Bovine Vaccines and Herd Vaccination Programs

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With the increasing size of today's cattle operations and the extensive movement of cattle, disease exposure continues to occur at a high rate. These exposures often put pressure on the efficacy of the vaccines used and may give field experience as to how well they can protect cattle. The wide diversity in uses of cattle and management practices makes a single vaccination protocol impossible for all cattle production systems. Today it is even more important to scientifically choose a vaccine or design a vaccination program based on good information. When designing programs, several variables must be considered[1]:

- The presence and degree of challenge of the particular diseases on the farm or ranch (Boxes 48-1 and 48-2)
- Management practices on the facility that support or hinder vaccination programs
- The times or ages when disease problems occur and whether the diseases are associated with any stressors
- The immune system components necessary to afford protection against various diseases
- Some basic immunologic concepts
- The information available on products being considered and the source and quality of the information
- Required vaccines for a particular use of the animal (e.g., 4-H shows)

Challenge

The level of disease challenge and the degree of protection continually fluctuate. Biological variability makes the degree of protection different in every vaccinated animal. The same is true for the level of exposure to a pathogen. Overwhelming challenge can override immunity and lead to disease even in well-vaccinated animals.[2]

Timing of Disease

On many farms, certain diseases occur at consistent times. Timing may give some insight into stresses that occur in the management of the cattle. Correcting these stresses can have a positive impact on vaccination and lessen animals' susceptibility to disease. This type of history is also helpful in determining the timing of vaccinations, a concept that is often underused in veterinary medicine. Knowing when a problem historically has occurred allows vaccinations to be scheduled when they will induce maximum immune responses in preparation for expected challenges.

Assessing Vaccine Efficacy

The efficacy of a vaccine can be extremely difficult for the practitioner to assess. Traditionally, serologic data showing pre- and post-vaccination titers has been equated with protection. For many diseases, however, the correlation is poor between the antibody measured and the protection generated by the vaccine in the animal.[3] Recently a study comparing BVDV protection showed an inverse relationship between antibody levels and the ability of the vaccines to prevent development of persistently infected calves.[4] Cell-mediated immune function tests have been added to show a more complete stimulation of the immune response after

vaccination.[5] Although these tests provide more information about the vaccine, they still do not answer the basic question of how well a vaccine truly protects. This question can be answered only by well-designed challenge studies. There are many examples of well-designed studies involving both viral[6,7] and bacterial[8,9] agents. To assess a challenge study, the following information is needed:

1. Trial design, including animal characteristics
2. Statistical analysis of the results
3. Determination of whether statistical differences are biologically important
4. Route of administration of the challenge
5. Characteristics of the challenge organism
6. Consistency of the challenge model with the desired protection sought (e.g., respiratory vs. reproductive protection)
7. Method of clinical score assignment
8. Level of disease seen in the control unvaccinated cattle
9. Publication of the results in a peer-reviewed article

Unfortunately, the challenge model is not well established for many diseases. Field trials are even harder to assess but are valuable for judging the effectiveness (i.e., efficacy in a particular situation) and efficiency (i.e., cost-effectiveness) of a vaccine[10] (Boxes 48-3 to 48-12; also see Boxes 48-1 and 48-2). Several good references on field trial analysis are available.[11,12] Recently the Center for Veterinary Biologics (CVB) began giving vaccines different labels depending on the strength of the efficacy data submitted to them in the licensing trials.

Cattle Vaccines

Bovine vaccines tailored for use against 8 viral diseases, more than 28 bacterial pathogens, and 1 protozoal disease (trichomoniasis) are currently federally licensed in the United States (Table 48-8). These vaccines have been designed to aid in preventing a myriad of diseases in cattle, including reproductive, respiratory, generalized septicemic, and toxic (endotoxic and exotoxic) diseases. The vaccines have demonstrated some degree of protection against the pathogen for which they were designed, but they may not have proved protective against all the various syndromes known to be caused by a specific infectious agent. The challenge models for each pathogen and the release requirements for each vaccine are monitored by the Veterinary Biologics division of the USDA's Animal and Plant Health Inspection Service (USDA/APHIS) and can be found in Book 9 of the Code of Federal Regulations.

During gestation the bovine reproductive system, with its multilayered placenta, leaves the fetus in a naive environment susceptible to infection. Abortions may be due to infection of the placenta, inflammation of the ovary, death of the fetus, or disruption of the cervical plug. It is therefore difficult to achieve protection against reproductive diseases. Vaccination must minimize the amount or duration (or both) of the viremia or septicemia, or it must prevent the pathogen from moving through the cervix or crossing the placenta. Only a few currently licensed vaccines have proved protective against the reproductive forms of various diseases, and the duration of immunity they afford has not been established.

Each manufacturer's development and production of cattle vaccines is different, so the composition of vaccines varies substantially among manufacturers. Outlines of production are proprietary for each manufacturer, but some information can be found in technical and marketing materials. For example, some viral vaccines are grown on bovine-derived kidney cell lines, and

others are grown on porcine-derived kidney cells. Some vaccines are grown only on calf serum, whereas others are grown on both calf and fetal calf serum. Variability is seen in the strain or strains chosen for the vaccine, number of growth cycle passages chosen for attenuation, growth medium, and number of viral or bacterial particles in the vaccine.

Three types of vaccines represent the basic technologies currently available in cattle viral and bacterial vaccines[2,13-17]:

1. *Modified live (attenuated) vaccines* contain living bacterial or viral organisms. These organisms usually are collected from a field disease case and then grown in abnormal host cells (viruses) or media (bacteria) to change or attenuate the pathogen. Each completed replication cycle is known as a *passage*, and the changed pathogen then is administered back to the animal to determine if it is still virulent. After several passages the pathogen begins to lose virulence factors because it cannot cause "disease" in the unnatural host cells. Once the pathogen can no longer cause "disease" in the target species, it is tested to see if it can confer protection. The final vaccine is usually passed a number of times beyond the passage where virulence disappears in order to reduce the risk of reversion to a virulent pathogen. These vaccines require good quality control to reduce the risk of a contaminant entering the vaccine.
2. *Inactivated (killed) vaccines* are easier to develop because virulence after growth is not a problem. The same pathogen is isolated from a disease outbreak. The pathogen is grown and then chemically or physically killed. The inactivation is usually achieved either by adding a chemical to the pathogen or by using ultraviolet rays. The major concern with inactivation is the potential loss of important epitopes. An adjuvant is normally added to inactivated vaccines to heighten the immune response. The vaccine is then tested for efficacy.
3. *Genetically engineered vaccines* have been genetically altered, usually through a mutation. This mutation may be induced by several different methods, but the resulting bacterium or virus has different properties that may alter virulence or growth characteristics. Most of these vaccines are modified live mutants (e.g., temperature-sensitive viral vaccines or streptomycin-dependent *Mannheimia/Pasteurella* vaccines), but inactivated marker vaccines are also genetically engineered. These vaccines have been engineered to delete a gene and cause an immune response deficient in antibodies to a certain epitope; this allows diagnostic methods to distinguish between vaccine and natural exposure responses (e.g., gene-deleted infectious bovine rhinotracheitis [IBR] vaccines).

Once its efficacy has been established, the vaccine is put through a series of experiments to determine the minimum dose required to achieve adequate protection, called the *minimum immunizing dose* (MID). The vaccine will contain more than the MID to ensure that it contains at least the MID at the expiration date found on the label. In effect, a vaccine's efficacy is not determined by the final product used by the veterinarian but at a reduced level of immunogens from the amount contained in the final vaccine.

Autogenous Vaccines

In addition to the vaccines licensed by the USDA, several companies will make autogenous vaccines for use by veterinarians and cattle owners. These vaccines do not fall under any particular USDA/APHIS guidelines and are usually derived from cultures (e.g., viral or bacterial) isolated from specimens submitted by the particular farm. Such vaccines can be used only on that

particular facility and cannot be sold for use on other farms. These vaccines are not tested for efficacy or safety, and the components found in the vaccines may vary from batch to batch; this adds some element of risk when they are used. Nevertheless, this type of vaccine may be an option to consider when federally licensed vaccines are unavailable for a specific farm problem.

Maternal Antibody Interference Revisited

It is an accepted belief that maternal antibodies can block immune responses from vaccination. This belief has been based on a procedure of vaccination followed by a titer evaluation in the vaccinates. Many studies have shown that vaccinated animals may not display increased antibody levels if high levels of maternal antibody to that antigen are present. However, recent studies have shown that both B-cell memory responses and cell-mediated responses can be stimulated despite high maternal antibody for the same antigens.[18-20] Seropositive calves vaccinated at a young age with modified live (MLV) bovine herpesvirus type 1 (BHV-1), parainfluenza type 3 (PI-3), and/or bovine respiratory syncytial virus (BRSV) vaccines have shown higher antibody responses on revaccination than control calves vaccinated only at the second date. These young vaccinates typically do not show increased antibody responses after the initial vaccination in the presence of high maternal antibody. Cell-mediated immune responses, as indicated by antigen-specific T-cell blastogenesis, have been demonstrated in the face of high maternal antibody levels[21] when attenuated BRSV and BHV-1 vaccines were used. Similar responses have been reported in laboratory animals as well.[22-24] One study also demonstrated higher levels of protection at challenge if calves were vaccinated with a modified live BRSV vaccine.[20] It is clear from these studies that maternal antibody interference with vaccines is not as absolute as once thought. The animal's immune status, the specific antigen, and the presentation of that antigen should be considered when designing vaccination programs in which maternal antibody may be a factor.

Impact of Stress

Stress affects the immune system of all cattle, as can a number of other factors. The release of corticosteroid that occurs during the birthing process has a dramatic impact on the newborn's immune system. Newborns also have a higher number of suppressor T cells than adults.[2] These factors and others dramatically diminish systemic immune responses for the first week of life.[25] Other stresses should be avoided at vaccination time to maintain the integrity of the immune system. Procedures like castration, dehorning, weaning, and movement have to be considered as stressors in cattle, and all have the potential to temporarily diminish immune system functioning.[26-28]

Systemic vaccinations should be avoided during high-stress times because of these diminished responses and because vaccination at such times may even have undesired effects.

Booster Importance

It is important to follow the label directions for administering vaccines. Many inactivated vaccines and some modified live BRSV vaccines require a booster before protection is complete. The first time an inactivated vaccine is administered, the primary response occurs. This response is not very strong, is fairly short-lived, and is predominantly composed of IgM antibodies (Fig. 48-1). The response seen after a booster vaccination is called the *secondary* or *anamnestic response.* This response is much stronger, of longer duration, and is primarily composed of IgG

antibodies.[2,12] If the booster is given too early, the anamnestic response does not occur, and if too much time elapses before the booster is given, it acts as an initial dose, not as a booster.

With most MLV vaccines (except for some BRSV vaccines), the primary vaccination also stimulates the secondary response without the necessity of a booster, because the virus or bacterium is replicating in the animal.

Adverse Reactions

Adverse reactions are a risk with any vaccination and can be categorized as one of the following two primary types of hypersensitivities[2,4,29-34]:

1. *Type I (immediate) hypersensitivity* is mediated by IgE stimulation and release of granules from basophils and mast cells. This reaction is seen within minutes of vaccination and often begins with shaking or sweating. Most of these animals respond to IV injections of epinephrine. Every vaccine can occasionally elicit an anaphylactic reaction. Cattle should always be kept under observation for at least 30 minutes after administration of a vaccine. Epinephrine should be administered at a dosage of 1 mL of 1 : 1000 solution per 50 kg of body weight, preferably by IV injection, at the first sign of weakness, staggering, or dyspnea. With most vaccines, anaphylactic reactions occur no more often than 1 case per 5000 to 10,000 doses administered. The rate of occurrence may be much higher after administration of *Salmonella, E. coli,* and some *Moraxella bovis* bacterins, which may have high levels of endotoxin.
2. *Type III (immune complex) hypersensitivity* is mediated by attachment of an antibody-antigen complex to complement and the ensuing activation of the complement cascade. The resultant reaction may occur locally or systemically. The reaction may be delayed, as the complexes form and the cascade begins, or subsequent, as products begin to exert their effects. The signs are similar to those of an immediate hypersensitivity reaction, and the treatment is administration of epinephrine.

One of the more common reactions seen in cattle has been associated with the endotoxin and other bacterial components found in most gram-negative vaccines.[32-35] Currently, there are no requirements for monitoring or reporting the amount of endotoxin found in cattle vaccines, and the level of endotoxin may vary dramatically between vaccines and between serials of the same vaccine. Furthermore, the potency of endotoxin varies among different gram-negative bacteria. This type of reaction is seen primarily in Holsteins because of a genetic predisposition and may be seen after administration of any gram-negative bacterin. The signs vary depending on the farm's or the individual's sensitivity to gram-negative bacterial components. The number or potency of the gram-negative fractions in vaccinations administered simultaneously are also instrumental in causing these reactions. As a general rule, no more than two gram-negative vaccines should be administered to dairy cattle on the same day because of the possibility of adverse reactions, which may include anorexia and transient decreases in milk production, early embryonic death, abortion, and gram-negative bacterial shock (endotoxic shock), which requires treatment with flunixin or ketoprofen, steroids, antihistamines, and fluids.

Site reactions are common sequelae to many vaccines. These granulomas are usually caused by overreaction to the adjuvants, but they may also be directly aimed at the antigen or antigens. This has been a major focus of beef quality programs and has generated a push to have all vaccines labeled and to have them administered SC to avoid damaging the muscle.

Finally, some vaccines may affect appetites post-vaccination. This impact continues to be an area of concern and active research, particularly in stressed cattle and neonates.[36-41]

Read the Labels
The vaccine label is a wealth of information that is approved by the CVB/APHIS. The CVB evaluates the supportive efficacy data supplied by the vaccine manufacturer and decides whether the vaccine can be licensed or not. They also determine what type of efficacy claim can appear on the vaccine labels and in advertising. Included are dosage, route of administration, precautions, timing, indications, storage information, withdrawal period, and shelf life. As found in Veterinary Services Memorandum 800.202 (June 2002), the CVB also does some preliminary rating of vaccine efficacy by granting one of five level of protection statements (in order of highest efficacy to lowest): Prevention of infection, Prevention of disease, Aid in the prevention of infection, Aid in disease control, Other miscellaneous claims. The label can be a good starting point for comparing vaccines.

Newer immunologic concepts in cattle vaccination
The terms of dominant antigen, antigen interference and immunodominance have been used interchangeably to describe a unique phenomenon of the immune system. The term immunodominance has become the accepted term in human immunology and textbooks have been written on the subject.[42] Immunodomination is defined as the process whereby immune expression or recognition of one epitope or antigen influences the recognition of a second distinct epitope or antigen.[43] This prioritization of epitopes by the immune system has been widely studied and many articles have been published. While most studies have focused on the occurrence of immunodominance in immune responses to the multitude of epitopes within a specific antigen (virus or bacteria; there are continued studies on the interactions between different antigens. On any bacteria or virus only .2% of the possible epitopes have any measurable immune response.[44] This also extends to interactions between concurrent administration of different vaccines. [45,46]

Immunodominance has been shown to occur via several different mechanisms. These include:

1. Dominant epitope processing blocks antigen presenting cells from the antigen presentation of subdominant epitopes.[43]
2. Dominant epitope T cells block expansion of subdominant T cells (CD4+ and CD8+)[3]
3. Dominant epitope processing using Tcell synaptic molecules to be used and exhausted and/or the release of defective synaptic molecules, thereby blocking attachment of subdominant T cells.[42]
4. Shifting of subsets of CD4+ subsets toward antiviral or antibody formation [45,46]

One of the first published cattle studies demonstrating the potential for interactions between cattle vaccines was published in the Canadian Journal of Veterinary Medicine in 1992.[47] The authors demonstrated that vaccination with a modified live bovine herpesvirus 1 (infectious bovine rhinotracheitis virus, BHV-1) vaccine blocked the *Mannheimia haemolytica* vaccine response. The same phenomena of modified live BHV-1 vaccine over *Mannheimia hemolytica* vaccine response was observed in a vaccine field trial performed by Kansas State University.[48] More recent studies have compared the serologic responses to *Mannheimia hemolyica* bacterins with co-administration of attenuated BHV-1 (MLV and TS) supported the earlier findings; however, immunodominance was not shown if the BHV-1 vaccine was

administered intranasally or upon subsequent vaccination.[49-50] Antigen interaction has been shown with several other vaccines as well.[51-53] More research is needed to continue to understand these interactions and how they pertain to developing vaccine program strategies.

Another new immunologic concept also started in human immunology and is now being researched in veterinary immunology is prime boost vaccine strategies. This concept involves priming the immune system to a target antigen delivered by one vector, route, or mechanism, and then selectively boosting this immunity by re-administration of the antigen in the context of a second and distinct method.[54] This is considered heterologous versus traditional homologous boostering. Several papers have highlighted the power of prime-boost strategies in eliciting protective cellular immunity to a variety of pathogens and have demonstrated efficacy in humans.[55] The key strength of this strategy is that greater levels of immunity are established by heterologous prime boost than can be attained by a single vaccine administration or homologous boost strategies. Recent studies in veterinary medicine have demonstrated the prime boost concept.[56-59] These and other studies indicate that this area of vaccination strategy is poised to make tremendous progress.

Summary

Designing a vaccination program requires a good history of the individual farm and a basic understanding of the immune system. Vaccines that should be considered for routine or optional use in various classes of pastured beef cattle, feedlot cattle, and dairy cattle are listed in Boxes 44-3 to 44-12. The vaccines chosen should be supported by good, solid efficacy studies (and by effectiveness and efficiency studies if possible) to ensure that the product can fulfill the needs of the farm or ranch (see Table 44-8). Management decisions may be made that do not maximize the potential of the product chosen, and realistic expectations of all products should be well explained to the producer before the vaccines are administered. The owner should be involved in the vaccine decision-making process, and all information on the product should be shared.

Establishing good baseline immunity of replacement heifers and the foundation vaccination program can have dramatic effects on the health and profitability of the herd, so such programs must be well planned.

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This review provides a framework for the establishment of rational bovine herd vaccination programs. Information is provided that can assist in the selection of specific vaccine products and the establishment of appropriate schedules for their administration. Advantages, disadvantages, indications, and contraindications of vaccine options are discussed. PMID: 2178739. Types of vaccine. Vaccination is the most effective way of preventing viral diseases. While attenuated and inactivated virus vaccines are still the â€œwork horsesâ€ of veterinary practice, third generation products are now complementing and, in some cases, replacing them.Â An optimal vaccination program depends on both the characteristics of the vaccine and the epidemiology of the agent. Vaccine characteristics include the proportion of protected vaccinates, the duration of protection and the coverage achieved in a population by the program (herd immunity). The most important parameter is the reproduction figure Ro (as explained above).Â A microorganism can be eliminated from a population when the herd immunity level reaches or exceeds 67%, which is attained nowhere in cats.