TIME TO
VACCINATE

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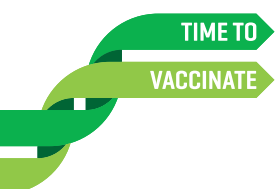# The importance of preventive health and vaccination programmes in ruminant production

MSD
Animal Health

The importance of preventive health and vaccination programmes in ruminant production

Contents

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.

> **the power to resist infection whether natural (innate) or acquired (as by vaccination)**

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.

All cells of the immune system originate in the bone marrow. A common lymphoid progenitor gives rise to cells that mature in the 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.

(Tizard, 2013)
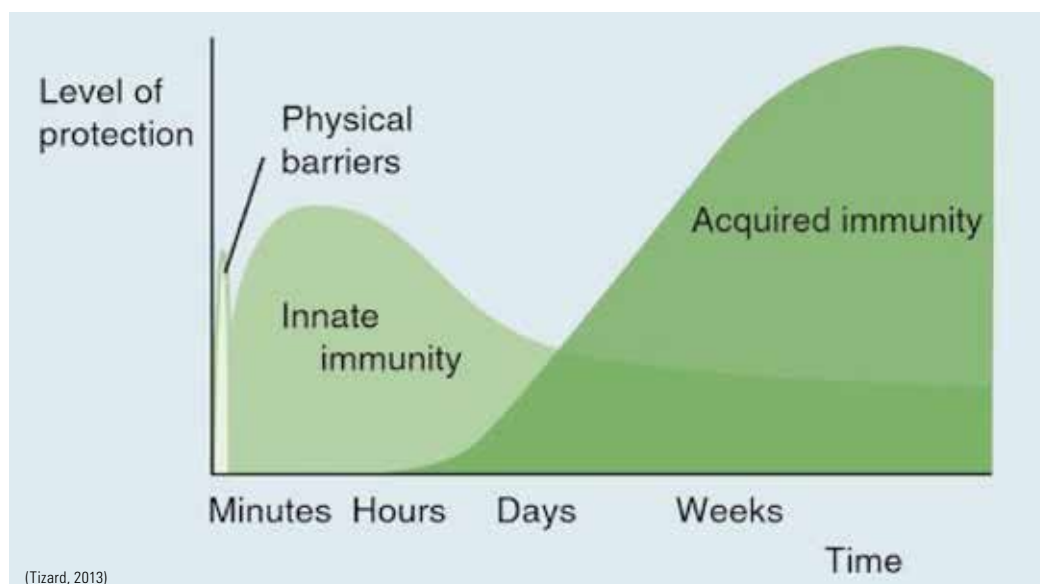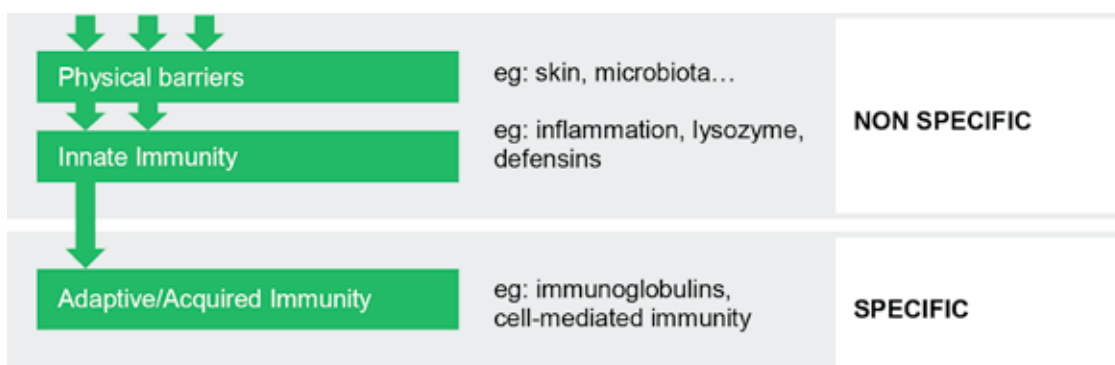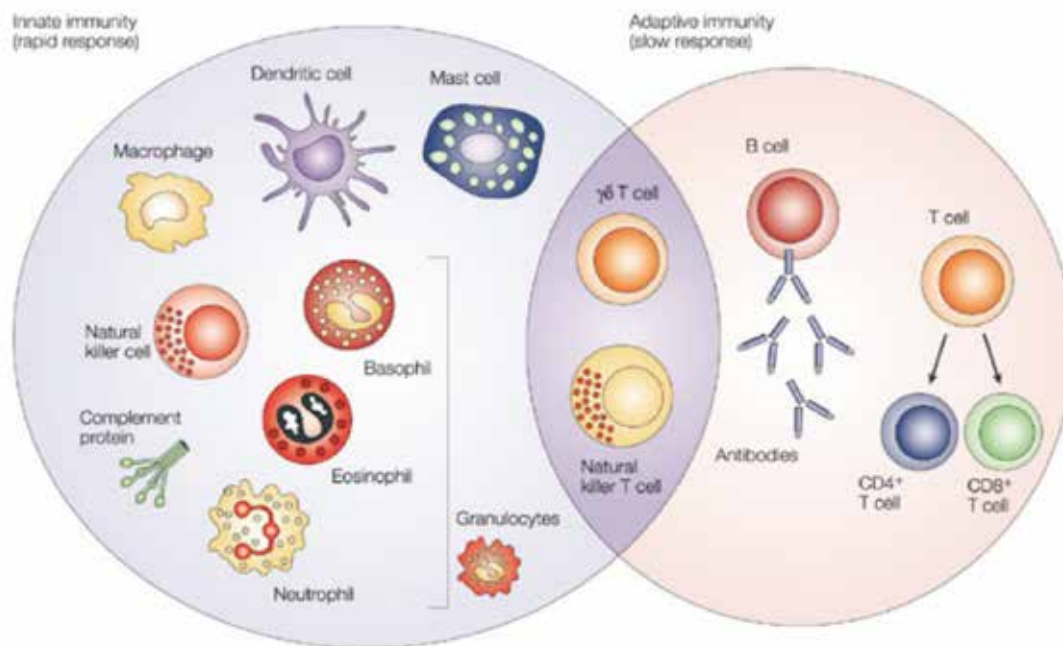
2.1.1 The innate immune system

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 infec-tions, 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 frontline 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 expansion) 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 cyto-kines, 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.
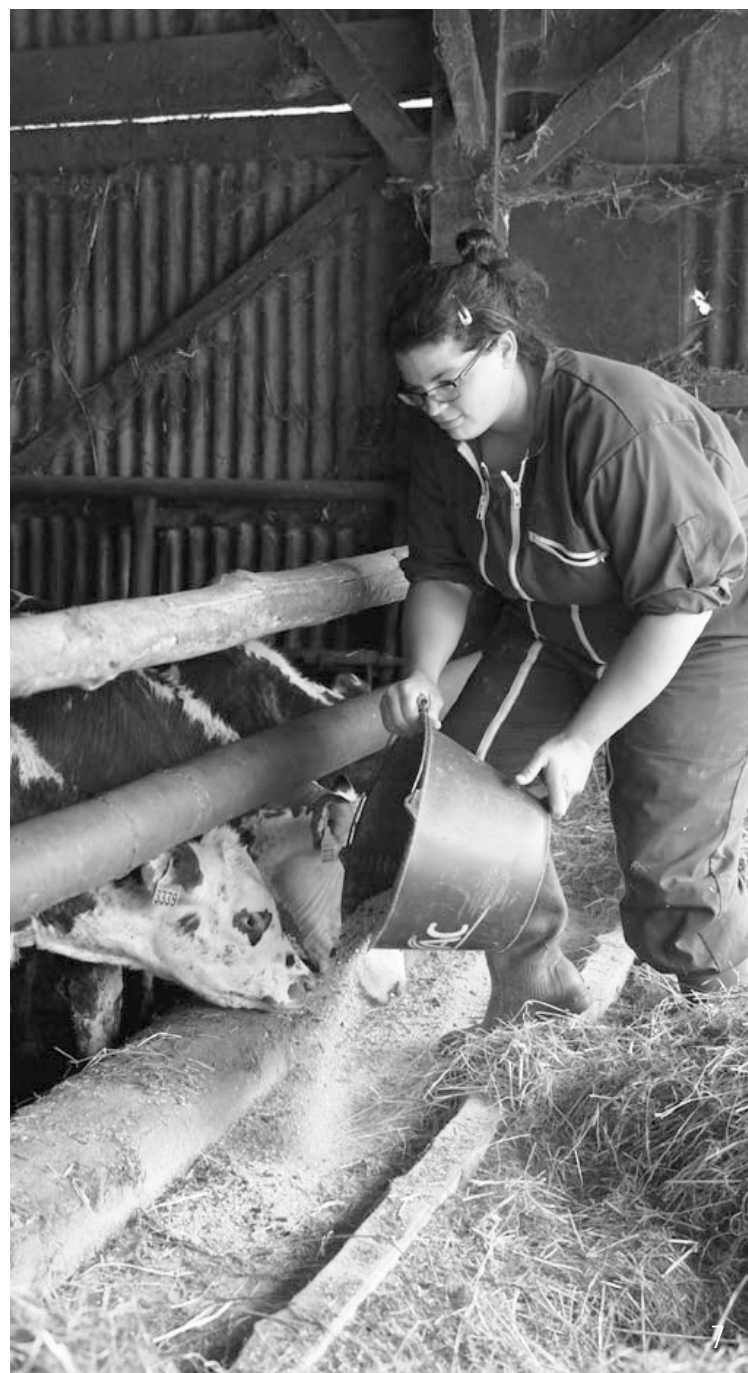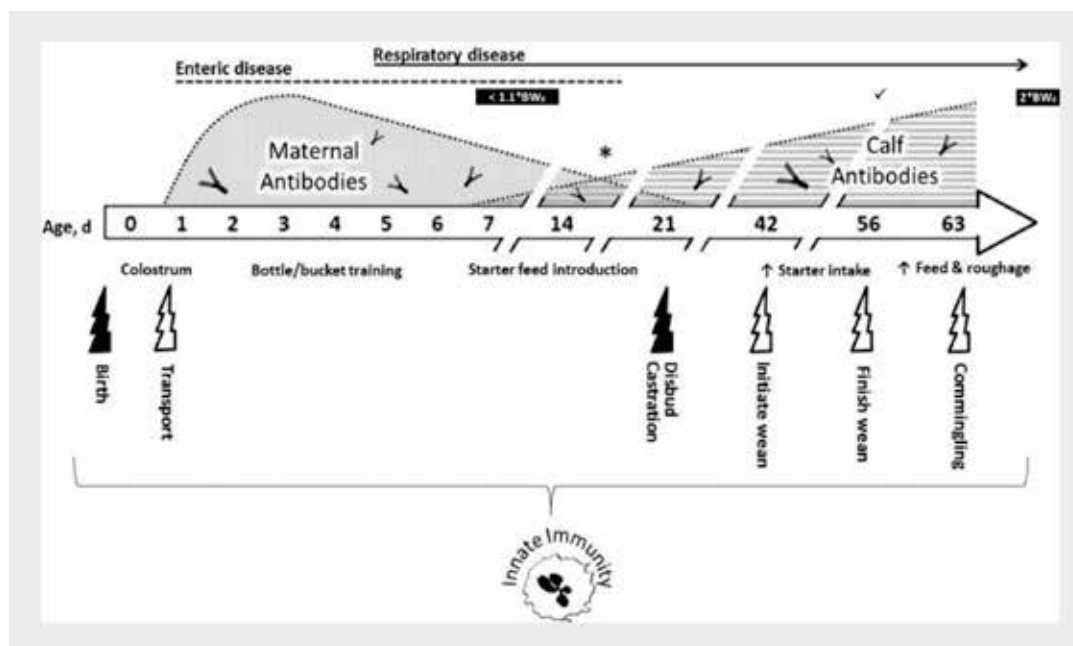
The orchestration of the different types of immunity overtime results in the protection of the young animal.

For example, in the second week of life of calves, the neonatal animal is at risk for disease as antibody levels are lower due to waning levels of colostral antibodies and insufficient production and development of its own immunity (diagram above (Hulbert and Moisa, 2016)). 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

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.

> **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**

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 endoge-nous 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.

Cu/Zn or Mn
Superoxide dismutase

$O^{2-} + O^{2-}$
Superoxide ion

$2H^+$

$H_2O_2 + 0^{2-}$
Peroxide

Catalase
(Fe)

$H_2O + O_2$

GSSG

$OH + H_2O$

NADPH

Se
GSH-Px
Glutahione peroxidase
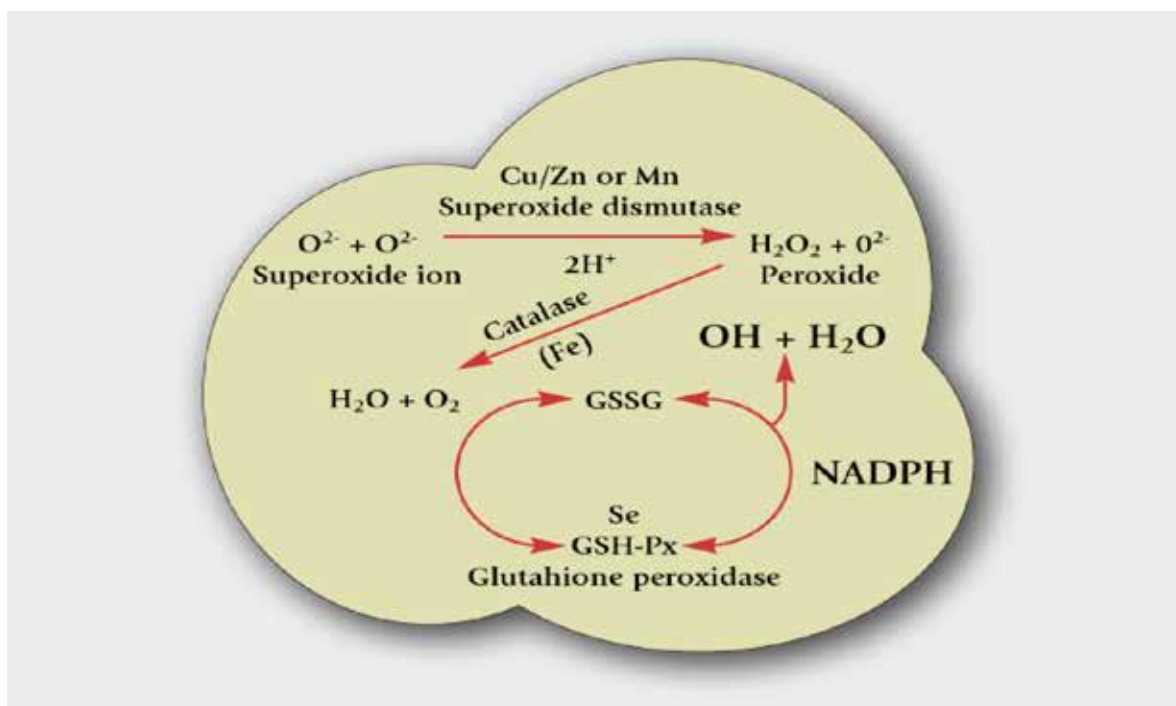
2.2.1.3 Nutritional factors in pre-weaned calves

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, haptoglobulin responses and an im-proved 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 mannanoligosaccharides 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, preintroduction 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 1.5-2m^2, between 150-200 Kg has 2-3m^2, and animals over 200 Kg has > 3m^2.

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

A herd health programme is a combination of sound management, good housing, good nutrition, good biosecurity and proactive health measures such as vaccination

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 increase 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

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.

The maintenance of good herd health and productivity is dependent on multiple factors. The factors are all inter-related and of importance. Depending on the farm system, location, size, management system, feed sources, etc, the challenges that are disturbing herd health will vary.

As you can note, vaccinations is one component of maintaining herd health, but if vaccinations are applied to systems where there are high risks, weaknesses or failures in other areas, then the vaccinations may not solve the health challenge, and the farmer may blame the vaccine, although there were other causes for vaccination failure.

A vaccination scheme alone is not a herd health programme. It is part of the holistic herd health programme

Herd health programme

Breed Genetics

External & Internal Biosecurity

Documentation & Benchmarking

Nutrition

Animal Welfare, Environment, Housing

Reproduction, Production

Disease diagnostics Vaccinations Treatments

Management Daily, weekly, monthly, yearly
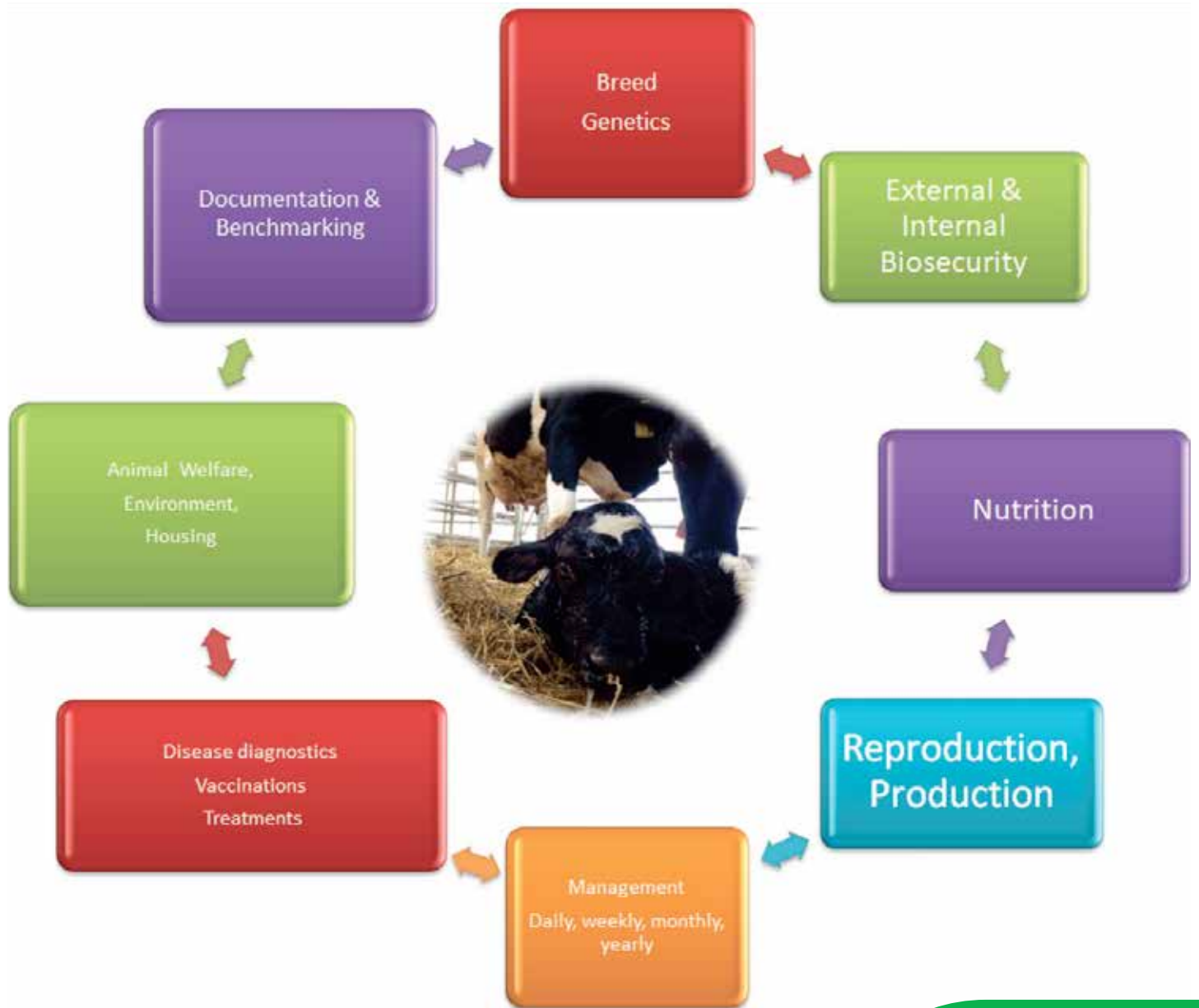
3. Basic concepts of vaccination

3.1 Why vaccinate?

The three main reasons to vaccinate are to increase immunity, reduce the spread of disease and eradicate disease. Furthermore, **with the increasing global threats of antimicrobial resistance in both animals and humans, vaccines are very important tools to reduce antimicrobial use and thereby slow down the emergence and spread of antimicrobial resistance. Vaccinations can also reduce production losses associated with disease and are therefore leading to a more sustainable animal production**.

> Main reasons to vaccinate:
>
> 1. **Increase immunity**
> 2. **Reduce the spread of disease**
> 3. **Reduce the impact of** (subclinical) **disease**
> 4. **Eradicate disease**

The purpose of a vaccination is to develop a specific immune response against the pathogenic agent so that the clinical effects (severity of the symptoms, mortality risk) of any infection with the wild-type agent can be greatly reduced. Use of vaccination is intended as a prevention strategy against a disease. A vaccination can pursue different goals: to obtain an immune response in the vaccinated animal, which then exerts its effect in the vaccinated animal or to raise antibodies to pass on via colostrum intake from dam to offspring in order to protect the young animal against infection or the negative consequences of the infection.

> **Treatment of disease is not as effective or as economical as prevention**

Treatment of disease is not as effective or as economical as prevention and in the European Union, the position is that 'Prevention is better than cure' (European Commission, 2007). Poor health status and subclinical disease are major causes of losses in all forms of ruminant production, including organic production (McConnel et al., 2008). Many disease conditions can be avoided or minimised by using management practices that reduce exposure to disease, lower stress, and include good hygiene and biosecurity (Leblanc et al., 2006; Marce et al., 2010). However, resistance to change, lacking financial resources often means that not all recommended management procedures are implemented. However, farmers often find that vaccination is relatively easy to implement and this is very important for any health intervention measure. It is possible to vaccinate against several viral, bacterial, fungal and parasitical diseases. A vaccination programme is an important element in a comprehensive, well-planned herd health control strategy. Farmers and their veterinary surgeons will always aim to ensure that animals are kept in the best state of health and welfare. While this aim should never be compromised, it is important to recognise that it is influenced by the profitability of the farming business. A farm specific vaccination programme in consultation with the veterinarian could greatly contribute to a reduction in both the severity and the prevalence of infectious disorders and can also lead to a reduction of the need for curative use of antibacterial agents.

3.2 When to vaccinate?

Vaccinations are generally undertaken when there is a real or perceived risk of infection. When the risk that a herd will get infected is high, or the infection in the herd is already established and the losses in productivity and health are financially high, or when the impact of a certain infection is very high even when the risk to get infected is moderate, then the recommendation will be to vaccinate, when safe and efficacious vaccines are available.

For example, bovine viral diarrhoea virus (BVDV) is prevalent in many Europeans countries and it is a disease with high economic losses, and therefore vaccination of cattle against BVD is certainly indicated in those countries. For certain diseases that are government regulations that determine vaccination protocols for farmers, such as foot-and-mouth disease and Bluetongue. For other programmes there may be national or regional industry-initiated systems that determine the vaccination protocols.

As herd size increases the risk of introduction of infection and spread within the herd increases. The larger herds usually have more animal introductions and animal contacts. Furthermore group housing and free stall systems increases contacts within animals on the farms. Therefore the risk that diseases will be introduced onto a farm and spread within a farm is increased. In these systems strategic vaccination programs have become a necessity in order to protect the animal from diseases.

In small dairies, there may also be a high risk of transmission of disease due to close contact between different animal age groups. Many small dairies are very tight for space, and many times the maternity pen is used as sick pen or the sick pen is adjacent to the maternity pen. Practical and immediate solutions to these structural challenges may be hard to find. In these situations, vaccination may assist a farmer in minimizing the spread and outbreak of diseases.

The decision of if and when to vaccinate and against what pathogen should always be done after consultation with the herd veterinarian (See section 4.1).

3.3 Herd immunity and reproductive ratio of disease

Herd immunity is a form of immunity that occurs when the vaccination of a significant portion of a population (or herd or flock) provides a measure of protection for animals that have not developed immunity. The risk of infection among susceptible animals in a population is reduced by the presence and proximity of immune animals. This concept can be explained in terms of the reproductive ratio (R), which is a measure of the transmission potential of a disease. It is the number of secondary infections produced by a typical case of an infection in a population that is totally susceptible. The basic reproductive ratio (R0) is affected by several factors: such as population density and contacts between animals, probability of transmission upon contact, duration of infectious period, etc. When R0 > 1 the infection will be able to spread in a population but when R0 < 1 the infection will die out in the long run. The effective reproductive rate (R) measures takes into account that some animals may be immune against disease through previous exposure to the pathogen or vaccination. The herd immunity threshold is the proportion of a population that need to be immune in order for an infectious disease to become stable in that community (R=1, each case of infection generates one new case of infection). If R < 1, then the infectious disease will be eliminated out of the population. For vaccines, the percentage of the population that needs to be vaccinated to protect the population can be calculated based upon the efficacy of the vaccine and the reproductive ratio. Furthermore, selective vaccination of high risk animals that are important in transmission can slow transmission in a population.

3.4 Vaccination classification

All vaccines aim to influence the animal's immune system mechanisms in order to stimulate future protection against a disease or diseases. This is achieved by either administering a live, but attenuated (non-virulent or little virulence) form of the infectious organism, or by administering a killed version of the organism or a modified toxin. A live virulent vaccine can also be used, where the timing of the vaccine administration induces immunity without causing severe disease. Vaccines may be classified according to the target species for disease control, by the disease or diseases they help control, type of vaccine or by their biological action. A **univalent vaccine** is prepared from a single strain of microorganism. **Multivalent or polyvalent vaccines** are prepared from cultures of two or more strains of the same species or microorganism. **Combination vaccines** take two or more vaccines that could be given individually and put them into one preparation and thereby protect against more than one pathogen. A marker or DIVA vaccine (Differentiating Infected from Vaccinated Animals) allows for the differentiation between an immune response due to natural infection and an immune response due to vaccination. There are cattle marker vaccines available for infectious bovine rhinotracheitis (IBR). Marker vaccines are important for herds with a designated "disease free status" and when trading with countries that are free from, or eradicating, these diseases.

Several vaccines (for example those against salmonellosis, leptospirosis, ringworm) also act as a safeguard to human health by reducing the risk of zoonotic infection. This helps to ensure the health of those working with cattle by lowering disease levels.

3.4.1 Live attenuated vaccines

Live attenuated vaccines contain a version of the living microbe that has been attenuated (weakened) in the laboratory so that it can't cause disease. They elicit strong cellular and antibody responses and may confer lifelong immunity with only one or two doses. Some disadvantages are: there is risk that an attenuated microbe in the vaccine could revert to a virulent form and cause disease, immune-suppressed animals may become sick and they are most sensitive to cold-chain failure. Live vaccines developed and produced by trustworthy companies are nowadays as safe as inactivated vaccines. Live, attenuated vaccines are relatively easy to create for certain viruses, whereas more difficult to create for bacteria. Serum free production of live vaccines (e.g. Bovilis IBR Marker Live) reduces risk of contamination with unwished pathogens

MSD-AH vaccines: Bovilis IBR Marker live, Bovilis Ringvac, Enzovax, Scabivax Forte, Toxovax, Bovilis Huskvac.

3.4.2 Inactivated Vaccines

Inactivated (killed) vaccines are created by killing the disease-causing microbe with chemicals, heat, or radiation and these vaccines are more stable than live vaccines, and may not require refrigeration. Most inactivated vaccines stimulate a weaker immune response than live vaccines, and may therefore require a two dose primary course as well as more booster vaccinations. Killed vaccines usually contain adjuvants (see 3.7), which is a substance that enhances the immunological effect to stimulate a greater immune response (and therefore protective effect) to the vaccine.

MSD-AH vaccines: Blackleg vaccine, Bovilis Bovipast RSP, Bovilis BVD Suspension, Bovilis IBR Marker Inac, Bovivac S, Footvax, Leptavoid-H, Ovipast Plus, Rotavec Corona.

3.4.3 Subunit Vaccines

Subunit vaccines include only the antigens that best stimulate the immune system, and not the whole microbe, and this approach can minimize adverse reactions to the vaccine. Subunit vaccines can contain anywhere from 1 to 20 or more antigens.

3.4.4 Toxoid Vaccines

For toxin-producing bacteria a toxoid vaccine can be produced to develop immunity to the toxin. A toxoid is a detoxified toxin. Vaccines against tetanus are examples of toxoid vaccines.

MSD-AH vaccines: Bravoxin 10, Heptavac P, Lambivac, Ovivac P Plus, Tribovax.

3.4.5 Conjugate Vaccines

A conjugate vaccine is a special type of sub-unit vaccine that can be used to trigger immunity to bacteria that have cell walls with polysaccharides. Polysaccharide coatings disguise a bacterium's antigens so that immature immune systems cannot recognize them.

3.4.6 DNA Vaccines

DNA vaccines can be created from microbes with a known DNA profile. These vaccines are promising as they can use the genes that code for the most antigens and they can be easy and inexpensive to produce. When the genes for a microbe's antigens are introduced into the body, some cells will take up that DNA. The DNA then instructs those cells to make the antigen molecules. The cells secrete the antigens and display them on their surfaces and the body's own cells become vaccine-making factories. So-called naked DNA vaccines consist of DNA that is administered directly into the body.

3.4.7 Recombinant vector vaccines

Recombinant vector vaccines are experimental vaccines similar to DNA vaccines, but they use an attenuated virus or bacterium to introduce microbial DNA to cells of the body. "Vector" refers to the virus or bacterium used as the carrier.

3.5   Adjuvants

Adjuvants are important components of vaccines used to elicit stronger, faster and longer last-ing immune responses to vaccines (Gerdts, 2015). They can enhance either antibody or cell-mediated immune responses. Most adjuvants are used with subunit and inactivated vaccines that are less immunogenic than live vaccines. Adjuvants can have a variety of effects on the outcome of vaccination such as: type of immunity, onset, magnitude and duration of immunity, multivalent vaccines, targeting of specific immune compartments, route of immunization, optimize use in neonates or high risk animals or during gestation. Adjuvants can have a cost sparing effect through antigen sparing and reduction in number of doses.

Most adjuvants cause some sort of tissue damage (local inflammatory response) which leads to the recruitment of immune cells and illicit a stronger immune response. The innate immune response is activated first and triggers a more specific (adaptive) immunity. Adjuvants can help in the type of signals that are triggered. Aluminium-based adjuvants, micro and nano particle formulations, oil-in-water/water-in-oil emulsions allow for a depot slow release of the vaccine. Saponins seem to induce T-cell and B-cell immune responses. Toll like receptor (TLR) ligands activates signalling pathways and proinflammatory cytokines and target dendritic cells. Particle-based adjuvants (nanoparticles/microparticles) are taken up by phagocytic antigen-presenting cells and allow vaccines to be delivered directly to mucosal cells allowing for oral or nasal routes of delivery. Liposomes are synthetic spheres of lipid layers that encapsulate the vaccine and release these by integrating in cell membranes. Virosomes are non-replicating delivery vehicles for vaccines. There are furthermore combination adjuvants.

3.6   Potential and limitations of vaccination

Vaccines are effective, convenient and efficient health intervention to:

- Stimulate the animal's own immune system to prepare it for future encounter of pathogenic organisms.

- Decrease animal diseases and suffering in animals.

- Prevent the transmission and the spread of zoonotic diseases between animals and hu-mans

- Improve the feed conversion and production efficiency

- Are generally safe and efficient

- Prevent and control infectious animal diseases epidemics

- Reduce antimicrobial use and decrease veterinary costs

- Reduce antimicrobial resistance and preventing multi-drug resistant infections such as from *S. aureus, C. difficile* and *E. coli* (Vaccines Europe, 2016).

- Provide increased food security and safety.

- Eradicate diseases ('Rinderpest", FMD, BVD, IBR) globally or regionally

Some limitations are:

- Vaccination development is costly and lengthy with stringent requirement for safety and efficacy by regulatory authorities.

- The time needed for vaccine development makes it difficult to respond to new pathogens quickly

- Antigenic shifts in pathogens may render some vaccines inefficacious in protecting animals.

- Vaccines do not prevent infection. Rather, they prime the immune system to provide a rapid and effective response following infection. The result is decreased disease severity and decreased transmission to other animals.

- Many management factors can limit the effectiveness of vaccination including nutrition, environmental conditions, parasites and exposure to disease.

- Inability of animals to mount an appropriate immune response. Animals in poor bodily condition, lacking in essential micro-nutrients, stressed or suffering from concurrent disease may not be able to mount an appropriate immune response following vaccination (See section 2.2.1).

- Over-crowding and poor sanitation increase the exposure to infectious agents which can overcome even high levels of immunity obtained through vaccines (See section 2.2.2 and 2.2.3).

- Helminths have been shown to suppress the immune system and may interfere with immune response to vaccination (See section 2.2.1.6).

- Inappropriate transport and storage may damage the vaccines. (See section 4.2)

- Failure to vaccinate all susceptible animals and administer booster vaccines leads to suboptimal herd immunity.

- Vaccinations cause occasionally side effects.

3.7   Vaccine - safety and efficacy in development and production

An effective vaccine needs to be highly "antigenic", meaning that it must strongly stimulate the immune system to respond rapidly in the correct way. However, the better a vaccine is at stimulating a protective immune response, the more likely it is that the immune system in an individual animal may respond in the wrong way. In general, the more effective a vaccine is, the less safe it is. This is a general rule and may not hold within one particular class of vaccines - for example a modified live vaccine may be more effective than a killed vaccine of the same virus, but the killed vaccine may be more likely to cause local reactions because of its adjuvant.

3.7.1   Safety

Prior to licensure, field safety studies are conducted to detect unexpected reactions and investigate the safety profile of the product. These studies are used to prove that vaccines are safe for commercial use. However, even a safe vaccine may still occasionally be associated with an adverse event.

Fortunately these are usually infrequent; however, post-licensure monitoring of adverse events is very important. Adverse events are comprised of more than adverse reactions. Lack of efficacy and problems with the product formulation are also considered adverse events.

3.7.2 Efficacy

Vaccine efficacy must be tested under representative conditions - or as close as possible. There are two general types of efficacy studies: serological testing and live animal challenge studies.

With serological testing, the vaccine efficacy may be evaluated by measuring the antibody titer produced in animals after vaccination. Titer testing looks at the ability of the serum antibodies to inactivate live viruses in cell culture – this is referred to as serum neutralization (SN) or virus neutralization (VN). Titer testing can be useful, but generally the challenge study is the most compelling and accepted means of evaluating vaccine efficacy.

Challenge studies are usually conducted with research animals in a controlled environment. Animals in these studies are typically vaccinated with the product being tested, then "challenged" with the actual disease weeks – or years – later. A control group of non-vaccinates is also challenged to determine whether the results were due to the vaccine – and what would happen to an unvaccinated animal challenged in the same way.

Vaccine duration of immunity (DOI) has become very important in recent years. In the past, most vaccines only had challenge data conducted a few weeks following vaccine administration. Yet they were still able to state "revaccinate annually" on the label. This changed in the mid 90's to a requirement that vaccines must demonstrate a duration of immunity identical to the interval stated on the label. DOI has now become very important for vaccines.

4. The logisitics of vaccination

4.1 How to get success with vaccination programme

Much of the failure of vaccination may be found in incorrect diagnosis of the health challenge, vaccine handling, administration and timing of administration, failure of stressed animals to mount a good immunity following vaccination, the multifactorial nature of infectious diseases, and the increased susceptibility of stressed animals to disease.

Therefore in order to have a successful vaccination programme it is essential to consider all the aspects of health and immunity as described previously. It is highly likely that the competence of the individual animal owner is sufficient to evaluate all factors necessary for a successful program, and therefore the herd veterinarian becomes a vital person to develop the herd vaccination scheme within the scope of a holistic herd health programme.

4.2 The veterinarian's role in the vaccination programme

The veterinarian has a pivotal role in all vaccination programmes and needs to dedicate sufficient time and resources to the entire vaccination scheme and related management factors. **The veterinarian has competence in the immunological components of the vaccination as well as the herd health and animal health factors that are essential to obtain a good vaccination response**.

The failure to take this pivotal role may lead to failure in vaccination protection as shown by a survey in Pennsylvania (Rauff et al., 1996). Most producers relied on their veterinarian for vac-cination information and vaccine purchases, but administered the vaccine to the cattle themselves and many producers did not vaccinate all susceptible groups of cattle or failed to administer booster vaccination. The survey indicated that although 82% of dairy

producers indicated that they routinely vaccinated their herds, only 27% of herds were considered adequately vaccinated.

The veterinarian has knowledge regarding the potential and weaknesses of a vaccine. The ideal vaccine should stimulate complete immunity providing 100% protection against disease, prevent shedding or excretion of the pathogen, and protect the foetus. The ideal vaccine is efficacious against all types of the pathogen and lead to a long duration of immunity. The ideal vaccine is a marker vaccine that is stable in transport and storage, has a long shelf-life, and is safe and easy to administer. The ideal vaccine does not exist, but nonetheless, there are several excellent vaccines, and a good knowledge of their characteristics, benefits and limitations is needed to protect animals/herds/production systems. The role of the veterinary profession in vaccination program is therefore emphasized.

The veterinarian can determine the need for vaccination and the ability for vaccines to reduce the current health challenges on a farm. This includes a good knowledge of the herd health history, diagnostic sampling of animals, the diseases challenges in the area, evaluation of specific risk factors and other management routines that might impact animal health.

The veterinarian can determine the health status of the animals to be vaccinated and the animal groups that should be vaccinated. As the vaccine relies on the animal mounting an adequate immune response it is important that the animal is not suffering any undue stress, or nutritional deficiencies or clinical disease as described above. The animal should be in good health and not suffering from any other disease. For example, parasites can influence the immune response to vaccination and there may be a need to deworm the animals 2 weeks prior to vaccination. Sufficient time must be allowed to elapse between vaccinating and exposure to the natural infection. Furthermore, it is important to understand the epidemiology of the disease in order to determine what animals should be vaccinated and at what time the vaccines should be administered.

The veterinarian has knowledge regarding the correct administration and timing of the vaccinations and the use of various vaccines in relation to one another in time. Different vaccines may stimulate an immune response in different

ways; therefore it is vital that the manufacturer's guidelines for injection and timing of vaccination are closely followed. It is important that the vaccines are administered according to instructions, such as intramuscular or subcutaneous injection. The mixing of various vaccines should not be done, unless specifically authorised (such as Bovilis BVD and Bovilis IBR Marker Live), as the safety and efficacy of the combined product could be adversely affected. The multivalent vaccines induce immunity against a number of pathogens or antigens and are highly effective at reducing diseases caused by a combination or range of pathogens. Similarly here, these vaccines may not be administered with other vaccines, unless specific information indicates that this is acceptable and suitable.

The veterinarian has competence, skills and ability to monitor the outcome of the vaccinations. The effect of some vaccination programmes can be monitored by taking milk or blood samples (serology) and assessing the antibody levels indicating that the animals have mounted an immune response (Go to 4.3). This response is similar to that produced to natural infection with the disease organism and the two are usually indistinguishable, unless a marker vaccine has been used.

4.3   Importance of the cold chain

It is very important that vaccines are kept at the indicated temperature, but unfortunately vaccines are too often subjected to temperature abuse, either too high temperatures or too low and even freezing temperatures, compromising the vaccine potency. A field study performed by Paul Williams, veterinary advisor MSD, indicated that farm refrigerator temperatures where vaccines were stored were frequently outside the correct temperature range for vaccines (between 2-8 °C)(Williams and Paixao, 2016). Paul Williams concluded that there is a need to raise farmers' awareness for correct vaccine storage temperatures. In order to minimize the risks of temperature abuse on farms, the vaccines should be stored on farm for a minimum amount of time in refrigerators with temperature controls.

4.4 Diagnostics

When using diagnostic tools to determine past or current infection status or immunity, it is important to understand the epidemiology of the infection and the statistical properties of the diagnostic tools (Fosgate, 2009). The number of samples that need to be taken is dependent on the estimated prevalence of disease, the desired confidence level of the sampling and the sensitivity and specificity of the diagnostic tool. **Sensitivity** and **specificity** are statistical measures of the performance of diagnostic tools that measures binary responses (such as presence or absence of disease). Sensitivity refers to the test's ability to correctly identify infected animals, whereas the specificity is the ability to correctly identify non-infected animals. Diagnostic sensitivity can be increased by targeting high risk animals. Statistical and epidemiological advice should be sought prior to commencing a new diagnostic program within a herd or group of herds.

Most diagnostic tools are aimed at detecting antibodies, indicating previous exposure to a specific antigen, either via natural infection or vaccination. Other tools aim at detecting the actual pathogens themselves.

Antibody detection sampling gives mostly historic results that an animal has been exposed to a pathogen and has mounted an immune response (seroconversion). Paired sampling with a time between sampling times can indicate current infection. Antibodies are mostly tested in sera, milk or other body secretions. It is important to differentiate antibodies that have been acquired through passive transfer of immunity through colostrum and antibodies acquired through vaccination or natural exposure to a pathogen. Marker vaccines can facilitate this differentiation. Laboratory analysis can involve neutralization assays, haemagglutination inhibition and ELISAs. It should be noted that vaccination success cannot always simply be measured as an antibody response, as there are vaccines that stimulate the cellmediated immunity and sometimes colostral immunity or other factors obscure the result (Mawhinney and Burrows, 2005).

Pathogen detection can indicate current infection. In order to optimize recovery of pathogens, the samples should be taken in the acute phases of disease, and for bacteria preferably prior to antimicrobial treatment. Specimens are mostly taken from tissue, body secretions (nasal/tracheal/broncheal secretions, milk) or faeces. These

samples are fragile, so they should be transported quickly and cooled in appropriate and indicated transport media to the laboratory. Laboratory analysis may involve traditional bacterial culture, virus isolation in cell culture, ELISA, PCR or other genotypic method. Culture methods traditionally have a low sensitivity, whereas the other methods may have higher sensitivity but lower specificity.

- Neutralization assays are the gold standards of measuring antibody levels as it also provides a functional level evaluation.

- ELISA (Enzyme Linked Immunosorbent Assays) are standardized and efficient methods for large number of samples where liquid samples are added to antibody-coated microwell plates (96-well plates) and binding is measured through a colorimetric system. There are various types of ELISA tests such as Direct ELISA, Blocking ELISA, Competition ELISA and Indirect ELISA. The response, usually an optic density is categorized as a yes/no, based upon a cut-point definition. It is important to realize that the cut point definition can lead to both false positives as well as false negatives.

- PCR (Polymerase Chain Reaction) involves the detection of specific nucleic acids of the pathogen concerned, and they can be DNA or RNA (RT-PCR: reverse transcript PCR), and real time PCR also known as quantitative polymerase chain reaction (qPCR) can give quan-titative or semi-quantitative results.

Advantages and disadvantages of laboratory methods for identifying enteric pathogens have been described briefly (Cho and Yoon, 2014). The diagnosis of pathogens involved in respira-tory disease is difficult and the ability to differentiate field strains from vaccination strains requires extensive skills and competence (Fulton et al., 2016; Fulton and Confer, 2012). It should be noted that regardless of diagnostic technique, the detection of a potential pathogen in a sample does not necessarily indicate a causal agent for disease.

5. Momentum and situation in EU

5.1 Data on how much vaccines or how many animals are vaccinated

There are different veterinary medicinal products authorised in the Member States of the EU (Eudrapharm, 2017) There is large variability between European Union countries in various vaccines available and registered (Videnova and Mackay, 2012). **A study by MSD AH in 2016 indicates that actual cattle vaccination penetration rate is low, between 10% and 45% in Europe**. The survey of non-compulsory vaccination in selected European countries indicates that BRD vaccination ranges from 14% in France, 22% in the UK, 33% in Germany to over 80% in Spain and Italy. Neonatal vaccination rates show a different national pattern with a low 5-6% vaccination in Spain and Italy, 14% in UK and Germany and 30% in France. Vaccination coverage in countries where BVD vaccines are available is reported to be 20%.

5.2 Political and regulatory trends and hurdles to vaccination

5.2.1 Regulatory Bodies and rules regulating vaccination in the EU

Research on vaccines and access to the market in the EU falls under the remit of a number of regulatory bodies at global, European and national levels.

The World Organisation for Animal Health (OIE) publishes standards for veterinary vaccine production and the requirements for recognition of disease-free status. All 28 EU Member States are members of the OIE; as such they follow the organisation's standards detailed in the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (OIE, 2016a). This sets out the general principles of laboratory management and vaccine production, as well as disease-specific chapters providing detailed standards for the manufacture of vaccines for the OIE listed diseases. In May 2015, the OIE adopted its 6th strategic plan for the period covering 2016-2020 (OIE, 2016b). Included among the plan's strategic objectives were "the application of new and rapidly

evolving technologies related to standards development, including diagnostics and vaccines, and the ability of the OIE to access expertise in these technologies." These will be a focus of the upcoming working period.

The European Commission (EC) produces legislation to guide livestock vaccination within the 28 EU Member States. In the light of the Foot and mouth disease outbreak in the UK in 2001, an evaluation of existing complex and fragmented legislation for managing disease prevention and control and to reduce the economic impact of disease outbreaks was initiated. The Animal Health Strategy, which ran from 2007 until 2013, was organised around the principle that "prevention is better than cure" and, prompted the single regulatory framework. In March 2016, the EC adopted the new 'Animal Health Law' (AHL) (European Commission, 2016), which will enter into force in 2021. This Regulation lays down the general principles and rules relating to the control of transmissible animal diseases as a single regulatory framework. The detailed provisions, particularly those regarding vaccination and vaccine banks, are being adopted through secondary legislation until April 2019.

The new AHL places a greater focus on disease awareness, preparedness and control. It proposes a framework promoting a more coherent use of vaccination. It introduces a listing, categorisation and prioritisation for diseases that will require EU intervention. The majority of serious diseases will be subject to EU-mandated control measures such as the use of vaccines; depending on the seriousness of the disease in question, eradication measures may be voluntary or compulsory. Under certain conditions (i.e. relating to the internal market), Member States can take additional measures. The list will be regularly updated to integrate new scientific evidence. The AHL also provides a wider legal framework for establishing banks of antigens, vaccines, master seed sticks and diagnostic reagents that take into account the needs of Member States and storing a large number of vaccines for more diseases. Rules for emergency vaccina-tion are also introduced, which will allow rapid access for Member States tackling epidemics, economies

of scale and reduced administrative burden. The AHL also provides a closer alignment to international standards, particularly those of the OIE.

5.2.2   Market authorisation for vaccines

There are two routes to market authorisation for veterinary vaccines in the EU. **National authorities** can authorise for their respective markets or the European Commission can do so centrally for the EU based on a **European Medicines Agency (EMA)** evaluation. Vaccines developed using biotechnology must use the centralised EMA route; novel products usually do so (European Commission, 2004a). In 2014, the European Commission undertook a revision of veterinary medicines legislation in 2014 (European Commission, 2014). The new rules would help streamline marketing authorisation procedures, allowing companies to place and maintain a medicine on the entire EU market. These proposals are currently being reviewed by European legislators.

The EMA Network Strategy to 2020 identifies the increased availability of veterinary medicines as a priority (EMA, 2015a). This prompted EMA and the EU Heads of Medicines Agencies (HMA) to organise a workshop in March 2015 on requirements for the authorisation of veterinary vaccines within the EU. As a result, the EMA and HMA drew up an action plan to facilitate timely access for new or improved veterinary vaccines. EMA's Committee for Veterinary Medicinal Products established a joint steering group in February 2016 to oversee the implementation of the plan. The following elements are based on the workshop recommendations (EMA, 2015b):

- To develop proposals for increasing communication, cooperation and transparency in developing scientific and administrative guidelines;

- To propose specific training for assessors to enhance the consistency of assessment; developing a list of diseases for which vaccines are not available;

- To develop lists of diseases where vaccines are not currently available and therefore required, together with clear expectations of what would be needed for their authorisation;

- To examine the list of factors (Annex 2 of report) that industry believes are constraining the availability of vaccines within the EU;

- To explore reduction of data requirements for Minor Use Minor Species (MUMs);

- To take the opportunity of the current revision of the veterinary medicines legislation to identify best practices on how vaccines are assessed in other regulatory areas and the level of requirements that should apply.

The **EU reference laboratories (EURLs)** in the animal health sector are responsible for coordinating methods of diagnosing diseases in Member States, assisting in the diagnosis of disease outbreaks, collaborating in researching methods for diagnosis, and training on diagnosis (European Commission, 2004b). EURLs provide the European Commission with assistance on diagnosing animal diseases outbreaks.

The EU requires each Member State to designate a **National reference laboratory** for each EURL, which would be responsible for coordinating the activities of official laboratories responsible for analysing samples, organising comparative tests and appropriate follow-up, ensuring dissemination of information and assisting in implementing coordinated control plans.

5.2.3 Impact on Trade

The impact of vaccination on trade of recent developments seems likely to be positive. Increased economic and ethical concerns have led to a change in emphasis. Inoculation against major transmissible diseases as the default approach, rather than mass culling of herds, infected or not, will inevitably increase demand for vaccines in the years to come.

Other developments brought about by adoption of the AHL will also improve trade opportunities. These include increased harmonisation of international standards, steps to reduce the fragmentation of the EU market for vaccines, along with measures for emergency vaccination in the case of disease outbreaks. EU rules presented and coordinated by the European Commission cover the health of animals transported to, from, and within the EU.

Also in the AHL, the new provisions aim at increasing convergence with international (OIE) standards on animal health such as compartmentalisation, requirements for export and added flexibility. The OIE acts as the World Trade Organization reference organisation for standards relating to animal health. The extension of vaccine banks to more diseases, facilitating their access in case of disease outbreak will also favour trade by reducing the number of animals destroyed or slaughtered.

5.2.4 Hurdles to vaccination

However, there will be limits. Any increase in use will be driven principally by disease outbreak, rather than attempts at universal uptake. Although movement of animals within the EU will be a factor, countries that are currently disease-free will wish to maintain that status. Such countries will be reluctant to allow vaccinated animals to enter, given that even when inoculated, they can remain a vector for transmission. For similar reasons, disease-free countries will be unlikely to invest in vaccination programmes. Their disease-free status

may give them a competitive advantage when it comes to exporting; vaccination programmes could compromise this.

However, the overall impact will on balance be positive for vaccination. An existing lack of clarity on responsibilities and definition of veterinary services risked Member States taking divergent interpretations, rendering the attribution of duties incoherent. The AHL should better distribute these duties, coordinate disease surveillance more effectively. This in turn should help clarify the compulsory and voluntary aspects of the rules, thus improving alignment and predictability of the uptake of animal vaccination in the EU.

5.3 Vaccination and environmental impact and greenhouse gases

There are high demands on our animal production to minimize environmental impact such as greenhouse gases and effluent waste. All food has an environmental impact, regardless of the production system, and a sustainable agricultural system must meet food needs while minimizing social, economic and environmental impact. Life Cycle Assessment (LCA) is a standardised approach to evaluate resource use and environmental emissions of a production system or product. LCA has been applied in agriculture to examine the total greenhouse gas (GHG) emissions associated with products such as milk. The US EPA estimates that animal agriculture contribute approximately 9% of total greenhouse gas emissions (EPA, 2017). The FAO estimates total emissions from global livestock as: 7.1 Gigatonnes of CO_2-equiv per year, representing 14.5% of all anthropogenic GHG emissions (FAO, 2017). On commodity-basis, beef and cattle milk are responsible for the most emissions, respectively, contributing 41% and 20% of the sector's overall GHG outputs. However, modern industrialized dairy practices may require fewer resources than dairying in the 1940s with 21% of animals, 23% of feedstuffs, 35% of the water, and only 10% of the land required to produce the same 1 billion kg of milk and a 41% reduced carbon footprint per litre milk (Capper et al., 2009)

Nonetheless, **the beef and dairy industry need to contribute to the goal to be sustainable, which means "meeting the needs of the present without**

compromising the ability of future generations to meet their own needs". Thus, the application of sustainable agricultural practices that maximize efficiency to produce more food with fewer resources is critical. Improving 'produc-tive efficiency' (milk/meat output per resource inputs) is the mechanism by which a dairy or beef herd can mitigate environmental impact. This involves decreasing the maintenance require-ments of the production system, which includes everything from heifer rearing to lactation performance. Improved breeding and animal health interventions to allow herd sizes to shrink (meaning fewer, more productive animals) is thereby one method to reduce GHG. As an example, the daily nutrient requirement of lactating cows comprises nutrients and energy needed for maintenance and nutrients needed for milk production.

Since the maintenance need does not change as production changes, a cow that produces more milk will use less energy per litre milk than a cow that has a lower production (for example, a cow producing 7 kg/day requires 2.2 Mcal/kg of milk, whereas a cow yielding 29 kg/day needs only 1.1 Mcal/kg of milk). **The impact of disease prevention on production efficiency can only be indirectly demonstrated through the evidence that optimal heifer health and growth yields a higher performance lactating cow, and losses due to mortality or early culling are decreased**. Thereby all measures that minimizes sub-clinical and clinical disease will contribute to minimizing the environmental impact and vaccination programs can be seen as one tool for a sustainable more environmentally friendly production.

6. Financial benefits of vaccination

6.1 Impact of disease on performance and productivity

The costs of disease have many times been underestimated or ignored in financial analysis of animal production. The costs of subclinical infection and failure to reach full productive potential are to a large extent ignored. The cost implications of some of the multifactorial diseases in cattle and sheep are poorly documented and not easily quantifiable due to the inability to attribute the performance losses to the exact causes and due to the time lag between disease and productive life. However, more and more studies are calculating the impact of clinical and subclinical disease on future productivity.

> ### The costs of sub-clinical infection and failure to reach full productive potential are to a large extent ignored

Disease is very many times a major factor for suboptimal growth, due to decreased feed intake, decreased feed efficiency and increased metabolic needs for immune functions. The strong impact of preweaning weight gain on future lactation performance has been shown in numerous studies. A metaanalysis of all relevant studies indicated that for every 100 gram extra daily gain preweaning a heifer will produce 155 Kg more milk in the first lactation (Soberon and Van Amburgh, 2013).

> ### For every 100 gram extra daily gain preweaning a heifer will produce 155 Kg more milk in the first lactation

A dynamic programming model of a dairy replacement herd, showed that the average age at first calving affected the net costs of raising replacement heifers; reducing the age at first calving by 1 month lowered the cost of a replacement program of a 100 cow herd by $1400 or 4.3% (Tozer and Heinrichs, 2001). A UK study of the costs associated with heifer rearing estimated that each extra day in age at first calving increased the mean cost of rearing during pregnancy by £0.33/d and an additional month would result in an additional £91.6 (Boulton et al., 2015). The total cost of rearing young dairy cattle in the Netherlands was estimated as 1567€ per successfully reared heifer (Mohd et al., 2012). Reducing the age of first calving by one month reduced the total cost between 2.6% and 5.7%. **The rearing costs of a heifer that experienced disease at least once were on average 95€ higher than those of healthy heifers**.

This section describes some major diseases, quantifies the most recent estimates of the economic impact and when possible, show cost benefit analysis of reducing the level of the major endemic ruminant diseases. These examples do not diminish the importance of other diseases and vaccination programmes such as OIE list A diseases (FMD, Bluetongue), IBR, emerging diseases or other.

6.2 Bovine Viral Diarrhoea (BVD)

The Bovine Viral Diarrhoea virus (BVDV) is a pesti virus that is endemic in cattle populations worldwide and results in substantial losses to the dairy and beef industries (Weldegebriel et al, 2009). The virus can cause various types of disease in the animals. There are two different genotypes of BVDV; BVDV Type 1 and BVDV Type 2. In Europe, the BVDV Type 1 genotype predominates but there have been isolations of BVDV Type 2 in some countries. The most important effect is that it can cause infertility and abortions, affect the unborn calf and lead to mucosal disease (MD). BVD virus can also cause diarrhoea in acute or transient infection which is usually mild but occasionally severe enough to cause death, even in adult cattle. Transient BVDV infection is also

associated with immune suppression and may contribute to the BRD and other diseases.

The main risk of infection comes from persistently infected (PI) cattle. If a naive non-infected cow is infected in her first 110 days of gestation, the calf may be born persistently infected (PI). The dam of a PI calf may test negative and this is important to consider when buying pregnant heifers/cows (Troyan cow). This PI calf is immune-tolerant to BVDV and thus has no antibodies against the virus and it can shed large quantities of virus throughout its life (Coria and McClurkin, 1978). PI animals may go undetected for several years and if PI heifers are bred they will always give birth to PI calves. PI animals may develop a fatal mucosal disease (MD) with bloody diarrhoea, fever and mucosal lesions in the mouth, as well as ulcerations at the muzzle, the nose, the rim of the hoof and in the interdigital cleft. The animals usually die within 3 weeks. Animals that are infected with BVDV after birth are referred to as 'transiently infected' and these usually show no signs of disease and eliminate the virus within a few weeks.

6.2.1.1 BVDV control programs and surveillance

In many countries there are control programmes for BVDV. In some countries non-vaccination approaches have been implemented whereas in other countries there are programs including vaccination strategies (Stahl and Alenius, 2012). There are several vaccines available on the market but vaccination as a stand-alone measure has never been shown to improve the epidemiological situation (Moennig and Becher, 2015) . The key component of a control pro-gramme is removal of PI animals, biosecurity and vaccination of all breeding animals with a vaccine that has been proven to be able to prevent the birth of PI calves (vaccines that include foetal protection in their claims).

A practical approach can be the use of an inactivated BVDV vaccine in combination with a test for antibodies against nonstructural proteins (NS). The vaccine exhibits properties of a marker vaccine where animals usually remain seronegative after vaccination but develop NS specific antibodies after field virus infection. With this approach, a field virus infection with BVDV can be monitored by measurement of NS antibodies in blood or (bulk) milk samples, even in a vaccinated herd.

6.2.1.2 Costs and benefits of prevention and control

The substantial costs of BVD for the industry have been evaluated in numerous studies and countries. A systematic review including 44 studies in 15 countries over the last 30 years indi-cated that direct losses ranged from $0.50 to 688 US dollars (USD) per animal, and average direct losses per naive dairy cow were $25 higher than per beef cow (Richter et al., 2017). The majority of economic assessments had been performed in Europe, and countries recording direct losses were more likely to carry out voluntary or compulsory control and eradication programmes. The studies that included mortality, morbidity, premature culling and/or reinfection in the economic calculation demonstrated higher direct losses and may thereby be more correct estimates of total costs. Immunosuppression and reproductive failure are often neglected in economic analyses and this may lead to underestimated BVDV costs (Gunn et al., 2004).

The UK has performed most cost estimates of BVD globally. Already in 1998, it was estimated (Paton et al., 1998) that 65% of UK herds had encountered the virus and had a detectable antibody titre and 95% of the national herd had been exposed to the virus at some point. In 2003, BVDV was calculated to cost the UK beef and dairy cattle industry approximately £40 million per year placing the disease as the third highest cause of loss after mastitis and lameness (£180m and £54m per year, respectively). The major costs were due to mortality and premature culling (£23 million), and abortion and stillbirth (£12 million), and other under £2 million included other fertility problems, control costs and monitoring costs (Bennett and Ijpelaar, 2003).

The costs of BVD in **beef cow-calf herds** are also high. The cost of a BVD outbreak in a Scottish commercial suckler herd with no immunity to the virus has been estimated at £37 per cow as a result of infertility and abortion alone (Gunn et al., 2004). The costs of BVD were attributed to various reproductive losses (44%), PI heifers and cows (16%), PI calves (19%), abortions (9%), immunosuppression of calves (7%) and congenital defects/growth retardation (5%). These estimates did not include costs of treating disease conditions associated with or resulting from BVD infection, nor the losses associated with reduced growth rates and higher variable costs. Some farmers may treat for these ailments oblivious to the fact that the main cause of them is the BVD virus. Undetected BVD is a massive threat to the performance and financial viability of any herd.

It is clear that BVDV infection has huge financial implications and thereby eradication and control within a herd will result in benefits. **Bovilis® BVD vaccination** has been shown to improve fertility in BVD infected dairy herds (Mawhinney et al., 2005). A study of 3 herds where virus was actively circulating indicated lower rates of insemination per pregnancy, more than doubled conception rate in first service, lower calving to conception rates and overall higher conception rate (Smith et al., 2014). A stochastic model was designed to calculate the cost-effectiveness of biosecurity strategies for BVDV in cow-calf herds. Results indicated that importing pregnant animals and stockers increased the financial risk of BVDV. Strategic testing in combination with vaccination decreased the risk of high-cost outbreaks in most herds.

6.3   Bovine respiratory disease (BRD)

BRD is primarily a multifactorial disease of young and growing cattle. The factors that significantly predispose cattle to BRD include stress related to stocking, moving or mixing cattle, poor ventilation or draughts, sudden climatic changes or extreme heat or cold, mixing various age groups, nutritional deficiencies, colostrum deficiency, and poor feed hygiene. These stresses lead to infection by primary pathogens which cause lung damage and disease. The primary viral pathogens include Bovine Respiratory Syncytial Virus (BRSV), Parainfluenza-3 virus (PI3), and Infectious Bovine Rhinotracheitis (IBR). The viral damage to the lungs paves the wave for various bacterial pathogens, such as *Mannheimia haemolytica, Pasteurella multocida* and *Haemophilus somnus, Arcanobacterium pyogenes, Fusobacterium necrophorum, Histophilus somni* and *Mycoplasma bovis* (dispar, argini, etc.).

BRD can affect cattle of all ages but it is predominantly seen in young cattle. Affected animals are highly infectious and shed large quantities of virus and bacteria through nasal discharge. Symptoms include reduced feed intake, fever, nasal discharge, coughing, strained breathing (pumping), depression and lethargy and possible death.

6.3.1   BRD – health and productivity consequences

Bovine respiratory disease (BRD) is costly to farmers, impacts animal welfare and results in high quantities of antimicrobial use in cattle worldwide (Barrett, 2000). Surveys by USDA

Aphis esti-mate that (BRD) to account for 25% of preweaned dairy heifer calf deaths, and it is the leading cause of death in weaned heifer calves, accounting for 45% of calf death losses. Respiratory disease accounts for 16 % of total beef calf death loss and 6 % of total breeding cattle death loss on cow–calf operations (Callan and Garry, 2002).

BRD is usually the major disease challenge in beef operations and feedlots. It is not only calves with clinical symptoms that are affected by BRD, as shown by a feedlot study in Colorado (Wittum et al., 1996) where 30% of the steers were treated for BRD. There was no mortality, but being treated for clinical disease was associated with a 10 kg reduction in gain as well as the labour and drug costs. However, at slaughter a surprising 70% of the calves that had never shown signs of clinical illness had lung scaring indicating that they had had subclinical pneumonia. These sub-clinically affected calves, representing 50% of the steers, gained 20 kg less than their herd mates without lesions. Numerous other studies document lower average daily gains (ADG) from cattle with lung lesions at packing plants that were not treated for BRD compared with cattle with normal lungs. Data indicate that BRD lowers daily weight gain on average by 91 grams/day, and lowers the carcass grading (Barrett, 2000; Griffin, 2014). These results indicate that preventive measures such as vaccination will benefit the whole herd, and not only decrease the number of clinically sick calves.

There are many productivity consequences of BRD in dairy herds. A study in 18 dairy herds in New York State, USA, indicated that for each additional week of pneumonia in calves reduced total body weight gain during the first 3 months by 0.8 kg (Virtala et al., 1996). In Ireland, pre-weaning growth rates in calves that been reported to decrease 8% for calves experiencing pneumonia, 18% for calves with diarrhoea and 29% for calves with both disease conditions (Magnier, 2014). A Dutch study indicated that BRD in dairy heifers increases the risk of mortality directly after the disease episode by up to 6 times and reduces growth during the first 6 months of life with up to 10 kg (Van der Fels-Klerx HJ et al., 2001). In addition, BRD can increase mortality in later stages of the rearing period, and age and likelihood of dystocia at first calving.

Survival to maturity and age at first calving were studied in heifer calves from 34 Holstein dairy farms in Ontario, Canada.

Heifers that had been treated for pneumonia during the first three months of life were 2.5 times more likely to die after 90 days of age than heifers which had not been treated for pneumonia (Waltner-Toews et al., 1986). A Spanish contract rearing facility found that heifers that experienced 4 or more BRD cases before first calving had 1.9 times greater odds of not completing the first lactation than those that never experienced BRD (Bach, 2011).

The effect of calfhood morbidity on age at first calving was investigated in 948 heifer calves in 21 herds in the vicinity of Cornell University. Heifers without respiratory illness as calves were twice as likely subsequently to calve and calved 6 months earlier when compared to those with respiratory illness as calves (Correa et al., 1988). In an AFBI herd in Ireland, chronic calf pneumonia resulted in a 5% and 10% reduction in first and second lactation milk yield. The association of owner-diagnosed calf diseases with the length of the lactating herd life was evaluated over a ten-year period in 25 New York Holstein dairy herds (Warnick et al., 1995; Warnick et al., 1997). The only factor that seems to influence lactation performance was dullness, and this could likely be linked to sub-clinical respiratory disease. Studies of the impact of calf morbidity on future lactation performance may be biased by the fact that sick heifers may die, be sold or culled early.

6.3.2   BRD – financial consequences

The costs of BRD to the industry are substantial. The costs of respiratory disease to the industry are estimated in the range of £50 to £80 million per year (Potter and Aldridge, 2010). The cost of BRD in dairy heifers has been estimated at £3824-4732/100 calves at risk (Barrett, 2000; Esslemont, 1998). The direct costs in a dairy herd are attributed to; treatment costs, treatment labour and veterinary costs. The longer term costs in animals that recover are seen as; fibrosis, loss of functional lung capacity, reduced weight gain, delayed conception, reduced milk production and earlier culling or premature death. In 2007, the National Disease Infor-mation Services (NADIS) in the UK estimated the cost to be £60 million. In 2016, NADIS has estimated the cost as £30 for a mild case and up to £500 when the afflicted animal dies (Scott, 2016). The average cost of an outbreak from a detailed survey of 12 outbreak cases during 2010 was calculated as a minimum of £43 per ill calf in the herd (Wright, 2012). A target live weight

gain to 6 months – of 0.7kg/day can often be reduced to 0.4kg/day after respiratory infection.

6.3.3   BRD- vaccination benefits

The cost benefit of vaccinating cattle against respiratory disease based on a group of 25 calves would be £1890 based on a cost of disease of £2040 (Wright, 2012). This estimate does not include costs for improved housing or changes to management to reduce the incidence of res-piratory disease. It is cost effective to administer vaccine at housing for young stock where pneumonia is a known risk; however it should not be done in isolation because nutrition, ventilation, stress and stocking densities all play a crucial role in reducing pneumonia.

A study in multiple Dutch white veal farms evaluated the influence of vaccination with Bovilis Bovipast (MSD Animal Health) on antimicrobial use and performance (Vahl et al., 2014). Vaccination with Bovipast significantly reduced (14.5% reduction) the daily treatments with antibiotics and the highest level of reduction was seen in the first 2.5 months on the farms. The Bovilis Bovipast vaccinated animals also had significantly less bromohexine treatments. With increasing emphasis on antibiotic free production, vaccinations are not only cost-effective but also part of a 'prudent use of antibiotics' concept.

6.4   Bovine Enteric Disease

Infectious enteric disease is a primary challenge in preweaned calves. The gut of the calf is developing, as is the immunity and microflora, and during this development phase the gut is more sensitive to pathogenic microbes as well as dietary factors that can cause disease. Infectious diarrhoea remains one of the big health challenges in both the beef and dairy industries. It has been estimated that diarrhoea accounts for more than half of all calf mortality on dairy farms (Gulliksen et al., 2009; NAHMS, 1994), and diarrheal disease may pave the way for other systemic diseases such as respiratory disease.

Infectious enteric disease is nearly always a multifactorial condition. The symptoms of enteric disease include diarrhea, dehydration, depression, weakness, fever or cold extremities,
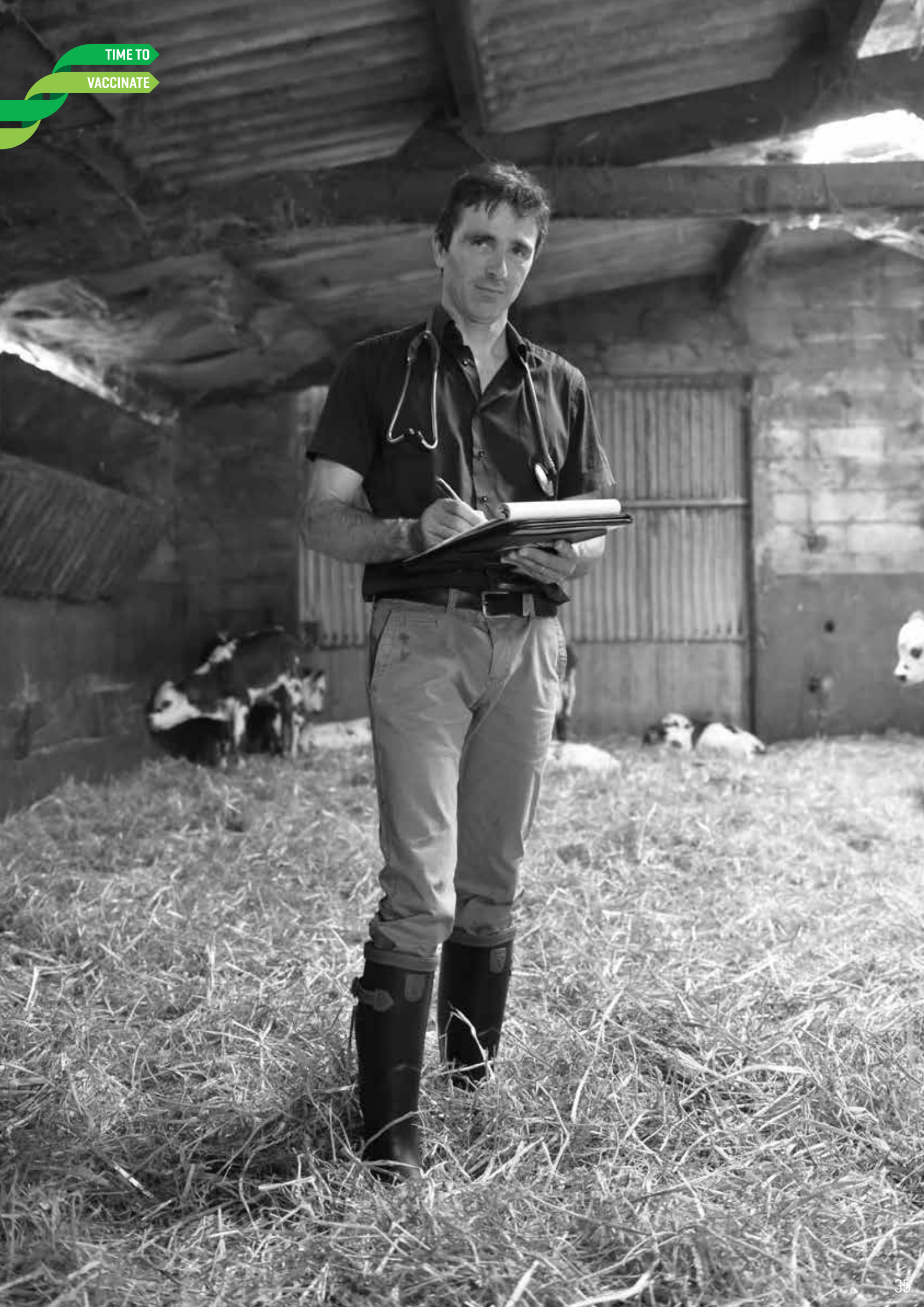
loss of suckle reflex and metabolic acidosis. Therefore in any discussions regarding pathogens involved, the multi-factorial nature of the disease may not be forgotten, and the ability to reduce the exposure of infection with one pathogen, may be critical to maintaining gut health.

Currently, enterotoxigenic *Escherichia coli* (ETEC), *Cryptosporidium parvum*, rotavirus, and corona virus appear to be the most significant infectious causes of neonatal calf diarrhoea. In older and adult cattle Clostridium perfringens (various types) can cause enteric disease with acute morbidity and mortality or more extensive herd level problems.

A Spanish study of diarrhoeic dairy calves under 1 month of age found rotavirus in 42% of calves and concurrent presence of other pathogens was found in many calves (Garcia et al., 2000). In rotavirus positive diarrhoea cases they found that calves had 20.4% for corona virus (20%), 85.2% for *Cryptosporidium* (85%), 16.7% for F5+ *E. coli* (17%). A study in young Dutch dairy calves about the prevalence, prediction and risk factors of enteropathogens in normal and non-normal faeces (Bartels et al., 2010) indicated that *Clostridium perfringens* was found in 54% of diarrhoea calves, *C. parvum*

in 43%, whereas *E. coli* and Corona virus were rarely found. In a study of diarrhoeic dairy calves under 3 weeks of age in Switzerland, the prevalence of *C. parvum* was 55%, rotavirus was 59%, coronavirus was 8% and ETEC was 6%. The main causes of scouring and the incidence on UK beef farms sampled through MSD Scour Check during 2009 were: Rota virus (37%), Corona virus (28%), E. coli (5%), *C. parvum* (30%), and less commonly *Coccidia spp* and *Salmonella spp.*

6.4.1.1 Impact of enteric disease on growth and productivity

Enteric disease in calves is very prevalent and has long term consequences in terms of animal growth rate, future lactation productivity and longevity. Calf diarrhoea has been estimated to be the associated with 53-57% of all calf mortality (Cho and Yoon, 2014). However costs can be five times that figure when calves die as a result of scour (DEFRA, 2008). The cost of an outbreak of scour in suckler calves was estimated in 2008 to be on average £33 per at risk calf (DEFRA, 2008). Growth can be reduced substantially and 60% of the costs of diarrhoea are associated with reduced weight gain. In Ireland, pre-weaning growth rates in calves have been reported to decrease, 18% for calves with diarrhoea and 29% for calves with both diarrhoea and respiratory disease (Magnier, 2014).

Survival to maturity and age at first calving were studied in Canadian Holstein heifers (Waltner-Toews et al., 1986). Heifers that had been treated for scours were 2.5 times more likely to be sold and 2.9 times more likely to calve after 900 days of age than other heifers. In an Agri-Food and Bioscience Institute (AFBI) herd in Ireland, calves that had diarrhoea resulted in a 12 kg reduction in live weight at 18 months, and delays in calving (Morrison et al., 2013). A Swedish study of heifers in 107 dairy herds found that heifers that had contracted mild diarrhoea pre-weaning was associated with an estimated 344 Kg reduction in first lactation 305d milk production (Svensson and Hultgren, 2008). The authors speculated that this was most likely due to reduced growth and possibly association with respiratory diseases.

6.4.2   Costs associated with enteric disease

Since antibiotics are not effective against virus and antimicrobial agents have limited efficacy against cryptosporidium the treatment of enteric diseases in calves with these products is not successful. The use of antibiotics for common enteric disease may even lead to increased enteric disease due to a disturbance in the gut microbiota that may be associate with reduced growth performance (Berge et al., 2009b). Berge calculated that extensive use of antimicrobials for preweaned calf diarrhoea was furthermore associated with an increased treatment cost of $10 dollars per calf. The best way to reduce the impact of these enteric

diseases is through a preventive programme involving good nutrition, management and boosting immunity through vaccinations.

6.4.3   Vaccination against enteric diseases

6.4.3.1 Rota-Corona - *E. coli*

Vaccinations of pregnant dams 12 to 3 weeks (for Rotavec Corona) prior to calving to prevent coronavirus, rotavirus and *E. coli* K99 infections in calves have been shown to be an effective way of decreasing neonatal enteric disease in dairy and beef calves through the increased levels of antibodies in the colostrum. It is important to note that vaccination of dams will only be effective if the colostrum from the vaccinated cows is correctly fed to the calf. In dairies, the colostrum should be hygienically harvested as soon as possible after birth, and 3 to 4 litres directly fed to the calf (at least within 4 hours). The highest quantity IgG (colostrum IgG > 50 g/L) available should be used for first feed and excess good quality colostrum from immunized cows should be frozen for other calves when the dam does not have sufficient high quality colostrum. Furthermore in order to assure good uptake of immunoglobulins in the calf a clean calving environment, hygienic colostrum handling and prevention of hypothermia is important. A colostrum supplementation of the milk or milk replacer during the first few weeks of life can decrease diarrheal disease (Berge et al., 2009a), and

an enhanced immune protection can thereby be provided by using colostrum from Rotavec Corona vaccination of dams before calving.

The total cost of scour outbreak in a 100 cow suckler herd, assuming 90 calves born, has been estimated around £5794 (Wright, 2012) and the benefit for herd when vaccinating with Rotavec Corona has been estimated to be £4225. These estimates did not include changes to husbandry and management to reduce the incidence of scour.

6.4.3.2 Salmonella

Salmonellosis can have a significant impact on health, growth, and production as well as in certain countries trade restrictions and movement restrictions are placed on herds with salmonellosis. In calves, *Salmonella enterica serovar* Dublin is associated with diarrhoea, septicaemia, arthritis, pneumonia, chronic ill thrift and ultimately increased calf mortality. *Salmonella Dublin* triggered abortions is often seen in infected herds and result in significant costs (O'Leary, 2014). The Teagasc (Animal and Grassland, Research and Innovation Centre) in Ireland has estimated that a spring-calving herd of 100 cows can lose over €9400 due to reduced milk yield (6% less milk produced). Vaccinations have been shown to cost-effective to reduce losses due to abortions and production losses (Agriland, 2015).

6.4.3.3 Clostridiosis

Clostridial bacteria are significant pathogens of livestock globally associated with various disease conditions. The bacteria are part of the normal flora of cattle and only become problematic when other stress factors such as dietary changes, injury, management changes, parasitism, or other lead to toxin production by the bacteria. Some of the most common conditions are *enterotoxemia (C. perfringens* type A-D and *C. sordelli*), Malignant oedema/Gas gangrene (*C. novyi* type B, *C. perfringens* type A, *C. septicum, C. chauvoei, C. Sordelli*), tetanus (*C. tetani*), blackleg (*C. chauvoei*), infectious bacillary hemoglobinuria (*C. heamolyticum*). Vaccines containing inactivated organisms as well as toxoids such as Bravoxin 10 provide antigens to 10 types. This vaccine can be used as a general insurance against the most common clostridial diseases and the vaccination programme can be tailored to the herd risk.

6.5   Ovine diseases

6.5.1   Footrot

Footrot is a common cause of lameness in sheep with high economic impact. Footrot is a highly contagious bacterial disease caused by *Dichelobacter nodosus* which infects the interdigital skin and surrounding soft and hard horn of a hoof, often resulting in severe lameness. Lame animals that are in pain spend less time feeding than their healthy counterparts due to increased laying time. Failure to feed adequately will have many effects. This reduced feed intake may lead to suppressed growth in young animals (Nieuwhof et al., 2008), reduced lambs per ewe, metabolic diseases in late pregnancy, and poorer libido and fertility in rams.

Reducing lameness to a minimum requires multiple preventive measures including, genetic selection of sound feet, culling of lame ewes, foot bathing, trimming, biosecurity measures in-cluding quarantining of new arrivals, vaccination and early diagnosis and treatment of lame animals with antibiotics and anti-inflammatory medicines. Studies indicate that foot bathing and trimming results in high costs per flock and parenteral antibiotics then were resulting in better results for the owner (Winter and Green, 2017). Since routine antimicrobial use is not globally responsible, alternatives such as biosecurity and vaccination are advisable.

The cost of lameness has been estimated at £10 per ewe. A five point plan has been de-veloped to reduce footrot problems to a minimum (2%). The five points include bi-annual vaccination, culling badly or repeatedly lame animals, quarantine of incoming animals, treating clini-cal cases early, and minimize infection spread at gathering and handling (AHDB, 2015). Imple-menting a programme to reduce the incidence of footrot from 10% to 2% could have a cost benefit of £4.4 per ewe in the flock.

6.5.2   Abortion – Toxoplasma, Enzootic abortion and Campylobacter

The major infectious agents causing abortions in sheep are *Campylobacter sp, Chlamydia abortus, Toxoplasma sp, Listeria sp, Brucella sp, Salmonella sp*, and border disease virus. The con-sequences of these infections are; more barren ewes, aborted and stillborn lambs, weak non-viable lams or reduced

performance in surviving lambs, and sick ewes post abortion.

The cost of enzootic abortion (*Chlamydia abortus*) and toxoplasmosis in the UK flock was estimated to be £20 million and £12 million respectively (Bennett and Ijpelaar, 2003). These estimates included loss of production, cost of treatment, control and monitoring but did not include the costs associated with human health.

Some farmers believe that abortions are inevitable, and accept an ongoing low level of abor-tion (e.g. 2 to 5% of ewes). However, non-infectious abortion is likely to affect less than 1% of well managed ewes. Some farmers mitigate the losses from infectious abortion by purchasing spare lambs from other farmers to foster on to ewes that have had non-viable lambs. This practice risks introducing other diseases into the flock, and may mask the losses from abortions and stillbirths.

The cost of an abortion outbreak in a 500 ewe flock if 50 ewes were affected would amount to a loss of £6080.

These calculations assume that the ewe is kept rather than culled (if ewes abort with Toxoplasma or Campylobacter there is no need to cull since they develop immunity to the disease but with enzootic abortion culling would be advised and costs would be higher). Increased flock biosecurity could significantly reduce the losses from these diseases. Enzootic abortion is most commonly introduced to a flock with purchased ewes, so it is advised that farmers keep purchased replacements separate from the main flock until after lambing - even if they have been vaccinated.

There are very effective vaccines available for enzootic abortion and toxoplasmosis. There are two vaccines available for enzootic abortion (Enzovax) and one vaccine available for Toxoplasma (Toxovax). Spending £6.50 per replacement can avoid losses of £12.16 per ewe in the flock. On most farms, a ewe will only need to be vaccinated with the two different abortion vaccines (Toxovax and Enzovax) once in her productive lifetime. In an enzootic abortion storm, some farmers choose to inject breeding ewes with

an oxytetracycline antibiotic to reduce the severity of the outbreak. This is an effective control method in the face of an outbreak of enzootic abortion but should not be used as a replacement for vaccination.

6.5.3   Clostridiosis

Clostridial diseases are a serious threat in sheep farming and many times associated with acute disease and death. The bacteria are naturally found in the animal environment and gut, and during times of dietary stress or injury the growth conditions for the various species can become favourable and result in the production of extremely potent toxins that are many times lethal. Parasites such as liver flukes can predispose to. All cases of clostridial disease are fatal despite treatment, except for a small percentage of cases with early treatment of malignant oedema and blackleg. The

costs associated with the disease are mainly associated with mortality. Clostridiosis can result in 50% mortality of lambs and sheep on a farm. A good vaccination program with multivalent clostridial vaccines can greatly reduce production losses associated with clostridial disease.

The reference lists shows all references used in **Whitepaper: 'The importance of preventive health and vaccination programs in ruminant production '**.

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