Fundamental Considerations in Developing Vaccination Protocols

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Abstract

A tremendous amount of time, effort and expense is placed on vaccination programs in the cattle industry. Recent surveys of vaccination practices in the U.S. suggest that many producers are not effectively vaccinating their animals for optimum immunity. Development of an effective vaccination program requires a thorough understanding of vaccine immunology. Antigen processing and presentation are key mechanisms of an appropriate immune response and affect the type of response that can be expected from different types of vaccines. Modified live vaccines provide effective humoral and cytotoxic immunity that is long lived. Killed vaccines can provide effective humoral immunity when appropriate adjuvants are used. New concepts in antigen presentation and adjuvants will undoubtedly improve the immune response elicited by future killed vaccines. Vaccination programs should adopt a concept of strategic vaccination in order to provide the most effective immunity to the animals prior to stress or exposure. Vaccination programs may be monitored in the field by evaluating specific serological responses. This information can be used to compare vaccines and vaccination programs as well as provide information that can be used to differentiate vaccine responses from recent infection. While vaccines are instrumental in decreasing disease incidence and severity, there are inherent risks. Adverse reactions include systemic responses to endotoxin, anaphylactic and anaphylactoid reactions, vaccine induced disease, and reproductive effects including infertility and abortion. These risks can be minimized by appropriate use of vaccines. Ultimately, we expect vaccines to be efficacious and provide a positive economic return to the producer.

Introduction

Development of vaccination protocols is one of the most challenging services provided by bovine practitioners. There are many considerations that impact the structure and implementation of bovine vaccination protocols including safety, efficacy, necessity and economics. This is compounded by the fact that while we are expected to provide unbiased professional advice, we are both distributors and consumers of vaccine products and must somehow develop informed and knowledgeable judgments. How does a busy practitioner stay abreast of current vaccine developments and published literature? How does one evaluate and critique the information provided by the biological company marketing the product? In the end, we are often left scratching our heads asking ourselves "am I truly giving the best recommendations for the producers and their animals?"

As we are all aware, there is no single correct vaccination protocol. Vaccination protocols must be tailored to the individual producer, geographic location, industry sector, physical facilities and husbandry practices. In many cases, a vaccination protocol may need to be changed due to changes in disease frequency or introduction of a new disease. In this session, we will touch on several topics related to vaccine use and evaluate the recent and historical literature related to those issues.

Current Status of Vaccination Programs

Perhaps the most concerning aspect of vaccine usage is that the cattle industry appears to be doing a poor job at following the most basic recommendations. National surveys (NAHMS, http://www.aphis.usda.gov/vs/ceah/cahm/index.htm) of dairy, cow-calf and feedlot producers indicate that vaccine usage varies widely with an overall low level of use in the cow-calf sector and higher usage in the dairy and feedlot sectors. It is estimated that less than 30% of producers are utilizing vaccines in a way that would provide optimum immunity for their herd. There are many opportunities to undermine the potential benefits of vaccination (Table 1). The first and foremost rule of vaccine usage is to follow the manufacturer's labeled recommendations. The most common mistake in this regard is not providing an appropriate booster to a primary vaccination. This is a

Table 1. Practices that decrease the efficacy of herd vaccination programs.

Not vaccinating all susceptible animals
Not following manufacturers' labeled recommendations
Not vaccinating incoming animals
Vaccinating in the face of maternal immunity
Vaccinating animals under stress
Vaccinating in the face of a disease outbreak
Vaccinating too late relative to anticipated exposure or stress
Failing to provide appropriate booster to primary vaccination
Providing primary booster too early or too late
Inappropriate vaccine choice
Improper vaccine handling

significant concern for killed vaccines but may also apply for some modified live vaccines such as bovine respiratory syncytial virus (BRSV). In general, primary boosters should be administered within 3 to 4 weeks of initial vaccination in order to elicit an appropriate amnestic response. The amnestic response may be decreased when the primary booster is administered within 2 weeks or after 8 weeks of primary vaccination. As is many times the case, we would be far better off if we simply addressed the fundamental issues and recommendations in animal husbandry rather than trying to look for the new and novel solution or the "magical" vaccination protocol. Excellent reviews of vaccines and vaccination programs are readily available.

Vaccine Immunology

It is important to understand the immunological mechanisms of immunization in order to provide informed recommendations on the use of vaccines. Differences in antigen processing and presentation play a dramatic role in the type of response observed with different types of vaccines. Controversy concerning the use and efficacy of killed, modified live, or mucosal vaccines continues in spite of the large volume of literature pertaining to current vaccines. Important issues such as safety, immunological response, immunological interference, duration of immunity and efficacy continue to baffle researchers and clinicians alike. It is important to understand the basic mechanisms of the immune response to the different types of vaccines in order to make informed assessment of the relative benefits and risks of each vaccine type.

Antigen Processing and Presentation directs the fundamental framework of the immunological response to a vaccine (Figure 1). Extracellular antigen (exogenous antigen processing) is processed and presented to the immune system by antigen presenting cells (APCs) such as macrophages, dendritic cells and

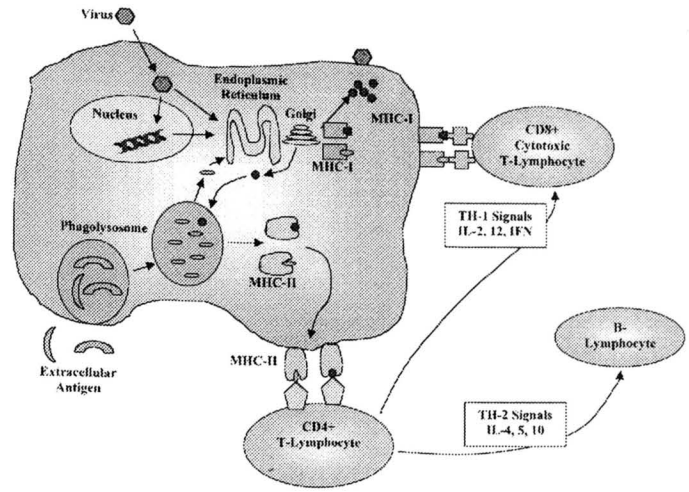

Figure 1. Exogenous and endogenous antigen processing pathways.

B-lymphocytes. These cells continually recognize and phagocytose foreign as well as self-antigen. Several tissue and molecular signals activate and direct the action of APCs. In general, APCs are activated through cytokine signals in areas of tissue injury. Without these signals they remain relatively inactive. Once activated, APCs will engulf and process both foreign and cellular debris found in that local environment. Foreign antigens can also be marked for phagocytosis by unique carbohydrate moieties on glycoproteins or by opsonization with complement molecules or immunoglobulin. Once phagocytosed, the antigens are digested within the phagolysosome. Digested antigen peptides then bind to MHC class II molecules and are presented on the surface of the antigen presenting cell for T-lymphocyte (CD4+) recognition and activation. These activated T-lymphocytes release additional cytokines that direct the character of the immune response (antibody mediated or cytotoxic immunity).

Antigens that are synthesized in the cell (i.e both self and viral antigen) are processed and presented by a different pathway often termed endogenous antigen processing. In this pathway, cellular or viral messenger RNA is translated and proteins are processed through the endoplasmic reticulum and the Golgi apparatus of the cell. Some of these proteins are digested and bind to MHC class I proteins. The MHC I-peptide complex is transported and presented on the cell surface. Peptides presented by MHC I complexes signal cytotoxic T-lymphocytes (CD8+) that bind the complex. All cells, including antigen presenting cells, continually sample and present intracellular proteins by this pathway.

In general, extracellular antigen undergoes exogenous antigen processing (MHC-II) and intracellular antigen undergoes endogenous antigen processing (MHC-I). However, there are mechanisms by which

extracellular antigens can be shunted to the endogenous pathway and intracellular antigens can be shunted to the exogenous pathway.

Antigens presented by MHC-I or II complexes have the opportunity to stimulate an immune response. Antibody mediated immunity is stimulated when B-lymphocytes bind extracellular antigen and receive the proper signals from CD4+ T-lymphocytes that are activated by MHC-II presented antigen. Cytotoxic immunity is stimulated when CD8+ T-lymphocytes bind MHC-I complexes and receive the proper signals from activated CD4+ T-lymphocytes. In both cases, the effecter lymphocytes (B-lymphocytes or cytotoxic T-lymphocytes) must receive **TWO** signals. If only one signal is encountered, the effecter cell will either not respond, or may die by apoptosis. This two-signal process is the basis for self-antigen recognition and clonal selection that occurs during immune system development in the fetus. During fetal development B- and cytotoxic T-lymphocytes are continually exposed to self-antigen but not to the second signal provided by CD4+ T-lymphocyte. These cells ultimately die prior to birth.

Killed Vaccines rely on the presentation and uptake of a large purified antigenic load to the immune system. The antigens must be administered in such a way that they are recognized and phagocytosed by antigen presenting cells. APCs perform best when they are "activated" and that is the key to proprietary adjuvants. Adjuvants are chemicals that help improve the uptake and presentation of antigens and stimulate the character and quality of the immune response. They can do this by 1) stimulating activation of APCs, 2) making the antigens appear "tasty", or 3) directing the type of immune response (i.e. humoral vs. cytotoxic). Most conventional adjuvants simply activate APCs by inducing local tissue damage, thus the local injection reactions and swellings observed with many vaccines. New more novel methods of antigen presentation such as immune stimulating complexes (ISCOMs), liposomes, fusion proteins (C3b), DNA vaccines, and cytokines (IL2, IL4, IL6, IL12) have also been employed on a research basis and to a lesser extent in commercial vaccines.

The antigens of killed vaccines are phagocytosed by APCs and primarily processed for antigen presentation by MHC II molecules (exogenous pathway). The MHC II-peptide complexes stimulate CD4+ T-lymphocytes that respond by releasing specific cytokines that activate effecter lymphocytes (B-lymphocytes or CD8+ T-lymphocytes) (Figure 2). Some of the antigens from the vaccine are recognized by immunoglobulin on the surface of circulating B-lymphocytes. If the B-lymphocyte binds antigen **AND** is exposed to the proper cytokine signal from stimulated CD4+ T-lymphocytes, then the B-lymphocyte will become activated, undergo clonal expansion and differentiation to immunoglobulin secreting plasma cells. Some of the antigen taken up by the APC may be diverted to the endoplasmic reticulum and Golgi where it is processed and presented with MHC I molecules for activation of cytotoxic (CD8+) T-lymphocytes. This is the mechanism by which killed vaccines can stimulate some cytotoxic immunity. The degree of cytotoxic immunity is governed by many factors including the type of antigen. While killed vaccines can produce some cytotoxic immunity, most immunologists believe this immunity is not as strong or durable as that produced by modified live vaccines.

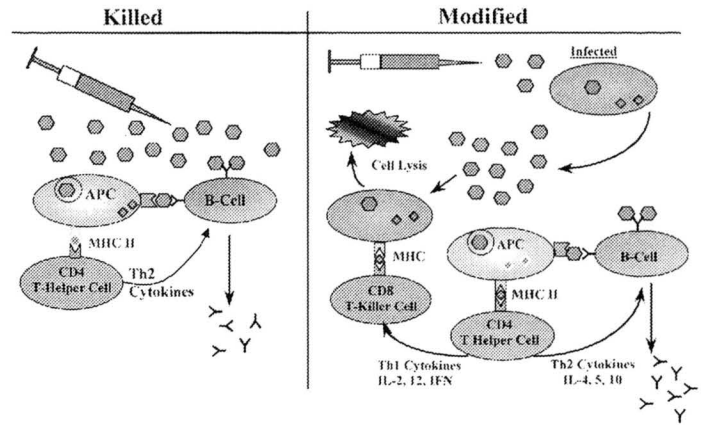

Figure 2. Comparison of immune stimulation with killed and modified live vaccines.

Modified Live vaccines provide a more "natural" method of antigen presentation and immune system stimulation. These vaccines rely on administration of a relatively low antigenic load that then multiplies and stimulates the immune system in a fashion similar to natural infection. It must be emphasized that, with the exception of mucosal vaccines, these attenuated agents are administered by an "unnatural" route and therefore do not necessarily stimulate the same character of immune response as natural infection. Modified live viral vaccines effectively stimulate both humoral and cytotoxic immune responses (Fig 2). Because of their prolonged replication, they can generally stimulate and effective immune response with a single vaccination. One exception to this rule is modified live BRSV vaccines that do not effectively replicate in the muscle tissue and thus need to have a primary booster. It is generally considered that modified live viral vaccines provide stronger and more prolonged immunity compared to killed viral vaccines. This concept is being challenged with the development of more effective adjuvants and methods of antigen presentation.

Mucosal Vaccines are generally attenuated live vaccines that are administered intranasally or orally. They have the advantage that they are applied in a manner similar to the normal route of infection. As such, they have the ability to stimulate a mucosal immune

response, along with a humoral and cytotoxic response. This is an important characteristic as the various types of immune responses have different roles in controlling infection. Mucosal, or secretory IgA, immunity has the potential to neutralize infectious agents at the site of entry and actually prevent infection. In addition, mucosal immunity can dramatically decrease local tissue spread, shedding and transmission to other animals. Humoral (IgM, IgG) immunity has limited ability to actually prevent infection but it is very effective at limiting tissue spread and viremia by neutralizing free virus or bacteria. Humoral immunity can also help clear infected cells by antibody dependant cellular cytotoxicity. Cytotoxic immunity is only of significance for intracellular agents (i.e. viruses, some bacteria and protozoa). Cytotoxic immunity will not prevent infection but is very important in clearing intracellular infections. Understanding the relative importance of the different types of immune response is important in evaluating and comparing different types of vaccines and their applications.

Strategic Vaccination

We are all familiar with the concept of strategic deworming but we often fail to recognize that the same principles hold true for vaccination programs. A prudent and efficacious vaccination program must be based on a sound understanding of the relationship between the population at risk, the specific disease conditions and the protective efficacy of the induced immunity. The vaccination protocol should be administered in such a way that it provides the greatest immunity to the animals at risk within the management framework of the individual production unit.

Prior to establishing a vaccination protocol one must determine what agents are considered significant production and economic threats to the individual livestock facility. Veterinarians have the knowledge, training and experience to provide the best recommendations in this regard. There are several infectious agents that are considered endemic, have sufficient health and economic threat, and have reasonably efficacious vaccines available that they should be recommended for every bovine livestock facility. Other infectious diseases have limited geographic range or are observed sporadically enough that they do not necessitate routine vaccination even though the vaccines are reasonably efficacious and economical under restricted conditions. Finally, there are many other agents that have localized geographic distribution, cause limited morbidity and economic impact, are best controlled by proper husbandry, or do not have sufficiently efficacious vaccines to warrant their use. In all cases vaccines should be used judiciously and their use should be reevaluated periodically with regard to each facility and current understanding of vaccine immunology and infectious disease control.

The Goal of Vaccination

Vaccination is used to stimulate an immune response that provides some degree of protection against infectious disease. It must be remembered that vaccination does not imply immunization and that immunization does not imply protection. Further, it is critical to identify the population of animals that each vaccine is intended to protect. For example, the common 4-way viral and clostridial vaccines are used throughout all sectors of the cattle industry. However, different populations of animals are at higher or lower risk than others for the specific disease agents contained in these vaccines. In addition, the disease condition of concern for a given etiologic agent may vary based on age and use. While 4-way viral vaccines serve to protect from both respiratory disease and reproductive loss, our level of concern for these different conditions varies by the age of the individual animal and industry sector. Is the goal to protect the adult from overt clinical disease or reproductive wastage? Is the goal to protect the fetus from infection? Is the goal to protect the neonate? What is the duration of previous vaccination or natural immunity and are boosters necessary? These are some questions that should be asked when assessing vaccination protocols

In general, neonatal immunity is best obtained through passive transfer of maternal colostral antibody. Colostrum contains predominantly IgG1 antibodies and these antibodies afford a certain amount of systemic immunity for different diseases. While IgG1 is resecreted at a low level to mucosal surfaces, it does not provide as good of protection as an active IgA response. Rarely does passive antibody prevent infection. Rather, it prevents overt clinical disease by limiting the invasion, replication, tissue spread, shedding and duration of an infection. It does this by neutralizing infectious agents or "marking" them for destruction in the extracellular space or along mucous membranes.

The importance of colostral antibody differs for different etiological agents and industry sectors. For example, enteric disease caused by K99 enterotoxigenic *E. coli* can be effectively prevented by administration of colostrum containing antibody against the K99 pili antigen. This disease occurs in the immediate postnatal period when gastrointestinal lactogenic immunity (free antibody in the lumen of the intestinal tract) is present for any animal receiving quality colostrum. Coronavirus and rotavirus enteritis occur later and can also be prevented by colostral antibody. However, differing industry practices have a dramatic effect on the efficacy of maternal vaccination. While vaccination of

the dam will provide increased colostral antibody for absorption, the most effective prevention for coronavirus and rotavirus requires antibody within the lumen of the intestinal tract for a prolonged period of time. Resecretion of colostral IgG1 antibody may not be sufficient for adequate protection. Thus, dairy calves that are given colostrum only during the immediate neonatal period are not protected as effectively as beef calves that continue to nurse the dam.

Vaccination of animals for clostridial diseases serves many different purposes. Clostridial enteric diseases (*Cl. perfringens* types A, C, and D) are a significant concern in all calves. These agents are endemic throughout the country. Adult cattle routinely have sufficient titers following previous vaccination or exposure and provide some degree of passive immunity to the calves. While adult cattle are generally not at specific risk for these diseases, vaccination of pregnant dams will provide superior protection for the neonate. Alternatively, muscle clostridial (*Cl. chauvei, septicum, sordelii)* diseases are typically observed later in life. While passive transfer may not be required for the neonate, vaccination and active immunity is very important from 4 to 24 months of age. After 12 to 24 months of age, most animals are immune through previous exposure or vaccination and may not require additional vaccination. The liver clostridial diseases (*Cl. novyi* type B and D) are really only of concern in animals over 4 months of age on wet or swampy pasture. These diseases tend to have specific geographic distribution and are of concern throughout the life of the animal. While the vaccine for these is efficacious, it is only necessary for a specific population of animals based on the likelihood of exposure.

The goal of vaccination for the common viral respiratory and reproductive diseases (BHV-1, BVDV, PI-3, BRSV) can be equally diverse. Protection of the calves through colostral antibody may be more important for beef calves that are raised in groups than for dairy calves that are initially raised in calf hutches. Stocking densities and housing conditions may influence the risk for the calves. Most adult cattle are protected from overt clinical disease from these agents through previous exposure or vaccination. However, their effective immunity will wax and wane allowing for periodic subclinical infections. These subclinical infections can result in reproductive loss through infertility, early embryonic death, or abortion. Fetal infection can occur without noticeable clinical signs in the cow thus allowing for fetal BVDV infection and the development of persistently infected calves. If the goal is to protect the cow and fetus, vaccination prior to the breeding season is most appropriate. However, if the goal is to protect the newborn calf, then precalving vaccination is most efficacious.

These examples demonstrate how knowledge of the disease, the animals at risk, the differences in husbandry practices, and the different disease manifestations all affect the development of a vaccination protocol.

Establishing Expected Vaccination Response

It is important to have an appreciation of the expected vaccination response for a given protocol within a given herd. In many cases, knowledge of humoral responses in groups of animals will help evaluate a given vaccination protocol. In addition, knowledge of the expected vaccination response will help differentiate vaccine-induced titers from natural disease. This can be tremendously helpful when investigating infectious disease outbreaks. Serological testing is inexpensive and can be easily performed on selected groups of vaccinated cattle. In general, ten animals should be evaluated at the same time. Blood samples should be obtained prior to vaccination and approximately two weeks following vaccination. Not only will these post-vaccination titers provide information on the efficacy of the vaccine program, they can also be used to compare alternative programs or new vaccines that become available.

Exposure and Stress

One of the major failures of vaccination programs is that the vaccines are administered under conditions that do not allow ample opportunity for the development of an effective immune response. The classic example of this is the use of vaccines on entry into feedlots for the prevention of respiratory disease. Animals entering the feedlot are exposed to many animals from different sources in a confined and stressful environment. In most cases, significant exposure has occurred prior to vaccination. Stress from transportation, socialization, adaptation to a new environment, feed and water restriction, and dietary changes contributes to decreased responsiveness and immunity following vaccination. In many cases, there is not sufficient time to mount an effective immune response. While vaccination may be justified in preventing disease later in the feeding period, it has limited benefit in preventing disease during the first two weeks following processing. The time from vaccination to effective immunity varies with different vaccines. Whenever possible, vaccination should be administered at a time when stress is minimized and at least two weeks prior to anticipated exposure to infectious agents.

Immunological Interference

We know that maternal antibody will interfere with a standard vaccine response. Maternal antibody interference is different for different types of vaccines and

agents. Modified live vaccines tend to produce active immunity at an earlier age than do killed vaccines. Intranasal modified live vaccines will elicit an immune response earlier than intramuscular vaccination. The majority of animals will not mount a detectable humoral immune response until after 2 months of age. The difficulty in developing a protective immune response prior to weaning is a significant problem in dairy calves. More recent protocols have advocated vaccination with modified live intramuscular viral vaccines at 1-2 weeks and again at 5-6 weeks of age. There is limited information regarding the efficacy of this approach in the literature. A recent trial at Colorado State University did not show evidence of significant humoral antibody response in calves vaccinated with this protocol (unpublished data). Previous research has shown some evidence of a priming effect on the immune system in calves vaccinated at 10 days of age. However, when these animals are vaccinated again at 4-6 months of age, there does not seem to be a difference in vaccine response between vaccinated animals and unvaccinated controls (unpublished data). Thus, it does not seem likely that early calfhood vaccination provides significant immunological benefit for weaned calves.

Vaccine induced immunological interference may also affect the response to successive vaccination. Again, there is limited data regarding this phenomenon in the literature. It appears that cattle that have received previous vaccination with a modified live vaccine have erratic and suboptimal serum antibody responses to successive vaccination with modified live vaccines of the same type. However, killed vaccines appear to stimulate an effective humoral response following appropriate vaccination with either a modified live or a killed vaccine. It has been argued that humoral antibody from previous vaccination interferes with the modified live vaccine response. However, this theory is counter to the response observed when vaccinating in the face of passive maternal immunity. Alternatively, cytotoxic immunity stimulated by previous vaccination with a modified live vaccine may interfere with replication and immune stimulation following administration of successive modified live vaccines. Killed vaccines contain high antigenic mass and would not be affected by a cytotoxic response. Thus, they appear to provide more effective stimulation of the humoral immune response when used as an annual booster vaccination (unpublished data). The specific implications of this phenomenon still need to be evaluated. However, it would appear that annual booster with killed vaccines provides a more consistent and higher antibody response than modified live vaccines.

Safety

Several questions should be entertained regarding vaccine safety. What types of adverse reactions can occur? Which types of vaccines are safer? What animals are at risk of vaccine induced disease? To what degree do modified live vaccines shed and is this of concern for commingled cattle? What vaccines contain significant endotoxin levels? What is the significance of anaphylactic/anaphylactoid reactions?

There are many adverse reactions that can be encountered with vaccine use. These reactions include local tissue inflammation, endotoxin reactions, anaphylactic or anaphylactoid reactions and clinical disease. In some cases, these reactions have had dramatic impact on the acceptance and use of specific vaccines. Vaccines are designed to stimulate a biological response and these adverse reactions are an inherent drawback of this process. As indicated above, antigen presenting cells work best when they are activated. One of the purposes of vaccine adjuvants is to stimulate an inflammatory response in order to activate antigen presenting cells. This reaction often contributes to the local tissue lesions observed with many killed viral, bacterin and toxoid vaccines. Modified live vaccines can also produce local tissue inflammation through the action of the attenuated organism(s) contained in the vaccine.

In addition, endotoxin contained in the vaccine can cause both a local and systemic response. Many conventional vaccines contain endotoxin, either as a fraction of the specific antigens or as contaminants. Occasionally, severe systemic endotoxin reactions are observed following vaccination in cattle. These reactions are characterized by weakness, lethargy, fever, respiratory distress, inappetence, and occasionally death. Abortion may be occur several days to weeks following the incident. The effect is often seen in multiple animals when multiple vaccines, especially vaccines containing gram-negative antigens, are used. The reactions most often occur 30 minutes to several hours after vaccination. Severe endotoxin reactions may be treated by administration of non-steroidal anti-inflammatory drugs (i.e flunixin meglumine) and/or steroids.

Endotoxin reactions must be differentiated from classical anaphylactic or anaphylactoid reactions. Both anaphylactic and anaphylactoid reactions result in mast cell degranulation, mediator release (histamine, bradykinin, SRSA), and acute systemic hypotension. By definition, anaphylactic reactions are an IgE mediated immune reaction to antigens contained in the vaccine product. These antigens can be the vaccine specific antigens, the adjuvant or other carrier components or contaminants. Anaphylactoid reactions are not mediated by IgE. In these cases, components of the vaccine directly induce mast cell degranulation. Anaphylactic/anaphylactoid reactions are typically observed within minutes of vaccination. The animal will become acutely recumbent and demonstrate an elevated heart rate and respiration rate. Increased vascular permeability with resulting pulmonary edema

may be observed in cattle. Treatment with epinephrine and steroids should be instituted immediately. Anaphylactic/anaphylactoid reactions occur sporadically as isolated cases in individual animals. Rarely are multiple animals affected at the same time.

There will always be concern over reversion or vaccine induced disease with modified live vaccines. There are numerous documented situations where modified live vaccines are contaminated by a secondary virulent agent and in spite of higher vaccine standards, such contamination can still occur. Current modified live BVDV and BHV-1 (IBR) vaccines have the potential to induce abortion in pregnant cattle. These vaccines are not labeled for use in animals commingled with pregnant animals for fear of shedding and induced abortion. However, this practice is used by some producers and veterinarians with success. There are clear instances where vaccine virus has lead to infection and abortion in commingled cattle. Recent studies show that some intramuscular modified live vaccines may not shed significant vaccine virus to commingled cattle. At this time, administration of attenuated BVDV and BHV-1 vaccines to animals commingled with pregnant cattle must be approached with caution. The degree of shedding is likely to be different for vaccines from different manufacturers. When this practice is utilized, the veterinarian and producer must be certain that the pregnant cattle have been adequately vaccinated in order to prevent possible infection and abortion.

While attenuated BVDV vaccines are highly efficacious, vaccine induced mucosal disease has tarnished their reputation. Vaccine induced mucosal disease occurs when a persistently infected animal is vaccinated with an attenuated BVDV vaccine that contains a cytopathic virus. This condition does not require that the vaccine strain be antigenically homologous to the non-cytopathic PI virus. Spontaneous recombination between the cytopathic vaccine virus and the non-cytopathic PI virus can result in a cytopathic virus that is antigenically homologous to the PI strain. Clinical signs of vaccine induced mucosal disease are delayed at least one week post vaccination.

Modified live viral vaccines also have the potential to infect the ovaries and cause reproductive failure during the breeding season. It is currently recommended that modified live BVDV and BHV-1 vaccines are used at least 30 days prior to breeding.

Vaccine Efficacy

In simplistic terms, the USDA requires that all vaccines are safe and elicit a measurable immune response. Unfortunately, immune response does not always equate with disease protection. Numerous studies attempt to examine vaccine efficacy in either experimental challenge, or field trials. Experimental challenge studies have the advantage of better control over exposure conditions. These studies will often use challenge exposure that is know to cause disease and thus can more effectively demonstrate differences between protected and unprotected individuals. However, these challenges are often in excess of what is observed during natural exposure. It is tremendously difficult to design and implement appropriate field vaccination trials that will consistently show vaccine efficacy. A recent review of bovine respiratory vaccine field trials shows that many of these studies are flawed in some way. Appropriate field studies must contain a valid control group, randomization of treatments, blinding of evaluations, adequate statistical power and clinically relevant outcomes.

While many vaccines may show efficacy under controlled challenge experiments, one must be cautious in extrapolating these results to field conditions. In general, if a vaccine shows efficacy under controlled challenge conditions, it will probably offer some degree of protection in the field. The question is whether the degree of protection is clinically significant under the differing management and exposure conditions encountered in the field. Field conditions tend to have more variability in exposure to infectious agents. This level of exposure is difficult to control for from year to year and between groups of animals housed in separate facilities or pastures. Often, the amount of clinical disease experienced is not sufficient to provide statistically meaningful results. For these reasons, it is difficult to get a clear appreciation of how a vaccine will perform in a specific group of animals. It is also important to appreciate that while vaccines may show only limited benefit under conditions of low disease incidence, they may be of high value in preventing or decreasing the severity of disease during a severe outbreak. Unless there is sufficient data to suggest otherwise, it is usually reasonable to expect up to a 30% reduction in disease incidence and disease severity if the vaccine has demonstrated a relevant immune response and/or protection from experimental challenge.

Vaccination Economics

Fundamentally, vaccines are utilized to decrease the incidence and severity of disease and thus decrease the associated treatment costs and production losses. Occasionally, useful information regarding the economic benefit of vaccination can be obtained from clinically relevant field trials. From a production-oriented standpoint, the cost effectiveness of a vaccine is dependent on four factors:

1) Vaccine Cost (VC): The cost of the vaccine supplies and labor.

2) Disease Incidence (DI): The incidence of the disease you are trying to prevent.

3) Disease Cost (DC): The average treatment and production cost of the disease in an affected animal.

4) Vaccine Efficacy (VE): The decrease in incidence and severity associated with the use of the vaccine.

Taken together, **A VACCINE PROGRAM IS COST EFFECTIVE IF**

VC < Cost Benefit of Vaccination = DI x DC x VE

To determine the economic benefit of a vaccination program, one must evaluate each of these factors. The cost of vaccination (VC) is fairly straightforward and includes the total cost per animal of each dose of vaccine used to help control a disease condition, additional supplies (syringes, needles, etc.), and the labor required to administer the vaccine.

The disease incidence (DI) is the percentage of animals that develop a disease during a given time period. Accurate and detailed records are essential in obtaining an accurate estimate of disease incidence. Along with knowing the incidence of the disease process, some information concerning the specific etiology must also be obtained through thorough physical examination, postmortem examination, serology, or specific viral and/or bacterial cultures of acutely affected animals. In some cases disease incidence and etiology may be extrapolated from published data.

The disease cost (DC) is perhaps the most difficult factor to accurately determine. It depends on many variables including drug costs, veterinary costs, labor, decreased growth, decreased milk production, decreased fertility, culling rate, case mortality rate and the economic value of the animal. However, given some thought, one can make fairly reasonable estimates. Careful evaluation of morbidity and treatment costs with the producer will usually provide sufficient information to make realistic estimates of disease cost.

Vaccine efficacy (VE) is a difficult factor to determine and is dependent on a number of variables including the specific vaccine product, the vaccination program, production characteristics, management practices, age, immune status, nutrition and even the disease incidence. Most current vaccines do not specifically protect against infection but rather decrease clinical disease severity and death loss. Vaccine efficacy can be defined as **the percentage reduction in morbidity**. Vaccine efficacy can be as low as 0% or as high as 80%. In some instances you may have sufficient data to determine an accurate estimate of the vaccine efficacy based on disease incidence before and after instituting a vaccination program. In other cases you may need to rely on published research, manufacturer data, or clinical experience from other livestock operations. When specific data is not available it is reasonable to assume a vaccine efficacy of 30%.

True vaccine efficacy is an extremely complex variable that is dependent on numerous interrelated factors independent of the specific vaccine used. Both disease incidence and case morbidity may be attenuated to different degrees by the vaccine. For example, a vaccine may reduce disease incidence by 50%, disease severity (and thus case treatment cost) by 20%, and case mortality rate by 100%. In such a situation it may be difficult to set a single value for vaccine efficacy. A more rigorous approach would be to separate these different values and multiply them by their specific related disease components to determine a more detailed analysis of the overall cost benefit. For example:

$$\text{Cost Benefit} = (VE_1)(DI) \times [(VE_1)(DC_1) + (VE_2)(DC_2) + \ldots + (VE_n)(DC_n)]$$

From a practical standpoint, it is often not necessary to become so detailed in the evaluation of most vaccines in order to provide useful assessment for the producer. It is interesting that as one evaluates different vaccination programs, the use of rough estimates for vaccine efficacy and disease cost will often identify which vaccination programs provide significant cost benefit, marginal cost benefit or negative economic return.

There are additional considerations that provide value to vaccination programs. One important concept is the use of vaccinations as "insurance" against devastating losses. While disease incidence may be at an acceptable level without vaccination, the potential for new disease introduction is always present and could result in catastrophic losses that may be prevented by the use of an appropriate vaccination program. The type 2 BVDV outbreaks in dairy cattle that were observed in the early 1990s is a prime example of how non-vaccinated and inappropriately vaccinated herds were susceptible to high morbidity and mortality. Another economic consideration is the value of vaccinated animals at market. Many livestock buyers place a higher value on vaccinated livestock. Establishment of known vaccination status is important when purchasing dairy cattle as well as feedlot cattle. However, the level of economic incentive remains controversial and can fluctuate dramatically with changing livestock markets.

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