Effective Immunization of Cattle

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Vaccinology has changed significantly since many of the vaccines we have today for all animals including cattle were originally developed. Our understanding of the immune system has improved and expanded so now many aspects of immunology can be explained at the cellular and molecular level. Additionally, major discoveries have been made in the areas of cell and molecular biology, bacteriology, and virology which provide greater insight into the nature of the organisms against which vaccines are designed. Veterinary vaccinologists only recently have begun to take advantage of many of the advances made in the basic sciences. Transferring and applying the new scientific knowledge from modern biology to vaccinology has been slow and difficult because vaccinology, like most of medicine, remains as much an art as a science. Vaccinology tends to be driven more by tradition and current wisdom than by scientific principles. It is a discipline that since its beginnings more than 200 years ago, has prospered through empiric approaches both for human and veterinary vaccines. The early success in the development of vaccines to control many diseases that once caused significant morbidity and mortality clearly demonstrated that an understanding of immunology or any other basic science was not a prerequisite for a vaccine to be successful. However, those successes were for diseases that are easily and effectively controlled by the immune system. Unfortunately, the diseases that remain, present significant challenges to vaccinologists, since the empiric methods of the past will not work. The diseases that remain are complex and not easily controlled by the immune system. To produce the vaccines for the future and to design better delivery systems a better understanding of basic immunology as well as a better understanding and utilization of certain advances made in molecular and cell biology, genetics, biochemistry, microbiology and parasitology will be required. Perhaps equally important for modern vaccinologists to understand and consider will be subjects like economics, epidemiology, public health, management practices, animal husbandry and animal (including human) behavior, if new and improved vaccines are to be developed for the diseases which continue to cause significant problems. The diseases not only include those caused by viruses and bacteria, but also parasitic diseases. Development of highly effective and safe vaccines based on all of the best scientific information available will achieve little or nothing if the vaccines are not used appropriately.

Thus the challenges for vaccinologists into the 21st century will be to develop vaccines that are: 1) truly needed, 2) as safe as possible, to avoid immediate or future health problems for the vaccinees and non-vaccinated contacts, 3) effective in preventing disease in the vaccinees and possibly effective in reducing the threat of disease for non-vaccinated individuals, 4) cost effective (e.g. do not cause production losses that are greater than the savings expected from the vaccine) and, 5) stable and easily administered, so they readily reach the target population that will benefit by receiving them.

The Immune System

An understanding of the immune system provides a basis for understanding the nature of vaccine immunity. Two major types of immunity prevent or limit infectious diseases. The two types are: 1) non-specific or innate immunity and 2) specific or adaptive immunity. Adaptive immunity is characterized by specificity and memory and it is adaptive immunity which is primarily or exclusively stimulated when an animal receives a vaccine. Ironically, in nature, it is innate or non-specific immunity that prevents a majority of the pathogens from infecting and/or causing disease in animals. Innate immunity is important because it is the first line of defense and is immediately activated in response to inherent or elaborated chemical substances of the infectious agent. Although current vaccines rarely

have a significant beneficial effect on innate immunity, immunomodulators (non-specific immune stimulants) and some new experimental vaccines and drugs are being targeted toward enhanced innate immunity as a nonspecific method for disease prevention. As will be readily evident from future discussions, certain of these innate factors also play a role in specific immune responses. Notable among the soluble factors playing an important role in both systems are the interferons (IFNs), certain of the other cytokines (e.g. IL-1, TNF) and complement components. Cells involved in both innate and adaptive (specific) immunity are, to a limited extent, neutrophils and natural killer cells, and more critically, monocytes and macrophages.

The development of the specific immune system has been defined for several mammalian species. In cattle the genetic information for an adaptive immune system is present in the fertilized egg and within days the developing embryo has hematopoietic stem cells in its yolk sac. By the end of the first month of gestation, hematopoiesis occurs in the fetal liver. The pluripotent stem cells in the liver are capable of eventually differentiating into mast cells, basophils, megakaryocytes, erythrocytes, eosinophils, neutrophils and monocytes, and critical for the development of the adaptive immune system, they differentiate into the various types of lymphocytes. Early in the second month of gestation lymphoid stem cells migrate from the liver to the developing bone marrow and certain cells migrate to the thymus for further maturation. Shortly after the bone marrow becomes populated with the lymphoid stem cells, the bone marrow becomes the main source of future lymphoid cells that migrate to the thymus. The B lymphocytes mature in the bone marrow under the influence of the stromal reticular cells and the T cells mature and are educated in the thymus. "Education" refers to the immune system's cell-based discrimination between self and non-self. In the thymus, most T cells with anti-self specificity are eliminated or suppressed so that an immune response does not develop to self antigen because an immune response directed toward self antigen can lead to autoimmune disease. Those T cells responsive to foreign antigens that provide cell mediated immunity (T cytotoxic cells and T helper[1] effector cells), those that regulate (Tr) or suppress (Ts) the immune response and those that provide help for B cells (T helper[2] cells) leave the thymus to populate the peripheral lymphoid tissues. In addition to B cell maturation in the bone marrow, the Peyer's Patches are the site of B cell development for mucosal humoral immunity. The B cells that migrate to mucosal sites from the Peyer's Patches produce primarily IgA that is secreted onto mucosal surfaces. Bone marrow, thymus and Peyer's Patches are referred to as central, or primary lymphoid tissues. However, these are not the sites where the lymphocytes encounter antigens. Instead, the primary lymphoid tissues are connected through blood and lymphatic channels to lymph nodes, spleen and lymphoid tissue found in the skin and at mucosal surfaces primarily of the gut, lung, and genital tract. These peripheral, or secondary lymphoid organs, are the sites where lymphocytes meet antigen. The mature, immunocompetent, but antigen naive cells are continually seeded from the primary lymphoid organs to secondary organs where they encounter antigens and perform their specific effector functions. By the 6th to 7th month of gestation the adaptive systemic immune system is well developed in the bovine fetus. However, the mucosal system lags behind, not maturing until just before or just after birth. However, for a few days to a few weeks after birth depending on the way the calf is handled (e.g. kept on the cow or moved to a hutch on farm vs. transported to sales barn, sold and placed in new environment) the immune system is significantly suppressed primarily by stress related hormones, especially cortisol.

By 2 to 4 weeks of age, the adaptive immune system should have recovered from these transient periods of immunosuppression, and if passively acquired maternal antibody (PAMA) is not present to interfere with active vaccine immunity, most calves should be able to develop immune responses to many of the vaccine antigens and the important epitopes on the antigens. However, most calves will have PAMA to many of the vaccine components, thus the vaccine will not immunize to provide protective immunity. To ensure the vaccine is given at an age when PAMA no longer interferes, it is necessary to vaccinate at 3 months of age or older. To help ensure an optimal immune response to those components of a multi-component vaccine that are of greatest concern for the young animal, vaccines with a limited number of components are recommended first followed with more complex vaccines. Then a few weeks later follow with vaccines containing additional components instead of trying to vaccinate for everything at one time. Between 3 to 6 months of age, the bovine immune system is fully functional, interference by maternal antibody has disappeared, and the immune system should remain at optimal levels for many years.

The antigen specific defense mechanisms, such as those triggered by vaccines or pathogens are dependent on the T and B cells found in the peripheral lymphoid tissues. Initiation of an adaptive immune response requires antigen presentation by special cell types called antigen presenting cells (APC's) of antigenic determinants (epitopes) to T and B cells with receptors that are antigen epitope specific. With an understanding of the development of the immune system and how it functions in a vaccination program can be developed that hopefully will provide the best protection from specific diseases.

Therefore, questions that should be asked when designing a bovine vaccination program to get optimal immunity would include the following:

1. What is the earliest age to vaccinate?
2. How often should the first series of vaccinations be administered?
3. Which vaccines are necessary?
4. What type of vaccine should be used?
5. What route of vaccination is most effective?
6. How often does the animal need to be revaccinated after the primary series of vaccines?
7. What is the efficacy of current vaccines against challenge?
8. What are the risks of the vaccine causing economic loss?
9. Are vaccines being used that aren't needed?
10. What can we expect in the future?

Each of these questions will be addressed in the presentation.

Abstracts

Prognostic indicators for toxic mastitis in dairy cows

M. J. Green, P. J. Cripps, L. E. Green
Veterinary Record (1998) **143**, 127-130

During a three-year study, 54 cows with toxic mastitis were examined and a number of clinical and laboratory measurements were taken. Twenty-five (46.3 per cent) of the cows died, and in comparison with those which survived, they had a significantly higher packed cell volume (PCV) ($P<0.01$), longer eyelid skin tent time ($P<0.01$) and lower rectal temperature ($P<0.01$). In a model designed to predict the probability of survival, these variables correctly predicted survival in 84 per cent of cases and death in 73 per cent of cases. The cows with toxic mastitis had a significantly higher PCV than a normal cohort of cows sampled at the end of the study.

Cattle-to-cattle transmission of *Mycobacterium bovis*

E. Costello, M. L. Doherty, M. L. Monaghan, F. C. Quigley, & P. F. O'Reilly
Veterinary Journal (1998) **155**, 245

Twenty steers which were positive to the single intradermal comparative tuberculin test were divided into 10 groups of two, and each pair was housed in an individual loose-box for a year with one steer which was negative in the tuberculin test. Five of the groups were fed a restricted diet for part of the time. All the cattle were then slaughtered and examined postmortem. Four of the in-contact animals became infected; one had a tubercle on a retropharyngeal lymph node, and *M bovis* was isolated from the other three from lymph nodes which showed no visible lesions. Two of the latter animals showed no detectable cell-mediated immune response. There was no indication that the dietary restriction had any effect on the transmission of the disease.