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IMMUNOLOGY AND PREVENTION OF INFECTION IN FEEDLOT CATTLE

James A. Roth, DVM, PhD, and Louis J. Perino, DVM, PhD

Maintaining healthy animals requires an immune system that is functioning optimally. The immune system consists of a complex set of cells and molecules that help the animal resist infection. It can be divided into native immune components and acquired immune components. The native immune components work to prevent infection in newly exposed animals. They can function without previous exposure to the pathogen. The native defense components are very important in the first hours and days after exposure to viral or bacterial pathogens. The native defense mechanisms, especially phagocytic cells, are very susceptible to having suppressed function due to stress, viral infection, inadequate nutrition, low-level infection with coccidia or parasites, or exposure to certain toxins. When the native defense mechanisms are impaired, the animal rapidly becomes susceptible to severe infection.

The acquired immune system consists of antibody as well as effector and memory lymphocytes (B cells, T-helper cells, cytotoxic T cells, and gamma-delta T cells) which provides stronger immunity to specific pathogens than native defense mechanisms can provide by themselves. One of the main ways the acquired immune mechanisms help to improve immunity is by increasing the efficiency of the native defense

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From the Department of Microbiology, Immunology, and Preventive Medicine, College of Veterinary Medicine, Iowa State University (JAR), Ames, Iowa; and the Division of Agriculture, West Texas A & M University (LJP), Canyon, Texas

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mechanisms. The acquired immune system can be stimulated by effective vaccination. It takes 1 to 2 weeks after vaccination or exposure to the virulent organism before the acquired immune system is fully functional. Maintaining optimal immune function for the prevention of infectious diseases requires good management practices to prevent suppression of the immune system and sound vaccination practices to induce optimal acquired immunity. This article briefly reviews the basic types of immunity, the factors relevant to feedlot cattle that have been shown to suppress immune function, and what is known about the basis of protective acquired immunity against the common bovine respiratory pathogens that cause significant losses in feedlot animals.

TYPES OF IMMUNITY

Native Defense Mechanisms

The native defense mechanisms include enzymes in the saliva and tears, acids in the stomach, fatty acids in the skin, and normal flora at mucosal surfaces. Native defense mechanisms also include the complement system and phagocytic white blood cells which are capable of killing some bacteria and viruses. These native defense mechanisms are functional immediately when an infectious agent enters the body even if an animal is not vaccinated. The complement system and phagocytic cells work more efficiently in a vaccinated animal, however. Those bacteria and viruses that are capable of producing disease have evolved ways to avoid being easily killed by the native defense mechanisms. In order for an animal to be adequately protected from economically important infectious diseases, it must have either been previously exposed to the disease or vaccinated against the disease so that it developed humoral immunity, cell-mediated immunity, or mucosal immunity.

Humoral Immunity

Humoral immunity is due to the presence of either immunoglobulin G (IgG) or IgM in the bloodstream. When an animal is vaccinated, B lymphocytes respond to the vaccine by producing IgM- and IgG-class antibodies. These antibodies are proteins that circulate in the bloodstream and can attach to the infectious agent when it is encountered in the blood or in the tissues. Antibodies alone are not capable of killing infectious agents. The presence of circulating IgG and IgM may help to control disease by:

1. Agglutinating infectious agents, thereby reducing the number of infectious particles (for viruses) and facilitating removal by phagocytosis
2. Binding to and neutralizing toxins
3. Binding to the infectious agent and blocking attachment to cell surfaces
4. Binding to the infectious agent and initiating the classic pathway of complement activation
5. Opsonizing infectious agents and facilitating phagocytosis

6. Mediating attachment of cytotoxic cells to the surface of infected cells so that the infected cells may be destroyed by antibody-dependent cell-mediated cytotoxicity

Some disease-causing organisms, however, are resistant to control by these activities of circulating antibodies. These organisms must be attacked and destroyed by the cell-mediated immune system or controlled by the secretory IgA system.

Cell-Mediated Immunity

The term *cell-mediated immunity* refers to immunity mediated primarily by T lymphocytes. The T lymphocytes have two basic methods for protecting animals from disease. Some lymphocytes called "cytotoxic T cells" make contact with cells presenting foreign antigens on their surface such as viral antigens or antigens from some intracellular bacteria. The T cells specifically recognize the foreign antigens and kill the cell that has them on its surface. This effectively prevents virus from replicating in the cell. The second method that T cells use to fight infection is to secrete cytokines. Cytokines are glycoprotein molecules that activate other cells of the immune system to be more aggressive. This includes macrophages, neutrophils, and natural killer lymphocytes. The activated macrophages and neutrophils are more efficient at killing bacteria, especially facultative intracellular bacterial pathogens like brucella, mycobacteria, salmonella, and listeria. The activated natural killer cells are more efficient at killing virus-infected cells. The T cells that secrete cytokines to enhance killing by macrophages, neutrophils, and natural killer cells are called "T-helper 1" cells. T lymphocytes are also essential for secreting cytokines which control the type and amount of antibody produced by B lymphocytes. These T cells are called "T-helper 2" cells. Therefore, production of a normal antibody response requires T-lymphocyte help. The activity of the T-helper 2 cells is not usually considered to be part of cell-mediated immunity.

Mucosal Immunity

Protecting the animal from infection on mucosal surfaces such as the intestinal tract, respiratory tract, mammary glands, and reproductive tract is especially difficult for the immune system. The antibodies responsible for humoral immunity and the white blood cells responsible for cell-mediated immunity are found in the bloodstream and in the tissues to some extent, including submucosal surfaces; however, they are not found on some mucosal surfaces. Therefore, they can help to prevent invasion through the mucosal surface but are not very effective at controlling infection on the mucosal surface. On some mucosal surfaces such as the lower respiratory tract, reproductive tract, and mammary gland, where IgG and white blood cells are found in relative

abundance, they are able to provide a significant amount of protection, but they are not able to function as effectively as in the bloodstream and tissues. Protection on mucosal surfaces is due, in large part, to a special class of antibody called "secretory IgA." Secretory IgA tends to be produced in response to pathogens that enter through a mucosal surface. Secretory IgA is secreted onto mucosal surfaces, where it may bind to mucus and be present in fairly high concentrations. Secretory IgA is resistant to destruction by the proteolytic enzymes on mucosal surfaces that are capable of breaking down IgA and IgM. IgA is the predominant immunoglobulin found in the milk of monogastrics and is important for protecting the gastrointestinal tract of the neonate from pathogens. In ruminants, IgG1 is the predominant class of antibody in the milk for protecting the gastrointestinal tract of the newborn. Mucosal surfaces of ruminants tend to have high concentrations of IgG1 as well as IgA.

IMMUNOSUPPRESSION AND DISEASE SUSCEPTIBILITY

The bovine respiratory disease (BRD) complex has been extensively investigated in recent years, and numerous vaccines and antibiotics have been developed and prescribed for its control. Despite these efforts, BRD is still a major problem, and its pathogenesis and etiology are incompletely understood. Respiratory disease is particularly prevalent during the first 45 days after calves have been weaned, transported, and placed in a feedlot (i.e., shipping fever).⁴⁹

The economically important clinical signs, lesions, and death loss in shipping fever usually can be attributed to bacterial pneumonia due to *Pasteurella haemolytica*, *Pasteurella multocida*, or *Haemophilus somnus*. These bacteria are commonly found in the nasopharyngeal area of healthy animals. Under normal conditions, the bacteria are unable to move into the lower respiratory tract and cause pneumonia. In fact, the lungs of normal healthy cattle can withstand a challenge with surprisingly large numbers of these bacteria without serious consequences. If the animal is stressed, however, has a respiratory viral infection, or is otherwise immunosuppressed, a severe pneumonia can be established by a relatively small number of bacteria. These observations have led to the concept that BRD has a multifactorial etiology involving a complex interaction between stressors, viruses, and perhaps other immunosuppressive factors that act separately or together to suppress the defense mechanisms in the lung and predispose the animal to bacterial pneumonia.

Distress

There is ample evidence that environmental, physical, or psychological stress (distress) can lead to increased susceptibility to disease and that the increased susceptibility is at least partially due to alterations

in immune function.^{54, 55} A general bodily response to distress is the release of adrenocorticotropin from the anterior pituitary gland, which stimulates the adrenal cortex to increase the synthesis and secretion of cortisol (hydrocortisone). Cortisol is responsible for many (but not all) of the effects of distress on the immune system. Several stressors that are sometimes associated with the introduction of cattle to a feedlot have been proven to result in increased plasma cortisol levels. These conditions include castration and dehorning, weaning, handling, forced exercise, acute pain, and transportation.^{2, 23, 41, 97, 99, 102} There is evidence that high plasma cortisol concentrations affect several aspects of host defense,⁸⁹ including decreased antibody response to primary immunization, decreased lymphocyte function leading to impaired cell-mediated immunity, and an inhibition of phagocytic cell ability to enter the tissues and destroy bacteria. The levels of endorphins, catecholamines, insulin, glucagon, growth hormone, prolactin, thyroid hormones, and melatonin are also altered by stress. These hormones may alter immune function as well, but their effects on the immune system are not understood as well as those of cortisol.

A very important effect of elevated cortisol concentration or the administration of pharmacologic doses of glucocorticoids (e.g., dexamethasone) is the recrudescence of herpesviruses such as bovine herpesvirus 1 (BHV1). BHV1 can be recrudesced in otherwise healthy cattle by stress or dexamethasone treatment; this can be done even if the animal has an antibody titer. The recrudescence of a latent BHV1 infection in an animal under stress can lead to the spread of BHV1 throughout a herd. Like other herpesviruses, BHV1 is harbored in a latent state in animals that have recovered from an initial infection. Even a modified live virus (MLV) vaccine strain can be recrudesced and shed under the influence of glucocorticoids.⁸⁰

One clinical application of dexamethasone has been in the treatment of cattle suffering from bronchial pneumonia to reduce the inflammatory response in the lungs. A short-term improvement in clinical signs often occurs; however, experimentation has shown that when dexamethasone administration was combined with antibacterial and antihistamine therapy for the treatment of bronchial pneumonia in cattle, the outcome was a poorer response to treatment, more relapses, and greater death losses. This occurred because in decreasing the inflammatory response in the lung, the dexamethasone also impaired the activity of the host defense mechanisms, thus allowing increased bacterial replication.¹⁷ In general, glucocorticoids should not be used as a part of the treatment regimen for BRD unless the inflammatory response in the lung is life threatening or the clinician is confident that the antimicrobial agent being used can control the bacterial infection.

Viral Infection

The best evidence that viruses play an important role in predisposing to bacterial pneumonia comes from epidemiologic data indicating

that a recent serologic conversion to a respiratory virus is associated with bacterial pneumonia and from challenge experiments in which cattle are infected with a virus and then infected a few days later with an aerosol of *P. haemolytica* or *P. multocida*.⁹⁰ The cattle that are preinfected with either BHV1, parainfluenza 3 (PI3) virus, or bovine viral diarrhea (BVD) virus develop a severe bacterial pneumonia, although the nonvirus-infected control cattle are able to clear the bacteria from their lungs. These viruses may have a number of effects on the antibacterial defense mechanisms in the lung, including impairment of mucociliary clearance, suppression of phagocytic cell function, and interference with lymphocyte function. The relative importance of each of these effects is not known, but it is probably a combination of activities that is responsible for the predisposition to bacterial pneumonia. Studies have shown that simultaneous infection with BVD virus and bovine respiratory syncytial virus (BRSV) can synergistically increase the pathologic effects of each individual virus.⁵⁷

A number of respiratory viruses of cattle can inhibit mucociliary clearance in the ciliated respiratory epithelium (e.g., BHV1, PI3 virus, BVD virus, BRSV).⁹⁰ Decreased mucociliary clearance is often cited as a primary reason for greater susceptibility to bacterial pneumonia. Evidence suggests, however, that this is not as important as impairment of bactericidal mechanisms within the lung. This conclusion is based on the observations that the rate of bacterial killing within the healthy lung greatly exceeds the rate of mucociliary transport out of the lungs and that the period of increased susceptibility to bacterial pneumonia does not coincide with the timing of the inhibition of mucociliary clearance after viral infection.⁴⁸

The current consensus seems to be that suppression of the function of phagocytic cells in the lungs (both alveolar macrophages and neutrophils) is a primary factor in predisposing to bacterial infection. The phagocytic cells are essential for killing bacteria that find their way to the lower respiratory tract and removing them from the lung. The alveolar macrophage is the predominant phagocyte in the healthy lung and is very important in surveillance and removal of foreign material (including bacteria) from the alveoli. If the alveolar macrophages are unable to control the infection or if the lung is exposed to a large challenge dose of bacteria, neutrophils migrate into the alveoli and bronchioles rapidly, and they soon (within a few hours) become the predominant cell type. Neutrophils are quite active phagocytically and have potent bactericidal mechanisms, including the generation of toxic oxygen products (e.g., hydrogen peroxide, superoxide anion, hydroxyl radical) and the release of cationic antibacterial peptides and hydrolytic enzymes. In addition to being bactericidal, these products also can damage pulmonary tissue. If the infection is not brought under control relatively rapidly, the neutrophils can induce considerable damage in the lung.

There is evidence that BHV1, PI3 virus, BVD virus, and BRSV can each impair alveolar macrophage function.⁹⁰ BHV1 and BVD virus also

can inhibit neutrophil function.⁹⁰ The effects of PI3 virus and BRSV on neutrophil function apparently have not been determined. An important aspect of alveolar macrophage and neutrophil function is that they can be activated by cytokines secreted by T lymphocytes. When these phagocytes are activated, they become more "aggressive" and are more effective at controlling bacterial infection. By interfering with lymphocyte function, the BRD viruses may inhibit alveolar macrophage and neutrophil activation and leave the animal more susceptible to bacterial pneumonia.

The BVD virus has been shown to inhibit aspects of lymphocyte,^{51, 82, 93} macrophage,⁵⁹ and neutrophil^{92, 93} function; to impair bacterial clearance from the blood⁸⁷; to lessen the ability of calves to clear BHV1 from the lung⁸⁴; and to facilitate pulmonary infection with *P. haemolytica*.⁸³ At least one MLV vaccine strain of BVD virus also was shown to be capable of suppressing lymphocyte and neutrophil function.⁹¹ The suppression of neutrophil function lasts for 3 to 4 weeks after infection with either a virulent or MLV strain. Cattle that were given adrenocorticotrophin to increase their serum cortisol levels at the same time that they received MLV BVD vaccine had more marked suppression of neutrophil function than cattle that received either the modified live BVD virus or the adrenocorticotrophin only.⁹¹ This implies that stress and the BVD virus act synergistically to cause an immunosuppression that is worse than either would cause alone. The clinical importance of immunosuppression by currently used MLV BVD vaccines is unknown. It is probably not a problem when used in healthy animals under good management conditions.

The bovine immunodeficiency virus (BIV) is a lentivirus that has antigenic and genetic homology with the human immunodeficiency virus. The true prevalence of BIV infection of cattle in the United States is unknown. Various serologic surveys have detected infection rates from 4% to 18%.¹⁰⁵ Experimental infection with BIV has been associated with changes in circulating lymphocyte numbers,¹⁵ alterations in monocyte function,^{77, 95, 96} and decreases in neutrophil function.^{31, 32} These changes were relatively minor, however, and experimental BIV infection has not been shown to lead to a clinically apparent immunodeficiency syndrome. The potential impact of naturally occurring infection with BIV on susceptibility to diseases in feedlot cattle is still unknown.

Several other viruses have been associated with the BRD complex, including bovine adenovirus, coronavirus, DN599 herpesvirus (Movar), rhinoviruses, reoviruses, and bovine parvovirus.^{90, 104} Little is known about the immunosuppressive effects of these viruses in cattle; however, it is logical to assume that infection with any of them may render cattle more susceptible to bacterial pneumonia.

Mycoplasma Infection

Mycoplasma species (*Mycoplasma bovis*, *Mycoplasma dispar*, and ureaplasmas) also may be important factors in the etiology of BRD. Infection

with these agents that is uncomplicated by any other factors usually results in subclinical pneumonia. The mycoplasmas probably play a larger role in BRD as predisposing factors to secondary bacterial infection than as primary pathogens.¹⁰¹ Infection with *M. bovis* has been reported to enhance the severity of pneumonia caused by *P. haemolytica*.⁴⁶ The mechanisms by which mycoplasmas predispose to secondary infection are not clear, but induction of inflammation, impairment of lymphocyte function, inhibition of mucociliary transport, and inhibition of neutrophil function all have been suggested as possible contributing factors.⁹⁰

Nutrition

Nutrition plays an important role in maintaining optimal immune function and resistance to BRD. This topic is covered in another article in this issue.

Parasitism

Immunosuppression due to the administration of glucocorticoids to cattle has been shown to exacerbate clinical signs of coccidiosis.⁷⁶ In addition, there is evidence that coccidiosis itself is immunosuppressive and predisposes to secondary infection. The feeding of coccidiostats to feedlot cattle has been associated with reduced shedding of coccidial oocysts and with reduced morbidity⁶⁵ and mortality³³ from respiratory disease. Subclinical and clinical coccidiosis has also been shown to suppress neutrophil function in cattle.⁹⁴

Substances secreted by nematodes progressing through larval stages have been shown to suppress proliferation of bovine lymphocytes.³⁶ Therefore, controlling coccidiosis and parasites in feedlot cattle is important for maintaining optimal immune function and resistance to infectious disease.

CHARACTERISTICS OF PROTECTIVE IMMUNITY TO BOVINE RESPIRATORY DISEASE PATHOGENS

Bovine Herpesvirus 1

BHV1, also referred to as "infectious bovine rhinotracheitis" (IBR), is an alpha herpesvirus. The characteristics of protective immunity against BHV1 are similar to those against other alpha herpesviruses. Antibody titers as measured by a serum neutralization (SN) test can protect the animal against infection. The evidence for this is that the passive antibodies that a calf receives from the colostrum can provide solid protection against infectious challenge. The passively acquired antibody can

also prevent an MLV vaccine from inducing an antibody response in a calf. This maternal antibody blockage of an MLV vaccine can even occur if the serum neutralizing titer is very low. If the calf receives a lot of colostrum with a high titer against BHV1, it may be 6 to 8 months old before it is capable of responding to an MLV vaccine by the production of antibody. Even though the MLV vaccine may not induce an antibody response, it is possible that it may induce a memory response in the face of maternal antibody so that if the calf is subsequently exposed to the virulent virus, it may be capable of responding more rapidly to the viral challenge and have some degree of protection. There is evidence to indicate that vaccination in the presence of maternal antibody against pseudorabies virus in pigs (another alpha herpesvirus) stimulates immunologic memory even though an antibody response does not occur. This immunologic memory has been shown to provide partial protection against disease challenge with pseudorabies virus in pigs.¹¹¹ There is also evidence that the same is likely to be true for MLV BHV1 vaccines used in the presence of maternal antibody in calves.^{30, 70}

An important characteristic of herpesviruses is that after an animal recovers from disease, it is latently infected with the virus for the rest of its life. The virus resides in ganglia of nerves in a quiescent state. Even MLV BHV1 vaccine has been shown to latently infect cattle.⁸⁰ The immune system is not capable of clearing this latent infection. If the animal is stressed or treated with glucocorticoids later in life, the virus is likely to recrudescence and be shed even if the animal has a high serum neutralizing antibody titer.^{80, 98, 106} Therefore, serum neutralizing antibody can prevent infection, but it cannot prevent recrudescence and shedding of the latent BHV1. The latently infected animal that is shedding BHV1 may not show any clinical signs but is a source of infection for other animals in the herd.

Once an infection with BHV1 is established, a cell-mediated immune response is probably needed in order to bring the infection under control. Cytotoxic T lymphocytes are thought to be important in controlling the infection.

There do not seem to be important antigenic differences between BHV1 isolates. Immunity to one isolate of BHV1 or one vaccine strain of virus appears to provide good cross protection against all field isolates. Therefore, an SN titer measured against any BHV1 virus in the laboratory will more or less equally neutralize any other BHV1 virus. An antibody titer determined by enzyme-linked immunosorbent assay may or may not measure protective (serum neutralizing) antibodies depending on the nature of the antigen used in the enzyme-linked immunosorbent assay.

Bovine Viral Diarrhea Virus

SN antibody titers approximately greater than 1 to 32 have been shown to protect against disease induced by BVD virus.¹¹ A major problem, however, in immunity to BVD virus is that there is a great deal

of antigenic diversity among BVD virus isolates.²⁷ The BVD virus, like most other RNA viruses, has a high mutation rate, resulting in almost unlimited antigenic diversity among isolates. The E2 gene of BVD codes for the GP53 protein. This is the major surface glycoprotein and is immunodominant for antibody production. It is a major epitope for virus neutralization. The E2 gene represents one of the hypervariable regions of the BVD virus genome. This hypervariability may be due to selective pressure from the immune system.²⁶ The heterogeneity of the GP53 protein (and other less important virus neutralizing epitopes) limits the ability of an antibody response to one strain of BVD virus to protect against a wide array of other possible strains that the animal may be exposed to. The SN antibody titer of a single serum sample may vary from 10- to 100-fold depending on which BVD virus isolate is used in the SN assay.^{12,27} The animal is probably protected against the isolates that the serum can neutralize at a titer of approximately 1 to 32 or greater, but the antibody in the serum cannot protect against the other isolates of BVD virus. In a field outbreak, it is impossible to predict which antigenic type of BVD virus the animal is going to be exposed to. There is apparently no single vaccine strain of BVD virus (or even a combination of vaccine strains) that is capable of providing cross-protective SN antibody titers against all potential virulent BVD virus isolates that may be encountered.

Little is known about the role of cell-mediated immunity (either cytotoxic T cells or T-helper 1 cells) in protection against BVD virus-induced disease. It is likely that cell-mediated immunity is important for recovery from infection. It is quite possible that cell-mediated immunity, especially that provided by cytotoxic T lymphocytes, provides better cross-protective immunity between different BVD virus isolates than antibody does. If this is true, an animal that has developed cell-mediated immunity has better protection against BVD virus challenge. Because MLV vaccines are more likely to induce cytotoxic T lymphocytes than are killed vaccines, they may provide better cross-protective immunity to a variety of BVD virus isolates. This hypothesis fits the commonly held perception that MLV vaccines provide better immunity to BVD virus than killed vaccines, but it remains to be proven experimentally. Recently, two separate genotypes of BVD virus have been defined,⁸⁸ type 1 and type 2. The type-2 BVD viruses have the potential to produce severe acute infection even in adult animals. The homologous genotypes tend to induce better cross-neutralizing antibody titers than the heterologous genotypes. A type-1 MLV BVD vaccine has been shown to provide protection from a virulent challenge with a type-2 BVD virus,²² probably due to cross-protective cell-mediated immune responses.

A critical factor in controlling BVD virus infection in a herd, and probably in the cattle population as a whole, is to prevent infection of the fetus and development of persistently infected calves. There are scant data on the ability of vaccines administered to the cow to prevent infection of the fetus if the cow should become exposed to virulent BVD virus. There have been some experiments conducted using killed BVD

virus vaccines in cows that were subsequently challenged with virulent BVD virus during pregnancy. In most cases, these vaccines did not provide adequate immunity to prevent fetal infection. In one experiment using three doses of a killed vaccine, evidence of fetal protection from experimental challenge was obtained.¹³ Considering all of the evidence, it is likely that a killed vaccine inducing a titer of greater than 1 to 32 in the cow against a particular isolate of BVD virus can protect the fetus from becoming infected; however, there are likely to be strains of BVD virus that are antigenically different from the vaccine virus, which the cow and fetus are not protected from. It is possible that an MLV vaccine administered to the cow prior to pregnancy may provide better cross-protective immunity against a variety of isolates as described above. Nevertheless, the authors are unaware of any experiments demonstrating that an MLV vaccine administered to a cow is capable of protecting the fetus from infection. Fetal protection experiments are expensive to perform but are needed to answer important questions regarding vaccine efficacy.

Bovine Respiratory Syncytial Virus

Circulating antibody does not seem to provide good immunity against BRSV-induced disease. The evidence for this is the observation that calves with passive antibody are not usually protected from BRSV-induced infection or disease; however, calves that recover from disease are protected from reinfection, at least for a while.⁶⁰ The nature of protective immunity is not clearly understood, but there is some evidence to suggest that a strong IgA memory response is associated with protection and that a cytotoxic T-lymphocyte response to the F protein of BRSV may protect from disease. In one series of experiments in which calves with and without maternal antibody were primed with live BRSV via the respiratory tract, protection was associated with a strong and rapid mucosal antibody memory response after challenge but not with serum or mucosal antibody present at the time of challenge.⁶¹

A problem with BRSV vaccination and immunity is that maternal antibody does not provide good protection, but it does interfere with active immunization of the calf as assayed by antibody production.⁶⁰ This presents a real problem, because BRSV tends to cause disease in calves that are too young to effectively vaccinate because of maternal antibody. Additional research is needed to further characterize the nature of protective immunity to BRSV and to develop vaccines that can effectively immunize a young calf in the presence of maternal antibody.

Pasteurella haemolytica

In recent years it has been shown that antibody against *P. haemolytica* leukotoxin and surface capsular antigens is important to help protect

calves against *P. haemolytica*-induced pneumonia.^{18, 19, 37, 72} When measuring antibody titers against *P. haemolytica*, it would be best to measure both the antileukotoxin antibody titer and the anticapsular antibody titer, because these titers correlate best with immunity when a calf is directly challenged in the lung with *P. haemolytica*. Lymphocytes from mediastinal lymph nodes of calves vaccinated with an MLV *P. haemolytica* vaccine or recovered from *P. haemolytica* challenge secreted gamma interferon when stimulated with outer membrane proteins of *P. haemolytica*. This is an indication that calves develop T-helper 1 cell-mediated immune responses to *P. haemolytica*. Protection against pneumonic lesions more closely correlated with antileukotoxin antibody responses than with lymphocyte gamma interferon production, however.²⁵

An important component in the pathogenesis of naturally occurring *P. haemolytica* pneumonia is colonization of the upper respiratory tract.³⁴ *P. haemolytica* can be isolated in low numbers from the upper respiratory tract of normal healthy calves. Viral infection or stress may allow the *P. haemolytica* in the nasal and pharyngeal areas to grow to large numbers, leading to inhalation of microcolonies deep into the lung. These microcolonies then may successfully avoid the immune defenses in the alveolus and produce severe pneumonia. Little is known about the ability of current vaccines to inhibit colonization of the upper respiratory tract by *P. haemolytica*. Further research is needed to design and test vaccines that are capable of preventing or reducing upper respiratory colonization by *P. haemolytica*.

Haemophilus somnus

Not much is known about the nature of protective immunity to *H. somnus*-induced pneumonia. *H. somnus* has a number of potential virulence factors that have been studied, including endotoxin, antibody binding proteins, surface nucleotides, and a hemolysin.^{21, 112, 114} It is likely that antibody against these potential virulence factors may help to protect the calf against *H. somnus*-induced pneumonia; however, there are scant data to support this hypothesis. In addition, there are two proteins that have been isolated from *H. somnus*, a 40-kD protein and a 31-kD protein, that have been implicated as important antigens for inducing immunity.^{38, 113}

The role of T-helper 1 cells or a secretory IgA response in protection from *H. somnus*-induced pneumonia has not been thoroughly investigated. There is evidence that gamma interferon, which can be produced during a T-helper 1 cell immune response, can help to protect the calf against *H. somnus*-induced pneumonia.¹⁶

VACCINES

We use both live and killed vaccines. The advantages of one are usually the disadvantages of the other. MLV vaccine attributes include

strong long-lasting immune response achieved with fewer doses, less reliance on adjuvants, possible stimulation of interferon production, stimulation of the effector component of cell-mediated immunity (cytotoxic T lymphocytes), and the fact that the bacteria or virus may look and behave more like the pathogenic form of the organism. Some advantages of killed vaccines are that they are more stable in storage and are unlikely to cause disease as a result of residual virulence or reversion. Numerous brands of vaccines provide a variety of combinations of live and killed antigens. These include IBR virus, BVD virus, PI3 virus, BRSV, *Pasteurella sp.*, and *H. somnus* antigens.

IBR virus vaccines are available in MLV form for intramuscular, subcutaneous, or intranasal use as well as in killed and chemically altered virus forms for intramuscular use. Intramuscular MLV vaccines are thought to quickly induce immunity following proper administration of a single dose. Intranasal MLV vaccines induce immunity at the mucosal surface through stimulation of acquired mucosal immunity and production of interferon. They may be used safely in calves suckling pregnant cows and can induce immunity in the face of residual maternal antibody titers. They are, however, more difficult to administer. Killed virus vaccines require two doses administered at a 14- to 28-day interval in order to induce immunity. Along with higher cost and concerns about shorter duration of immunity, this makes them less practical to use in a typical feedlot setting.

In a review of IBR virus vaccine clinical efficacy studies, results were positive or neutral; however, none were negative.⁸¹ The studies date to 1958 and 1974 and may not apply to current cattle feeding management practices in North America. In a field trial using IBR MLV vaccine at arrival, the incidence of upper respiratory disease was reduced from 17.2% in 3371 unvaccinated calves to 1% in 3345 vaccinates (RR=16; $P<0.0000$).¹⁵ A well-designed trial using IBR MLV vaccine given on arrival failed to show benefits in health performance.²⁴ Another report that failed to show IBR virus vaccine efficacy involved additional antigens and is discussed in the section on multiple antigens. The current consensus is to include IBR virus in preconditioning and arrival vaccine regimens.

BVD virus vaccines are available in MLV and killed virus forms, and they are one of the most controversial vaccines used in cattle in the United States. The lack of large-scale efficacy trials, widespread infection in the cattle population in the United States, the presence of persistently infected cattle that subsequently develop mucosal disease, and the emerging role of heterologous and novel strains of the virus all combine to create confusion and controversy. There is no clear consensus concerning use. Measurements of certain immune parameters suggest that immunosuppression following use of MLV may be a concern⁹¹; however, the lack of complications following its use in large numbers of cattle suggests that these may not be of practical concern.²⁹ The use of MLV may be of greater concern in highly stressed cattle, but well-controlled studies evaluating this are not available. As is the case with BHV1, dose

and timing requirements of killed BVD virus vaccines are a severe limitation in most feedlot settings.

There are no reliable peer-reviewed reports of field trials examining the clinical effects of BVD virus vaccines in North American beef cattle based on research that uses scientifically valid methods with clinically relevant outcomes.⁸¹ Use is based on extrapolation from challenge or licensing data and personal preference.

A main concern with BVD is fetal infection with resulting abortion, congenital defects, or the development of persistently infected carriers that are a constant source of infective virus.^{4, 10, 85} The virus can cross the placenta in susceptible pregnant cattle and result in fetal infection either through exposure to the field virus or through the improper use of intramuscular BVD MLV vaccines.¹⁰⁸ 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.⁶²

Current information does not conclusively document the duration of protection following natural infection or the use of BVD MLV vaccine, although available information indicates that infection confers more than a single year of protection to the fetus.^{28, 53, 58, 71, 85} Seronegative cattle vaccinated with BVD MLV vaccine 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.⁷⁸

Critical studies comparing the ability of BVD MLV and killed 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 BVD MLV vaccine prior to breeding.^{10, 28, 45, 53, 85} To ensure a response, the vaccine should be administered to replacement heifers two or more times between weaning (6 to 8 months of age) and breeding.^{10, 45, 53} 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 MLV vaccine 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.^{20, 56} The importance of the specificity of circulating antibody and effects on cellular immunity due to viral mutation are largely unanswered at this time.

A temperature-sensitive, BVD MLV vaccine was shown to be safe and to induce seroconversion in pregnant cattle.⁶³ A killed Singer-strain vaccine prevented clinical signs following intravenous challenge.⁶⁸ Pregnant cows vaccinated with a polyvalent killed BVD virus vaccine and challenged at 80 days of gestation showed resistance to fetal infections compared with nonvaccinated controls.⁴³

The long duration of immunity and the cross protection between serotypes following the use of MLV vaccines make them preferable for use in beef breeding herds. The opportunities for 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.⁵³ Depending on the circumstances of each herd, annual, biannual, or less frequent MLV vaccine injections to cows between calving and breeding may be recommended.

BRSV vaccines are available in MLV and inactivated virus forms. Because recovery from natural infection with respiratory syncytial virus does not engender protective immunity in most species, it is unlikely that vaccination can prevent subsequent infection. Nevertheless, it may still be possible for vaccination to attenuate clinical signs of subsequent infections and reduce time to recovery. One experimental challenge of a small number of calves showed that passive antibodies reduce the pathology associated with BRSV.⁸ Moreover, there are reports of improvement in gain and feed efficiency.³ Mixed results are reported from studies investigating clinical efficacy of BRSV vaccination of calves on arrival. A statistically significant benefit of BRSV vaccination was shown in auction- or market-purchased and transported calves, with vaccinated calves being two times less likely to be treated for BRD complex (OR=2.0, $P<0.00001$). Freshly weaned and transported calves were 1.4 times less likely to be treated for BRD complex (OR=1.4; $P<0.001$). A statistically significant benefit of BRSV vaccination was not shown in the two classes of calves with low morbidity. These included preconditioned calves ($P=0.11$) and freshly weaned calves that were not transported ($P=0.75$).⁴² In a Canadian study, results of five separate trials designed to assess BRSV vaccine efficacy were equivocal for calves vaccinated before weaning; however, reduction of treatment rate was reported in calves vaccinated on arrival. No benefit was found for vaccination on arrival of yearling cattle.¹¹⁰ Two additional trials involving calves^{5,73} and one trial involving stocker cattle⁵⁰ failed to demonstrate a benefit of BRSV vaccination on arrival. Although there is evidence to support BRSV vaccine usage in naive or mismanaged calves, inclusion in vaccine regimens is not universal.

Studies show that PI3 virus compromises the innate defenses of the respiratory tract.^{64, 86} Because many older cattle arriving at feedlots are likely to be immune, the value of PI3 virus vaccination in yearling cattle is questionable. Vaccination may be valuable in preweaning or arrival programs for less immunologically experienced calves. There are no reliable peer-reviewed reports of field trials examining clinical effects of PI3 virus vaccines in North American beef cattle based on research that uses scientifically valid methods with clinically relevant outcomes.⁸¹ As a practical matter, it is difficult to select a multivirus BRD vaccine that does not include PI3 virus, making its inclusion less of an issue.

Findings reported in the literature are equivocal on the use of more recently available *Pasteurella* sp. vaccines before and on feedlot arrival.

The largest body of *Pasteurella sp.* vaccine data exists for *P. haemolytica* toxoid. Three studies have shown statistically significant reduction in morbidity or mortality in calves administered a *P. haemolytica* toxoid on arrival.^{7, 40, 66} Nevertheless, two clinical trials showed no significant effects when the same vaccine was given on arrival⁶⁹ or 3 weeks before shipment or arrival.¹⁰⁷ Health performance in vaccinates was not affected negatively in any report.

There are individual reports on various other commercial or experimental *Pasteurella sp.* vaccines. These include reports of significant efficacy in field studies of a streptomycin-dependent live *Pasteurella sp.* vaccine⁵² and an intradermally administered live *P. haemolytica* vaccine.¹⁰⁰ Alternatively, a field study of a *P. haemolytica* capsular antigen vaccine failed to show significant health effects⁴⁴ as did a study using a tissue culture-derived *P. haemolytica* bacterin.³⁵

For some currently available *Pasteurella sp.* vaccines, there are no reliable peer-reviewed reports of field trials examining clinical effects in North American beef cattle based on research that uses scientifically valid methods with clinically relevant outcomes. There are reports of lack of field efficacy with earlier *Pasteurella sp.* bacterins.^{1, 75} There is also a report of increased health problems following vaccination with earlier *Pasteurella sp.* bacterins⁹; however, this study did not mention whether treatment assignment was random, and the experimental unit is unclear, making the validity of the data analysis suspect. Because of dose and timing requirements for optimal immunity (7–10 days following a 14- to 21-day booster dose) their value should be compromised when used only in a feedlot arrival program. Paradoxically, the available data support the use of *P. haemolytica* toxoid on arrival. The current consensus is that it is best to administer at least the priming dose and sometimes the booster dose before weaning.

As with other vaccine antigens for BRD prophylaxis, results of field trials evaluating the efficacy of *H. somnus* bacterins have been conflicting. One group of investigators has reported negative effects of a single vaccination with a commercial *H. somnus* bacterin in that significantly more animals in groups of calves vaccinated once were treated for respiratory disease compared with groups of unvaccinated control calves or groups of calves vaccinated twice at a 21-day interval.⁷⁴ These findings are in conflict with earlier reports by these authors that no significant difference in the number of animals treated was found between groups of calves immunized once with a commercial *H. somnus* bacterin and groups of nonimmunized control calves.⁷⁵ Conversely, these investigators had reported earlier that morbidity (number of animals treated for respiratory disease) was significantly reduced in groups of calves vaccinated with a commercial *H. somnus* bacterin on arrival at the feedlot and revaccinated 21 days later compared with morbidity of groups vaccinated twice with a bivalent *P. haemolytica*, *P. multocida* bacterin or unvaccinated controls.¹

The ability of *H. somnus* vaccine to reduce BRD in feedlots in the United States may be limited by the low incidence and sporadic nature

of the disease.⁴⁵ Although studies demonstrate vaccine efficacy, most have shown vaccine efficacy using septicemic challenge.¹⁰³ Some have shown efficacy in experimental respiratory challenge.^{14, 39} To date, however, efficacy has not been unequivocally demonstrated in well-controlled trials in a US field setting. It is logical to assume that these vaccines are subject to the same dose and timing limitations as *Pasteurella sp.* vaccines. There is no clear consensus on usage.

Field trials have been carried out with vaccinates receiving multiple antigens, making it impossible to determine the effects of individual antigens. These can be subdivided into two broad groups: vaccine administered at or near the time of feedlot arrival and vaccine administered several weeks before feedlot arrival. Assuming valid design, execution, and analysis, interpretation of the first group is fairly straightforward. Some studies of arrival vaccination suggest that it does not affect or may even compromise health performance. A well-designed study using IBR MLV and PI3 virus vaccine along with a *P. haemolytica* toxoid failed to show health performance benefits.⁶ This is supported by findings in a multiyear observational study in Ontario, Canada, which reported that administration of respiratory vaccines (IBR virus, IBR-PI3 virus, or IBR-PI3-*Pasteurella sp.* virus) to calves vaccinated within 2 weeks of arrival was associated with an increased risk of mortality (RR = 2.4).⁶⁷ In contrast, subcutaneous vaccination with a *P. haemolytica* and *H. somnus* vaccine on arrival reduced BRD complex morbidity from 41% to 29%.¹⁰⁹

The second type of mixed antigen study is when vaccines are administered several weeks before feedlot arrival. These are often part of a preconditioning or preweaning study. Because an unvaccinated but similarly managed group is rarely included in these studies, the effects of management interventions such as preweaning and bunk acclimation are totally confounded with vaccine effect. Hence, it is impossible to know which intervention accounts for improvements in health performance.

OPTIMIZING VACCINATION

Vaccine injection only ensures that the animal has been exposed to the antigens contained in that vaccine; it does not ensure that a protective immune response ensues. The two key components required for successful immunization are an efficacious vaccine and an immunocompetent animal.

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 pathogens require each individual in a population to be immune for the vaccine to be efficacious. One example is an infectious but noncommunicable disease such as tetanus. For other pathogens, especially those that are highly contagious, reducing the number of susceptible animals below a critical threshold may be suffi-

cient for the vaccine to be efficacious by preventing a disease outbreak, that is, the concept of herd immunity.

A vaccine may seem to be ineffective if it does not contain antigens that induce protective immunity to the disease-causing agent currently challenging the calf. There are respiratory pathogens that can influence calf health for which no vaccines are available such as *Chlamydia sp.*⁷⁹ There are situations where antigenic differences between strains and species of pathogens or changes in antigens that the organism displays may compromise vaccine efficacy. One example of this is the genetic and antigenic instability of BVD virus.²⁰ This instability was thought to contribute to the failure of repeated annual doses of inactivated virus vaccine to protect animals from infection.⁵⁶ For many infectious agents of cattle, immunologically important antigens are relatively stable.

A more likely cause of vaccine ineffectiveness is improper storage or handling. We must store and administer vaccines according to the manufacturers' recommendations or risk reducing their efficacy.

Once we have done everything to properly care for the vaccine and the equipment, we must carefully administer the vaccine. Training sessions should be conducted to ensure that personnel are knowledgeable about the proper locations and techniques for vaccine administration.⁴⁷ Intramuscular injections should not be made behind the calf's front leg. The subcutaneous route should be used whenever allowed by label instructions. As a general rule, the smallest needle through which the product is easily delivered should be used. For thin watery products, an 18-gauge needle works well. Strict attention to proper restraint and changing needles to keep them sharp is critical if using 18-gauge needles. Needle length should be adjusted for calf size and injection route. Intramuscular injections should be given with a 1.5-in needle, except in the case of small calves in which a 1-in needle should be used. Subcutaneous injections should be made with a needle shorter than 1 in. Needles should be changed whenever they become dull, barbed, or bent. A clean needle should be used when refilling syringes to avoid contaminating the vaccine bottle. Good handling facilities help minimize injection site reactions by ensuring that cattle are adequately restrained, thereby preventing movement should a calf struggle during an injection.

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. Disinfectants inactivate MLV vaccines, so we must properly clean and rinse all equipment that comes in contact with vaccine.

Timing of vaccine administration can also influence our perception of vaccine effectiveness. If an animal is incubating a disease or if it is exposed to the disease-causing agent soon following vaccination, it may get sick, and the vaccine seems to be 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 immune animals. When cattle are assem-

bled in close quarters, the amount of disease agent to which they are exposed may be quite large, resulting in disease even in immune animals.

In summary, specific vaccine recommendations should be made by the veterinarian familiar with the management of the operation, including type of cattle handled and disease problems typically experienced. There are few cookbook solutions. Fine-tuning the program by including or excluding certain vaccines requires the identification of 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 immunocompetence and timing of vaccine administration is as important as selecting the correct antigens and types of vaccines used.

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Address reprint request to

James A. Roth, DVM, PhD
MIPM, College of Veterinary Medicine
Iowa State University
Ames, IA 50011

e-mail: jaroth@iastate.edu