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Review

How well do vaccines for *Bordetella bronchiseptica* work in dogs? A critical review of the literature 1977–2014

John A. Ellis *

Department of Veterinary Microbiology, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK, Canada

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ABSTRACT

Bordetella bronchiseptica (*Bb*) has long been causally associated with respiratory disease in dogs. Parenteral and intranasal vaccines for this pathogen have been in common use since their development in the late 1970s and early 1980s and recently a commercial oral *Bb* vaccine has become available. Overall, the literature (comprising experimental infection models and field studies) documents the efficacy of these vaccines in stimulating disease-sparing mucosal and systemic immune responses that can be associated with reduced growth of *Bb* in vivo. However, many of the published studies are limited by flaws in experimental design, most notably a failure to consider the biological and statistical implications of the 'pen effect'. Many questions related to the longevity of vaccine induced immunity against *Bb* and the impact of natural exposure on herd immunity remain unanswered.

Introduction

Bordetella bronchiseptica (*Bb*), a Gram-negative aerobic coccobacillus, is one of a myriad of infectious agents causally associated with the canine infectious respiratory disease (CIRD) syndrome, or kennel cough (Ford, 2006). It colonizes ciliated epithelia and incites inflammatory disease in the respiratory tract of dogs and other species, including humans (Goodnow, 1980).

Bb has been recognized as a pathogen in CIRD since the early 1900s, when it was wrongly implicated as the cause of canine distemper (Ferry, 1910). However, for much of its history *Bb* was considered a secondary invader, until investigators at the University of Glasgow fulfilled Koch's postulates, establishing its primacy as a canine pathogen in the early 1970s (Wright et al., 1973). Since then, there have been several excellent reviews of the biology of *Bordetella* spp., and the pathogenesis of *Bordetella* spp. infections, including *Bb* and the closely related human pathogen, *B. pertussis* (*Bp*) (Goodnow, 1980; Bemis, 1992; Keil and Fenwick, 1998; Mattoo and Cherry, 2005). In contrast, although vaccines against *Bb* are commonly used in small animal veterinary practice, and controversy concerning the comparative efficacy of routes of administration of *Bb* vaccines is long-standing, there is a dearth of critical assessment of the *Bb* vaccine literature. The following is an attempt to remedy that deficiency.

Parenteral vaccines (Table 1)

Whole cell (WC) bacterins

Shortly after the 'reassessment' of *Bb* as a primary respiratory pathogen, the group at the University of Glasgow performed a series of studies (McCandlish et al., 1976; McCandlish and Thompson, 1978a, 1978b) in the mid to late 1970s, using 8-week-old *Bb* sero- and culture-negative farm-raised collies that were vaccinated with heat inactivated (HI) *Bb* twice intramuscularly (IM) at 14-day intervals, and then individually challenged (2 weeks after the second vaccination) by aerosolizing a virulent field isolate of *Bb*.

In their first experiment with HI *Bb* alone as the vaccine, both vaccinated ($n = 6$) and unvaccinated ($n = 6$) dogs developed clinical signs typical of kennel cough. Although vaccinates had moderate titers of *Bb*-agglutinating serum antibodies (>1:256) at challenge, and the onset of disease was delayed by up to 5 days compared with controls, there were no differences in the incidence of signs, *Bb* isolation results, or respiratory lesions between groups. In contrast, when the same vaccine was adjuvanted with aluminum hydroxide and dogs were similarly vaccinated, all six control dogs developed typical signs of kennel cough, whereas, 4/6 vaccinates remained free of clinical signs, and two had less severe respiratory disease than controls. Vaccinates had no lesions of tracheobronchitis and markedly reduced amounts of *Bb* in the respiratory tract, compared with severe tracheobronchial lesions and pneumonia in controls. In a third unique study (McCandlish and Thompson, 1978c), nine dogs were vaccinated with the same adjuvanted HI *Bb* bacterin and were subsequently placed in a single pen with four unvaccinated controls, and five unvaccinated controls that had been challenged, as before. The five experimentally infected dogs and the four in-contact control

* Tel.: + 1 306 966 7052.
E-mail address: john.ellis@usask.ca.

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Table 1
Studies of injectable *Bordetella bronchiseptica* vaccines.

Vaccine (reference)	Study population	Parameters tested	Results and limitations
Experimental INJ WC *Bb* heat-inactivated vaccine (McCandlish and Thompson, 1978a)	Seven vaccinated seronegative 8-week-old 'farm dogs'; six controls	Challenge 2 weeks after vaccination; *Bb* isolation; *Bb*-agglutinating serum antibodies	High *Bb* antibodies in vaccinates, no apparent differences between vaccinates and controls in clinical signs, *Bb* isolation Limitations: No statistics
Experimental INJ WC *Bb* formalin inactivated, alum-adjuvanted vaccine (McCandlish and Thompson, 1978b)	Six vaccinated seronegative 8-week-old collies; six controls	Challenge 2 weeks after vaccination; *Bb* isolation; *Bb*-agglutinating serum antibodies	Reduced disease, reduced lesions, reduced *Bb* shed, high *Bb* antibodies in vaccinates compared with controls Limitations: No statistics
Experimental INJ WC *Bb* formalin inactivated, alum-adjuvanted vaccine (McCandlish and Thompson, 1978c)	Eight vaccinated seronegative 8-week-old collies; nine controls	Contact challenge with five infected controls 2 weeks after second vaccination; *Bb* isolation; *Bb*-agglutinating serum antibodies	Reduced disease, reduced lesions, reduced *Bb* shed, high *Bb* antibodies in vaccinates compared with infected and naïve contact controls Limitations: No statistics
Experimental INJ *Bb* formalin inactivated, carbopol-adjuvanted vaccine (Bemis et al., 1977)	Four vaccinated seronegative Beagles; three controls	Challenge 3 weeks after second vaccination; *Bb* isolation; *Bb*-agglutinating serum antibodies	High *Bb* antibodies in vaccinates, no apparent differences between vaccinates and controls in clinical signs, *Bb* shed Limitations: Small sample size, no statistics
Pre-licensing INJ WC *Bb* glutaraldehyde inactivated vaccine (Brown et al., 1989, US patent)	39 vaccinated 8- to 20-week-old seronegative 'mongrel' dogs; 14 controls 9000 client owned dog safety study 12 dog antibody interference study	Challenge 2 weeks after second vaccination; *Bb* isolation; *Bb* agglutinating serum antibodies	Reduced disease, reduced lesions, high *Bb* antibodies in vaccinates compared with controls; *Bb* isolated from both groups 1/400 local or transient systemic adverse reaction rate in safety study No interference in antibody responses in two component (*Bb* + MLV CPIV) vaccine Limitations: No quantitation of *Bb*
Pre-licensing INJ *Bb* antigen extract vaccine (Shade and Rapp, 1982)	41 vaccinated 6- to 14-week-old seronegative 'mongrel' dogs; 16 controls 444 client owned dog safety study	Challenge at undisclosed time after second vaccination, Bb isolation	Variation in development of clinical signs, some reduction in clinical signs in vaccinates vs. controls; reduced *Bb* shed in vaccinates 6/444 dogs transient lameness (1); depression (5) Limitations: Inconsistency of *Bb* challenge; no immunological data
Commercial INJ *Bb* antigen extract vaccine (Bronchicine, Zoetis) (Ellis et al., 2014)	Seven vaccinated seropositive 2- to 3-year-old Beagles; one contact control	*Bb*-reactive serum IgG, IgA, bactericidal antibodies 2 weeks after first and second vaccinations	Increased anamnestic IgG, IgA and bactericidal antibodies after first vaccination; no change in contact control Limitations: Small sample size

Bb, *Bordetella bronchiseptica*; WC, whole cell; INJ, injectable (parenteral); CPIV, canine parainfluenza virus; CAV2, canine advenovirus-2; IN, intranasal; MLV, modified-live virus; CIRD, canine infectious respiratory disease.

dogs developed kennel cough and had lesions of severe tracheobronchitis with consistently high amounts of *Bb*. In contrast, 6/8 vaccinates remained free of clinical signs, two had less severe, shorter duration kennel cough, and all had reduced *Bb* and no tracheobronchial lesions compared with controls.

These studies, using robust challenge models including contact transmission, reproduced typical clinical disease (including spontaneous coughing and characteristic lesions), and documented proof of the principle that parenteral vaccines could stimulate *Bb* disease-sparing responses, similar to that reported for WC *Bp* bacterins in humans (Mattoo and Cherry, 2005). However, the mechanism of protection was not determined. Although lack of statistical analyses limited these studies all data are accessible, and apparent differences between groups were almost certainly statistically as well as biologically significant.

Importantly, vaccinates and controls were housed within the same air space. This precluded the possibility of a 'pen effect', which is a systemic effect other than the treatment, such as an environmental factor, that can impact the overall outcome of the experiment (St-Pierre, 2007). An experimental design that fails to consider a pen effect limits the analyses to descriptive statistics, mean and standard deviation, so that differences amongst groups cannot effectively be measured (St-Pierre, 2007). If animals must be housed in separate groups, then the pens should be replicated, and randomized. An adjustment for grouping must also be accounted for in analyses. If researchers do not apply appropriate statistics to account for potential systematic differences between treatment groups that results from housing experimental groups separately then this pen effect can bias outcomes. These and other critical concepts such as observer bias (Buhles and Kass, 2012) have apparently not been applied in many of the studies considered in this review article, thereby impacting the interpretation of study results.

In another early published study (Bemis et al., 1977), a formalin-inactivated, carbopol-adjuvanted *Bb* WC bacterin was tested in seven 6- to 12-week-old Beagles. Three weeks after two IM vaccinations, four dogs had a group mean serum *Bb*-agglutination titer of 1:256 and were aerosol challenged along with three unvaccinated control dogs. Three of four vaccinates and 2/3 controls developed clinical signs; there were no differences in the amounts of *Bb* isolated from tracheas. Unfortunately, the small number of dogs and scant details on the experimental design, housing, and results make it difficult to draw conclusions from this study. To the best of the author's knowledge none of these early bacterins were commercialized.

Although no adverse reactions were reported following administration of the experimental *Bb* bacterins, there were poorly documented clinical observations and perceptions that these or similar bacterins caused local or systemic reactions, so limiting their