ASSESSMENT OF AVAILABLE VACCINES FOR BOVINE REPRODUCTIVE PATHOGENS

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INTRODUCTION

Infectious agents can be responsible for early embryonic death, abortion, teratogenesis, and weak calves. Importantly, these same signs of disease may be attributed to noninfectious causes (Table 1). As diagnosis of an etiologic agent occurs in less than a majority of reproductive losses,[1] vaccination practices are often instituted without a supporting laboratory diagnosis. Unfortunately, this tendency to vaccinate without diagnosis of reproductive pathogens can produce a waste of economic resources, an unrealistic sense of protection and a means of pathogen transmission.[2] This presentation will review availability and reproductive efficacy data of vaccines for bovine reproductive pathogens.

Table 1. Causes of abortion in cattle.

Bacterial causes	Viral Causes	Protozoal Causes	Fungal Causes	Toxic Causes
1. Leptospira	1. IBR (Bovine herpes)	1. Tritrichomonas	1. Aspergillus fumigatus	1. Nitrates
2. Brucella abortus	2. BVD	2. Neospora spp.	2. Mucor spp.	2. Poison hemlock
3. Listeria	3. Bluetongue	3. Sarcocystis neuroni	3. Mortierella wolfii	3. Lupines
4. Campylobacter	4. Vesiviruses			4. Tobacco
5. Salmonella				5. Ponderosa pine
6. Haemophilus			Other Causes	
7. Ureaplasma			1. Epizootic bovine abortion	
8. Mycoplasma			2. Genetic	
9. Chlamydia			3. Environmental	
10. Anaplasma			4. Trauma	

1. Leptospira interrogans sensu lato **(species)** *hardjo, pomona, canicola, icterohemorrhagiae, szwajizak* **(serovar)**

Hardjo-bovis and *Hardjo-prajitno* (genotype= sub-serovar) These sub-serovars are responsible for host-maintained infections while other serovars cause incidental infections. These host-maintained serovars cause insidious reproductive losses throughout gestation (abortion rates of 3-10%), yet are much more economically significant than are causes of incidental infections. While most vaccines contain *hardjo-prajitno*, *hardjo-bovis* is most commonly isolated in the field. *Hardjo-bovis* is maintained throughout persistent infections in the proximal renal tubules of the kidneys and is associated with extensive shedding in urine. *Hardjo-prajitno* is associated with clinical mastitis and severely decreased milk production. *Hardjo-prajitno* is not maintained in the proximal renal tubules of the kidney and thus is associated with minimal shedding in urine. *Hardjo-prajitno* does exhibit a predilection for the genital tract and is thought to be an important cause of infertility. With *Hardjo-prajitno*, venereal transmission is the most common route of infection. Appropriate diagnostic samples include maternal serum (serology by macroscopic agglutination test [MAT]), fetal serum (serology by MAT), fetal kidney and fluids

(immunofluorescence testing), maternal urine (culture or darkfield microscopy) and paired serum samples from 10 herdmates in contact with aborted material. Most leptospira bacterins were approved years ago when efficacy was proven by vaccinating cattle, challenging with a virulent serovar, then looking at recovery rate from the kidneys in vaccinates versus controls. A newer vaccine is purported to have field data for fetal protection but currently has limited availability.

Table 2. Available *Leptospira* vaccines

Manufacturer	Vaccine	Dosage	2 Doses Initially	Route		Slaughter Withdrawal
				IM	SQ	
Agrilabs	Lepto 5	2 mL		√	√	21 days
	Pre-Vent 6	2 mL		√	√	21 days
Pfizer	Lepto Ferm-5	2 mL		√		21 days
	Stay Bred VL5	2 mL	√	√		21 days
	Spirovac	2 mL	√		√	
Fort Dodge	TriVib 5L	5 mL	√		√	60 days
Merial	Lepto 5	2 mL	Recommended	√		21 days
Boehringer Ingelheim	Lepto 5	2 mL	Recommended	√	√	21 days
Novartis	Vib Shield L5	2 mL	Recommended	√	√	21 days
Durvet	Lepto 5	2 mL		√	√	21 days
Intervet	Lepto 5	2 mL		√	√	21 days
Premier Farmtech	Lepto 5	2 mL			√	21 days
Aspen	Lepto 5 Vaccine	2 mL		√	√	21 days
Colorado Veterinary Products	Lepto 5	2 mL		√	√	21 days

2. Campylobacter fetus ssp. venerealis

Infection mainly causes temporary infertility or early embryonic death, but may cause sporadic abortions. Abortions due to *C. fetus* spp. *venerealis* have been recorded between the fourth and eighth month of gestation. The agent is only transmitted venereally in cattle. Fertility usually returns 4 to 8 months after initial infection. The organism may survive in the cervix through a full gestation. When herd history reveals infertility, preputial smegma, semen, fetal fluid, placenta and vaginal discharge can be submitted for culture. Samples should be submitted in anaerobic transport media.

Vaccines for Campylobacter have proven efficacy in protecting heifers from reproductive losses associated with this bacteria. Two injections of vaccine, 6 weeks apart, are recommended for treatment of young *C. fetus*-infected bulls.

Table 3. Available *Campylobacter* vaccines.

Manufacturer	Vaccine	Dosage	2 Doses Initially	Route		Slaughter Withdrawal
				IM	SQ	
Agrilabs	Pre-Vent 6	2 mL		√	√	21 days
	Vibrio Lepto 5	5 mL	For Campylobacter	√	√	21 days
Pfizer	Vibrin	2 mL			√	60 days
	Vibrio-Leptoferm-5	2 mL	√	√		21 days
Fort Dodge	TriVib 5L	5 mL	√		√	60 days
Boehringer Ingelheim	Vibrio-Lepto 5	5 mL	√	√		21 days
Novartis	Vib Shield	2 mL		√	√	21 days
Durvet	Vibrio-Lepto 5	5 mL	For Campylobacter	√	√	21 days
Intervet	Vibralone-H-L5	5 mL	√	√		21 days
Premier Farmtech	Vibrio-Lepto 5	5 mL	For Campylobacter	√	√	21 days
Aspen	Vibrio-Lepto 5 (Oil)	2 mL		√		60 days
	Vibrio-Lepto 5	5 mL		√	√	21 days

3. Hemophilus somnus

This bacterial agent is associated with thromboembolic meningoencephalitis, polyarthritis, respiratory disease, and reproductive infections. This agent is thought to cause weak-calf syndrome or stillbirths more often than abortions. Lesions are associated with a necrotizing to necrosupparative placentitis and changes associated with the fetal brain. This agent also has a controversial role in causing infertility. *H. somnus* is part of the normal bacterial flora of the male and female bovine genital tract. Therefore, pure cultures of this organism are considered necessary to incriminate it in causing abortion in the cow. Appropriate diagnostic samples include fetal fluid, placenta and vaginal discharge. Criteria for diagnosis include: (a) nearly pure culture in stomach content or tissues, (b) lesions of inflammation present, and (c) no other more likely cause for the abortion is found. Vaccination may improve fertility and decrease the number of abortions caused by this agent.

Table 4. Available *Hemophilus* vaccines.

Manufacturer	Vaccine	Dosage	2 Doses Initially	Route		Slaughter Withdrawal
				IM	SQ	
Agrilabs	Somnumune	2 mL	√	√	√	21 days
Pfizer	Somubac	2 mL	√		√	21 days
Fort Dodge	Triangle 9 +HS	5 mL	√	√		21 days
Boehringer Ingelheim	Bar Somnus	2 mL	√	√		21 days
Novartis	Somnu Shield	2 mL	√	√	√	21 days
Intervet	Somnutech	2 mL	√	√	√	21 days
Aspen	Somnumune	2 mL	√	√	√	21 days

4. Infectious bovine rhinotracheitis (Bovine herpesvirus 1)

Bovine herpesvirus 1 (BHV-1) carried in blood leukocytes can become localized in placental vessels. Subsequently, BHV-1 kills the fetus within 24 hours after entry. Abortions commonly follow the respiratory and conjunctival forms of the disease. The virus may be diagnosed with fluorescent antibody test on fetal kidney or lesions in the fetal liver and adrenal. A four-fold rise in titer may be noted from abortion to 2 weeks but viral titers are seldom of help in diagnosis because the dam may be infected for months prior to aborting and may actually have a decreasing titer following abortion. Duration of carrier state is probably for the life of the animal. In an abortion storm, up to 60% of the herd may abort due to this virus. The aborted tissues are uniformly dark red as a result of hemoglobin imbibition. BHV-1 is still the most frequently diagnosed viral cause of abortion in North American cattle. This virus may remain latent in the trigeminal and sacral ganglia. Fetuses may serve as a source for transmission of disease. This virus may also be associated with a necrotizing oophoritis with localized inflammation in the corpus luteum. Lesions within the fetus include foci of necrosis in the liver, spleen, adrenal glands, lung, and kidneys. This virus may be transmitted venereally even via cryopreserved semen. Vaccination can be effective in preventing disease but may not prevent infection or viral latency. Use of modified-live vaccines may cause a temporary infertility due to follicular necrosis in seronegative cows. Vaccination with a modified live BHV-1 vaccine has been shown to protect against abortions.

5. Bovine viral diarrhea virus (BVDV)

Brain, eye, and hair abnormalities have been noted in infected fetuses. Herd infections with BVDV can be diagnosed with sera from colostrum-free calves or sera from unvaccinated calves > 4 months old. Timing of infection is critical to cause birth defects or persistently infected animals. May be transmitted in the semen. Virus is not usually present in fetuses or newborns that have sustained teratogenic viral damage. However, these calves do exhibit a precolostral anti-BVDV antibodies.

To a degree, the importance of BVDV as a pathogen and the costs of living with it are further manifested by the large number of licensed vaccines (>140) that are used (Table 5).[3] However, it should be understood that vaccination has provided inconsistent protection.[4,5] Vaccination of cows has been particularly unreliable in protecting the developing fetus from infection, and the result can be the birth of offspring that serve as reservoirs and shed BVDV for life.[6-8] Other challenges for development of vaccines are the wide antigenic diversity among field strains and the immune suppression associated with live vaccines.[7] Modified live vaccines have also resulted in infection of ovarian tissue and thus might negatively impact fertility.[9]

Table 5. Available vaccines for bovine viral diarrhea virus.[10]

Manufacturer	Vaccine	Modified Live (MLV) or Killed	Type 1 BVDV Subtype	Type 1 BVDV Biotype	Type 1 BVDV Strain	Type II BVDV Biotype	Type II BVDV Strain	Additional Claims	Approved for Pregnant Cows	Dosage	2 Doses Initially	Route IM	Route SQ	Slaughter Withdrawal
Boehringer Ingelheim	Elite 5™	Killed	1a	cp	Singer	cp	296		√	5 mL	√	√		21 days
Intervet	Horizon® 4 Plus	Killed	1a	cp	C24V	cp	296		√	5 mL	√	√	√	21 days
AgriLabs®	Master Guard™ 5	Killed	1a	cp	C24V	cp	296		√	5 mL	√	√	√	21 days
Merial	Respishield™ 4	Killed	1a	cp	Singer				√	5 mL	√	√	√	21 days
Fort Dodge®	Triangle® 4+type II	Killed	1a	cp	Singer	cp	5912		√	2 mL	√	√	√	21 days
Pfizer	CattleMaster® 4	Killed	1a	cp	5960				√	2 mL	√	√		21 days
			1	ncp	6309									
Novartis	ViraShield® 5	Killed	1a	cp	KY22	ncp	TN 131		√	5 mL	√	√		60 days
Biocor	Surround™ 4	Killed	1a	cp	Singer				√	5 mL	√	√	√	21 days
			1b	ncp	NY									
Boehringer Ingelheim	Express™ 5	MLV	1a	cp	Singer	cp	296		∅	2 mL	√	√		21 days
Pfizer	Bovi-Shield™ 4+L5	MLV	1a	cp	NADL			Fetal protection	Provisional	2 mL	For BRSV	√		21 days
Fort Dodge®	Pyramid® 4	MLV	1a	cp	Singer				∅	2 mL		√	√	21 days
Merial	Reliant® 4	MLV	1a	cp	NADL				∅	2 mL	Recommended	√		21 days
Intervet	Frontier™ 4 Plus	MLV	1a	cp	C24V	cp	296		∅	2 mL	For BRSV	√	√	21 days
AgriLabs®	Titanium™ 5	MLV	1a	cp	C24V	cp	296		∅	2 mL	For BRSV	√	√	21 days
Schering-Plough	Jencine® 4	MLV	1	ncp	WRL			Fetal protection	∅	2 mL		√	√	21 days
Biocor	Herd Vac™ 3	MLV	1a	cp	Singer				∅	2 mL		√	√	21 days
Boehringer Ingelheim	Breed-Back™ FP	MLV	1a	cp	Singer	cp	296	Fetal protection	∅	5 mL		√		21 days

The wide antigenic diversity among field strains is due to the inability of the viral RNA polymerase to correct misincorporated nucleotides. This lack of proofreading ability results in a high frequency of base substitutions in BVDV, approaching 1 error for every 10,000 nucleotides polymerized or an average of 1.25 nucleotide changes during each replication of the viral genome.[11] Thus the genome of BVDV is not a single defined entity, but an average or consensus of a heterogeneous population of molecules. This strategy of replication generates genomes with potentially greater fitness and ability to survive under altered environmental conditions. This explains why some genotypes of BVDV such as type 1B appear to more commonly play a role in the bovine respiratory disease complex, while type 2 BVDV is more commonly involved in severe acute disease.[10,12]

Due to the negative impact of BVDV on animal health and the inconsistency with which vaccines have been able to control infection, several countries (Denmark, Finland, Norway, Sweden, the Shetland Islands and Slovenia) have initiated eradication programs.[13-17] Furthermore, in November, 2001, the American Academy of Veterinary Consultants approved the following position statement: "The beef and dairy industries suffer enormous losses due to the effects of bovine viral diarrhea virus (BVDV) infection. The highly mutable nature of BVDV and the emergence of highly virulent strains of BVDV contribute to limited success of present control programs. Also, persistently infected cattle are the primary source of infection, and effective testing procedures are available to identify those infected carriers. Therefore, it is the resolve of the Academy of Veterinary Consultants that the beef and dairy industries adopt measures to control and target eventual eradication of BVDV from North America." Thus, there is informed support for development and implementation of eradication programs for BVDV in this country.

As the beef and dairy industries strive to eventually eradicate BVDV, vaccination and biosecurity must play equal roles in achieving this goal. Vaccines for BVDV will soon conform to the Center for Veterinary Biologics policy (Notice No. 02-19; 9/5/02) concerning vaccine claims for protection against the reproductive effects of bovine virus diarrhea virus. Claims will henceforth by type-specific (i.e., BVDV Type 1 or Type 2) under the following categories:

1. "Aids in the prevention of abortion:" This claim must be supported by studies in which abortions occur in an acceptable proportion of the nonvaccinated control cattle. Protection is evidenced by lack of abortion in vaccinated cows.
2. "Aids in the prevention of persistently infected calves:" This claim must be supported by challenging pregnant cattle at 75-90 days of gestation and performing virus isolation procedures on tissues from all fetuses on, or after, 150 days of gestation. Protection is evidenced by lack of virus isolation from fetuses obtained from vaccinated cows.
3. "Aids in the prevention of fetal infection" or "Aids in the prevention of fetal infection including persistently infected calves:" This claim may be supported by generating data to support the claim for "aids in the prevention of persistently infected calves" AND challenging a separate group of pregnant cattle at approximately 180 days of gestation and evaluating the fetuses (or calves) at, or after, ≥220 days of gestation. Serology and virus isolation procedures must be performed. Protection is evidenced by lack of detection of virus and antibodies from fetuses obtained from vaccinated cows.

Appropriate use of vaccination and biosecurity could produce control and eventual eradication of bovine viral diarrhea virus in North America.

6. Tritrichomonas fetus

This pathogen may cause abortions from breeding up to 7 months of gestation but usually abortions occur in the first half of gestation. Inflammation of vagina, cervix and endometrium produces a hostile intrauterine environment. Abortions may be most common in older cows with partial immunity. The organism may be found in pyometral discharge, placental fluids or fetal stomach contents. Cows may retain the organism for 150 days. Within infected herds, control of this pathogen may be achieved by using only 1 to 3 year-old-bulls. This agent is associated with a high incidence of early embryonic death between 18 and 60 days of gestation. By one year after recovery, cows are certainly susceptible. There is a vaccine available for *Tritrichomonas foetus* (Trichguard or Trichguard Plus [Ft. Dodge]). The vaccine stimulates cows to clear the infection in a matter of weeks (vs. months in unvaccinated cows). No vaccine efficacy has been shown in bulls.

7. Neospora spp.

Abortions due to *Neospora spp.* typically occur during the early second trimester, but can occur throughout gestation. Lesions considered to be virtually diagnostic for *N. caninum* are nonsuppurative encephalitis with foci of necrosis and gliosis, nonsuppurative myositis, hepatitis, and most consistently myocarditis. Aborted fetuses usually are autolyzed or mummified. Protozoal zoite cysts with a thick wall or free zoites in the brain parenchyma may be noted. In the California diagnostic lab, 18-19% of all submitted fetuses are diagnosed with Neospora infection. Abortions due to this pathogen are more common in drylot dairies. There is a vaccine available for Neospora caninum (NeoGuard [Intervet]). The vaccine has been shown to reduce abortions associated with challenge of animals using a *N. caninum* preparation.

Reference List

(1) Kirkbride CA. Etiologic agents detected in a 10-year study of bovine abortions and stillbirths. J Vet Diagn Invest 1992; 4:175-180.

(2) Niskanen R, Lindberg A. Transmission of bovine viral diarrhoea virus by unhygienic vaccination procedures, ambient air, and from contaminated pens. Vet J 2003; 165(2):125-130.

(3) Ridpath JF, Neill JD, Frey M et al. Phylogenetic, antigenic and clinical characterization of type 2 BVDV from North America. Vet Microbiol 2000; 77(1-2):145-155.

(4) Polak MP, Zmudzinski JF. Prevalence of bovine viral diarrhea virus infection in bulls in artificial insemination centers in Poland. Vet Microbiol 1999; 64:253-257.

(5) Houe H, Baker JC, Maes RK et al. Prevalence of cattle persistently infected with bovine viral diarrhea virus in 20 dairy herds in two counties in central Michigan and comparison of prevalence of antibody-positive cattle among herds with different infection and vaccination status. J Vet Diagn Invest 1995; 7:321-326.

(6) Campen HV, Woodard L. Fetal infection may not be preventable with BVDV vaccines. J Am Vet Med Assoc 1997; 210(4):480.

(7) van Oirschot JT, Bruschke CJ, van Rijn PA. Vaccination of cattle against bovine viral diarrhoea. Vet Microbiol 1999; 64:169-183.

(8) Van Campen H, Vorpahl P, Huzurbazar S et al. A case report: evidence for type 2 bovine viral diarrhea virus (BVDV)-associated disease in beef herds vaccinated with a modified-live type 1 BVDV vaccine. J Vet Diagn Invest 2000; 12:263-265.

(9) Grooms DL, Brock KV, Ward LA. Detection of cytopathic bovine viral diarrhea virus in the ovaries of cattle following immunization with a modified live bovine viral diarrhea virus vaccine. J Vet Diagn Invest 2000; 10:130-134.

(10) Fulton RW, Ridpath JF, Saliki JT et al. Bovine viral diarrhea virus (BVDV) 1b: predominant BVDV subtype in calves with respiratory disease. Can J Vet Res 2002; 66(3):181-190.

(11) Donis RO. Molecular biology of bovine viral diarrhea virus and its interaction with the host. Veterinary Clinics of North America-Food Animal 1995; 11(3):393-423.

(12) Carman S, van Dreumel T, Ridpath J et al. Severe acute bovine viral diarrhea in Ontario, 1993-1995. J Vet Diagn Invest 1998; 10:27-35.

(13) Houe H. Epidemiological features and economical importance of bovine virus diarrhoea virus (BVDV) infections. Vet Microbiol 1999; 64:135-144.

(14) Lindberg AL, Alenius S. Principles for eradication of bovine viral diarrhoea virus (BVDV) infections in cattle populations. Vet Microbiol 1999; 64:197-222.

(15) Ferrari G, Scicluna MT, Bonvicini D et al. Bovine virus diarrhoea (BVD) control programme in an area in the Rome province (Italy). Vet Microbiol 1999; 64:237-245.

(16) Synge BA, Clark AM, Moar JA et al. The control of bovine virus diarrhoea virus in Shetland. Vet Microbiol 1999; 64:223-229.

(17) Grom J, Barlic-Maganja D. Bovine viral diarrhoea (BVD) infections--control and eradication programme in breeding herds in Slovenia. Vet Microbiol 1999; 64:259-264.