Review - The role of *Histophilus somni* in the bovine respiratory disease complex

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SUMMARY

Histophilus somni, besides being firstly isolated as the cause of thromboembolic meningoencephalitis, is nowadays regarded worldwide as one of the primary bacterial causes of bovine respiratory disease (BRD), as well as of some reproductive and cardiovascular diseases in both beef and dairy cows, leading to health impairment, economic losses, and higher need of antimicrobial treatments. Even if *H. somni* is usually found as a commensal bacterium in the respiratory and reproductive tracts of cattle, some external conditions, such as stress related immunosuppression and previous action of other pathogens, can induce *H. somni* to become pathogenic.

Even if there still is a lack in the knowledge about the precise mechanisms of its pathogenicity, several virulence factors have been identified that can explain its pathogenicity. The high variability in the genetic aspect of the antigens exposed on the bacterial surface, their ability to undergone to phase variation and to bind the antibodies, as well as its ability to form a biofilm, to acquire iron as a nutrient and to bind some of the host's immunoglobulins (IgGs) through the expression of outer membrane proteins (OMPs) are some of the main virulence factors that can both trigger its pathogenicity and reduce the effectiveness of the immune defences and of some treatment options. Indeed, the treatment of symptomatic diseases caused by *H. somni* is difficult, due to both the high variability in the antigens expressed as well as due to the difficulty in intervening promptly at the onset of the first symptoms and in identifying affected animals early in the course of disease.

In any case, the efficacy of the treatment with antimicrobial is scant and vague, even if it has a good susceptibility toward many antimicrobials *in vitro.* The use of prevention strategies such as specific vaccinations against *H. somni,* and against the main pathogens related to BRD, such as *M. haemolytica* or Bovine Respiratory Syncytial Virus, common cofactors for *H. somni*, may be beneficial as an approach to control *H. somni* outbreaks. Indeed, even if the mechanisms of protective immunity against *H. somni* are still not so well understood, antibodies are likely to be an important part of the protection system, and vaccination is thus used as the primary way to counteract *H. somni*.

However, the high genetic variability of the antigens, as well as their ability to undergo to phase variation, and the intrinsic differences between specific respiratory or urogenital strains, can reduce the efficacy of the vaccines. Some improvements in the efficacy of vaccines can be done by using innovative technologies such as reverse vaccinology, to be able to find a higher number of target genes that encode for more surface proteins, that are more likely to be potential antigenic vaccine candidates.

The aim of the present work was to give an overview of the main clinical syndromes associated with *H. somni*, as well as on the current knowledges about epidemiology, transmissions ways, virulence determinants, host-immune response and treatment and prevention strategies.

KEY WORDS

Histophilus somni, bovine respiratory disease, virulence factors, pathogenicity, thromboembolic meningoencephalitis, pneumonia.

INTRODUCTION

Respiratory and reproductive diseases are the most common and severe diseases, respectively in beef and dairy cows, that can cause significant economic losses and welfare impairments, due to a reduction in the productivity as well as an increase in morbidity and in the need of antimicrobial treatments to counteract and resolve it [1-3]. Also, the incidence and severity of diseases during the preweaning and weaning period in both beef and dairy calves can significantly alter the survival rate and their future productivity, impacting the overall farm efficiency and profitability.

Considering the relevant economical losses, the welfare impairment as well as the need to counteract the problem of antimicrobial resistance, the incidence of bovine respiratory disease (BRD) and of reproductive diseases must be contained, with alternative strategies that allows to use less antibiotics [4]. Knowing the causes and predisposing factors of both BRD and reproductive diseases is the basis to understand how both to contain them and which are the main focal points to consider.

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The BRD, common in beef cattle and also in pre-weaned and weaned dairy calves, has a multifactorial etiology, including predisposing factors related to the host, such as sex, weight and age, and the management, such as transport, temperature and nutritional management, and causative infectious agents [57].Relatively to the infectious agents of BRD, they are both viral and bacterial, such as *bovine herpesvirus type 1, bovine adenovirus, bovine viral diarrhoea virus, bovine coronavirus, bovine respiratory syncytial virus, bovine parainfluenza virus, Pasteurella multocida, Mannheimia haemolytica, Mycoplasma bovis* and *Histophilus somni* (*H. somni*) [8]. It is common to detect more than one causative agents during an outbreak, suggesting BRD is often polymicrobial [9-10]. Microorganisms such as *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma spp.* are consistently regarded as the primary bacterial causes of BRD [11].

The most common reproductive diseases in dairy cows have a multifactorial etiology, with age, number of lactation, feeding strategy in the dry period and also incidence of dystocia at calving as the host and management related factor, while several infectious agents like bacterial (*Brucella abortus, Campylobacter fetus, Salmonella spp etc*), viral (*bovine herpesvirus type 1, bovine adenovirus, bovine viral diarrhoea virus*), and other agents (protozoon, chlamydial and fungal) are known to have direct impact on reproductive health of dairy cows [12]. Also, *H. somni* was correlated with the incidence of reproductive diseases such as suppurative vaginitis, cervicitis, and endometritis, often acting as door opener for other pathogens [13]. *H. somni*, in the absence of stress factors that compromise immunity, leads a relatively non-invasive existence as a commensal of the mucosal surfaces of respiratory and reproductive tracts of beef and dairy cattle [14].

H. somni was initially identified in 1960 as the cause of thrombotic meningoencephalitis-myelitis (TME) in cattle but it has been recognized as the cause of numerous other pathological manifestations including pleuropneumonia, myocarditis, otitis, conjunctivitis, but also reproductive disorders such as vaginitis, endometritis, orchitis, mastitis, infertility, and abortion [14-18].

The predominant pathological manifestations of *H. somni* are those affecting the respiratory system, which pertain to the BRD complex in beef and dairy cattle, even if it is also correlated with reproductive diseases [14]. Furthermore, a more severe form of disease, known as the "septicaemic form" was detected in preweaned and weaned calves, when the infection is spread from the lungs to other organs, like heart and brains, causing sudden death [19]. Moreover, the respiratory symptoms caused by *H. somni* are similar to those caused by other pathogens, but *H. somni* is harder to treat and control.

The aim of the present work was to give an overview of the main clinical syndromes associated with *H. somni*, with a specific attention on pneumonia and its etiopathogenesis and anatomopathological findings, as well as on the current knowledges about epidemiology, transmissions ways, virulence determinants, and host-immune response. Considerations related to the main preventive and treatment strategies are also presented.

LITERATURE REVIEW

The literature search was performed using the following databases: PubMed, ScienceDirect, Web of Science, CAB Abstracts Archive, and Google Scholar (consulted till May 2022). For the search, the keyword terms used included: *Histophilus somni (H. somni)*, *Haemophilus somnus (H.somnus)*, bovine respiratory disease (BRD), beef cattle, virulence factors, pathogenicity, thrombotic meningoencephalitis-myelitis (TME), pneumonia, preventive strategies, vaccine, lipo-oligosaccharides (LOS), phase variation, immunoglobulin binding proteins, histamine, biofilm, pathogenic and commensal, in different combinations.

EPIDEMIOLOGY, PREDISPOSING FACTORS, AND TRANSMISSION ROUTE

H. somni can be considered as a global problem for dairy and beef cattle farming, as it has been reported in many countries worldwide. Indeed, there have been records of histophilosis in the U.S.A. [20], Western Europe [17], Brazil [21], Argentina [22], Australia [23], Bulgaria [24], Czech Republic [25], Egypt [26], Japan [27], New Zealand [28], and South Africa [29].

H. somni related diseases affect preferentially young animals, from one week of age to 10 months, although the greatest number of cases are found from 4 to 10 months of age [17].

H. somni manifests its pathogenicity especially in newly arrived intensively reared beef cattle, but affects also, albeit less frequently, dairy calves, grazing heifers, dairy cattle [17]. Indeed, in intensive beef cattle farming, commingling, transport, handling, vaccination, overcrowding, changing in the diet as well as factor related to the climate, such as extreme temperature and humidity or abrupt changes in it, can act as a predisposing factor for the spread of *H. somni*, as well as for other pathogen involved in the BRD complex, due to a stress-related immunosuppression [4,14]. Indeed, most clinical cases occur between October and January, due to abrupt changes in the temperature as well as to extremely low temperature [30,31].

Transmission of the infection occurs through secretions from the respiratory system, such as cough and, in some cases, nasal mucus, especially in intensively reared beef cattle. Cough is the more effective vehicle of infection, considering that the bacterium usually colonizes and exert his pathological effects in the lower respiratory airways [32,33]. Urine is also a source of infection, especially in young calves within the first month of age. Whole blood can be another source of infection [33]. Also, secretions of male and female reproductive systems can represent a route of transmission in dairy and cow-calf farming systems [17]. Carrier animals, that do not manifest signs of disease, are also possible vehicle of transmission [33].

VIRULENCE FACTORS

Even if there is still a lack in the knowledge about the precise mechanisms which lead to the triggering of pathological symptoms, several virulence factors/mechanisms have been identified in *H. somni* that can explain its ability to cause all the various pathologies to which it is related, as well as to escape the immune defences.

Adherence to endothelial cells

H. somni can colonizes the surface of the mucous membranes and attaches to bovine endothelial cells (BECs) [33]. Likely, non-

pilus adhesins are involved in the adherence of the organism to the cell surface [34]. A bacterial surface protein, p76, would play a role in adherence [35]. Also, the capacity to form biofilm is involved in the ability to adhere to the mucosal surface [36].

Lipo-oligosaccharides: production, phase variation, sialylation, and apoptosis of endothelial cells

As other Gram-negative bacteria, *H. somni* express a variety of structures on the outer leaflet of the outer membrane, such as lipopolysaccharide (LPS) that are known as bacterial endotoxins. Those LPS has also been termed lipo-oligosaccharides (LOS) [14]. The LOS of *H. somni* provides critical protection to the bacterium against host defences, may act as an adhesin, and is an endotoxin that cause inflammation [37]. LOS is also involved in the activation of the complement, resulting in an increased chemotaxis of inflammatory cells to the site of inflection [38]. Moreover, LOS have an endotoxic activity toward the bovine endothelial cells (BECs), through the effect of its lipid-A component and through the release of reactive oxygen intermediates (ROIs) [39,40]. Consequently, LOS induces apoptosis in the BECs cells [39]. LOS is also reported to be involved in the activation of platelets, another function that is correlated to the etiology of thrombosis and vasculitis [38]. Moreover, the activation of platelets by LOS also induces the production of proinflammatory molecules by the endothelial cells, such as cytokines, causing vascular inflammation and damages that can lead to TME [41].

Furthermore, LOS of *H. somni* can undergo several modifications that lead to an increased variability and continuous changing in the antigen expression by the bacterium, that allows it to escape the host immune defences.

Also, *H. somni* can incorporate neuraminic acid into its LOS. This process, known as sialylation, may block the binding of antibodies to certain epitopes and enhances the resistance to the bactericidal activity of serum [37,38].

Outer membrane proteins (OMPs): transferrin-binding and immunoglobulin-binding proteins

H. somni express a wide range of outer membrane proteins (OMPs) that are involved in the host-parasite relationship and in its pathological functionality.

Indeed, some OMPs, are considered as antigens and are consequently accessible to the host defences and involved in the immune responses [14,38]. Moreover, there is a strong variability in their molecular characteristics which can reduce the efficiency of the host immune responses against them, while increasing the ability of the organism to cause infection [34,42].

Other important OMPs are transferrin-binding proteins (Tbps) that bind the bovine transferrin. *H. somni* is thus able to acquire iron, an important nutrient used for bacterial growth, also making it unavailable to the host [33,34,38].

H. somni also express several immunoglobulin-binding OMPs (IgBPs). Those IgBPs recognize and bind the IgGs, consequently enabling them, allowing thus to evade the host immune defences, resulting in a higher serum resistance [38].

Histamine production

H. somni can synthesize and secrete histamine [38,43]. Besides being a proinflammatory molecule, histamine on the surface of *H. somni* could bind to histamine receptors located on the endothelial cells of the lungs, causing vasoconstriction, stimulation of vagal afferent nerves and mucus glands, and increased permeability of bronchial epithelium. Consequently, histamine production can aggravate the pneumonia mediated by *H. somni* [43]. Moreover, histamine enhances IgE production leading to bronchoconstriction [38,44].

Resistance to intracellular killing

Neutrophils phagocytize *H. somni*, but *H. somni* can inhibit their killing ability once engulfed [33]. This ability allows *H. somni* to survive inside the neutrophils, also escaping the other host defences. It would contribute to the invasion of other tissues and to the establishment of chronic and multisystemic infections [14,33].

Biofilm

Bacterial biofilms are aggregation of bacteria held together by self-produced polymer matrix mainly composed of polysaccharides, such as exopolysaccharide, secreted proteins, and extracellular DNAs. Those bacteria form a highly structured and organized community. The constitution of bacterial biofilms allows to colonize also different sites, where they cannot live as single bacterium. Moreover, biofilm enhance the resistance of the bacteria to both the host defences and to the antimicrobial treatment, acting as a complicating factor in many bacterial infection [36,45-47]. It was demonstrated that *H. somni* can form a biofilm both *in vitro,* and *in vivo* in his natural host [36,46] Moreover, the biofilm created by *H. somni* can be used also by other pathogens, such as *Pasteurella multocida*, to persist in the host and escape immune defences, especially during chronic BRD [10]. Moreover, large biofilm-like aggregates of *H. somni* were detected on the luminal surface of the cardiac microvascular endothelium in natural cases of *H. somni* myocarditis [30]. Also, in concomitance with those biofilm-like aggregates, the endothelial cells were damaged and degenerated [30].

CLINICAL DISEASES

The pathological picture attributable to *H. somni* is complex and includes neurological, respiratory, cardiac pathologies and symptoms affecting the reproductive system [14]. The original disease manifestation associated with *H. somni* was thrombotic meningoencephalitis-myelitis (TME). However, nowadays, there is a predominance of manifestations affecting the respiratory system and myocardium [17,31]. Sometimes, two or more symptomatology related to *H. somni* can occur contemporaneously [30].

Clinical diseases associated with *H. somni* occurred either in peracute, acute, subacute, and chronic forms. The neurological forms are usually peracute or acute while the respiratory and cardiac ones are usually subacute or chronical, even if those pathologies can lead to death [30,33].

Thrombotic meningoencephalitis-myelitis (TME)

Originally called thromboembolic meningoencephalitis, it is now recognized that endothelial damage and thrombosis, rather than embolism, is central to the pathogenesis of the disease [15,48]. In the ’80, TME affected on average 11% of feedlot cat-

tle in the U.S.A. with an average mortality of about 1.1% [49]. Nowadays, neurological disease, including TME, affect 1.1% of feedlot cattle in the U.S.A [30,50]. Cases of TME were also detected in Italy, with an average mortality of 3-4% in beef cattle and 5-6% of veal calves [17]. TME affect primarily fattening beef cattle, between 6 to 12 months and, to a lesser extent, dairy calves [30,51]. *H. somni*, in the case of TME, does not behave like a contagious disease even if, during an outbreak, different cases can occur in the herd [30].

Clinical signs and symptoms are typical of acute meningoencephalitis with lateral recumbency, depression, anorexia, excitement, irritability, fever, head tilt, nystagmus, strabismus, blindness, coma, convulsions, and sudden death [30,33,52]. One of the typical signs of TME is the presence of closed ore semi closed eyes, that gives rise to the common phrase of "sleeper syndrome" and to the denomination "*somni*" [30].

Classical lesions of TME, such as multifocal haemorrhages with necrosis and fibrinopurulent meningitis, can be found in the brain or in the spinal cord [30,53,54]. Moreover, in case of TME, the cerebrospinal fluid is cloudy and blood-tinged [30,55].

Pneumonia

The incidence of pulmonary disease associate to *H. somni* is gaining interest in the last years, becoming the most frequent and impactful form of histophilosis in beef cattle farming [30,33]. Indeed, *H. somni* is a component of the BRD complex. *H. somni* was identified as the third most important bacterial pathogen found in BRD in one Midwestern study (1994-2002), with *Mannheimia haemolytica* ranked first (46.3 % of isolations), followed by *Pasteurella multocida* (34.7 %), and *H. somni* (19.0 %) [56]. Moreover, Cirone et al., found out a 40% percentage of beef cattle that were positive to *H. somni* at the arrival in Italy and a 100% percentage of positivity four days after the arrival [8]. Often, the symptomatology is driven by more than one single pathogen, with commensal pathogens, such as *H. somni* acquiring virulence characteristics after the first action of others pathogen [57,58]. Up to 60 % of cattle with pneumonia in which *H. somni* is detected at necropsy were infected also by other respiratory pathogens [59]. Nevertheless, *H. somni* can also cause BRD alone [30].

Pulmonary forms are frequent in intensively reared beef cattle and especially in the most critical phases, where the stress-related immunosuppression is more frequent, peaking within the first 2 weeks after the arrival [5,30]. Moreover, pneumonia caused by *H. somni* can represent the first step of a complex of diseases, that due to septicaemia, can lead to the other pathologies related to histophilosis, such as myocarditis [53].

Clinical signs and symptoms are those typical of BRD: tachypnoea, fever, cough, nasal discharge, depression, and anorexia.

Anatomopathological lesions are more frequent in the case of acute pneumonia and can develop mainly in three principal forms: anteroventral fibrinosuppurative bronchopneumonia, fibrinosuppurative bronchopneumonia associated with pleuritis and interstitial pneumonia [30].

These lobular lesions are bilateral and affect cranial-ventral portions of the lungs. Affected parenchyma is consolidated and grey or red to grey, with intraluminal exudate in the small airways. Also, multiple small abscesses can be detected in the bronchioles. Mediastinal and tracheobronchial lymph nodes can be mildly edematous [30].

Conversely, interstitial pneumonia, that is caused mainly by septicaemia and endotoxemia, is characterized by intra-alveolar edema and haemorrhage, with heavy and red lungs due to edema [60].

Myocarditis

The incidence of the myocardial form is also increased in recent years, even if is considered rare and sporadic. Myocarditis caused by *H. somni* affect mainly intensively reared fattening beef cattle, occurring on average sixty days after the arrival and, often, as a follow up of a pulmonary symptomatology [61]. Breathing difficulties, intolerance to exertion, cyanosis of the tongue and fever are the most common symptoms, even if it is possible to have cases of sudden death without previously showing any symptoms [17,30].

The anatomical cardiac lesions associated with *H. somni* are myocardial infarction, myocarditis, and fibrinous pericarditis [17,30]. Usually, those lesions are located in the left ventricular myocardium and affect one or both of its papillary muscles [30]. Signs of acute forms include areas of 1-3 cm of purple haemorrhage, while subacute and chronic lesions are fibrotic and characterized by apoptosis and necrosis of the endothelium and of the cardiocytes [30].

Other

In addition, even with a lower incidence and spread, infection with *H. somni* can result in reproductive failure and abortion [62], infertility [63], arthritis [64] and mastitis [65] with varying degrees of frequency and severity [14,33].

Indeed *H. somni* can colonize the bovine reproductive tract, both in male and female causing vulvovaginitis, endometritis, cervicitis, and abortion [33, 62,66,67].

Moreover, even if the udder is not an important site of *H. somni* colonisation, Hazzlet et al. [65] observed that some cases of chronical and subclinical mastitis can be related to its infection.

PROTECTIVE IMMUNE RESPONSE

The mechanisms of protective immunity against *H. somni* are still not so well understood, but antibodies are likely to be an important part of the protection system, and vaccination is thus used as the primary way to counteract it [38].

Indeed, *H. somni* was once thought to be a facultative intracellular pathogen, that consequently require the reaction of macrophages but, besides being phagocyted by them, *H. somni* survive inside and destroys them within hours in vivo [32,38]. Therefore, it is more like an extracellular parasite than a facultative intracellular one.

Classically, antibodies are most important in protection against extracellular pathogens. Moreover, early *in vivo* studies demonstrated that convalescent serum, extracted from pneumonic cattle affected by *H. somni*, protects other animals against *H. somni*-induced acute pneumonia [32,38]. The protection was correlated with both high IgG1 and IgG2 antibody titers, but between the two types, IgG2 showed a trend toward better passive protection [32,38]. Moreover, IgG2 are also the most produced after vaccination [38, 68-69]. Therefore, it was proposed that IgG2 antibodies might have the major role in counteracting the infection and in reducing the spread of the pathogen in the organism. Corbeil et al. [70] also compared the protective ability of different IgG2 isotypes and showed that IgG2a are the most important and active against *H. somni*- induced pneu-

monia.
Conversely, in case of reproductive diseases and abortion caused by *H. somni,* IgM were the most frequently and abundantly detected, but they declined soon after the infection [38].
H. somni has been shown to persist for 6-10 weeks in the lungs of challenged calves, despite the presence of systemic as well as local *H. somni*-specific antibodies [32]. This indicates that humoral immune responses may not be adequate in clearing *H. somni* infections. However, these calves were shown to clear a second *H. somni* challenge within three days [32]. Therefore, it is possible that the induction of cell-mediated immune responses, in addition to IgG2- and IgA-mediated humoral immune responses, is important in developing a complete protection against *H. somni*. However, the current understanding of cell-mediated immune responses against *H. somni* is limited.
In summary, previous research indicates that challenged or vaccinated calves have moderate levels of resistance against subsequent *H. somni* infections, and that vaccination could be used to protect cattle against certain manifestations of disease due to *H. somni*.

PREVENTION AND TREATMENT

Antimicrobial treatment

The treatment of symptomatic diseases caused by *H. somni* is problematic, due to the difficulty in intervening promptly at the onset of the first symptoms and in identifying affected animals early in the course of disease because of its often rapidly fatal nature and of the similarity with the symptoms caused by other pathogens. Florfenicol (20 mg/kg, IM, repeated in 48 hours, or 40 mg/kg, SC, once) may be the antimicrobial of choice if histophilosis is the tentative diagnosis in an individual animal. In any case, metaphylactic mass medication can be an alternative management practice to reduce the spread of infection when recognized cases of *H. somni* are present at the farm level. In this way is possible to identify affected animals early in the course of disease. In any case the efficacy of the treatment is still scant and vague, even if it has a good susceptibility toward many antimicrobials *in vitro,* including florfenicol, tilmicosin, tulathromycin, tetracyclines, trimethoprim-sulfadoxine, fluoroquinolones, and ceftiofur [71]. But the results *in vivo* showed that the efficacy is low, variable, and scant. Indeed, long acting oxytetracycline did not reduce the risk of mortality due to *H. somni* [72-73]. According to Welsh et al. [56], *H. somni* has a variable susceptibility to spectinomycin and sulfachloropyridizine. However, it is highly susceptible also to other antibiotics of regular use, such as ampicillin and tetracycline [56, 74].

Vaccination

Since antibodies are the main protective and counteracting mechanism to cope with *H. somni*, vaccination is still the best way to protect cattle from the infection. Indeed, attempts have been made for decades to control *H. somni* infection by vaccination [75]. Various preparations of formalin-killed commercial bacterins for prophylaxis against *H. somni* diseases are available from major pharmaceutical companies. Commercial vaccines for *H. somni* include killed cells or outer membrane proteins that have helped prevent infectious thrombotic meningoencephalitis and pneumonia caused by *H. somni.*
However, there are many different possible type of *H. somni*, with also different origins in the body, namely the uterus or the nasal discharges, aspects that can lead to a high variability in the type of antigens exposed on the bacterial surface, and consequently to the possible inefficacy of some specific vaccines [76]. Moreover, another problem related to the role of antibodies in counteracting *H. somni* is his ability to undergo to phase variation of the LOS [76]. Therefore, it is plausible that an assortment of *H. somni* lipoprotein and LOS antigens are crucial inside the vaccine, to generate active immunity [76].
Nowadays, some improvement in the efficacy of vaccines can be done by using reverse vaccinology, as proposed by Madampage et al. [77], to be able to find a higher number of target genes that encode for more surface proteins, that are more likely to be potential antigenic vaccine candidates.
It is also likely that vaccination against other BRD pathogens such as *M. haemolytica* or bovine respiratory syncytial virus, common cofactors for *H. somni*, may be beneficial as an approach to control *H. somni* outbreaks in feedlot cattle [30]. Outside Europe there are several options for combined vaccines but in Europe there is only one inactivated vaccine available containing *H. somni* in combination with *Mannheimia haemolytica* leukotoxin.
In a field trial performed in feedlot calves, vaccination of calves on arrival with a vaccine containing *Mannheimia haemolytica* leukotoxin combined with bacterial extracts of *M. haemolytica* and *Histophilus somni*, significantly ($p < 0.05$) increased *M. haemolytica* and *H. somni* serum antibody titers and reduced bovine respiratory disease (BRD) morbidity [78]. Another field trial conducted in a crossbreed beef cow-calf herd the vaccination of beef cows once at 4 weeks prepartum significantly ($P < 0.05$) increased passive antibody titers to *M. haemolytica* and *H. somni* in their calves [79]. In addition, calves vaccinated at 1 and 2 months of age in the face of maternal antibodies to *M. haemolytica* and *H. somni* had significantly ($P < 0.05$) higher antibodies to *M. haemolytica* and *H. somni* at 4 and 6 months of age than did unvaccinated calves [76].

CONCLUSION

Histophilus somni is consistently regarded as one of the primary bacterial causes of BRD, and was also correlated with the incidence of reproductive, cardiological and neurological diseases, often acting as door opener for other pathogens. However, nowadays, there is a predominance of manifestations affecting the respiratory system and myocardium.
Even if there still is a lack in the knowledge about the precise mechanisms which lead to the triggering of pathological symptoms, several virulence factors/mechanisms have been identified in *H. somni* that can explain its ability to cause all the various pathologies to which it is related, as well as to escape the immune defences.
The treatment of symptomatic diseases caused by *H. somni* is difficult, due to the difficulty in intervening promptly at the onset of the first symptoms and in identifying affected animals early in the course of disease because of its often rapidly fatal nature. In any case the efficacy of the treatment is still scant and vague, even if it has a good susceptibility toward many antimicrobials *in vitro.*
Mechanisms of protective immunity against *H. somni* are still not so well understood, but antibodies are likely to be an im-

portant part of the protection system, and vaccination is thus used as the primary way to counteract *H. somni*. It is also likely that vaccination against other BRD pathogens such as *M. haemolytica* or bovine respiratory syncytial virus, common cofactors for *H. somni*, may be beneficial as an approach to control *H. somni* outbreaks.

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