General Session II

"Infectious Disease: Old Problems, New Approaches"

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Bovine Vaccines: Which work best and what's new or coming?

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A vaccine can be defined as an attenuated microorganism, a killed microorganism, or a part or product of a microorganism which is administered to an animal for the prevention, amelioration or treatment of an infectious disease. There are a wide variety of vaccines available to the bovine practitioner for use in cattle, and therefore selecting the most appropriate vaccines for a particular situation can be difficult.

The effectiveness and suitability of a vaccine depends upon the nature of the immune response it generates and on the role that the immune system may play in preventing or regulating the infectious process of a particualr microorganism.

The basic steps involved in the infectious process of any microorganism include: 1) Exposure to the host followed by attachment or absorption of the microorganism to the host tissue, 2) Penetration and/or replication of the microbe at this site of entry, and 3) Spread of the microbe to other sites with tissue destruction and/or toxin production. During steps 2 and 3, shedding of the infectious agents usually occurs with subsequent spread to other susceptible animals.

A protective immune response can interfere with any of these three steps, but clearly the ideal vaccine would consistently induce a life-long immune response that would inhibit the initial infectious step, attachment or absorption. Unfortunately, there are no vaccines currently on the market which uniformly accomplish this. That is, vaccines do not always protect an animal from infection of a microorganism. Rather, vaccines usually protect the animal from spread of the agent after an infection has occurred, or they protect from the clinical disease caused by the microbe.

The immune response can be divided into the humoral (antibody) or cellular (lymphocyte) system. The humoral system can be further divided into a local and a systemic response to a microbe. These responses differ in the predominant class of antibody produced. In catte, IgA and IgG_1 classes of antibodies characterize local immune responses on mucous membranes, while IgM and IgG antibodies predominate in a systemic immune response. Cellular immunity, on the other hand, can be divided into 1) lymphocytes that produce factors called lymphokines that assist other cells, including white blood cells, such as macrophages in the elimination of pathogens, or 2) lymphocytes that can kill altered cells, such as virally infected cells. These antigen-specific killer cells are called T cytotoxic lymphocytes (Tctl). Different types of vaccines will stimulate the immune system somewhat differently. The nature of the vaccine will determine what aspects of the immune response are stimulated.

Vaccines can be divided into three general types; those that are composed of a live microorganism (such as attenuated strains of virus or genetically engineered virus), those made up of a killed microbe usually treated chemically, or those made up of a portion or subunit of the microbe (such as the hemagglutinin molecule of influenza). Killed and subunit vaccines are generally administered IM, and induce an immune response that is less broad, and many times shorter in duration than the response normally seen following exposure to a replicating organism. These vaccines generate good levels of antibody circulating systemically, but they do not stimulate Tctl production, nor do they effectively stimulate the mucosal immune system. In contrast, live viral vaccines, but not live bacterial vaccines, can induce Tctl immunity. Although Tctl activity is an important protective immune mechanism in some viral infections such as BHV-1, it may not be important in other viral infections, such as bovine respiratory syncitial virus, and these cells play no role in protective immunity to bacteria or their toxins.

Table 1 lists some bovine pathogens and indicates the

protective immune response to the pathogens. When both antibody and Tctl activity function in protection, it is not to be implied that both are absolutely required for protection. Rather, it should be viewed that both aspects function together in protection from the microorganism.

Table 1. The protective immune response to assorted bovine pathogens

Microbe	Antibody	Lymphokine producing lymphocytes	Tctl
BVD	X		
IBR (BHV-1)	X		X
PI-3	X		
BRSV	X		?
Pasteurella	X		
Leptospirosis	X		
Hemophilus	X	X	
Mycobacteria (Johnes)		X	

There are a variety of factors (aside from safety and economic issues) of a pathogen and the corresponding immunity that are important to consider in the selection of an effective vaccine. Table 2 lists some of these factors.

Table 2. Factors in vaccine selection

1. Are the protective antigens in the vaccine capable of stimulating protective immunity?
2. Does the vaccine protect against most or all variants of a particular pathogen?
3. What is the duration of the immunity?

Protective antigens- Immunity to a given pathogen is the key to protection. A significant consideration in evaluating a vaccine is whether the immunity induced by the vaccine is directed to protective antigens. For example, the important protective antigens for BHV-1 are the surface glycoproteins. These molecules are responsible for attachment of the virus to epithelial cells, a requirement for infection. A vaccine that would fail to induce a response to these glycoproteins, but would cause a high level of immunity to other BHV-1 proteins would not protect cattle against the virus. Similarly, an immune response against a bacterial toxin may be much more important for protection against disease than a strong immune response to the structural proteins of the organism itself. This is commonly recognized when one thinks about human and animal vaccines for tetanus, where the immunogen is an attenuated toxin (rather than C. tetani). It may be evident, then, that knowledge about protective antigens are necessary for effective vaccine development. This knowledge is especially important when parts of a microbe are used as the vaccine rather than the entire agent. However, even when the entire organism is used as the vaccine, the protective antigen may be present in too low a concentration for effective immunization, or the antigen may be in an altered state as a consequence of chemical inactivation procedures so that the response is not adequate.

Protection against variant microorganisms- Another vaccine concern is whether the vaccine can protect against the variants of a given pathogen that are present in a given locale. For example, it is now established that there are multiple BVDV serotypes. Vaccination of cattle with one serotype can induce protection against that particular serotype. However, this protection is limited for other BVDV serotypes. Therefore, for this virus, and many other microorganisms, the vaccine should induce a broad enough immunity to protect against the various variants.

Duration of immunity- Some viral vaccines are capable of inducing very long-lived, if not permanent immunity. For example, live polio virus vaccine can produce an immunity of very long duration in human beings.

In contrast, some vaccines, especially subunit vaccines, induce immunity that is much shorter in duration. An example of this is the immunity produced by tetanus-toxoid. The exact mechanism for this difference is poorly understood. Fortunately, in the case of some pathogens, it may not be necessary to induce permanent immunity to benefit from vaccination. When disease is primarily one of age dependence, such as Corona virus, or if the life span of the animal is short, as with veal calves, permanent immunity would not be required. Immunity to bacteria or their toxins are of short duration (months) and therefore, these vaccines will require revaccination to maintain protective levels of immunity.

Future Vaccines- Traditional live attenuated and killed vaccines have been effective over the last several decades in moderating the severity of many diseases in cattle, and in limiting the economic losses to farmers that result from many of these diseases. However, these vaccines do not prevent the initial infection of cattle, or the spread of the infectious agent throughout the cattle population. The techniques of molecular biology have allowed us to identify not only the individual molecules that make up a virus or bacteria, but to identify discrete portions on each molecule, called epitopes, that are the targets of the immune response. This knowledge has led to some very creative strategies that are now pursued in the design of more effective vaccines. It is known for example, that BHV-1 has three glycoproteins on its outermost surface that are the primary targets of the bovine immune response. Antibodies directed against epitopes on these molecules can completely neutralize the infectivity of the virus in laboratory assays. The genes for each of these glycoproteins have been molecularly engineered into bovine cells and large

quantities of purified BHV-1 glycoprotein can be produced to be used as subunit vaccines. This vaccination strategy will eliminate the need to expose cattle to live BHV-1 and can be manipulated to allow distinction between a vaccinated and an infected animal; a useful feature in following the spread of disease in a region or in confirming that an animal is disease free. Another strategy for BHV-1 vaccination is the creation of a strong immune response on the mucosal surfaces. BHV-1 normally enters cattle via the nasal or vaginal membranes. BHV-1 glycoproteins could be used in such a way as to preferentially induce a strong local immune response in the nasal mucosa. Secretions present on these surfaces following vaccination contain antibody specific for BHV-1, and the virus could be neutralized before it has a chance to infect the epithelial cells that are coated by these secretions. This approach to vaccination could prevent infection of individual animals and most importantly interrupt the cycle of spread of the virus to other animals.

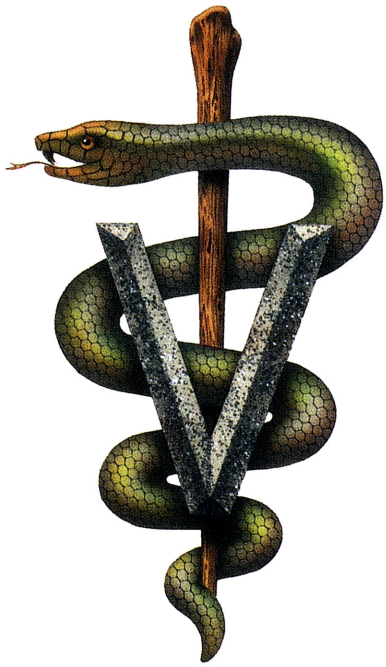
Vaccines of the future also may include the use of novel fusion proteins created by genetic engineering techniques. These are small portions of one virus or bacteria (usually the protective epitopes) chemically joined with portions of molecules from other viruses or bacteria to form a hybrid string of protective epitopes. These may be further joined to a "binding molecule", usually a piece of a toxin that is responsible for docking on to the surface of cells. Such vaccines would be capable of directing a highly specific, efficient immune response to multiple pathogens and could be incorporated into a replicating vehicle, such as adenovirus or vaccinia virus, to enhance the stimulation of cell-mediated immune response.

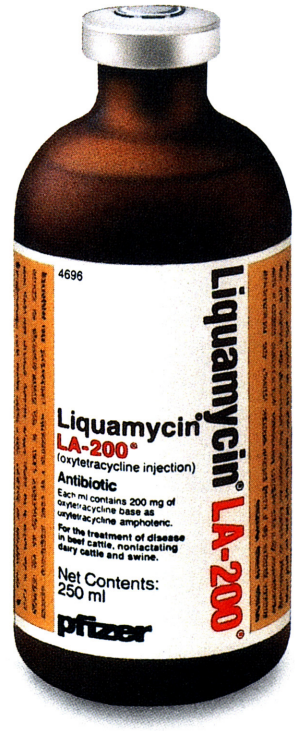
Many other novel approaches to vaccination are being proposed and tested and the references listed at the end of this article should provide the interested reader with a sampling of these diverse and unique strategies.

The past two decades of intensive research into the molecular structure of viruses and bacteria, and the nature of the immune response to them now provide the basis for creative intelligent design of more effective vaccines against the common pathogens of cattle.

References

1. Arnon, R. (1985). Synthetic peptide vaccines. *Immunochemistry of Viruses. The Basis for Serodiagnosis and Vaccines:* 139-151. 2. Belsham, G.L., E.C. Anderson, P.K. Murray, J. Anderson, T. Barret (1989). Immune response and protection of cattle and pigs generated by a vaccinia virus recombinant expressing the F protein of rinderpest virus. Veterinary Record 124: 655-658. 3. Chase, C.C.L., B.A. Israel, K. Carter-Allen, and G.J. Letchworth III (1988). Expression and affinity purification of recombinant bovine herpesvirus 1 glycoproteins. J. Tissue Culture Methods 11: 75-81. 4. Etlinger H.M., D. Gillessen, H.-W. Lahm, H. Matile, H.-J. Schonfeld, A. Trzeciak (1990). Use of prior vaccinations for the development of new vaccines. Science 249: 423-425. 5. Israel, B.A., R.L. Marshall and G.J. Letchworth III (1988). Epitope specificity and protective efficacy of the bovine immune response to bovine herpesvirus 1 glycoprotein vaccines. Vaccine 6: 349-356. 6. Issacson, R. (1985). Development of vaccines for bacterial diseases using recombinant DNA technology. Avian Diseases 30: 28-36. 7. Mosier, D.A., A.W. Confer, R.J. Panciera (1989). The evolution of vaccines for bovine pneumonic pasteurellosis. Research in Veterinary Science 47: 1-10. 8. Obijeski J. (1985). Vaccines produced by recombinant DNA technology. Veterinary Viral Diseases:142-148. 9. Radostits, O.M., I.R. Littlejohns (1988). New concepts in the pathogenesis, diagnosis and control of diseases caused by the bovine viral diarrhea virus. Journal Canadian Veterinarian 29: 513-528. 10. Tizard, I. (1990). Risks associated with use of live vaccines. Journal American Veterinary Medical Association 196: 1851-1858. 11. Zanetti, M., E. Sercarz and J. Salk (1987). The immunology of new generation vaccines. Immunology Today 8: 18-25.





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