ANTIBIOTIC STEWARDSHIP AS A DRIVER OF LEGISLATIVE, REGULATORY, AND CONSUMER AGENDAS

Mike Apley
Kansas State University
Antimicrobial Timeline

- 1910 – Arsphenamine (Salvarsan) – 1912 Neosalvarsan
- 1935 – Prontosil (sulfanilamide)
- 1942 - Benzylpenicillin
- 1948 - Chlortetracycline
- 1949 - Chloramphenicol
- 1949 – Neomycin - aminoglycosides
- 1949 – Neomycin - streptogramins
- 1955 – Vancomycin - glycopeptides
- 1955- Vancomycin - streptogramins
- 1959 – Virginiamycin - streptogramins
- 1959 – Virginiamycin - streptogramins
- 1960 – Metronidazole
- 1960 – Metronidazole
- 1968 - Clindamycin - lincosamides
- 1968 - Clindamycin - lincosamides
- 1970 – Cephalexin - cephalosporins
- 1970 – Cephalexin - cephalosporins
- 1978 - Norfloxacin - fluoroquinolones
- 1978 - Norfloxacin - fluoroquinolones
- 1985 – Imipenem - carbapenems
- 1985 – Imipenem - carbapenems
- 1992 - Benzylpenicillin
- 2000 - Linezolid - oxazolidinones
- 2003 - Daptomycin - cyclic lipopeptides
- 1985 – Imipenem - carbapenems
- 1978 - Norfloxacin - fluoroquinolones
- 1970 – Cephalexin - cephalosporins
- 1959 – Virginiamycin - streptogramins
- 1955 – Vancomycin - glycopeptides
- 1949 - Chloramphenicol
- 1948 - Chlortetracycline
- 1935 – Prontosil (sulfanilamide)
- 1910 – Arsphenamine (Salvarsan) – 1912 Neosalvarsan

Commercial availability for first member of major antimicrobial groups
“But I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient.

There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.”
SO OUR RESPONSE HAS BEEN....?
First

Second

Third

Fourth

Fifth

Penicillins

Phenicols

Tetracyclines

Fluoroquinolones

Cephalosporins
Macrolides

Ketolides

Triamilides

Azalides
Potentiated!!

Sulfas

2nd and 3rd Penicillins
Basic Realities

- Antimicrobials...
  - don’t cure the animal by themselves (but may be a substantial portion of clinical outcome determination)
  - don’t make a clinical outcome difference in all cases
  - can cause damage to the animal themselves
  - can alter both the pathogen and normal microbiota populations, resulting in changes in our ability to treat future cases
What do we use in food animals?
Reuters Special Report: Poultry Firms Systematically Feed Low-Dose Antibiotics to Flocks (9-16-2014)
Sharp Increase Seen in Sales of Antibiotics for Use in Farm Animals

October 2, 2014, 6:10 pm ET by David Hoffman and Emma Schwartz
## Antimicrobial Drugs Approved for Use in Food-Producing Animals Actively Marketed in 2012

Sales and Distribution Data Reported by Drug Class

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Annual Totals (kg)</th>
<th>% Subtotal</th>
<th>% Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domestic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>273,536</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>27,654</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ionophores</td>
<td>4,573,795</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>218,140</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Macrolides</td>
<td>616,274</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Penicillins</td>
<td>965,196</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Sulfas</td>
<td>493,514</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>5,954,361</td>
<td>41%</td>
<td>40%</td>
</tr>
<tr>
<td>NIR</td>
<td>1,495,959</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>14,618,428</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td><strong>Export</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIRE</td>
<td>139,173</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td>14,757,601</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 7

ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS<sup>1</sup> ACTIVELY MARKETED IN 2012
DOMESTIC SALES AND DISTRIBUTION DATA
REPORTED BY MEDICAL IMPORTANCE, ROUTE OF ADMINISTRATION, AND DRUG CLASS

<table>
<thead>
<tr>
<th>Route</th>
<th>Drug Class</th>
<th>Annual Total (kg)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>% Subtotal</th>
<th>% Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed</td>
<td>Sulfas</td>
<td>90,972</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5,085,178</td>
<td>57%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>Other Drugs&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1,070,301</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
<td>195,043</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Lincosamidines</td>
<td>72,187</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Penicillins</td>
<td>753,510</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Sulfas</td>
<td>283,909</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
<td>782,959</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Other Drugs&lt;sup&gt;3&lt;/sup&gt;</td>
<td>26,233</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Water</td>
<td>Cephalosporins&lt;sup&gt;1&lt;/sup&gt;</td>
<td>27,654</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Sulfas&lt;sup&gt;1&lt;/sup&gt;</td>
<td>118,633</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
<td>86,224</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Other Drugs&lt;sup&gt;5&lt;/sup&gt;</td>
<td>300,300</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Other Routes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Subtotal</td>
<td>8,893,101</td>
<td>100%</td>
<td>61%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not Currently Medically Important&lt;sup&gt;4&lt;/sup&gt;</th>
<th>All Routes&lt;sup&gt;6&lt;/sup&gt;</th>
<th>All Drugs&lt;sup&gt;10&lt;/sup&gt;</th>
<th>5,725,327</th>
<th>39%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Routes&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Grand Total</td>
<td>14,618,428</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS

ACTIVELY MARKETED 2009-2012

SALES AND DISTRIBUTION DATA

REPORTED BY DRUG CLASS

Domestic/Export and Drug Class

Annual Totals (kg)

2009
2010
2011
2012
<table>
<thead>
<tr>
<th>Antimicrobials or classes listed as Highly Important in Guidance 152</th>
<th>Antimicrobial</th>
<th>Growth promotion</th>
<th>Prevention</th>
<th>Therapy</th>
<th>Any reason ‘yearly basis’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlortetracycline</td>
<td></td>
<td>83,331</td>
<td>206,076</td>
<td>217,622</td>
<td>507,029</td>
</tr>
<tr>
<td>as Chlortetracycline alone</td>
<td></td>
<td>942</td>
<td>14,673</td>
<td>3,784</td>
<td>19,398</td>
</tr>
<tr>
<td>as Chlortetracycline/Sulfathiazole/Penicillin G (CSP)</td>
<td></td>
<td>2,735</td>
<td>3,663</td>
<td>1,148</td>
<td>7,546</td>
</tr>
<tr>
<td>as Chlortetracycline/Sulfamethazine/Penicillin G (ASP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lincomycin</td>
<td></td>
<td>356</td>
<td>4,246</td>
<td>20,844</td>
<td>25,446</td>
</tr>
<tr>
<td>Neomycin</td>
<td></td>
<td>4,068</td>
<td>2,632</td>
<td>16,394</td>
<td>23,094</td>
</tr>
<tr>
<td>as Neomycin/Oxytetracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td></td>
<td>2,615</td>
<td>31,699</td>
<td>97,547</td>
<td>131,862</td>
</tr>
<tr>
<td>as Oxytetracycline alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as Neomycin/Oxytetracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
<td>471</td>
<td>7,336</td>
<td>1,892</td>
<td>9,699</td>
</tr>
<tr>
<td>as Chlortetracycline/Sulfathiazole/Penicillin G (CSP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as Chlortetracycline/Sulfamethazine/Penicillin G (ASP)</td>
<td></td>
<td>1,367</td>
<td>1,832</td>
<td>574</td>
<td>3,773</td>
</tr>
<tr>
<td>Virginiamycin</td>
<td></td>
<td>26,108</td>
<td>54,858</td>
<td>493</td>
<td>81,459</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td></td>
<td>1,068</td>
<td>46,906</td>
<td>22,786</td>
<td>70,761</td>
</tr>
<tr>
<td>Tylosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as Tylosin alone</td>
<td></td>
<td>25,641</td>
<td>37,893</td>
<td>91,160</td>
<td>154,694</td>
</tr>
<tr>
<td>as Tylosin/Sulfamethazine</td>
<td></td>
<td>7,500</td>
<td>149</td>
<td>3,460</td>
<td>11,109</td>
</tr>
</tbody>
</table>

64% of medically important use

66% of medically important P and T

15% 39% 46% 165,803

**Notes:**
- Only potentiated sulfonamides are listed in Guidance 152, Appendix A.
- The tetracycline class representative in Guidance 152, Appendix A is tetracycline.
- The lincosamide class representative listed in Guidance 152, Appendix A is clindamycin.
- The streptogramin class representative in Guidance 152, Appendix A is dalbopristin/quinupristin.
- The macrolide class representatives listed in Guidance 152, Appendix A are erythromycin, azithromycin, and clarithromycin. Antimicrobials are grouped according to classification or lack of classification in Appendix A of FDA/CVM guidance 152.
WHAT IS THE CONTEXT WITHIN WHICH WE CONSIDER THE MEDICAL IMPORTANCE OF ANTIBIOTICS?
CDC Resistance Threats 2013

- Threat level of **URGENT**
  - *Clostridium difficile*
  - Carbapenem-resistant Enterobacteriaceae
  - Drug-resistant *Neisseria gonorrhoeae*
Threat level of Serious

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida*
- Extended spectrum β-lactamase 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
Threat level of Concerning
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*
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: *Enterocococcus faecium* and *Enterococcus faecalis*.
- *Streptococci*: *Strep. zooepidemicus* and *Strep. Equi* in horses, *Strep. canis*
- *Escherichia coli*
- *Salmonella*
- *Pseudomonas*
Antimicrobial multidrug resistance and coresistance patterns of *Mannheimia haemolytica* isolated from bovine respiratory disease cases—a three-year (2009–2011) retrospective analysis

Brian V. Lubbers,¹ Gregg A. Hanzlick

Abstract. Bovine respiratory disease continues to be the most important ailment of feed yard cattle. While the disease is multifactorial in nature, therapy continues to target the primary bacterial pathogens, *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*. A survey of records from a single diagnostic laboratory was conducted to evaluate the percentage of *M. haemolytica* isolates that were resistant to multiple antimicrobials and if coresistance patterns could be detected. All susceptibility test results for *M. haemolytica* recovered from lung tissues of cattle were eligible for inclusion in the survey. There were no isolates over the course of the analysis that were resistant to all 6 antimicrobials, primarily due to a lack of resistance to ceftiofur. In 2009, just over 5% of isolates were resistant to 5 or more antimicrobials (pan-resistant). In 2011, more than 35% of the *M. haemolytica* isolates were characterized as pan-resistant. Significant antimicrobial coresistance patterns were only seen with oxytetracycline and tilmicosin; bacterial isolates that were resistant to either oxytetracycline or tilmicosin were more likely to be resistant to at least one other antimicrobial. The mechanisms by which *M. haemolytica* is developing multidrug resistance warrant investigation if antimicrobial utility in the therapy of bovine respiratory disease is to be preserved.
Figure 2. The percentage of *Mannheimia haemolytica* isolates, by year, that were resistant to 0, 1, 2, 3, 4, and 5 antimicrobials, respectively. Isolates in the 0 column would be considered pan-susceptible isolates. There were no isolates resistant to all 6 antimicrobials over the course of the survey.

Table 1. Antimicrobial coresistance patterns of *Mannheimia haemolytica* isolates in the current study.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Odds ratio*</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrofloxacin</td>
<td>0.71</td>
<td>0.32–1.58</td>
<td>0.41</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>1.43</td>
<td>0.63–3.25</td>
<td>0.40</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>3.52</td>
<td>1.07–11.61</td>
<td>0.04</td>
</tr>
<tr>
<td>Spectinomycin</td>
<td>1.08</td>
<td>0.48–2.44</td>
<td>0.86</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>2.64</td>
<td>0.97–7.17</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Odds ratio is the odds of an isolate being resistant to 1 or more other antimicrobial given resistance to the antimicrobial listed compared to the odds of an isolate being resistant to 1 or more other antimicrobials given the isolate is not resistant to the antimicrobial listed.

We can’t conclude anything from D-lab trends?
So, is it all OK?

- Does documenting that antimicrobial resistance has been around for eons before we humans started using antimicrobials make the current selective pressure “OK”?
IF WE CHOOSE TO CONSERVE ONE INPUT, THEN WE MUST NOT CONSERVE ANOTHER (OR OTHERS)
Food Animal Production System
Evolution Pressures

Disease
Water
Animals
Environment
Land
Price
Labor
Fuel
Regulations

“The System”
POLICY SOUP HAS JUST A DASH OF DATA FOR FLAVORING

Extralabel use restrictions on cephalosporins?

Guidance 209?
| CTC: 10 mg/lb BW for up to 5 days | Treatment |
| CTC: 400 g/ton to provide 10 mg/lb per day in calves up to 250 lbs | Prevention/Control |
| TC: 22 mg/kg for 3-5 days in calves | |

| OTC: 0.5 to 2.0 g/hd per day | |
| CTC: 350 mg/hd per day in beef cattle under 700 lbs | |
| CTC: 0.5 mg/lb per day in beef cattle over 700 lbs | |
| CTC: 350 mg/hd per day in beef cattle | |
| CTC: 25 - 70 mg/hd per day in calves 250 – 400 lbs | |
| CTC: 70 mg/hd per day in growing cattle over 400 lbs | |
| CTC: 0.1 mg/hd per day in calves up to 250 lbs | |

These are not all of the CTC, TC, and OTC indications, but are selected to illustrate the regimen range.
“IF WE JUST UNDERSTOOD ALL OF THE DATA THE WAY FORWARD WOULD BE CLEAR”
“However, the Agency believes that it is not limited to making risk determinations based solely on documented scientific information, but may use other suitable information as appropriate.”
The Executive Order directs the Secretary of HHS, in consultation with the Secretary of Agriculture, to establish a Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, to be composed of leading non-governmental experts.
The Overton Window

- Unthinkable
- Radical
- Acceptable
- Sensible
- Popular
- Policy

Prohibition of **therapeutic** uses of medically important antimicrobials
Prohibition of **prevention and control** uses of medically important antimicrobials
Prohibition of **growth promotion** uses of medically important antimicrobials

Question: What is the evidence that separates any of these 3 categories as to the effect of this use on antimicrobial resistance in human therapeutics?
So, where to from here

- Realities
  - I don’t think sales of antimicrobials for food animals are going to change significantly due to 209 and 213
  - A usable, acceptable method of end-user antimicrobial use to evaluate actual applications of antimicrobials in food animals isn’t going to be in place before December, 2016.
    - Even if it could, what was the baseline?
Realities

- Routine prevention and control will be the next highly scrutinized use...
  - when our only metric is reduction in use
The days of verbal treatment protocols are gone
The days of unacceptable treatment records are gone
The days of nontransparent use of antimicrobials in food animals are coming to an end
Neither veterinarians or producers can be passive in these efforts.
Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.

Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains.
The veterinary profession is not only going to be responsible for all medically-important antimicrobial uses in food animals...

we are going to be accountable
How Things Work

Expect these relationships to tighten
Veterinarians should have control of all uses of antimicrobials in animals.

Emphasize veterinary education on optimal use of these resources.

Duration of therapy research is an absolute requirement

Continue the emphasis on prevention of infectious disease
So where to from here

- Revisit efficacy research for many of the preventive applications (especially administered to a group through feed and water) to see if we actually still make a difference.
- Enforce our current regulations!!
- Include data and the correct analysis in the decision process
- It is reasonable to monitor both antibiotic resistance and antibiotic use (also reasonable to have a plan for analysis)
The Bottom Line for Veterinarians

- Will we retain our relevancy to antimicrobial use decisions in food animals, or...
- will we just sign authorizations based on a regulatory formulary developed out of political pressure exerted on regulatory agencies?
Tapping unsustainable groundwater stores for agricultural production in the High Plains Aquifer of Kansas, projections to 2110

David R. Steward, Paul J. Bruss, Xiaoying Yang, Scott A. Staggenborg, Stephen M. Welch, and Michael D. Apley

Departments of Civil Engineering, Kansas State University, Manhattan, KS 66506; Department of Environmental Science and Engineering, Fudan University.

The impacts of reduced pumping on corn and cattle production. So far, 30% of the groundwater has been pumped and another 39% will be depleted over the next 50 y given existing trends. Recharge supplies 15% of current pumping and would take an average of 500–1,300 y to completely refill a depleted aquifer. Significant declines in the region’s pumping rates would occur over the next 15–20 y, yet irrigated agricultural production might increase through 2040 because of projected increases in water use efficiencies in corn production. Water use reductions of 20% today would cut agricultural production to the levels of 15–20 y ago, the time of peak agricultural production would extend to the 2070s, and production beyond 2070 would significantly exceed that projected without reduced pumping. Scenarios evaluate incremental reductions of current pumping by 20–80%, the latter would result in a 10% decrease in production. Human activity has a significant impact on the structure and function of the earth (13), and changes driven by economic development and population growth occur faster than our understanding (14). We developed integrated methods to forecast groundwater depletion into the future, to relate the impacts of pumping on the crop and livestock sectors, and to study the impacts of changes in water use on agricultural production. We show that water limitations will begin to have a significant impact on food production over the next few decades; yet, the changes we might implement today could significantly alter future possibilities.

An Integrated System with Groundwater Depletion Supplying Irrigated Corn and Cattle Production

The consequences of aquifer depletion are studied in a region of