Why I Recommend The Vaccination Of Cattle For BVD

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In the last few years, probably no one bovine immunization has received more discussion than bovine virus diarrhea (BVD) vaccination. However, in the light of more intensive field studies, laboratory evidence of its importance in bovine respiratory disease (BRD) and abortions, greater knowledge of immunology, use of different strains of the BVD virus for production of vaccine and improved methods in the production of BVD vaccines, I believe we need to re-examine and re-evaluate the importance of BVD vaccination.

First let us review the history of BVD. It was first reported in 1946 and 1953. The more common clinical cases that we saw were those of an acute contagious condition of the alimentary tract that produced pathological lesions from the tip of the nose to the anus. Today we see very few of these text book cases. One might ask then what is the significance of this agent and why should I consider vaccination against this viral agent if the classical syndrome is seldom seen.

Today many cases of BVD are inapparent or are being misdiagnosed because the first or primary symptom of the disease is no longer diarrhea and diarrhea in fact is the last symptom to appear. In most instances the diarrhea does not appear until 6-8 days after the onset of the disease or when the temperature starts to decline. The disease today is most often seen as an abortion in breeding animals or in combination with other pathogens of the BRD complex. Serologic evidence shows that a high percent of cattle in the U.S. are sero positive for BVD.[1]

Amstutz[2] reported in a recent DVM article that a survey done by Crandell and Mellah showed a high percent of cattle in Illinois were infected with the BVD virus. Their survey revealed the following:

	Herds		Animals	
IBR	104	54.8%	271	39.9%
BVD	94	72.3%	272	59.2%
PI[3]	79	72.2%	228	60.1%

Because of this widespread infection rate which occurs in the cattle population, in spite of the low rate of apparent clinical disease, the disease is now considered to be one of the most prevalent diseases of cattle in the U.S.

From 1971 - 1976 a study was made on the BRD complex on 1,837 feeder cattle shipped to a Texas feedlot. These cattle represented 23 groups gathered in the Southeastern United States. On arrival, nasal secretions, blood and feces from 10 groups were checked for BVD virus shedding. Forty percent of these cattle were shedding BVD virus. None of the groups were shedding infectious bovine Rhinotracheitis (IBR) virus.

Serologic profiles revealed that a high percent of these incoming cattle were sero-positive for BVD virus but 11-46% of these animals would be susceptible to infection with BVD virus.[3]

As can be seen from this survey, the BVD virus may be one of the most important factors in the BRD and the economical loss from its impact in BRD should be a major concern of cattle producers and feeders.

In the U.K. 50% of the cattle population is serologically positive, while 90% of the cattle population in Australia were sero-positive for BVD.[4]

In the past when we diagnosed the classical BVD mucosal syndrome by symptoms and clinical signs of the disease, we did not know about the most significant pathogenic effect of BVD virus; that is its ability to replicate in and damage lymphoreticular tissues.[5],[6] which causes a depletion of lymphoid cells and a persistant infection in the leukocytes of infected animals.

This can result in a significant suppression of the animals non-specific and specific defense mechanisms brought about mainly by the immuno-suppressive effect primarily of the T Cells. This can create a lag in the initiation of the animals immune response. Due to this delay in response, organisms which might have been mildly pathogenic or non-pathogenic may establish themselves and become pathogenic. With this synergism between BVD virus and other potential pathogens a more severe disease can result than either pathogen alone could cause.[1] An example of this is the mild pathological changes that occur in the lung of the bovine when exposed to *P. haemolytica* alone. If the animal has a BVD infection and then exposed to *P. haemolytica,* severe lung damage can be found when the animal is necropsied.[7] Other agents that could produce the same clinical conditions in the presence of BVD infection could be IBR, PI[3], *Mycoplasma* and *Hemophilus somnus.* Many of these mixed infections result in chronic BRD.

The foregoing data, I believe, suggests to us that the measures we have used in the past to control BVD have

failed or are inadequately applied. A major part of this inadequacy is probably due to the practicing veterinarian not vaccinating for BVD and not vaccinating when he should because of his fear of post-vaccinal reactions, which may result in the MD Complex.

Lambert[8] most recently reviewed this problem and stated that available evidence indicates that the incidence of post-vaccinal BVD problems is less than 1% of vaccinated animals and that this failure was contributed to or associated with failures or deficiencies in the immune mechanism of individual animals and not to the vaccine. Support for this I believe can be found when evaluating serum from calves with mucosal disease (MD). Only two of the twelve calves showing clinical signs of MD showed evidence of a significant production of antibodies against the BVD virus. The specificity of the immune failure is evident from the fact that there were significant antibody titers against IBR virus in the infected cattle.[9]

Where then has the scare that most veterinarians have about BVD vaccination come from?

As stated earlier, BVD is often undiagnosed and udoubtedly many cattle are vaccinated while incubating virulent BVD virus as well as other infectious agents and thus the vaccine was blamed for the post-vaccinal disease. At the same time, animals receiving BVD vaccine during or following stress from weaning, transportation, environmental changes, dehydration, or while being treated with corticosteroids likewise may fail to respond immunologically.

Without a doubt a certain number of post-vaccinal reactions or post-vaccinal breaks of BVD are vaccine related. I believe that this is one of the main factors that has made many practitioners hesitate about using a BVD vaccine. No practicing veterinarian likes to admit to product failure particularly if he or she used the product or recommended its use.

Let us now take a brief look at what could have happened to cause a vaccine related safety problem. In the making of a modified live virus (MLV) vaccine there are three distinct entities involved in the production and manufacture. They are: 1) the cell culture system, 2) the nutrient medium and 3) the working seed virus. All three of the components must be free of contaminating or extraneous adventitious viruses to produce a vaccine that is pure, safe and efficacious.

Let us first look at the cell culture system. The cell culture system does nothing more than provide a vehicle for the growth and multiplication of the working seed virus, so that a serial or batch of modified live viral vaccine can be produced. There are three cell culture systems used in the industry today. They are primary cells, diploid cells, which are normal primary cells that can be passed up to ten times, and stable cell lines. A biological manufacturing plant does not produce these cell culture systems or types, but makes modified live vaccine grown on or in primary cells, diploid cells or stable cell lines.

Primary cells are taken directly from an animal and are cultured in the laboratory. The disadvantage here is that because of the lack of subculturing and because of the limited time these cells are in the lab, it is possible that a latent BVD may be missed in the testing of primary cells. Smithies and Moderman[10] reported at the 18th American Association of Veterinary Laboratory Diagnosticians Meeting that bovine embryonic kidneys used in the preparation of primary and secondary tissue cultures are themselves sometimes carrying noncytopathic BVD virus. They found that 13 of 133 or 10% of pairs of bovine fetal kidneys obtained from a local packing plant were contaminated with BVD virus when propagated in a truly virus free fetal calf serum.

Dr. Phillips[11] National Veterinary Services Laboratory, reported at the 1972 AABP Meeting that 2,682,820 doses of IBR vaccine which were grown on bovine primary fetal calf kidney cells and nourished with bovine fetal calf serum were withheld from the market from July 1, 1971 to June 30, 1972 because of contamination of BVD virus.

As you can see from the foregoing explanation, when vaccines are produced on primary cell culture, there is a chance of picking up a latent BVD virus.

With the use of stable cells much more freedom from a contaminating or latent BVD virus is provided because they must be at least eleven sub-passages or more and the laboratory would have time to do more thorough testing.

Now let us take a look at the nutrient medium that is used to keep these cells growing. The nutrient medium is a mixture of nutrients such as amino acids, vitamins and a serum used to feed the cells of the cell culture system during vaccine production. If fetal calf serum is used as the nutrient media there is always a risk of contaminating bovine virus, particularly the bovine virus diarrhea virus.

Smithies and Moderman[10] also reported at the 18th annual meeting of the AAVLD that their laboratories had found that a high percent of commercially prepared fetal calf serum contained noncytopathic BVD virus. During a four year period, they examined 19 lots of commercially prepared fetal calf serum obtained from different companies and found that 14 of the 19 lots or 75% contained BVD virus. The sad thing about this is that all 14 of these serum lots had been advertised as "Virus Screened." The foregoing data, I believe, substantiates the fact that the serum supplying the nutrient medium can also be a source of contaminating BVD Virus.

The third component that is needed to produce a vaccine is the working seed virus. All companies engaged in the manufacture and sale of biologicals for interstate trade are required to have their vaccines pass the Master Seed Lot Principle Test. The following procedures are required in the Master Seed Lot Principle Testing 1) identity, 2) sterility, 3) purity, 4) safety, 5) antigenicity and 6) immunogenicity.

Several effective vaccines for the prevention of bovine virus diarrhea are being marketed. All have been produced from the NADL or Oregon C24V Strains of BVD virus and have been grown on primary cells, diploid cells or in cell

lines. Although these vaccines are effective in preventing BVD infection in cattle, post-vaccination reactions may occur when biological manufacturers employ some of the methods previously discussed in its production.

In the last two years, a BVD vaccine has been marketed that is manufactured from the Singer Strain of BVD virus.[9] This strain was isolated from the Singer Sewing Machine Farm in Maryland, thus the name Singer Strain and was subjected to years of research by the National Animal Disease Center and has been proven to be of a low pathogenicity, extremely safe and yet is highly antigenic due in part to the high amount of soluble antigen produced from the Singer Strain infected cells. It has also proven to produce less leukopenia than the NADL or C24V.[12]

For evaluation,[13] the Singer Strain Virus was incorporated with IBR and PI^3 virus grown in BT cells. Twenty sero-negative calves to BVD were inoculated 10 subcutaneously (SC) and 10 intramuscularly (IM) with a 2 ml dose of vaccine containing 10% of the minimum virus concentration required for the final product.

In the evaluation of a BVD vaccine it is necessary to show that it is antigenic or immunogenic, does not produce a febrile response, produces no shedding of the virus from the animal receiving the vaccination and particularly with the bovine virals, that a leukopenia is not produced. Figure I shows the average antibody (AB) response in 20 calves to a 1/10 dose of Singer Strain BVD virus administered IM or SC, compared to the AB response of five nonvaccinated contact controls before and after intranasal (IN) challenge with virulent National Veterinary Services Laboratory (NVSL) Strain of BVD Virus.

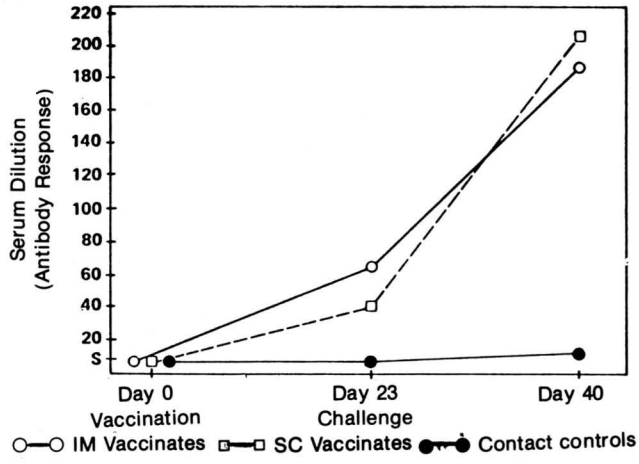

Fig 1. Average antibody response in 20 calves given a 1/10-dose of Singer Strain BVD virus IM or SC, compared to response of 5 nonvaccinated contact controls, before and after in challenge with virulent NVSL strain BVD virus.

As can be seen from Fig. 1, both vaccinated groups whether vaccinated IM or SC produced adequate antibody against the BVD virus. It also shows that the vaccinates were not shedding the virus because of the lack of a significant antibody titer in the controls.

Figure 2 shows the temperatures of the vaccinates and contact controls prior to and after challenge with virulent BVD virus 23 days after vaccination with a 1/10 dose of Singer Strain BVD virus.

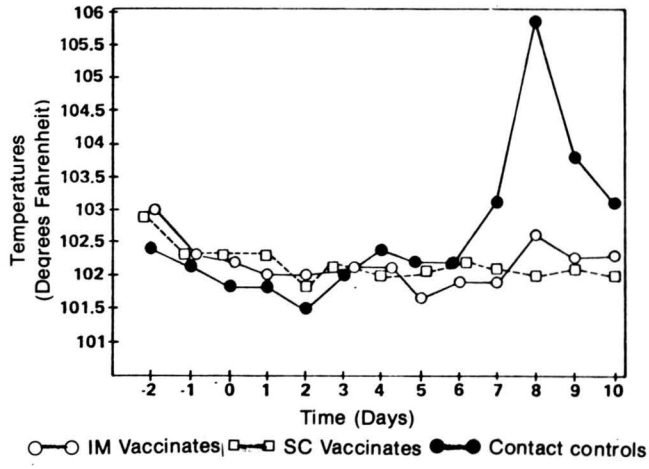

Fig 2. Average temperature response in 20 calves challenged (day 0) with virulent BVD virus 23 days after vaccination with a 1/10-dose of Singer Strain BVD virus, compared to postchallenge temperature response of 5 nonvaccinated contact controls.

As Chart 2 clearly illustrates, the vaccination of the calves with the Singer Strain of BVD virus causes no febrile reaction at the time of vaccination nor was any temperature increase noted after challenge. The control calves showed a

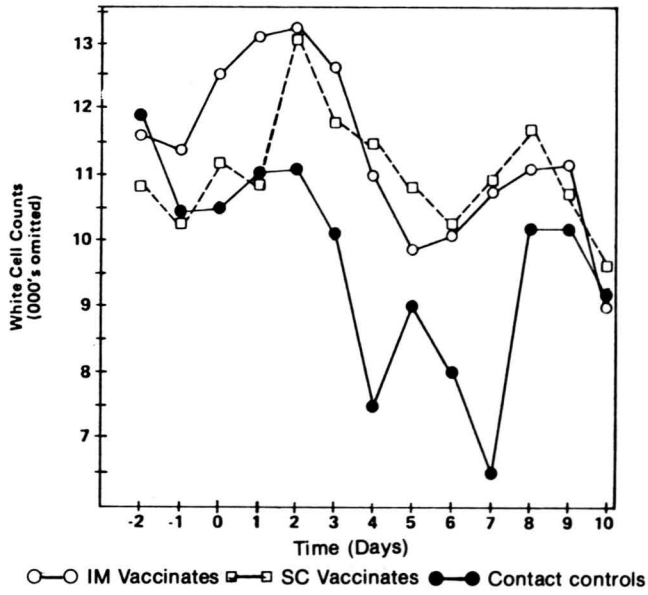

Fig 3. Average blood leukocyte counts in 20 calves challenged (day 0) with virulent BVD virus 23 days after vaccination with a 1/10-dose of Singer Strain BVD virus, compared to postchallenge blood leukocyte counts of 5 nonvaccinated contact controls.

temperature rise approximately seven days post challenge.

Some MLV vaccines at times may produce a leukopenia in the vaccinates after vaccination. Figure 3 shows the white cell counts of vaccinates and controls prior to and post virulent virus challenge.

Notice the severe leukopenia that developed in the controls post vaccination. The total WBC counts were markedly less for controls than for the vaccinates 4 - 7 days post challenge.

In the early evaluation of the Singer Strain of BVD virus, a safety test was performed to show the safety of this strain of BVD virus. This test consisted of giving eight calves parenterally 10 full field doses of the vaccine containing the Singer Strain BVD virus only. All animals remained clinically normal during the experiment. Rectal temperatures and total WBC counts remained within normal limits.

Field Trial:

The true test of any biological is its performance in the field. A clinical field trial was conducted on a sandhill ranch in western Nebraska.[14] Two hundred thirty-five Hereford, Angus and crossbred calves (200 steers and heifers and 35 bulls) were used in this field trial. The cattle were maintained in a dry lot and were fed on a ration consisting of a mixture of alfalfa and grass hay with a protein supplement. At the conclusion of the trial, the animals were placed out on native sandhill range.

All animals were serologically negative or had no demonstratable antibodies to IBR or BVD prior to inoculation parenterally with a field dose of the vaccine. Approximately eleven weeks later, representative serum samples were collected and tested for IBR and BVD serum antibodies. The entire group was kept under close observation during the entire period for any untoward effects from the vaccination.

Results:

No adverse reactions were observed clinically in any animals vaccinated during the eleven weeks the clinical field trial was in progress. Representative serum samples collected at the end of the observation period were tested and demonstrated average antibody titers of 1:21 for IBR and 1:742 for BVD.

Similar testing as was done in this herd for safety and immunogenicity of the Singer Strain Vaccine was duplicated in at least six separate and distinct cattle herds totaling in excess of 2,000 head.

Up to now we have discussed only the effect of BVD virus on calves and feedlot cattle. I believe that we should spend a few minutes and discuss the role that BVD plays in reproduction and on the neonate.

We know that BVD contributes to a certain percent of the abortions that occur in the pregnant bovine. Again from the data of Smithies and Moderman;[10] they report that tissues taken from 1,033 aborted fetuses from field cases, seventy-five or 7.5% were positive for BVD Virus. However, data that they have accumulated over the past 6 - 7 years show the percentage of abortions due to BVD virus to be more like 10%.

The BVD virus may affect the pregnant cows in various ways. There may be fetal death, resorption of the fetus and return to heat or abortion if the infection occurs during the first trimester. If the infection occurs in the second trimester and there is a full term pregnancy, the newborn calf may have cerebellar hypoplasia, necrotic dermatitis or alopecia. If the infection occurs after 180 days pregnancy, or in the last trimester, a normal healthy calf may be born, probably due to the fetus's ability at this age to produce antibodies against the BVD virus.[1]

BVD virus has been isolated from the feces and intestines of calves ranging in age from one week to 1 - 2 months.[15] A BVD - Salmonella or BVD - *E coli* infection is especially bad for the new born calf. The BVD complex has also been incriminated in the "Weak Calf Syndrome."[12]

Corea and McClurkin[16] found that neonatal calves congenitally infected with BVD virus were unthrifty and seldom survived more than a couple of months. If a calf did survive, it was usually persistently infected with the virus and became chronically affected with the disease.

While discussing BVD in breeding animals, the question often comes up why and when can we vaccinate these animals. We all know that it is best not to use a MLV vaccine on pregnant animals. However, recent research has shown that the dangers of using a MLV BVD vaccine on pregnant cows may not be as great as once thought.

Losses from repeat breeding and neonatal disease caused by BVD might be prevented by assuring that all animals are sero-positive to BVD prior to breeding.

Concerning the efficacy of vaccinating breeding cattle for BVD, McClurkin and coworkers[17] reported the following: Although bulls semen contained BVD virus when sero-positive cows were bred, normal calves were born. When sero-negative heifers were bred, they became sero-positive to BVD virus within two weeks. One heifer aborted, three continued to have estrus cycles until titer was 1:128.

A 1:128 titer in a cow is sufficient to protect the fetus from BVD virus in bull semen or from a BVD virus infection in the herd during the first half of gestation.

A second question that arises often from BVD vaccination is "Can I vaccinate calves that are nursing pregnant dams?"

At this time, there is no evidence to show that vaccinating a calf (six months of age) and leaving it with its pregnant dam will result in shedding of the virus and abortion in the dam.[12, 18]

While on the subject of vaccination, the next question might well be, "When is the right time to vaccinate calves for BVD?" The best answer to this is as in all diseases; vaccinate before the disease strikes. We have proponents for vaccination of calves after 6 - 7 months of age because their

arguement is that the calf would still have maternal antibodies at a younger age and we would just waste time and vaccine. Such a concept fails to consider that approximately 50% of the calves at this age are not protected by maternal antibody and are fully susceptible to BVD infection if exposed to the virus.[8] Possibly this is where the so-called BVD vaccination break has come from. These 6 - 8 month old calves had lost their maternal antibody and when vaccinated, were actually incubating the disease from contact and natural exposure. McClurkin[12] reported to me that his work shows that maternal antibodies do not interfere with the ability of the new born calf to respond to BVD vaccination.

Another area of disagreement on the time of vaccination for BVD is whether to vaccinated feeder cattle at the time of arrival or to wait and vaccinate 2 - 3 weeks after arrival. Recent work that was done by Dr. Caley[19] showed that when stressed calves were vaccinated at arrival, they did reduce the incidence of sick calves; which allowed the owner more time to get on with the business of feeding calves. Dr. Caley stated "the quicker you can vaccinate for BVD and IBR, the less trouble you'll have, for vaccination tends to bring the disease situation to a climax and prevent continuous spreading from one to another."

In summary, I would say that BVD is recognized in all states in cow-calf herds, dairy herds and in the feedlot.

Therefore vaccination of normal healthy cattle is recommended and without hazard. In stressed or exposed cattle, the BVD virus destroys tissue in the lymphoid germinal centers depleting the production of lymphocytes. Thus if post-vaccinal troubles develop, it is often the animals' condition, not the vaccine.

Bovine Virus Diarrhea vaccines have been available commercially since 1964. Until recently the vaccines utilized either the Oregon C24V Strain or the NADL Strain of the BVD virus. You now have a third choice and that is the Singer Strain. This strain is produced on a homologous stable cell line. The nutrient medium contains equine serum which eliminates any possibility of a latent or adventitious bovine virus caused disease developing. It is non-shedding, is highly antigenic because of the high amount of soluble antigen present, produces no leukopenia or febrile response and can be administered SC or IM. There have been over two million doses sold in the last two years and no adverse reactions have been related to its use.

In 1967 the J.A.V.M.A. published an article on BVD vaccination that stated the following: Since the post-vaccinal condition is highly sporadic and is generally low in morbidity, it is not considered to be of sufficient significance to merit serious concern in not using the vaccine."[20]

If this was so in 1967, then in 1979, with the increased knowledge we have about the disease and its pathogenicity and the improvements in vaccine production, I can think of no reason for not vaccinating for BVD.

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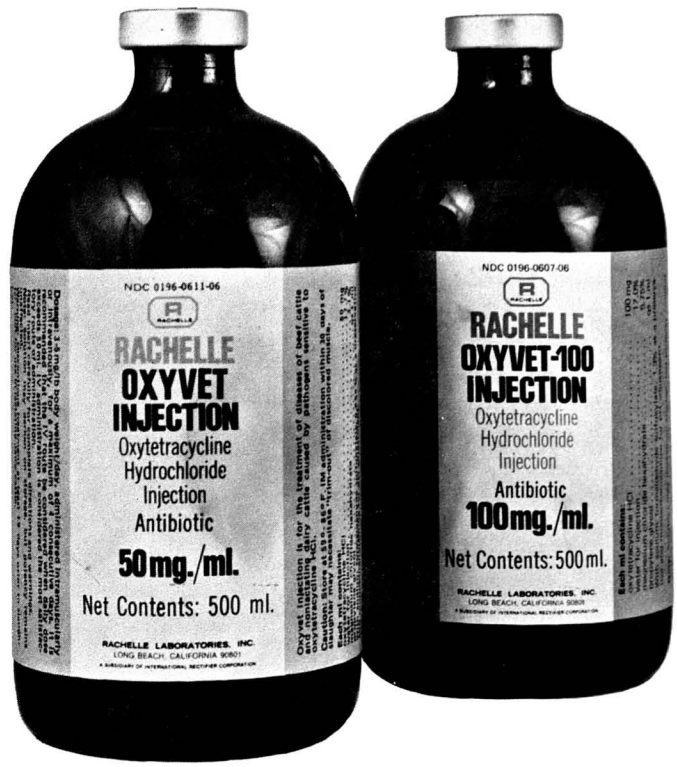

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