The Antibiotic Paradox: What’s the Scoop with Animal and Human Poop?

Kuldip Kumar, Ph.D
Soil Scientist - MWRDGC
Pharmaceuticals in Environment

- Antibiotics – Therapeutic or Non Therapeutic
  - Antibacterial Compounds in PCPs
  - Steroid Hormones
  - Drugs – Prozac, ……Antidepressants
  - Contraceptive pills
  - Blood Lipid-Lowering Agents
  - Beta Blockers
What Is An Antibiotic?

Antibiotics are powerful medicines that can kill bacteria and only bacteria.

Antibiotics do not work against viral infections like colds or the flu.
Discovery of penicillin

Alexander Fleming
1928
Nobel Prize, 1945

Discovery of sulfa drugs

Gerhard Domagk
1932
Nobel Prize, 1939
### Structure and Chemical Properties of Few Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Molecular Weight</th>
<th>Log $K_{OW}$</th>
<th>Solubility</th>
<th>$pK_a$</th>
<th>Metal Complexation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>444.43</td>
<td>0.4</td>
<td>30 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>333.1</td>
<td>3.5</td>
<td>5 g/L</td>
<td>7.1</td>
<td>n.a.</td>
</tr>
<tr>
<td>Tylosin</td>
<td>917.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- $K_{OW}$: Octanol-water partition coefficient.
- Solubility: g/L at 25°C.
- $pK_a$: Effective pKa values.
<table>
<thead>
<tr>
<th>Class/Group</th>
<th>Mechanism of Action</th>
<th>Mechanism of Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides,</td>
<td>Inhibits protein biosynthesis</td>
<td>Inactivation of antibiotic by enzymic modification</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Lactums, Glycopeptides</td>
<td>Inhibits cell wall biosynthesis</td>
<td>Reduced permeability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced affinity for target</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrolysis</td>
</tr>
<tr>
<td>Macrolides, Chloramphenicol</td>
<td>Inhibits protein biosynthesis</td>
<td>Reduced affinity for antibiotic target</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Inhibits DNA replication</td>
<td>Alteration in target</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased cell permeability</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Inhibits folic acid biosynthesis</td>
<td>Metabolic bypass of inhibited reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overproduction of antibiotic target</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Inhibition of RNA synthesis</td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Polymixins</td>
<td>Disruption of bacterial membranes</td>
<td>Altered cell permeability</td>
</tr>
</tbody>
</table>

Pre-antibiotic age

- Tuberculosis and pneumonia responsible for 25% of deaths in US (1900)
- More people died in wars due to infection than to actual traumatic injury
“...the greatest news event of World War II may well be the discovery and development...of penicillin.”

- “miracle drugs”
- “wonder drugs”
- “magic bullets”

⇒ The Golden Age
1940s: Limited to therapeutic usage

Late 1940s and 50s: Moore et al. (1946), McGinnis (1950), and others
- Improve feed efficiency
- Increase growth rates

Antibiotic use in livestock production
- Therapeutic
- Growth promotion
- Prophylactic
Antibiotics in the Environment

- National and local reconnaissance surveys
- 200 sites
  - 50% of surface water samples contained 1+ antibiotic
- Source?
## Antibiotics Detected in Drinking Water (Khetan and Collins, 2007)

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Antibiotics</th>
<th>Water</th>
<th>City/Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>165 ng/L</td>
<td>Clofibric acid</td>
<td>Tap</td>
<td>Berlin, Germany</td>
</tr>
<tr>
<td>258 ng/L</td>
<td>Carbamaepine</td>
<td>Finished</td>
<td>Atlanta, USA</td>
</tr>
<tr>
<td>ng/L levels</td>
<td>Sulfonamide, tetracycline, macrolides, quinolones</td>
<td>Point-of-use</td>
<td>10 cities in Canada</td>
</tr>
<tr>
<td>ng/L levels</td>
<td>Several antibiotics like fluro-quinolones, sulfonamides, tetracyclines etc.</td>
<td>Finished</td>
<td>North Carolina, USA</td>
</tr>
</tbody>
</table>
Are VETERINARY MEDICINES Causing Environmental Risks?

Des Moines Register
Swissinfo Apr 27, 2003

Environmental Science & Technology/ Aug. 1, 2000
Major Concerns Regarding Antibiotic Usage

- Antibiotics appearing in potable waters
- Antibiotics appearing in food supply
- Emergence of Antibiotic resistant bacteria

The major pathway is thru the land application of manure or biosolids.
Antibiotic Production and Use

Institute of Medicine
- 50 M pound produced per year
  - 60% Human medicine
  - 40% Agriculture uses
    - 32% Non-therapeutic
    - 8% Therapeutic

Union of Concerned Scientists
- 35 M pound produced per year
  - 13% Human medicine
  - 84% Agriculture Uses
    - 78% non-therapeutic
    - 6% Therapeutic
  - 3% Pets

K.M. Shea, 2003
## Antibiotics Approved by the FDA for Subtherapeutic Livestock Usage

<table>
<thead>
<tr>
<th>Antibiotics Approved for Subtherapeutic Livestock Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprolium</td>
</tr>
<tr>
<td>Bacitracin</td>
</tr>
<tr>
<td>Bambermycins</td>
</tr>
<tr>
<td>Carbadox</td>
</tr>
<tr>
<td>Clortetracycline</td>
</tr>
<tr>
<td>Erythromycin</td>
</tr>
<tr>
<td>Laidomycin</td>
</tr>
<tr>
<td>Lasalocid</td>
</tr>
<tr>
<td>Limcomycin</td>
</tr>
<tr>
<td>Monensin</td>
</tr>
<tr>
<td>Oxytetracycline</td>
</tr>
<tr>
<td>Penicillin</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Roxarsone</td>
</tr>
<tr>
<td>Tiamulin</td>
</tr>
<tr>
<td>Tylosin</td>
</tr>
<tr>
<td>Virginiamycin</td>
</tr>
</tbody>
</table>

*Identical/similar to human drugs*

Kumar and Gupta, 2003

USGS Report
Non-therapeutic Use of Antibiotics in Animal Production

**Dose:** 1-400 g/ton of feed

**Purpose:**
- To increase the ability of animal to absorb nutrients
- To reach the market weight on time
- To prevent the outbreak of diseases

Kumar et al., 2004; J. Environ Quality
Drug Portal to the World

adapted by Daughton from Ternes (April 2000)
## Proportion of Antibiotics Excreted in Urine and Feces

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>% Excreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines</td>
<td>75-80</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>60</td>
</tr>
<tr>
<td>Quinacrine</td>
<td>10</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>40</td>
</tr>
<tr>
<td>Tylosin, Monensin, Erythromycin</td>
<td>50-90</td>
</tr>
</tbody>
</table>

*Kumar et al., 2005; Adv Agron., Vol. 87*
### Concentration of Antibiotics in Different Manures

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Conc. mg/kg or mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines (Chlor, Oxy, Tet)</td>
<td>0.1-200</td>
</tr>
<tr>
<td>Tylosin</td>
<td>0.1 – 7.9</td>
</tr>
<tr>
<td>Monensin</td>
<td>1.0-5.0</td>
</tr>
<tr>
<td>Sulfamethazine</td>
<td>3.3-8.7</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.2-5.0</td>
</tr>
<tr>
<td>Nicarbazine</td>
<td>35.1-152.1</td>
</tr>
<tr>
<td>Sulfathiazole</td>
<td>0.1-12.4</td>
</tr>
</tbody>
</table>

Kumar et al., 2005; Adv Agron., Vol. 87
## Concentration of Antibiotics in Biosolids and Sewage sludge (Jones-Lepp and Stevens, 2007)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Media</th>
<th>Amount detected (mg/kg dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Sewage sludge</td>
<td>2.3-2.4</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Sewage sludge</td>
<td>2.1-2.4</td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Sewage sludge</td>
<td>0.001-0.16</td>
</tr>
<tr>
<td></td>
<td>Millorganite</td>
<td>0.014</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Sewage sludge</td>
<td>0.0003-0.063</td>
</tr>
<tr>
<td></td>
<td>Millorganite</td>
<td>0.0009</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Class A &amp; B biosolids</td>
<td>nd-0.041</td>
</tr>
<tr>
<td><strong>Sulphonamides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sewage sludge</td>
<td>nd – 0.197</td>
</tr>
<tr>
<td><strong>Trimethoprim</strong></td>
<td>Class A &amp; B biosolids</td>
<td>nd – 0.133</td>
</tr>
<tr>
<td><strong>Tetracylines (District)</strong></td>
<td>Class A &amp; B biosolids</td>
<td>nd – 0.171</td>
</tr>
</tbody>
</table>

nd—not detected
Swine Facility-CAFO
(Concentrated Animal Feeding Operation)
Relative Use of Biosolids, Manures, and Fertilizer (million tons dry weight) in US.

<table>
<thead>
<tr>
<th></th>
<th>Biosolids</th>
<th>Manure †</th>
<th>Fertilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produced</td>
<td>6.9</td>
<td>133</td>
<td>50</td>
</tr>
<tr>
<td>Land Applied</td>
<td>2.8</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>Fecal Coliform</td>
<td>~500,000 MPN/g</td>
<td>5-30 million colonies/g</td>
<td>-</td>
</tr>
<tr>
<td>Salmonella</td>
<td>&lt; 7 MPN/4g</td>
<td>3100 organisms/g</td>
<td>-</td>
</tr>
</tbody>
</table>

†Kumar, K., et al. 2005.
“Risks” – 40 times greater manure than biosolids?

Manure

“Manures have been used since beginning of time, and they have been used for so long that people don’t think about comparing risks and benefits – *manures are simply accepted and they have been for over 2000 years*”

Biosolids

YET “*for biosolids, it appears that risks associated with their use are no greater than – and, in many cases, may in fact be less than – risks associated with manure use*”
Finally, may be the solution lies in MTPs (Manure Treatment Plants) just like we have WWTPs (Waste Water Treatment Plants)
Fate and Transport of Veterinary Antibiotics in the Environment

Solid Beef Manure

Liquid Hog Manure

University of Minnesota has been in the lead
Antibiotic Losses from Manure Application

- Surface runoff
- Leaching

Staples (turkey and swine)
Lancaster, WI (swine and beef)
Lamberton (swine)
Drainage and Runoff Plots

Legend:
- Primary tile line (Diameter=10.2 cm)
- Second tile line (Diameter=12.7 cm)
- Non-porous tile line (Diameter=10.2 cm)
- Berm and plastic barrier
- Surface inlet
- Monitoring wells

MP+M: Moldboard plow & Manure
MP+U: Moldboard plow & Urea
CH+M: Chisel plow & Manure
CH+U: Chisel plow & Urea
Surf-N-Sub Plot Set-up
Monitoring Well

- Surface runoff outlet
- Surface runoff tipping bucket
- Tile line
- Tile line tipping bucket
- Sump pump
Winter and Snowmelt Scenes
Antibiotics Applied in Manure

- **Manure applied**: 46.23 m$^3$/ha
  
  
  - (4000 gallons/ac)

- **Chlortetracycline**: 5.0 mg/L of manure
  
  - = 231 grams/ha (0.21 lbs/ac)

- **Tylosin**: 5.6 mg/L of manure
  
  - = 259 grams/ha (0.23 lbs/ac)
Antibiotic Losses

- No losses of dissolved chlortetracycline in surface runoff or through tile drainage
- No losses of dissolved tylosin in tile drainage
Dissolved Tylosin Losses via Surface Runoff

<table>
<thead>
<tr>
<th>Event</th>
<th>Manure [mg/ha]</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 July</td>
<td>47</td>
</tr>
<tr>
<td>4 August</td>
<td>4</td>
</tr>
<tr>
<td>9 August</td>
<td>114</td>
</tr>
<tr>
<td>22 August</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
</tr>
</tbody>
</table>

0.07% of tylosin applied
Adsorption Isotherm - Batch Studies

Webster clay loam - 34% clay

Kumar et al., 2003
Chlortetracycline (CTC) and Tylosin (TYL) Remaining in the Soil (Webster clay loam) after 1 Year

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0-15 cm g/ha</th>
<th>15-30 cm g/ha</th>
<th>Total (g/ha) (% of applied)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYL -MP-M</td>
<td>76</td>
<td>41</td>
<td>117 (45%)</td>
</tr>
<tr>
<td>TYL -CP-M</td>
<td>91</td>
<td>56</td>
<td>147 (57%)</td>
</tr>
<tr>
<td>CTC -MP-M</td>
<td>84</td>
<td>16</td>
<td>100 (43%)</td>
</tr>
<tr>
<td>CTC -CH-M</td>
<td>117</td>
<td>26</td>
<td>142 (62%)</td>
</tr>
</tbody>
</table>

antibiotics not detected below 30 cm depth.
## Antibiotic Half-life (Days) During Composting of Turkey Manure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CHLOR-TETRACYCLINE</th>
<th>MONENSIN</th>
<th>TYLOSIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Management</td>
<td>1</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>High Management</td>
<td>0.9</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Vessel</td>
<td>0.8</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>

Holly Swanson and Kuldip Kumar, 2008
Cowazaky
Another Energy Solution
Summary

- Land application of manure is a major pathway of spread of antibiotics in the terrestrial environment.
- Composting may reduce residual antibiotic concentrations in manure.
- The overall contribution of biosolids may be relatively small.
Land application of manure and biosolids may result in antibiotics entering the food chain?
What is the Concern?

- Residues entering the food chain
- **Potential adverse effects** †
  - Development and spread of antibiotic resistance
  - Acute effects from allergic/ toxic reactions
  - Chronic effects from prolonged exposure
  - Disruption of digestive system functioning
- Not regulated (unlike animal residues)

Organic farming

US veg: not so organic?

By Jennifer Rohn

Reports that US growers of organic vegetables may be contaminating their produce with antibiotic-laden manure raises questions over the quality of the ‘organic’ produce imported into the UK from the US every year.

Certified organic farmers in the US can use untreated manure from livestock treated with antibiotics and other drugs. But researchers from the University of Minnesota have shown that urine. Many farmers, conventional and organic, routinely recycle this waste as fertiliser.

Although it is known that these substances can leach into the environment, no one had checked whether they are incorporated into vegetables. Kuldip Kumar and colleagues at the University of Minnesota planted corn, cabbage and green onions in soil treated with manure from pigs fed antibiotics, and several weeks later were able to measure chlortetracycline in the edible plant tops.

human microbial diseases ineffective. Kumar believes that hormones may also be taken up by vegetables grown in raw manure.

According to Holly Givens of the Organic Trade Association of America, nearly 60% of organic farmers use raw manure ‘frequently or regularly’. Other organic growers compost their manure first, and there is a mandatory time lag between manure spreading and harvest. But as little is known about how composting and time limits affect
Plants

Corn

Lettuce

Potato
Discussion

Antibiotic uptake†
- No uptake of tylosin (Bigger molecule)
- Sulfamethazine: 0.008-0.100 mg kg\(^{-1}\) (ppm) fresh weight
- Chlortetracycline: 0.002-0.017 mg kg\(^{-1}\) (ppm) fresh weight

Overall recovery of sulfamethazine and chlortetracycline in plant tissues was <0.1% applied in manure
- >70% in soil (i.e. not fully degraded)

Differences due to:
- Antibiotic structure/ chemistry
- Biomass & concentration
- Physiology
- Crop stage

Discussion

U.S. Food and Drug Administration Regulations †

- Animal residues: <0.1 mg kg\(^{-1}\) (ppm)
- Plant residues: NO REGULATION
  - Current study
  - <0.1 mg kg\(^{-1}\) (ppm) fresh weight
  - >0.1 mg kg\(^{-1}\) (ppm) dry weight

- Potential for food supply contamination (low levels)
- Organic farming implications

Regulatory Purposes – Maximum Residue Levels (MRLs)

MRLs (antibiotics) in animal tissues < 1 mg kg\(^{-1}\) fresh weight.
Sulfamethazine MRL = 0.1 mg kg\(^{-1}\) fresh weight of animal based products.
Acceptable Daily Intake (ADI) for Veterinary Pharmaceuticals (JECFA, 2006)

ADI value indicates the level of chemical that can be ingested daily over a lifetime without health risk.

Antibiotics ADI = 50 \( \mu g \) kg\(^{-1} \) body weight
Sulfamethazine was stable for 6 h in boiling water but not in hot oil ($t_{1/2} = 120$ min at 180 °C and 5 min at 260 °C).

Sulfamethazine spiked into raw pork was also found to be stable during a variety of common cooking processes (casseroling, roasting, grilling, pressure cooking, microwaving, and frying).

Oxytetracycline was not stable in water, oil, and cooking processes.
Summary

Manure

- Chances of antibiotics getting into plant based foods from manure applied soils are low
  - Very low concentrations
  - Actual health impact not known (low risk)

Biosolids

- Concentrations of antibiotics are way lower compared to manure to begin with.
- Not applied for use in human food crops in IL.
Bacterial Resistance to Antimicrobials
“...the greatest news event of World War II may well be the discovery and development...of penicillin.”

“miracle drugs”
“wonder drugs”
“magic bullets”

⇒ The Golden Age

Life Magazine (Aug. 14, 1944)
The Golden Age

 dez 1969, Surgeon General of United States: “It is time to close the book on infectious diseases”
 dez Smallpox - global eradication, last case in 1977
 dez 1990, TB and pneumonia caused less than 4% of deaths
 dez Measles - record low level in 1995

<table>
<thead>
<tr>
<th>Country</th>
<th>Azithromycin %</th>
<th>Penicillin %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>18.9</td>
<td>18.9</td>
</tr>
<tr>
<td>France</td>
<td>54.2</td>
<td>35.4</td>
</tr>
<tr>
<td>USA</td>
<td>35.4</td>
<td>28.7</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>82.9</td>
<td>64.3</td>
</tr>
<tr>
<td>Australia</td>
<td>16.8</td>
<td>13.6</td>
</tr>
</tbody>
</table>
Antibiotic Resistance

- **Susceptible = sensitive**
  - MIC is at a concentration attainable in blood or other appropriate body fluid using usually recommended dosages

- **Resistant**
  - MIC is higher than normally attainable levels in body fluids

- **Intermediate (moderately sensitive, moderately resistant)**
  - MIC is between sensitive and resistant levels, may be able to treat with increased dosage
The Golden Age has ended
Factors Associated with the Spread of Antibiotic-Resistant Bacteria

- Inappropriate use of antibiotics
  - Worldwide overuse
    - Extensive use in upper respiratory infections
  - Incomplete or incorrect therapeutic regimes
  - Availability of antibiotics without prescriptions
- Failure of hospital infection control policies
- Widespread use of antibiotics as a “growth enhances” in animal agriculture
- Increased opportunities for clonal dissemination of antibiotic-resistant bacteria both within and outside the hospital setting
  - Global dissemination of particular strains
Consequences of Antibiotic-Resistant Bacteria

- Change in the approach to the administration of “empiric antibiotic therapy”
- Increased number of hospitalizations
- Increased length of hospitalizations
- Increased morbidity and mortality
  - Emergence of strains totally resistant to all available antibiotics
- Choice of more expensive or more toxic therapeutic alternatives
- Increased costs by ~ 5 billion dollars
How did we get here?
Timeline of antibiotic resistance

- 1942 - penicillin available
- 1942 - penicillin resistant S. aureus
- 1940’s-1950’s - chlorampenicol, tetracycline, erythromycin resistance
- Early ‘60s - β-lactamase resistant penicillins available
- Late ‘70s - MRSA arose (methicillin resistant S. aureus)
- 1997 - first vancomycin resistant Enterococcus reported
- July 2002 - CDC reported first case of vancomycin-resistant S. aureus in US
It Can Happen to Anybody!

Oakland Tribune

Drug-resistant bacteria turns cut into life threatening ordeal

Critics: Drugs overused in people, animals

By Matt Carter

MURFreesboro — Investors have long said the secret to success is being able to diversify — and it seems to be working for the drugs industry. The latest in a series of drugs for the treatment of drug-resistant bacteria has been approved by the FDA.

The new drug, called Staphis, has been given to thousands of patients in the United States. It is the first to be approved for use in patients with drug-resistant infections.

The drug works by blocking an enzyme that helps bacteria to grow. It is now being tested in patients who have been infected with drug-resistant bacteria.

The FDA has approved the drug for use in patients who have been treated with antibiotics and who have not responded to treatment. It is also being studied for use in patients with drug-resistant infections who have not responded to other treatments.

Rosie writes about the nasty infection that could have killed her

“Staph is no laugh!”

Rosie writes about the nasty infection that could have killed her

7/4 Blowout recipes, 500 recipes, all-Americans plus

“Survivor” beauty essentials, what they wish they’d packed

cute Patootie kids’ room

If you want to wear summer outfits
How do they do it?
Pssst! Hey kid! Wanna be a Superbug...?
Stick some of **this** into your genome...
Even **penicillin** won’t be able to harm you...!

It was on a short-cut through the hospital kitchens that **Albert** was first approached by a member of the Antibiotic Resistance.
Genetics of Resistance

- **Intrinsic**
  - Proteins or impenetrable

- **Acquired**
  - Chromosomal mutation and selection
  - Plasmid-borne resistance
  - Transposition (Transposons)
  - Integrons
Plasmid Transfer of Antibiotic Resistance genes

Bacterial cell resistant to ampicillin

R-plasmid

sex pilus

Bacterial cell sensitive to ampicillin

Resistant to ampicillin

Bacterial cell sensitive to ampicillin
How do plasmids acquire new genes?

TRANSPOSITION - "jumping genes"
How do transposons acquire new genes?

INTEGRONS - gene capture and expression systems

“natural” genetic engineering
### Mechanisms of Chromosomal Resistance

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β-lactamase Action on Amoxycillin

β-lactamase
How do bacteria resist the action of antibiotics?

- Penicillins
- Tetracyclines
- Sulphonamides
- Permeability
- Inactivation
- Active efflux
- Altered target
Question?

What is the role of antibiotic feeding on development of antimicrobial resistance on the farm?
Percent Antibiotic Resistance Bacteria – Swine Farms

**Manure**

- Tet-20
- Tyl-10
- Mon-6

**Soil**

- Tet-20
- Tyl-10
- Mon-6

**Dog**

- Tet-Tetracycline
- Tyl-Tylosin
- Mon-Monensin
Feeding antibiotics may lead to increased resistance in manure and soil and may be transferred to dogs.
Laughter is the best medicine ––
I guess entertain them
Evolution of Antimicrobial Therapy in a Nutshell

- Yr 2000 B.C.  “Here eat this root”
- Yr A.D. 1000  “That root is heathen. Here, Say this prayer”
- Yr 1850  “That prayer is superstitious. Here drink this potion”
- Yr 1920  “That potion is snake oil. Here swallow this pill”
- Yr 1945  “That pill is ineffective. Here take this penicillin”
- Yr 1955  “OOPS, Bugs mutated. Here take this Tetracycline”
- Yrs 1960-07 more  “Forty seven more OOPS’s Here, take this powerful antibiotic”
- Yr 2010… “The Bugs have won! Here eat this root”
What do we do now?
Patient Guidelines

- Don’t insist on antibiotics when your doctor says they are not needed.
- If you are prescribed drugs, take the full course.
- Never hang on to unfinished prescriptions with the intention of using them for new ailments.
- Never share antibiotics with others.
- Keep a diary of antibiotic use.
Physician Guidelines

- Reduce inappropriate use of antibiotics
- Meticulous infection control, especially in hospitals and long term care facilities
- Reduce use of broad spectrum antibiotics, use narrow spectrum antibiotics when possible
- Urge patient compliance
- Increase surveillance
Federal Intervention

- FDA proposes ban of two poultry drugs (10/27/00)
  - Fluoroquinolones
  - Abbott has pulled drug, Bayer has not

- New antibiotics
  - Zyvox (linezolid) - active against MRSA, VRE
    - FDA approved 4/00
  - Synercid - active against MRSA
    - FDA approved 9/99
    - Turkeys fed virginiamycin have Synercid-resistant bacteria
Roadblocks

- Research and development of new antibacterial can take 15-20 years and cost over $500 million.
- Pharmaceutical companies want largest usage from products
- Farmers and ranchers resist bans on agricultural use
Not Over Yet

But there are serious concerns about the decreasing effectiveness of antibiotics because of increased antibiotic prevalence and emergence of antibiotic resistance in the environment.
Which bacteria are of greatest concern for antibiotic resistance?
Streptococcus pneumoniae

- Most common cause of bacterial pneumonia, also causes meningitis, bacteremia, >7 million ear infections per year,
  - 10-40% are caused by DRSP (drug-resistant S. pneumoniae)
- Until late 1970’s, readily killed with penicillin
- Now, up to 30% are penicillin resistant
**Enterococcus**

- **1987** - Van-R Enterococcus - England and France
- **1989** - NYC
- **1991** - 38 US hospitals
- **1992** - lab transfer to *Staphylococcus*
- **1993** - 14% patients in ICU with VRE
Staphylococcus aureus

- Methicillin resistance common
- Vancomycin susceptibility decreased
  (VISA - vancomycin-intermediate S. aureus)
- VRSA - vancomycin resistant S. aureus
Neisseria gonorrhoeae

- More than 50% are resistant to penicillin or tetracycline or both
  - in SE Asia, ~98% are penicillin resistant
- Resistance to ciprofloxin increasing
- Gonorrhoea increases shedding of HIV, may also increase susceptibility
Mycobacterium tuberculosis

- 1/7 new TB cases is resistant to isoniazid and rifampin (5% die)
- Cost of treating one person with multidrug-resistant TB is 100 times greater than the cost of treating non-resistant cases.
  - NYC spent $1 billion to control outbreak of multidrug-resistant TB in early 1990s
- All known resistance due to mutation
  - Therefore, multiple drugs beneficial
Escherichia coli

Resistance to fluoroquinolones

- 1983-1990, all were susceptible (92 strains)
- 1991-1993, 11/40 were highly resistant to 5 different quinolones