

## **HEALTH AND BIOSECURITY CONCERNS TO IMPROVE BEEF CATTLE REPRODUCTION**

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Maintaining the health of animals in a beef breeding herd is critical to insure optimum herd productivity since the major contributor to overall herd performance is the reproductive rate. Because of this level of importance, it is essential to carefully monitor all aspects of herd reproduction on a production year basis in order to monitor each year's production and make good management decisions.

Since reproduction is the basis of herd productivity, the effects of suboptimal health or disease is the primary cause of reduced performance. We should define "disease" as any deviation from normal in an individual animal. This includes non-infectious and infectious causes of disease. Physical injury, management or environmental stress, toxic agents or nutrient deficiencies alone or in combination with infectious agents can contribute to disease and, in turn, reduce reproductive performance.

The risk of introducing infectious diseases into a herd can be reduced by following good management practices. The term "biosecurity" has recently been used to address the areas related to disease prevention, containment, and control within a herd.

### **Components of Biosecurity**

In this discussion, herd biosecurity will be covered under four parts: (1) to reduce or eliminate the source of disease; (2) to minimize disease transmission; (3) to maximize each animal's ability to resist disease; and (4) to record animal health and productivity parameters to monitor herd health and permit early detection/control of problems.

#### *1) Reduce the source of disease*

A common source of disease in beef cow herds is through contact with other cattle. Some additional risks are involved through other livestock species, visitors, feed, water, manure and purchased semen as well as less apparent sources such as dogs, cats, rodents, birds, and other wildlife. This is especially true in regard to several primary reproductive disease agents that are primarily spread by close or direct animal contact and makes it important to determine the individual and herd of origin health status of new animals before herd entry. In all cases an appropriate quarantine, testing, and pre-entry immunization program should be mandatory for all animals prior to herd entry, even if they originated in the same herd. It is advantageous to plan and manage breeding programs and pastures to minimize exposure, including fence-line contact with neighboring livestock. Avoiding visitor and vehicle contact with livestock, being aware of potentially contaminated feed or water sources, and sound sanitation practices are an important part of breeding herd management. A specific consideration in breeding herd biosecurity is the potential of introducing disease through the use of outside semen or embryos. As a general rule, national semen suppliers conform to specific standards for certified semen but smaller bull studs may

provide collection and freezing services without a complete health protocol.

2) *Minimize disease transmission*

It is best to avoid commingling various age or management groups within herds, especially prior to breeding and calving. Maintaining separate management groups whenever possible can limit the spread of disease within a herd. The common use of livestock equipment without proper cleaning and disinfection can also be an avenue for disease exposure. Finally, the proper handling of livestock waste and carcass disposal is an important part of herd biosecurity.

3) *Maximize the animals ability to resist disease*

Individual animal disease resistance is of paramount importance in the prevention and control of certain reproductive diseases. Obviously, animals should be fed an adequate diet based upon NRC requirements and management stress should be avoided whenever possible to assure a healthy animal that can respond to disease challenges. This form of disease resistance or immunity is known as innate or natural disease resistance. Another important part of disease resistance is that from “induced or acquired” immunity. It is important to realize that even though animals may recover from the initial challenge of an infectious agent and become somewhat resistant, they may also become carriers of the disease and be a source of infection for other herd mates.

4) *Record animal health and productivity parameters to monitor herd health and permit early detection/control of problems*

Good records are invaluable for monitoring all aspects of herd reproductive outcomes and animal health. They provide a basis for comparing year to year variation and can be important documents for monitoring subclinical disease effects such as marginal nutrient deficiencies on the breeding herd. Small variation in final results are expected but significant decreases in reproductive rates should be examined and the cause corrected if efficient production is to be maintained.

An early diagnosis permits the institution of immediate control practices and minimizes the spread of disease between animals. For example, detection of repeated estrus during the breeding season is better than detection of delayed pregnancy or pregnancy failure and detection of abortion problems is preferable to waiting to find cows that fail to calve, in terms of diagnostic and control measures.

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## **“IMMUNIZATION OF THE BEEF COW AND ITS INFLUENCE ON FETAL AND NEONATAL CALF HEALTH”**

### **Brief Synopsis**

Improving the immunity of the dam is critical to optimizing the health of the gestating cow and fetus and the perinatal calf. Vaccine use, by itself, 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 non-self 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 the immune response 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 disease 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 includes 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.(Abbas 1991) Depending 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 two to four 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 non-self 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 and/or the net effects of these two cell types, or 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, since they come from 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. Most commonly it is 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 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. The differences 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 immunoglobulin,(Butler 1982) 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 immunoglobulins 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.(Osburn 1981)

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.(Schultz 1974) 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.(Osburn 1982) Lymph nodes begin to form at around 60 days and the size of all fixed lymphoid organs increases as gestation progresses.(Schultz 1974)

Bovine fetal lymphocytes demonstrated a suboptimal response to mitogens at 75-80 days of gestation. 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.(Jensen 1988) 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.(MacLachlan 1984) These fetal lymphocytes did demonstrate a response to mitogens (plant glycoproteins used in vitro to stimulate lymphocytes in a nonantigen specific manner). 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.(Hein 1988) Newborn calves can reject skin grafts just as vigorously as adults, indicating the CMI develops in the bovine by the time of birth.(Billingham 1957)

Granulocytes appear in the fetal blood at day 130 of gestation.(Schultz 1974) 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.(Enright 1981)

### **Neonatal Immunity**

Once a normal calf is born, the most important determinant of its immunocompetence is the timely consumption of colostrum.(Perino 1992) The virtually agammaglobulinemic calf receives large amounts of passive IgG1 via intestinal absorption during the first 12 to 24 hours of life.

Serum IgG1 is trapped by receptors on mammary epithelial cell of the dam, transported through these cells and secreted into the colostrum in the acinar ducts.(Banks 1989) In gestating dairy cows there is a gradual decrease in the serum levels of IgG1 during the weeks prior to parturition, then a gradual increase during the following weeks.(Kiddy 1974)

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.(Menanteau-Horta 1985) By 100 days of age (five half-lives), 97% of the maternal antibody will be gone.(Banks 1982) 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.(Menanteau-Horta 1985)

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.(Riedel-Caspari 1991) Calves fed colostrum leukocytes isolated from heifers immunized with *M. bovis* had increased lymphocyte blastogenesis to PPD between 3 and 21 days compared to calves fed colostrum cells from control heifers.(Duhamel 1986)

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.(Hein 1991) 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. Newborn calves were able to respond to soluble protein antigens, chicken RBC, and a bacteriophage at birth.(Banks 1982) 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 immunoglobulin responses to whole-cell antigen regardless of age. In contrast, modified-live *S. dublin* vaccine given to calves at one to three weeks of age stimulated anti-LPS immunoglobulins, although the response was not as rapid and was of lesser magnitude than that of older calves given Salmonella bacterin.(Roden 1992) The practical implication of these observations is that not only will the effects on vaccination of

the newborn or young calf be affected by their passive immune status, but also by 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 routinely done 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, 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 or 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 its simplicity, these, along with some environmental considerations, 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; virus vaccines may stimulate interferon production; stimulation of the effector component of cell mediated immunity (cytotoxic T lymphocytes); and the bacteria or virus may look 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 (BHV1) is a widespread disease primarily affecting the respiratory and reproductive systems.(Blood and Radostits, 1989-IBR) The respiratory form, BHV1 type 1, referred to as infectious bovine rhinotracheitis (IBR) may terminate pregnancy at any stage of gestation.(Chow 1964, Miller 1991) It may contribute to neonatal losses in calves from susceptible dams.(BLOOD and Radostits, 1989-IBR) 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.(Miller, 1991 VM/SAC; Miller, Whetstone, et al. 1991

The use of intramuscular modified-live vaccine at the correct time of the production cycle provides protection against respiratory signs and abortion in cattle.(Blood/Radostits 1989-IBR, Chow 1971, Kahrs 1977, Hjerpe, Saunders 1972) It does not prevent latency induced by aerosol exposure to four ml of  $10^{6.5}$  TCID<sub>50</sub> of virulent BHV1/ml.(Narita M et al.) Animals with passive immunity from immune dams may fail to respond to vaccination before six months of age but the cellular immune function may be primed.(Brar et al. 1978;

Menanteau-Horta 1985) The vaccine should be administered a minimum of one additional time approximately one 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.(Chiang et al., 1990; Smith et al. 1990) Intravenous administration of a five ml of cell culture medium containing from  $10^{6.5}$  to  $10^{7.3}$  TCID<sub>50</sub>/ml of one of four vaccine strains of BHV1 on post-breeding day 14 resulted in infertility in four of eight heifers.(Miller 1989) Failure of a single injection of modified-live agent to immunize may be due to improper handling, storage, or administration. The importance of a solid immunity 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.(Kahrs 1981) Immunity of long duration follows infection by virulent virus or by modified-live injection.(Chow 1971) This would include protection of the fetus from transplacental infection in most cases.(Kendrick 1971, Kahrs 1981, Blood/Radostits 1989-IBR)

Recent work indicates that BHV1 type 2 virus administered to seronegative pregnant heifers did not cause abortion.(Miller, 1991, AJVR) This may indicate a possible use of BHV1 type 2 virus for an intramuscular modified-live product that could improve safety and still provide a durable immunity. Similarly, thymidine kinase-negative mutants of Cooper (Miller 1991) and Los Angeles (Kit 1986) 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.(Talens et al 1989)

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.(Blood/Radostits 1989-IBR, Tizzard) 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.(Blood/Radostits 1989-IBR) The duration of immunity has not been determined following use of intranasal immunization and it is more difficult to properly administer than intramuscular products.(Hjerpe) The use of an intramuscular modified-live vaccine at the next opportunity following intranasal immunization increases the likelihood of a durable immunity. The use of 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.(Blood/Radostits 1989-IBR, Hjerpe, Kahrs 1981)



### **Bovine Virus Diarrhea Virus - BVDV**

The BVDV is distributed worldwide and has a high rate of prevalence based on serology.(Radostits 1988) 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.(Baker, Radostits, Blood/Radostits 1989-BVD) Studies have reported a serious effect on conception if local BVDV infection occurs by experimental inoculation (Grahn, Whitmore) or following natural service with a persistently infected bull.(McClurkin) 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.(Radostits 1988) 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.(Brownlee, Bolin 1985, Moennig) 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.(Duffel, Kendrick, Kahrs 1981, Radostits, Moerman 1993)

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.(Trautwein 1986) If this occurs during the first six 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.(Liess 1987) 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.(Orban 1983)

Critical studies comparing the ability of modified-live and killed BVDV vaccines to protect the fetus in field situations are not available. At the current time, it is believed that optimum protection of the beef breeding herd is dependent on active immunization with modified-live BVDV vaccine prior to breeding.(Duffel et al., Radostits 1988, Kahrs 1981, Hjerpe, Blood/Henderson) To insure a response, the vaccine should be administered to replacement heifers, two or more times between weaning (six to eight months of age) and breeding.(Kahrs 1981, Hjerpe, Blood/Radostits 1989-BVD) The final injection should be at least one 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 so as 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.(Corapi 1990, Kelling 1990) The importance of specificity of circulating antibody and effects on cellular immunity due to viral mutation are largely unanswered at this time.

A temperature-sensitive, modified-live BVDV vaccine was shown to be safe and induce seroconversion in pregnant cattle.(Lobmann M, et al.) A killed Singer-strain vaccine prevented clinical signs following intravenous challenge.(McClurkin/Coria 1980) Pregnant cows vaccinated with a polyvalent killed virus BVDV vaccine and challenged at 80 days gestation showed resistance to fetal infections compared to nonvaccinated controls.(Harkness 1987)

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.(Kahrs 1981) 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.

**Insert:** Recent information from challenge studies indicates solid fetal protection to Type I BVDV and moderate protection from Type II BVDV is conferred through immunization with a pre-breeding Type I modified live virus vaccine. (Cortese et al. 1998; Brock/Cortese 2001).

### **Campylobacteriosis - (Vibriosis)**

This venereal disease of beef cattle is characterized by temporary infertility and sometimes abortion.(Carroll; Ball et al.) 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.(Dekeyser) It is also possible to have local immunity without a rise in serum antibody.(Wilkie et al., 1972; Dekeyser) These factors may be responsible for partial immunity which in some cases of exposure results in delayed conception or early conception with low-grade infections that may result in later abortions.(Dekeyser) Following infection of naive animals, the organism is usually eliminated from the animal within four to five 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.(Hoerlein; Dekeyser) Effective immunization using oil adjuvanted vaccine<sup>1</sup> requires a sensitizing dose, followed one month prior to breeding, by a second injection, and then annual boosters approximately one month prior to natural service for all breeding females.(Hoerlein/Carroll; Carroll/Hoerlein; Ball et al., VCNA)

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.(Clark 1975; Fivaz: Vasquez) The use of 2.5 times the recommended dose, twice the first year followed by annual boosters one month prior to breeding has been shown to be effective in eliminating carriers.(Vasquez, L et al.) Generally, oil adjuvanted products (Freund's incomplete adjuvant) are preferred because of more durable immunity following single annual boosters.(Hoerlein and Carroll, Ball) Products in aluminum hydroxide adjuvants generally induce less durable immunity and, to be effective, should be given ten days prior to a limited breeding season.(Berg) The oil adjuvanted product requires an annual booster, preferably one month prior to breeding.(Carroll) Modification of these recommendations for the

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<sup>1</sup> Vibrin<sup>®</sup> - Smith Kline Beecham, Exton, PA

prevention and control of campylobacteriosis, such as immunization of only part of the cow herd, 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. (Blood/Radostits 1989-LEPTO p759) The most common isolate in the United States is serovar hardjo genotype hardjo-bovis. (Miller DA 1991) This genotype of hardjo is antigenically different from the hardjo-prajitno genotype identified in Europe and currently used in the multivalent vaccines. (LeFebvre 1987) Although the serovar in the multivalent vaccine produced circulating antibody following one or two doses it was not protective against experimental conjunctival challenge. (Bolin/Theirman et al. 1989) Further studies using an experimental vaccine derived from a hardjo-bovis isolate also failed to prevent infection and urine shedding when challenged in a similar manner. (Bolin/Zuermen 1989 and Bolin 1991)

In endemic areas frequent immunization with multivalent antigens containing the specific serovar is recommended. (Ellis 1986) In the majority of beef herds not in endemic areas, less frequent immunization of animals is usually practiced. Previous information indicated that annual vaccination in closed herds and every six months in endemic areas was protective. (Hansen 1977) Recent studies revealed fetal infection, stillbirths, weak calves, and apparently healthy calves shedding the organisms in urine following challenge of immunized pregnant cattle at four to six months of gestation. (Bolin 1989) 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. (Miller DA 1991; Ellis WA; Bolin 1991)

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. (Hansen, 1977) 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. (Kimsey 1986) The disease is generally insidious in onset due to 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. (Johnson, Kvasnika)

Resistance and immunity to natural tritrichomonas infection are similar to other pathogenic organisms causing local infection of the reproductive tract such as campylobacteriosis. (Skirrow-a) Infected animals gradually develop enough immunity to remain pregnant and eventually eliminate the infection in four to seven months. (Abbit,

Skirrow-b) 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.(Kimsey et al. 1980) 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.(Clark 1974) Clinicians should not be lulled into a complacent attitude towards testing young bulls because of this characteristic. *Tritrichomonas fetus* has been cultured from essentially any age bull.(Grotelueschen DM, personal communication, August 1993)

Controlling the disease by immunization has been studied and a commercial vaccine<sup>2</sup> is currently available. Immunization of bulls appears to have limited application under most situations.(Clark 1983, 1984) Immunizing breeding females has resulted in more rapid elimination of infection and a reduction in early abortion when compared to controls.(Kvasnicka; Schnackel) 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.(Kvasniska; Hjerpe; Schnackel)

Management is critical to control trichomoniasis, regardless if vaccine is used. Due to 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.(Abbitt, Ball, Berry 1985, Mickelsen) Prevention and control of the disease require management decisions based on epidemiologic characteristics of the disease and have been reviewed.(Ball)

### **Haemophilus Somnus**

*Haemophilus somnus* can innocuously colonize the healthy genital mucosa of the cow.(Kwiecien 1992) It has also been associated with genital inflammatory disease (Hoblet 1989) and abortion (Firehammer 1959) in cows. *H. somnus* associated reproductive diseases have been reviewed.(Kwiecien 1991)(Miller 1983)

Corbeil, et al. were able to experimentally induce abortion using an intravenous challenge of large numbers of organisms.(Corbeil 1986) Commercial (Williams 1978) and experimental (Stephens 1984) *H. somnus* vaccines have been shown to attenuate the effects of intravenous challenge. While 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.(Kaneene 1987) 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.(Patterson 1986)

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 observed with many diseases. Brucellosis,

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<sup>2</sup> Fort Dodge Laboratories Inc, Fort Dodge, IA

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 due to requirements for interstate shipment and sale of replacement heifers. Although the vaccine has been shown to be efficacious in the past there is less information regarding the reduced dosage now recommended.(Hjerpe) 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, it would likely be cost 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.(Corapi 1990) This instability was thought to be the cause of the failure of repeated annual doses of inactivated virus vaccine to protect animals from infection.(Kelling 1990); however, for many infectious agents of cattle, the immunologically important antigens are relatively stable.

A more likely cause of vaccine ineffectiveness is improper handling, as was mentioned in the discussion of IBR. 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, etc.

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 carefully administer the vaccine. 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/disease history. As previously mentioned, the immature immune system found in a calf is not able to respond to vaccines as well as the immune system in adult cattle.(Banks 1982)(Roden 1992) Even though the bovine fetus is capable of recognizing and responding 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.(Gasbarre 1985) 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 more 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 disease has been described in other species and speculated on 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, etc. 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.(Gwazdauskas 1978)(Pollock 1992) Lymphocyte function is suppressed in transported calves.(Filion 1984)(Blecha 1984) 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. Usually it 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. Not only does each animal have a unique immunologic history but each animal 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 are the results of the marketing and management systems inherent in the cattle industry of the United States. Often we 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 that are present in an operation. This requires good records, complete postmortems, 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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## NOTES

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