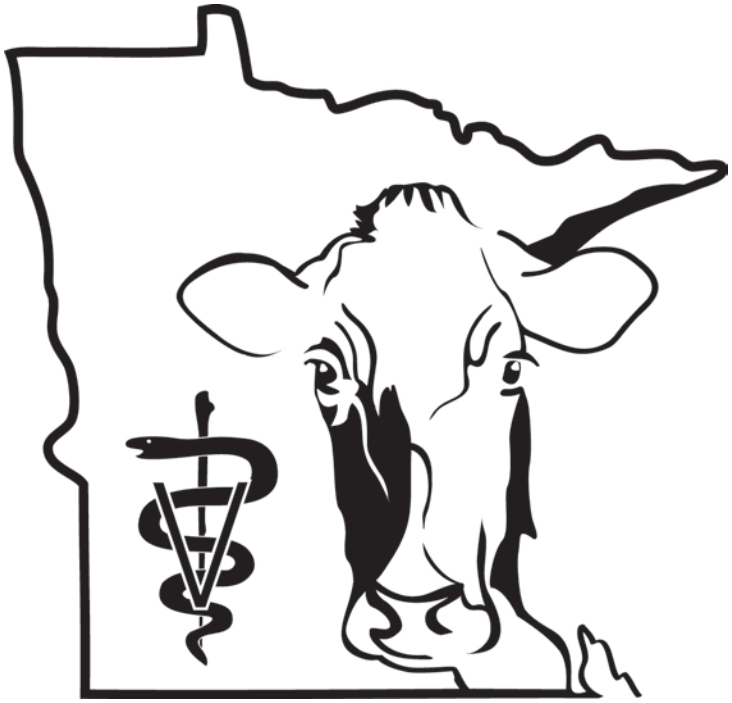
THIS ARTICLE IS SPONSORED BY THE
MINNESOTA DAIRY HEALTH CONFERENCE.

UNIVERSITY OF MINNESOTA

College of Veterinary Medicine

VETERINARY CONTINUING EDUCATION



ST. PAUL, MINNESOTA
UNITED STATES OF MINNESOTA

CERTAIN FACTORS TO CONSIDER WHEN DESIGNING A BOVINE VACCINATION PROGRAM

Dr. Ronald D. Schultz
Professor and Chair
Department of Pathobiological Sciences
School of Veterinary Medicine, University of Wisconsin-Madison
Madison, WI 53706

Why, when we are vaccinating cattle more than ever before, are we failing to immunize?

VACCINATE
The process of inoculating a vaccine into an animal. Does not imply an immune response has occurred

IMMUNIZE
The process of inoculating a vaccine into an animal and the animal responds with a detectable immune response. Does not imply protective immunity has developed

Some would blame the vaccines, which can be at fault, others would blame the animals, sometimes they cannot respond, but frequently the real problem is a failure to apply the basic principles of immunology in the vaccination program. Sometimes we forget what we have learned about immunology, sometimes incorrect information was provided on the basic principles of an effective vaccination program or at times new information has changed the way we should use vaccines.

Now more than at any other time, because there are so many vaccines to choose from, the basic principles of vaccination must be applied for your program to work as effectively as possible. The goal of every vaccination program is to enhance protection from important infectious diseases the vaccines are designed to prevent.

Objectives of Immunization

1. Produce a good humoral, cellular and local immune response similar to natural infection.
2. Produce protection against clinical disease and reinfection.
3. Give protection over several years, preferably a lifetime.
4. Result in minimal immediate side reactions (e.g. reduced milk production, weight loss, infection of the fetus with abortion, congenital anomalies or persistent infections).
5. The vaccine can be administered simply in a form acceptable to the producer and practitioner.
6. Cost and benefits of administration of vaccine should clearly outweigh the cost and risk of natural disease.

An obvious failure in the design a vaccination program would be to use a vaccine that does not contain antigens to the pathogens that may case disease in your herds. Therefore, the first decision in the process of designing a vaccination program is choosing the correct vaccine(s). Too often the response on the part of the producer or the practitioner will be, "well I want to protect against all diseases, therefore, let's use all vaccine(s) available". This is the first fundamental error in designing a vaccination program, for several reasons. One must understand there are not now, nor will there be in the future, vaccines to prevent all infectious diseases. Secondly, if there were vaccines for every known bovine pathogen, vaccines alone would not be capable of preventing each and every one of the diseases they cause. Third, vaccination at times can do more harm than good. There are many reasons for vaccination failures.

Possible Reasons for Vaccination Failure

1. The serotype of organism in the vaccine is different from the infecting serotype, thus immunity is incomplete. For example, it is our experience that none of the BVDV vaccines protect against reinfection and/or disease for all the different serotypes of BVDV in the field. This is true of certain other viruses (e.g. Bluetongue Virus).
2. Due to a contaminated environment, exposure to a high amount of infectious agent overwhelms the immune system regardless of the vaccine used.
3. The immune system is compromised due to immunosuppressive factors associated with poor or inadequate management (e.g. nutritional deficiency, transportation stress, vaccine induced immunosuppression or poor ventilation).
4. The vaccine may prevent disease but not infection, or spread of the infectious agent (e.g. Bovine Herpes Virus), thus non-vaccinated animals become infected and may develop disease.
5. The vaccine is not immunogenic, or provides inadequate protective cellular and/or humoral immunity.
6. Colostral antibody interferes with active immunity. This is the most important cause of vaccination failure in young animals.
7. Often the most important cause of failure is the design of the vaccination program.

One needs to use vaccines as a **"Management Tool"** to improve the general health of the animal so that when and if an animal is exposed to a potential pathogen, the level of exposure is low, the animal is in good health and the animal has previously been immunized with the correct vaccine. Inadequate management leading to a high level exposure, a compromised immune system in a stressed animal or failure to properly immunize puts the animal at increased risk to infection and subsequent disease. Another important factor in preventing disease that is difficult to control at present, but will become a mechanism in the future to enhance resistance to infectious diseases is genetic selection. It should be possible in the early part of the next century (approx. 10 to 15 years), to selectively breed or produce with biotechnology, animals with increased resistance to many of the important diseases of cattle. However, until genetic methods are in place we need to practice the best immunization principles currently available to reduce the cost of infectious diseases. Those practices at times will include a recommendation **not to use any vaccine.** The decision to use a particular vaccine must be based on careful consideration of the expected benefits vs. potential risks.

Vaccine Production

> The production of vaccines is part science and part art. There are so many factors to be taken into account that the production must rely on intuition and empirical experience almost as much as on rational deductions. Biotechnology has not changed the art of making a good vaccine, it has only modified the science and cost.

One of the most important considerations in designing a vaccination program, after the specific vaccines have been selected, is timing. When should the vaccine be administered? Incorrect timing of vaccination is the greatest cause for vaccines failing to immunize. Timing includes such considerations as: 1) the effects of maternal (colostral) antibody on active immunization, 2) the period of time between injection of vaccines that require multiple doses and 3) the age of the animal when the disease most often occurs, 4) age, as it relates to the competence of the immune system.

Maternal Antibody, or the antibody acquired by the calf from absorption of colostral antibody during the first 24 to 48 hours after birth has a profound suppressive effect on active immunization to most vaccines. Maternal antibody prevents the vaccine from immunizing for variable periods of time after birth. The period of time the colostral acquired antibody interferes with active immunization depends on the amount of antibody present in the dam and the amount of colostrum absorbed, and the amount of antigen in the vaccine and the route of vaccination, thus every animal is different. A paradox exists since this passively acquired antibody is essential for survival of the calf, since the calf receives the protective effects of the maternal antibody experience, but the maternal antibody must decline or disappear before most vaccines can actively immunize. In Table 1 you will find the ages at which certain vaccines are able to immunize various percentages of calves. As is shown in Table 1, immunizing a group of calves that are one to two weeks old with an intramuscular vaccine containing IBR would result in approximately 5% to 10% of the vaccinated calves developing an immune response. In contrast, if the calves had been first vaccinated at 12 to 14 weeks of age with the same vaccine, approximately 80% or more of the calves would be actively immunized. The reason for these differences in efficiency of immunization is the amount of maternal antibody present at the time the vaccine is given, which is much higher in the one week old group than the 12 week group. If most of the calves have antibody (1 to 2 weeks), then few will be immunized, whereas if few or none have antibody (3 months) almost all (or all) will be immunized. As shown in Table 1, for certain vaccines (e.g. BVDV) maternal antibody can interfere with active immunization in some animals for up to 6 months after birth. The information in Table 1 shows that to ensure that your vaccination program for BVDV stimulates an immune response, the animal should be vaccinated after 6 months of age even if it is vaccinated at an earlier age. This is the reason why I recommend a BVDV vaccination program that includes giving vaccine between the ages of 9 months to 16 months (or 30 days prior to breeding) regardless of when other BVDV vaccination may have been given.

Table 1 Effect of Maternal Antibody on Active Immunization for BHV-1, PI-3 and BVDV Vaccines

BHV-1 (IBR) or PI-3 Vaccination Schedule
Effect of Maternal Antibody on Immunization

Age	Non-Infectious (Killed) 2 Doses	MLV (IM) 1 Dose	MLV(IN) /Dose
Birth to 2 wk.	5%*	10%	25%
2 wk to 1 mth	15 to 30 %	20 to 40%	50%
1 mth to 2 mth	35 to 45%	50 to 75%	75%
2 mth to 3 mth	50 to 65%	75 to 90%	>90%
3 mth to 4 mth	70 to 80%	>90%	>90%
> 4 mth	>80%	>90%	>90%

* Values are approximate percentage of calves that will be immunized when vaccinated at various ages.

BVDV Vaccination Schedule
Effect of Maternal Antibody on Immunization

Age	Non-Infectious 2 Doses	MLV 1 Dose
Birth to 1 mth	5%*	10%
1 mth to 2 mth	25%	35%
2 mth to 3 mth	45%	55%
3 mth to 4 mth	60%	70%
4 mth to 5 mth	75%	80%
5 mth to 6 mth	80%	90%
>6 mth	>80%	>90%

* Values are approximate percentage of calves that will be immunized when vaccinated at various ages.

It should also be noted from Table 1 that the type of vaccine used will in part determine when an animal can be actively immunized. We, and others, have found that intranasal IBR/PI-3 will immunize at an earlier age than intramuscular modified live (MLV) IBR/PI-3 vaccines. Also, modified live viral vaccines for IBR/PI-3 will immunize at an earlier age than non-infectious (inactivated or killed) virus vaccines. The reasons for the differences between local and parenteral vaccines are due to the fact maternal antibody is at lower concentration at mucosal surfaces, therefore, when an intranasal IBR/PI-3 vaccine is given there is less antibody to interfere with local infection and viral replication. It is important to remember that infection is essential if there is to be activation of the immune system with modified live vaccines. The reason for this is that there is a

small amount of viral antigen in MLV vaccines, thus infection is required for immunization. A modified live vaccine can immunize at an earlier age because a few viral particles escaping the maternal antibody can infect cells, to produce additional antigen which stimulates an immune response. In contrast, a non-infectious (killed, inactivated) vaccine cannot infect or produce new antigen, therefore, if maternal antibody interferes with the first dose of vaccine there is not enough antigen to stimulate an immune response. When a second dose of vaccine is given 2 to 3 weeks later, instead of stimulating an already primed immune system you get a primary response, which requires another dose of vaccine 2 to 3 weeks later to get the desired immune response. Unfortunately, most producers and practitioners do not want to vaccinate this often. Furthermore, it is not desirable to have an animal susceptible to infection for this prolonged period of time. Importantly, it will often be at least 3 weeks to a month later, (approximately one week or more after the second dose of vaccine) before one gets significant protective immunity from non-infectious vaccines. The many different types of viral vaccines are listed in the table below.

Types of Viral Vaccines

Live-virus vaccines	
Virulent	Delivered by an unnatural route or at a safe age
Attenuated	Naturally occurring or derived by serial passage in eggs or cell culture
	Genetic manipulation possible: temperature-sensitive, cold-adapted, or deletion mutants; or gene reassortants
Non-Infectious Vaccines	
Killed/Inactivated Vaccines	Partially purified suspensions of virus, inactivated by chemical or physical treatment
Protein vaccines	
Subunit	Partially purified protective protein extracted from virons
"Cloned"	Protein derived by recombinant DNA technology, in bacteria, yeast, or mammalian cell line
Synthetic peptide	Critical epitopes of protective protein synthesized chemically
Virus-vectored vaccines	A virus, e.g., vaccinia virus, is used as a vector for the gene specifying the protective antigen

Maternal antibody is not the only thing interfering with active immunization in a young (6 months or less) animal, therefore, other factors, can and do prevent optimal immunization. The multitude of other factors, such as stress, poor nutrition, genetics of the animal, vaccine immunosuppression, rarely completely prevent an immune response (Table 3). Instead they tend to cause the immune response to be less effective or incomplete, thus the animal may lack complete immunity. If these partially immunized animals are exposed to the pathogen they would be at higher risk of being infected and developing clinical disease than animals with complete protective immunity. There are many other causes of vaccination failure (Table 2).

Table 2 Causes of Vaccination Failure

CAUSES OF VACCINATION FAILURE*

Host Factors	Vaccine Factors	Human Error
Maternal Antibody interference	Improper storage	Exposed at time of vaccination
Immunodeficiencies/ Immunosuppression	Inactivated during handling	Improper mixing of products
Pregnancy Age: very young or old	Vaccines do not protect 100% of population	Concurrent use of microbials Simultaneous use of antisera
Pyrexia, hypothermia Incubating disease at time of Vaccination	Disinfectant used on needles and syringes Wrong strain of pathogen	Too frequent administration (<2 week interval) Disinfection of skin?
Drugs: cytotoxic, glucocorticoids	Improper or inadequate adjuvant	Too long between multiple doses during primary vaccination (> 8 weeks) Wrong route of administration
Anesthesia?	Too little antigen	Wrong vaccine

*? = uncertain

This brings us to the second important consideration of when you should vaccinate. If a modified live vaccine is given, only one dose would be required to immunize if there is no interference by maternal antibody. Thus, if one gave two doses of a modified live vaccine, they could be given at any interval since the time between doses is not critical and one should get effective immunity from at least one of the two doses. For example, if the first dose of IBR/PI-3 was given at 2 weeks and maternal antibody prevented active immunization the second dose at 3 months would cause an active immune response if maternal antibody was gone. This is in contrast to non-infectious vaccines (killed/inactivated/sub unit) vaccines. For almost all non-infectious vaccines, 2 or more doses are required to induce a protective immune response. The period of time or interval between those doses ideally should be 2 to 3 weeks. Less than 2 weeks and more than 4 weeks between doses likely will lead to failure of the non-infectious vaccine to immunize optimally, if at all. This is something that is critical in designing an effective

vaccination program with non-infectious vaccines. It is also important to understand that if maternal antibody interferes with the first dose of a noninfectious vaccine, the second dose will often fail to immunize even if given when all maternal antibody had disappeared. In the example above with modified live IBR/PI-3, if you followed the same schedule with noninfectious IBR/PI-3 as you did with MLV, you would fail to immunize, because when the first dose of vaccine was given at 2 weeks the animal would not respond due to maternal antibody interference, if you gave the second dose at 3 months the animal would not respond because: a) the first dose did not activate the immune system and b) the period of time between doses, even if the first dose had activated the immune system was not optimal. The only way to ensure active immunization with a non-infectious viral vaccine in this example is the following. In an attempt to immunize at an early age you would have given the first dose at 2 weeks and the second dose at 4 to 5 weeks. You would then have given the second series of immunizations, to ensure that the animal is actively immunized, at 3 months (12 weeks) and again at 14 to 15 weeks. This is an obvious disadvantage for noninfectious vaccines, but if you use them you need to strictly follow these recommendations or you will be making a major contribution to "Why Your Vaccination Program Doesn't Work"! Also it is important to understand that if you fail to immunize when the two doses of a non-infectious vaccine are first given, reimmunization annually with a single dose of a non-infectious vaccine will also fail to immunize. Therefore, you could vaccinate for the life of the animal (e.g. 2 doses as a calf, annually with one dose) and not induce a protective immune response. If this animal is never naturally exposed to the pathogen in the environment it can remain serologically negative. We have recognized some of these animals when performing routine serological testing. Experimentally, these animals were shown to lack both cellular and humoral immunity, because they were susceptible to challenge with the pathogen. However, if vaccinated properly with either modified live vaccine or two doses of non-infectious vaccine given 3 weeks apart the animals should develop an immune response. When vaccinated, these animals developed antibody at levels similar to animals vaccinated for the first time, thus showing they were immunocompetent. If these animals had been naturally exposed and developed severe disease, it would have been assumed the vaccine was not effective. However, instead the vaccine was not the problem, the vaccination program was the problem.

The third consideration with regard to timing of the vaccination is a failure to immunize prior to infection with the pathogen. This is especially important for diseases of the neonate. Diseases during the first few weeks of life (e.g. from birth to 6 weeks) may not be effectively controlled by vaccination of the calf, because the calf will not develop immunity to a vaccine at a time early enough to prevent infection or disease. Therefore, the two alternatives available are: 1) enhance the immunity of the dam prior to parturition or 2) immunize the fetus in utero at 225 to 250 days of gestation. The first method currently is the only practical method, but the second method would, based on experimental studies, be more effective. The most effective and safest method to increase the antibody response prior to parturition would be to use a non-infectious vaccine at approximately 7 to 7½ months of gestation and to give a second dose of the vaccine 3 weeks later. The second dose which would be administered approximately two to three weeks later and about a month prior to parturition should help to increase the amount of antibody, at the appropriate time for antibody to be selectively transferred into the colostrum. This practice is most effective for bacterial vaccines (bacterins) since the viral vaccines often fail to increase the antibody titer. The diseases of greatest concern during the early neonatal period are neonatal enteric pathogens (eg. E. coli, coronavirus

and rotavirus), but other bacteria and viruses can and do infect and cause disease during this period. Therefore, management procedures that include, but are not limited to: 1) ensuring the calf receives an adequate amount of colostrum as soon after birth as possible, 2) keeping the calf in a clean and dry environment and 3) separating the calf from other cattle, would significantly reduce the likelihood of infection and disease. These management measures would also help the vaccines used in the neonate be more effective in preventing disease of the neonate and allow you to get the animal immunized before it is exposed to significant numbers and types of pathogens.

STRESS
Decreased Immunity With Increased Susceptibility to Disease

Another concern with regard to timing of vaccination is the status of the immune system when the vaccine is given. Although immune competence develops very early in gestation for the bovine species, the immune system is compromised at the time of birth. The endogenous steroids that are elevated to initiate parturition, the stress associated with birth, extreme temperatures, and the exposure to a large numbers of antigenic insults in a "dirty new world" severely compromise the immune system of the calf for at least three days before and up to one week after birth. Because of the immunosuppression associated with these and many other factors, the likelihood of successfully immunizing the calf during this perinatal period is significantly decreased. Therefore, any and all calves vaccinated during the first week of life must be reimmunized at a later age if you expect your vaccination program to provide some level of protection. A program that includes immunization of animals only in the first week of birth leaves more than 90% of the animals without a detectable active immune response, regardless of whether modified live or non-infectious vaccines are used.

THE GREAT DEBATE:
Which Vaccine Is BEST?

The fourth important consideration in designing a vaccination program is deciding when to use a modified live vaccine or when to use a non-infectious vaccine. There are numerous advantages and disadvantages for both (see Table 3). The major advantage of a modified live vaccine is efficacy. Modified live vaccines in general give the best systemic and local, cellular and humoral immunity that an be achieved by a vaccine. However, under certain circumstances, modified live vaccines should not be used. Examples of when certain modified live vaccines should not be used are during pregnancy. For example, modified live intramuscular IBR vaccines (with the exception of the chemically altered temperature sensitive IBR in Cattlemaster®) should not be used because they can and will cause abortion in animals that are susceptible to IBR virus. There are other modified live IBR vaccines that can be safely used in pregnant animals such as intranasal IBR/PI-3 like Nasalgen®, Nasamune® and TSV-2® and the Intramuscular IBR virus in Cattlemaster®. Currently none of the modified live BVDV vaccines are recommended for use in pregnant animals. There may be other times that modified live virus vaccine are not recommended, but it would be difficult, if not impossible, to show experimentally that they would cause overt disease in any of those circumstances. Certain problems can occur after vaccination with modified live vaccines, such as decreased milk production, development of disease, going off feed, increased

body temperatures that may or may not have been caused by the vaccine. Many times problems blamed on vaccines only occur in one herd or at most in a few herds out of the hundreds or thousands of vaccinated cattle. When such a small number of herds are affected one needs to consider concurrent infection at the time of vaccination, the stress of vaccination making the disease worse or the disease appearing shortly after vaccination especially if it is in sub-clinical incubation phase at time of vaccination. The other problem that has been shown to occur on rare occasions is an increase in virulence of the vaccine strain, thus the vaccine does cause a problem. However, when that occurs it will be more widespread and can often be associated with a specific lot # of vaccine. This increased virulence of vaccine causes disease in certain animals in most vaccinated herds. Although there are precautions that need to be taken, such as not using certain modified live vaccines in pregnant animals, there have been very few problems proved to be associated with modified live vaccines during the last 5 years especially when one considers the number of doses of vaccine given to cattle. Other advantages and disadvantages of a modified live vaccines vs. non-infectious vaccine are shown in Table 3.

The advantage of a non-infectious vaccine is that it does not contain live viruses or live bacteria. Unlike modified live vaccines where the vaccine component must infect the animal to immunize, the non-infectious vaccines must have enough virus and/or bacteria to immunize the animal when inoculated multiple times. Because there should be nothing in the non-infectious vaccine that is live or infectious, these vaccines are believed to be safer and are known to be more stable than the modified live vaccines (Table 3). However, there are many disadvantages with the current non-infectious vaccines. They fail to induce certain forms of systemic cellular immunity and provide only limited or no local (e.g. mucosal) humoral or cellular immunity. They are much more likely to cause hypersensitivity reactions because of the increased amount of antigen required to make the vaccine immunogenic, because adjuvants are present and because they often contain more non-specific factors from cell culture, media and preservatives. Adjuvants are required to stimulate immunity with non-infectious vaccines. These hypersensitivity reactions, if systemic, can kill the animal when not treated quickly. They can also cause abortion in pregnant animals, they can cause animals to go off feed, or cause decreased milk production, create febrile reactions and/or cause local or systemic swelling with or without granuloma formation. Also it is important to remember that non-infectious vaccines induce an immune response that is of shorter duration than would be induced by a modified live vaccine to the same infectious agent. For example, immunity to modified live viral vaccines is generally for the lifetime of the animal and at a minimum for three to five years. In contrast, the duration of immunity with most non-infectious vaccines is from less than one year to as long as three years. Immunity to non-infectious bacterial vaccines (bacterins) is shorter than immunity to modified live bacterial vaccines and immunity to bacteria in general is much shorter than immunity to viruses.

It is often said that non-infectious vaccines are safer than modified live vaccines, but I prefer to consider them "less likely to cause disease as a result of infection at the time of vaccination." When they cause hypersensitivities or when they fail to provide protective immunity at mucosal surfaces or when the duration of immunity is shortened, thus placing the vaccinated animal at increased risk to infections in a relatively short

Table 3 Advantages and Disadvantages of Attenuated Live-Virus and Non-Infectious Vaccines

Parameter	Vaccine Type	
	Attenuated (Modified) Live-Virus	**Non-Infectious (Inactivated, Killed)**
Route of Administration	Natural[a] or Injection	Injection
Antigen per dose	Low	High or Moderate
Cost	Low	High or Moderate
Number of doses needed	Single[b]	Multiple
Need for adjuvant	No	Yes
Duration of immunity	Many Years to Life	Months or Years[c]
Antibody response	IgG; IgA[d], IgM	IgG, IgM
Cell-mediated response	Good	Uncertain, general no CTL response
Heat liability[e]	Yes[f]	No
Interference	Occasional[g].	No
Side effects	Occasional mild signs	Occasional to frequent local or general reactions
Dangerous in pregnant animals	Some	No (but caution is required since hypersensitivity or stress may cause problem)
Reversion to virulence	Possible	No

[a]Oral or respiratory, in certain cases.
[b]For some live vaccines a second dose may be required
[c]But satisfactory with some inactivated vaccines.
[d]IgA if delivered via oral or respiratory route or if agent replicates locally.
[e]Especially in hot climates
[f]Stabilizers added to vaccine, plus maintenance of "cold chain" delay inactivation.
[g]If administered by oral or respiratory route.

period of time, I have difficulty considering them safer. The one situation where the non-infectious vaccine would be safer is when the virulence of a modified live vaccine increases and causes disease since a non-infectious vaccine cannot become virulent or cause an infectious disease. An exception may occur when a non-infectious vaccine becomes contaminated with a live agent (e.g. BVDV). The other time non-infectious vaccines would be safer than modified live vaccines would be when used in a pregnant animal.

As discussed briefly above, non-infectious vaccines are less likely to immunize than are modified live vaccines when the vaccination program is not planned correctly and followed closely. **It is essential that you understand more clearly the principles of vaccinology if you use a non-infectious vaccine than when you use a modified live vaccine especially if you want your vaccination program to succeed.**

It is my experience that a major cause of vaccination failure in cattle during the past 10 to 15 years was the switch to non-infectious vaccines, with the concurrent practice of following the same vaccination program that was used successfully with modified live vaccines. Unfortunately many of the principles that apply to non-infectious vaccines were not understood or at best poorly understood and the programs with certain non-infectious vaccines failed to give long lasting protective immunity. Non-infectious vaccines generally require multiple doses of vaccine to immunize and the vaccines should be given two to three weeks apart. If the first dose fails to prime the immune system due to interference (e.g. maternal antibody) the second dose will not immunize and a third dose will need to be given two to three weeks after the second dose. If one fails to administer a second dose or if the second dose of vaccine is given too soon after the first dose (less than two weeks), or too long (greater than six to eight weeks) after the first dose, there may be poor or often no detectable immunity. Annual revaccination with a non-infectious vaccine is required to maintain a memory response. In some cases multiple doses may be required at revaccination, however, usually only one dose is required at the time of revaccination. Therefore, unlike the situation for modified live vaccines where immunity to viruses generally persists for the life of the animal, immunity to non-infectious vaccine is short-lived. Unfortunately there are many herds and/or animals where there is only one chance to immunize thus, those animals should not be given a non-infectious vaccine. It would be better to save your money and time and not vaccinate, rather than give one dose of non-infectious vaccine. Non-infectious vaccines are most effective in stimulating a systemic humoral immune response, primarily a classic IgM response followed by IgG. Certain cellular immune responses (e.g. Cytotoxic lymphocytes) are not stimulated at all by non-infectious vaccine or others are stimulated poorly (e.g. certain lymphokine production by T effector cells). Mucosal or local humoral immunity may not occur or may be minimal since local activation of antibody synthesis requires antigenic stimulation at the local site. Thus with inactivated vaccines, systemic antibody must reach the mucosal surfaces through transudation from the serum if protection is to occur. Similarly, local cellular immune responses are not likely to be stimulated by non-infectious vaccines. If cytotoxic lymphocytes or local antibody or local cellular immunity are important in protecting against clinical disease, non-infectious vaccines are not likely to provide significant protection or certainly not protection equivalent to MLV vaccines. In contrast, a modified live vaccine to those same pathogens are likely to be more effective because MLV vaccines should stimulate cytotoxic lymphocytes and a local humoral and/or cellular immune response. An additional concern about non-infectious vaccines is that the

specificity of the immune response is more narrow than it would be to a modified live vaccine. For example, when a non-infectious vaccine is prepared after a virus was grown for 5 days in culture, many of the early viral antigens are not present in the culture material used to prepare the vaccine and only the late viral antigens or the intact viron may be present. In contrast a modified live vaccine will cause an infection that stimulates an immune response to antigens produced throughout the cycle of infection, thus they induce more complete immunity.

You should be asking yourself, if I use non-infectious vaccines when and how should they be used? I think the following principles should be applied. If you want the most effective immune response, use modified live vaccines when you first immunize a young animal. Don't use non-infectious vaccines first if you want the modified live vaccine to immunize, since the systemic immune response from the non-infectious vaccination will generally prevent the modified live vaccine from infecting (which is absolutely necessary) thus you will not stimulate an immune response. Non-infectious vaccines are generally more effective in stimulating a secondary immune response than a modified live vaccine, due to the increased amount of antigen in the non-infectious vaccine. Therefore, if you feel that annual or booster vaccinations are required and they are for most bacterial vaccines and a few viral vaccines, non-infectious vaccines are more likely to be effective in providing a secondary response than are modified live vaccines. **Most annual revaccinations with modified live viral vaccines do not stimulate a secondary immune response!** As explained above, the only way a modified live vaccine can stimulate an immune response is for the agent in the vaccine to infect the animal and replicate or reproduce itself. It is generally not possible for the vaccine agent to infect and replicate in an immune animal, therefore, no secondary immune response occurs when a modified live vaccine is given annually. Two doses of a non-infectious vaccine are not required when used to revaccinate an animal that developed its initial immunity from a modified live vaccine, but two or more doses can be given if you are vaccinating an animal that was initially immunized with a non-infectious vaccine or if you are trying to increase the antibody to be transferred in the colostrum for passive immunity to neonatal diseases. IgG_1 is the predominant immunoglobulin subclass in bovine colostrum and milk and most of it is derived from the serum IgG_1. Therefore, non-infectious vaccines should be effective since they are best at stimulating systemic antibody of the IgG class.

Table 4 Facts to Remember About MLV and NI Vaccines

Modified Live Vaccines (MLV)	Killed-Inactivated Non-Infectious Vaccines
1. Provide Longer duration and more complete immunity than (Non-infectious vaccines.	1. Provide short lived systemic immunity.
2. Cellular and secretory immunity should be produced.	2. Cellular and secretory immunity poor.
3. Do not require multiple vaccinations for immunologic memory.	3. Require multiple vaccinations for active immunity.
4. Often do not require revaccinating or require fewer revaccinations during life of an animal.	4. Often require re-vaccination to ensure immunologic memory.
5. Rarely cause hypersensitivities, but may be virulent for certain individual animals or revert to virulence.	5. Often cause hypersensitivity reactions.
	6. Cannot cause disease even in immunologically compromised animal.

An effective vaccination program is one that is an integral part of an excellent management program. The vaccination program must be designed to provide the greatest opportunity for the vaccine to immunize the majority of animals to infectious agents causing significant clinical disease. An effective vaccination program can most often be accomplished when a modified live vaccine is used for initial immunization and non-infectious vaccines are used for revaccination. My specific recommendations for dairy calves can be found in Table 5.

Table 5 Vaccination Schedule

Dairy Calves - Vaccination Schedule	
AGE	**VACCINE**
2 wk to 1 month	Intranasal BHV-1/PI-3, BRSV*
2 to 3 month	Intranasal BHV-1/PI-3, Lepto-5 Way BRSV*, Haemophilus*, Pasteurella*
3 to 4 month	MLV-BVDV, Lepto-5 Way, Haemophilus*, Pasteurella
>6 month to breeding Age	MLV-BVDV

*I don't routinely recommend these vaccines (bacterins), but if you feel you need to use them this is the age that they should be administered.

BRSV - Modified Live Virus (MLV)
Haemophilus somnus
Pasteurella - Toxoid

Frequently Asked Questions about BVDV

R.D. Schultz, Professor and Chair
Department of Pathobiological Sciences
School of Veterinary Medicine, University of Wisconsin-Madison

1. Q. What is BVDV?

   A. BVDV is classified as a *Pestivirus*, a genus of the *Togaviridae*. As the name implies, it is a real pest! There are many differences in the BVDV, but they are all related. There are two biotypes, non-cytopathic (CPE) and cytopathic (CPE) there is Type 1 serotype with many different strains and both biotypes and type 2 serotype with many strains and both biotypes.

2. Q. Is BVDV related to viruses of other animal species?

   A. It is most closely related to a virus causing disease in sheep called Border disease and the disease of swine known as Hog Cholera. BVDV infects all ruminant species.

3. Q. Is BVDV a relatively new viral infection of cattle.

   A. No it has probably been in cattle for many years. It was first recognized by Olafsen et al. in 1946. Baker et al. isolated the virus in 1954. We have heard recently a lot about type 2, but it is very similar to the BVDV that has been around for years. It is slightly different antigenically from the Type 1.

4. Q. Does BVDV always cause clinical disease?

   A. No, only in certain animals or certain herds. Infection with this virus is most often sub-clinical. I would estimate 60 to 75% of infections cause little or no clinical disease.

5. Q. What are the clinical signs of disease caused by BVDV.

   A. They vary from mild to severe enteritis of adult cattle, respiratory disease, lameness, ulceration of various mucosal surfaces to congenital anomalies, abortions and increased susceptibility to other diseases from immunosuppression.

6. Q. What percentage of dairy cows are serologically positive for the BVD virus?

   A. About 70% of all cows and approximately a similar percentage or higher (perhaps 90%) of all herds have antibody positive animals. Good epidemiologic data are not available and these percentages are based on herd surveys we have done and samples we have collected in Wisconsin as part of surveys for other diseases. Prevalence for beef cattle would be lower based on studies we have done on cow/calf operations in Alabama.

7. Q. If I have one infected animal in my herd will all others get infected?

   A. Yes and No. Yes if that one animal is a persistently infected animal, no if the animal is acutely infected.

8. Q. Why is there this difference in infectivity?

   A. Persistently infected animals shed a lot of virus for a lifetime, acutely infected animals shed virus for only a few days.

9. Q. Do all animals that are once infected keep the virus for life similar to animals infected with IBR virus (latent infection)?

   A. No, BVDV does not cause latent infection. Fetuses infected during the first 100 days of gestation with certain strains of non-CPE BVDV become infected for life. These are the persistently infected (PI) animals which is different from latent infection with IBR because a PI animal is always shedding virus!

10. Q. How common are PI animals?

    A. About 1% or less of all cattle are PI and approximately 15% of all herds will have one or more PI animals based on our studies and studies of others. The most infected herd we found was one herd out of 1,000 tested where 17% of the animals in that specific 100 cow herd were PI.

11. Q. How do PI animals get in a herd?

    A. They are born into the herd and/or they are purchased. If you have female PI animals, their calves will always be PI. If you have dams infected with a particular strain of the non-CPE BVD during the first 100 to 120 days of gestation that calf will be PI animal.

12. Q. What is the most likely way BVDV is brought into a herd and its introduction into the herd will result in serious economic consequences from clinical disease?

    A. Purchasing a persistently infected or actively infected animal and putting it directly into a herd that has never been vaccinated, never had sub-clinical BVDV infection, or has been improperly vaccinated. Large numbers of animals of all ages can die from severe BVDV disease. Also those animals that get sick, but don't die may be severely affected by decreased milk production, weight loss, and they may show increased susceptibility to other infections ("poor doers").

13. Q. Will introducing a PI animal into a herd always cause clinical disease.

    A. No, not if the animals are immune, they are likely to be immune if they have been vaccinated with modified live virus (MLV) vaccines or have had subclinical infections.

14. Q. How can I prevent this problem from occurring?

A. 1. Don't introduce new animals into your herd without first testing them for persistent or acute BVDV before bringing them into the herd.

2. Isolate the new animals after you introduce them, then test and remove animals positive for BVDV. (This is the procedure used by AI Centers that are members of the National Association of Animal Breeders [NAAB]).

3. Vaccinate your animals with a ML BVDV once or twice between 6 months of age up to 30 days prior to breeding or with killed vaccine if bred. When you use killed vaccine in calves be sure they are vaccinated after six months with two doses of killed vaccine waiting two to four weeks between each dose. You should then wait at least two weeks after the second dose of killed vaccine before bringing new animals into the vaccinated herd.

4. When using killed vaccine in the herd to be sure you have protection vaccinate all animals in the herd 2 to 4 weeks prior to introduction of new animals. This is not necessary for herds where MLV vaccine is used in calves (up to breeding age). Don't use semen from an AI center that doesn't test for PI in their bulls. (All the AI centers that belong to the NAAB test their animals and eliminate PI bulls.)

15. Q. Are all these methods equally effective in keeping BVDV from entering a herd and causing significant disease.

A. No, the only absolute way to prevent the problem is to not bring animals into the herd and to use semen only from AI centers that do not have bulls with PI. However, to date we have never seen a major outbreak of BVDV with adult animals dying in a herd that uses ML BVDV vaccines. However, we have seen outbreaks in herds using only killed BVDV vaccines.

16. Q. If I use a herd bull to breed could he be a source of BVDV.

A. Yes, the worst possible situation you could have is a PI bull in your herd used for natural breeding. AI breeding with semen from a PI bull appears to cause no problem in a BVDV serologically positive (vaccinated) cow, but will cause infection in a serologically negative cow which could lead to infection of the fetus, and/or disease in the adult cows.

17. Q. How can I test for presence of animals persistently infected with BVDV.

A. 1. Virus isolation
2. Nucleic Acid Probe
3. Animal Inoculation - Herd Screen
4. Serologic Testing

We had been using the Probe method but now use an animal inoculation test for herd screens.

18. Q. Are all BVDV the same?

    A. No, there are differences among the various isolates, strains, types, etc., two biotypes and two serotypes. Each are capable of causing different diseases depending on the animal (age, sex, genetics) and the amount of virus the animal encounters.

19. Q. Do the vaccines available for BVDV all work the same?

    A. No, there are major differences between the killed and the modified live vaccines. The modified live (ML) are most effective but cannot be used in pregnant animals. Also, when ML vaccines are used in a PI animal they will sometimes cause mucosal disease or in certain young calves (< 8 months of age) will cause them to go off feed for a few days. The vaccine effects seem to be a more serious problem when BVDV is given with other vaccines, especially BRSV and *H. somnus*, or in certain groups of animals. We are not sure why there is such a different response among animals to the BVDV vaccines.

20. Q. Are MLV vaccines able to provide better immunity and longer lasting immunity than the killed vaccines?

    A. Yes, we have found all of the ML vaccines to be more effective than any of the killed BVDV vaccines, and we have tested most if not all of them. However, the MLV are not without their problems. The perfect vaccine has not been made yet, nor will it ever be made for anything, especially BVDV, but the MLV give better immunity than the non-infectious vaccines.

21. Q. What do you recommend for vaccinating calves and open heifers.

    A. We recommend MLV vaccine be used for the first series of vaccinations in calves older than 6 months and heifers up to 30 days prior to breeding. After immunizing with MLV vaccines killed vaccines can be used as booster vaccines on an annual basis. Don't use killed vaccines first if you plan to use MLV vaccines.

22. Q. Will use of BGH interfere with BVDV vaccines?

    A. No.

23. Q. Will use of BGH enhance the clinical disease caused by BVDV?

A. No, not to our knowledge.

24. Q. Will BVDV infection be made more severe if the infected animal is vaccinated with other things?

A. BVDV infection may enhance the severity of other infections since it is immunosuppressive for certain animals.

Also it would appear that other viruses and bacteria or their products could make clinical disease with BVDV more severe. Vaccines with BRSV and *H. somnus* and perhaps other vaccine or bacterins with *E. coli* or Pasteurella may make the disease worse. However, this is only speculation and the reasons for increased severity of disease when these combinations of vaccines are given are not known but are being studied in my laboratory.

25. Q. Can animals vaccinated with BVDV become infected and/or develop disease when exposed to BVDV?

A. Yes, the killed vaccines are not as effective as MLV, thus animals vaccinated with killed vaccines are more susceptible to infection and disease, but even animals that have been vaccinated with MLV can become infected or reinfected if they are in constant contact with BVDV especially if they are in contact with a PI animal. The animals are not likely to develop clinical disease but their fetus may become infected and go on to be a PI animal, develop congenital abnormalities or die and be aborted.

26. Q. Do some ML-BVDV vaccines work better than others.

A. Yes, but we can't tell you which one, because it depends on the strain of BVDV that infects your herd. However, regardless of the MLV vaccine you use it should provide some protection, especially from severe clinical disease, but the protection may not be complete. The BVDV is very complex and no vaccine can give complete protection from possible challenges. For example, if a PI animal is allowed to remain in a herd, the herd will have disease problems caused by BVDV regardless of your vaccination program.

27. Q. Can ML-BVDV be shed at time of vaccination.

A. Yes, some BVDV in certain vaccines are shed, whereas other seem not to be shed.

28. Q. Will the vaccine strain of BVDV that could be shed cause clinical disease, PI, etc.

A. If the herd is/was vaccinated with the same vaccine then there will be no problem. If the herd has not been vaccinated pregnant animals may get infected and fetal problems could occur. However, the only way you could cause PI is if you had an ML-BVDV vaccine with non-CPE virus.

29. Q. Can I have a herd that is free of BVDV?

A. It would be possible but it may be difficult to keep a herd BVDV-free. My experimental herd has animals that have been BVDV-free for many years. It is, however, possible to have a vaccinated herd that is free of BVDV disease. In fact, most of our herds are that way.

30. Q. What about this BVDV called Type II? (2)

A. This is a type of BVDV that differs significantly from the many different strains or serotypes of the other, so-called Type I BVDV. Some strains of the Type II seem to cause a more severe hemorrhagic disease due to its ability to cause thrombocytopenia. Disease was first seen in veal calves, however, we currently see little or none of this disease today in calves, but have seen the Type II appear in adult cattle causing clinical disease which can be very severe in unvaccinated herds. Type II has probably been around for 10 years or more.

31. Q. Do animals vaccinated with current BVDV vaccines develop immunity to Type II BVDV?

A. Yes, it appears that there is cross protective immunity to the Type II as there is among the strains of Type I, but just as there is incomplete immunity with all vaccines for all strains of Type I there is incomplete immunity against all Type II strains with current vaccines. The MLV vaccines give better protection than killed vaccines against Type II, as they do against the Type I. Apparently at least one killed BVDV vaccine, had by chance, a Type I and a Type II BVDV in it, but I don't know if that killed vaccine is better than other killed vaccines. I know it didn't perform any better than other killed vaccines when I challenged with a "cocktail" of Type I BVDV strains.

32. Q. If Type II BVDV is introduced into a herd that has been immunized with a MLV will there be severe disease from the newly introduced Type II?

A. No, you may get some subclinically infected animals, but you won't get severe disease with adult mortality.

33. Q. When does the severe disease outbreak occur if Type I or Type II BVDV is brought into the herd.

A. Under certain unknown conditions severe disease with certain strains of Type I or Type II will occur after introduction of infected animals into an unvaccinated herd, or a herd only vaccinated with killed vaccines. The real intriguing question is why does severe disease only occur in some susceptible herds and not in others even when they haven't been vaccinated. No one has the answer, but it may have something to do with the strain of BVDV, other infections that may be present and/or vaccines being given as well as the genetics of the animals.

34. Q. Does BVDV cause immunosuppression.

A. Yes, but we have shown that not all strains of BVDV are as immunosuppressive as each other and not all animals are as susceptible to immunosuppression as others. Therefore, both the genetics of the animal and the virus determine the severity of immunosuppression.

35. Q. Can BVDV be introduced into a herd through infected wildlife (e.g. deer)?

A. It is possible, but wildlife are not a common source of BVDV. We find a low percentage of white-tailed deer in Wisconsin to have antibody to BVDV.

36. Q. What about other domesticated species, are they a likely source of BVDV infection for cattle.

A. The most likely domestic species to be infected with BVDV other than cattle is sheep. However, our serological results suggest that sheep are rarely infected. Cattle, fetal bovine serum, vaccines, embryos and bovine semen are the most likely sources of BVDV infection.