Optimising herd-vaccination programmes: timing is key

Isabelle Truyers DVM DipECBHM, area veterinary manager, Zoetis, discusses basic principles of bovine immunology and vaccinology as well as factors impacting on the immune system function of periparturient cows that can affect the optimal timing for vaccination

With expansion and further intensification of production in the Irish dairy industry, it is inevitable that risks associated with livestock diseases such as infectious bovine rhinotracheitis (IBR), Johne's disease, Salmonella and leptospirosis, for example, will be exacerbated. This expansion, often in combination with tighter calving patterns, has not only increased milk output and improved productivity, but also contributed to an acute shortage of farm workers in Ireland. This could have consequences for the sustainability of our farming systems, the safety of the food chain and human health. In this context, it is important that, as gatekeepers of livestock health, bovine practitioners understand how various animal factors, such as nutritional status, stress and co-existing disease can impact on immune-system function and an animal's response to disease and vaccination. Nowadays, controlling livestock diseases through vaccination forms an integral part of herd-health management and, when used in conjunction with other management tools, vaccines can both reduce the risk and the impact of disease in cattle herds. However, when it comes to ensuring good immunity, timing can be critically important to helping guarantee optimal efficacy of vaccination strategies.

UNDERSTANDING THE IMMUNE RESPONSE TO VACCINATION

Immune response can be defined as 'all phenomena that result from the specific interaction of cells of the immune system with antigen'. Lymphocytes are the basic components of the immune system involved in response to vaccination and the immune system's organs are all of those which produce or contain lymphocytes (Wilkie, 1974).
Thymus and bone marrow are primary organs that have a controlling or regulatory function.

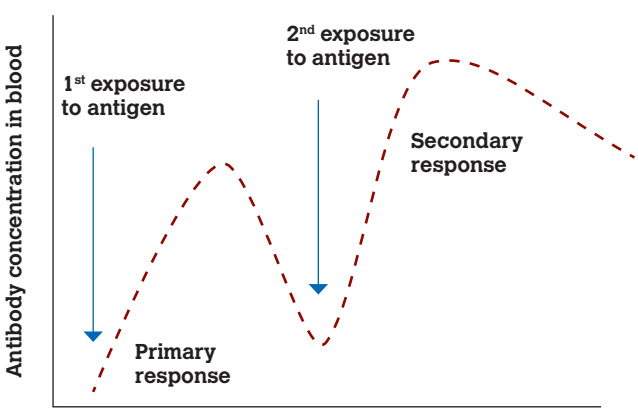

Figure 1. Correlation of antibody titres to the various phases of the vaccine response.

The spleen and lymph nodes are the principle secondary organs but individual lymphocytes or lymph follicles in any tissue can function in immune response. The relationship between primary and secondary organs is one of conditioning uncommitted lymphocytes within primary organs for export to secondary organs as immunologically functional cells.
In general:

- Bone marrow-dependant B-lymphocytes generate humoral immune responses. B-lymphocytes, upon interaction with antigen, proliferate and differentiate morphologically to become memory B cells or antibody-producing plasma cells.
- Thymic derived T-lymphocytes function in cellular immune responses. Cellular immunity involves the activation of antigen-specific cytotoxic T-lymphocytes, phagocytes and the release of various cytokines in response to an antigen.
- In summary, the immune system responds to antigen in two ways and most vaccines trigger both B and T cell responses. The presence of antibodies can be detected by classic serological reactions; however cellular immune response is not so readily assayed but is also of primary importance.

THE HUMORAL IMMUNE RESPONSE OF CATTLE

When stimulated parenterally by a suitable amount of antigenic material, ie. a vaccine, the humoral immune response or antibody synthesis proceeds after a lag period. Antibodies can be detected in the serum of cattle and titres continue to rise, often to reach peak at four to five weeks following administration of the vaccine (primary response). After this, titres gradually decline to baseline levels if antigenic stimulation is terminated. However, a second injection of antigens results in further antibody synthesis following a shortened lag period and a higher maximum titre is attained more quickly and for a greater duration (secondary response) than following the primary response (see Figure 1). The secondary response is a manifestation of immunological memory. *Note that this generic pattern may not apply to live vaccines often triggering long-term antibodies for extended periods of time (Siegrist, 2008).*
The magnitude of vaccine antibody responses is modulated by numerous determinants such as the nature of the vaccine antigen and its intrinsic immunogenicity, the use of an optimal dose of vaccine antigen (experimentally determined), route of administration, the presence of a vaccine adjuvant and the immune competence of the host

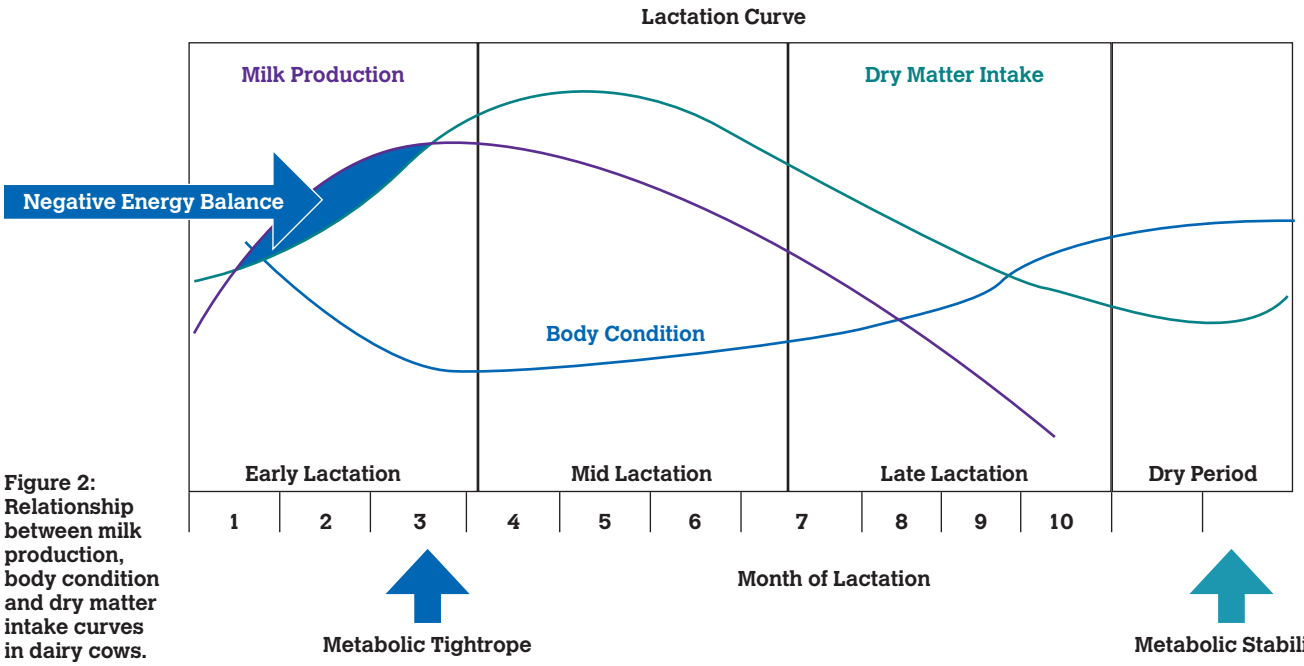

Figure 2: Relationship between milk production, body condition and dry matter intake curves in dairy cows.

(Siegrist, 2008).

THE CELLULAR IMMUNE RESPONSE OF CATTLE

The tendency is often to relate efficacy of immunisation to the presence of serum antibodies however, there is more to protective immunity than the peak of vaccine-induced antibody titres. Cellular or T-cell vaccine responses are elicited in parallel to humoral or B-cell responses.

Naïve T cells convert into activated effector T cells after encountering antigen-presenting cells (such as dendritic cells, macrophages and B cells in some circumstances). Activated effector T cells fall into three functional classes:

- Antigen-specific cytotoxic T cells – kill infected target cells such as virus-infected cells and cells with intracellular bacteria by apoptosis (without using cytokines)
- Th1 cells – produce interfereon (IFN)-alpha and tumour necorsis factor (TNF)-alpha, participating in the elimination of intracellular pathogens both directly (cytokine responses) and indirectly via their support to macrophage activation, enabling them to destroy pathogens, and induce B cells to produce strongly opsonising antibodies
- Th2 cells – primarily function to stimulate B cells to produce various antibody isotypes
- The activation of naïve T cells in response to antigen, and their subsequent proliferation and differentiation, constitutes a primary immune response. At the same time as providing effector T cells, this response generates immunological memory in the form of memory T cells that protect from subsequent challenge by the same pathogen. Memory T cells are long-lived cells that give an accelerated response to antigen and require activation by antigen-presenting cells with co-stimulatory activity in order to regenerate effector T cells.

Vaccine-mediated immunity is often multifactorial and the best protection is likely to be elicited by the combination of strong humoral and cellular immune responses. Protective immunity provided by the most successful vaccines will likely be a combination of residual persisting antibody, production of increased (local and systemic) levels of antibody by memory B cells, and active immune-surveillance for infected cells by rapidly proliferating T cells. The relative contributions of these different immune-cell subsets are context-dependent and vary depending on the attributes of the vaccine (ie. live/attenuated, inactivated) as well as the biology of the pathogen in question (Siegrist, 2008).

TRANSITION PERIOD OF COW-IMMUNE FUNCTIONS

The periparturient or transition period, defined as the period from three weeks pre- to three weeks postpartum, is marked by several changes in the immune system function of dairy cows as a consequence of the physiological demands of colostrogenesis, parturition and lactogenesis. It is a well-documented fact that dairy cattle suffer from suboptimal immune responses during this period. The combined effects of multiple stressors incurred as a result of nutritional deficiencies, calving and transition to the milking herd can both increase and prolong the magnitude of this immunosuppression, further increasing susceptibility to disease and negatively impacting on the animal's ability to overcome disease and recover (Aleri et al, 2016).

NUTRITIONAL STATUS

Negative energy balance (NEB) is regularly observed in dairy cows after calving because the energy from dietary sources does not meet the energy demands of lactation (see Figure 2). The pro-inflammatory and inhibitory effects as a consequence of the accumulation of non-esterified fatty acids (NEFA) are well-documented. High concentrations of circulating NEFA have been shown to negatively impact on appetite stimulation in the brain and are linked to elevated concentration of circulating glucocorticoids stimulating the release of other pro-inflammatory mediators which inhibit immune function (Aleri et al, 2016). Therefore, cows that

lose a significant amount of body condition in early lactation due to NEB will have a decreased ability to respond to an infectious disease or vaccination. The immune system of the periparturient cow is also sensitive to inadequate dietary vitamin E, selenium, and trace minerals, such as zinc and copper (Goff, 2008).

STRESS

The act of calving is a 'stressful event' for dairy cows and induces the production of glucocorticoids, mainly cortisol. Circulating cortisol levels influence immune responsiveness by directly inhibiting T-cell proliferation, T-cell development, modifying the action of complement molecules and by interfering with antibody function. In addition, circulating glucocorticoids also reduce the surveillance activity and immune response capacity of neutrophils (Aleri et al., 2016). Aside from calving, a number of other activities that take place in the transition period, like moving and regrouping, can also increase cortisol levels. Stress, and consequentially, changes in circulating cortisol levels around calving are therefore thought to play a critical role in the development of immunosuppression (Aleri et al, 2016).

CO-EXISTING DISEASE

Metabolic diseases, such as milk fever and ketosis, exacerbate immunosuppression in the periparturient period; often resulting in close to 60-80% loss of immune function. Several other so-called metabolic disorders, such as retained placenta and metritis, may actually be manifestations of a poorly functioning immune system. Preventing milk fever and ketosis can help prevent major loss of immune function and, therefore, reduce incidence of diseases, such as retained placenta, that occur secondary to a poorly functioning immune system (Goff, 2008).In a study by Santos et al (2010), only 55.8% of 5,719 dairy cows evaluated were considered healthy and did not develop disease in the first 60 days postpartum. Incidence of diseases was high with 14.6% calving-related problems, 16.1% metritis, 20.8% clinical endometritis, 21.0% fever, 12.2% mastitis, 10.4% ketosis, 6.8% lameness, 2.8% digestive problems and 2.0% pneumonia. In addition, 27.0% of the cows were diagnosed with a single-disease event, whereas, 17.2% had at least two disease events in the first two months of lactation. One of the consequences of disease is that cows have reduced appetite and lose more body condition, further enhancing NEB and its impact on immune system function.

CHALLENGING THE STATUS QUO

Traditionally, vaccines against bovine diseases such as IBR and Leptospirosis are often administered in spring when most cows are in early lactation. This was recommended because either IBR vaccines with a six-month dosing interval were being used or because this was indicated on the vaccine's datasheet. However, one has to question whether those cows, which are most at risk of peripartum disease due to their immunosuppressed state, are likely to respond most optimally to vaccination? True efficacy data on vaccination of cows during a period of immunosuppression are lacking but in a study by Walz et al (2015), which compared the effect of revaccination with either live or inactivated multivalent viral vaccines on reproductive performance in primiparous dairy cows in early lactation, it was noted that response, as defined by increases in virus-specific antibody titres, could be considered less than ideal.

In addition, around half of the annual workload in Irish seasonal calving herds is carried out during the three months of busy spring activity. With calving, calf-care and cow condition as priorities, it makes sense to have a rethink about other work traditionally carried out at this time of year, if at all possible. Recent data on vaccine sales suggests that over 70% of vaccines for breeding cows in Ireland are used between February and April. With progressive developments in research and vaccine effectiveness, it is now possible to switch to more flexible yearly-vaccination programmes to prevent some of the common infectious diseases of cattle in Ireland. Take IBR for example; we now know that herds can also be fully protected against IBR with the use of the simple yearly Rispoval IBR vaccination programme. Using this proven yearly IBR programme not only reduces the amount of time and effort required to vaccinate the herd but the yearly booster vaccination can also be carried out at a different time of year (ie. winter) when there aren't the metabolic demands of lactation imposing a strain on cows' immune systems. It is now also possible to boost cows against leptospirosis at any time of year; it doesn't have to be done in the spring as Spirovac has no timing restriction and can be given any time of year.

CONCLUSION

With increasing demands on cows and labour shortages in the Irish dairy industry, farm animal practitioners can play a pivotal role in reducing the pressure on our farming systems by reconsidering the timing of herd vaccination programmes. Simple yearly Rispoval IBR vaccination and Spirovac for the control of leptospirosis offer greater flexibility without compromising on efficacy.

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