Raising a preventive shield


Written by Dr. Anna Catharina Berge DVM, MPVM, PhD
Dr. Geert Vertenten DVM, PhD
June 2017
Content

1 Introduction.................................................................................................................... 3
2 Immunity in ruminants................................................................................................... 3
   2.1 Basic description of immunity in ruminants............................................................... 3
       2.1.1 The innate immune system.............................................................................. 5
       2.1.2 The adaptive immune system........................................................................... 5
       2.1.3 Development of immunity in the young animal.............................................. 6
   2.2 A holistic approach to optimal health..................................................................... 7
       2.2.1 Gut Health and Nutrition.................................................................................. 8
       2.2.2 Biosecurity......................................................................................................... 11
       2.2.3 Stress Reduction................................................................................................. 12
       2.2.4 The important role of the herd veterinarian..................................................... 13
1 Introduction

Immunity has been defined as ‘a condition of being able to resist a particular disease especially through preventing development of a pathogenic microorganism or by counteracting the effects of its products’, or in simpler terms it is ‘the power to resist infection whether natural (innate) or acquired (as by vaccination)’ (Merriam Webster, 2017). A strong powerful immunity is therefore crucial to maintain health in our current animal production, where multiple types of pathogens are continually challenging the health, welfare and productivity of our animals. As Webster’s dictionary implies, vaccinations play a great role in optimizing the animal’s power to resist disease. Vaccination is the administration of antigenic material (a vaccine) to stimulate an individual’s immune system to develop adaptive immunity to a pathogen. The vaccine contains either inactivated or attenuated forms of the pathogens, or purified highly immunogenic components of the pathogen. On a population basis, vaccinations have led to the eradication and control of many animal and zoonotic diseases. Vaccines are indispensable tools to prevent potentially dangerous infectious diseases and to maintain animal welfare and the productivity of animal production. Vaccine use within disease prevention and eradication programmes has optimized animal production, health and welfare, and contributed to a highly efficient production system.

A good knowledge of the immune system, disease situation, productivity and goals of the farm are necessary to set up a successful vaccination programme, and the farm veterinarian has a big role to play in developing, executing and monitoring the programme. The aim of this white paper is to create a better understanding of the role of immunity and vaccinations for the maintenance of good herd or flock health and productivity and for a more sustainable animal production with minimal negative environmental impact. The white paper gives important examples of how vaccines can generate a return on investment, minimize environmental impacts, and achieve other productivity goals so as to create an understanding that vaccination is an essential tool for all farmers in order to optimize the herd/flock’s capability to resist infection. This paper is not intended to cover every single disease and vaccination program, but to use some good examples of the value of vaccination in our ruminant production systems.

2 Immunity in ruminants

2.1 Basic description of immunity in ruminants

The immune system of animals can be described as two interactive systems; the innate system and the adaptive (acquired) system (Janeway et al., 2006; Tizard, 2013). The innate immunity is composed of the first physical barriers that prevent infectious agents such as skin, commensal microflora and self-grooming, and the non-specific inflammatory response. The Adaptive (or acquired) immunity is composed of the pathogen specific antibody (immunoglobulin) production and the cell-mediated immune response. The innate immunity provides a rapid response within minutes of attack by pathogen, whereas the adaptive immunity can take days to week to fully develop. The immune system can be divided into a series of anatomically distinct compartments, each of which is
specially adapted to generate a response to pathogens present in a particular set of body tissues. The mucosal associated lymphoid tissue (MALT) is located where most pathogens invade near the surface of intestines, skin, airways etc. The peripheral lymph nodes and spleen responds to pathogens/antigens that have entered the tissues or spread into the blood.

(Tizard, 2013)

All cells of the immune system originate in the bone marrow. A common lymphoid progenitor gives rise to cells that mature in the spleen and bone marrow (B-cells) and those that mature in the thymus (T-cells). A myeloid progenitor gives rise to granulocytes (neutrophils, eosinophils, basophils), monocytes that differentiate into macrophages.
2.1.1 The innate immune system

The innate system consists of natural barriers of the body such as the skin, the stomach with its low pH, enzymes, tears and the white blood cells (macrophages and neutrophils) and complement. The macrophages and neutrophils continually monitor the body for invading organisms or infections, and they are thereby called ‘first responders’. Neutrophils are the most abundant and important phagocytic cell and they are found in the blood stream until recruited to an infection site. Macrophages are found in the tissues. Eosinophils and mast cells are mainly involved in the defence against parasites. Neutrophils and macrophages identify pathogens by distinct pathogen-associated molecular patterns, using specific receptors called Toll-like receptors. They engulf the pathogen, and secrete cytokines and other substances that causes inflammation and therefore these are known as inflammatory cells. Beneficial microorganisms in the intestine and respiratory tract (the microbiota) that compete against invading pathogens are also an important part of innate immunity. By providing this front-line barrier, the innate system provides the time required by the adaptive immune system to develop an antibody response against a specific pathogen, usually several days to several weeks. The innate immunity may be strengthened or weakened by factors such as; wounds, dehydration, nutritional status, genetics, and stress. With a functional innate system, most of the pathogens encountered by an animal do not cause disease.

2.1.2 The adaptive immune system

The adaptive immune system consists of white blood cells (T and B lymphocytes) that provide long-term protection against disease through production of specific antibodies (immunoglobulins) and cell-mediated immunity. B-cells and T-cells bear unique receptors for a specific antigen (that has been generated by somatic gene rearrangements). When a naive lymphocyte has been activated (now called lymphoblast) it starts dividing about 2-4 times every hour for 3-5 days (clonal expan-
sion) to generate about 1000 effector cells. B-effector cells can produce and secrete up to 2000 antibodies per second, and the T-effector cells can destroy infected cells or activate other parts of the immune system. The antibody (immunoglobulin) consists of a constant (C) region, hinged to two arms in Y-shape that has the variable (V) antigen specific region. The C-region can be assembled in various forms to create different antibodies (IgG, IgM, IgD, IgA and IgE) that have different properties and functions in the body. IgM is initially expressed during the B-cell activation and it has low affinity for antigens compared to IgG that is found in high abundance in serum.

The T-cells are needed to control intracellular pathogens (such as virus) and to activate B-cells to most antigens (cell-mediated immune response). The T-cells have only one antigen recognition site and the receptor is always attached to the cell. The cell-mediated immune response depends on interaction between T-cells and body cells bearing the antigen that the T-cells recognize. The T-cells recognize the body cells that have been infected by pathogens such as virus and virus inside are using the cell machinery to replicate. The T-cells can kill the infected cells before the virus replicates and release is complete.

T-helper cells influence and modulate a variety of leukocyte responses through secretion of cytokines, proteins or peptides that stimulate or interact with other leukocytes. T-helper type 1 cells are mostly involved in intracellular bacteria and protozoa responses, whereas T-helper type 2 cells are involved in extracellular parasites including helminths. Memory T-helper cells can retain the antigen affinity of the originally activated T cell.

Activated effector cells have a limited time span and once antigen is removed they undergo programmed cell death, and only a few remains as an immunological memory, which ensures a more rapid and effective response on a second encounter, and thereby provides lasting protective immunity. A second encounter with the same specific antigen will generate a more rapid response and antibodies with higher affinity. It is this immunological memory that is the basis of vaccination that prevents re-infection with pathogens that have been repelled successfully by an adaptive immune response.

2.1.3 Development of immunity in the young animal

Ruminants have a chorio-epithelial placenta that prevents the transfer of maternal immunoglobulins to the foetus in the uterus. The immune system is fully developed at birth, but immature and the maturation of the immune system is slow with adult immunity seen around 5 to 8 months of age in the calf. There are high numbers of phagocytic cells at birth but their function is decreased. Complement in calves is from 12% to 60% of adult levels at birth and does not reach adult levels before 6 months of age. T cells (CD41, CD81 and TCRgd1 cells) do not reach peak levels until the animal is 8 months of age. This does not mean that a young calf/lamb cannot respond to antigens, but the response is weaker, slower, and easier to overcome. Therefore the calf is highly susceptible to disease pathogens, more clinical disease is seen due to pathogens and therefore increased disease shedding and spread (Cortese, 2009).

Neonatal ruminants are highly dependent on passive transfer of immunity from the dam through colostrum. Colostrum is the first source of liquid, energy, nutrients, vitamins, immunoglobulins and various bioactive substances that the calf will ingest (McGrath et al., 2016). The effect of the various components of colostrum on health and growth cannot always be separated from each other and they should be kept in mind, even when evaluation of colostrum feeding in calves/lambs mostly
is a measure of passive transfer of immunity in the form of immunoglobulins. The maternal antibodies protect the calf against pathogens and disease during the time that the young ruminants own immune system is evolving.

For example, in the second week of life of calves, the neonatal animal is suffering from low levels of immunoglobulins due to waning levels of colostral antibodies and insufficient production and development of its own immunity (Diagram above). However, colostral passive transfer of immunity has a big impact of calves for a very long period.

If animals are vaccinated in the presence of high levels of maternal antibody to that antigen, they may not display increased antibody titres after vaccination. However, attenuated vaccines and some inactivated vaccines using adjuvants that stimulate cell-mediated protective mechanism can elicit the formation of B-cell memory responses and cell-mediated immune responses in the face of maternal antibody (Cortese, 2009; Ellis et al., 2013). Furthermore, there are some intranasal vaccines that stimulate the mucosal associated lymphoid tissue (MALT) that also are effective in the presence of colostral-derived immunity.

2.2 A holistic approach to optimal health
Prevention of disease requires a multi-dimensional holistic programme that takes into account factors ranging from pathogen exposure level on the farm to optimized animal immunity. A farmer may be considering vaccination as an option to prevent disease, but it is also essential to manage other risk factors for disease introduction and spread as well as factors contributing to sub-optimal immune responses to vaccination when setting up a disease prevention programme.
2.2.1 Gut Health and Nutrition

Optimal nutrition is important in order for animals to optimize immunity and mount an appropriate response to vaccination. Sufficient protein, energy, minerals and vitamins are all required to develop and maintain a strong immune system. Specific vitamins and minerals associated with optimal immune function include vitamin A, vitamin E, selenium, copper, and zinc. It is very important to assure that the animal’s basic energy, macronutrient and micronutrient requirements are met in order to assure that the animal can properly respond to disease challenge. In neonatal animals, malnutrition can considerably contribute to a poor immune response, and thereby disease and death (Griebel et al., 1987).

A healthy gut has been defined as a ‘the absence/prevention/avoidance of disease so that the animal is able to perform its physiological functions in order to withstand exogenous and endogenous stressors’ (Kogut and Arsenault, 2016). A healthy gut is a key to a healthy animal, and more and more emphasis is placed on optimizing gut health in our production animals (Kogut and Arsenault, 2016). A healthy gut involves a number of physiological and functional components including digestion and absorption of nutrients, host metabolism, energy production, a balanced gut microbiota, mucus layer, barrier function and the mucosal immunity.

2.2.1.1 The microbiota

The microbiota refers is an "ecological community of commensal, symbiotic and pathogenic microorganisms" found in and on animals. Although the gut microbiota has been the focus of most research, microbiota in other organs such as the respiratory tract and udder are of importance for health.

A diverse microbial population colonizes the sterile gastrointestinal tract during and after the birth. This complex microbiome plays an important role in the mucosal immunity and overall health. The gut microbiota is not only essential for development and maturation of the mucosal immune system but also the nutrition and health of the animal. There are significant associations between the early microbiota, development of the mucosal immune system, and the growth and health of newborn calves (Malmuthuge et al., 2015). There is increasing focus on determining the microbiome of the udder of lactating animals, as this may also be a key to reducing mastitis, which is one of the biggest health challenges of the dairy industry.

2.2.1.2 Trace element nutrition

Optimal mineral and vitamin nutrition are essential for good immune function and health. Clinical deficiencies of trace minerals and vitamins may produce clinical signs associated with nutrient deficiencies such as slow growth and failure to thrive, but subclinical deficiencies are more common and more difficult to detect, yet may result in broader economic losses (Galyean et al., 1999; Kegley et al., 2016). The incidence and duration of disease is subject to so many extraneous influences that the contribution of the micronutrients can easily be masked (Finch and Turner, 1996). At times of physiological stress (such as weaning, transport, comingling and calving), when feed intake is reduced the mineral and vitamin requirements may be increased. Health problems that are exacerbated by mineral or vitamin deficiencies include bovine respiratory disease (BRD), footrot, retained placenta, metritis, and mastitis.
Trace elements nutrition is a key factor in preventing oxidative stress. Many micronutrients have antioxidant properties through being components of enzymes and proteins that benefit animal health. Antioxidant enzymes are responsible for preventing damage to cell contents and membranes by radical oxygen metabolites. Superoxide dismutase (SOD), along with catalase and glutathione peroxidase (GSH-Px) protects cell contents while vitamin E is an antioxidant located in the cell membrane. The trace minerals Cu, Zn, Mn, Fe and Se are important co-factors for these enzymes. Neutrophils isolated from ruminants deficient in Cu or Se have reduced ability to kill ingested bacteria in vitro. Vitamin E and Selenium have been shown in numerous studies to improve both antibody dependent and cellular immunity against various pathogens and thereby decrease both disease incidence and duration (Finch and Turner, 1996).

Organically bound minerals (chelated compounds) may improve uptake and availability to the body of the animal.

2.2.1.3 Nutritional factors in pre-weaned calves
The most critical nutritional factor influencing health and productivity in ruminants is the first colostrum meal as discussed above (see 2.1.3). Numerous studies and publications have evaluated the importance of colostrum for short term health, and increasing evidence is indicating that the colostrum meal will impact future milk production and longevity of dairy cattle (Faber et al., 2005). There are many studies indicating that a larger volume of colostrum as soon as possible after birth will improve passive transfer of immunity (PT) from the dam to the calf. However, colostrum administration must always be emphasized in all ruminant production. A study of US dairy heifer health indicated that up to 31% of dairy heifer mortality during the first 21 days of life could be prevented by optimizing colostrum feeding (Wells et al., 1996). A study in the United Kingdom evaluating growth rates during rearing and its effect on age and body weight (BW) of replacement heifers at first calving found that growth the first 6 months of life was on average 0.66 Kg/d for heifers having been fed...
less than 3 litres of colostrum versus 0.83 Kg/d for heifers fed more than 3 litres (Brickell et al., 2009). A study in 68 Brown Swiss heifers compared the effects of feeding two versus four litres of high quality colostrum within the first hour of birth (Faber et al., 2005). At the time of conception, the heifers fed four litres colostrum had significantly higher daily weight gain (1.03 ± 0.03 kg/d) compared to heifers fed two litres (0.80 ± 0.02 kg/d) and they conceived half a month earlier. The heifers fed four litres produced 500 Kg more milk in first and second lactation and there was 16% less involuntary culling in these heifers compared to the heifers fed 2 litres. Therefore, a large emphasis needs to be placed on colostrum management in herd health programmes, where it is recommended that a calf is fed at least 3-4 litres of high quality colostrum as soon as possible after birth, followed by a second colostrum feed 6-8 hours later.

The pre-weaned calf nutrition is very important to provide the calf with energy and nutrients to optimally develop the immune system. Many dairy calves are not fed sufficient quantities milk or milk replacer during the preweaning period, especially during the first few weeks of life. This problem is exasperated during times of cold-stress and disease challenges. Malnutrition has a negative impact on immune system, both with regards development and response to vaccination. A Minnesota study were calves were fed either 4 litres of a milk replacer (20% protein/20% fat) or 4 litres of pasteurized waste milk indicated that morbidity and mortality was greatly reduced in the calves on the pasteurized waste milk (Godden et al., 2005). This was very likely due to the higher protein and energy content and composition of the cow milk compared to the milk replacer. A Canadian study indicated that calves subjected to protein energy malnutrition had a delayed response in IgG and interleukin-2 compared to control calves receiving maintenance requirements feed, and this could be attributed to a numerical and functional deficiency of T-helper cells (Griebel et al., 1987). Another study indicated that feeding calves a higher plane of milk replacer nutrition could improve various immune functions such as neutrophil oxidative burst, haptoglobin responses and an improved innate immune response post-weaning (Ballou, 2012). A higher plane of pre-weaning milk replacer nutrition has also been linked to an improved immune response and increased resistance to Salmonella enterica serovar Typhimurium (Ballou et al., 2015).

2.2.1.4 Nutritional factors in weaned heifers and animals intended for beef

In beef cow calf operations, a good start in life with early access to high quality colostrum is as important as for dairy operations to minimize disease and mortality. A cohort study in 1,568 crossbred beef calves showed that calves with serum IgG concentration < 2400 mg/dl were 1.6 times as likely to become ill before weaning and 2.7 times as likely to die before weaning as calves with higher serum IgG concentrations (Dewell et al., 2006). Furthermore, calves with serum IgG concentration of at least 2700 mg/dl weighed an estimated 3.4 kg more at 205 days of age than calves with lower serum IgG concentration.

Studies of BRD in steers has indicated that several nutritional factors influence immunity (Galyean et al., 1999). Feeding diets with higher levels of concentrate typically improve performance by newly weaned or received cattle, as does feeding diets supplemented with protein; however, these diets may increase the rate and severity of BRD. Vitamin E and supplemental Zn, Cu, Se, and Cr may be beneficial for decreasing BRD morbidity.
2.2.1.5 Nutritional factors in lactating/adult animals

Immunosuppression in the periparturient period of cows has been linked to nutrition, metabolic imbalance and stress (Ingvartsen and Moyes, 2013; Janeway et al., 2006; Sordillo, 2016). Altered nutrient metabolism and oxidative stress can interact to compromise the immune system in transition cows. In dairy cattle, high levels of supplemental Zn are generally associated with reduced somatic cell counts and improved foot health, possibly reflecting the importance of Zn in maintaining effective epithelial barriers (Kegley et al., 2016).

Nutritional status during the dry period can also influence calf immunity. By boosting maternal gut immunity, colostrum quality can be improved. Franklin et al. showed that dry cows supplemented with mannan-oligosaccharides during the dry period, had an increased vaccination response to a Rotavirus/Corona/E. coli vaccination that resulted in higher levels of rotavirus-antibodies in colostrum and in the calf and a tendency for higher levels of passive transfer of immunity (Franklin et al., 2005). A study in Belgian blue white cattle indicated that supplementing the dry cows and lactating cows with organic selenium resulted in improved health and performance in the calves receiving colostrum and milk from their dams (Guyot et al., 2007). In sheep production it has similarly been shown that optimizing ewe nutrition is a key to reducing morbidity and mortality in lambs (Dwyer et al., 2016).

2.2.2 Biosecurity

Biosecurity is a system to prevent infectious diseases from entering and spreading on the farm. It is founded on three pillars: sanitation, isolation and traffic control. External biosecurity entails measures that prevent the introduction of pathogenic organisms onto a farm, and internal biosecurity relates to measure that prevents the spread of pathogens within the farm.

Biosecurity measures are important to minimizing disease in cattle, and both internal and external biosecurity measures must be used in combination with other management strategies that address the many other risk factors (Wells, 2000). Various combinations of biosecurity measures can be applied to individual farms to help decrease the morbidity and mortality attributed to respiratory disease (Callan and Garry, 2002).

External Biosecurity: The highest risk of introduction of disease is through the introduction of live animals. A closed herd producing its own replacements is the optimal management for live animals. When that is not an option, careful sourcing of animals, pre-introduction testing and quarantine with further testing is recommended. Vaccinations may be used to prevent effects of introducing some diseases, and is thereby a biosecurity tool. Good practices for people visiting the farm also need to be in place, with strict rules for visitors and their vehicles and good hygiene at all levels. It is important to assure that cattle/sheep on pastures do not come into contact with animals from other farms, and farm and trade shows represent another biosecurity risk. Furthermore, vermin and insect control are part of biosecurity measures. In beef cattle production, preconditioning is an external biosecurity tool preparing calves to enter the stocker/finisher phase of the beef industry. This process typically includes management activities such as weaning, supplemental nutrition, dehorning, castration, and implementation of an animal health program (deworming, foot care and vaccinations). Preconditioning can reduce stress and improve immunity and as such facilitates the introduction of new animal into the farm, and decreases risk of disease through the strategic deworming and vaccinations.
Internal Biosecurity: To prevent diseases from spreading in the barn, management of groups and housing is essential where young animals are segregated from older animals, and sick animals are segregated from healthy animals. Sanitation is also important, everything on the farm needs to be kept as clean as possible; equipment, environment, clothing etc. Mechanical cleaning and the use of disinfectants will help in reducing pathogen levels along with hygienic feed management. Furthermore, the manure management system needs adequate removal, treatment and storage to reduce pathogen loads. Vaccination may prevent the spread both between and within a farm, and as such vaccination can be considered part of biosecurity measures. However, poor vaccination routines with repeated use of vaccination equipment and re-useable needles can also be a biosecurity risk.

When pathogens involved in disease are enzootic in the general cattle population, biosecurity practices aimed at the complete elimination of exposure are often impractical. Several husbandry and production management practices can be used to minimize pathogen shedding, exposure, and transmission within a given population. The air quality may have a huge impact on respiratory diseases, and indoor housing facilities with shared air spaces may facilitate the spread of numerous respiratory disease virus and bacteria. The relative humidity should be 55-75% and less than 5 ppm ammonium. A draft free environment is important and the air speed should be less than 0.25 m/s for calves under 4 months and less than 0.5 m/s for older animals. The air flow should furthermore be in the direction from younger to older animals. The environment should furthermore be as dry as possible and good drainage and timely removal of manure from the environment is important to decrease pathogens that can cause diseases such as enteric disease, mastitis and foot problems.

Shared drinking and eating places may also be an important method of spread of pathogenic organisms. In automatic milk feeding systems and in calf groups, the nipples can be a source of disease-spread and the number of nipples per calf, frequency and method of sanitation and replacement are all important factors to minimize pathogen spread. Overcrowding or too large groups may contribute increased opportunity for spread of disease-causing agents. It is recommended that a calf under 150 Kg has 1.5-2 m2, between 150-200 Kg has 2-3 m2, and animals over 200 Kg has > 3 m2.

2.2.3 Stress Reduction
Stressors are conditions or factors that disturb the body’s homeostasis, and they will elicit coordinated, physiologic responses within the body in an attempt to re-establish homeostasis, primarily through activation of various endocrine, nervous and immunologic pathways (Carroll and Forsberg, 2007). Animal stress is a very important risk factor for most infectious diseases. Stress may be due to parturition, dietary changes, transport, within farm location changes, surgical interventions (de-horning, castrating, surgery), social group systems, overcrowding environmental conditions, etc (Hulbert and Moisa, 2016). As much as possible, the various stressors need to be minimized and care need to be taken to not impose additional stress in times of immune challenge. To minimize stress there should not be many management and nutritional changes at the same time and the changes should be as gradual as possible. For example, abrupt feed changes should be avoided, changes in group sizes should be gradual, and vaccinations should be avoided when the animals are going through stressful changes. For beef cattle, vaccination on arrival to the feedlot may in-
crease both morbidity and mortality and decrease weight gain (Griffin et al., 2016). This indicates that multiple stressors (such as transports, comingling of animals, handling, feed and water deprivation) can overwhelm the animal’s immune system, and this is very important to consider in vaccination programmes.

2.2.4 The important role of the herd veterinarian

A herd health programme is a combination of sound management, good housing, good nutrition, good biosecurity and proactive health measures such as vaccination. The aims of the herd health programme and the achievable goals should be determined, and a strategic plan is needed to obtain optimal herd health and productivity. A holistic approach is necessary and attention needs to be paid to all risk factors and a risk management programme needs to be established where interventions are included and prioritized to reduce disease risk to a minimum. A herd health programme takes time and expertise to develop, and the herd veterinarian has competence and a key role to play in directing the efforts. A vaccination scheme alone is not a herd health programme. It is part of the holistic herd health programme and should be considered as one tool to optimize health rather than being thought of as a separate entity. The vaccination scheme is heavily dependent on the overall herd health and should be tailored to the individual operation by the herd health veterinarian, who seeks appropriate expertise from vaccine providers as well as other expert advice when necessary.

References

The reference lists shows all references used in Whitepaper: 'The importance of preventive health and vaccination programs in ruminant production'. Visit our website timetovaccinate.com to download the full whitepaper.

Reference List


DEFRA. 2008. Cattle rearing to 10 months of age. in .


Wiliams, P., and G. Paixao. 2016. There is a need to raise farmers' awareness of correct vaccine storage temperatures. Pages 167 in World Buiatrics Congress.


Time to Vaccinate is an initiative from MSD Animal Health to provide information and share experiences about vaccination as a preventive tool for ruminants. Visit our website timetovaccinate.com to download the full whitepaper 'The importance of preventive health and vaccination programs in ruminant production'.