Beef Cow Immunity and Its Influence on Fetal and Neonatal Calf Health*

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Abstract

Improving the immunity of the dam is critical to optimizing the health of the gestating cow and fetus as well as the perinatal calf. Vaccine use alone is inadequate. Strategic management decisions, including types and timing of vaccination, are required. These require a knowledge of the host - pathogen relationship, including immune mechanisms, pathogenesis, and epidemiology. This article selectively reviews the immune system of the cow and fetus during gestation and explores the use of active immunization of the dam as a management tool to control certain reproductive diseases in the beef herd.

Introduction

The successful outcome of pregnancy requires the dam to have, and the fetus to develop, functional immune systems; yet both must tolerate the other. In this immunologic balancing act, the dam must protect the fetus from maternal infections but not reject the fetus. The fetus must attain the ability to differentiate self from nonself but not respond to antigens of the dam. Finally, the dam must produce a high quality colostrum and the precocious calf must consume it in sufficient quantity soon after birth. Superimposed on the immunologic interactions of the cow and fetus/calf are our attempts to manipulate their immune responses through management and vaccines. There are few well-designed and executed clinical trials in the scientific literature to evaluate the clinical efficacy of many vaccines. This discussion selectively reviews the immune system of the cow and fetus during gestation and the use of active immunization of the dam to control certain reproductive diseases in the beef herd.

Immune Defenses of the Reproductive Tract

The reproductive tract of cattle is one of several mucosal interfaces between the animal and the environment. At these mucosal interfaces, much of the early interaction between the host and the pathogen occurs. Not surprisingly, these systems with extensive mucosal surfaces, such as the reproductive, respiratory, and gastrointestinal tracts, are also the sites of many of the significant diseases of cattle.

The primary function of the immune system at mucosal surfaces is to prevent pathogens from entering the body. This function can be severely compromised by the other physiologic roles of the mucosal surface such as absorption. There are differences in the mucosal surfaces within the reproductive tract; for example, the normal vagina has a resident microflora while the healthy uterus is normally sterile. The defense systems at the reproductive mucosal surfaces include both innate and acquired immunity.

The innate immune system is usually the first line of protection at the reproductive mucosal interface. It includes physical barriers, such as the epithelium, mucus, and the sometimes closed cervix; humoral factors, such as complement, lysozyme, lactoferrin, and peroxidase; and some cellular responses mediated by macrophages, polymorphonuclear neutrophils, and natural killer (NK) cells. The mediators of innate immunity are not antigen specific and do not require immunologic priming.

Acquired immunity is mediated by lymphocytes and is the type of immunity we attempt to manipulate with vaccines. Lymphocytes, along with some accessory cells, are responsible for recognizing foreign substances, responding to them, making soluble factors such as interleukin and interferon, killing infected and foreign cells, and producing antibodies. In contrast to innate defenses, acquired defenses are antigen specific, antigen driven, and mediated by antibodies, cytotoxic T lymphocytes, and cytokines produced during an immune response.

Acquired Immune Response

An acquired immune response may be divided into three phases: cognition, activation, and effect.[1] Depend-

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ing on the immunologic experience of the animal, these phases take a varying number of days to occur and the response will not be maximal for 2 to 4 weeks after exposure to antigen.

The acquired immune response is initiated by the recognition of a foreign substance called antigen. This can be a virus, bacteria, toxin, or any other nonself substance. During the cognition phase, antigen-presenting cells process and present the antigen to lymphocytes for recognition.

The activation phase is the sequence of immune events that occurs as a result of the cognition phase. Lymphocytes undergo two major changes in response to antigens: (1) They proliferate, leading to expansion of the clones of antigen-specific lymphocytes and amplification of the immune response, and (2) they differentiate to cells that function to eliminate foreign antigens.

The effector phase of immune responses is the stage in which antigen-activated lymphocytes perform functions that lead to elimination of the antigen. This includes production of antibodies by B lymphocytes and elimination of infected cells by cytotoxic T lymphocytes.

Different subtypes of lymphocytes have specific functions in the overall immune response. Some, called helper cells, are responsible for producing and releasing factors that turn on the immune system. Others, called suppressor cells, are able to turn off the immune response. The balance between the number or the net effects of these two cell types — helper/suppressor ratio — is important in determining the ability of the animal to respond to a vaccine. Certain lymphocytes are able to recognize and destroy cells that have been infected by viruses or bacteria. These are known as killer or cytotoxic cells and are important in an animal's ability to fight intracellular infections. The cells mentioned above — helper, suppressor, and cytotoxic cells — are all part of the cell-mediated immune system and are lumped under the general classification of T lymphocytes because they all originate in the thymus.

The phrase "cell-mediated immunity" (CMI) can have several meanings, especially regarding modified-live and killed vaccines. This inconsistent usage has resulted in confusion. In its most general usage, the term CMI can include any immune phenomenon mediated by a cell. In more specific usage, it includes only effects mediated by cytotoxic T lymphocytes. It is most commonly used to describe any effect mediated by a T lymphocyte. This includes the effects of T helper, T suppressor, and T cytotoxic cells. During the activation stage of the immune response, a T helper cell response is a normal and necessary part of antibody production from B lymphocytes.

Indirect measures of immune function that assess T helper cell function, such as lymphoproliferation, are likely to show a positive response even if the effector component of CMI, cytotoxic T lymphocytes, is not stimulated. For example, following administration of a modified-live bovine herpesvirus 1 (BHV1) vaccine to a naive animal, virus replication occurs. The immune system responds to this "infection" as outlined above. T helper cells are activated, cytokines are produced, antibody titer rises, and cytotoxic T lymphocytes "see" virus infected cells and are primed. In response to a killed vaccine all of this would occur as well, except the immune system would not be exposed to virally infected cells. The practical implications of these differences would vary from pathogen to pathogen and are difficult to assess, but may partially account for the differences noted in the immune responses to modified-live versus killed virus vaccines.

The cells responsible for the production of antibodies are called B lymphocytes. When B lymphocytes are presented with a foreign substance they recognize (cognition phase), they undergo repeated divisions and eventually mature into antibody-producing lymphocytes (activation phase). The increased number of activated lymphocytes producing antibodies results in elevation of the antibody titer of the animal to the inducing antigen (effect phase). We use this increase in antibody titer to evaluate the effectiveness of a vaccine; however, as we have briefly discussed, antibody response comprises only one part of a very complex process. In the ruminant, immunoglobulin (Ig) G is a major secretory Ig,[22] and, like secretory IgA, has been shown to be capable of defending mucosal surfaces.

Fetal Immunity

The ruminant fetus is particularly susceptible to infectious agents for three reasons: 1) the syndesmochorial placentation does not allow passive transfer of maternal Ig during pregnancy, 2) the fetal immune and accessory systems are immature and therefore not fully functional, and 3) the fetal environment provides factors or cells which are conducive to microbial replication.[86]

Fetal immunocompetence develops during gestation. Lymphocytes have been observed as early as 42 days of gestation in the bovine fetal thymus, day 45 in the fetal blood, and in the spleen and bone marrow by 55 days.[95] Lymphocytes that contain IgM were demonstrated by day 59 and those containing IgG, by day 145 of gestation. IgM is not observed in the serum until day 130 of gestation.[87] Lymph nodes begin to form at around 60 days and the size of all fixed lymphoid organs increases as gestation progresses.[95]

At 75 to 80 days of gestation, bovine fetal lymphocytes have a suboptimal response to mitogens (plant glycoproteins used *in vitro* to stimulate lymphocytes in

a antigen-nonspecific manner). The lymphoproliferative response increases and, by 120 days of gestation, the response to mitogens for many fetuses is in the range of values obtained for lymphocytes from normal adult cattle.[51] Lymphocytes from bovine fetuses inoculated with *Mycobacterium bovis* at approximately 125 days of gestation are not stimulated by purified protein derivative of *M. bovis* (PPD) at 20 or 50 days post-infection, whereas lymphocytes taken from adult cattle at similar intervals after *M. bovis* inoculations are stimulated by PPD.[70] These fetal lymphocytes did demonstrate a response to mitogens. When fetal lymphocytes obtained by cannulation of the thoracic duct after day 121 of gestation were stimulated with a mitogen, they displayed patterns of secretion of the cytokine interleukin-2, a potent activator of T and B lymphocytes, indistinguishable from those of similarly treated lymphocytes from an adult animal.[46] Newborn calves can reject skin grafts just as vigorously as adults, indicating the CMI develops in the bovine by the time of birth.[10]

Granulocytes appear in the fetal blood at day 130 of gestation.[95] The fetal ruminant inflammatory response differs from that of the adult. Observations of inflammatory lesions occurring in a variety of infectious diseases show a fetal response composed primarily of monocytes and macrophages, while the response induced in the adult is a predominantly polymorphonuclear leukocyte reaction.[37]

Neonatal Immunity

Once a normal calf is born, the most important determinant of its immunocompetence is the timely consumption of colostrum.[89] The virtually agammaglobulinemic calf receives large amounts of passive IgG_1 via intestinal absorption during the first 12 to 24 hours of life.

Serum IgG_1 is trapped by receptors on mammary epithelial cells of the dam, transported through these cells, and secreted into the colostrum in the acinar ducts.[7] In gestating dairy cows, there is a gradual decrease in the serum levels of IgG_1 during the weeks prior to parturition, then a gradual increase during the following weeks.[59]

The duration of protective titers following passive transfer is a function of dose and timing. The half-life of IgG in cattle is around 20 days.[73] By 100 days of age (five half-lives), 97% of the maternal antibody will be gone.[6] However, residual passive antibody must be considered when designing calf vaccination programs, because, depending on the pathogen and the vaccine, even low residual titer may interfere with immunization.[73]

Colostrum also contains leukocytes that can influence the immune response of the newborn. Compared to calves fed cell-depleted colostrum, calves fed complete colostrum showed no decrease in lymphocyte numbers in the blood on the second day of life, uniform blastogenic response to a mitogen, slightly enhanced antibody formation against sheep erythrocytes, and a high spontaneous proliferation of mononuclear cells during the first week of life.[92] Calves fed colostral leukocytes isolated from heifers immunized with *M. bovis* had increased lymphocyte blastogenesis to PPD between 3 and 21 days compared to calves fed colostral cells from control heifers.[35] Thus, colostral leukocytes appear to be absorbed from the gut and to be able to affect the immune function of the calf. The impact of colostral leukocytes on neonatal morbidity and mortality has not been examined.

The lymphoid systems of cattle and sheep contain a large number of gamma-delta ($\gamma\delta$) T cells, in contrast to the lymphoid systems of humans and mice. This is especially true in neonates where $\gamma\delta$ T cells comprise 60% of the T cell pool.[47] These cells are found in the epidermis, intestinal epithelium and lamina propria, the basal layers of the stratified squamous epithelium of the tongue and esophagus, the pseudostratified epithelium of the trachea, and the transitional epithelium of the bladder. Based on their tissue distribution and circulation patterns, the most probable function of $\gamma\delta$ T cells is the protection of epithelial surfaces, which may be a particularly vital role in the precocious bovine neonate.

Newborn calves cannot respond to all antigens with the same magnitude. In one study,[6] newborn calves were able to respond to soluble protein antigens, chicken red blood cells, and a bacteriophage at birth. However, antibody to certain bacterial, protozoal, and viral antigens was not produced or did not appear until 14 to 30 days of age. *Salmonella* bacterin administered to Holstein calves starting at 1 to 19 weeks of age failed to elicit antibody responses to the lipopolysaccharide (LPS) cell-wall antigen in calves less than 12 weeks old but did stimulate Ig responses to whole-cell antigen regardless of age. In contrast, modified-live *S. dublin* vaccine given to calves at 1 to 3 weeks of age stimulated anti-LPS Ig, although the response was not as rapid and was of lesser magnitude than that of older calves given *Salmonella* bacterin.[93] The practical implication of these observations is that the effects of vaccination on the newborn or young calf can be affected by both their passive immune status and the specific antigens in question.

Immunization Considerations

Vaccine-induced immunity is one of several management tools available to the veterinarian to help livestock achieve optimum productivity through disease prevention, control, and eradication. Disease surveillance is a critical part of each herd program to determine

need and evaluate the effectiveness of each immunization procedure. This surveillance requires accurate monitoring of clinically affected animals and should be done routinely on breeding females that do not become pregnant or fail to calve, as well as herd sires. Additions to the herd should be from known sources and be examined, tested, immunized, and isolated for an accepted time before being mixed with the herd. Duration of isolation is dependent on the source of the cattle and the disease(s) of concern. Other risk factors that should be considered are animals in surrounding herds, common grazing agreements, other species that may be carriers, and the use of frozen semen or embryos from outside herds.

We manipulate the immune system in two ways — management decisions and vaccines. The two key components required for a successful immunization are an efficacious vaccine and an immunocompetent animal. Despite the simplicity of the concept, along with some environmental considerations, these are the basis for all vaccination successes. Vaccine failures arise from inattention to details in these critical areas and are discussed later.

Both live and killed vaccines are in use. The advantages of one are usually the disadvantages of the other. Modified-live vaccine attributes include strong, long-lasting antibody response achieved with fewer doses; less reliance on adjuvants; possible stimulation of interferon production by virus vaccines; stimulation of the effector component of cell-mediated immunity (cytotoxic T lymphocytes); and the bacteria or virus may appear and behave more like the pathogenic form of the organism. Some of the advantages of killed vaccines are that they are more stable in storage and they are unlikely to cause disease due to residual virulence or reversion. Some vaccine considerations that impact the health of the fetus and the calf are discussed below.

Bovine Herpesvirus 1 (BHV1)

Bovine herpesvirus 1 is a widespread disease primarily affecting the respiratory and reproductive systems.[14] The respiratory form, BHV1, referred to as infectious bovine rhinotracheitis (IBR) may terminate pregnancy at any stage of gestation,[26,76] and may contribute to neonatal losses in calves from susceptible dams.[14] A strain that may interfere with conception is BHV1 type 2, which causes the disease known as infectious pustular vulvovaginitis (IPV). The IPV form affects the genital mucosa of heifers and bulls and, if severe, may interfere with conception by reduced mating activity but does not appear to cause abortion.[76,77,79]

The use of intramuscular modified-live vaccine at the correct time of the production cycle provides protection against respiratory signs and abortion in cattle.[14,25,48,53,94] It does not prevent latency induced by aerosol exposure to 4 ml of $10^{6.5}$ $TCID_{50}$ of virulent BHV1/ml.[84] Animals with passive immunity from immune dams may fail to show an antibody response to vaccination before 6 months of age but cellular immune function may be primed.[20,73] Vaccine should be administered a minimum of one additional time approximately 1 month before breeding to insure stimulation of the immune system.

Achieving successful immunization while avoiding complications requires proper timing of administration and handling of vaccine. Vaccination at the time of breeding with intramuscular modified-live vaccines may seriously decrease the conception rate in susceptible cattle.[24,99] Intravenous administration of a 5 ml of cell culture medium containing from $10^{6.5}$ to $10^{7.3}$ $TCID_{50}$/ml of one of four vaccine strains of BHV1 on post-breeding day 14 resulted in infertility in four of eight heifers.[78] Failure of a single injection of modified-live agent to immunize may be due to improper handling, storage, or administration. Solid immunity to BHV1 of long duration that minimizes the chance of a sporadic natural infection at critical stages of reproduction or production is essential for a well managed breeding herd.

Declining immunity may be stimulated by natural infection, reactivation of latent virus, or the administration of modified-live vaccine. The annual use of intramuscular modified-live IBR products is unnecessary.[55] Immunity of long duration follows infection by virulent virus or by modified-live injection.[25] This would include protection of the fetus from transplacental infection in most cases.[14,55,58]

Recent work indicates that BHV1 subtype 2b virus administered to seronegative pregnant heifers did not cause abortion.[79] This may indicate a possible use of BHV1 subtype 2b virus for an intramuscular modified-live product that could improve safety and still provide a durable immunity. Similarly, thymidine kinase-negative mutants of Cooper[80] and Los Angeles[62] strains of BHV1 may also be useful as vaccines as they did not cause abortion when administered to pregnant cattle. *In utero* inoculation of a modified-live BHV1 vaccinal strain into the fetus and the amniotic fluid via right flank laparotomy resulted in vaccine related abortion in one of nine cows, while 4,543 pregnant cows administered the same virus intramuscularly had no reported incidence of vaccine related abortion.[101]

Since the modified-live products must replicate (cause infection) in order to stimulate immunity, caution should always be used in planning the herd vaccination program to avoid the exposure of susceptible or nonvaccinated animals. Viral shedding has been a concern as a source of infection to susceptible animals with modified-live vaccines.[14,102] The use of intranasal modified-live vaccine offers a safe alternative in

nonvaccinated pregnant or stressed cattle and is recommended for use in bulls which are to be used in artificial insemination programs with frozen semen.[14] The duration of immunity has not been determined following use of intranasal immunization and it is more difficult to properly administer than intramuscular products.[48] The use of an intramuscular modified-live vaccine at the next opportunity following intranasal immunization increases the likelihood of a durable immunity. Additional modified-live immunizations may be necessary under certain situations and should be carefully planned for each herd.

The use of killed IBR vaccines has increased because of safety concerns related to modified-live vaccines. Critical studies demonstrating the ability of killed BHV1 vaccines to protect the fetus are not available. Since repeated injections are necessary, it may be difficult to avoid periods of susceptibility due to low levels of immunity during some stages of production.[14,48,55]

Bovine Virus Diarrhea Virus - BVDV

The BVDV is distributed worldwide and has a high rate of prevalence based on serology.[91] The main concern for the beef breeding herd is fetal infection with resulting abortion, congenital defects, or the development of persistently infected carriers that are a constant source of infective virus.[4,13,91] Studies have reported a serious effect on conception if local BVDV infection occurs by experimental inoculation[42,104] or following natural service with a persistently infected bull.[71] Following local infection, susceptible animals seroconverted due to systemic infection, resulting in immunity.

Confusion and controversy have surrounded the disease syndromes caused by BVDV since the first modified-live vaccine became available.[91] Fortunately, research during the past few years has unclouded much of the confusion related to the spread of BVDV and the cause of the severe or chronic "mucosal disease" form.[18,21,82] Current information does not conclusively document the duration of protection following natural infection or the use of modified-live BVDV vaccine, although available information indicates that infection confers more than a single year of protection to the fetus.[34,54,58,83,91]

The virus can cross the placenta in susceptible pregnant cattle and result in fetal infection either through exposure to the field virus or the improper use of intramuscular modified-live BVDV vaccines.[103] If this occurs during the first 6 months of pregnancy, fetal losses or immune tolerance may result. Fetal infection during the last trimester of gestation usually results in the birth of an immune, seropositive, healthy calf.[68] Seronegative cattle, vaccinated with modified-live BVDV in the last trimester of pregnancy, had calves that seroconverted as fetuses whereas over 90% of cattle that were seropositive had calves that did not, indicating that transplacental infection of previously exposed dams did not occur.[85]

Critical studies comparing the ability of modified-live and killed BVDV vaccines to protect the fetus in field situations are not available. It is believed that optimum protection of the beef breeding herd is dependent on active immunization with modified-live BVDV vaccine prior to breeding.[13,34,48,54,91] To insure a response, the vaccine should be administered to replacement heifers, two or more times between weaning (6 to 8 months of age) and breeding.[13,48,54] The final injection should be at least 1 month before breeding in order to avoid detrimental effects on conception. Although not documented, the use of different strains or serotypes of modified-live vaccine virus for each injection has been proposed to expand the range of cross protection. The genetic and antigenic instability of BVD virus may result in the emergence of isolates that have reduced antigenic cross-reactivity.[19,31,57] The clinical importance of specificity of circulating antibody and effects of viral mutation on cellular immunity are unclear at this time.

A temperature-sensitive, modified-live BVDV vaccine was shown to be safe and induce seroconversion in pregnant cattle.[69] A killed Singer-strain vaccine prevented clinical signs following intravenous challenge.[72] Pregnant cows vaccinated with an experimental polyvalent killed virus BVDV vaccine and challenged intranasally at 80 days gestation showed improved resistance to fetal infections versus nonvaccinated controls.[45]

The long duration of immunity and the cross protection between serotypes following the use of modified-live vaccines make them preferable for use in beef breeding herds. The opportunities for a planned vaccination at noncritical stages of production and during times of minimal stress are available. This makes infection from field strain viruses during critical periods of fetal development less likely. If immunity has declined enough to permit natural infection, it may stimulate an immediate immune response without severe disease consequences and this may be the basis for maintaining long-term immunity.[54] Depending on the circumstances of each herd, annual, biannual, or less frequent modified-live virus vaccine injections to cows between calving and breeding may be recommended.

Campylobacteriosis - (Vibriosis)

This venereal disease of beef cattle is characterized by temporary infertility and, sometimes, abortion.[5,23] It continues to interfere with optimum reproductive rates in a number of beef herds, in spite of the availability of effective vaccines, from a failure to develop and

utilize adequate herd vaccination programs. (Grotelueschen DM, Hudson DB, personal communication, May 1993)

The immunity induced by parenteral injection is somewhat different from natural infection. Circulating antibody may not provide protection against venereally transmitted microorganisms that invade the reproductive tract directly.[33] It is also possible to have local immunity without a rise in serum antibody.[33,106] These factors may be responsible for partial immunity that, in some cases of exposure, results in delayed conception or early conception with low-grade infections that may result in later abortions.[33] Following infection of naive animals, the organism is usually eliminated from the animal within 4 to 5 months as local and systemic immunity develop. Active immunization confers adequate protection for a high reproductive rate but does not prevent local vaginal infection of the dam.[33,50] Effective immunization using oil adjuvanted vaccine (Vibrin®, SmithKline Beecham, Exton, PA) requires a sensitizing dose, followed by a second injection 1 month prior to breeding and then annual boosters approximately 1 month prior to natural service for all breeding females.[5,23,50]

Immunization of bulls has been shown to be of value in preventing the carrier state even though they may mechanically transmit the organism for a short time.[28,40,104] The use of 2.5 times the recommended dose, twice the first year, followed by annual boosters 1 month prior to breeding has been shown to be effective in eliminating carriers.[104] Generally, oil adjuvanted products (Freund's incomplete adjuvant) are preferred because of more durable immunity following single annual boosters.[5,50] Products in aluminum hydroxide adjuvants generally induce less durable immunity and, to be effective, should be given 10 days prior to a limited breeding season.[8] The oil adjuvanted product requires an annual booster, preferably one month prior to breeding.[23] Modification of these recommendations for the prevention and control of campylobacteriosis, such as immunization of only part of the cow herd or only bulls, or failure to utilize booster injections at the correct time, may result in decreased effectiveness.

Leptospirosis

Leptospira interrogans serovars *hardjo* and *pomona* have been reported to be the most frequent cause of abortion in cattle.[12] The most common isolate in the United States is serovar *hardjo* genotype *hardjo-bovis.*[75] This genotype of hardjo is antigenically different from the *hardjo-prajitno* genotype identified in Europe and currently used in the multivalent vaccines.[67] In one study,[15] the serovar in the multivalent vaccine produced circulating antibody following one or two doses, but it was not protective against experimental conjunctival challenge. Further studies using an experimental vaccine derived from a *hardjo-bovis* isolate also failed to prevent infection and urine shedding from conjunctivally challenged cattle.[16,17]

In endemic areas, frequent immunization with multivalent antigens containing the specific serovar is recommended.[36] In the majority of beef herds not in endemic areas, less frequent immunization of animals is usually practiced. Previous information indicates that annual vaccination in closed herds and every six months in endemic areas is protective.[44] Recent studies revealed fetal infection, stillbirths, weak calves, and apparently healthy calves shedding the organisms in urine following challenge of immunized pregnant cattle at 4 to 6 months of gestation.[15] Based on this information, it may be beneficial to administer booster injections of vaccine again during midterm pregnancy in an attempt to reduce fetal losses in later gestation and the perinatal period.

Immunization of bulls with booster injections immediately prior to breeding season may be considered due to the reported incidence in bulls, possible venereal transmission, and the potential of reducing urine shedding following natural infection.[17,36,75]

It is difficult to fully justify immunization of the majority of beef cattle herds based solely on the reported incidence and currently available information on vaccine efficacy. It is possible that local immunity could permit improved reproductive rates even though infection is present and the dam sheds the organism in urine.[44] Further study regarding the benefit of immunization may answer these questions.

Trichomoniasis

Reproductive losses due to infection by *Tritrichomonas fetus* result primarily in delayed fertility but are also associated with abortion, pyometra, and reduced calving rates in limited breeding seasons.[61] The disease generally is insidious in onset because a single or limited number of infected animals initiating the disease in a susceptible herd. The disease is widespread in the range areas of the western United States and has been diagnosed as a significant cause of infertility in some beef herds for more than 50 years.[52,63]

Resistance and immunity to natural tritrichomonas infection are similar to other pathogenic organisms causing local infection of the reproductive tract such as campylobacteriosis.[97] Infected animals gradually develop enough immunity to remain pregnant and eventually eliminate the infection in 4 to 7 months.[2,98] This is important for control of the disease in herds with limited breeding seasons since infected pregnant females rarely remain infected until the next

breeding year.[60] Bulls are the primary source of disease and, with the possible exception of artificial insemination, are the only method of spread. Once exposed, older bulls are more likely to remain infected than young bulls.[27] Clinicians should not be lulled into a complacent attitude towards testing young bulls because of this characteristic. *T. fetus* has been cultured from essentially any age bull. (Grotelueschen DM, personal communication, 1993)

Controlling the disease by immunization has been studied and a commercial vaccine (Trichguard®, Fort Dodge Laboratories Inc, Fort Dodge, IA) is currently available. Immunizing bulls appears to have limited application under most situations.[29, 30] Immunizing breeding females has resulted in more rapid elimination of infection and a reduction in early abortion compared with controls.[64, 96] Further studies are needed to provide additional information on efficacy and evaluation from an economic standpoint. Vaccination is currently recommended for controlling the disease in infected or high-risk herds.[48,64,96]

Management is critical to control trichomoniasis, regardless whether vaccine is used. Given the relative ease, accuracy and cost of diagnostic surveillance of herd bulls and open females for trichomoniasis, it should be a routine practice in beef herds.[2,3,5,9,74] Prevention and control of the disease require management decisions based on epidemiologic characteristics of the disease and have been reviewed.[5]

Haemophilus somnus

Haemophilus somnus can innocuously colonize the healthy genital mucosa of the cow.[66] It has also been associated with genital inflammatory disease[49] and abortion[39] in cows. *H. somnus* associated reproductive diseases have been reviewed.[65,81]

Corbeil *et al* were able to induce abortion experimentally using an intravenous challenge of large numbers of organisms.[32] Commercial[107] and experimental[100] *H. somnus* vaccines have been shown to attenuate the effects of intravenous challenge. Although intrauterine infusion of *H. somnus* resulted in increased serum anti-*H. somnus* antibody titer and transient genital inflammatory lesions, it provided no protection against challenge five months later.[56] Similarly, vaccination with an anionic antigen of *H. somnus* induced an increase in serum antibodies but did not increase antibodies at the vaginal mucosa or provide protection to challenge.[88]

There are no reports documenting reduction of *H. somnus*-induced infertility or abortion in vaccinated cattle in the refereed literature. Despite anecdotal reports of efficacy, gaps in our understanding of the epidemiology of *H. somnus*-induced reproductive disease and lack of demonstration of vaccine efficacy make it difficult to justify recommendation of vaccination.

Additional Vaccines

Several additional vaccines are available that may influence the outcome of a successful breeding herd health program. Nearly all diseases may indirectly affect reproduction by interfering with the normal physiologic processes. Brucellosis, caused by *Brucella abortus*, is currently of limited distribution in the United States due to eradication efforts. Vaccination of replacement heifers is recommended under most circumstances because of requirements for their interstate shipment and sale. Although the vaccine has been shown to be efficacious in the past, there is less information regarding the reduced dosage now recommended.[48] Federal guidelines will dictate future use of this vaccine.

Optimizing Immunization

As stated at the outset, injection of a vaccine only ensures that the animal has been exposed to the antigens contained in that vaccine, not that a protective immune response will ensue. The two key components required for a successful immunization are an efficacious vaccine and an immunocompetent animal. We will briefly discuss why one of these components may be missing, resulting in an apparent vaccine failure.

Achieving a protective immune response to every pathogen in every animal in a population is probably impossible for several reasons. Even if it were possible, its cost would be prohibitive. Based on their pathogenesis, some disease agents require each individual in a population to be immune for the vaccine to be efficacious. An example would be an infectious, but noncommunicable, disease like tetanus. For other pathogens, especially those that are highly contagious, reducing the number of susceptible animals below a critical threshold may be sufficient for the vaccine to be efficacious by preventing a disease outbreak. This is the concept of herd immunity.

Our goal in herd immunization is to raise the level of immunity in a sufficient number of animals to prevent epidemics and the catastrophic monetary losses associated with them. This means that individual animals may still become ill, especially if other factors are present that reduce their level of disease resistance. In a population of immune animals, disease transmission is reduced as disease resistance increases. This reduces, but does not eliminate, the chances of a disease with high morbidity or mortality. Paradoxically, individual animals can still become ill when the vaccine is successfully stimulating an effective level of herd immunity.

There are pathogens that can influence fetal and/

or neonatal calf health for which no vaccines are available, such as *Neospora*-like protozoa and *Ureaplasma*. There are situations where antigenic differences between strains and species of pathogens or changes in the antigens the organism displays may compromise vaccine efficacy. A previously mentioned example of this is the genetic and antigenic instability of BVD virus.[31] This instability was thought to be the cause of the failure of repeated annual doses of inactivated virus vaccine to protect animals from infection.[19,57] For many infectious agents of cattle, however, the immunologically important antigens are relatively stable.

A more likely cause of vaccine ineffectiveness is improper handling, as was mentioned in the discussion of BHV1. Vaccines must be stored and administered as recommended or their efficacy will be reduced. Special care must be taken with any live vaccine, either viral or bacterial, to prevent inactivation of the vaccine by exposure to extreme temperature, ultraviolet radiation, disinfectants, and other harmful environmental factors.

Sanitation is an important component of any vaccination plan and helps minimize injection site reactions and abscesses. Contamination of a multidose container can result in vaccine inactivation and injection site problems. Some disinfectants will destroy vaccines, so care must be taken to properly clean all equipment that comes in contact with the vaccine.

Once we have done everything to make certain that the vaccine and the equipment are properly cared for, we should administer the vaccine carefully. Ensuring our personnel are knowledgeable about the proper locations for vaccine administration, changing needles at intervals or whenever they become barbed or bent, and having good handling facilities help minimize injection site reactions.

Timing of vaccine administration can also influence our perception of vaccine effectiveness. If an animal is incubating a disease or is exposed to the disease-causing agent soon following vaccination, sickness may result and the vaccine will appear ineffective. It takes several days for an animal's immune system to respond to a vaccine and for the animal to be protected, especially if the calf is immunologically naive.

Experimentally, if we give enough of the disease-causing organism, we can cause disease even in animals that have immunity. When cattle are assembled in close quarters, the amount of disease agent that they are exposed to may be quite large, resulting in disease even in immune animals.

Individual animal responsiveness can affect vaccination success or failure. Not all animals are able to respond to vaccines, for a variety of reasons including age, nutrition, genetics, stress, and previous vaccination and disease history. As previously mentioned, a calf's immature immune system is not able to respond to vaccines as well as the immune system in adult cattle.[6,93] Even though the bovine fetus is able to recognize and respond to antigens before birth, the immune system does not reach its peak function until around puberty. Much later, immunocompetence wanes with old age.

The previous nutritional status and parasite burden of a calf or cow can affect their overall physiology and their immune responsiveness. Parasites have been shown to produce immunosuppressive substances as they progress through their larval molts.[41] Since the immune system is a part of the larger organism — the cow or calf — nutritional deficiencies in energy and protein are likely to compromise both overall physiology and immune function. Trace minerals and vitamins are thought to play an important role in maintaining an optimally functioning immune system, although this is incompletely understood and the practical implications are even move obscure.

Genetics contribute to an animal's ability to respond to a vaccine, although markers in cattle that would indicate good or poor responders have not yet been found. Genetic predisposition to infectious disease has been described in other species and speculated upon in cattle.

Stress is an important factor in determining the ability of the animal to respond to vaccines and comes from a variety of sources, including transport, nutritional changes, weaning, handling, and so on. The relationships between stressors and disease resistance have been speculated on for centuries. In the nineteenth century, Pasteur noted that placing a chicken's legs in cold water increased its susceptibility to anthrax. Similar relationships have been described in cattle. Weaning reduces antibody responses in calves.[43,90] Lymphocyte function is suppressed in transported calves.[11,38] Efforts should be made to minimize as many different stressors as possible to increase the chances that an animal can respond to the vaccine.

The concept of additive stressors is especially relevant when discussing the immunologic sequelae of distress. It usually is not a single stressor that debilitates the immune system; more often, the cumulative effects of a series of mild and moderate stressors experienced over a period of hours to days depress immune function below a threshold that prevents an effective immune response from occurring. Each animal has a unique immunologic history and varies in its response to these stressors resulting in the spectrum of morbidity and response to vaccine that we frequently see in cattle.

Once we appreciate the importance of the additive stressor concept, along with some of the interactions of distress and immune function, it becomes apparent that a positive intervention

point for health managers is identifying and minimizing preventable stressors. Many distresses that cattle encounter result from the marketing and management systems inherent in the cattle industry of the United States, and we often can have little impact on such stresses. However, an objective examination of our management strategies will reveal that many controllable stressors are tolerated in the interest of economics or convenience.

Conclusion

Specific vaccine recommendations should be made by you, the veterinarian familiar with the operation, the type of cattle handled, and the disease problems cattle typically experienced. There are few cookbook solutions. Fine tuning the program by including or excluding certain vaccines requires working to identify the specific disease entities present in an operation. This requires good records, complete postmortem examinations, and a good diagnostic support system. Effective management to optimize the immunocompetence of the cow and the timing of administration of the vaccine is as important as selecting the correct antigens and type of vaccines to be used.

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