Alternatives to Antibiotics

Cyril G. Gay, DVM, PhD
Senior National Program Leader
Animal Production and Protection
Agricultural Research Service
United States Department of Agriculture
cyril.gay@ars.usda.gov
Consumer Reports’ poll says Americans want antibiotic-free meat

Greg Henderson, Editor, Associate Publisher, Drovers CattleNetwork | Updated: June 21, 2012

Farm Use of Antibiotics Defies Scrutiny

JOURNAL NATURE: FARMERS SHOULD REIN IN ANTIBIOTIC USE WORLDWIDE

By Helena Bottemiller

The prestigious journal Nature this week called antibiotics in agriculture, adding to the growing public health advocates seeking reforms. “If far of antibiotics for... Read more >>

By Editorial Board, Published: July 10
Antibiotic usage in food animals

- Therapeutic - treatment of diseased animal
- Prophylactic - disease prevention at times of stress when infection rates rise, such as shipping, weaning
- Metaphylactic - therapeutic and prophylactic herd use in the face of a disease outbreak
- Growth promotion – accelerate growth of healthy animals
- Regardless of personal opinions:
  - Increasing concern with antibiotic resistance
  - Increased regulation – likely ban of some antibiotics
- Examination of alternatives to conventional antibiotic use is warranted
- Goal – improve animal health, welfare and production efficiency
Alternatives to Antibiotics

International Symposium
Alternatives to Antibiotics (ATA)
Challenges and Solutions in Animal Production

The World Organisation for Animal Health (OIE)
12 Rue de Prony, 75017
Paris, France
25-28 September, 2012

www.ars.usda.gov/alternativesstoantibiotics
The objectives of this symposium was to 1) highlight promising research results and novel technologies that provide alternatives to antibiotics, 2) assess challenges associated with their commercialization and use, and 3) provide actionable strategies to support their development.
Symposium Organization
Five Major Topics

1. Alternatives to antibiotics: lessons from nature
2. Immune modulation approaches
3. The gut microbiome
4. Alternatives to antibiotics for growth promotion
5. Regulatory pathways to enable the licensing of alternatives to antibiotics
What are alternatives to antibiotics?

Drugs, biologics, biotherapeutics, feed additives

Host derived antimicrobials, defensins, probiotics, prebiotics, bacteriocins, phytochemicals, acidifying agents, heavy metals, bacteriophages, bacteriophage lysins, small interfering RNAs, naturally occurring antibacterial lytic enzymes, recombinant and hyperimmune therapeutic antibodies, immune enhancers, Toll-like receptor agonists, cytokines.

www.ars.usda.gov/alternativesstoantibiotics
The aim of this session was to review novel biocontrol approaches for preventing and/or treating bacterial pathogens (and where applicable viral and parasitic pathogens) in food animal production.

www.ars.usda.gov/alternativestoantibiotics
Host derived antimicrobials
“Innate host defense”

- Present in all organisms
- Ancient
  - Snake: cathelicidin
  - Frog: plastrin
  - Insect: cecropin
- Limited repertoire of molecules
- Rapid acting
- Broad specificity
- Constitutive and stimulated secretion

“The first line of defense against infection”
Chicken cathelicidin 2 (Cath-2)

- Cationic (+9)
- 26 amino acids
- Amphipathic

Henk P. Haagsman
Department of Infectious Diseases and Immunology, Utrecht University, The Netherlands
CATH-2 is produced by chicken heterophils

Van Dijk et al., 2009a
Conclusions

• *Salmonella enteritidis* infections of chickens result in accumulation of CATH-2 positive heterophils at the site of infection
• CATH-2 is microbicidal against Gram (-), Gram (+) bacteria, yeasts and fungi
• Truncated CATH-2 analogs are antimicrobial
• CATH-2 and derived peptides induce cytokine production in a chicken macrophage cell line
• CATH-2 dampens the LPS-induced inflammatory response
• Prophylactic or therapeutic treatment of chickens with CATH-2 significantly reduced *Salmonella* survival in the crop
Bacteriophage

Animal virus
e.g., Influenza, HIV

Plant virus
e.g., Tobacco mosaic virus

Bacteriophage
e.g., T1, T2

Specific

Human
Poultry
Swine
Bacteriophage

- Discovered by Felix d’Herelle in 1917
- Infect and replicate in bacterial cells
- Host specific infections
- Must enter and exit bacterial host cell
- Lytic cycle
- Lysogenic cycle
- DNA phage
- RNA phage
Bacteriophage as an Intervention?

- Felix d’Herelle explored using phage solutions to treat dysentery in humans
- Phage solutions supplied to Russian soldiers during World War II
- Republic of Georgia has been using phage therapy since the 1940s
- In 2011, US FDA approved *E. coli* phage for using on food
- Possible therapy for treating multi-drug-resistant strains of bacteria

http://www.cfsan.fda.gov/~dms/opabacqa.html
Bacteriophage concerns?

Restriction modification – degradation of phage DNA upon infection

CRISPR – clustered regularly interspaced short palindromic repeats

Immunogenicity – antibodies developed against phage during treatment

Resistance – mutations in bacterial genes needed for adsorption and lysogeny

Lateral Gene Transfer – virulence factors

Bacteriophage Resistance Mechanisms
Bacteriophage Gene Products

- Phage genomics and proteomics to search for potential novel antimicrobials
- Bacteriocins shown to reduce *Campylobacter*
- Bacteriophage lytic enzymes
  - Amidase
  - Muramidase (Lysozyme)
  - Endopeptidase
- Recombinant lytic enzymes (amidases) shown to be lytic against *Clostridium perfringens*
- Challenges - Need efficient and cost-effective expression system

Seal et al. *Arch Virol* 156:25, 2011
• Need to define the mechanism(s) of action!!!
• Need to conduct scientific studies to determine the efficacy and safety of these products
• Need to conduct studies under field conditions
• Determine the product profile (label claims): treatment, prevention, or growth promotion?
• Can these products be manufactured in a cost effective manner?
• How will these products be administered?
The aim of this session was to address novel drug-free alternative strategies to enhance innate defense mechanisms by modulation of innate immune pathways or activation of conserved innate immune sensing molecules of the host immune system.
Diversity of stimuli can bind host conserved recognition receptors (PRRs= Pattern Recognition Receptors) and stimulate immune response
Recent studies have shown that dietary supplementation with phytonutrients such as safflower leaf, plum, anethol, mushroom, capsaicin, cinnamaldehyde, turmeric, garlic… enhance innate immunity.  

Some phytochemicals (essential oils) interact with host PRRs and initiate inflammatory immune response.

PRRs and downstream signaling components are molecular targets for dietary intervention strategies using phytochemicals to reduce PRR-mediated inflammation.

- Innate immune response
  - Host resistance
  - Wound healing

- Dysregulated immune response
  - Cancer
  - Atherosclerosis
  - Insulin resistance

Bioactive phytochemicals

PAMPS
(Pathogens, diets)

DAMPS
(Necrotic cell products)

Level of PRR activation

Inflammation
NUTRIGENOMICS

Up regulated

Down regulated

5 ppm carvacrol
3 ppm cinnamaldehyde
2 ppm Capsicum oleor.

Primary infection
E. Maxima

Secondary infection
E. Maxima

Kim, DK et al., 2010. Poul Sci 89:68-81
SOME CONCLUSIONS FROM THE ATA SYMPOSIUM

SESSION 2

- Need veterinary immunological reagents to characterize function
- What is the product profile (label claims): treatment, prevention, or disease resistance?
- Need more basic research
SESSION 3

The Gut Microbiome and Immune Development, Health and Disease

Recent advances are demonstrating that the microbiota plays a key role in health and disease. The aim of this session was to attempt to capture state-of-the-art results in farm animals and humans to assess how microbiome analysis is helping to solve disease problems.

www.ars.usda.gov/alternativesantibiotics
Microbiome and Metagenomic Analysis

Microbiome or Virome

DNA → RNA

Metagenomics → Metatranscriptomics

16s Survey → Metabolomics
Intestinal Microbiome

- Bacteria, fungi, viruses, protozoa, helminths
- Bacteria $10^{11}$ cells/gram
  - Firmicutes
  - Bacteroidetes
  - Proteobacteria
- Bacteria primarily associated with mucus and macromolecular food matrix (fiber)
- Composition varies
  - In different portions of GI
  - In different animals
### Alternatives to antibiotics to modify microbiome

<table>
<thead>
<tr>
<th>Science of nutrition</th>
<th>Science of disease</th>
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<tbody>
<tr>
<td>- Improved feed efficiency</td>
<td>- Prevent intestinal diseases</td>
</tr>
<tr>
<td>- Improved growth rates</td>
<td>- Reduce inflammation</td>
</tr>
<tr>
<td>- Assess alternative feeds</td>
<td>- Prevent colonization of foodborne pathogens</td>
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<td>- Reduce shedding of pathogens</td>
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<td>- Increase disease resistance</td>
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A number of the products discussed during the symposium impact the gut microbiome.

Do we need to culture and characterize gut microorganisms or do we just need to identify them?

Do we need to just shift specific populations that are associated with beneficial effects or do we need to characterize the mechanisms by which gut microorganisms modulate disease and health traits?

Need to integrate nutrition, health, and disease research.
The aim of this session was to explore novel approaches that can be used as alternatives for antimicrobial growth promoters in poultry, swine, ruminant, and aquaculture production. A key aim of this session was to improve knowledge on mechanisms of action of the growth-promoting characteristics of the proposed approaches.
Alternatives to the Use of Antibiotic Growth Promotores in Ruminants

S. Calsamiglia
Dept. Ciència Animal i dels Aliments
Universitat Autònoma de Barcelona
sergio.calsamiglia@uab.es
Intestinal Microbiota Associated with High Feed Conversion Efficiency in Chickens

Rob Moore
Australian Animal Health Laboratory
• Need to understand mechanisms of action to maximize the effect of alternatives to antibiotics for growth promotion
• The active ingredients needs to be defined to ensure quality and reproducibility of expected effect of the product under field condition
• Current knowledge of mechanisms of action for growth promotion of certain alternatives to antibiotics may be greater than what we knew about antibiotics used for production
SESSION 5

Regulatory Pathways to Enable the Licensing of Alternatives to Antibiotics

The aim of this session was to review the regulatory pathways in different regions of the world to license alternatives to antibiotics. Regulatory challenges that are faced in taking new molecules from discovery to commercial production was reviewed. This session also covered how to seek approval for labeling claims that are new with specific focus on claims that a product is able to reduce the use of antibiotics.

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Alternatives to antibiotics will be regulated as drugs, biologics, feed additives, or possibly all of the above.

Alternatives to antibiotics must be developed according to national and international standards and meet requirements for efficacy, safety, and quality.

Regulatory processes are in place to enable and facilitate the licensing of alternatives to antibiotics.

Need to engage regulatory agencies early in the process.

Some conclusions from the ATA Symposium:

- Alternatives to antibiotics will be regulated as drugs, biologics, feed additives, or possibly all of the above.
- Alternatives to antibiotics must be developed according to national and international standards and meet requirements for efficacy, safety, and quality.
- Regulatory processes are in place to enable and facilitate the licensing of alternatives to antibiotics.
- Need to engage regulatory agencies early in the process.
GOING FORWARD

• Need to link academia, government researchers, feed industry, pharmaceutical industry, regulatory agencies, and livestock industries

• Stakeholders and scientific community need to define the scope of the research, development, and applications of alternatives to antibiotics
OIE GLOBAL CONFERENCE
ON THE RESPONSIBLE AND
PRUDENT USE OF
ANTIMICROBIAL AGENTS
FOR ANIMALS

International Solidarity to Fight against
Antimicrobial Resistance

Paris (France), 13–15 March 2013

http://www.oie.int/eng/A_AMR2013/introduction.htm
OIE Global Conference on the Prudent Use of Antimicrobial Agents for Animals
International Solidarity to Fight against Antimicrobial Resistance

Paris (France) 13 – 15 March 2013

FIRST ANNOUNCEMENT

BACKGROUND

Antimicrobial agents are essential tools for protecting animal health and welfare. They also contribute to satisfying the increasing world demand for safe food of animal origin, such as milk, meat and eggs. To ensure sustainability of livestock production, the efficacy of antimicrobial agents must be preserved through their responsible and prudent use.

Antimicrobial resistance is a global human and animal health concern that is influenced by both human and non-human usages of antimicrobial agents. The human, animal and plant sectors therefore have a shared responsibility to minimise antimicrobial resistance selection pressures on human and non-human pathogens and to contain antimicrobial resistance illustrating the One Health approach.

The OIE has worked actively for more than a decade on veterinary products, including antimicrobial agents, and developed a strategy for its activities in this area. Given that antimicrobial resistance is often an animal and human health issue, the OIE works closely with all its Member Countries, as well as with international organisations such as WHO, FAO and the Codex Alimentarius Commission.

The OIE has developed international standards and promotes the responsible and prudent use of antimicrobial agents in terrestrial and aquatic animals, as it is crucial to safeguard their therapeutic efficacy for both animals and humans.

The OIE’s standards also address the surveillance of antimicrobial resistance and the monitoring of quantities of antimicrobial agents used in food producing animals. The OIE standards provide guidance for OIE Member Countries to appropriately address the risk of the emergence or spread of resistant bacteria.

Several of these OIE standards and the OIE list of antimicrobials of veterinary importance, already adopted by all Member Countries, are currently under revision to incorporate recent scientific developments with the participation of WHO and FAO.

OBJECTIVES

The conference will in particular:

- present an overview of the current situation regarding antimicrobial use in animals and antimicrobial resistance;
- inform on initiatives taken by the OIE and other international organisations to promote prudent and responsible use of antimicrobial agents in animals at a national, regional and international level;
- promote good governance practices including national legislation and regulatory frameworks for import, registration, distribution and use of quality veterinary drugs worldwide, by using the OIE PVS Pathway in evaluating and strengthening national Veterinary Services and their compliance with OIE standards;
- encourage international cooperation to help all Member Countries to effectively implement measures for responsible and prudent use of antimicrobial agents in animals;
- foster and strengthen cooperation with Veterinary Statutory Bodies and the veterinary profession for the respect of OIE standards on prudent use in animals worldwide;
- explore the opportunities to improve data collection in animal antimicrobial usage and antimicrobial resistance;
- present research on new molecules and scientific findings on the alternatives that could be used in animal production replacing antimicrobial agents.

Contact: scientific.dept@oie.int
Thank you!

cyril.gay@ars.usda.gov
www.usda.ars.gov