



Research Gap Analysis Workshop

National Animal Disease Center

Ames, Iowa

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Cattle Working Group Report

As we consider research into alternatives to antibiotics, our group stressed the need to ensure that new technologies be both safe and efficacious. Especially important to any antibiotic alternative and their use in food animals is that these agents pose no food safety risk down the line.

An important and over-arching consideration for research was to develop a better understanding of the sources of variability within the cattle industry. Nationally, both beef and dairy cattle production systems are highly diversified with cattle being raised in a variety of ecosystems and environments. Future research should encourage innovative approaches to eliminate disease risk factors for the diseases and pathogens listed in our table. Increased understanding of the bovine immune system is needed to allow future advances in modulation of the host's response to pathogens. Understanding of host-pathogen interactions is needed to develop modalities that optimize the ability of cattle to counteract pathogen escape mechanisms that provide the organism a means to avoid inducing an optimal immune response. In addition, the development of basic knowledge regarding how the microbiome affects the wellness and innate immune defenses of cattle is needed.

Antibiotic use is often applied in the cattle industries for a wide variety of diseases (Table 1). Several of which involve contributions from environmental stressors and management practices, as well as interplay between multiple viral and bacterial pathogens. As such, this often makes prevention and treatment difficult and less than optimal. Levels of antibiotic use may be higher for certain critical diseases in cattle. Many of the alternatives to antibiotics currently available suffer from limited

or unproven efficacy. Development of alternatives to antibiotics is dependent upon basic research to better define the processes important to pathogenesis.

Table 1: Major Diseases in Cattle where Antibiotic Use is Most Often Applied

Key syndrome	Primary Agents	Level of Antibiotic Use	Non-antibiotic products in use today	Non-antibiotic products limitations	Priority for research for alternatives to antibiotics
Enteric Diseases	<ul style="list-style-type: none"> <i>Escherichia coli</i> <i>Salmonella</i> <i>M. avium subsp. paratuberculosis</i> <i>Cryptosporidium parvum</i> Rotavirus and coronavirus 	Mod	<ul style="list-style-type: none"> Vaccine Feed additives Lactic acid bacteria Probiotics 	<ul style="list-style-type: none"> Timeliness of vaccines Colostrum management 	
Respiratory Diseases	<ul style="list-style-type: none"> <i>Manheimia haemolytica</i> <i>Pasteurella multocida</i> <i>Histophilus somni</i> 	High	<ul style="list-style-type: none"> Vaccine Zelnate 	<ul style="list-style-type: none"> Timeliness of vaccines Bacterial infection secondary to viral Better diagnosis 	High
	<ul style="list-style-type: none"> <i>Mycoplasma bovis</i> 	High	<ul style="list-style-type: none"> Vaccine 	<ul style="list-style-type: none"> Better understanding of basic pathogenesis 	
Reproductive Tract Diseases	<ul style="list-style-type: none"> Metritis (various) 	High	<ul style="list-style-type: none"> Therapeutic antibodies Immunomodulators Imrestor 	<ul style="list-style-type: none"> Effect on milk withdrawal Better understanding of basic pathogenesis 	
	<ul style="list-style-type: none"> <i>Leptospira sp.</i> 	Low	<ul style="list-style-type: none"> Vaccines 	<ul style="list-style-type: none"> Multiple serovars Short-lived efficacy Cost 	
Mastitis	<ul style="list-style-type: none"> <i>Escherichia coli</i> <i>Streptococcus uberis</i> <i>Staphylococcus aureus</i> (others) 	High	<ul style="list-style-type: none"> Vaccines (J5) Imrestor Teat sealant 	<ul style="list-style-type: none"> Limited efficacy No alternatives to antibiotics in dry-off 	High
	<ul style="list-style-type: none"> <i>Mycoplasma bovis</i> 	High	<ul style="list-style-type: none"> 	<ul style="list-style-type: none"> Need for basic research Reproducible model 	
Lameness	<ul style="list-style-type: none"> Polymicrobial (<i>Treponema sp.</i>) <i>Fusobacterium necrophorum</i> (foot rot) 	High	<ul style="list-style-type: none"> Vaccine Foot baths 	<ul style="list-style-type: none"> Environmental impact of foot baths 	High
Food Safety/ Slaughterhouse condemnations	<ul style="list-style-type: none"> <i>E. coli</i> O157:H7; other STEC <i>Salmonella sp.</i> Liver abscesses (<i>Fusobacterium sp.</i> and <i>Arcanobacterium sp.</i>) 	High	<ul style="list-style-type: none"> Vaccine (Canada) NP51 <i>Lactobacillus</i> probiotic 	<ul style="list-style-type: none"> Need for basic research 	High
Vector borne	<ul style="list-style-type: none"> <i>Anaplasma marginale</i> 	Mod	<ul style="list-style-type: none"> Vaccine (not approved) 	<ul style="list-style-type: none"> Vaccine efficacy 	High
Pink Eye	<ul style="list-style-type: none"> <i>Moraxella bovis/ M. bovoculi</i> 	Mod	<ul style="list-style-type: none"> Vaccine Fly tags 	<ul style="list-style-type: none"> Multiple pathogens Reproducible model 	High

New and innovative alternatives to antibiotics are currently included as research initiatives for USDA and other funding agencies. There are several types of antibiotic alternatives, we have broadly classified four: immunomodulators, bactericidal agents, nutrients, and molecular genetics. Each of these has several specific examples; some that are currently the subject of ongoing research, whereas research is needed for others. We rank each of these areas of potential research in Table 2. Basic studies in these areas would have application throughout the cattle industry as well as within other commodity groups.

Table 2: Types of Alternatives of Antibiotics and Research Priority

Type of Alternative	Example	Research Priority
Immunomodulators	Cytokines / chemokines	High
	Innate defense molecules	High
	Vaccines	High
	NSAIDS	High
	Adjuvants	High
	Therapeutic antibodies	High
Bactericidal Agents	Bacteriophages	Medium
	Antibacterial lytic enzymes	Medium
Nutrients	Prebiotics / probiotics	High
	Organic acids	Low
	Essential oils	Low
	Phytochemicals	Medium
	Colostrum qc	High
Molecular Genetics	siRNAs / small ncRNAs	Medium
	Genetic testing/selection/modification	High
	Transcriptome	High
	Metabolome	High

In order to better focus the resources directed toward animal research, we propose the following list of strategic research priorities that have the purpose of generating alternatives to antibiotics in the beef and dairy industries (Table 3):

Bovine respiratory disease complex is an important health problem in both the beef and dairy cattle industries. The cattle industry has a history of use of medically important antibiotics for prevention and treatment of the disease.

Liver abscesses are a significant management problem for the beef industry and are a cause for slaughterhouse condemnation. Currently, treatment for this condition involves use of a medically important antibiotic.

Mastitis and metritis are two of the largest health concerns in the dairy industry causing billions of dollars in loss revenue annually. Treatment of these diseases accounts for the majority of antibiotics used in the dairy industry.

Anaplasmosis treatment is currently dependent on medically important antibiotic use for prevention and control. This is a disease with multiple vectors that is seasonal in many areas of the United States.

Table 3: Proposed Research Priorities

Disease	Antibiotic Use	Alternatives to Antibiotics	Research Needed
Bovine Respiratory Disease Complex	High	Limited	Although vaccines are available, consistency of use, timing of delivery, and ease of implementation at appropriate stages may hamper progress in control of this disease complex. We believe research in modulating the immune system and improving efficacy, delivery, and cost effectiveness of vaccines is critical to progress in combatting BRD.
Liver abscesses	High	Unavailable	Currently, treatment for this condition involves use of a medically important antibiotic. We believe that this disease would benefit from basic research characterizing the rumen microbiome under different conditions (i.e. specifically rumen acidosis).
Mastitis and metritis	High	Limited	We believe that research to understand the development of both disease processes and to enhance host immunity may aid in their prevention. Potential alternatives include the use of immunomodulators and innovative vaccine technologies. Methods to provide rapid involution of the mammary gland at drying off should be explored. Improved understanding of the pathogenesis of metritis and mastitis.
Anaplasmosis	High	Limited	There is a current vaccine but it is less than effective and does not provide cross protection against antigenic variation. Research to improve host immunity through immunomodulators and immunostimulants should be pursued.

The exploration of innovative strategies to minimize the risks of animal disease as well as the discovery of novel products that may serve as alternative agents to antibiotics is an ongoing process to improve our antibiotic stewardship. Preserving the efficacy of antibiotics against pathogens encountered in both human and veterinary medicine and effectively treating, preventing and controlling disease becomes the ultimate goal. Research priorities defined here for cattle may be used to create a future portfolio of “alternatives to antibiotics” research projects essential for ensuring optimal cattle health and improved disease management.