Choosing a New Vaccine: A Solution or a Potential Problem

Robert Tremblay, *DVM, DVSc, Diplomat ACVIM*
Technical Services Veterinarian, Boehringer Ingelheim (Canada) Ltd.

Abstract

Vaccination is an integral part of disease prevention and control programs in dairy and beef production systems. Despite widespread acceptance of vaccination, many aspects of vaccination are controversial. Veterinarians are often confronted with implementing or changing vaccines and vaccination programs without having access to adequate information. This paper addresses controversial issues related to the implementation of modified–live viral vaccine programs and the selection of BVD and BRSV vaccines.

Introduction

Despite widespread adoption of vaccination,[42,43] data supporting the use and efficacy of vaccination in field situations is scarce, even for common diseases, such as bovine respiratory disease (BRD) syndrome.[33] Research on the benefits and disadvantages of changing vaccines or changing vaccination programs is even more uncommon in the scientific literature. Recently, results of trials evaluating different combinations of vaccines have been reported.[15] These give some guidance for the responses that might be expected if changes were made to vaccination programs.

Veterinarians and producers may wish to change vaccines or vaccination programs for any of several reasons. Biomedical reasons for change include:

- Perceived lack of efficacy of the existing vaccine or vaccination program;
- Perceived superior efficacy or broader range of protection provided by a different vaccine or vaccination program (for example: selecting a vaccine with more BVD viral antigens or with BVD antigens different from the existing vaccine or program);
- Adoption of products with claims of efficacy different from existing products or programs (for example: introduction of vaccines with label claims to protect the fetus against BVD virus rather than to protect only against acute BVD);
- Implement a vaccination program to use different vaccines in combination;
- Implement a vaccination program that is easier for producers to use;
- Unacceptable prevalence or severity of adverse reactions with the existing vaccine or vaccination program.

In addition to biomedical reasons, there may also be commercial reasons to change vaccines and vaccination programs. A common commercial reason is to provide an improvement in the cost-to-benefit ratio for the vaccination program. This often occurs in situations where formal cost-benefit analyses are possible because the risk of disease is high, as in beef feedlots.[40]

In the absence of an overt failure of the existing vaccine or vaccination program, it is difficult to determine if efficacy will be improved by changing vaccines or vaccination practices. Unlike therapy where success or failure may be obvious, in most cattle production systems, prevention or control cannot be readily assessed in the absence of failure. One can never be sure if the absence of signs of disease results from the success of the program, from the absence of the infectious agent or from absence of the risk factors that often contribute to disease. This uncertainty in assessing vaccines and vaccination programs has fueled debate and research about the protection provided against major pathogens by different vaccines and vaccine programs.

BVD Virus: Genetic Diversity, Vaccine Efficacy and Vaccination Programs

Much controversy has revolved around the impact of the genetic and antigenic diversity of bovine viral diarrhea (BVD) virus on the ability of vaccines and vaccination programs to protect against the major clinical manifestations of infection. BVD virus exists in only one serotype although there is substantial antigenic variation in isolates from field cases of BVD.[5,14,28] BVD virus also exists in at least two genotypes, BVD type 1 and BVDV type 2. Each genotype can be further subdivided into subgenotypes such as subgenotypes 1a and 1b.[32,36,37] As the name implies, the types or groups of BVD virus were originally differentiated based on variations in their genetic material. Differences in the anti-

genic properties between isolates of different genotype were identified subsequently.[6,11,25]

When type 2 BVD virus were first described following the BVD epizootic of 1993-1994, there was concern that vaccines containing only type 1 vaccines may not protect against disease caused by the newly recognized type 2 BVD viruses. Assessing the field efficacy of vaccines is difficult. Cross neutralization assays suggested that commercial inactivated and modified-live vaccines provoked antibodies that cross-reacted with a range of BVD virus.[11,25] Unfortunately, the production of cross-reacting antibodies may not equate with protection against naturally-occurring disease.

Examination of data from farms in the Canadian 1993-1994 outbreaks suggested that lack of compliance with vaccination recommendations rather than lack of cross-protection by existing type 1 BVD vaccines was the main contributing factor in herds with outbreaks of severe BVD.[7] Subsequently, a series of studies has been reported documenting the ability of vaccines containing type 1 BVD viruses to provide protection against clinical disease (acute BVD) following experimental challenge with virulent type 2 BVD viruses.[13,18,22] The extent of cross protection under field conditions and the extent of cross protection of the fetus in pregnant cows provided by commercial vaccines containing only type 1 BVD viruses is less clear.[4] It is very difficult to compare the relative efficacy of commercial vaccines across fetal challenge studies because there is no standard methodology. However, in challenge studies, commercial vaccines containing both genotypes of BVD virus may provide greater protection of the fetus than vaccines containing only a type 1 BVD virus.[4,10,12,23,30]

While there are significant antigenic differences between genotypes, the importance of possible antigenic differences in subgenotypes is less clear. Questions have arisen regarding the ability of BVD vaccines containing subgenotype type 1a antigens to protect against naturally-occurring disease due to subgenotype type 1b BVD viruses.[26,27] There are only limited data to support this concern. BVD viruses associated with outbreaks of respiratory disease were more frequently found to be type 1b BVD viruses and BVD viruses isolated from BVD virus-infected cattle were more frequently type 1b viruses.[27,41] Until the distribution of genotypes among field isolates of BVD virus is determined, it will be difficult to evaluate the significance of differences in isolates from diagnostic laboratories. Even if it is found that type 1b BVD viruses are more prevalent in vaccinated diseased cattle than in the general population, there is limited antigen choice among commercially available vaccines as currently only one vaccine contains a type 1b BVD virus.

It appears that the need for broad protection from a BVD vaccine depends on the type of the clinical protection that is required. Research suggests that, except in high risk situations, a broad range of antigens may not be necessary if the objective is to prevent acute BVD. Limited data suggests that protecting the fetus is more difficult and may require the use of vaccines with an expanded range of antigens or increased antigen content.

If protection against a broader range of genotypes is needed, it is not apparent how this can be best achieved. When the objective of the vaccination program is to provide protection for breeding females, then an obvious change in vaccination would be to select a vaccine that carries a label claim for fetal protection. At present this means most veterinarians will select an MLV vaccine containing both type 1 and type 2 BVD viruses. Ideally, the veterinarian would select the vaccine with documented high efficacy. Unfortunately, because the methodology for fetal trials is not consistent from study to study, there is no real way to compare different products unless both vaccines were assessed in the same study. There are differences between studies not only in trial design, but also in how the level of protection is calculated. Some studies choose to exclude cattle that came up open during the trial from any calculation of protection. This actually allows the possibility of eliminating cattle from the study even though they may have lost a fetus to BVD virus infection. In some studies where the rate of fetal infection in unvaccinated control cattle is not 100%, the authors often fail to adjust the calculated level of protection in the vaccinated cattle to account for the fact that the actual risk of fetal infection was not 100%. In other words, veterinary practitioners do not actually know the relative efficacy of different products with similar label claims and may not be improving efficacy by changing vaccines.

Practitioners should also be aware that a label claim for protection against both type 1 and type 2 BVD virus does not necessarily mean that both genotypes of BVD virus are present in the vaccine. It means, only that the type 1 BVD virus in the vaccine has been shown to provide some cross-protection to experimental challenge with a type 2 BVD virus.

If the objective of the vaccination program is to protect against acute BVD, the choice is even less clear. One could also select an inactivated or MLV vaccine that contains both genotypes of BVD virus, but is there evidence that you can accomplish better or broader efficacy using combinations of vaccines? It has been proposed that it is inappropriate to administer a primary series with inactivated vaccine if you intend to boost with an MLV vaccine.[39] In fact, research has shown that the interaction between different vaccines is much too complex to permit such a blanket recommendation. In some studies, superior protection has been achieved by boosting cattle with an MLV after initial vaccination

with an inactivated vaccine.[24,47] This cannot be a general recommendation though as there are differences in serologic responses depending on which inactivated and MLV vaccines are used. Not all combinations of vaccines yield the same outcome.[15] Veterinarians need information on the immune response to a specific combination of vaccines before recommending the use of that combination in the hope it will provide a greater or broader range of protection against BVD virus. Practitioners should also be aware that changing to a different BVD vaccine does not necessarily mean that they will be changing to a different antigen. In fact there are a limited number of strains of BVD virus used in vaccines.[26] Vaccines manufactured by different companies may very well contain the same BVD viral strains, although the amount of virus included in different company's vaccines may be quite different.

BRSV Vaccine Efficacy

The controversy over the extent of protection provided by vaccines is not limited to BVD vaccines. The efficacy of bovine respiratory syncytial virus (BRSV) vaccines has also been controversial.[1,16,17,39] Until relatively recently, there had been no way to evaluate clinical efficacy because there were no challenge models that produced clinical disease and lesions similar to those in naturally-occurring disease.[44,46] Discussions on efficacy of BRSV vaccines were generally based on studies of the immune response following challenge or on the response to vaccination with experimental vaccines. The controversy was fueled by the lack of a complete understanding of the nature of protective immunity to BRSV.[16,31] Based on research of the basic immune response to BRSV, it had been proposed that inactivated vaccines were unlikely to provide protection against naturally-occurring respiratory disease.[1,17,39] This would suggest that although commercial inactivated vaccines had met the regulatory standard for efficacy, they may not be efficacious enough to prevent naturally-occurring disease. Should veterinarians recommending the use of inactivated vaccines change their recommendation to MLV vaccines to take advantage of their perceived greater efficacy?

As with many conclusions formulated using data of research on the basic immunology of infection, the proposal that inactivated vaccines did not protect was contradicted by subsequent research that studied actual disease. When inactivated BRSV vaccines were assessed in challenge models that closely mimicked naturally-occurring disease, they were found to protect against both clinical disease and the development of lung lesions.[19,21] Commercial modified-live vaccines were also found to protect in these challenge models.[20,45] It remains to be determined if there are differences between the protection provided by inactivated or modified-live vaccines in naturally occurring disease. It also remains to be determined if there are differences in the duration of the immunity induced by inactivated and modified-live BRSV vaccines. As yet, there are not sufficient efficacy data to justify a wholesale change in BRSV vaccination protocols to promote the wider use of MLV vaccines.

Changing to an MLV Vaccine-based Program

One of the most common changes in vaccines and vaccination programs is to change from inactivated to modified-live vaccines in breeding cows and heifers. This change might be undertaken for a number of reasons. In addition to the efficacy improvements, noted above, another reason is to improve compliance with vaccination recommendations. A major problem with programs using inactivated vaccines is the widespread lack of compliance among producers who use inactivated vaccines.[8,34,42,43] Failure to give a primary series with inactivated vaccines and failure to regularly administer annual boosters with inactivated vaccines are common. It is unclear what protection is obtained if no primary series is given, however, this type of lack of compliance was identified as a factor in dairy and beef herds affected by the BVD epizootic in Ontario in 1993-1994.[7]

Compliance is less an issue with MLV vaccines because a single dose is sufficient as a primary series for the major viral antigens. The interval between consecutive boosters is also less critical because only one dose of MLV vaccine is sufficient to boost the major viral antigens even when it has been more than a year since the previous vaccination.

There are concerns associated with introducing some MLV vaccines into management systems where recently vaccinated cattle come into contact with unvaccinated pregnant cattle. IBR viruses used in some vaccines can retain sufficient virulence to induce abortion in pregnant cattle. A number of studies have been undertaken to show that the risk of shedding from recently vaccinated cattle is low.[9,29,38] These studies are useful but difficult to interpret. They do not actually estimate the risk of shedding of vaccine viruses. They only suggest that shedding does not occur above a detection threshold determined by the design of the trial. In general, it is difficult to conclusively prove that an event, such as shedding of vaccine virus, does not occur, when it appears to be rare. In any case, assuring that the pregnant cattle are vaccinated before implementing the MLV vaccination program in non-pregnant cattle will even further reduce the risk.

Concern has been raised about using more than one BVD virus in MLV vaccines. The hypothesized risk is that the two cytopathic vaccine viruses may recom-

bine to generate new non-cytopathic BVD viruses. As with post-vaccination shedding, it is difficult to prove that recombination cannot occur, but it appears to be an unlikely risk. Genetic recombination of BVD viruses has been reported, but only in persistently infected cattle. In these cases, the recombination involved a recombination of the persistently infecting non-cytopathic virus with a different cytopathic virus to create a new cytopathic BVD virus and mucosal disease.[2,3,35] This is quite a different process from the hypothesized recombination of the two cytopathic viruses present in MLV vaccines to create a new non-cytopathic BVD virus. This type of recombination has never been reported. In addition, if recombination occurs in persistently infected cattle, the immunotolerance of the persistent infection may permit survival and replication of recombinant BVD viruses (JF Ridpath, pers com, 2005). In acutely infected cattle, the tendency is for all BVD viruses to be cleared by the immune system, which would limit the potential for survival of any viruses even if they were created through recombination.

The decision about introducing MLV vaccines then becomes a tradeoff between the potential benefits of increased protection and more easily attained compliance and the risks of introducing vaccine virus into a herd or of generating new BVD viruses through recombination.

Conclusion

It is difficult for practicing veterinarians to formulate science-based vaccination recommendations because they are bombarded with recommendations that are often formulated from very limited data. Ideally vaccines and vaccination program should be evaluated in field trials. Unfortunately field trials are almost impossible to conduct in situations where the risk of disease is not easily predictable. In these cases, evaluation of vaccine efficacy in challenge models is probably the best alternative. When challenge trials are not possible, either because no suitable challenge model exists or because challenge studies do not lend themselves to evaluation of the duration of immunity, indirect outcomes such as serology may be the only data available. Serologic studies should only be used for diseases where protection can be correlated with the serologic outcome that is measured. Ideally, serologic studies should be conducted with the same vaccines that will actually be included in the vaccination program.

To reduce the possibility of misunderstanding, veterinarians should provide their recommendations to use specific vaccines and to implement vaccination programs in writing. A copy of the "vaccination prescription" should be included in the clinic's permanent record for that client.

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