BORDETELLA BRONCHISEPTICA AND RESPIRATORY DISEASE IN SWINE

Samantha J. Hau¹, Susan L. Brockmeier²
¹ National Animal Disease Center, ARS, USDA, Ames, IA
Corresponding Author (susan.brockmeier@usda.gov)
Bordetella bronchiseptica is an ubiquitous pathogen of swine causing respiratory infections including rhinitis, tracheitis, bronchitis, and pneumonia. It spreads quickly between animals, especially during commingling of naïve animals with subclinical carriers. B. bronchiseptica causes disease through the production of virulence factors, such as adhesins and toxins, which is coordinated by the BvgAS system. In addition to causing primary disease, B. bronchiseptica can exacerbate viral respiratory infections and predispose animals to other bacterial respiratory pathogens, which increases the clinical significance of B. bronchiseptica colonization. Disease is currently managed with antibiotic treatments and vaccination strategies; however, colonization is difficult to clear and animals can remain colonized and shed B. bronchiseptica long term, acting as a source of infection for naïve animals within a herd.
Bordetella bronchiseptica causes respiratory disease in swine that can impact both the upper and lower respiratory tracts. Disease has a rapid onset, with clinical signs developing 2-3 days post-exposure (11). B. bronchiseptica is associated with a high morbidity and low mortality, spreading rapidly within a group of animals but resulting in low death loss (12-14).

Swine diseases caused by B. bronchiseptica include: rhinitis, bronchitis, tracheitis, and pneumonia.

Bordetella bronchiseptica is the causal agent of Non Progressive Atrophic Rhinitis, and it causes tracheitis, bronchitis and pneumonia.

Bordetella bronchiseptica is a primary cause of rhinitis in pigs, which can present as mild rhinitis, nonprogressive atrophic rhinitis, when B. bronchiseptica is the sole etiologic agent, or progressive atrophic rhinitis, when B. bronchiseptica infects with toxigenic Pasteurella multocida. The interaction of B. bronchiseptica with the nasal mucosa leads to inflammation (rhinitis) and epithelial changes including squamous metaplasia, ciliostasis, or loss of ciliated cells (15, 16). Over time, disease progresses to atrophic rhinitis, in which the boney trabeculae of the turbinates is replaced with fibrous connective tissue through the action of the dermonecrotic toxin (DNT) produced by B. bronchiseptica (17-19). With B. bronchiseptica as the sole etiologic agent, the disease is nonprogressive, affecting predominantly the ventral scrolls and turbinates, which can take weeks to resolve (15, 20-24); however, when B. bronchiseptica interacts with toxigenic strains of P. multocida, disease is more severe (25-27). The P. multocida toxin (PMT) and DNT act synergistically to cause more severe atrophy of the turbinates, which can result in septal deviation (25, 28). Rhinitis presents with clinical signs of sneezing, nasal discharge, and ocular discharge. As atrophic rhinitis progresses, atrophy of the turbinates can be visualized at necropsy and during coinfection with P. multocida, can lead to brachygnathia, lateral deviation of the snout (Figure 1), and/or epistaxis (11).

Bordetella bronchiseptica is also capable of causing inflammation of the airways resulting in tracheitis and bronchitis. Similar to disease associated with the nasal mucosa, B. bronchiseptica interacts with the ciliated epithelial cells in the trachea and bronchi causing ciliostasis and epithelial changes (15, 16). This reduces the clearance by the mucociliary escalator causing accumulation of mucus in the airways, which may provide a niche for secondary bacteria and predispose the animal to pulmonary infection (11). Uncomplicated tracheitis and bronchitis present with a dry, non-productive cough that can be paroxysmal in nature (11).

Pulmonary infection with Bordetella bronchiseptica results in suppurative bronchopneumonia (29)(Figure 2). It can act as the primary etiologic agent in young pigs and in older pigs it generally contributes to the severity of the Porcine Respiratory Disease Complex (PRDC) through interaction with other bacteria and viruses in mixed infections (6, 29-33). The necrosis and tissue damage associated with B. bronchiseptica pneumonia is induced by the action of DNT, without which pneumonia does not develop (18, 19). Pneumonia caused by B. bronchiseptica results in red-to-plum areas of cranioventral consolidation in the lungs that are associated with hemorrhage, necrosis, and neutrophil infiltration (29). Over time, the lesions undergo fibrosis and become grey-to-tan in color and more firm (29). The most prevalent clinical sign of B. bronchiseptica pneumonia is coughing and it can be difficult to discern the cause without further diagnostics.

Figure 1. Fattening pig with lateral deviation of the snout. Source: HIPRA.
Bordetella bronchiseptica is a predisposing factor for other diseases. 

Bordetella bronchiseptica is also capable of increasing the severity of respiratory disease caused by viral pathogens and predisposing pigs to secondary infection with other bacterial pathogens. The impact of B. bronchiseptica on respiratory disease associated with PRDC has been investigated using coinfection models with several viral agents (12, 32, 34, 35). Disease associated with Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), influenza A virus (IAV), and Porcine Respiratory Corona Virus (PRCV) is exacerbated by coinfection with B. bronchiseptica (32, 34-37). B. bronchiseptica was found to increase lesion severity and prolong disease resolution when contributing to a viral respiratory infection, which may be associated with elevated and sustained cytokine response during coinfection of viral agents and B. bronchiseptica (12, 32, 34-37). B. bronchiseptica has also been shown to enhance colonization and disease with other bacterial agents (25, 27, 31). The association between B. bronchiseptica and P. multocida has been well studied as it relates to progressive atrophic rhinitis, where toxigenic P. multocida is better able to colonize and contribute to disease in animals with established B. bronchiseptica infection (25, 27). Additionally, P. multocida is less capable of causing pneumatic lesions as the sole agent or during PRRSV coinfection; however, when P. multocida is associated with PRRSV and B. bronchiseptica, more severe pneumonia develops (37). B. bronchiseptica also predisposes animals to disease with Streptococcus suis, promotes colonization with Haemophilus parasuis, and may contribute to the persistence of Actinobacillus pleuropneumoniae in the respiratory tract (31, 38-40). Coinfection of pigs with B. bronchiseptica and S. suis increases the prevalence of pneumonia as well as increasing the incidence of systemic infection with S. suis (38, 39). Coinfection of B. bronchiseptica and H. parasuis increases the burden of H. parasuis in the nasal cavity (31). Finally, biofilms produced by B. bronchiseptica may provide a niche for the survival of other pathogenic bacteria in the nasal passageways, as has been seen with A. pleuropneumoniae in vitro (40).

Although Bordetella bronchiseptica is ubiquitous within the swine industry, this organism is not a commensal and the differences in severity of B. bronchiseptica disease are associated with the age and immune status of the animal, environmental conditions, coinfections, and variations in B. bronchiseptica isolates. Younger animals tend to develop more severe nasal and pulmonary lesions during B. bronchiseptica infection (11, 41). B. bronchiseptica disease is also impacted by immune status and passive immunity, with piglets from vaccinated or naturally infected sows having delayed onset and/or reduced severity of lesions; however, these animals still become colonized with B. bronchiseptica (29, 41, 42). Environmental conditions, such as poor air quality, can exacerbate disease with B. bronchiseptica as well as coinfections with other pathogens, both bacterial and viral. Differences in isolate virulence also contribute to differences in disease presentation and a broad range of virulence has been detected (lethal dose 50 variation of 100,000 fold in inbred mice) (43, 44). These differences have been attributed to variation in virulence factor production (43-45); however, even with less virulent isolates, B. bronchiseptica predisposes animals to secondary infections and, when present, B. bronchiseptica should not be considered a commensal.
Bordetella bronchiseptica infection begins with attachment of the bacterium to the respiratory epithelium, with preferential adherence to ciliated cells in the mucosa (15, 46). Through this interaction and toxin production, B. bronchiseptica causes ciliostasis and the extrusion of ciliated epithelial cells (15, 16, 29), which contributes to mucus accumulation within the respiratory tract. B. bronchiseptica causes inflammation of the epithelium, leading to epithelial metaplasia and necrosis and the infiltration of immune cells (15, 16, 29), which contributes to persistent infections in bacteria such as B. bronchiseptica (49).

The pathogenesis of B. bronchiseptica infection is associated with the coordinated implementation of various virulence factors that are regulated by the BvgAS (Bordetella virulence gene) system (50). This system functions as an on/off switch regulating the virulence genes of B. bronchiseptica and enabling phenotypic modulation that allows the bacterium to succeed as it cycles between the environment and the host (11, 50, 51). The Bvg+ state is induced by an elevation in temperature during the transition of B. bronchiseptica from the environment to infecting a host (50, 51). The virulence factors induced by the BvgAS system are generated in two phases: “early” and “late”. Early genes induced by BvgAS function predominantly in adherence and aid the bacterium in establishing host infection. Late genes induced by BvgAS include toxins and virulence factors which cause tissue damage and are involved in host evasion. At environmental temperatures in the Bvg- state, B. bronchiseptica has elevated expression of genes involved in motility and urease production, while virulence factors are repressed (52, 53). Bvg- B. bronchiseptica also show greater adherence to swine epithelial cells than Bvg+ cells (54, 55), this is thought to assist in the persistence of Bvg- cells in the respiratory tract until BvgAS can be induced. The BvgAS system can also become locked in the “off” condition through phase variation, in which frameshift mutations prevent the expression of BvgAS and the transition of the bacterium to the pathogenic state (11). These Bvg-locked bacteria are readily cleared by the innate immune system and do not establish infections in the swine host (14).

Bordetella bronchiseptica virulence factors

Bordetella bronchiseptica produces a host of virulence factors that function in adherence, host tissue damage, and immune evasion. Adhesion is mediated by a group of adhesins that work in concert to promote B. bronchiseptica colonization. Filamentous hemagglutinin (FHA), fimbrial proteins, and pertactin are all thought to contribute to adherence through multiple binding specificities that extend the range of ligands (48, 56-61). Toxin production by B. bronchiseptica contributes to tissue damage and immune evasion. One prominent toxin is DNT, which is essential for the bony changes associated with nonprogressive atrophic rhinitis and the necrosis associated with pneumonia (17-19, 62, 63). The production of DNT is essential for B. bronchiseptica to cause disease in swine and many swine isolates of B. bronchiseptica have enhanced DNT production due to the presence of mutations in the coding sequence upstream of the gene (64). This genetic change may represent host-adaption of swine isolates to causing disease in pigs. Another important B. bronchiseptica toxin is tracheal cytotoxin (TCT). TCT is produced by the bacteria during cellular proliferation as a breakdown product of peptidoglycan remodeling (65). When released from the cell, TCT interacts with lipopolysaccharide in the outer cell membrane to induce ciliostasis and extrusion of ciliated epithelial cells from the mucosa (16, 29, 65). Because TCT is produced during cell wall remodeling, it is constitutively produced and its production is not impacted by the BvgAS system. The last major B. bronchiseptica toxin is adenylate cyclase toxin (ACT). ACT has adenylate cyclase activity and induces cellular lysis through pore formation (66, 67). ACT can lyse many cell types, but the primary targets of ACT are phagocytes (68). Through its interaction with immune cells, ACT is able to modulate cytokine production and alter the serum and secretory antibody response (58, 69, 70). Immune modulation and tissue damage are also mediated by effectors of the type 3 secretion system (T3SS) produced by B. bronchiseptica. The T3SS functions in the translocation of effector proteins from
The bacterium into the host cell cytosol (71). The effector proteins contribute to immune evasion and tissue necrosis (72-74), and the T3SS is important in the progression and persistence of pneumonia (13, 74, 75).

The presence of B. bronchiseptica in the respiratory tract and the progression of disease contributes to the development of secondary bacterial infections through several mechanisms. First, the interaction of Bordetella bronchiseptica with epithelial cells is mediated through the production of adhesins, which can be pirated by other bacteria, such as P. multocida, to enable attachment to the nasal epithelium (11). For the interaction between B. bronchiseptica and P. multocida, this occurs independently of DNT production and the tissue damage associated with rhinitis (76). Second, ciliostasis associated with B. bronchiseptica infection inhibits mucociliary clearance leading to the accumulation of mucus within the respiratory tract (16, 29). This provides a niche for secondary bacterial pathogens to adhere and thrive during B. bronchiseptica infection. Additionally, the epithelial damage associated with B. bronchiseptica infection leads to increased loss of nutrients that can be utilized by other bacterial pathogens during colonization. Finally, multispecies biofilms can be generated by B. bronchiseptica and other bacteria, such as A. pleuropneumoniae, to provide added protection and nutrients within the nasal cavity (40), thereby increasing the survival and risk of infection with both bacterial species.

### TRANSMISSION

Bordetella bronchiseptica is highly infectious and spreads rapidly throughout a herd to infect most animals (12-14). The bacterium spreads through direct contact between infected sows and their piglets as well as between pigs after comingling. B. bronchiseptica can also spread via aerosols between animals without direct contact (12-14, 77), which is promoted by the sneezing and coughing associated with the progression of disease. After acute disease resolves, B. bronchiseptica colonization persists for several months and infected animals can serve as a reservoir for newly introduced, naive animals (78). Bordetella bronchiseptica is also able to persist in the environment with a half-life of 1-2 hours at ambient temperatures and 75% relative humidity and is known to survive weeks in soil or water (77, 79, 80), which indicates fomites may also play a role in transmission. Although there are no documented cases of transmission to swine from other animal species, B. bronchiseptica has been isolated from wildlife found in close proximity to swine (81) and is a common cause of disease in other domesticated mammals (1), which may allow them to act as a reservoir for B. bronchiseptica infection.
Bordetella bronchiseptica grows readily on blood agar plates; however, because B. bronchiseptica is a slower-growing organism, it can be difficult to identify without the use of a more restrictive media to prevent overgrowth of contaminating bacteria. Assessing the role of B. bronchiseptica in the disease process can also be difficult due to the mixed nature of many infections. B. bronchiseptica can be detected through isolation and biochemical identification from nasal swabs, or in cases of pneumonia from lung tissue samples or washes from pigs with pneumonia. Additionally, a polymerase chain reaction (PCR) target has been developed that has shown 100% specificity and sensitivity for B. bronchiseptica (82). More recently the use of oral fluids has compared favorably to the use of nasal swabs for detecting B. bronchiseptica via PCR at the herd level, improving the ease of sample collection (83, 84). Collection cards that lyse the bacteria and capture and stabilize the DNA for transport and storage at room temperature have also been used successfully to detect B. bronchiseptica in oral fluids (85). Atrophic rhinitis prevention programs can also be assessed using a snout scoring system, in which turbinate atrophy is quantified using a transverse sectioned snout (11) (Figure 3).

**Figure 3.** Routine evaluation of the nasal turbinates in the slaughterhouse and in nursery animals is now the best way of confirming or ruling out Progressive or Non-Progressive AR, respectively. Source: HIPRA.
Control of *Bordetella bronchiseptica* has been accomplished primarily with antibiotic treatments and vaccination to develop protective immunity. *B. bronchiseptica* tends to be susceptible to chlortetracycline, oxytetracycline, and enrofloxacin, all antibiotics approved for the treatment of bacterial agents associated with PRDC, but not specifically *B. bronchiseptica* (86). Resistance to β-lactams, including ampicillin and ceftiofur, is widespread making them ineffective in treating *B. bronchiseptica* (8, 87, 88). While antibiotics have been useful in reducing pneumonia and clinical signs associated with *B. bronchiseptica* infection, they are not effective in clearing the upper respiratory tract of infection and animals continue to shed *B. bronchiseptica* after treatment (11). Atrophic rhinitis control often utilizes antibiotic treatment using a combination of tetracycline and trimethoprim-sulfonamide of the piglets and/or sow around weaning or farrowing; however, resistance to trimethoprim-sulfa antibiotics is becoming more common in *B. bronchiseptica*, making this treatment less effective (87). In addition, the trend to reduce antibiotic usage in animal production in general, and more specifically as a disease prevention measure, may result in a reemergence of overt atrophic rhinitis lesions in herds.

Vaccination as prevention and control of AR

Vaccination against *Bordetella bronchiseptica* in swine typically utilizes whole cell bacterins often including inactivated *P. multocida* toxin to provide better control of progressive atrophic rhinitis. **Although vaccination with bacterins does not provide sterilizing immunity, it can prevent clinical signs, lower bacterial numbers, and limit the severity of disease with *B. bronchiseptica*** (89-91). Only natural infection has been shown to provide total resistance to reinfection, probably due to induction of both serum IgG and mucosal IgA, which are important for clearance of the lung and upper respiratory tract respectively (92-96). Modified live vaccines are not widely available for swine but may be more likely to mimic natural immunity through induction of a mucosal immune response; however, this would be dependent on the mechanism of attenuation and length of persistence in the respiratory tract and thus is strain/vaccine dependent. In addition, attenuated *B. bronchiseptica* strains colonize the nasal cavity and may still predispose animals to infection with other respiratory pathogens (76, 97). Systemic antibody responses tend to be higher in animals parenterally vaccinated with bacterins compared to naturally infected animals or animals given intranasally administered attenuated vaccines (89). Thus bacterins are preferred for sow vaccination protocols, which involve vaccinating animals pre-farrow and rely on passively acquired maternal immunity to limit the severity of disease in piglets (98). **Reduction of the prevalence of infection, bacterial load, and severity of nasal lesions, as well as increased weight gains have been demonstrated in piglets from *B. bronchiseptica* bacterin vaccinated sows.** As is often the case, active vaccination of piglets can be complicated by the presence of maternal antibodies and vaccination at one and four weeks of age in maternally immune piglets has been employed with mixed results (89, 99). It is reasonable to suggest that vaccination against *B. bronchiseptica* may also reduce infection or severity of disease with secondary pathogens, nevertheless additional research into the effectiveness of vaccination in preventing enhanced disease with coinfection models using *B. bronchiseptica* and other respiratory pathogens is needed.
CONCLUSION

*Bordetella bronchiseptica* is a widespread, highly infectious cause of respiratory disease in swine. Disease varies from mild, subclinical infections to severe pneumonia or atrophic rhinitis. The presence of mild and subclinically infected animals causes *B. bronchiseptica* to be an underreported contributor to respiratory disease in pigs. *B. bronchiseptica* also exacerbates viral respiratory infection and enhances colonization and/or disease with other bacterial pathogens, which makes the full impact of *B. bronchiseptica* on swine respiratory health difficult to discern. Vaccination can improve clinical health and improve performance, but control of *B. bronchiseptica* can be challenging due to the difficulty in fully clearing the bacterium using vaccines and antibiotics. Further research should aim to better understand the mechanisms by which *B. bronchiseptica* contributes to enhanced disease with other respiratory pathogens and to determine whether vaccination can improve our ability to control both *B. bronchiseptica* infection and its contribution to secondary disease.
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