

BOVINE VIRAL DIARRHEA AND BOVINE VIRAL DIARRHEA VIRUS (BVDV)

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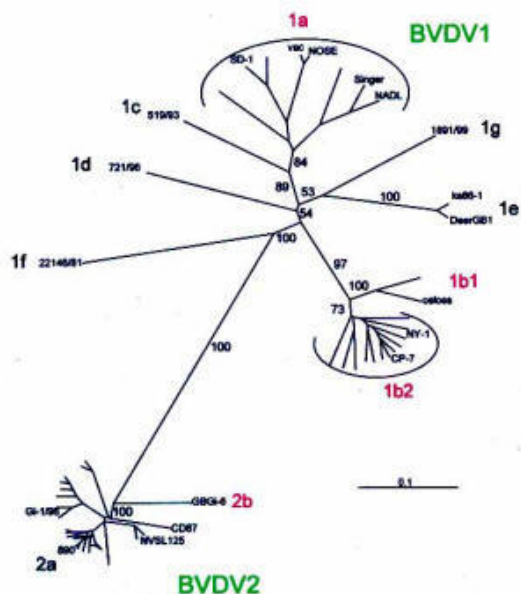
PATB 4110

Diseases of Food Animals and Horses, 2005

Two lectures in this course focus on a single disease. One dealt with rabies. The other is on bovine viral diarrhoea virus (BVDV). I am devoting a full lecture to this topic because:

- It is a major cause of abortion, perinatal death and weak calves in Wyoming. It is the single most important virus we deal with in cattle. In a survey that the former laboratory director Dr. Woodard undertook of our case archives, 27% of all aborted fetuses submitted to the WSVL were infected with BVDV. Elsewhere in the country the number is lower (1 - 5%) although in [England](#) the number is similar to Wyoming's. Finding BVDV in the fetus does not mean it caused abortion (a hole in the window and a fly in the room does not mean the fly made the hole in the window) - we find it in calves that have clearly died of other conditions, including genetic diseases. But detecting BVD in a fetus from your herd means that the agent is circulating. Odds are that the finding is meaningful.
- It can be a source of ill thrift in older cattle. When they develop a syndrome called **mucosal disease**, they generally die.
- It is a co-factor in pneumonia (BRD)
- The virus has a sophisticated ecology. Understanding it will give you some sense of how "clever" viruses can be as they attempt to evade mammalian immune surveillance. It is well adapted in that it causes little disease in adult animals, yet has evolved a mechanism to cause vertical as well as horizontal infection.
- This disease can be eliminated regionally or nationally by targeting its Achilles' heel - the occurrence of **persistently infected cattle** (called PIs). Such cattle can now be detected and culled.
- The agent is widely vaccinated for. I would like you to understand the limitations as well as benefits of vaccinating cattle for BVDV. Bottom line: vaccinate for BVDV, ideally with a modified live virus product (MLV), but understand that biosecurity and test-and-cull are more important than vaccination in keeping the virus out of your herd.
- There is a large amount of complicated information put out by vaccine companies on BVD. Not all of it is accurate, to put it mildly. If you have this disease in your herd, you need to have a basic understanding of how this disease works. Please do not rely on vaccine companies for the full story. The complexity of its life cycle and the abuse of the scientific literature should not blind you to the need to look critically at claims that one vaccine is superior to another.
- The US approach has been: vaccinate. Several European countries eschewed vaccination and instead focused on voluntary (producer-run) biosecurity and test-and-slaughter programs. Unlike the US, BVD is now virtually eradicated in several Scandinavian countries. It's not a coincidence Scandinavia is the natal home of the Vikings.

THE VIRUS



Phylogenetic tree taken from a recent paper by Dr. Ed Dubovi ([J Vet Diagn Invest 17: 10 - 15, 2005](#)), who has done much of the critical field work on BVDV. Note that there are multiple genotypes, the principal ones being 1a, 1b (split between 1b1 and 1b2 subgenotype) and another other distinct lineages, genotype 2. There are other type 1 genotypes (c, d, e, etc). The ones to remember are genotypes 1a, 1b, and 2, since these are the common ones, and are represented in vaccines.

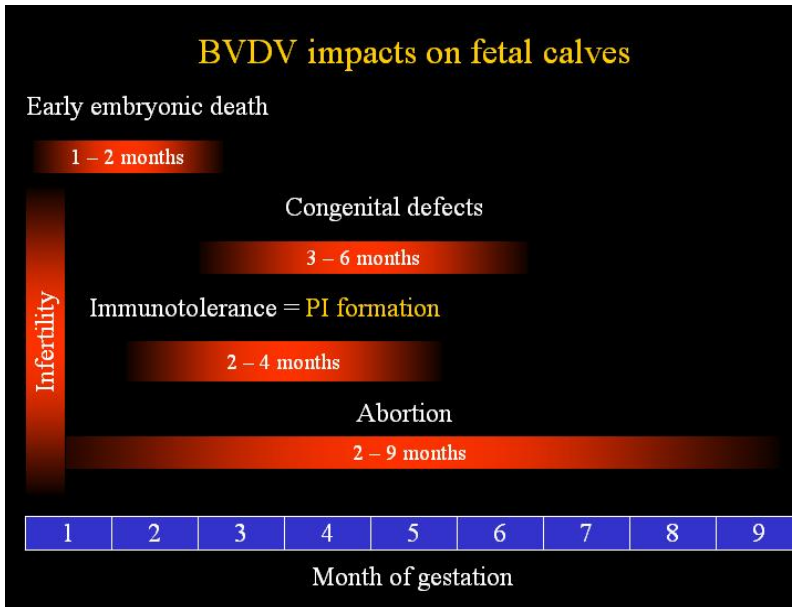
Bovine viral diarrhea was first recognized in 1946 in New York. At that time it was one of the few viral diseases that was identified in cattle as a cause of diarrhea, hence the inappropriate exclusionary term bovine viral diarrhea virus. It is a bit like denominations calling themselves *The First Christian Church* or *First United Methodist Church* a mere 2,000 and 200 years after the birth of Christ and John Wesley, respectively. Nevertheless the name stuck. Obviously, other viruses cause viral diarrhea in cattle.

This pestivirus is a single stranded RNA agent. It therefore is prone to mutations resulting in multiple variants. The principal **genotypes** based on RNA sequences are the **type 1a, 1b and 2**. This is important since most vaccines, until recently, contained only BVDV 1a (e.g., NADL and Singer strains). When BVDV-2 was first recognized in Canada, it was associated with a severe, often fatal disease. Vaccine companies incorporated additional strains into their products. You will see advertising that specifies which strain(s) is present in a product. It is now clear that type 2 BVDV is **NOT** invariably associated with bleeding disorders. One doesn't have to have a type 2 strain in a vaccine for cross-protection against type 2 genotypes. Nevertheless, having attenuated strains that mirror those in the field is likely to be helpful. **The current consensus is that having both type 1 and type 2 genotypes in the vaccine is important.**

This is a relatively fragile virus, since it is enveloped. It survives poorly in the environment. Its survival strategy is to infect calves *in utero* during a particular gestational window, which is before the immune system can distinguish self from non-self. The end result is that the fetal calf accepts BVDV surface antigens as "self" and does not clear the virus. Assuming the fetal calf survives the initial infection, when it is born it is infected for life (which may not be long - see below). Such infected calves are **persistently infected (PIs)**. **Identifying and eliminating PI calves is the most important way at present to control the disease in herds.**

Viral strains can also be described in terms of **biotype**: whether they are **cytopathic** (CP) or **noncytopathic** (NCP). Cytopathic means that one can see the damage it does to cells infected in the laboratory. Noncytopathic means one can't recognize this effect. Noncytopathic viruses are an especial nuisance since infected cells don't look sick, and it is common for batches of laboratory-grown cells to be contaminated with NCP BVDV. There have been several spectacular episodes where BVDV got into viral vaccines and caused a major problem. In truth, whether a strain of BVDV is cytopathic or noncytopathic is in the eye of the beholder - it comes down to the experience of the laboratory technician checking cells, since the effects can be subtle. The NCP concept is important in that persistently infected calves have only the NCP strain in their system.

EFFECT ON EMBRYO AND FETUS



There is substantial overlap in terms of impacts of BVDV on the fetus. These are shown above (after [Grooms: 2004, Vet Clin N Am Food Anim Pract 20\(1\): 5-19](#)). A simplification is that disease occurs in the following sequence gestationally: infertility and early embryonic death; immunotolerance with formation of PIs; congenital defects; infection with questionable effects on calf in first year of life. Abortion may occur at any time. Experimentally this tends to occur in the first trimester, but in beef cattle operations the ones that are recognized are later in gestation (>6 months)

The principal effects that we recognize in association with BVDV are:

1. **Abortion** - this may occur at *any* gestational age. We tend to recognize it in fetal calves at >6 months, but this may just reflect the small size of early aborted fetuses, and therefore the ease with which they can be found. A typical abortion rate following introduction of BVDV into a naive herd is 5 - 20%. As with most infectious agents, the biggest problem tends to be in the pregnant heifer cohort. The fetus dies 10 - 30 days after infection and is expelled up to 50 days later. Fetuses may therefore be rotten and the virus inactivated, so we tell producers that just because we can't grow the virus does NOT mean BVDV was not responsible. In an abortions we often have to culture multiple aborted calves before we can be sure it is/is not BVD.

2. Formation of **persistently infected calves**. These are generally infected between 90 and 130 days gestation just as immunocompetence is developing. Some researchers think they can be infected and formed a little earlier (60 days and up) and that it is rare for PIs to occur after 100 days. A proportion of infected calves otherwise destined to be PIs die and are expelled. PI calves may or may not look abnormal at birth. Dr. Cornish is about to publish an important study on PI calves. When those animals were in the laboratory, the bulk of them identified at weaning did not look too bad, but their growth rates were poor. **ONLY THE NCP BIOTYPE OF BVDV RESULTS IN PI CALVES.** Some PI calves have a characteristic "coyote-head" appearance, but you cannot rely on this to spot PI animals. Some look completely indistinguishable from healthy herdmates.

3. **Congenitally defective calves**. These occur when they are infected after about 130 days. Overlap with the PI-formation stage exists. At 130 days the fetus begins to have a working immune system, and it is likely that the inflammation that now becomes possible is responsible for some or all of the tissue damage that results in a defective newborn calf. The number of defects is large and essentially any organ system can be affected. Lesions of the brain and eyes predominate. Congenital defects were relatively common due to BVDV in my experience in England, and remain beloved by authors of pathology and virology text books due to their striking nature in the brain, such as cerebellar hypoplasia, But in Wyoming we see few overtly defective BVDV calves that make it to full term.

4. Three other forms are seen: **infertility/low conception**, due to death of the oocytes or poor survivability of embryos; **early embryonic death** (< 2 months) due to infection of the embryo and/or damage to the uterine mucosa; and calves that are **congenitally seropositive** (= infected *in utero* and survived to term) but have few or no abnormalities. Vaccine company literature tends to emphasize such calves, but [data](#) are limited establishing that such calves are a major part of the disease spectrum of BVD.

EFFECT ON CALVES FOLLOWING BIRTH

BVDV is generally a mild pathogen in neonatal calves, with some exceptions. Typical BVDV infections in calves and adults are high morbidity, low mortality affairs. Generally the virus moves through a herd without being noticed. Animals have a mild fever, a clear nasal discharge, and a transient drop in their white cell count that signals immunosuppression. The virus is in their system for 6 - 8 days. Animals recover, and have a fairly robust immunity.

The exceptions are:

1. **BVDV is part of the BRD complex.** There are several studies out of western Canada documenting that the virus is found with some consistency in lungs of feeder cattle dying of BRD. The fact that it is there does not clarify its exact role. It may be a pneumotropic strain, or it may be acting as an immunosuppressant. We do see it in some pneumonia cases, but - at least in range cattle it is not a major factor.
2. It can cause a **mild diarrhea** in baby calves, and exacerbates rotaviral diarrhea.
3. **Severe outbreaks of diarrhea**, such as those that were seen when the disease was first recognized in NY, are seen from time to time. Such outbreaks are associated with ulcerative lesions in the gastrointestinal tract, and are usually due to a type 2 BVDV. I have not recognized this in Wyoming.
4. There are strains of BVDV that cause a marked reduction in the number of platelets (**thrombocytopenia**). Affected calves bleed easily: they have blood diarrhea, nose bleeds (epistaxis), and blotchy hemorrhages in skin and other tissues. It can be fatal. We have not seen this in Wyoming.
5. **Mucosal disease** is a sporadic disease that affects only PI. Such calves are infected with a second type of BVDV (invariably a cytopathic strain) and develop a severe, invariably fatal ulcerative disease of the gastrointestinal tract. Most but not all PI calves will develop mucosal disease. A high proportion of PI calves will develop mucosal disease in their first few weeks in feedlots. They can also develop mucosal disease as a result of vaccination, and following spontaneous mutation of NCP to CP.
6. **Localized infections in bulls, BVDV contamination of germplasm and contamination of bovine fetal serum.** BVDV does some odd things. One of them is its ability, in a small number of bulls, survive in testicular tissue for up to 7 months following acute infection, presumably because the testis is an immunologically privileged site and it is slow to clear infection. PI bulls can also look sufficiently good and have semen of adequate quality that they may be used for AI semen. This is not a common event, but be aware that semen from AI bulls can contain BVDV and infect cows. Detecting BVDV in semen, especially when undiluted, is not an easy task. Semen has several properties that make it difficult to check it for viral infection, especially if it is an RNA virus. Semen inhibits viral replication (so there is not a lot there), destroys cell cultures (so we can't use cell cultures to grow up the virus), and inhibits reverse transcriptase (which is used in one of the more sensitive tests we use to detect viral RNA). BVDV is "sticky" and it will attach to the surface of fertilized eggs and early embryos. There are several reports of BVDV being introduced to countries with embryos intended for implantation. An added complication is that batches of fetal bovine serum (FBS) can be contaminated by BVDV. Anywhere between 20 and 49% of FBS batches are contaminated. Since FBS is used with *in vivo* derived embryos and *in vitro* fertilization, and the benefits of using FBS are lost if it is irradiated to inactivate BVDV, it is possible to introduce the virus into embryos.

DETECTING BVDV

There are multiple systems to detect the presence of BVDV in a herd, and I will not inflict all of them on you - this is a rapidly developing field. We are now close to a point when it is cost-effective to

screen entire herds for PI animals, and have done so in the recent past. At \$3/animal it is expensive, but this cost is coming down as new methods come online.

There are several tests you need to be aware of. One is based on examining ear notches (**ear notch test**). PI calves have enormous amounts of virus in all tissues, including skin. The virus can be detected in skin either by using a specific antibody and then examining it as on a slide or in an enzyme linked immunosorbent assay (ELISA). Another is a polymerase chain reaction (**PCR**) test, which allows distinction between the various types of BVDV - this is important for epidemiological studies, where it is necessary to find out if all animals were exposed to the same virus. The gold standard for viral diagnosis is **virus isolation**. This is however slow and requires good laboratory technique. It can't be used in suspected PI calves aged between 1 - 4 months, since maternal antibodies in the circulation mask the presence of virus.

BVDV AND RELATED PESTIVIRUSES IN WILDLIFE

Pestiviruses resembling BVDV occur in wildlife, and several of these isolates were made in Wyoming ([mule deer](#) and [pronghorn](#)). We still know little about these isolates and what they do. Additional work is needed on them (ideally, by inoculating pregnant cattle to see if they cause mischief). In the experience of the WSVL, BVDV is more likely to be introduced by PI calves than wildlife.

CONTROLLING BVD

This has three components: biosecurity, vaccination and test-and-cull PIs. It is worth remembering that the Scandinavian countries (Norway, Sweden, Finland and Denmark) have decided to license no BVDV vaccines. Instead they focused on biosecurity and test-and-cull. They have been astonishingly successful. It started in 1993 in Sweden as a voluntary program run by producers. By 2002, 93% and 88% of all dairy and beef herds in Sweden were certified BVD free.

- a. Biosecurity - keeping BVDV out
- b. Vaccination - keeping resistance high

BVD is one of the principal diseases that producers in Wyoming vaccinate against. More than 180 USDA-licensed BVDV vaccines are commercially available - a remarkable number. The vaccines, particularly MLV products, are moderately effective. **THEY DO NOT PROVIDE COMPLETE PROTECTION AND YOU CAN'T RELY ON VACCINES ALONE.** Most producers are not aware that, although they use the products to protect the calf *in utero*, the products don't have to be tested for their ability to provide fetal protection - they are mostly tested in adult animals to see if they reduce the (minimal) clinical effects of BVDV in adult cattle. Some products (e.g., Pfizer's [Bovi-Shield® FP™](#) line) have been tested to establish an ability to protect the fetus, and therefore have a fetal protection (**FP**) claim. In vaccination-challenge trials, efficacy of various companies' products ranges from 25 - 100%. Note that less successful vaccination-challenge trials performed by or for companies are unlikely to be published in the scientific literature since it give competing companies an edge. The 25 - 100% protection is an upper-end estimate for protection. In one study done by Pfizer, pregnant cattle previously vaccinated with a type I BVDV and challenged at 75 days gestation were protected to a variable degree, depending on whether the challenge (virulent) strain was type 1 (= 88% protection) or 2 (= 58% protection), respectively. We've seen large outbreaks of BVDV on common grazing allotments (for example, an episode seen in [Weston County](#) some years ago) where cattle vaccinated against type I BVDV were then infected when pregnant with either a killed product, or a MLV product to which they have been previously exposed

Possibly, vaccinate calves at branding in late spring. This is one time when it may be appropriate to give a killed product. There is a good chance that maternal antibody will interfere and reduce efficacy, so this needs to be repeated by

Vaccinating calves at, or better still several weeks before, branding time (5 - 7 months of age). ed with type 2.

A common vaccination strategy is:

Vaccinate heifers with MLV two months before breeding

Vaccinate cows with MLV two weeks before breeding

Possibly, boost cows

c. Detecting and culling PI calves

This is best done using the ear notch test. A small piece of skin is taken from the ear and examined by one of several methods in a laboratory. Some laboratories claim that one pattern of staining indicates that PI calves have a stereotyped distribution of virus in tissue, and that acutely infected (or vaccinated) calves have little or no viral antigen in skin. A recent study done in our laboratory by Dr. Cornish has added a little wrinkle to this - some acutely infected calves can have viral antigen in their skin for months. But for all intents and purposes, if a calf has viral antigen in its aural skin, it is very likely to be a PI and should be culled. Culling in this instance does not mean taking it down to a sale barn and selling this little time bomb to one of your neighbors - the ethical thing to do is to humanely euthanize the PI calf. The dam of any PI calf should also be tested. If you detect a PI in your herd, it may be time to test everyone. There are strategies to test pooled milk (dairy cows) and serum (beef cows - not quite as convenient) to establish the status of herds. This is likely to be a focus of research over the next few years in order to bring down the costs of testing herds.

SUMMARY

1. Bovine viral diarrhea virus is an important, common cause of reproductive loss in Wyoming beef herds.
2. In addition to infertility, early embryonic loss, congenital defects and perinatal loss, infection during a specific gestational window (90 - 130 days), before the immune system is functional, results in persistently infected calves that perpetuate infection into the next generation. This is a classical example of vertical (one generation to the next) infection.
3. Persistently infected animals are the main source of infection in herds. Some will die when superinfected with a cytopathic strain of BVDV, causing a distinctive clinical syndrome called mucosal disease. In some ways this is beneficial: they are eliminated from the herd.
4. Most PI calves are born to non-PI dams. A small proportion of PI calves are born to PI dams. If you have a PI calf, you **MUST** test to dam to make sure she too is not a PI, although the chances of this are low.
5. BVD is controlled primarily by 1. good biosecurity; 2. detecting and eliminating PIs and 3. vaccination.
6. There is a bewildering range of vaccines for BVD. They are in fact based on a small number of virus isolates (i.e., vaccines from different companies may contain the same strain). They are either inactivated or MLV. As a general rule, MLV are better, but these should be give to cattle before they are bred. Use a vaccine that will give some protection against type 1 and type 2 genotypes. Pfizer has a vaccine line that can be given to pregnant animals, but **COWS MUST HAVE BEEN VACCINATED ONCE PREVIOUSLY WITH THAT VACCINE BEFORE IT IS SAFE TO GIVE THEM THE MLV WHEN PREGNANT**. Competing companies are likely to get similar products on the market (i.e., can be given to pregnant cows) over the next five years.

7. Even with a good vaccination program, don't assume BVDV will not enter your herd. We've seen herds with up to one third of all the calf crop being PI, in spite of excellent vaccination programs. We presume they were exposed to strains of BVDV that were only distantly related to the vaccine strain, and therefore the level of protection was poor. This does not mean the vaccine you used was "bad" - it is just the nature of a beast that exists in many strains.

8. Detecting one animal with BVDV may mean you have an appreciable problem. On ranches where we have gone in and tested everyone, and in spite of owners seeing little overt disease, there have been major benefits in terms of a healthy calf crop in subsequent years, provided the PIs were culled. The owners were getting used to a high incidence of calf scours and pneumonia, and not associating it with underlying BVD.

8. Some vaccine have a Fetal Protection claim This is good, since it means that testing was done to establish the level of protection of calves when their dams were experimentally vaccinated and then challenged. But challenge models have limitations. They can't completely address the range of viral strains in the field. Such studies can be configured by time of exposure and dose to ensure the product looks good in promotional literature. Not all of these studies are published, so it can be hard (or impossible) without getting the company data to evaluate the integrity of the challenge model that was used.

8. You can't detect all PI calves based on physical appearance alone (the coyote-calf look). There are various methods to detect PIs, such as virus isolation from blood, or various skin tests.

DO'T