Applied feedlot immunology

Breck D. Hunsaker, DVM, PhD
Feedlot Health Management Services USA, Preston, ID 83263

Abstract

Outcomes such as health performance, growth performance, and feed efficiency – outcomes that are clinically relevant and economically important to beef cattle producers and veterinarians involved in production medicine are the most clinically relevant and economically important outcomes by which to evaluate immune function in beef cattle populations. Although substitution indicators like serum antibody titers, lymphocyte proliferation assays and other laboratory assays may be indirectly related to the health and performance of the populations of interest, they are not directly correlated with the economically important outcomes essential to the financial health of the beef cattle businesses for which food animal veterinarians provide service.

A number of factors or events impact immune function of cattle that are received and fed in North American feedlots. These include, but are not limited to, weaning, commingling, transportation, arrival processing surgical procedures, nutritional status and environmental conditions. The expression of immune function in terms of health performance, growth performance, and feed efficiency, during the feeding phase is affected by not only arrival conditions and procedures conducted at feedlot arrival or management during the feeding phase, but the background and history of management prior to feedlot arrival. These are the most economically important measures of immune function.

Key words: beef, feedlot, immunology

Résumé

Les résultats comme la performance sanitaire, la performance de croissance et l'efficacité de l'alimentation sont importants d'un point de vue clinique et économique pour les producteurs de bovins de boucherie et pour les vétérinaires en médecine de population. Ils sont donc les plus pertinents cliniquement et économiquement afin d'évaluer la fonction immunitaire dans les populations de bovins de boucherie. Bien que d'autres indicateurs, tels les titres sériques d'anticorps, le dosage de la prolifération des lymphocytes et d'autres analyses de laboratoire, puissent être indirectement reliés à la santé et à la performance dans des populations d'intérêt, ils ne sont pas directement corrélés avec les résultats économiquement importants qui sont essentiels à la santé financière des élevages de bovins de boucherie auprès desquels les vétérinaires offrent leurs services.

Plusieurs facteurs ou évènements ont un impact sur la fonction immunitaire chez les bovins accueillis et engraissés dans les parcs d'engraissement en Amérique du Nord. Parmi ceux-ci on retrouve le sevrage, le regroupement, le transport, les procédures chirurgicales à l'arrivée, l'état nutritionnel et les conditions environnementales. L'expression de la fonction immunitaire durant l'engraissement au niveau de la performance sanitaire, de la performance de croissance et de l'efficacité de l'alimentation n'est pas seulement affectée par les conditions lors de l'arrivée, les procédures menées à l'arrivée au parc d'engraissement ou par la régie durant l'engraissement mais aussi par le contexte et le type de régie adopté avant l'arrivée au parc d'engraissement. Ce sont les mesures de la fonction immunitaire qui sont les plus pertinentes économiquement.

Introduction

Immune function is a term often used interchangeably with serum antibody response, leukocyte or lymphocyte responses, responses of endogenous immunomodulatory molecules such as interleukins or tumor necrosis factor (TNF), among others. However, these are actually substitution indicators for actual immune function, which is expressed as health performance, growth performance, and feed efficiency – outcomes that are clinically relevant and economically important to beef cattle producers and veterinarians involved in production medicine.[26,30] Although substitution indicators may be indirectly related to the health and performance of the populations of interest, they are not directly correlated with the economically important outcomes essential to the financial health of the beef cattle businesses for which food animal veterinarians provide service.

Immunity is often categorized as innate (non-specific) or acquired (specific). Innate immunity is inherent and is not enhanced through stimulation following exposure to antigen, while acquired immunity elicits a response that is quicker and increasingly stronger following exposure. Recent developments in understanding protective immunity have been described. These developments are intriguing and help to elucidate the biological mechanisms underlying protective immune function.

A number of factors or events impact immune function of cattle that are received and fed in North American feedlots. These include, but are not limited to, weaning, commingling, transportation, arrival processing surgical procedures (dehorning, castration), and environmental conditions (dust, weather, extreme temperatures). The expression of immune function in terms of health performance, growth performance, and feed efficiency, during the feeding phase is affected by not only arrival conditions and procedures conducted at feedlot

arrival or management during the feeding phase, but the background and history of management prior to feedlot arrival. This involves not only the antigens included in vaccines given, but also the timing and routes of the vaccines administered. Specifically, management of the vaccination program is as important as the vaccines themselves.

Technological approaches to diagnosis of disease relevant to feedlot production have been described.[32,36] The objective of these technologies is to enhance sensitivity and specificity of diagnosis of infectious disease in order to fine-tune treatment selection and timing of treatment. Diagnosis of disease is made by measuring feeding behavior and core body temperature changes using infrared thermography.

Also important in the ability of an animal to respond to an antigen is the metabolic status associated with the status of minerals essential to protective immune function. Selenium, copper, cobalt, and manganese have been shown to be important in the ability of an animal to respond to antigens exposed to in the form of vaccination or natural exposure.

It is interesting that vaccine technology has evolved and applications have been developed for a number of species. However, although technologies are available, bovine medicine has not taken advantage of these advances. Recently, we've seen approval of an immunomodulator[a] that may provide an opportunity for further advancement of technology in relation to enhancing or filling gaps in normal immune function.

Protective immune function is complex and involves management of immune responses through sound nutrition, timing of presentation of antigens, and management of procedures that minimally inhibit normal, protective responses.

Recently described immune responses

Immune function has been categorized as innate and acquired immunity. Innate immunity consists of physical and chemical barriers, non-specific phagocytes, macrophages and neutrophils, the complement system, interferon, natural killer (NK) cells, and TNF. Acquired, specific immunity is comprised of humoral and cell-mediated functions. Humoral immunity is found in fluids such as serum, tears, mucus, and bronchial secretions. Cell-mediated immunity (CMI) may be a misnomer, since humoral immunity is also mediated through cellular function, albeit a separate cell line, specifically B-cells. However, CMI is described as "trained" T-lymphocytes that eliminate and provide protection against intracellular pathogens and tumor cells.[16]

Cellular signaling in the form of pathogen receptor recognition (PRR) has been described.[37,41] PRRs comprise a group of cellular signaling pathways, which includes the highly studied toll-like receptors (TLRs). TLRs reportedly play important, and potentially critical roles in both innate and acquired branches of immune function.[13,37] While understanding these mechanisms helps to elucidate normal immune function, they are indirectly related to outcomes most directly relevant to cost-effective beef cattle production.

Management Practices

Hay et al[21] reported reduced risk of bovine respiratory disease development during the feeding phase if calves had been weaned in a yard vs pasture-weaned, had been fed grain ("bunk broke"), and had been vaccinated against BVDV1 or *Mannheimia haemolytica* prior to feedlot entry in Australian feedlots.

Passive Transfer

Dewell et al[12] reported that calves with lower (<2,400 mg/dl) serum IgG1 had 1.6 times higher likelihood of morbidity, 2.7 times higher likelihood of mortality, and weighed 7.38 lb (3.35 kg)/hd less at weaning than calves with serum IgG1 > 2,700 mg/dl during the pre-weaning period. No significant association was reported between perinatal serum IgG1 and feedlot health or growth performance.

Earlier, Wittum et al[45] had reported that calves with inadequate plasma protein (<4.8 g/dl) had 3.0 times higher likelihood of overall morbidity and 3.1 times higher likelihood of respiratory tract morbidity during the feedlot phase.

While the feedyard doesn't have control over cow-calf practices, such as colostrum and passive transfer management, calves coming from sources with attention to detail in this area have a higher probability of better health and growth performance. Therefore, the feedyard and the consulting veterinarian can use historical health and feeding performance to make current and future purchasing decisions.

Commingling

The scientific literature is sparse on the immunologic impact of commingling cattle populations. Step et al[39] reported that commingling reduced growth performance and increased risk of development of respiratory disease with increased treatment cost and numerically higher mortality due to infectious causes (i.e., respiratory disease). However, statistical power was not reported in the event failure to find statistically significant differences, and the study only covered a 42-day receiving period.

Weaning

A 2-step weaning process reportedly reduced weaning stress and enhanced immune response when measured using the laboratory outcomes BHV-1 shedding, serum haptoglogin levels, interferon-gamma, and leukocyte tumor necrosis factor following experimental BHV-1 challenge when compared to abrupt weaning and transportation.[20]

Weather

Month, year placed, days on feed (DOF), arrival body weight, BRD risk code, gender, size of cohort, wind chill temperature, temperature change, and maximum wind speed have been reported to be associated with morbidity in feeder cattle.[2,7] Briefly, September and October placements had significantly higher BRD morbidity than November placements,

lighter placements (500 to 600 lb (227 to 271 kg)/hd) were at greater risk of BRD treatment than heavier placements (700 to 800 lb (318 to 363 kg)/hd), high-risk placements were about 3X more likely to require BRD treatment than low-risk placements, and smaller placement cohorts (< 91 hd) were at lower risk of BRD treatment than larger cohorts. Additionally, interactions between wind speed, temperature change, and wind chill were reported to be associated ($P < 0.05$) with BRD morbidity, as measured by number of daily treatments for BRD.

Transportation

Arthington et al[1] reported that transported calves had greater weight loss and an increase in acute-phase proteins compared to non-transported calves. Reporting clinically relevant outcomes, Cernicchiaro et al[8] found that shrink following transportation was associated with morbidity, mortality, hot-carcass weight, and average daily gain which were significantly modified by gender, season, and mean arrival body weight.

Vaccination

Traditionally, it had been accepted that vaccinated cattle populations would be effectively protected against challenge pathogens; however, it has since been shown that other factors, such as commingling, nutrition, period of time since weaning, weather, and transportation conditions play a role in the health of the population that may compliment or overwhelm protection provided through vaccination.

Herd immunity is an important principle that affects the health of a population based on reduced numbers of susceptible animals, reduced pathogen load due to shedding, duration of pathogen shedding, and a higher infectious dose required to cause disease.[40]

Antigens

Respiratory vs other pathogens

Vaccination against respiratory pathogens – both viruses and bacteria – has been the central theme for providing immunity to calf, feeder, and feedlot cattle populations. Ancillary antigens administered include, but are not limited to, clostridial agents, leptospiral antigens, anaplasma antigens, mycoplamal antigens, among others that may vary by region, history, and anecdotal effects.

MLV vs KV

Modified-live (MLV) BHV-1 has been shown to be more effective in protection against IBR than killed virus vaccines. This has also been extrapolated for BVDV vaccination, with the basis being protection of the fetus in a simulated challenge mode.[19,33] The onset of immunity has been reported to be dramatically reduced for MLV vaccines, with protection provided in 3 days post-vaccination in 1 study and by 5 days post-vaccination in another.[46] Alternatively, killed vaccines generally require a booster and rely on antibody production, which requires more time to provide protection.[40]

Route of Administration

Vaccines in beef cattle production are generally administered parenterally, i.e. subcutaneously. This is done more for ease of delivery than for effectiveness. Immunity following parenteral administration of vaccines varies with the antigen, the disease targeted for protection, and conditions of vaccination. Immunologically and biologically, it may make more sense to deliver antigen at the site of natural challenge, i.e., mucosal surfaces.[40]

Parenteral

Perino and Hunsaker[30] provided a thorough review of the scientific literature that reported clinically relevant outcomes using sound scientific methods such as blinding, a contemporaneous control group, randomization, and appropriate statistical analysis of results, among others. In this review of 22 reports that met these criteria, 10 reported field efficacy of the vaccines investigated. Positive results were reported for BRSV, *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*.

Hunsaker and Tripp[23] later reviewed the scientific literature to update the previously published review article. In this later review, it was reported that 21 articles met the criteria of the review, which were the same as those outlined above for the previous review. Of the qualifying articles, 10 were from studies done in beef cattle. Of these, 7 reported efficacy under field conditions for cattle vaccinated against BRSV, *Clostridium* spp, bovine coronavirus, *Fusobacterium necrophorum*, *Mannheimia haemolytica*, and *Moraxella bovis*. Results for antigens that showed field efficacy were often equivocal, i.e., there may have been multiple studies done wherein some reported efficacy, while others did not.

Intranasal

Ellis et al[15] reported that clinical efficacy of immune response to intranasal vaccination in an experimental challenge study may be equal to that of parenterally delivered vaccine. Onset of immunity for antigens delivered by the intranasal route was reported to be established by day 3 post-vaccination in a dual challenge model with bovine herpesvirus-1 and *Mannheimia haemolytica*; however, the challenge exposure began on day 3, so prior protection could not be stated.[24] Todd[43] stated that calves vaccinated intranasally with BHV-1 were protected against experimental IBR challenge as early as 48 hours post-vaccination; however, no data were provided to support this finding, only statements of findings. In a study designed to compare IN vaccination with parenteral vaccination (IM), it was reported that no difference was found in ADG, DMI, or morbidity as measured by the number of BRD treatments; however, feed:gain ratio was increased in cattle vaccinated by the IM route.[14] Although this study was done under natural challenge conditions,

the duration of the study was only for the 28-day receiving period. Therefore, economic outcomes relevant to feedyard production could not be calculated.

In summary, intranasal vaccines have been available for nearly 5 decades, but there are no reports in the public domain of field efficacy under conditions of natural challenge. Nonetheless, as stated by Stokka,[40] it makes biologic and immunologic sense to deliver antigen at the site of challenge. There are in-house data from studies done in large pens, under commercial feeding conditions, investigating protection against natural challenge that support this hypothesis.[b]

Intradermal

Hunsaker et al[22] provided a thorough review of the scientific literature on the intradermal route of vaccination in domestic animals. ID vaccination is reported to be an appealing alternative to other routes of administration based on beef quality issues, without compromising effectiveness. However, reliable and consistent delivery of the antigen to a consistent depth in the dermis may not be achievable in a commercial setting. Dean et al[11] reported that intradermal vaccination against tuberculosis challenge using a CMG-primed adenoviral vectored vaccine provided more consistent and strongest immune response of the different routes of administration examined.

Oral delivery

Oral vaccines have been investigated experimentally, using genetic engineering to develop recombinant bovine pathogen sequences into plant genome. To date, these vaccines are not available commercially since efficacy has not been shown.

Timing of Vaccination

Exposure to antigens prior to disease exposure has been documented to be most effective in reducing infection and disease, which is logical considering the time requirement for development of a protective immune response. Furthermore, antibody response requires the most time to develop when compared to other components of protective immunity, such as innate immunity and cell-mediated responses. This is particularly important for immunity against bacterial agents and associated leukotoxins.[40] Hence, it may require an adjustment in expectations for protection immediately following vaccination at arrival to the feedlot, unless previous natural exposure or exposure through vaccination has occurred.

Kirkpatrick et al[25] reported that vaccination with IBRV, BVDV1, BVDV2, PI3, BRSV, *M. haemolytica*, and *P. multocida* antigens was effective in improving health performance when compared to unvaccinated control calves, with no difference seen between calves vaccinated at 67 days of age at the time of primary vaccination vs 167 days of age. This implies that vaccination at the time of branding is not detrimental in terms of eliciting a protective immune response at a time when maternal immunity would expected to be present.

Revaccination has been well-defined and described by Stokka et al[40] in a review of the scientific literature relevant to vaccination of cattle populations. Little benefit has been reported for re-vaccination as an isolated effect.

Nutrition

Mineral status

Chromium has been reported to reduce morbidity, as measured by numbers of treatments for respiratory disease, and modulate weight loss in the face of LPS challenge.[4] *Copper* has been reported to play an important, if not crucial, role in immune function; however, Galyean[16] reviewed the literature to find little compelling evidence of benefit to copper supplementation in stressed calves. *Selenium* has been reported to be essential in supporting adequate immune function;[29] however, review of the literature for reports of clinically relevant outcomes in selenium-supplemented cattle being prepared for feedlot entry is unrewarding.

Zinc-supplemented cattle reportedly had improved growth performance, but no change in clinically relevant health performance outcomes.[14]

Energy

Duff et al[14] reported in a review of the literature that a higher-concentrate ration fed during the receiving period had a negative impact on health performance as measured by clinical morbidity, but a positive effect on feeding performance. They indicated that it was not cost-effective over the entire feeding period to reduce concentrate and increase roughage during the receiving period, even with the benefit found in morbidity. However, Gifford et al[18] reported that growth performance and feeding performance could be compensated with additional days on feed.

Gifford et al[18] also reported that the metabolic cost of inflammatory responses and immune function had a liability on feeding performance and carcass characteristics, measured by hot-carcass weight and marbling.

Protein

Galyean et al[16] indicated that protein deficiency has negative implications on protective immune function. This position was based largely on substitution indicators (e.g. serum antibody responses) reported in protein-supplemented cattle vs non-supplemented cattle prior to feedlot entry. These authors describe a paradoxical response, using clinically relevant outcomes, wherein crude protein (CP)-supplemented cattle have greater dry matter intake, greater gain, but also greater rectal temperature and clinical signs of respiratory disease. However, no mortality outcomes (crude mortality, BRD mortality, infectious mortality, etc.) were reported. Little has been reported since this time to dissect the question of immune function impact of protein-supplementation in studies reporting clinically relevant outcomes. However, Gifford et al[18] described the metabolic protein demand based on inflammatory response.

Biotechnology

Genetically engineered vaccines

In the peer-reviewed refereed scientific literature, there are reports of efficacy of experimental vaccines developed using genetic engineering technology against bovine herpesvirus-1 (BHV-1), bovine respiratory syncytial virus (BRSV), *Brucella abortus*, and *Salmonella* spp using experimental challenge models and reporting substitution indicators, such as serum antibody response and reduction in viral shedding. In some cases, clinically relevant outcomes, such as reduction in severity of clinical illness scores under experimental challenge conditions, are reported.

Recombinant

A recombinant vaccine was reportedly developed by integrating BVDV sequences into ginseng plant DNA. However, although humoral and cell-mediated responses were reported following vaccination, no clinically relevant outcomes were reported under natural-challenge field conditions.[17] Although recombinant technology has been used to elicit immune responses to foot-and-mouth disease virus (FMDV),[27] *Brucella abortus*[42] and *Mycoplasma mycoides* when laboratory outcomes or substitution indicators are measured under experimental challenge conditions, there are no reports in the peer-reviewed, refereed scientific literature investigating field efficacy in feedlot cattle populations. Prysliak et al[31] reported that conserved protein sequences of *Mycoplasma bovis* failed to protect feedlot cattle from experimental challenge as measured by weight gain, rectal temperature, survival proportion, and lung lesion development.

There have been recent advances in experimental plant-made viral bovine vaccines against foot-and-mouth disease virus (FMDV), bovine rotavirus (BRV), bovine viral diarrhoea virus (BVDV), bluetongue virus (BTV), and bovine papillomavirus (BPV). However, there have been no commercially available recombinant vaccines developed for use in feedlot cattle.[35]

Gene-deleted mutant

Chowdhury et al[10] reported that a gene-deleted mutant experimental vaccine with deletions or modifications at 3 gene loci provided superior protection and immunologic substitution indicators following experimental challenge compared to unvaccinated control calves or an experimental vaccine with a gene-deletion at only 1 locus.

Subunit vaccines

Babiuk et al[3] presented a novel vaccine approach in 1996 and predicted that subunit BHV-1 vaccines would launch a new generation of vaccines and revolutionize vaccine regimes used in cattle. While this seemed promising, based on developed technology, limited progress has been made after 20 years in commercializing genetically engineered vaccines such as recombinant strains, gene-deleted mutant strains, and subunit sequences. However, recent work has been done to investigate genetically engineered vaccines under experimental conditions, reporting substitution indicators, and in some cases, protection against experimental challenge.

A commercially available *Mannheimia haemolytica* bacterial extract-toxoid has been developed and made commercially available. This vaccine is comprised of subunit *M. haemolytica* outer membrane protein and recombinant leukotoxin. Clinical efficacy investigating clinically relevant outcomes under field challenge conditions is underway.

Immunomodulators

Van Engken et al[44] reported that oral meloxicam had negative impact on immune indicators such as interleukins, interferon production, CD surface molecule expression, and expansion of T-cell subsets; however, no clinically relevant outcomes were reported.

Zelnate DNA immunostimulant[a] is a non-antibiotic DNA sequence that mimics infection, thereby stimulating nonspecific innate immune responses. Results of manufacturer-sponsored studies designed to investigate field efficacy are equivocal. A third-party, independent field trial designed to investigate field efficacy of Zelnate DNA immunostimulant and report clinically relevant outcomes under field conditions has recently been published.

Conclusions

Immune function in cattle received at the feedlot can be optimal based on attention to detail regarding prior management including adequate passive transfer, weaning practices, effective immunization based on timing and appropriate vaccination, transportation, season and associated weather during the receiving period, commingling, and nutrition. The driving question becomes whether it is cost-effective for the feedlot to pay premiums for cattle managed to enhance immune function prior to feedlot arrival at a level that warrants implementation of these management practices for the cow-calf producer.

Seeger et al[38] reported results of a study designed to find the actual market value of management practices that enhance immune function during the feeding period. This study used reports of sales of calves sold on a video livestock auction service from 1995 to 2009. Calves in the sale are categorized as having been vaccinated once or vaccinated and re-vaccinated, vaccinated and weaned, or unvaccinated. Calves designated and marketed as having pre-sale management including vaccination, weaning prior to feedlot arrival, and bunk breaking yielded a premium of 3.7 to 7.3% of the base price. In today's marketing environment, assuming a 500 lb (227 kg) calf is valued at $150/cwt, this returns an additional $2.06 to 10.95/100 lb (45 kg) bodyweight to the producer. However, this does not come at no additional cost or risk to the producer. Using elementary calculations to

estimate these costs, without feed mark-up or interest, but including a basic yardage charge to cover additional labor, fuel, and repairs, and an estimate of mortality for the backgrounding period, it likely costs the producer approximately $12/100 lb (45 kg) BW to manage calves at weaning time in a manner that enhances immune function, based on reports in the literature cited in this review.

Participation in pre-feedlot management programs varied in the study reported by Seeger et al[38] from 3.2 to 53%, depending on the level of management and the year of the study. From the feedlot's perspective, it makes sense to purchase cattle that have been managed to enhance the probability of optimal immunity prior to sale. However, from the producer's perspective, implementation of additional management practices must return on investment. Based on the results of this study, even for years with the highest return vs baseline, the management practices that enhance immune function prior to feedlot entry are unlikely to return on the investment of the cow-calf producer. Hence, the cow-calf producer must rely on more intangible benefits of these management practices, such as reputation and buyer relationships.

Endnotes

[a]Zelnate DNA immunostimulant, Bayer Animal Health, Shawnee Mission, KS

[b]Feedlot Health Management Services, Okotoks, AB, Canada. Unpublished data.

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