Combination Vaccines for Cattle

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Introduction

Since the first immunization against enterotoxemia by Louis Pasteur in 1877, vaccines have played a significant role in the control of bovine diseases. Foot and mouth disease, respiratory disease and neonatal diarrhea vaccines have been used successfully for many years.

Multivalent vaccines are common practice in many species, including human. Vaccines protecting against five diseases in a single injection have been developed for use in children (diphtheria, tetanus, whooping cough, polio and Haemophilus b meningitis). Likewise the puppy vaccines include several viruses and leptospira in one product. In cattle, most vaccinations against neonatal diarrhea or clostridium are done worldwide with products containing several valencies. In North America, large combinations have been developed to control bovine respiratory disease in the feedlots. However, the use of such biologicals is not common practice in Europe.

In this paper we will review the reasons for and against the use of the combined vaccine and the results obtained with such products in the control of bovine respiratory disease and bovine enteritis.

Reasons to Use Multivalent Vaccines

Several pathogens may act in synergy

Secondary bacterial infection has long been recognized as a major complication of acute viral respiratory disease.[14] Bovine viral diarrhea virus (BVD), bovine herpesvirus 1 (BHV-1) and Bovine parainfluenza 3 (PI3) virus may play a predisposing role for *P. haemolytica* or *P. multocida* infections. This was demonstrated under experimental conditions[6, 15] and was confirmed under field conditions.[7] More recently two viruses, bovine respiratory syncytial virus (BRSV) and BVD were shown to have synergistic effects in an experimental study.[9] Calves challenged with BVD and RSV sequentially had more clinical signs and lung lesions than animals challenged with only one of the viruses.

Likewise, the severity of neonatal diarrhea may be related not only to the virulence of the infectious agent, but also due to the presence of multiple infections.[1] If two viruses co-infect an animal and have different sites of replication, the combined effect may be more severe than if they infected the animal individually. The presence of a viral-bacterial synergistic interaction is another important factor.

Concurrent viral infection

Simultaneous rise of antibodies to 15 different pathogens has been observed in the same diseased cattle.[8] Furthermore, several viruses have been isolated at the same time from the nasal cavities or lungs of sick calves.[11] Those evidences show that mixed infection with two or more agents occur.

Different strains or serotypes of pathogens

Various serotypes, strains or serovars of virus or bacteria can cause the same disease in the same geographic area without any reliable technique to predict which one will be involved in an outbreak. Type I and Type II BVD can illustrate that purpose for North America. Antigenic variation can also occur.

Convenience

Convenience could also be a major driver for the use of a combination vaccine. It is easier to administer all products in one injection than to reload a syringe several times.

Difficult differential diagnostic

In many outbreaks of either respiratory disease or neonatal diarrhea, it is difficult to determine with precision the etiology of the disease. When confronted with the task of developing a prevention plan for the future, the veterinarian may often be forced to use broad combination vaccines.

Cost

The livestock industry is driven by cost like any other business. Combinations of antigens allow some

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cost reduction from the manufacturer bill and the labor. It may also minimize the risk of injection site reaction by diminishing the number of injections.

Reasons Not to Use Multivalent Vaccines

Cost

A multivalent vaccine costs more than a monovalent vaccine. If protection against only one pathogen is required, it will be a waste of money to use large combinations.

Interference between fractions

The immune system has limitations on the number of antigens it can process efficiently at the same time. The consequences could be an interference between fractions of a combination vaccine resulting in a less than optimum response for each fraction. However, the regulatory guidelines for licensing of new products in the European Union guarantee that biologicals sold on the market are effective. For example Tables I and II illustrate the lack of interface between BRSV and BVD antigen in a commercial vaccine (Rispoval RS/BV, Pfizer, Inc.).

Table 1. Lack of interference between BRSV and BVD fractions in a combination vaccine. Response to BRSV antigen measured by seroneutralization and reported as geometric mean titers (seven animals per group)

Vaccine/Days	Day 1	Day 21	Day 35
BRSV monovalent	1.0	3.0	58.0
BVD Monovalent	1.0	1.0	5.9
BRSV/BVD Combination	1.0	4.0	95.1

Table 2. Lack of interference between BRSV and BVD fractions in a combination vaccine. Response to BVD antigen measured by seroneutralization and reported as geometric mean titers (seven animals per group)

Vaccine/Days	Day 1	Day 21	Day 35
BRSV monovalent	1.0	1.0	1.0
BVD Monovalent	1.0	1.1	52.5
BRSV/BVD Combination	1.0	2.4	78.0

Safety concerns

In theory the more antigens in a product, the larger are the chances of a local or systemic reaction. The protein/endotoxin/adjuvant contents play a role in various side effects observed with vaccines, such as local irritation, allergic reaction endotoxic shock. A negative effect on the immune system is also a potential risk.

Veterinarian's professional judgment

In many cases the veterinary practitioner knows the farm and its history and can recommend the proper vaccine to be used. The use of large vaccine combination should not replace good management practice and the right prescription.

When properly used, the combination vaccines are a viable option for the control of some diseases. Two of the most damaging diseases for the cattle industry are respiratory disease and neonatal diarrhea. We will review successively the use of a multivalent vaccine in the control of these diseases.

Bovine Respiratory Disease

Vaccines available

In response to a complex etiology vaccine, manufactures have developed various combinations of multivalent products. The following vaccines are available as monovalent or in different associations:

- *P. haemolytica*
- *P. multocida*
- *H. somnus*
- Bovine herpesvirus 1
- Bovine respiratory syncytial virus
- Bovine viral diarrhea virus
- Bovine parainfluenza III virus
- Bovine adenovirus
- *Dictyocaulus viviparus*

Intranasal vaccination

Vaccines containing, in various combinations, BHV-1, PI-3 and Adenovirus 3 have been developed by vaccine manufacturers for use intranasally. Some viruses have been mutated by treating an attenuated culture with acid. Amongst these mutant viruses, those incapable of multiplying at the normal body temperature were selected. These temperature-sensitive viruses can replicate in the nasal passages when the temperature is at least five degrees Celsius below normal core body temperature but not in other tissues at normal body temperature. Such vaccines are designed to stimulate local mucosal immunity. Under experimental conditions, challenge 21 days after revaccination (with PI-3 and Adeno-3) resulted in a reduction of the multiplication of PI-3 and bovine adenovirus in the upper respiratory tract in the presence of local and systemic antibodies.[16] Furthermore, during an outbreak of PI-3 pneumonia in a commercial calf rearing unit, the incidence of pneumonia was lower and the number of days of elevated temperature, as well as the number of treatments, were significantly reduced in groups vaccinated intranasally with a combination product against BHV-1 and PI-3 virus.[13]

Systemic vaccination

More than 130 vaccines with different combinations, including viruses and bacteria, were available to US veterinarians and cattle producers here in 1995. The choice is much more restricted in the EU.

The viruses included in the combinations are BHV-1, BVD, BRSV, and PI-13. The vaccines can be based on modified live viruses, inactivated viruses, or a combination of both. In experimental challenge experiments, calves vaccinated with two doses of BHV-1, PI-3, BVD, and BRSV vaccine developed serum-neutralizing antibodies against those viruses, were protected against clinical signs of IBR, and the shedding of PI-3 virus was significantly reduced if compared with a placebo.[12] Furthermore, no drop in leukocyte count was observed after challenge with BVD virus and no evidence of serological interference was found.

In a large field study involving 6,988 calves, the addition of BRSV to a BHV-1, BVD, PI-3 vaccine resulted in a significant reduction of the morbidity rate for bovine respiratory disease.[4]

The available vaccines are either administered twice at 2-4 week intervals or only once. For young calves, the administration can happen during the preconditioning program, at weaning before transportation, at the auction barn, or upon arrival at the feedlot.

In a recent study conducted in collaboration between researchers at AFRC in Compton UK and Pfizer scientists, calves four months of age were vaccinated twice, three weeks apart with a part live (BRSV, PI-3) part inactivated adjuvanted (BVD, IBR) vaccine. Clinically vaccinated animals showed significantly less nasal discharge and fever following challenge with IBR virus Table III.

Table 3. Reduction of clinical signs after challenge with BHV-1 of calves vaccinated with a placebo or an experimental multivalent vaccine, Rispoval 4 (Pfizer Inc.)

	Clinical scores		
Groups	Number of calves	Nasal discharge	Fever
Vaccine	9	6	3
Placebo	9	33	36

Four of the nine control animals challenged with BVD became viraemic. None of the vaccinated animals were viraemic. Furthermore, the mean duration of leukopenia in those calves was less in vaccinated than in control animals (4 and 9.2 days respectively).

After the challenge with BRSV the virus was isolated from the nasopharynx of two of nine vaccinated animals compared with six of nine control animals. Mean duration of virus shedding and mean titer was also less in vaccinated compared with control animals Table IV.

Table 4. Reduction in virus shedding after experimental challenge with BVD of calves vaccinated with a placebo or our experimental vaccine.

	Shedding in nasopharynx				
Group	Number of Calves	Mean duration (days)	Number of calves	Mean titer	Number of days
Vaccine	9	1.0	1	1.65	2
Placebo	9	2.0	6	2.28	10

Likewise the mean duration and mean titer of the PI-3 virus shed were reduced in vaccinated calves.

In commercial vaccines, virus can be found in association with various bacteria showing tropism to the respiratory tract: *P. haemolytica* and *multocida* and *H. somnus*. An experimental vaccine associating *Mycoplasma dispar and Mycoplasma ovis* with BRSV and PI-3 has been tested successfully under field conditions with a significant reduction in mortality and morbidity.[5]

Respiratory pathogens have also been associated with other antigens such as various serovars of leptospira or species of clostridium. Up to 18 antigens have been combined.[2] For such vaccines, the safety profile and the potential interference between fractions should be a major decision factor prior to use. The vaccine users have the possibility to inject lesser combinations at the same time, for example the four viruses + *P. haemolytica*.

The use of multivalent vaccines is a basic tool used to reduce the risk of bovine respiratory disease in calves. Although it is difficult to prove that they guarantee a significant return on investment for all cases, the role of such vaccines is now well established in reduction of mortality and morbidity for BRD.

Neonatal Diarrhea

Vaccines available

Following the same logic as for respiratory disease, the following antigens are present in various combinations in vaccines to be administered to pregnant heifers or cows in order to obtain passive protection of the calves through maternal antibodies:

- Bovine rotavirus
- Bovine coronavirus
- *E. coli* (different serotypes)
- *C. perfringens* type C

Furthermore, a vaccine containing bovine rotavirus and coronavirus has been used for many years in young

calves at birth and various vaccines containing salmonella have been developed for use in calves.

Use of combined vaccines

Two published studies demonstrate the potential benefits of multivalent vaccines. Since it is difficult to test these under experimental conditions, field studies are used.

In the first study conducted in large beef cattle (2,000 animals), cows were vaccinated either with a placebo or an inactivated oil adjuvanted rotavirus--*E. coli* vaccine.[3] Morbidity due to diarrhea among calves from dams in the vaccinated group was significantly reduced when compared to the placebo group (Table V).

Table 5. Reduction in morbidity due to diarrhea in calves from dams vaccinated with a placebo or a rotavirus *E. coli* vaccine

	Years		
Groups	1986	1987	1988
Vaccine	34%	23%	15%
Placebo	77%	67%	34%

In the second example, 783 pregnant cows from 22 herds in France were vaccinated 15 to 90 days before calving and at the day of calving with an inactivated vaccine against Rotavirus, Coronavirus and four antigens of *E.coli* or a placebo.[10] A significant reduction in the incidence of neonatal diarrhea was observed (Table VI).

Table 6. Morbidity rates in calves after vaccination of their dam with vaccine containing Rotavirus, Coronavirus and *E. coli.*

Groups	Morbidity rate
Vaccine	4%
Placebo	17.5%

Hyperimmunization of the dam to increase the level of antibodies in milk above the threshold level required to prevent infection with various pathogens associated with good management practices is still one of the best prevention methods.

Recent advances in recombinant DNA technology and delivery systems such as pulse release should provide more efficacious vaccines in the near future.

Conclusion

In the control of various bovine diseases, combined or in the future combinable vaccines have a significant role to play. They should not, however, replace good management practices. Furthermore, the role of the prescribing veterinarian deciding which products should be used under what circumstances remains crucial for the success of any prevention plan.

Summary

Multivalent vaccines are used commonly for the prevention of human and animal diseases. However, they should not be used in replacement of good hygiene or good management practices but only after careful considerations based on epidemiology, convenience, cost, difficulty of differential diagnosis, best interest of the animals and their owners. Combination vaccines on the market today have been tested for their safety and efficacy during their development, leading to a government license for sale. Any combination vaccine that passed the rigorous procedures of the EC directive 92/18 could be used with the same benefits as a monovalent product. Several biologicals are available in Europe to control bovine respiratory disease and neonatal diarrhea. The veterinarian should use her or his judgement in selecting the right product for a specific customer.

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