Mannheimia haemolytica in Bovine Respiratory Disease (BRD): A Pathway to Optimal Protection

Bimeda® Biologicals

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CATTLE

KEY HIGHLIGHTS

1. *M. haemolytica* is the most important and commonly isolated bacteria isolated from fatal cases of BRD.
2. *M. haemolytica* biotype A serotypes 1 and 6 are the most commonly isolated serotypes from pneumonic bovine lung tissue with serotype 1 being most prevalent and serotype 6, the second most prevalent which accounts for approximately 12-30% of pneumonic lung cases.
3. Due to differences in surface antigens among *M. haemolytica* serotypes, cross-serotypic protection provided by commercial vaccines that only contain A1 and/or leukotoxoid is limited.
4. Protective immunity against *M. haemolytica* requires both serum antibodies that neutralize secreted leukotoxin and antibodies that bind to surface antigens.
5. The PRO-BAC™ line of vaccines are the only commercially available vaccines that contain *M. haemolytica* A1 and A6 as well as a quantified level of leukotoxin for optimal protection.

Bovine Respiratory Disease (BRD) is a multifactorial disease that arises from a combination of environmental stressors such as transport, weaning, inclement weather, host immunity status and from the effects of infectious viruses and bacteria.[1] Significant losses are attributed to BRD in both the beef and dairy industries.[2,3] *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis* are the most common bacteria associated with bovine pneumonia. *M. haemolytica* is the most important and commonly isolated bacteria isolated from fatal cases of BRD.[4]

There are twelve different serotypes of *M. haemolytica* based on capsular antigens, all of which are biotype A. Serotypes 1 (A1), 2 (A2) and 6 (A6) are the most prevalent serotypes in cattle globally. These three serotypes are not always pathogenic and are frequently isolated from the nasopharynx of healthy cattle. Serotype A2, which is a major cause of pneumonia in sheep, is largely considered a commensal organism in cattle although it can be capable of causing disease.[5] *M. haemolytica* A1 and A6 are the most commonly isolated serotypes from pneumonic bovine lung tissue with A1 being most prevalent and A6 , the second most prevalent serotype, accounting for approximately 12-30% of pneumonic lung cases.[1,4-8]

Pathogenic serotypes of *M. haemolytica*—if not stopped by the host's innate immune system—produce a number of virulence factors that enable them to colonize and proliferate in the animal's lungs causing infection and subsequent disease. The virulence factors produced by *M. haemolytica* include capsular polysaccharides (CPS), lipopolysaccharide (LPS), adhesins, outer membrane proteins (OMPs), iron-binding proteins, secreted enzymes, endotoxin, and the ruminant-specific repeats-in-toxin (RTX), leukotoxin (LKT). Because *M. haemolytica* pathogenesis depends on the production of these virulence factors, an effective immune response—either innate or developed through vaccination—must target these factors in order to provide adequate protection from disease.[9] Immunity against *M. haemolytica* requires both serum antibodies that neutralize secreted LKT **and** antibodies that bind to surface antigens or OMPs.[4]

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Leukotoxin is considered the most important virulence factor in *M. haemolytica*-induced pneumonia due to its many pathologic effects on leukocytes. Although there is some genetic diversity among LKT molecules, LKT-neutralizing antibodies against one *M. haemolytica* serotype usually neutralize LKT from another *M. haemolytica* serotype.[9] Several authors have shown that antibodies against *M. haemolytica* A1 LKT will cross-neutralize the toxin prepared from other serotypes. However, Conlon et al. demonstrated that vaccination with recombinant LKT alone failed to stimulate protection against experimental *M. haemolytica* challenge.[4]

Pandher et al. demonstrated 21 surface exposed immunogenic OMPs in *M. haemolytica* A1 using protease treatment and Western blotting. Although specific surface antigens required for immunity are not fully understood, high antibody responses to outer membranes, as measured by ELISA, and to several specific OMPs, as measured by quantitative Western Blotting, consistently correlated with resistance to challenge with virulent *M. haemolytica* A1.[4] Shewen and Wilkie demonstrated that vaccine immunity to *M. haemolytica* required both LKT-neutralizing antibodies and opsonizing antibodies to surface antigens. Because antibody responses to CPS and LPS do not appear to correlate with protection against a *M. haemolytica* challenge, surface proteins are the more likely targets for stimulating the production of opsonizing antibodies.[9] Due to differences in surface antigens among serotypes, cross-serotypic protection provided by commercial vaccines that only contain A1 is limited.[4,9]

Few studies have been published utilizing commercially available *M. haemolytica* A1 vaccines with a *M. haemolytica* A6 challenge. Confer et al., in an attempt to enhance vaccine-induced immunity, added recombinant *M. haemolytica* A1 PlpE to two commercial A1 vaccines (One Shot® and Presponse® HM) and subsequently challenged vaccinates with *M. haemolytica* A6. PlpE is a 45 kDa outer membrane lipoprotein of *M. haemolytica* to which high antibody responses correlated with resistance against experimental challenge.

PlpE is surface exposed and immunogenic in cattle, and anti-PlpE antibodies promote complement-mediated killing of the bacterium. Sequencing studies of PlpE from numerous A1 and A6 isolates have demonstrated homology between PlpE from these two serotypes. In the study conducted by Confer et al., the results indicated a 16.4% reduction in lung lesion scores when rPlpE was added to One Shot compared to One Shot alone, which was not significant ($p=0.06$). Lung lesion scores were reduced by 34.1% when rPlpE was added to Presponse HM compared to Presponse HM alone. This difference was significant ($p<0.05$).[4] Based on the findings of this study, the use of commercial vaccines that include only *M. haemolytica* A1 does not adequately equip vaccinates with protection against *M. haemolytica* A6 which has been isolated in up to a third of pneumonic bovine lung tissue.

Other studies that have looked at cross-serotypic protection for the two major *M. haemolytica* serotypes isolated from BRD cases are limited and include several experimental vaccines as well as other ruminant hosts such as, sheep and goats; however, none have shown complete cross protection between *M. haemolytica* A1 and A6.[9] This data suggests that a more relevant, complete immune response that better protects cattle from *M. haemolytica* infection could come from the use of a multivalent whole cell *M. haemolytica* vaccine that includes both A1 and A6 serotypes.

Conversely, the most used bacterial vaccines that are commonly relied on for protection against *M. haemolytica* contain only A1 isolates and some only contain leukotoxin, which has been shown to be only partially protective.[10] To be more exact, all of the commercially available USDA-licensed vaccines for *M. haemolytica* currently on the market only contain A1 isolates and/or leukotoxin with the exception of Bimeda Biologicals' PRO-BAC line of vaccines. Each of the PRO-BAC vaccines include **BOTH** A1 and A6 isolates and, in order to gain their USDA license, had to demonstrate efficacy against both of the most commonly isolated serotypes. PRO-BAC vaccines also contain a quantified level of leukotoxin and are made using a variety of proprietary production methods to maximize the expression of bacterial virulence factors to help elicit the most comprehensive immune response. The PRO-BAC vaccines come ready-to-use (require no chute-side mixing) adjuvanted with Reveal ATS™. Unique to Bimeda Biologicals, Reveal ATS, which stands for Antigen Transport System, is paramount in presentation to the immune system and protects the antigens from existing circulating antibodies. Post-injection reactions that can occur after the use of a killed Gram-negative vaccine are limited by the ability of Reveal ATS to limit the dispersion of free endotoxin into the animal. There are several versatile presentations of PRO-BAC vaccines available that, in addition to *Mannheimia haemolytica* Serotypes A1 and A6, contain other economically relevant pathogens namely *Pasteurella multocida, Histophilus somni,* and *Salmonella typhimurium.*

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®Presponse HM is a registered trademark of Boehringer Ingelheim

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