“Improving Antimicrobial Use in Food Animal Production: Alternatives, Options and Incentives”

APUA-sponsored National Stakeholder Meeting
May 6-7, 2012, Omni Shoreham Hotel, Washington, DC

Purpose:
To establish a forum for open discussion among major stakeholders regarding feasible, concrete approaches to promote judicious use of antibiotics, in order to both preserve their efficacy to treat disease and ensure a safe, stable and affordable food supply.

Objectives:
- To evaluate feasible alternatives to current non-therapeutic/preventive antimicrobial use in food animal production, specifying barriers and opportunities;
- To propose incentives to promote improved practices and so minimize the need for use of antimicrobials;
- To propose an action plan, based on identified solutions.

Meeting Proceedings – Transcript Notes

Stuart Levy, Meeting co-chair, and President of APUA, welcomes the group – a full schedule, with APUA staff, Carol Cogliani and Sophie Matte presiding.

Joann Lindenmayer: Meeting co-chair and facilitator offers her pleasantries & thanks; described her role as a facilitator – not to express an opinion – and hoped that everyone felt comfortable in expressing their opinions and perspectives and hopes that we can all learn something from the meeting. She then elaborated on the meeting process. The point is to engage in dialogue and generative listening. (Explains the method to encourage dialogue.) Making non-judgmental statements – rather I feel uncomfortable with what you said. It is also important to identify underlying assumptions. She explained that except for the working groups, all of the sessions would be taped. Everyone will have an opportunity to review all material before it goes into a report. The expected outcomes are recommendations that we can agree on. Put assumptions in a parking lot. Ask people to take a piece of paper and 1) write down a group that best characterizes the stakeholder group that they belong to, 2) other group that least represents your perspective, and 3) one myth the other group holds about your group. She felt this exercise to be very enlightening.

1st presentation
Stuart B. Levy, MD

Opening Keynote: Ecology of Antibiotic Resistance
Drug resistance equation- bacteria have a fantastic ways of accumulating genetic material.
If you add an antibiotic a particular kind of bacteria will become more prominent. Bacteria exchange genetic material via plasmids, transposons, transducing phages, also via conjugation. 50 - 80% of antibiotics are used in animals. Antibiotic treatment of farm animals has an impact on fruits and soils – wildlife can pick it up.
Scientific evidence indicates a ripple effect from animal to person and backward (cites Marshall & Levy article in Clinical Microbiology Reviews, 24:4:718-733).

Emergence of resistance
- Stuart cited the farm study (1970s) where he raised chickens from eggs to adults—gave half the chickens feed laced with oxytetracycline and the other half feed without tetracycline. They took fecal samples – as weeks went by you saw the emergence of resistance to multiple antibiotics – some of which were not even used. Resistance is all over - they could not track it to its source. The frequency of tetracycline resistant bacteria in human fecal samples was between 80 and 100% in 35% of the samples taken from farm families, 10% from neighbors, and 5% from Boston. No one was taking antibiotics in the farm family.
- Amboseli Park, Kenya, where baboons were consuming human garbage at the lodge. There was a tremendous difference between the lodge group of baboons and the wild baboons (Alto & Hook). Almost 80% of the lodge group was 20% or more resistant; here the plasmids were small and plentiful. In the wild baboons, < 20% was 20% or more resistant; in this case, there were a small number of large plasmids – clearly reflective of the environment in which the wild baboons partake of their food. The lodge group –rummaging in the refuse—picked up resistance from antibiotics used by people—a secondary effect.

Antibiotic use has a global environmental impact. They are ecologic drugs, which “can alter the microbiology and levels of resistance vs. susceptible bacteria in any given environment.” Antibiotic use – preserving the power is goal and mission of APUA with chapters in 66 countries. Antibiotic use in the new millennium—“it shouldn’t be a war but making peace with bacteria.”

The U.S. Regulatory Framework

2nd presentation
William T. Flynn, DVM, MS
FDA’s Strategy for Promoting Judicious Use of Medically Important Antimicrobials in Food Producing Animals

Dr. Flynn’s objective is to present components of strategy to move forward. Three documents: Guidance 209, Draft Guidance 213 and the Veterinary Feed Directive (VFD).

Guidance 209
- Draft Guidance #209 issued in 2010 and finalized in 2012 -- policy statement that relates to concerns about antibiotic use today.
- Underlying principles- Using drugs in both humans and animals contribute to antimicrobial resistance. The focus today is on use in animals. Try to use drugs more judiciously and minimize resistance
- Two key principles: limit use of medically important (in humans) antimicrobials to uses deemed necessary- such as treatment /therapy and increase veterinary oversight. The focus is on antibiotics used for growth promotion and feed efficiency – used in food and water. There hadn’t been a requirement for close involvement of a veterinarian heretofore

Draft Guidance 213 – out for comment until July 12
- Offers details on implementation of Guidance 209- directed to the pharm. industry on how to align with guidance
- How to update product label – updating improved use
- Specifies data requirement for new therapeutic uses
- Timeline: drug sponsors to reply within 3 months after finalization of 213; phase in changes within 3 years of finalizing the guidance
- Proposed (expanded) definition of medically important drugs: all drugs listed in Guidance 152 (Appendix A) and include the following drugs used as AGPs: penicillins, tetracyclines, macrolides, lincosamides, streptogramins and aminoglycosides
- Potential new therapeutic indications when AGPs are withdrawn for treatment, control (signs of disease), and prevention (at risk for disease, no clinical signs evident)
  - Data required for approval of new uses
  - Requirements for prevention use: defined daily dose/duration, specific target(s), veterinary oversight

Veterinary Feed Directive
- Drug marketing status changed from OTC to Rx or VFD – to include veterinary oversight – not require direct vet. involvement in drug administration
- Changes planned to streamline process involving record keeping & transmission of VFD form
- FDA has a concern on assuring that veterinary services reach those producers in remote/underserved locations

3rd presentation
Thomas R. Shryock, PhD

Regulatory Approach for Veterinarian Directed Medicine

Need antibiotics because we need healthy animals to enter the food chain –100% more food will be needed in 50 years time and 70% of this food must come from efficiency improving technology. Veterinary oversight of antibiotic use is consistent with AVMA objectives. Approved antibiotic label indications: therapeutic – treatment, control and prevention. Production uses are non-judicious. Need to think of population medicine. Timing of administration is a key difference between individual vs. group treatment. Tom advised against using terms he considers undefined: overuse, misuse, inappropriate use, sub-therapeutic use, non-therapeutic use, routine use which are “value judgment terms”. Regulatory actions focus on a subset of food-borne bacteria (salmonella, campylobacter) that may become resistant to antibiotics and will affect people through the food chain and cites NARMS data.

ASM 2008 Colloquium Report:
- Prudent use to prevent development of new forms of resistance
- Find a way to co-exist with antimicrobial resistance: develop strategies to prevent new resistance
  - Effectively treat patients with resistant infections
  - Manage resistant strains in environmental reservoirs

Summary
- Disease prevention – primary goal —“with judicious use of antibiotics only when necessary, is best way for animal producers and vets to co-exist with resistance”.

4th presentation
Chandler Goule

The National Farmers’ Union Perspective(s) on Current Legislative Activity

The National Farmers Union (NFU), founded in 1902, represents 250,000 family farmers, ranchers, and fisherman in 50 states (2nd largest farm organization in the US)—grassroots organization. NFU policy on antibiotic use:
- Use antibiotics for treatment of disease and for disease prevention during periods of stress; unless FDA proves that the product is unsafe
- Supports producers’ rights to treat animals with antibiotics to address herd health concerns
- Calls for more research and evidence-based legislation (although he incorrectly cited Danish evidence); production systems not comparable between US and Denmark;
Asks that legislation target specific antibiotics—not entire classes—knocks Slaughter's legislation.

Conclusion

Organic production is one way to address the problem but it is not affordable for all consumers & even animals raised organically get sick. Chandler recommends judicious use; follow on-label use; strike a balance between organic and conventional production.

5th presentation

Katherine Feldman, DVM, MPH, DACVPM

The AAPHV: Challenges Representing the Diversity of Perspectives of Public Health Veterinarians

Dr. Feldman came to the meeting today to learn more about the issue. She is the immediate past president of AAPHV—a umbrella for any veterinarian, who is interested in public health can join. The organization was started in the mid-1940. In 2008, AAPHV revised its priorities:

- Promote science & practice of public health, epidemiology and preventive medicine
- Provide an expert forum for discussion of important public health issues in the veterinary profession and develop recommendations and health resolutions
- Advise Board of Directors & respond to policy inquiries; develop a pathway for policy development; solicit priorities to publish one position statement annually—Policy work group
- Continue to grow, n=229; diverse membership—a strength but a challenge to create a unified policy statement.

Food Industry: Perspectives and Opportunities

6th presentation

Beef Industry—National Cattlemen’s Beef Association (NCBA)

Michael D. Apley, DVM, PhD, Dipl. ACVCP

Antimicrobial Use in Beef Cattle Production

There is a range of doses chlortetracycline (CTC), TC, OTC used for prevention/control, treatment and feed efficiency. Dr. Apley is concerned about evidence (re: short term, high dose, low dose/long duration). Ionophores are used to increase efficiency of energy and nitrogen metabolism in rumen/animal and retard feedlot disorders.

The biggest challenge is at weaning. There is almost no placental transfer in calves (unlike humans)/In cow/calf production, neonatal enteric disease poses a challenge

Preventive practices include:

- Pre-calving vaccination
- Movement strategies—separation of younger calves from older calves in perinatal period to avoid disease transmission
- Nutritional programs (trace elements) to assure colostrums quality and amount
- Monitoring for adequate intake of colostrums
- Early vaccination of calves

In the feedlot phase, respiratory disease is responsible for 75% of morbidity.

Feedlot preventive practices include:

- Extensive vaccination programs
- Antimicrobial administration to selected high risk groups (at risk for an outbreak)
- Cattle flow: backgrounding programs (intermediate step between weaning & feedlot)
- Nutritional management
- Cattle handling strategies to reduce stress
Research needs
- Genetic markers for disease resistance; subsequent breeding programs on disease resistance
- Novel immune system modulators
- Improved methods to identify pathogen isolates to aid in understanding pathogen population dynamics

7th presentation
Dairy Industry
Mike Lormore, DVM, MS, MBA
Livestock Veterinary Medicine: a Focus on Animal Health, Food Safety and Performance

The principal focus of livestock veterinarians is to develop systems to minimize disease risk, maximize food quality and safety, and optimize animal performance for long-term viability. These goals are accomplished through using epidemiological methods/tools and routine health monitoring. Healthy animals are central to productivity, and the need for therapeutic intervention is a failure in disease prevention. According to FAO, livestock disease reduces global productivity by 20%.

Major diseases of dairy cattle
Youngstock: enterics, pneumonia, parasites
Lactating Herd: mastitis, metritis, pneumonia, lameness, metabolic diseases

Classes of antibiotics available for both humans and animals:
Aminoglycosides, cephalosporins (1st-2nd, 3rd, 4th), Macrolides (not ketolides), quinolones/fluoroquinolones, Tetracyclines (not tigecycline), ansamycins critically imp. for horses

Disease Prevention:
Facilities designed for:
- Proper ventilation
- Animal hygiene
- Protection from her mates
- Waste management systems designed to reduce exposure to environmental pathogens
- Cooling systems (heat stress 68-70 degrees)
- Milking Systems designed to reduce bacterial load and mechanical transmission of pathogens and in-line diagnostics for early disease detection.

Cow management systems and processes:
- Biosecurity systems, proper nutrition, proper milking procedures
- Management systems: transition cow, calving, colostrum, work flow protocol designs
- Vaccination protocols
- Personnel training
- Risk assessment

Treating Sick Animals:
- Training for accurate disease identification, drug selection & treatment protocol.
- Effective treatment of sick animals, with adherence to withdrawal times.

Salmonella and *E. coli* O157 pose special problems which require special measures: biosecurity to minimized spread and in the case of *E. coli* – nutrition management, vaccination and post-harvest methods to further reduce end product contamination.

Going forward:
- Continued focus on systems development
• Expanded role of veterinarians as key part of management team
• Employee training
• Active research – including development of early detection systems and SMART data analysis systems

A limited arsenal of antibiotics is necessary in managing animal health – when animals are sick or at high risk of contracting disease.

8th presentation
Pork Industry
Paul Sundberg, DVM, PhD, Dipl. ACVPM
Swine Health and Production: Issues Management and Program Development in Disease Prevention

Pork Quality Assurance (PQA) program was introduced in 1989 as an education program to raise awareness among producers on how to avoid product residue. Site assessment and animal well being were added to the program in 2005, so named PQA Plus. The goal is ongoing improvement and is a three step process: certification, site status (improvements from assessment implemented), and verification. This program provides information about on-farm good production practices (GPPs) to promote pork safety and pig health and include a valid veterinary/client/patient relationship (VCPR) to guide judicious use of antimicrobials and so minimize AMR. The market has supported the program – as part of a requirement for pig delivery.

The GPPs include the following components:
• Efficient/effective herd health management plan
• Responsible antibiotic use: take appropriate steps to reduce use; use only when measurable benefit; use guidelines – Take Care Responsible Use
• Record keeping: identify & track all treated animals; maintain records
• Proper storage and labels for all drug products and medicated feed
• Education of all animal caretakers on proper health & safety procedures to protect human food supply
• Development & implementation of animal caretaker training program
• Proper swine care to promote swine well-being.

All major packers require their producer suppliers have the PQA Plus certification (of education, not practice). To date, 55,000 pork producers are certified and 18,000 sites (83% of U.S. pork production) have been assessed for program implementation. An independent survey (assessment) has verified that 95% or> have implemented components of PQA plus, including having a valid VCPR and up-to-date medication and treatment records.

He/Pork Checkoff has developed a biosecurity guide for pork producers to promote more cautious behavior and reduce risk of new disease being introduced to a herd. Pork production 30% more with 40% decrease in herd size – Biosecurity and management have contributed to increasing productivity.

With respect to antimicrobial use, Paul cites Apley reference (2006 NAHMS data) – 1.6 million pounds of antibiotics/year are used for production and prevention (cf. UCS 2001 figures – 10.3 million pounds)

Paul concludes that antibiotics are an important tool for animal health. Antibiotic use is minimized (because it is a production cost) through ongoing improvements in animal husbandry, veterinary care and biosecurity.

9th presentation
Poultry Industry (no abstract or slides- transcript only)
Chet Utterback
Antimicrobial Use and Infection Prevention and Control in Poultry Production

Chet has been manager of the poultry research farm ($3.2 million) at the University of Illinois, Urbana-Champaign for 26 years – and has been working in poultry for his entire life (8 years previous in a large commercial operation). He receives 25 calls per year- from people who have backyard chickens- by the time they get analyses it would have been too late. Half the flocks will be dead by the time the results are analyzed. Most of these birds will not enter the food chain. He treated the birds with bacitracin-laced feed and they were ok – by the time results were available. People with a small number of birds will not take them to a vet. If these birds remain untreated – they can be the source of small outbreaks that will be spread – doesn’t think they should do away with ability of farmer to contact a vet. by phone for advice. He uses monensin as a coccidiostats on the farm. Dr. Yvette Johnson is the species veterinarian for the farm. Chet has even done research on coccidiosis and never had it spread to anywhere else in the farm. Chet maintains that a veterinarian is not needed if a farmer knows what he/she is doing. He uses flavomycin before using bacitracin- feed. They find that birds do so much better with this regimen, before they start them on a research trial.

Q&A/Discussion – Transcript

Joann summarizes perspectives. Food security and animal health highlighted. Everyone is trying to find a balance between perspectives on either end of the antibiotic use issue (not necessarily at this meeting). There are differences of opinion –on evidence. Prevention – what does it mean? Education – how to assess whether this has been effective? Interesting alternatives heard. There are different challenges between large and small producers. Should solutions be tailored to producers –specific guidelines? She opens the floor for questions. Stuart answers a question from Diane Kull on farm study. A clear ecologic effect. Animals were not distant – they are on same farm.

Stuart: thinks it is fantastic about actions taken to limit antibiotics on the farm. He comments on the amount of antibiotic referred to by Paul Sundberg (and differences between) giving an antibiotic to one animal versus a large number of animals. Selection density is a big factor - doesn’t have to be a therapeutic amount to select for resistance.

Martin Wierup: appreciates Paul's presentation. When you calculate the amount of antibiotic used in US – US use six times more antibiotics than Denmark. What do you think of this? Paul refers Martin to Mike Apley's publication. Numbers are in the same range based on the Kansas State estimate – and are comparable to the upper range of Denmark’s figures. Paul didn’t have the paper at hand that addressed antibiotic/kg of meat produced. (M. Apley et al. “Use Estimates of In-Feed Antimicrobials in Swine Production in the United States” Foodborne Pathogens and Disease, Vol. 9, No. 3, 2012)

Scott Brown to Stuart Levy: dose per animal lower- 100g/100 animals, 100 g/1 animal
Stuart: to some extent it was intuitive. Resistant bacteria outcompeted in one instance; at v. high doses You can have toxic effect; you don’t need a therapeutic amt. to get an ecologic effect. Selective pressure Single vs.100 animals. Issue has always been the use of antibiotics for growth promotion purposes.
Scott: Does antibiotic free mean ionophore free? He would like harmonization in definition of terms.. Antibiotics is a very broad term.

Martin- coccidiostats have an antibacterial effect- and cited the work of (Herman Goossens) – the big threat is in the amount (of antibiotic) used. His understanding is that the more drugs you use, the higher the risk for cross-resistance (selective pressure). There is a general correlation to the amount used.

Mike Apley: the amount has an effect. There are hierarchies- look at different groups – different interaction.
He was looking for data on duration and is uncomfortable – He has no illusion that after growth promotion – we shall be looking at prevention control. Thinks we need to collect data/evidence.

**Kumar to Chet:** backyard farmers can’t afford to take birds to the veterinarian. The bird might have something very serious, and there will need to be a veterinarian involved. **Kumar** asked about education. **Chet** agreed that it was not the best plan. People do unscrupulous things – they take sick birds to a state fair! **Chet** thinks another problem is that animals do not complete a full dose of antibiotics.

### Alternative Strategies

**10th presentation**

**H. Morgan Scott, DVM, PhD**

**Interventions to Prevent Resistance among Enteric Pathogens in Beef Cattle**

Morgan thinks that systemic intervention is required both to achieve reduced reliance on antibiotics overall, and to avoid the unintended consequences that may occur through haphazard application of antibiotic policies across multiple classes and uses of these products. He presents an alternative systems-based approach that relies on consideration of both the microbial ecology and epidemiology of enteric (pathogenic and commensal) bacterial in food production systems to identify and optimize potential interventions. Using research on fecal flora he describes an approach that may be applied in beef cattle production with a focus on changes both to host gut and production environment.

Antibiotic interventions not directed to the gut. Effects on gut are unintended consequences. (treating for respiratory pathogens and others). Speaks about variety of perspectives – humans take precedence, precautionary principle, and decreasing order of defensible use. Producers’ perspective: antibiotic therapy should be viewed as a last resort. - Moral & political and monetary economics. Perspectives differ even within the veterinary profession.

Strategies to prevent resistance- intervene to reduce exposure in the environment. See Meta-populations of AMR: ecological patch model concept: interaction of cattle, feed, and water (transmitted via feces). Potential interventions target host bacteria ('plasmid curing', select for competing strains), environment (change of conditions to favor susceptible bacteria), feed (direct- fed microbials) and water. He cites Guy Loneragan’s work on changes in US beef cattle enteric populations due to influence of the feedlot environment.

**11th presentation**

**Scott A. Brown, DVM, PhD, Dipl. ACVCP**

**Approaches to Reduce Risk of Infectious Diseases Losses in Livestock**

{Scott referred to the book: “Thinking – Fast and Slow”} Fast response based on gut-level emotion

Not addressing post harvest approaches. Guidance #152 template for data gathering and enables a company to decide whether or not to pursue further development on a drug.

Scott related Pfizer’s perspective- a science-based regulatory approach, with priority to protecting human health. Human and animal health are interlinked. Veterinarian involvement is central in establishing broad herd heath programs that include proper housing, vaccines, therapeutics, and nutrition. Pfizer believes that prevention and management practices are the first course of action in animal health. Several non-bacterial approaches to consider to reduce disease are:

- Animal side diagnostic tests
- Pre- and at-harvest pathogen reduction programs (food safety vaccines, irradiation of carcasses)
- Improvements in NARMS to enable it as a prevalence tool (probabilistic modeling of ABR)
- Veterinarian involvement in about all decisions concerning antimicrobial use
• Improved transportation-related biosecurity, and reduction of commingling with subsequent dispersal of animals

Other alternatives to consider (which require additional data and clarification on regulatory requirements) include:
• Direct fed microbials (see M. Scott)
• Amino acid and acidifiers
• Zinc and bacteriophages.

Best management practices (all in, all out, all clean in between together with on-farm husbandry education (Pfizer: Husbandry educator program in swine to reduce med. use and disease, and Join the Cause campaign for dairy producers) are essential to preventing infectious disease. **Graph: with the program in place, mortality reduced, medicine costs have gone down too! They also made money as they went along.** Ethical companies are investing in alternatives. Antibiotics (as well as new ones) will continue to be needed because animals (and people) will continue to get sick, despite management practices adopted.

12th presentation
**Yvette J. Johnson-Walker, DVM, MS, PhD**
*Infection Prevention and Control in the Poultry Industry: Current Trends and Future Directions*

The literature identifies the following benefits for using antimicrobials in livestock production: reduced production costs, enhanced food safety, improved animal welfare and environmental stewardship. Yvette Defines four categories of antimicrobial use in poultry production: growth promotion, prophylaxis (herd or flock at risk for disease), metaphylaxis (mass medication @ therapeutics doses to clinically normal animals in response to clinical disease in other pen/herds/flock mates), and therapeutic. In commercial poultry production, prophylaxis and metaphylaxis are important health management strategies, because in many cases of infectious disease, the first clinical sign noted is acute death. Furthermore, therapeutic administration occurs via water- and is not individual treatment. Enteric and respiratory diseases principally affect poultry. Necrotic enteritis (Clostridium perfringens) is an enteric disease with few clinical signs prior to death; and, E. coli is a source of respiratory infections in poultry (air sacculitis, rhinotracheitis, sinusitis, or pneumonia). Treating infected birds reduces suffering, minimizes economic losses associated with illness and prevents birds from farms with sick birds from entering the food supply chain.

There are concerns that new regulatory policies will act as a disincentive for new drug development, reduce production efficiency, increase incidence of infectious disease and limit the ability of veterinarians and farmers to treat and prevent disease. Currently there is a thrust toward alternative housing for poultry which will substantially increase the cost of production as well as expose birds to environmental pathogens/stressors. Some alternatives to antimicrobial growth promoters discussed are: organic acids, probiotics, prebiotics, enzymes and herbal products.

Dr. Johnson puts forth an approach to move forward via building consensus, focusing on common goals to protect public health, preserve antibiotic effectiveness, and assure food safety and affordability. The development of evidence-based, sustainable policies that have wide reaching ramifications (on production animals, animal husbandry workers, consumers, and the surrounding ecosystem) requires input from multiple stakeholders, with ongoing evaluation and revision as new information becomes available.

13th presentation
**Masoud Hashemi, PhD**
*Livestock Operation Systems and Ruminants’ Health*
Perspective – Dr. Hashemi began his work in Massachusetts as a nutrient management specialist advising dairy farmers – one-on-one. Then he started teaching sustainable crop and pasture management. Pasture works well in small or medium sized farms and this discussion does not pertain to large farms. Livestock are naturally grazing animals with digestive systems that function well on a grass diet. Allowed to graze, these animals enjoy a much healthier life than those animals confined to feedlots. Animals raised in confinement facilities are routinely treated with antibiotics to prevent disease outbreaks. Furthermore, grain-fed ruminants frequently suffer from acidosis, mastitis, and respiratory disease due to compromised immune systems. Traditional livestock producers often supplement animal feed with unhealthy sources of protein – chicken manure, restaurant food wastes, animal blood, whereas grazing animals derive all the necessary nutrients from plants. The nutrient value of pastures may be enhanced with the introduction of specific plant species - and the introduction of medicinal plants -such as fennel or milk thistle- may eliminate or reduce the need for antibiotics. He spoke of the value of a pasture-based system on sustainability- with a reduction of negative impact on the environment – air, water, soil.

14th presentation
Kumar Venkitanarayanan, DVM, PhD
Potentiating the Efficacy of Antibiotics against Multi-Drug Resistant Bacteria Using Plant Molecules

Salmonella Typhimurium DT 104 (DT) has become a major public health problem due to multi-drug resistance (ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracyclines). Since cattle, pigs and poultry are a reservoir for DT, people may become exposed to DT through the food supply. Hence there is a need to develop interventions to control DT in food animals. Dr. V. described a study to investigate the efficacy of plant-derived antimicrobials (PDA) such as resorcylic acid, carvacrol, thymol and eugenol or their combination for increasing the sensitivity of DT to five antibiotics. In addition, the authors also wished to delineate the potential mechanisms for enhancement of antibiotic sensitivity. Results indicate that these natural molecules both individually and synergistically increased the sensitivity of DT towards the antibiotics and may have a potential use for DT control in food animals.

15th presentation
Steven M. Kappes, Ph.D.
An Overview of USDA’s Activities Related to Antibiotic Resistance; Criteria to Consider in Evaluating Alternatives to Antibiotics in Food Animal Production

Antibiotic resistance is a complex problem that requires multiple solutions. The USDA plan to address AMR includes:

- Surveillance – on animal health (NAHMS), antimicrobial use (APHIS), and resistance prevalence and distribution: NARMS, APHIS, ERS (Economics of antimicrobial use),
- Management & technology
- Education & training veterinarians and producers on judicious use
- Prevention & Control: One Health Initiative; identification of factors to reduce transmission of resistant pathogens in veterinary, agriculture, and aquaculture; and formulation of best practices

A large potential to reduce the need of antibiotics exists and could be exploited by more research and development in the areas of food safety (processing technologies) and on antibiotic resistance and alternatives to antibiotics in animal health, specifically:

- the ecology of antimicrobial resistance in farm animals and the environment
- the host’s immune system – to develop effective vaccines and biotherapeutics and/or enhance vaccine efficacy
- genome sequencing of major food animals to identify animals with reduced susceptibility to specific diseases
Molecules of the innate immune system
Prebiotics and probiotics
Natural products- vit. D for mastitis
Bacteriophage, bacteriophage lysins.

The adoption of management practices may also aid in disease prevention by reducing stress and enhancing biosecurity. All of the above together with diagnosis, vaccination and interventions to reduce pathogenic load on food via antimicrobial treatments and lysins are alternatives to consider in lieu of antibiotics in food animal production.

16th presentation
Steven L. Solomon, MD
Prevention, Control and Treatment of Infectious Disease in Animals: The Role of Surveillance

Public health surveillance is the systematic collection, analysis and dissemination of health data to inform program planning, implementation and evaluation. The measure of success is in the outcome -- how well surveillance can be used to prevent and control disease. For the prevention and control of antimicrobial resistance, the goals of surveillance are:

- Describe scope and magnitude of problem
- Identify early the emergence of new resistance
- Monitor (ongoing) spread of antimicrobial resistance
- Evaluate effectiveness of prevention and control measures
- Monitor antimicrobial use
- Enable predictive modeling of emergence and spread

Surveillance of antimicrobial resistance is difficult to conduct and data difficult to analyze due to the complex interactions among different ecosystems –bacterial, animal, human and inanimate environments and the continual changes wrought upon these ecosystems by the use of antimicrobials. Monitoring the use of antimicrobial agents is critical to combating antimicrobial resistance and is considerably more difficult to implement on both a practical and a methodological basis. Nevertheless, surveillance can provide valuable data-- snapshots of current state and evidence of trends. Electronic records have the potential to improve surveillance capacity.

In the U.S., animal data sources are less developed than human data sources. (see chart of data types for human & animal health, p.3 slides). The Federal government operates several surveillance systems (see presentation of Dr. Kappes): incidence in humans, prevalence of antimicrobial resistant bacteria in food animals and retail meat, as well as antimicrobial use in select settings.

17th presentation
Martin Wierup, PhD, Dipl. ECVPH, Dipl. ECPHM
Strategies and policies in Scandinavia and EU for withdrawal of antimicrobials for growth promotion (AGP) and to further reduce their need for disease control

The withdrawal of AGPs (1995-99) in food animal production resulted in a significant reduction in the amount of antimicrobials used in animals in Sweden (65%), Denmark (45%), Norway (42%), and Finland (27%). In Denmark, there was a dramatic reduction in the animal reservoir of enterococci resistant to AGPs. WHO’s assessment in 2002, together with other studies, revealed the following findings in Denmark:

- Decrease in feed efficiency in broiler production largely offset by cost savings in AGP
- Temporary enteric diseases and decrease in growth rate with little to no negative effect noted in finisher production; 2010 studies indicate no long-term negative impact on swine production.
Total cost from birth to slaughter per pig was approx. one US dollar.
Antimicrobial usage per kg of pig produced decreased by 50% (1992-2008); AGP ban 1995-1999

In addition, a decrease in antimicrobial therapeutic use was seen in Norway and Sweden in 2003, while in Denmark usage was the same as the year prior to termination. In 2012, only 28% of broiler producers used any antimicrobials. A continuous focus on biosecurity and disease prevention can reduce usage further. The Netherlands has the goal of reducing usage in farm animals by 50%

The withdrawal of growth promoters was accompanied by disease prevention efforts together with a focus on judicious use of antimicrobials. The following prevention strategies were utilized in Europe:

- Disease surveillance
- Monitoring: use of antimicrobials and resistance
- Education: farmers, employers and veterinarians
- Guidelines
- Batch production – “all in all out”; batch farrowing & raising of pigs – simple, large positive effect
- Biosecurity: cleaning & disinfection between batches (Sweden/EU); in US, once/year at most!
  - Sweden organized control of Salmonella in broiler production since 1970 with antimicrobials (apart from coccidiostats) used in 6 of 3185 broiler flocks, each flock consisting of 20-30,000 birds (2011);
  - Reported human cases of salmonellosis were halved in Europe from 2006 to 2010 (197,000 to 99,000).
  - Low prevalence of Salmonella in both broiler and swine production in Scandinavia
- No economic incentive for prescribing antimicrobials

In Sweden, risk assessments are used to identify major hazards and guide actions regarding food and feed safety. Baseline studies, harmonized testing and results are reported to all Member States. EFSA (European Food Safety) is the Central agency in Europe, which provides scientific advice on existing and emerging risks.

Antimicrobial resistance is monitored and more needs to be done in monitoring antimicrobial use in animals. Thus far, 10 Member States provide this data, the analysis of which reveals a wide variation in usage between countries (8 – 188 mg/kg animal body weight), with Norway (lowest), Sweden, Denmark and Finland at the low end, and the Netherlands (highest), France and the U.S. at the high end (Grave et al. 2010).

Economic significance of disease prevention in swine production: the time from birth to slaughter is reduced by 30 days without AGP – 150 days, 180 days in conventional production, using SPF (Specific Pathogen Free) and well-implemented batch production.

Incentives for using prevention strategies are:
- Improve production economy and sustainability
- Avoid further ban on antimicrobial use in animals
- Gain consumer trust and demand

18th presentation
Steve Gilman
The Organic Farming Alternative to Antimicrobial Use in the Management of Livestock

* As related in an e-mail from Martin Wierup: SPF is a system introduced in Sweden 15-20 years ago, irrespective of the AGP ban, in which the “first generations of animals are born by caesarian section and then brought up normally in farms but with high biosecurity. They are free from most common respiratory and enteric infections, and therefore can grow much faster. …Batch production, introduced at the time of the AGP ban, can , when well-implemented, give the same magnitude of weight gain.”
NOFA- Northeast Organic Farming Association, established in 1971, is one of the oldest grassroots, organic farming organizations in the U.S. with seven independent state chapters totaling 5,000 members (diverse). NOFA has media outreach to 20,000 food system-aware citizens in the Northeast.

Organic practices and standards prohibit the use of antibiotics in livestock management. USDA's National Organic Program has developed strict standards that allow the use of antibiotics only to treat sick animals. If an antibiotic is required— that animal cannot be represented or sold as organic. Further use of sub-therapeutic doses of antibiotics or other drugs for growth promotion/production purposes are prohibited.

Organic production and standards focus on disease prevention and underlying causes and include:
- Beneficial management practices
- Proper nutrition and effective sanitation (use of manure in feed formulations is prohibited)
- Prohibit overcrowding
- Allow animals access to the outdoors: pasture and direct sunlight
- Choice of genetically diverse breeding stock (naturally less susceptible to disease)
- Quarantine incoming stock
- Maintain appropriate environment for specific animal species
- Certified organically grown- without synthetic fertilizers, GMOs, herbicides, pesticides
- Meat processed in certified facilities
- Organic farms are certified annually by USDA and 3rd party agents

Steve Gilman cites public health study indicating that withdrawing antibiotic use from large-scale Poultry farms can result in immediate and significant reductions in antibiotic resistance for some bacteria (Enterococcus faecalis, Enterococcus faecium) (Aug. 10, 2011).

19th presentation
Diane H. Kull
*Food Animal Production without the Use of Sub-Therapeutic Antibiotics*

Applegate, founded in 1987 by Stephen McConnell, is a company dedicated to the prudent use of antibiotics to maintain efficacy for human medicine. Their standards include:
- No antibiotics,
- High quality feed ingredients without animal by-products (100% veg. diet)
- Natural probiotics to boost digestive health
- Adequate space to raise animals
- Environmental enhancements to reduce stress and boredom
- Science-based improved production practices
- Mandatory annual farm audits.

Applegate sources from 1000 farm suppliers who produce pork, poultry and beef from livestock raised without antibiotics. Diane cited January 2009 USDA report that the economic and production benefits of antibiotics in animal feed can be largely achieved by improved cleanliness of animal houses and improved testing for diseases. Although prevention/management practices employed by Applegate can cost more than conventional farming (see above practices), consumers are becoming increasingly aware and willing to pay more for antibiotic-free products from livestock raised humanely. Double digit growth continues over 25 years, despite the economic downturn in the US. Diane maintained that 75% of Americans want the government to restrict the use of antibiotics on farms.
Perceived barriers to growth are:

- Supply of “no antibiotics used” protein
- Lack of education on antibiotic-free farming: agricultural colleges, conventional farming families
- Myth that raising antibiotic-free meat is not scalable.

20th presentation
Sean B. Cash
Incentives for Antimicrobial Reduction: The Role and Limits of Consumer Information

The use of sub therapeutic doses of antimicrobials in food animal production poses economic issues characterized by high external costs of antimicrobial resistance and asymmetric information between producers and consumers. External costs to society are often underestimated. Use of antimicrobials – economic benefits accrue to the producers. One way to overcome the asymmetry and promote voluntary consumer reductions in purchases of meats produced with antimicrobials is through certification and labeling schemes, e.g., “USDA organic” and “no antibiotics” labeling. Costs of verification and certification are typically paid by the consumer, covered through price premia. More labeling can put more pressure on industry if non-use becomes a new social norm, and can increase consumer awareness (and set new norms) of existing production processes, especially regarding organic standards. Despite the evidence that consumers are willing to pay more for antibiotic-free meat – this action is insufficient protection against the threat of antimicrobial resistance and is not a substitute for tighter, mandatory industry standards. Consumers undervalue risk of non-linear processes of antimicrobial resistance.

Afternoon Session
Reports from the Working Group and Overall Conclusions

Working Groups

Beef Cattle
Mike Apley
H. Morgan Scott
Kumar Venkitanarayanan
Steve Gilman
Steven Kappes

Dairy
Mike Lormore
Masoud Hashemi
Steven L. Solomon
Tom Shryock

Pork
Diane H. Kull
Martin Wierup
Scott A. Brown
Chandler Goule

Poultry
Katherine A. Feldman
Stuart B. Levy
Andrew N. Rowan
William T. Flynn

Poultry: Perspective from those outside the poultry industry
Group not clear about what antibiotics are being used in the industry

1. What are the most obvious/ specific targets for intervention for your industry –e.g., where a change in food production practices can make a significant, positive impact on both animal health status and antibiotic selective pressure? (and is compatible with implementing FDA Guidance 209, 213 and VFD) challenging area- smaller producers do not have all the capabilities of large producers; focused on low-dose & chronic use and not other scenarios

Aim is to reduce antibiotic need and use
That they would not be drugs used in human health
There would be a reduction in resistance rates; have to correlate with specific industry
2. Identify two alternatives: consider criteria: impact on the emergence and spread of antimicrobial resistance; shared health of humans, animals and the environment, economic viability, sustainability, feasibility and likelihood of implementation

Didn’t offer any alternatives – save for individual treatment.
- Minimize overall the use of antibiotics to optimize factors such as minimizing the need for growth promotion uses.
- Maximize the use of biosecurity, targeting the use of these antibiotics and vaccines

3. What are some of the barriers/opportunities available to promote a specific alternative? What incentives – economic or regulatory – can support/promote successful implementation?

Area that would be challenging: dealing with smaller producers, and them being able to operate the same way when limiting the use of antibiotics- this can be market driven
Smaller producers will not have all the capabilities of larger integrators; will not be able to operate in the same way in terms of avoiding the need for antibiotics; how to incentivize will be a challenge; perhaps they can distinguish their product – so that they can make a living

4. What priority, measurable improvements would you target in a 1-year plan? 3-year plan? What evaluation measures would you use?

Overall target
- Focus on phasing out medically important drugs used for growth promotion to the extent that those drugs are being used for growth promotion purposes
- Non re-use of bedding – how you would evaluate – the group discussed the best metric; look at decreases in overall use or absolute amount of drug being used; best indicator; if there were metrics that would indicate impact on core issue, which is contribution to resistance—that would be the better measure. Group said couldn’t speak on behalf of the poultry industry, as the participants hail from other stakeholder groups (government, veterinary association, animal welfare and academia).

Pork Industry: Chandler Goule
Disclaimer – no one in this working group is involved in the U.S. pork industry; EU colleague has experience

1. What are the most obvious/specific targets for intervention for your industry – e.g., where a change in food production practices can make a significant, positive impact on both animal health status and antibiotic selective pressure? (and is compatible with implementing FDA Guidance 209, 213 and VFD)

In the U.S. piglets are weaned around 21 days, increasing that to 28 days would be good and can do intervention
- Replacement animal evaluation to make sure that they are not bringing additional bugs
- All in-all out, batching, possibly keep pigs together all the way up to slaughter
- Reduce cross fostering – when you take piglets from one sow and give to another (only so many spigots)

Auction houses are problems:
- Do more online or video auctions to reduce co-mingling (more a beef issue, but it does occur)
- More individual direct contracting for replacements from one or the same source
- Vaccination on sows for piglet health

Experience with information technology (IT)/aging producers if we are to go to online
• Cost to feed, supplemental food programs
• Cost of housing conversion
• Logistics of online business trade structure
• Education, language barriers (and immigration), husbandry educator, increase employee retention rate (and educate them); there is a large turnover – institutional knowledge is going out the door; trained to recognize clinical forms of disease

2. Identify two alternatives: consider criteria: impact on the emergence and spread of antimicrobial resistance; shared health of humans, animals and the environment, economic viability, sustainability, feasibility and likelihood of implementation

Reduction in antibiotic use
• Record actual use
• Develop and actual baseline (to know how much antibiotics your are truly using)
• Increase employee education and retention

Discussion: Joann asked about the problem of employee retention
Mike Lormore: Hispanic labor handles 85% of work in dairy industry- lose people- better offer up the road; immigration a true issue & will have a significant impact in this country
Chandler Goule: education is becoming more and more important

3. What are some of the barriers/opportunities available to promote a specific alternative? What incentives – economic or regulatory -- can support/promote successful implementation? --

4. What priority, measurable improvements would you target in a 1-year plan? 3–year plan? What evaluation measures would you use?

3 year goal:
• Return to same number of days to market, before we reduced antibiotics and the same number of weanlings per sow before the reduction

Beef/Cattle Industry: Mike Apley

1. What are the most obvious/specific targets for intervention for your industry – e.g., where a change in food production practices can make a significant, positive impact on both animal health status and antibiotic selective pressure? (and is compatible with implementing FDA Guidance 209, 213 and VFD) (melded q. 1 and q. 2)

The primary antimicrobials used are the ionophores – salicin or monensin, bambermycin, which are not considered of primary concern to human medicine. As far as the growth promotion aspect, there is really minimal to be gained there.
• Beef-cattle respiratory pathogen ecology and interventions
• Pre-feedlot immune intervention
• Alternate systems – grass based systems; caveat – the actual dollars- add another year on to harvesting; it can be done -- a different economic model.
• Continued advancements in nutritional management
• Genetic selection for disease resistance
• Unique challenge: Not vertically integrated; the challenge is to vertically integrate based on data, not economics.
2. **Identify two alternatives:** consider criteria: impact on the emergence and spread of antimicrobial resistance; shared health of humans, animals and the environment, economic viability, sustainability, feasibility and likelihood of implementation.

Growth promotion aspect: minimal impacts on human health
Where you can generate a price signal is in backgrounded calves—they either go through a facility or an owner keeps them for 30-35 days and trains them to eat out of a bunk; vaccinates them, boosts them;

**Morgan Scott:** commented on modifying group treatment/metaphylaxis treat individual sick animals?

3. **What are some of the barriers/opportunities available to promote a specific alternative? What incentives—economic or regulatory—can support/promote successful implementation?**

**Incentives**
- A demonstrable efficiency gain and return on investment to the producer, e.g., any dollar investment would be offset in a decrease in antibiotic use and an increase in productivity—an obvious win-win deal
- A consumer price signal

**Opportunities/barriers**
- Preventive uses: metaphylaxis of a subset, not the whole group
- Barriers: need demonstrable efficiency gain (for the producer), or a consumer price signal

4. **What priority, measurable improvements would you target in a 1-year plan? 3-year plan? What evaluation measures would you use?**

**Goals:**
- Efficiency for profit to the producer
- Measurable output: specific drug pathogen interactions—would require a monitoring system to represent the prevalence. The impact on human health—is the final output and why we are here today. The output is to decrease disease *(in humans and animals)*. *(Stuart: This is reminiscent of poultry industry group—looking at commensals)*

**Dairy Industry:** Mike Lormore

1. **What are the most obvious/specific targets for intervention for your industry—e.g., where a change in food production practices can make a significant, positive impact on both animal health status and antibiotic selective pressure? (and is compatible with implementing FDA Guidance 209, 213 and VFD)**

They use ionophores in lactating cows and growing animals. They have a significant economic incentive to keep antibiotics out of lactating herds, because they have to throw all the milk out.

- Economic incentives are well aligned for limiting the risk of disease and use of antibiotics
- Targets for intervention: intramammary for mastitis; and parenteral applications in early lactation.
  - Education on disease identification and implementation of treatment protocols, disease prevention protocol, motivation to clean up drug residues in dairy cull cows. They are learning a lot about consistent treatment protocols. Where they are able to do this and do it successfully, they can significantly decrease the number of interventions made and improve outcomes. This/education is driven by primary care veterinarians and the herd health staff.
- Ongoing access to a lot of vaccines - constantly work on coming up with better treatment protocols and better vaccines.
- Management of cull cows (20% need treatment), residue avoidance (penicillin). 2.5 million go to beef market every year. 20% had pressure which landed them in the beef market when they did. Some of these animals have been treated shortly before ending up in the beef market. They have to do a lot to minimize the risks. The number one challenge from a residue standpoint is penicillin - which constitutes 30% - 40% of drug residues in cows. None of the penicillin used is on label. One of the things they learn at veterinary school is that penicillin does not work at the label dose. They need to know more about the withdrawal of this drug,
- They are putting animals in a 30 day feeding pen – working well.

2. **Identify two alternatives: consider criteria: impact on the emergence and spread of antimicrobial resistance; shared health of humans, animals and the environment, economic viability, sustainability, feasibility and likelihood of implementation.**

Need to have same industry standard, protocols
Labor specialization: better health, better outcomes, better productivity
They have as many herds as they did 10 -12 years ago—much consolidation has occurred in labor specialization.

3. **What are some of the barriers/opportunities available to promote a specific alternative? What incentives –economic or regulatory-- can support/promote successful implementation?**

Herd size (smaller herds have harder time of implementing protocols) not a fan of letting small herds go – to create problems for the rest of the market.
Experience and knowledge of handlers/herdsmen –doing things the same way their parents did
Incentive for doing this right (milk quality and residues); a big disincentive not to get it right – Economic pressure created

4. **What priority, measurable improvements would you target in a 1-year plan? 3-year plan? What evaluation measures would you use?**

One year plan:
- Continue recent efforts, education and training producers and processors on treatment protocols and avoidance of residues
- Improvement measure outcomes; can measure improvement in outcomes using treatment protocols. Most of dairy cattle go through 3 facilities – 35-40 contaminated carcasses. In 2011, only 2 adulterated carcasses in a 12 mo. period of time. They are moving in the right direction.

**Overall Conclusions:**

*Joann Lindenmayer (JL): Is there consensus on which approaches/incentives carry the most promise vis a vis effective implementation based on the reports on how to move forward?*

1-3 year outcome:
- Common theme around education at the farm level: husbandry education;
- Veterinary medical students and veterinarians –a target group to include for this whole issue.

Long-term outcome:
• Importance of the veterinary profession

M. Lormore (ML): Veterinarians are excited about participating in training; a totally different set of skills in terms of leadership, communication.

Scott Brown: continuing education on veterinary level has got to go together. Most of the producers in the U.S. will do an experiment on their own. They will try the husbandry educator, as long as they can see how it matters to them.

ML: Some producers are leaders. They are examples and when others see what they are doing, the ducks fall in line. Animals that go to auctions create higher risks; The information technology piece re: online trade may be a way to reduce risks.

ML: the auctions are a risk factor. He would love to find a more effective way on the dairy side.

M. Apley: have a substantial number of auctions on the beef side. If they do well enough, it is a price signal. Many want to buy direct.

JL: Is there a surveillance consensus? Do we need better surveillance?

Mike Lormore (ML) (Dairy) we would like to have a more integrated system to make valid observations – He would love to have the SMART systems – epidemiological systems. It is a huge opportunity. He has a lot of data on individual animals.

Mike Apley (Beef Cattle): Animals are individually identified in the feedlot. They can go back to exposure models – and what calf was next to what other calf --neighbors in the pen.

Bill Flynn: Surveillance: NARMS – still not a perfect system; opportunities for improvement. How can the data be used to detect trends in antibiotic resistance. FDA, USDA & CDC- NARMS is not in every state.

JL: Where would support come from?

ML: Industry will come up with the financial support, because there is economic value to having the system. It can be market driven. The challenge is in integrating data. The economics are not a barrier.

JL: What impact will consumer demand have on AB use?

Sean Cash: consumers are not so tuned in to the resistance issue. He thinks consumer perception does not correspond to the realities of public health.

Scott Brown: It depends on how much disposable income we have and competing priorities. We are a global economy. There is a large demand for protein. Japan is the number 1 export market.

ML: A certain number dedicated to organic. Ultimately there will be a balance by market. Organic adoption in Europe – supply greatly exceeded demand (15-20 years ago) – 12 -15%, In dairy industry – 3.5% volume milk is organic.

Andrew Rowan: It is a humane issue, not an organic issue.

ML: There are 25,000 management audits – handlers; Pfizer is looking for ways to assure consumers those animals are well cared for.

JL: an issue of quality of life.

ML: need standardization of label.

Dr. Stuart Levy, concluding the meeting, thanked everyone and said it had been more than we had hoped for. He had learned a lot and hoped that our paths would cross again. APUA plans to continue to provide a forum for diverse stakeholders’ discussion and consensus.

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