Overview

*Bordetella bronchiseptica* is one of the primary causative agents of canine infectious respiratory disease complex (CIRDC).

For pathogens such as *B. bronchiseptica*, which enters through the respiratory tract, the host’s defense relies heavily on mucosal immunity. Vaccination has played a key role in reducing or eliminating clinical signs of respiratory disease and controlling outbreaks.

Mucosal immunity varies substantially from systemic immunity in several fundamental ways and an understanding of these key differences is critical for optimal vaccination. Immune responses are divided into innate and adaptive responses. Innate responses act immediately requiring no previous contact with a pathogen to be effective but offer no future protection. Adaptive responses are capable of specific recognition of distinct pathogenic antigens and subsequent exposure leads to a more rapid and robust immune response. This is termed immunologic memory and is the basis for vaccination. Adaptive defenses comprise both humoral (antibody) and cell-mediated responses.

Brief review of mucosal immunity and relevance to mucosal vaccination

Activating a mucosal immune response relies on antigen being taken up and presented to mucosa-associated lymphoid tissue (MALT). In MALT, antigen is processed and presented to naïve B and T lymphocytes that subsequently proliferate and differentiate into effector and memory B and T cells. Activated B and T cells drain via efferent lymphatics to regional lymphoid tissue where they undergo imprinting to assist in returning to mucosal tissues. These markers allow effector and memory cells to preferentially migrate through the blood back to mucosal effector sites where they can respond to the initiating threat. Memory cells are particularly adept at homing back to mucosal sites which is critical if there is to be rapid protection after a second exposure to a pathogen.

Mucosal effector responses targeting pathogens include either immune exclusion or elimination. Immune exclusion results from production of secretory pathogen-specific IgA that prevents binding and entry of pathogens through the mucosal epithelial barrier. Other classes of antibody, in particular IgG, are present in serum and work after onset of infection in a process called immune elimination. However, pathogen invasion, damage, and activation of inflammatory pathways must allow for increased vascular permeability in order for IgG antibodies to extravasate and reach their target in mucosal tissues.
Immune response to natural infection with *B. bronchiseptica*

Many arms of the immune system respond to *B. bronchiseptica*, some helping to resolve host damage from infection while others are protective against future infection. B cells terminally differentiate into plasma cells and produce *B. bronchiseptica*-specific secretory IgA locally in the canine respiratory tract. Secretory IgA titers appear to be the best correlates for protection against this mucosal infection; IgA neutralizes *B. bronchiseptica* and prevents attachment and entry through the epithelial barrier. Not only does IgA appear to be required to reduce bacterial numbers in the upper respiratory tract, but it is also critical to prevent a subsequent infection. While serum IgG is most commonly measured in studies of canine bordetellosis, it may fall short in predicting protection from infection with *B. bronchiseptica*. For example, in dogs entering shelters, no protection from subsequent development of respiratory disease was noted in dogs having high versus low *B. bronchiseptica* serum IgG titers. Another study of natural infection showed dogs with high IgG titers were not protected from disease; that is, in dogs developing respiratory disease there was a lack of a correlation between development of disease and rising antibody titer. Serum IgG may play a role in established infection. Similarly, it is likely that cell-mediated immune responses, which have not yet been studied in canine bordetellosis, are also important for resolution of established infection.

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Immune response to natural infection

Mucosal pathogens like *B. bronchiseptica* differ from nonmucosal pathogens in the way they cause disease and interact with the host immune system. Because mucosal vaccines take advantage of mimicking the natural route of infection, they are thought to have the desired protection. The goal of vaccination against mucosal pathogens is to produce antigen-specific B and T memory lymphocytes from naïve lymphocytes. These lymphocytes will persist and reside or rapidly home to mucosal tissues to respond to a subsequent pathogenic threat. A number of peer-reviewed publications document efficacy of mucosally administered *B. bronchiseptica* vaccines (either as a monovalent antigen or as a multivalent antigen). Ultimately long-term protection induced by intranasal vaccination is associated with adaptive immune responses that increase mucosal secretory IgA with increasing IgA titers correlating with development of resistance to clinical infection. Dramatic decreases (89%–100% versus controls) in shedding with intranasal vaccination followed by experimental challenge have also been documented.

While topical administration of a vaccine may be necessary to promote strong mucosal immunity, mucosal vaccines are also capable of inducing systemic immunity. With respect to *B. bronchiseptica*, differences in mucosal and systemic serologic responses have been noted in a head-to-head comparison study of an intranasal versus injected *B. bronchiseptica* vaccine in the dog: the former induced both nasal IgA and systemic (serum) IgG whereas the latter did not generate nasal IgA in these studies.

Note that serum IgA is not the same as mucosal IgA and elevations in the former do not imply generation of a mucosal immune response.

Although the majority of studies focus on intranasal vaccination, efficacy has also been documented by oral vaccination. Oral administration of a modified live *B. bronchiseptica* vaccine via the buccal pouch was shown to be efficacious in a vaccine-challenge model in dogs. Mechanistically, similarities in nasal and oral vaccine routes are expected because:

1. Both the oral and nasal cavities share a common inductive site for generating adaptive immune responses; the cranial, oral, nasal-associated lymphoid tissue (CONALT), and routes of trafficking and imprinting.
2. In dogs, the nasal and oral cavities drain via efferent lymphatics to the same lymph node (medial retropharyngeal).
3. Secretory IgA correlates with clinical protection from *B. bronchiseptica* and is induced by mucosal vaccination.
Mucosal vaccines are highly effective at inducing pathogen-specific IgA that binds and removes antigen (“immune exclusion”). The *B. bronchiseptica*-specific IgA induced does not discriminate between the inhaled contagious pathogen and the attenuated vaccine strain given mucosally. While this might seem to be problematic in theory, boosting with mucosal vaccines does not result in all vaccine antigen bound by secretory IgA, especially if timing is close to the expected duration of immunity of the vaccine when IgA titers are decreasing. Importantly, protective immunity against a secondary exposure to respiratory pathogens is correlated with the presence of tissue-specific memory T cells.17

**Summary: Why mucosal vaccination has advantages**

Mucosal vaccination compartmentalizes pathogen-specific immune responses to the site of exposure of pathogenic entry and can stimulate systemic immune responses. Additionally, memory cells home to and reside in mucosal tissue for rapid secondary responses to pathogen. Prime-boost strategies can be effectively accomplished with mucosal vaccines. Collectively, these factors in conjunction with proven efficacy of mucosal vaccines against *B. bronchiseptica* provide a strong rationale for their use in susceptible populations of dogs.

**Can mucosal vaccines be used to boost immunity in dogs previously administered a mucosal vaccine?**

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**References:**