We can split this discussion into two parts, not necessarily unrelated. The first is what resistance challenges we might see in infectious diseases of food animals that arise from our use in animal agriculture. The second part is any effect we may have on human therapeutics.

These proceedings discuss
- The definition of resistance
- Selection for resistance
- Resistance challenges in human health
- Resistance challenges in veterinary species
- Transfer of resistance from animals to humans
- Tetracyclines as an example in cattle

To discuss the relevance of food animal antimicrobial use to human therapeutics, we first need to outline the resistance challenges in both human and veterinary medicine. This presentation attempts to summarize some of the major concerns in resistance development along with key articles explaining relevance, epidemiology, and prevalence. It is not intended to be an exhaustive review of the literature and the interested practitioner should use the cited literature herein as a basis for continued, extended reading. But before we can discuss resistance, we must define resistance.

**What kind of resistance are we talking about?**
We sometimes become confused as to the type of “resistance” we are talking about. As clinicians, you are concerned about clinical resistance, based on clinically derived breakpoints. These approved breakpoints are developed and approved by the Clinical and Laboratory Standards Institute Veterinary Antimicrobial Susceptibility Testing Subcommittee (CLSI VAST) based on the following.
- Clinical outcomes coupled with pathogen susceptibility data
- MIC distributions of wild type isolate collections
- Pharmacokinetic/pharmacodynamic modeling

These breakpoints are intended to give guidance on the probability of the antibiotic working on a combination of a pathogen, antimicrobial, disease, animal species, and specific treatment regimen. Once you deviate from any of these, the predictive value of the breakpoint is greatly diminished.

The second type of “resistance” is related to changes in population profiles of “wild type” susceptibility distributions. Instead of a clinical breakpoint, these are now referred to as an “epidemiological cutoff”. These cutoffs are defined to indicate a change from the original population minimal inhibitory concentration (MIC) distribution, and may be developed to indicate appearance of resistance genes. Regardless, they are not necessarily correlated to...
clinical response and it is very important to understand what changes based on epidemiological cutoffs convey in relation to clinical efficacy. One of the outcomes of using both epidemiological cutoffs and clinical breakpoints is that different monitoring systems may be declaring “resistance” at different MICs.

So where do resistant organisms come from?

Here is the basic question.

- Do resistant organisms develop from spontaneous mutations in your patient (or a population of patients, such as in some food animal applications) during antimicrobial use and then proliferate within the favorable climate of antimicrobial selection pressure?
- Or, are they already present at a low prevalence level and then proliferate in the new environmental “rules” imposed by the presence of antimicrobials (clonal dissemination and selection)?

My impression from the literature and sitting through and participating in meetings, debates, and outright arguments is that dissemination of resistant bacterial clones is a primary driver in what we are seeing in human and veterinary medicine. Spontaneous mutations can and do occur, but the rapid changes in resistance over broad areas, and also the similarities between isolates suggests that the spread of clones is a primary driver. Clones may be inaccurate in that it implies that it is the spread and proliferation of a single organism, when in fact what really matters is the spread and dissemination of genetic elements that code for resistance.

Another very basic concept is that selection for a resistant pathogen or bacteria may be due to an entirely different selection pressure than the antimicrobial in which we happen to be interested. Multiple-drug resistance mechanisms allow co-selection for resistance traits. And, it doesn’t even have to be an antimicrobial in the way we typically think of them. Co-selection by environmental disinfectants can co-select for antimicrobial resistance, as demonstrated for pine oil for *E. coli*, and triclosan for *Pseudomonas aeruginosa*. The presence of pathogens such as Vancomycin-Resistant Enterococci (VRE), *Pseudomonas*, and Methicillin-Resistant *Staphylococcus aureus* (MRSA) on surfaces, pagers, and stethoscopes has been well documented in human studies.

We don’t cause the original spontaneous mutations. But, once these mutations take hold in an environment, we are responsible for aiding in selection and spread. As Pogo said, “We have met the enemy and he is us”.

What are the challenges on the human side of medicine?

**Hospital acquired infections.** One publication gives us a quick look into the challenges in human hospitals. These data are from a Centers for Disease Control and Prevention (CDC) summary. The objective was to describe the frequency of selected antimicrobial resistance patterns among pathogens causing device-associated and procedure-associated healthcare-associated infections (HAIs) reported by hospitals in the National Healthcare Safety Network (NHSN). Data were collected on HAIs reported to the Patient Safety Component of the NHSN between January, 2006 and October, 2007. These HAIs included…
- Central line-associated bloodstream infections
- Catheter-associated urinary tract infections
- Ventilator-associated pneumonia
- Surgical site infections

Overall, 463 hospitals reported 1 or more HAIs: 412 (89%) were general acute care hospitals, and 309 (67%) had 200-1,000 beds. There were 28,502 HAIs reported among 25,384 patients. The 10 most common pathogens accounting for 84% of reported HAIs were…

- Coagulase-negative \textit{staphylococci} (15%)
- \textit{Staphylococcus aureus} (15%)
- Enterococcus species (12%)
- Candida species (11%)
- \textit{Escherichia coli} (10%)
- \textit{Pseudomonas aeruginosa} (8%)
- \textit{Klebsiella pneumoniae} (6%)
- Enterobacter species (5%)
- \textit{Acinetobacter baumannii} (3%)
- \textit{Klebsiella oxytoca} (2%)

As many as 16% of all HAIs in this report were associated with the following multidrug-resistant pathogens.

- Methicillin-resistant \textit{Staph. aureus} (8% of HAIs),
- Vancomycin-resistant \textit{Enterococcus faecium} (4%),
- Carbapenem-resistant \textit{Pseudomonas aeruginosa} (2%),
- Extended-spectrum cephalosporin-resistant \textit{Klebsiella pneumoniae} (1%),
- Extended-spectrum cephalosporin-resistant \textit{E. coli} (0.5%),
- Carbapenem-resistant \textit{A. baumannii, K. pneumoniae, K. oxytoca, and E. coli} (0.5%).

\textbf{“Bad Bugs, No Drugs” report of the Infectious Disease Society of America}

In 2004, the Infectious Disease Society of America (IDSA) came out with their “Bad Bugs, No Drugs” report.\textsuperscript{4} This report was updated in 2009, implicating the same organisms as primary challenges for antibiotic resistance in human medicine.\textsuperscript{5} The primary pathogens were termed the “ESKAPE” pathogens because they escape attempts at antimicrobial therapy.

\begin{itemize}
  \item \textit{Enterococcus faecium}
  \item \textit{Staphylococcus aureus}
  \item \textit{Klebsiella pneumoniae}
  \item \textit{Acinetobacter baumannii}
  \item \textit{Pseudomonas aeruginosa}
  \item \textit{Enterobacter spp.}
\end{itemize}
In the 2009 report, these pathogens were still implicated as being responsible for the majority of U.S. hospital infections. In addition, CDC data show rapidly increasing rates of infection due to Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant Enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa*. The report stated that more people now die of MRSA infection in U.S. hospitals than HIV/AIDS and tuberculosis combined. In addition, several very resistant Gram (-) pathogens are emerging as significant pathogens in the U.S. and around the world: Acinetobacter species, multidrug-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Klebsiella* species and *E. coli*. The carbapenems (e.g., imipenem and meropenem) are our most powerful beta-lactam antibiotics, and the appearance of widespread resistance to these antimicrobials is very alarming.

**Centers for Disease Control and Prevention Report – Antibiotic Resistance Threats in the United States, 2013**

The Centers for Disease Control and prevention recently released a report describing the major antibiotic resistance threats to human health. In this report, the major threats were classified as threat levels of urgent, serious, and concerning.

**Microorganisms with a threat level of urgent** – These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

*Clostridum difficile*
Carbapenem-resistant Enterobacteriaceae
Drug-resistant *Neisseria gonorrhoeae*

**Microorganisms with a threat level of serious** – These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*
Drug-resistant *Campylobacter*
Fluconazole-resistant *Candida*
Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
Vancomycin-resistant *Enterococcus* (VRE)
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant non-typhoidal *Salmonella*
Drug-resistant *Salmonella typhi*
Drug-resistant *Shigella*
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Drug-resistant *Streptococcus pneumoniae*
Drug-resistant tuberculosis
Microorganisms with a threat level of concerning – These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Resistance challenges in veterinary medicine (including zoonotic concerns):

Weese has published an excellent review of antimicrobial resistance issues in companion animals (2008). The primary organisms addressed in this review are as follows.

- *Staphylococcus aureus* and *Staphylococcus pseudintermedius*: both methicillin susceptible and resistant.
- Enterococci: *Enterococcus faecium* and *Enterococcus faecalis*.
- *Streptococci*: *Strep. zooepidemicus* and *Strep. Equi* in horses, *Strep. canis*
- *Escherichia coli*
- *Salmonella*
- Pseudomonas

The issue of MRSA highlights issues of zoonotic interactions from multiple veterinary species.

**Methicillin-Resistant Staph aureus (MRSA):** a 2008 review article has summarized literature on animal occurrence, including cattle, dogs, cats, sheep, chickens, horses, rabbits, seals, and psittacine birds. Significant research has been conducted evaluating the potential for exchange of isolates between people and their pets.

Kottler, et al., evaluated the prevalence of MRSA in people and pets in the same household. The sample consisted of one human nasal swab and one dog or cat nasal and fecal swab from 586 households. *Staph aureus* was classified as methicillin resistant (MRSA) or susceptible (MSSA). Pulsed-field gel electrophoresis (PFGE) and spa-typing were used to characterize the relatedness of *S. aureus* and MRSA between pets and humans. There was no difference in MRSA prevalence in households with human healthcare workers, veterinary healthcare workers, or without healthcare workers. The following table displaying prevalence of MSSA and MRSA in humans and pets is adapted from the publication.

<table>
<thead>
<tr>
<th></th>
<th>MSSA</th>
<th>MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>21.5%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Pets</td>
<td>7.9%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

In 4 of the 586 households (0.7%), the MRSA found in humans was the same strain as that found in the pet.
Faires, et al., evaluated the prevalence of concurrent infection in households where either a person or pet had a diagnosed MRSA colonization. In part 1 of the study, 22 households were identified as having an MRSA infection in a pet (19 dogs and 3 cats). In these households, 10 of 56 humans (17.9%) were also colonized with MRSA. In part 2 of the study, 8 households were identified where humans had MRSA cultures from dermal abscesses. In only 1 of these households was MRSA also isolated from a pet. In almost all cases of co-colonization or infection, the isolates were indistinguishable by PFGE.

O’Mahony, et al., evaluated MRSA isolates from dogs, horses, a cat, a rabbit, and a seal in Ireland along with isolates from 10 caregivers. The PFGE results for the equine MRSA isolates were indistinguishable from the results for those isolates originating from the caregivers for the horses.

Several studies have evaluated risk factors for infection with MRSA in companion animals. Faires, et al., evaluated risk factors for 40 MRSA infected dogs compared with 80 MSSA infected dogs. The highest prevalence of both infections was in ears and skin. The statistically significant risk factors for MRSA infection as compared to MSSA infection included the use of any antimicrobial prior to diagnosis (odds ratio 2.84), use of fluoroquinolones (OR 3.58), use of β-lactams (OR 3.58), or intravenous catheterization (OR 3.72).

A retrospective study in horses in Canadian and American referral hospitals evaluated MRSA infections in 115 horses. The infections originated both in the referral hospitals and in the community, with the frequency of both being approximately equal. Community acquired infections were significantly associated with previous hospitalization and previous gentamicin therapy. Hospital-acquired MRSA infections were significantly associated with infected incision sites.

Increasing attention in the literature has been paid to MRSA in swine and potential zoonotic concerns. There is extensive literature on types and occurrence of MRSA in farm workers. While swine workers and veterinarians have been demonstrated to have nasal carriage of the MRSA type found in swine herds, epidemiological studies suggest that colonization is primarily limited to those working with the swine and further transmission is limited to familial communities of these exposed workers. In the U.S., the human community-acquired outbreak strains are different from animal strains. In the Netherlands, a new type of MRSA (ST 398) is epidemiologically associated with pig and cattle farmers and is said to be > 20% of carriage in humans. MRSA has also been identified in bovine mastitis isolates. The authors of a 2012 study using single nucleotide polymorphisms (SNPs) to evaluate 89 CC398 MRSA isolates proposed that this MRSA originated in humans as a methicillin-susceptible isolate and then acquired tetracycline and methicillin resistance in livestock, but also lost phage-carried human virulence genes. MRSA CC398 has been documented to cause disease in humans, although it is not a major player in MRSA-associated disease in humans and appears to be a poor long-term colonizer.

MRSA is an example of a resistant organism (which may also be multi-drug resistant) that brings the issue of treating our veterinary patients together with concerns about the effect of this pathogen’s presence on our clients. There are no free lunches, as pathogens which have
developed resistance to one main line of therapy will likely also develop resistance to the next great thing in therapy.

Bovine respiratory disease pathogens: Another area of resistance concern involves the pathogens for bovine respiratory disease as displayed in isolates originating from high-risk calves in the United States. Lubbers and Hanzlicek published a retrospective analysis of Mannheimia haemolytica susceptibility results during 2009-2011 from the Kansas State Diagnostic Laboratory.20 The percentage of isolates showing resistance to at least 3 of our main classes of antibiotics used for BRD were 42%, 46%, and 63% in 2009, 2010, and 2011 respectively.

Has the transfer of resistance from food animals to humans been demonstrated?

The Pew Trust recently funded a paper which summarized evidence for a link between food animal use of antimicrobials and therapeutic resistance in humans.21 This paper, by Marshall and Levy, evaluated evidence for animal to human spread of antibiotic resistance. Ten references were cited which detailed some type of similarity between an isolate of a bacteria in food animals (5 papers for human colonization and 5 for infection) which were related to direct or indirect animal contact. Only one of these papers documented adverse effects in the humans, that being a Salmonella Newport hamburger-borne outbreak. These are basically what there is out there.

In my opinion, it is clearly shown that bacteria can be exchanged between animals and humans, either directly or through food, and that these pathogens may be resistant. The challenge relating to interpreting the effect and importance of these relationships is shown by the fact that few of the isolates shown in these references are included on the “ESKAPE” list.

Some notable quotes from this article include the following.

“In the above examples, the link to nontherapeutic antibiotic use in the farm animals is still circumstantial and largely implied, often because the authors do not report any statistics on farm use of antibiotics. Interpreting these studies is also difficult because of the widespread resistance to some drugs in bacteria of both animals and humans and the ubiquitous nature of resistance genes. Moreover, the same farmer may use antibiotics for both therapeutic and nontherapeutic purposes.”

“The complexities of the modern food chain make it challenging to perform controlled studies that provide unequivocal evidence for a direct link between antibiotic use in animals and the emergence of antibiotic resistance in food-borne bacteria associated with human disease.”

“While this concrete evidence is limited, a small number of studies have been able to link antibiotic-resistant infection in people with bacteria from antibiotic-treated animals. While not necessarily involving NTAs, these studies substantiate the considerable ease with which bacteria in animals move to people.”
We can agree on these passages. It certainly is hard to link the findings in these 10 references to specific drug uses. I especially agree that sorting out the uses for increases in rate of gain and feed efficiency is not based on any type of evidence.

“For example, a multidrug-resistant *Salmonella enterica* strain in a 12-year-old Nebraska boy was traced to his father’s calves, which had recently been treated for diarrhea. Isolates from the child and one of the cows were determined to be the same strain of CMY-2-mediated ceftriaxone-resistant *S. enterica*.”

“It is now believed that the 1992 multiresistant *Vibrio cholerae* epidemic in Latin America was linked to the acquisition of antibiotic-resistant bacteria arising from heavy antibiotic use in the shrimp industry of Ecuador (13, 156).”

My confidence in the authors being straight up about interpretation of the articles is shaken by the interpretation of the Salmonella article. In this reference, the authors of the original paper (Fey, et al.) didn’t do what I did; they didn’t actually visit the farms or interview any of the involved people.22 The facts are that only one, 1 gram vial of Naxcel was dispensed for treatment of the calves in the 4 affected herds, and that was only for the index case prior to culture and susceptibility results becoming available. How do Marshall and Levy know that the calves were treated, or that treatment contributed to the resistance of the Salmonella? They don’t, but is doesn’t stop them and many others from the insinuation that antibiotic use in food animals caused this resistant organism to be present. In fact, if the original authors would have done their field work, they would have found that geese were very prevalent on the calving grounds (a major flyway), that the isolate suddenly appeared in close temporal association in all herds, and that the isolate was gone the next year and not seen since. All of these point to a transient presence, most likely introduced by migratory water fowl. This organism was unable to find a niche due to antimicrobial use or any other factor. So, an article documenting the transmission of an enteric pathogen from a food animal population in which it was transiently present is now used as an indictment of antimicrobial use in animals.

The sum of evidence and the nature of the argument is best summed up by the following conclusion statement from the Marshall/Levy article.

“Data gaps continue to fuel the debate over the use of NTAs in food animals, particularly regarding the contribution and quantitation of commensal reservoirs of resistance to resistance in human disease. Nonetheless, it has been argued reasonably that such deficits in surveillance or indisputable demonstrations of animal-human linkage should not hinder the implementation of a ban on the use of nontherapeutic antibiotics.”

That is the essence of the argument. The cited reasonable argument is a letter to the editor. I am certainly not arguing that there is not a link between food animal bacteria and foodborne pathogens. Nor do I argue that there is no evidence to show that resistant organisms can travel through the food chain, or be directly transmitted to humans. However, we are establishing a level of evidence for evaluation of all uses of antimicrobials in food animals, not just growth promotant uses and the arguable classification of “nontherapeutic”, and this level of evidence for singling out individual use classes is troublesome.
**Tetracyclines as an example in cattle**

There are extensive, transmissible resistance genetic elements out there for the tetracyclines. A 2010 review of the tetracycline resistome noted 1,189 different reported resistance genes present in 84 bacterial genera, which included 354 bacterial species. These genes comprise 41 classes, with three major mechanisms.

- Actively pumping the drug out of the cell
- Enzymatic degradation of the drug
- Protection of the drug binding site

Another paper has documented the methods by which these genes are transferred between bacteria.

- Gram-negative and Gram-positive genes coding for tetracycline efflux are generally associated with plasmids.
- tet(S) and tet(O) encode for ribosomal protection and are located both in the chromosome and in conjugative plasmids.
- tet(M) and tet(Q) (also ribosomal protection) are typically associated with conjugative transposons.
- Other mechanisms include enzymatic inactivation (tet(X) and tet(37))
- Mosaic genes have also been described, which are combinations of individual genes (e.g., tet(O/32/O))

From these inputs, it is apparent that there are multiple options for tetracycline class resistance and that the mobility of these genetic options are well documented.

The next point for consideration is the breadth of regimens and the use classifications across these regimens. Here is the range of in-feed approvals for tetracyclines in cattle, with the highest dosing regimens at the top. These are spaced to illustrate the range of doses. (CTC = chlortetracycline, OTC = oxytetracycline, TC = tetracycline)
From this illustration, it is apparent that focusing on the rate of gain/feed efficiency claims as the “subtherapeutic” bogeymen implies that somehow there is a line where selection for resistant organisms increases or decreases based on label claims. Obviously, there is no science-based information to drive this assumption, but rather, in my opinion, it is based on selecting the most politically acceptable route for an initial removal of food animal antimicrobial uses. The challenge in allowing the rate of gain/feed efficiency antimicrobials to be removed based on the “precautionary principle” is that we then end up with this precedent in evaluating the prevention/control claims.

How can we put the dose ranges above in some kind of context as to the potential for selecting for tetracycline-resistant organisms? First, we need to evaluate what kind of dose it takes to alter the intestinal flora and/or select for resistant organisms in the gut. But, even before that, just how much tetracycline remains active in the gut anyway? My analysis of 7 published studies (rats, mice, humans, pigs) found a range of 0.2% to 13.4%, with an additional outlier showing 67% in rats.

These data were derived from experiments where they determined the actual active amount still functioning in gut contents or feces. Some difficulty is brought into this because we don’t know exactly how this varies between different areas of the gut, and the resulting effects in various areas of the gut. So right away it is apparent that the low doses have even less drug surviving to have an effect in the gut.

The next step is to determine just how much drug needs to be present, and active, in the gut to have an effect on the flora. Several studies have evaluated this level.
Carmen, et al. (2006) evaluated three concentrations of tetracycline in a chemostat system inoculated with human fecal flora. Concentrations of 0.15, 1.5, and 15 µg/ml were used in the systems, equivalent to daily doses of 0.025, 0.25, and 2.5 mg/kg per day in a 60 kg human (based on fecal concentration data by van Marwyck, 1958). Statistical analysis identified the lowest and middle concentrations as having no observable adverse effect on the bacterial population.

Perrin-Guyomard, et al. (2001) used a human-flora-associated (HFA) mouse model to evaluate water tetracycline concentrations of 0, 1, 10, and 100 mg/liter administered for 8 weeks. Upon further calculation, these are equivalent to doses of 0, 0.125, 1.25, and 12.5 mg/kg BW. The authors cited the highest dose as being capable of disrupting the capability to resist Salmonella infection by a resistant isolate. At the lowest dose, there were transient increases in percent resistant Bacteroides fragilis and Enterococci. These effects were more pronounced at higher doses.

Tancrede and Baraket (1987) administered 2, 20, or 2000 mg/day to human volunteers for 7 days. In 60 kg humans, this would be equivalent to 0.03, 0.33, 33 mg/kg per day. The low dose caused no change in % resistance in the dominant anaerobes. The two high doses did induce changes in resistance.

The gastrointestinal tract characteristics of the human and human flora associated mouse are obviously quite different from the bovine, but as our only means of evaluating this effect, we see a pattern in these 3 studies of daily doses of 0.25 and 0.03 mg/kg per day having no effect in two of the studies. In the other study, a dose of 1.25 mg/kg caused no change in the ability for resistant Salmonella to colonize the gut, while the low dose of 0.125 mg/kg per day caused some transient increases in resistant flora. These mixed results highlight the uncertainty in this type of modeling, but do support a conclusion that effects are dose dependant, and that the lowest doses cause the least effect.

Now let’s look at the dose ranges of tetracycline shown above and evaluate them in the light of calculated mg/kg per day.
CTC: 10 mg/lb BW for up to 5 days (22 mg/kg)
CTC: 400 g/ton to provide 10 mg/lb per day in calves up to 250 lbs (22 mg/kg)
TC: 22 mg/kg for 3-5 days in calves (22 mg/kg)

OTC: 0.5 to 2.0 g/hd per day (5.5 mg/kg for 500#)

CTC: 350 mg/hd per day in beef cattle under 700 lbs (1.9 mg/kg for 800#)
CTC: 0.5 mg/lb per day in beef cattle over 700 lbs (1.1 mg/kg)
CTC: 350 mg/hd per day in beef cattle (1.1 mg/kg for 700#)
CTC: 25-70 mg/hd per day in calves 250-400 lbs (0.62 mg/kg for 250#)
CTC: 70 mg/hd per day in growing cattle over 400 lbs (0.22 mg/kg for 700#)
CTC: 0.1 mg/hd per day in calves up to 250 lbs (0.002 mg/kg for 100#)

Rate of gain/Feed efficiency
Prevention or control claims
Treatment claims

Even with all the uncertainties of model application, it is apparent that singling out growth promotion claims as the most likely candidate for removal does not focus on the most likely culprits for changes in gut flora resistance. The growth promotion claims may have an effect, but we will have to address effects of the prevention/control claims sooner or later, and the precedents set for the growth promotion claims will follow us through to the others.

What actually happens when tetracyclines are put in the feed of cattle?

The effect of chlortetracycline addition to feed at 22 mg/kg per day has been shown to be transient when evaluated in light of resistance profiles of *E. coli*.27 In another study, including chlortetracycline in the feed for extended periods at a daily dose of approximately 0.03 mg/kg per day during a backgrounding and feeding phase in feedlot cattle increased the % of *E. coli* in the feces that were resistant to tetracyclines.28 A third study found that administration of chlortetracycline at 350 mg/head per day for 197 days caused a decrease in *E. coli* diversity and “…an increased linked inheritance of ampicillin and tetracycline resistance genes and prevalence of specific strains at day 197.”29

These studies demonstrate measurable effects of regimens that may or may not reflect actual use durations or doses in practice. However, the overall conclusion is yes, we can cause enteric flora changes with the tetracyclines in cattle.
Summary:

This presentation just scratches the surface of the literature as to the resistance challenges in human and animal health, and the interaction within the two. In my opinion, the major questions related to the use of antimicrobials in food animals are in relation to *Campylobacter*, *Salmonella*, and *E. coli*. The issue of MRSA is currently one of colonization with a more minor contribution to human disease from zoonotic sources, but this relationship bears watching in the future. However, it is obvious that food animal uses have little if any direct contribution to a large portion of the most critical human antimicrobial resistance issues.

In several parts of the world, the verdict has been returned on growth promotant uses of medically important (for human therapy) antimicrobials as evidenced by removal, or pending removal of these applications. Our next challenge will be to balance risk and benefit of antimicrobial uses for prevention and control of disease in food animals.

---


