh period as a result of the negative energy balance. The pathogenesis of this phenomenon is explained by the metabolic changes that occur when nutrient intake, particularly energy, does not meet production demands. In high-producing cows this metabolic disorder usually occurs from a few days up to 6 weeks post-calving, with the highest incidence occurring at about 3 weeks post-partum. Most high-producing cows undergo subclinical ketosis in early lactation when they are unable to consume enough energy to meet demands. Cows in negative energy balance are utilizing body fat and protein stores as a result of a drop in blood glucose concentration (glycemia). When fat molecules reach the liver, they are converted to ketones, and elevate ketone levels in the blood. High levels of blood ketone bodies interfere with the production of T cells and impair the chemotactic response

of leukocytes.[39] There is a link between elevated ketone levels and the risk of mastitis.[10] In addition, subclinical ketosis results in increased pro-inflammatory cytokine production, enhancing the cytokine storm (Figure 5).[8] The presence of subclinical ketosis in nearly 30% of fresh dairy cows suggests vaccination during this period is probably not the best approach and that vaccinating during the dry period might be a better alternative.

Evidence also exists that cows selected for high milk production traits, have unfavorable correlated responses in the functional capacity of immune function traits. There is sufficient genetic variation in these immunological traits among sires of high genetic merit for milk production.[6]

Another consequence of peripartum cows' feed disorders is hepatic lipidosis, a consequence of the fat cow syndrome. Upon vaccination, over-conditioned cows have lower humoral and cellular response when compared with cows with a low liver triacylglycerol (TAG) at day 14 after vaccination.[41] Cows in the transition period often face a challenge associated with low trace mineral levels. This is due to low dry matter intakes and stress, which causes excretion of trace minerals. Of particular concern are deficiencies in zinc, copper, chromium, manganese, cobalt, and selenium. The influence of these minerals on immunity was discussed above.

Conclusions

Management of the dairy cow 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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