The *Haemophilus somnus* disease complex (Hemophilosis): A review

Frederick W. Harris, Eugene D. Janzen

Abstract

***Haemophilus somnus* has long been associated with thrombotic meningoencephalomyelitis but has also been identified as the agent responsible for other clinical diseases including respiratory disease, reproductive problems, myocarditis, otitis, conjunctivitis, mastitis, and polyarthritis. Exposure to the bacteria is widespread and infection may occur via the respiratory tract from urogenital excretions and secretions.**

Diagnosis and treatment of hemophilosis may be easy or difficult depending on the manifestation presented, and special procedures must be taken to facilitate isolation of the organism. Satisfactory control measures are not available; vaccination is the only preventive measure demonstrating a beneficial effect.

Résumé

Une revue du complexe de la maladie à *Haemophilus somnus* (Hemophilose)

En plus d'être associé à la méningoencephalomyélite thrombosante, *Haemophilus somnus* a aussi été relié à d'autres entités cliniques incluant des maladies respiratoires, des problèmes de reproduction, des myocardites, des otites, des conjonctivites, des mammites et des polyarthrites. L'exposition à la bactérie est étendue et l'infection se propage par les voies respiratoires en provenance des excrétions et sécrétions urogénitales.

Selon la présentation clinique, le diagnostique et le traitement de l'hémophilose peuvent être plus ou moins faciles à établir. Certaines dispositions spéciales doivent être prises pour faciliter l'isolement de l'agent. Des mesures de contrôle satisfaisantes ne sont pas disponibles; la vaccination demeure la seule méthode efficace de prévention.

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Ecology

The "*Haemophilus somnus* disease complex" or hemophilosis is caused by the bacterium *Haemophilus somnus*. *Haemophilus somnus* was first recognized and identified in 1956 (1), as a cause of encephalitis, and has since been associated with other clinical problems in cattle. Numerous reviews describing the role of *H. somnus* in bovine disease are available (2-9).

Historically, the major *H. somnus* problem was considered to be the nervous system form variously called thrombotic meningoencephalomyelitis (TME); thromboembolic meningoencephalomyelitis (TEME); infectious thromboembolic meningoencephalomyelitis (ITEME); thrombo; or sleeper syndrome (1,10,11). However, fewer cases of TME are being encountered or reported each year. Instead, other disease conditions are becoming more prevalent and new manifestations are being identified. Because there are many different syndromes, they have been referred to as the "*Haemophilus somnus* disease complex" or "hemophilosis" (12).

Haemophilus somnus is a gram-negative pleomorphic bacterium that is not capable of prolonged survival outside the body. Experimentally it has been shown to remain viable at 23.5°C in nasal mucus or blood for at least 70 days and in vaginal mucus for up to five days (13). It does not survive in the environment for more than two hours in urine, but this route of transmission as an aerosol or aspirate may be important (13). *Haemophilus somnus* can also survive for extended periods of time in biological secretions at −70°C (13), which could allow it to overwinter.

Exposure is widespread and up to 25% of the cattle population may have serum antibodies to *H. somnus* (14,15). On some premises this can increase to as high as 50–100% (14,16). The reproductive tract should be considered the most likely reservoir of *H. somnus* (17). Females and males harbor *H. somnus* within their reproductive or urinary tracts (12,17-20) and can shed the organism in urine or discharges to contaminate the environment. Penmates could become infected by inhaling aerosolized particles containing the bacteria. It is also thought that routes of infection other than the respiratory tract, such as via Batson's veins (5,21), which course directly along the spinal column to the brain from the reproductive tract, are possible.

In vitro studies have established that bovine neutrophils are unable to kill *H. somnus*, and that *H. somnus* can replicate within bovine monocytes (22). Additional studies demonstrated that bovine alveolar macrophages and blood monocytes ingest but do not kill opsonized *H. somnus*. These findings suggest that the bacterium can persist and proliferate within these cells and contribute to the pathogenesis of hemophilosis (22).

Once *H. somnus* has localized, it causes endothelial cells of small blood vessels to separate and thus expose the underlying basement membrane. This activates the coagulation mechanism and results in the formation of a thrombus (23); hence the name "thrombo" that is sometimes given to the disease. The name TEME was likely truncated to thrombotic meningoencephalomyelitis (TME) after a previous review noted no evidence of embolic events in the pathogenesis of the disease (4). It is now considered that the lesion is an in situ thrombus and not a thromboembolism. Interruption of the blood supply results in destruction of tissues and development of clinical signs. Research has

Boehringer Ingelheim (Canada) Ltd., 977 Century Drive, Burlington, Ontario L7L 5J8 (Harris) and Department of Herd Medicine and Theriogenology, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0 (Janzen).

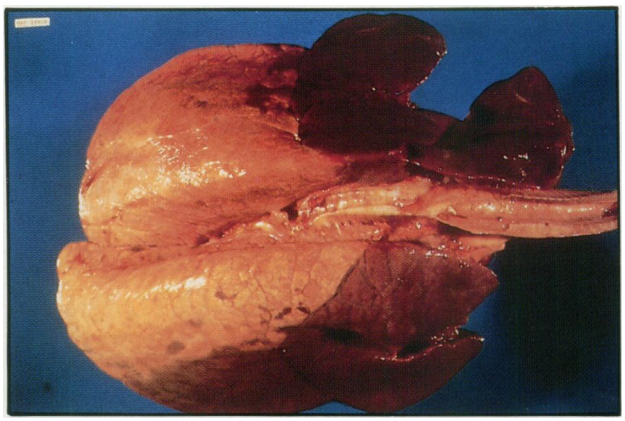

Figure 1. Clinical case of severe cranioventral pneumonia caused by *H. somnus*. (S. Groom — Alta Agr)

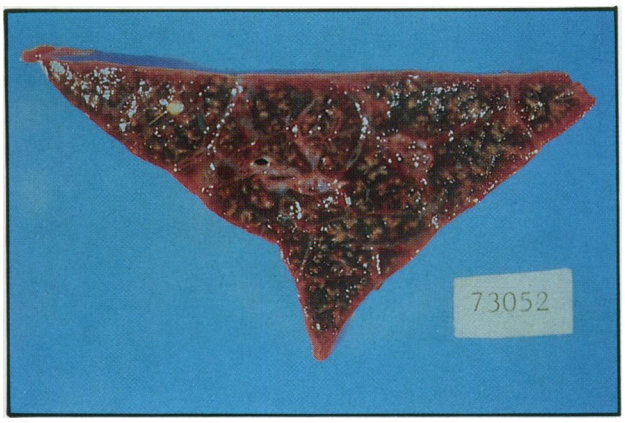

Figure 2. Suppurative pneumonia caused by *H. somnus*. (S. Groom — Alta Agr)

shown that intravenous challenge with as few as 40 colony-forming units of a virulent strain of *H. somnus* can produce septicemia in a susceptible calf (24). In this study, vaccinated calves were completely protected against intravenous challenge and 88% of 24 calves vaccinated with two doses of a *H. somnus* bacterin were completely protected against intracisternal challenge with the same virulent organism (24).

Although there is no major cultural, biochemical, electrophoretic or serological variation among isolates (18,19,25,26), there appear to be differences in virulence (17,27,28) and biotypes may exist within the species *H. somnus* (17-19). Laboratory challenge of calves by intracisternal inoculations with preputial and seminal isolates caused only mild, nonfatal, clinical meningitis, while the same challenge by an encephalitic isolate produced a fulminating, rapidly fatal, fibrinopurulent meningitis (17). Recent studies have identified an envelope surrounding bacteria in isolates from confirmed TME cases. This envelope, which is lost on subculture of the organism may have an influence on virulence (29,30-32).

To summarize, *H. somnus* resides in the reproductive tract of healthy animals and from this site the environment is contaminated. Exposed animals may inhale the bacteria and, under the proper circumstances, septicemia may develop and lead to localization in various tissues and development of disease.

Clinical manifestations

a) Reproductive or urogenital form

The reproductive tract is considered to be the ecological niche or reservoir of *H. somnus* (6,17). In bulls as well as steers, *H. somnus* is commonly isolated from the prepuce, although it can also be recovered from the bladder, accessory sex glands and ampullae (17,19,33). Except for infrequent reports of infertility (18,20,35) and poor semen quality (18,20), the organism does not seem to cause disease in these sites (12,17,19). However, it can contaminate semen and may be transmitted in untreated semen and, without proper control, this could be a mechanism of spread (12,17).

In female cattle, *H. somnus* can cause vaginitis, endometritis (36,37), infertility, and abortion. Abortions have been confirmed and produced experimentally at all stages of gestation (33-35,38-40). Calves from infected cows have been born weak or stunted and can die shortly after birth (41-43). *Haemophilus somnus* has frequently been isolated from the uterus, and in slaughterhouse studies *H. somnus* has been isolated from cases of endometritis (5). Some consider that genital infection can result in infertility, prolonged open intervals, and repeat breeding (2,5,34,44-49), but more research is required to confirm these theories.

Most female carriers of *H. somnus* will harbor the organism in the vagina and may or may not have vaginitis and cervicitis. When vaginitis and/or cervicitis are present, there may be a purulent vulvar discharge associated with infertility and repeat breeding. The most reliable location in the vagina for culturing the bacteria is the clitoral fossa, which frequently is the only site from which the organism can be isolated (RB Miller — personal communication).

b) Respiratory form

The respiratory form of *H. somnus* infection has been gaining in importance. The respiratory tract has been the reputed site of entry, producing the septicemic form, and *H. somnus* is now also known to cause disease in both the upper and lower respiratory tract.

In the upper respiratory tract, *H. somnus* can cause laryngitis as well as tracheitis (50). It is often the only bacterium isolated from the lesion, but there may also be secondary opportunists such as *Pasteurella*, *Actinomyces*, *Fusobacterium*, and *Clostridium* spp. present (50,51).

Many clinical descriptions of the disease report that lower respiratory tract disease often precedes outbreaks of TME (7,50,52-54). In case control studies, *H. somnus* has been found in pure culture in as many as 28% of the cases of pneumonic lungs examined microbiologically (55).

Haemophilus somnus alone is capable of causing a suppurative bronchopneumonia (55-58) (Figures 1 and 2) or may be a part of the classical "shipping fever complex" (53,55,56,59-61). Research studies have established that weaned calves inoculated intrabronchially with *H. somnus*, developed more severe clinical disease and pneumonic lesions, when previously infected with bovine respiratory syncytial virus (BRSV) (62) or infectious bovine rhinotracheitis virus (IBRV)

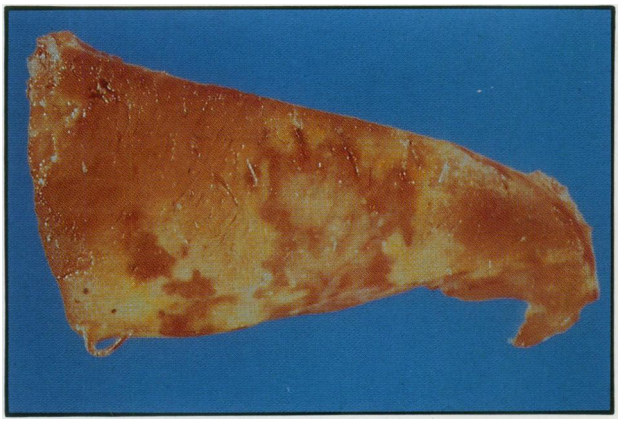

Figure 3. Focal myocardial hemophilosis. (S. Groom — Alta Agr)

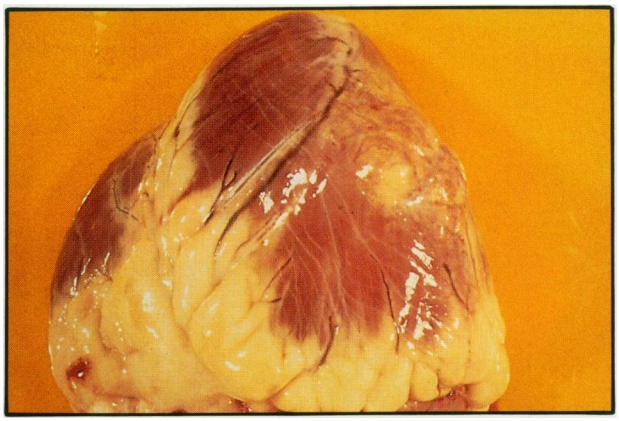

Figure 4. Left ventricular myocardial abscess caused by *H. somnus*. (T. Guichon)

(63). In some cases of pneumonic pasteurellosis, *H. somnus* may have been the primary pathogen but was not so identified because the more rapidly growing *Pasteurella* organisms or antimicrobial therapy masked the slower growing and more vulnerable *H. somnus*. *Haemophilus somnus* can cause severe fibrinous pleuritis (52-54,59), which may also rarely be found in conjunction with fibrinous pneumonia.

c) Septicemic form

Haemophilus somnus can gain entry to the circulatory system and then be distributed to various areas and organs of the body. *Haemophilus somnus* is known to localize in the brain, heart, skeletal muscle, joints, larynx, liver, and kidneys (10,11,52,54). Localization can, and usually does, occur simultaneously in one or more sites. The clinical signs vary depending on the affected area and resistance of the animal.

The nervous form is thrombotic meningoencephalomyelitis (TME). Affected animals are usually calves between six and ten months of age which have arrived in the feedlot three or four weeks previously. In the very early stage they have a high fever (>40.0°C) and, often, profound depression. The most important clinical finding is depression, which can be so severe that apparent blindness cannot be differentiated from true blindness. Ophthalmic examination reveals scattered retinal hemorrhages with ill-defined borders. Other signs which may be evident include: lameness, stumbling or knuckling of the hindlimbs, coughing, stiffness, incoordination, and swollen joints. Affected animals may become recumbent after a short period of ataxia and die soon afterward. In fact, some animals may die so quickly that they are presented to the stockman or attending veterinarian as cases of sudden death without previously observed clinical signs (52,54).

In the past few years however, septicemia with subsequent localization in sites such as the heart and joints have been reported with an apparent increasing frequency by practitioners (64). The result is that less TME and more myocarditis, arthritis, myelitis are apparently observed. The reasons for this are not completely understood but, may be due to two reasons. The early diagnosis and treatment of cases, and an increased implementation of vaccination programs and mass medication, may alter the expression of virulence of *H. somnus*. Therefore, rather than "sudden death", subacute lesions may develop. Secondly, the organism may have modified and adapted or strains of different virulence may have evolved through the process of natural selection. As the organism may have changed, the immune status of the host population may have varied as well. Because a large segment of the susceptible population is serologically positive to *H. somnus* (14,16), challenge from a virulent strain of *H. somnus* may result in a greatly modified expression of the disease.

One manifestation of the septicemic form that is observed more frequently is myocarditis. Traditionally, cardiac lesions in necropsy material were usually described as endocardial hemorrhages and pericarditis (1,10,11). Recently however, myocarditis lesions (Figure 3) which have yielded pure cultures of *H. somnus* have also been found (64,65). Affected animals may be yearlings rather than weaned calves and they often die suddenly. Some may have been chronically sick but others have appeared perfectly healthy. The lesion is usually located in the left ventricular free wall (Figure 4) and, may be quite large; small abscesses may only be evident when the ventricular wall is repeatedly sectioned (Figure 5). The cause of death is acute heart failure, and in addition to myocarditis there may be evidence of pulmonary congestion and edema (65) from left heart failure. These pulmonary findings can easily be mistaken for interstitial pneumonia (Figure 6), and unless the heart is properly examined the correct diagnosis may be missed. This manifestation is restricted not only to feedlot animals; affected cattle of varying ages and on pasture have also been described.

d) Other forms

Otitis has been reported in some feedlot cattle in which a copious clear yellow fluid draining from the ears of febrile animals yielded pure cultures of *H. somnus* (66). The ears of affected animals often droop and can influence the clinical impression and mislead the diagnostician regarding the degree of depression.

Chronic and gangrenous mastitis have been produced experimentally in dairy cows (67) and have been

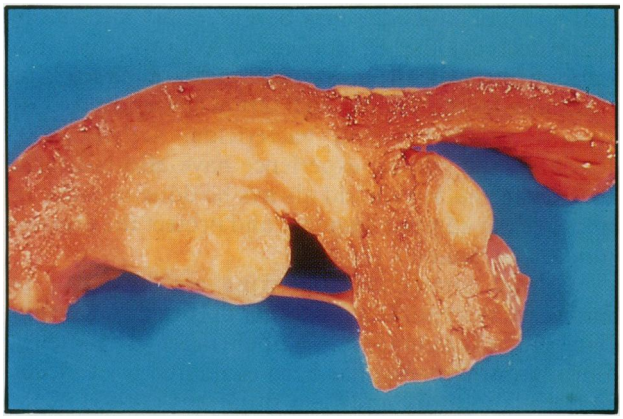

Figure 5. Section of myocardium with a clearly visible *H. somnus* abscess. (S. Groom - Alta Agr)

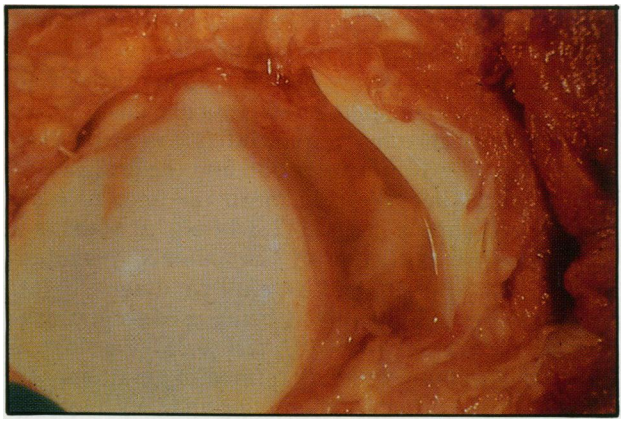

Figure 7. Fibrin in cloudy synovial fluid in the stifle joint of a steer affected with septicemic hemophilosis. (J. Orr — WCVM)

reported to occur in spontaneous clinical cases in both North America and Europe (68,69). Culture of the organism has usually been restricted to one quarter. Milk production was almost nonexistent and the secretion varied from blood-tinged and watery with small fibrin clots (69) to white, homogeneous (without clots and the consistency of yogurt) and without evidence of blood (68).

Pure cultures of *H. somnus* have been obtained from cases of conjunctivitis in herds with no previous history of either respiratory disease or TME (66,70). Clinically, conjunctivitis due to *H. somnus* resembles the conjunctivitis found in cases of infectious bovine rhinotracheitis (IBR) and the two diseases cannot be differentiated without the benefit of other clinical findings or diagnostic tests.

Following an outbreak of TME, lameness has been reported in animals not affected with the encephalitic form (18,52). Polyarthritis characterized by firm swellings of joints has been observed two days to several weeks following the TME outbreak. Multiple joints are usually involved and affected animals may exhibit lameness, stiffness, and knuckling at the fetlocks. At necropsy, affected areas demonstrate evidence of chronic arthritis characterized by excessive joint fluid and fibrinous clots (52) (Figure 7). In addition there may be congestion, edema, and petechial hemorrhages of the synovial membranes (52).

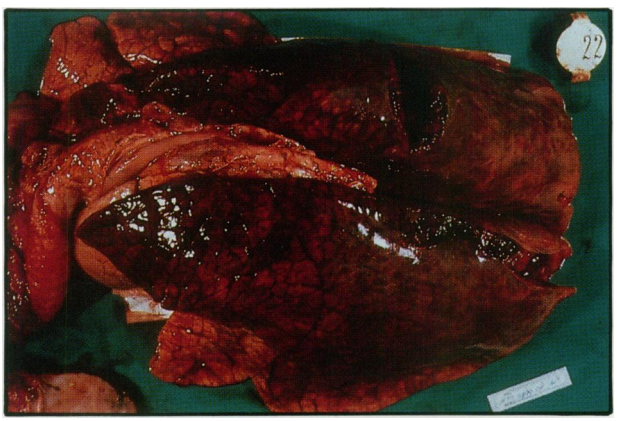

Figure 6. Pulmonary congestion and edema caused by *H. somnus* myocarditis. (S. Groom — Alta Agr)

Diagnosis

The diagnosis of the "*Haemophilus somnus* disease complex" may be easy, difficult, or impossible depending on the manifestation presented. For example, a calf dead of encephalitic hemophilosis may have secondary signs of bloat. In these cases, it is easy for even the experienced practitioner or pathologist to miss the diagnosis unless the brain, heart and lungs are examined histologically and microbiologically.

In the case of TME, small areas of hemorrhagic necrosis in the brain either grossly or histologically are diagnostic (1,8,10,11,52-54). Similarly, the ability to obtain pure cultures of *H. somnus* from the heart, joints, lungs, ears, conjunctival sacs and other affected areas is strongly indicative of hemophilosis. A blood culture may sometimes reveal *H. somnus* septicemia when TME is suspected in febrile calves that have not been treated with antibiotics (53). Additionally, some research microbiology laboratories have had considerable success culturing the organism from the urine of necropsy specimens (6,71). In some field cases this can be difficult unless samples are handled in the proper manner. *Haemophilus* spp. will not survive for a prolonged period in commonly used transport media, so swabs for bacterial culture should be fresh, moist and rapidly transported to the laboratory under refrigeration (72) or at room temperature. In addition, the laboratory should be advised to culture specifically for *H. somnus* to ensure use of the proper growth media and cultural conditions.

Pneumonia due to *H. somnus* remains a laboratory and necropsy diagnosis. When pneumonic lungs are sampled, a swab or tissue sample should be taken from the interface of healthy and diseased tissue where the living bacteria are most likely to be found (59). In addition, tissues from this same area should be taken, refrigerated but not frozen, and submitted to the laboratory. Standard formalinized samples should also be included. It is very important, but often impossible, to obtain all samples for culture from animals that have not been treated with antimicrobials, as treatment may destroy the bacteria and render their culture impossible (53); as well, other bacteria may be isolated. This is particularly important in pneumonia in which *Pasteurella* may remain even though *H. somnus* may have been the primary pathogen. In cases involving

polyarthritis, care must be taken to include *Mycoplasma bovis* (73) in the differential diagnosis.

Serological tests are available but do not provide all of the information required to make a diagnosis. Many animals experience inapparent infections or develop a carrier state, so seroconversion and the presence of a serological titer does not mean the animals have experienced clinical disease (2,8,14-16). If there is a significant rise in the titer of sick animals, this information will help support a definitive diagnosis (6). Currently there are two tests being used: a microagglutination test and an ELISA test (8,33). Serological tests are continuously being refined in an attempt to increase their accuracy and meaning and they may play a greater role in the future.

Treatment

Haemophilus somnus is very sensitive to most antimicrobials used at therapeutic levels. Oxytetracycline is used most commonly, but penicillin, erythromycin, and the sulfonamide drugs are also effective when assessed *in vitro* (25,61,74). Respiratory and reproductive diseases are therefore considered responsive to treatment, unless there are complicating agents such as *Pasteurella* spp., *Mycoplasma* spp., *Ureaplasma* spp., and viruses.

Response to treatment of the septicemic form is highly variable depending on the duration of the disease and the sites of localization. In the case of TME, antimicrobial treatment will be effective if it is begun before any signs of brain involvement occurs (10,54). Once CNS signs have developed, treatment is rarely successful and the animal usually dies or remains recumbent (52,54,75). In the case of joint involvement, antimicrobial treatment will be helpful but recovery is not usually complete. Myocarditis may not benefit from antimicrobial treatment (64). A diagnosis of myocarditis would rarely be made clinically, consequently, antimicrobial therapy would not usually be initiated. Cattle with otitis and conjunctivitis respond very well to treatment (66,70). Experience with treatment of mastitis is limited but indicates that affected mammary glands are not likely to return to normal (67-69).

Control and prevention

Satisfactory control measures are not available. When an outbreak is encountered, increased surveillance and immediate treatment with antibiotics has been the standard recommendation but has seldom been completely successful because the disease can progress so rapidly (76). In major outbreaks, mass medication with antibiotics in the feed or giving every animal in the pen an injection of a single sustained-action antimicrobial is often implemented, with variable success. In the long-term however this approach may not be useful in preventing hemophilosis because the carrier state may continue to exist in the reproductive and urinary tracts of some animals, and may allow for reinfection once the effectiveness of the antimicrobial has ceased.

The only preventive measure available is immunization prior to infection. Laboratory research suggests that humoral antibodies may be a necessary mechanism to protect against *H. somnus* infections, and that immunization with a bacterin does enhance this resistance by stimulating high serum concentrations of specific antibodies and bactericidal activity (77). Research and clinical experience have also indicated that revaccination should always be done in order to improve the immune response and protect the greatest number of animals (78-80).

Various commercial bacterins are available to immunize susceptible animals but only one *H. somnus* bacterin (Somnugen — Boehringer Ingelheim, Burlington, Ontario) has been evaluated for efficacy in both laboratory and field situations (78-83). Controlled laboratory studies have established that two doses of the bacterin were able to reduce morbidity and mortality when calves were challenged with a virulent strain of *H. somnus* by the intravenous, intracisternal, and respiratory routes (24,78,80). Thus, this bacterin has demonstrated effectiveness against laboratory challenge for TME as well as the pneumonic form of hemophilosis. Separate uncontrolled and controlled field studies carried out in feedlots have demonstrated that vaccination with two doses of the bacterin can reduce morbidity and overall mortality in addition to being cost effective (78,80-86).

Conclusion

Hemophilosis is a complex disease that has not been completely described or understood. While ongoing investigations into the various diseases produced by infection with *H. somnus* have provided many answers, some gaps in our understanding about the virulence of the organism, pathogenesis of hemophilosis, and manifestations of the disease remain. With continued commitment, additional research effort should provide more complete information allowing for better control and prevention in the future.

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