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VACCINATION TO CONTROL BOVINE RESPIRATORY DISEASE

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INTRODUCTION

Numerous vaccines are available to prevent and control bovine respiratory disease (BRD); however, it is not always clear whether BRD vaccines are actually useful as applied in the field. Moreover, it is not clear whether differences exist among available products. Supportive data from well-designed clinical trials are the best measure of efficacy of any vaccine. Unfortunately, few clinical trials have evaluated BRD vaccines in dairy calves or cattle; most published BRD vaccine trials have been completed in feedlots. Much more information is available from experimental challenge studies, which often use dairy calves as subjects. However, although experimental challenge studies can prove vaccine efficacy, the artificial nature of the experimental challenge study limits the degree to which results can be extrapolated to the field.

Because veterinarians are frequently presented with data in support of new vaccines, this presentation will begin with a short summary of information that should be considered when evaluating studies of vaccine efficacy. Published research regarding efficacy of vaccines for the major BRD pathogens will then be reviewed briefly. Reasons that BRD vaccines may fail (or appear to fail) will be discussed, and case examples of vaccine use to control BRD will be presented.

EVALUATING DATA SUPPORTING VACCINE EFFICACY

When presented with data supporting efficacy of vaccines, veterinarians should first consider the type of experimental trial they are evaluating: is it 1) a test of immune response as measured by in vitro testing, where antibody or cell-mediated immune responses in vaccinated animals are evaluated; 2) an experimental challenge trial; where cattle are vaccinated and then purposely exposed (challenged) with one or more infectious agents that cause BRD; or 3) a clinical trial, where cattle in a real production setting are vaccinated and then followed to see if the rate of naturally-occurring disease is different in vaccinated cattle as compared to a group of control cattle that were not vaccinated. Tests of *in vitro* immune response indicate that the vaccine can induce an immune response, and some measures of immunity (e.g., concentrations of serum neutralizing antibody) can be predicted to decrease disease in animals exposed to certain infectious agents. However, studies in which immune response alone is evaluated do not provide strong evidence that the vaccine will impact disease. Tests of *in vitro* immune response can be viewed as the foundation for future research. They provide preliminary information that is supportive, but more data are needed to determine if the vaccine really works in the field.

Experimental challenge studies provide the second level of evidence regarding vaccine efficacy. If a challenge study is carried out correctly, the results provide proof that the vaccine can prevent disease in at least an ideal setting. Experimental challenge studies showing proof of efficacy are required by USDA for licensure of vaccines; thus, any fully licensed vaccine has been shown to

prevent disease in an experimental challenge study. When evaluating an experimental challenge study, veterinarians should ask: 1) was a control group not receiving the vaccine included, were the cattle in the control group like the cattle in the vaccine group in every way (health, management) except for vaccine treatment, and did the controls develop meaningful disease after challenge; 2) were the differences in disease between the vaccinated and control groups both statistically significant and medically important; 3) was the vaccine used in a way similar to how it would be used in the field; and 4) was there a meaningful length of time between vaccination and challenge. If the answer to any of these questions is “no”, the trial may not provide quality evidence in support of the vaccine.

While experimental challenge studies, if correctly designed and executed, can provide strong evidence supporting the ability of a vaccine to prevent disease due to an infectious agent, a weakness of experiment challenge studies is that they are carried out in an artificial environment. Cattle are usually kept in isolation to protect them from any other infections during the trial. The challenge agent is usually administered in high concentration directly into the nose or lower respiratory tract, which is very different from the means by which cattle are naturally infected. Because of these and other factors, there are limits to the degree to which results from experimental challenge studies can be extrapolated to the field setting. An experimental challenge study is a better measure of efficacy than a study testing only *in vitro* measures of immune responsiveness, but it is not as good as a well-designed clinical trial.

Clinical trials are the best means of determining whether a vaccine is effective; this is because the effect of the vaccine on naturally occurring disease in animals in an actual production setting is measured. However, clinical trials are logistically complex, expensive, and subject to many variables which are difficult to control and which may impact the outcome of the trial. Because of this, relatively few clinical trials testing efficacy of BRD vaccines in situations typical of current U.S. cattle management have been published. Furthermore, most trials that have been published have been carried out in feedlots; thus there is a serious need for more clinical trials testing the efficacy of BRD vaccines in dairy calves or cattle.

When evaluating clinical trials testing BRD vaccines, veterinarians should ask:³1) were cattle randomly allocated to either the vaccine or control groups? This should be clearly stated in the description of the study; failure to randomize the groups can lead to serious bias which makes the results impossible to interpret. 2) Were meaningful measures of disease evaluated, and were people evaluating the cattle unaware (“blinded”) of their treatment status? If evaluators know which cattle are vaccinated and which are not, they may subtly (or not-so-subtly) change the way they look at the cattle and thus determine whether or not they are showing signs of sickness. Subjective outcomes are more subject to such bias, so if evaluators are not blinded, weigh objective measures of outcome (such as rectal temperature) more heavily than subjective measures (such as “difficult breathing”). 3) Did meaningful disease occur in any group? If meaningful disease did not occur, it will not be possible to tell if the vaccine had an effect. 4) Were there statistically significant and medically important differences between vaccinated and control cattle?

DO BRD VACCINES WORK?

Even if only published research evaluating experimental challenge studies and clinical trials testing currently available licensed BRD vaccines are considered, a complete review of the results are beyond the scope of this paper. However, a general summary may be made:

1. Most published research evaluates BRSV and *Mannheimia haemolytica* vaccines, either using experimental challenge studies or clinical trials. While currently available vaccines are usually effective in experimental challenge studies, sometimes they effectively decrease BRD and/or improve productivity in clinical trials, and sometimes they do not.
2. Relative to the published research regarding BRSV and *M. haemolytica* vaccines, less research has been published evaluating vaccines for IBRV (BHV-1), BVDV, *Histophilus somni*, and *Mycoplasma bovis*. For IBRV and *H. somni*, many of the trials were run 20 or more years ago and so may not represent current management in the U.S. While there are many reports of studies evaluating efficacy of BVDV vaccines in experimental challenge studies, the author is not aware of a clinical trial evaluating the use of a currently marketed BVDV vaccine to prevent BRD in a modern U.S. or Canadian production setting. While currently marketed vaccines for these agents are known to prevent disease in experimental challenge studies (which is required for their licensure), there is a great need for clinical trials to confirm the value of vaccines for these agents in preventing or controlling BRD in the field.
3. Very little research has evaluated vaccines for *P. multocida*, and to the author's knowledge, the published research is limited to a small number of experimental challenge studies.

In summary, some good quality evidence from clinical trials supports the point that BRSV or *M. haemolytica* vaccines can decrease disease or improve productivity of cattle in some cases, but not in others. A recent review of evidence of effectiveness of vaccination against *M. haemolytica*, *P. multocida*, and *H. somni* for mitigating BRD concluded that the published research supported efficacy for *M. haemolytica* or combined *M. haemolytica*/*P. multocida* vaccines but not *H. somni* vaccines.² More information is needed regarding other agents included in BRD vaccines. The fact that vaccines for BRSV and *M. haemolytica* (which have been the most rigorously tested) appear efficacious in some clinical trials but not others emphasizes the complex nature of assessing vaccine efficacy in a field setting.

An important point to remember is that when vaccines against BRD are tested in any type of experiment, it is quite rare for them to completely prevent infection in all cattle vaccinated—thus vaccinated cattle will likely still become infected even if they do not become as sick as unvaccinated cattle. And in some studies testing the efficacy of vaccines, even if vaccinated cattle become less sick than unvaccinated cattle, some of them still become sick. So vaccines should not be expected to completely prevent infection, or even completely prevent disease in all animals exposed; they should instead be viewed as a method to decrease the likelihood of infection or disease, and to decrease the severity of disease if it does occur. Veterinarians generally understand this, but we may not adequately communicate this to clients, leading to unrealistic expectations for vaccination. Other reasons BRD vaccines may fail are described below.

REASONS FOR APPARENT FAILURE OF BRD VACCINES

As noted above, clients should have realistic expectations of what BRD vaccination can accomplish. Given realistic expectations, if vaccinated cattle develop BRD, multiple possible causes should be considered. Possible causes of apparent vaccine failure are related to 1) the administration of the vaccine, 2) the ability of host to respond to vaccination, and 3) the nature of pathogen exposure. In category 1, apparent vaccine failure may be due to mishandling of vaccine (e.g., improper storage of live organism vaccines, use of residual product in a bottle reconstituted days to weeks previously, or chemical disinfection of multi-dose syringes leading to inadvertent inactivation of live vaccines); improper or careless administration, so that less than an optimum dose is delivered, or so that vaccine is not administered at recommended site (e.g., administration into nuchal ligament rather than cervical muscle, or intradermal rather than subcutaneous administration); concurrent administration of antibiotics with live bacterial vaccines; and incorrect timing of vaccination, such as vaccinating animals already incubating the disease, or failing to allow time for an immune response to vaccination prior to pathogen exposure, or administration of booster too soon, too late, or not at all. In general, if only a single vaccination is possible, modified live viral (MLV) vaccines should be used, as these nearly always give a stronger, more long-lasting response after only a single dose as compared to inactivated vaccines. If not given at a 2-4 week interval, even 2 doses of an inactivated product may not elicit optimal protective immunity.

In category 2, factors that may lead to apparent vaccine failure through inability of the host to respond to vaccination include the presence of very high levels of maternal antibodies (although some vaccines can immunize in the presence of moderate levels of maternal antibody);⁵ age of the animal, with very young calves (< 1 month) sometimes manifesting suboptimal immune responses; immunocompromise due to concurrent disease, poor nutrition, or high levels of stress; and genetic influences, which can be expected in a genetically heterogeneous population and which result in a continuum of responses to a given vaccine, such that some animals fail to respond as desired even when the majority of the population does. Finally, poor housing or husbandry may contribute to persistent problems with respiratory disease even in the face of an appropriate vaccination program.

In category 3, one must consider expected and actual pathogen exposure. Failure to vaccinate against pathogens to which animals are actually exposed may result in apparent vaccine failure. Regular postmortem evaluation with diagnostic microbiology may help confirm or rule out suspected pathogens and guide more rational vaccine choices. Strain variation of pathogens as compared to vaccine strains may impact vaccine success; BVDV is an example. Most mainstream BVDV vaccines contain both type 1 and type 2 BVDV to provide optimal immunity against both viruses. Nature of challenge may affect vaccine efficacy; even the immune response provided by a reliable vaccine can at times be surmounted by an overwhelming number of pathogens, an unusually virulent pathogen, or by concurrent exposure to additional pathogens unrelated to the vaccine. While the above points may appear obvious, it is important to consider and rule out these possibilities when a vaccine has failed to prevent BRD before making a quick switch to another brand or type of vaccine.

EFFECTIVE USE OF VACCINES TO CONTROL BRD

Vaccination should be one of multiple tools used to limit respiratory disease in cattle. When using vaccines, remember basic principles relevant to vaccine use: 1) animals need time to respond immunologically to a vaccine—roughly 3 to 14 days, depending on which aspect of the immune response is needed (serum or mucosal antibody, T cell responses, etc.). Don't expect much from vaccines given right at the time animals are exposed to infection. IBRV vaccines have been shown to provide protection within 3 to 5 days of administration, but this has not been well evaluated for other BRD vaccines. 2) Pay attention to recommendations on the vaccine label; if the label says a booster vaccine is required, optimal immunity will not be induced if the booster is not given. Many vaccines are labeled for single dose administration, but this is not universally true. 3) If an animal is already infected with a pathogen, vaccination against that pathogen is unlikely to be helpful. Think about when cattle are at risk for exposure and time vaccination so that the last dose occurs at least 1 to 2 weeks before exposure of the group is expected. 4) If an animal is vaccinated for a pathogen but it gets infected with a different pathogen, vaccination can't help. Many agents can cause BRD, so BRD in vaccinated cattle can be due to infection with other agents not included in vaccines. Vaccines for some pathogens that can cause BRD are not commercially available at this time (e.g., respiratory coronavirus).

In addition to selecting vaccines appropriate to the infection risks expected for a given group of cattle, and using those vaccines appropriately, biosecurity should also be used to limit the risk of BRD. A foremost principle of biosecurity is that newly introduced animals should be isolated from the rest of the herd for at least 2-4 weeks after purchase. Additionally, limit the age range in a group of cattle; a common finding in herds with BRD problems is the mixing of animals with a wide range of ages.¹ In such situations, older juveniles can amplify infectious agents and then spread them to younger or older naïve individuals. Evidence-based guidelines are lacking, but limiting the age range of calves in a group to no more than 60 days may help decrease the amplification and spread of BRD agents. Producers should also limit crowding to control BRD; BRD is often a problem when an unusually large numbers of cattle are brought together in close contact (due to severe weather, problems with facilities, etc.—not necessarily just due to new introductions).

In working to limit BRD, remember to control non-respiratory infections; animals with other infections (such as infectious diarrhea in calves) are more susceptible to BRD. Ensure optimal transfer of maternal antibody from colostrum: transferred maternal antibody is very important in limiting BRD (and other disease) in calves. If calves within the first month or two of life are developing BRD, pay particular attention to maternal antibody transfer in the herd, and factors that can affect it such as dystocia, severe weather, and dam nutrition. Nutrition of calves can play a role in BRD susceptibility through the impact of malnutrition on immune responsiveness. While supplementation of nutrients (such as vitamins and minerals) in excess of required amounts has not reliably been shown to prevent disease, correction of deficiencies of protein, energy, and certain vitamins and minerals has been shown to improve immune responsiveness in some situations. What is being fed to cattle may be important; some evidence indicates that high energy diets can increase the susceptibility of cattle to BRD.⁴

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