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Mannheimia haemolytica vaccines: Are we there yet?

Anthony W. Confer, DVM, MSc, PhD, Diplomate ACVP
Regents Professor & Sitlington Chair for Food Animal Research
Department of Veterinary Pathobiology, Center for Veterinary Health Sciences
Oklahoma State University, Stillwater, OK 74078-2007

Organism & disease

Mannheimia haemolytica (formerly *Pasteurella haemolytica* Biotype A) is a Gram-negative, non-motile, non-spore-forming, facultative anaerobic, weakly hemolytic coccobacillus, and a member of the family Pasteurellaceae. It is a common inhabitant of the nasopharynx of cattle and the major cause of severe, often fatal, fibrinous pleuropneumonia in bovine respiratory disease especially in weaned, stressed, beef calves.

Vaccine history

Attempts to make vaccines against what was then *Bacillus bovisepticus* go back as early as the 1920s where there was no distinction between what would become *M. haemolytica* and what would become *Pasteurella multocida.* With separation of those two bacteria and understanding that in cattle, *M. haemolytica* appeared to be the more important of the two bacteria in bovine respiratory disease (BRD), attempts to make vaccines were undertaken. Prior to the 1990s, bacterins were the only *M. haemolytica* vaccines available, and studies found that they were either generally ineffective or even enhanced disease in vaccinated cattle. Those negative findings along with the discovery of *M. haemolytica* leukotoxin as an important virulence factor and demonstration that immunity requires antibodies to leukotoxin and to surface antigens led to the development of new vaccines. In addition, the latter finding led to studies of various bacterial components to determine which surface antigens may be of importance.

Virulence factors/potential immunogens

Targeted areas of *M. haemolytica* study have been capsule, lipopolysaccharide, various adhesins, extracellular enzymes, outer membrane proteins, and leukotoxin (Table 1). Research has resulted in a database of information for understanding virulence factors, immune responses to the bacterium and potential immunogens that could enhance vaccine efficacy.

Vaccines

The importance of immunity to leukotoxin and to surface antigens in stimulating immunity led to studies of various types of potential vaccines and, in some cases, those studies led to marketing of newer vaccines. Vaccine studies have focused on individual native or recombinant antigens, bacterial extracts, live-attenuated or mutant organisms, culture supernatants, combined bacterin-toxoids, outer membrane vesicles, and bacterial ghosts (Table 2). Efficacy of most of these potential or marketed vaccines can be shown following experimental *M. haemolytica* challenge; however, efficacy in field trials is harder to determine due to the complexity of factors and etiologic agents involved in naturally occurring BRD. Current commercial vaccines are composed primarily of culture supernatant, bacterin-toxoid, or live mutant bacteria. Several of those can be augmented experimentally by addition of recombinant leukotoxin, sialoglycoprotease, or specific outer membrane proteins, and chimeric proteins composed of leukotoxin and surface antigens have been studied.

Table 1. Virulence factors, immunogens and potential immunogens of *M. haemolytica*			
Antigen	**Origin or source**	**Virulence Factor**	**Immunogenic**
Capsule	Surface	Antiphagocytic Adhesin	Weak
Filamentous hemagglutinin	Membrane	Adhesin	Strong
Fimbria	Surface	Adhesin	Strong
Gs60	Outer membrane and extracellular	Unknown	Strong
IgA1 & IgA2 proteases	Secreted	Unknown	Moderate
Leukotoxin	Secreted	Leukocyte necrosis & apoptosis	Strong
Lipopolysaccharide	Surface	Pro-inflammatory compound	LipidA –Weak Polysaccharide - Moderate
Lipoprotein 1	Membrane	Adhesin	Moderate
Metaloproteases	secreted	enzymatic	unknown
N-acety-D-gluosamine	Surface	Adhesion	Unknown
Neuraminidase	Extracellular	Hydrolyzes sialic acid residues on cell surfaces	Moderate
OmpA	Outer membrane	Adhesin Binds lactoferrin	Strong
OmpD15 (Omp85)	Outer membrane	Unknown	Weak
OmpP2	Outer membrane	Unknown	Weak
PlpE	Outer membrane	Unknown	Strong
PlpF	Outer membrane	Unknown	Strong
Serotype 1-specific antigen	Outer membrane	Possible adhesin	Strong
Sialoglycoprotease	Extracellular	Cleaves cell surface glycoproteins	Strong
Transferrin binding proteins A & B	Outer membrane	Remove iron from transferrin	Strong

Table 2. Various *Mannheimia haemolytica* vaccines tested under experimental and field trials

Vaccine type	Timeframe	Efficacy		Commercially available
		Experimental	Field	
Bacterin	Prior to 1990s	Variable	No	No longer
Sodium Salicylate extract	1980s	Variable	Unknown	No
Potassium thiocyanate extract	1980s	Variable	Unknown	No
Saline extract	1980s	Efficacious	Unknown	No
Live - attenuated	1980s	Efficacious	Efficacious or ineffective	No longer
Live – streptomycin-dependent	1985-present	Variable	Efficacious or ineffective	Parenteral or intranasal vaccination
Culture supernatant	1988 to present	Efficacious	Variable	Yes
Bacterin toxoid	1989 to present	Efficacious	Variable	Yes
Capsular polysaccharide	1990s	Variable or poor	Unknown	No
Proprietary extract	1990s	Efficacious	Somewhat efficacious	No longer
Recombinant chimeric protein	2001-present	Partially efficacious	Unknown	No
Ghosts	2003	Efficacious	Unknown	No
Recombinant single protein	2003-3006	Partially efficacious	Unknown	No
LKT-deficient mutant	2012-2013	Efficacious	Unknown	No
Outer membrane vesicles	2013-present	Efficacious	Unknown	No