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Assessment of available vaccines for bulls to prevent transmission of reproductive pathogens

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Summary
Immunization of bulls to prevent infertility or transmission of reproductive pathogens equates to the prudent use of available vaccines to achieve effective immunity prior to exposures that will infect reproductive tissues or negatively impact reproductive organs. The goal of this review is to concisely describe appropriate immunization for bulls used for natural breeding and semen production in the United States. Appropriate vaccination practices to prevent the transmission of Campylobacter fetus, Histophilus somni, Leptospira species, Tritrichomonas foetus, bovine viral diarrhea virus, infectious bovine rhinotracheitis virus (bovine herpesvirus-1), and bovine herpesvirus-5 are described. In the United States, licensed vaccines are not available or vaccination is usually contraindicated for Brucella abortus, Mycobacterium bovis, Mycobacterium avium subsp. paratuberculosis, and bluetongue virus. While some determinants may cause producers to neglect immunization of bulls for reproductive pathogens, informed practitioners can often minimize disease risks by recommending timely vaccination of future sires with appropriate vaccines.

Keywords: Pathogen, vaccination, immunization, venereal, infertility

Introduction
Effective and timely immunization of sires to be used for natural breeding or artificial insemination has the potential to prevent infertility or subfertility and transmission of some reproductive pathogens. Pathogens that should receive consideration when introducing new bulls in the United States include Brucella abortus, Campylobacter fetus, Histophilus somni, Leptospira species, Mycobacterium bovis, Mycobacterium avium subsp. paratuberculosis, Tritrichomonas foetus, bovine viral diarrhea virus (BVDV), bluetongue virus, infectious bovine rhinotracheitis virus (bovine herpesvirus-1; BHV-1), and bovine herpesvirus-5 (BHV-5). Unfortunately, vaccines for which efficacy and safety have been proven are only available to prevent the negative consequences associated with some of these disease causing agents. Effective vaccination strategies may be limited by the safety of available vaccines, the inability to administer vaccines at the appropriate time, and the lack of demonstrated efficacy to prevent reproductive sequelae.

Brucella abortus
Localization of field strains of Brucella abortus in the reproductive tract of the bull can result in orchitis, testicular degeneration and production of semen containing the bacteria. Vaccination of heifers between four and ten months of age is performed in the United States to mitigate perceived disease risks associated with B. abortus, minimize regulatory issues related to interstate transportation of breeding age animals, or increase market value of heifers. Bulls to be used for natural breeding should not be vaccinated unless the risk of exposure to B. abortus is very high. Intramuscular vaccination of six sexually mature bulls with strain RB51 did not result in shedding of the organism, prolonged colonization, or reproductive problems based on serial breeding soundness examinations during the five weeks after vaccination.1 As strain RB51 is essentially devoid of the O-polysaccharide chain, animals vaccinated with RB51 do not produce antibodies directed against the O-polysaccharide chain and can be distinguished from animals infected with field strains or vaccinated with strain 19. Clearly bulls should not be administered vaccines containing strain 19 as vaccination may cause orchitis, enduring testicular infections, and a seropositive status that cannot be differentiated from exposed bulls.1,2 Vaccination of bulls to be maintained in bull studs is rarely if ever indicated.

Campylobacter fetus
Infections of bulls with *Campylobacter fetus* subsp. *venerealis* are asymptomatic while infections of heifers and cows cause infertility and early embryonic death. As vaccination of bulls up to five years of age using a bacterin in an oil emulsion adjuvant is considered both protective and curative, vaccination prior to natural mating may be considered the least expensive method of biosecurity against *C. fetus*.

Unfortunately, vaccination may not result in every bull clearing the organism and some bulls may not clear the organism until more than six weeks after primary vaccination. While vaccines containing oil emulsion adjuvants may cause notable tissue reactions, *C. fetus* vaccines containing an aluminum hydroxide adjuvant have not demonstrated acceptable efficacy in a field trial involving heifers. Common recommendations for bulls that are considered to be at risk for exposure to and spreading of *C. fetus* subsp. *venerealis* involve an initial two-dose series of vaccinations (two to four weeks apart and at least 30 days before initiation of the breeding season) followed by annual vaccination.

**Histophilus somni**

The association of *Histophilus somni* (previously *Hemophilus somnus*) with endometritis, infertility, and abortion in cattle is controversial and may depend on the production of specific virulence factors by the bacterial strain. While field investigations attribute reproductive disease to introduction of bulls harboring this gram-negative coccobacillus, the efficacy of vaccination in preventing reproductive disease remains to be assessed and described. Unfortunately, the published body of evidence does not provide a consistent estimate of the direction and magnitude of effectiveness of the more common use of immunization to prevent respiratory disease due to *H. somni*.

**Leptospira species**

While pathogenic *Leptospira* species are mainly shed in urine, transmission of this opportunistic reproductive pathogen is possible via semen. While the serovar *pomona* is clearly associated with outbreaks of bovine abortion in North America, the association of North American *hardjo* types with bovine infertility has been diagnosed but is controversial. Vaccination strategies to prevent reproductive losses caused by *Leptospira* commonly focus on immunization of heifers and cows. While a controlled field trial in the United Kingdom demonstrated the ability of a *hardjo* vaccine to prevent infertility in vaccinated cows within naturally infected herds, a similar, large, randomized controlled field trial in the United States did not detect differences in pregnancy and calving rates between cows vaccinated with a hardjobovis vaccine and controls. Generalities regarding vaccine efficacy are to be avoided as research involving one 5-way pentavalent vaccine demonstrated lack of efficacy while research involving another 5-way pentavalent vaccine containing the same serovars and types of *Leptospira* demonstrated consistent protection against the same challenge strain and route of challenge. Depending on the potential for exposure of specific herds and regional considerations regarding association of *Leptospira* infection with reduced reproductive health, producers may choose to vaccinate bulls with a polyvalent product with the first dose administered after six months of age. In these situations, bulls often receive an initial two-dose series followed by annual revaccination. Bulls to be admitted or maintained in bull studs should not be vaccinated for *Leptospira species* as serologic status is used as the primary indicator of a possible ongoing infection.

**Mycobacterium bovis**

Transmission of *Mycobacterium bovis* via semen is possible. While much work focuses on the development and validation of safe and effective vaccines for *M. bovis*, a vaccine currently is not available for administration to cattle in the United States.

**Mycobacterium avium subsp. paratuberculosis**

While *Mycobacterium avium subsp. paratuberculosis* (MAP) has been isolated from testicular tissue and semen of infected bulls, venereal transmission has been considered to be of negligible importance. Vaccination of cattle in the United States for MAP is not common. One vaccine, Mycopar (Boehringer Ingelheim, Fort Dodge, IA), is limited to use in specific herds approved by state animal...
health officials. This approval varies among states and requires validation that MAP causes infections within the herd, negative tuberculin tests on all test-eligible animals, and a signed agreement by the herd owner and state animal health agency. With this approval, only replacement heifers and bull calves between one and 35 days of age are eligible to receive MAP vaccine. A protective effect of vaccination on MAP infection and clinical disease has been described.\textsuperscript{16} Except for extra-ordinary situations, vaccination of bulls is to be avoided as it increases the likelihood of testing positive for bovine tuberculosis via the caudal-fold skin test and Johne’s disease via antibody-based tests such as ELISA.\textsuperscript{16}

**Tritrichomonas foetus**

Infections of bulls with *Tritrichomonas foetus* are asymptomatic, while infections of heifers and cows with *T. foetus* cause transient infertility, early embryonic death, abortion, and pyometra. Vaccination strategies to prevent reproductive losses caused by *T. foetus* commonly focus on immunization of heifers and cows. One vaccine, Trichguard\textsuperscript{®} (Boehringer Ingelheim) which contains whole cell antigens, is licensed in the United States as an aid in the prevention of disease caused by *T. foetus*. In a randomized, controlled field trial, administration of two doses (three weeks apart) to heifers four weeks prior to a 45-day breeding season with infected bulls resulted in reduced embryonic and fetal losses and a shorter duration of infection.\textsuperscript{17} Research regarding immunization of bulls with various vaccines to prevent or cure infections with *T. foetus* has produced variable results.\textsuperscript{18-21} Systemic immunization with whole cell antigens has prevented colonization of the preputial and penile mucosa after experimental inoculation.\textsuperscript{18,21} Epidemiologic studies are not available to assess the reproductive impact of using immunized bulls in infected herds. If bulls are to be used for natural breeding in potentially infected herds, vaccination of bulls as well as heifers and cows can limit the economic impact of exposure to this pathogen. If vaccination is to be performed, two doses (two to four weeks apart) are recommended with the second dose administered four weeks prior to the breeding season.

**Bovine viral diarrhea virus**

Infections of cattle with BVDV can cause disease which ranges from subclinical to severe. To avoid contamination of semen with BVDV, bulls should be protected from persistent infection, a poorly timed acute infection, prolonged testicular infection, and persistent testicular infection.\textsuperscript{22} While appropriate immunization of the heifer or cow that will gestate the male fetus can prevent persistent infection of the resulting bull, vaccination of the bull cannot prevent persistent infection as this enduring infection of all tissues is initiated before approximately 125 days of gestation.\textsuperscript{22,23}

Immunization can prevent contamination of semen due to an uncontrolled acute infection initiated shortly before natural breeding or semen collection.\textsuperscript{24,25} Acutely infected bulls can shed BVDV in semen from two to 20 days after initiation of an acute infection.\textsuperscript{26} Two studies demonstrate that vaccination of bulls with a single dose of vaccine (Bovi-shield Gold, Pfizer Animal Health, Kalamazoo, MI or Express FP, Boehringer Ingelheim) containing cytopathic, modified-live strains of BVDV can prevent contamination of semen due to acute infections.\textsuperscript{24,25}

Acute infection of peri-pubertal and post-pubertal bulls with noncytopathic strains of BVDV can result in prolonged testicular infections.\textsuperscript{27} Research demonstrates that prolonged testicular infections can result in detection of viral RNA in semen for 2.75 years with infectious virus replicating in testicular tissue for 12.5 months after initiation of acute infections.\textsuperscript{27} While infectious virus can be detected in testicular tissue and viral RNA can be detected in semen for extremely long periods of time, the potential for viral transmission due to prolonged testicular infections appears to be limited.\textsuperscript{27} Two studies demonstrate that vaccination of bulls with a single dose of vaccine (Bovi-shield Gold, Pfizer Animal Health or Express\textsuperscript{®} FP, Boehringer Ingelheim) containing cytopathic, modified-live strains of BVDV can prevent prolonged testicular infections.\textsuperscript{24,25}

The characteristics of exposure to a noncytopathic field strain of BVDV that result in persistent testicular infections remain to be fully understood. Until our understanding advances, the potential for prevention of persistent testicular infections via vaccination is unknown. The initiating exposure for persistent testicular infections precedes seven months of age and results in seropositive bulls.\textsuperscript{28,29}
Persistent testicular infections result in contamination of semen with infectious BVDV for at least 11 months.\textsuperscript{28,29} The infectious virus excreted in contaminated semen readily transmits infection to artificially inseminated seronegative heifers or cows.\textsuperscript{30} Some caution is necessary to avoid undesirable consequences of vaccinating bulls for BVDV. Appropriately timed immunization of naïve bulls with a vaccine containing cytopathic, modified-live strains of BVDV is to be recommended. The initial dose of vaccine should be administered at least 28 days before introduction to the breeding herd to allow time for complete development of protective immunity and prevent the contamination of semen with BVDV due to the short-term, transient shed of modified-live BVDV in semen which occurs for up to 10 days after vaccination.\textsuperscript{24} Naïve bulls should not be administered the currently available modified-live vaccine containing noncytopathic BVDV as this vaccine has been demonstrated to cause prolonged testicular infections under field conditions.\textsuperscript{31}

**Bluetongue virus**

Infections with bluetongue virus may sometimes cause fever, facial edema, hemorrhages and ulceration of the mucous membranes and transmission via semen.\textsuperscript{8,32} Immunity to bluetongue is serotype-specific. While a recent European outbreak of bluetongue virus serotype 8 was rapidly controlled through voluntary and mandatory use of inactivated vaccines, vaccination in the United States should be avoided as immunization will result in a seropositive status for many years that will impede trans-boundary trade of semen.\textsuperscript{33} Modified-live vaccines developed for sheep should not be used in cattle because of the risk of transmitting vaccine strains via insect vectors.

**Bovine herpes virus-1**

Bovine herpes virus-1 causes economically significant respiratory and reproductive loss in cattle and can be transmitted via semen. Vaccination is commonly avoided in bulls to be admitted to bull studs as the resulting seropositive status may impede trans-boundary trade of semen. Vaccination of bulls to be used for natural breeding in the United States is considered prudent in many herds. Vaccines should be administered at least 28 days prior to introduction into the breeding herd.

**Bovine herpes virus-5**

Bovine herpes virus-5 (previously BHV-1.3) has been detected in semen of infected bulls using PCR and virus isolation techniques.\textsuperscript{36,37} Although genomic and pathogenic differences between BHV-1 and BHV-5 are quite consistent, the two related viruses display extensive serological cross-reactivity which can be evidenced in serum neutralization tests.\textsuperscript{38} Therefore, immunization measures to prevent contamination of semen with BHV-5 are the same as measures for BHV-1.

**Conclusions**

The implementation of appropriate immunization programs for reproductive pathogens can aid in the prevention of disease transmission. Bulls to be used for natural breeding in the United States should be prudently vaccinated for some reproductive pathogens. A combination of appropriate biosecurity measures and limited use of vaccines constitutes the basis for disease control programs for bulls entering or maintained in bull studs.

**References**