Antibiotic Resistance

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FAILURE

When Your Best Just Isn’t Good Enough.
Acknowledgments

• David G. White, PhD
  – Director National Antibiotic Resistance Monitoring System (NARMS) FDA, CVM

• Paula J. Fedorka-Cray, PhD
  – Research Leader, Bacterial Epidemiology and Antimicrobial Resistance (BEAR) Research Unit, USDA, ARS

• H. Morgan Scott, DVM, PhD
  – Associate Professor, Epidemiology, TAMU
Antimicrobial Resistance
Implications for the Food System

The Antibiotic Paradox
How the Misuse of Antibiotics Destroys Their Curative Powers
Second Edition

Stuart B. Levy, M.D.
**Words of Caution**

**The Nobel Prize in Physiology or Medicine 1945**
"for the discovery of penicillin and its curative effect in various infectious diseases"

Sir Alexander Fleming
Nobel Lecture, December 11, 1945
*Penicillin*

“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.”

The sample of Penicillium can now be found in the Science Museum, London
There are > 100 antibacterial agents currently approved for use in clinical medicine

However, resistance has followed each new antibiotic, albeit with varying time and frequency
The Biology of Antimicrobial Resistance

- Resistance precedes the use, and in some instances even the discovery, of antimicrobial agents.
- Historically, resistance emerged incrementally from low- to medium- to high-levels. Less true today, with MDR mobile DNA elements.
- Resistance typically develops from single to multiple phenotypes.
- Return to a susceptible microbial ecosystem following removal of drug is unpredictable.
Exceptions to the “Rule”

PENICILLIN USE [Nearly 60 Years]

S. aureus (n=144,531; 92% Resistant)
S. pneumoniae (n=8,632; 18% Resistant)

S. pyogenes (n=868; 0% Resistant)
E. faecalis (n=22,202; 1.7% Resistant)

Thornsberry, C., 2004. ASM.
Why are bacteria resistant to antimicrobials that perhaps have not been used?

- Intrinsic resistance
- Linkage of antibiotic resistance genes
- Selection of resistance determinant with broad specificity
- Other selection pressures present
  - e.g. disinfectants, heavy metals
Are these chemicals perturbing the cell membrane?

- Chlorine – up to 50 ppm
- Cecure – cetylpyridium chloride (CPC)
- Inspexx – per oxyacetic acid
- Safe$_2$O – acidified calcium sulfate
- Sanova – acidified sodium chlorite
- TomCO – CO$_2$ / chlorine system
- TSP – trisodium phosphate
Selection pressure: conflicting theories

“Resistance is Inevitable”
19th Century

Charles Darwin

“Resistance is Futile”
24th Century

The Borg
The Origin of Species by Means of Natural Selection, 1859
Charles Darwin

His theory of evolutionary selection holds, simply, that variation within species occurs randomly and that the survival or extinction of each organism is determined by that organism's ability to adapt to its environment.

“Survival of the Fittest”
Drug Resistance Equation

Resistance gene(s) in bacteria

+ Antimicrobial (selective agent)

Antimicrobial-resistant bacteria
The Cycle of Resistance

Resistance gene incorporated into Mobile DNA element

Resistance pre-existing?

SELECTION PRESSURE (antimicrobials, disinfectants, heavy metals)

Susceptible cells die

Resistance gene incorporated into Mobile DNA element

Antibiotic resistant bacterium

RESISTANCE TRANSFER transformation, conjugation, etc

Resistant strains survive the antimicrobial and divide
Dissemination of Antimicrobial Resistance
Dissemination of Antimicrobial Resistance
Use of Antimicrobials in Food Animal Production

- To treat diseased animals
- To control outbreaks of disease
- To prevent infections
- To promote weight gain and improve feed efficiency
  - most controversial, since drugs can be administered continuously to healthy animals
# Dissemination of Streptothricin Resistance in *E. coli*

Nourseothricin introduced in animal feed in 1983 in former East Germany

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<thead>
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</table>

Who is at Risk?

- Three year longitudinal study for AR *E. coli*
- 4048 human, 3429 swine samples
- Swine had higher rates of overall AR than humans
- Significant differences in AR between humans and swine
- Purchased boars > nursery piglets > breeding boars highest rates
- Slaughter workers > non-swine workers > swine workers

NDSU Animal Sciences

Scott et al, 2008 Appl Env Micro
Microbial Gene Exchange

- Pseudomonads
- Enterobacteriaceae
- Vibrio cholerae
- Campylobacter
- Staphylococci
- Enterococci
- Pneumococci
- Streptococci
Use of Antimicrobials in Food Animal Production and Potential Human Health Implications

- Antimicrobial-resistant zoonotic bacterial pathogens are selected, and food is contaminated during slaughter and/or preparation
  - After consumption of contaminated food, pathogen causes an infection that requires antibiotic treatment and therapy is compromised

- Antimicrobial-resistant bacteria non-pathogenic to humans are selected in the animal
  - After consumption of contaminated food, bacteria transfer resistance determinants to other bacteria in the human gut
  - Including both commensal and potential pathogens

- Antimicrobials remain as residues in food products
  - Which allows for selection of antimicrobial-resistant bacteria after the food has been consumed
Potential Consequences of Infections Caused by Antibiotic Resistant Pathogens

- Increased likelihood of treatment with inappropriate antimicrobial
- Increased morbidity and mortality
- Change of empiric therapy
  - potentially less effective, more expensive and more toxic
- Increased length of illness in the hospital
  - increased length of hospital stay
  - increased laboratory costs
  - increased infection control costs
Worldwide Resistance by Select Bacterial Pathogens

<table>
<thead>
<tr>
<th>Region</th>
<th>No. Isolates Tested</th>
<th>% Resistant</th>
<th>1997</th>
<th>1998</th>
<th>1999</th>
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<tr>
<td>MRSA</td>
<td>11,156</td>
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<td>22.4</td>
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<td>5.7</td>
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<tr>
<td>MDR - P. aeruginosa</td>
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<td>2.5</td>
<td>1.6</td>
<td>2.1</td>
<td>2.0</td>
<td>2.0</td>
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What is Responsible for the Widespread Dissemination and Diversity of Antimicrobial Resistance Phenotypes Among Bacteria?

- Plasmids
- Transposons
- Integrons
Transfer of Antibiotic Resistance

- **Plasmids**
  - R factors
  - Can possess multiple antimicrobial resistance genes, including other elements
  - Conjugative (mediate their own transfer)

- **Transposons**
  - “Jumping genes”
  - Can possess multiple resistance genes
  - Can move freely from chromosome to plasmid and vice versa
  - May be conjugative
Transfer of Antibiotic Resistance

- **Integrons**
  - “Gene catchers” Novel group of mobile DNA elements
  - Possess single or groups of antibiotic resistance genes in tandem (mobile gene cassettes)
  - Genes include β-lactamases, aminoglycoside modifying enzymes, sulfa/trimethoprim resistance, quinolone and chloramphenicol resistance
  - Can be plasmid mediated or chromosomal
  - 4 classes currently recognized

- **Common regions (CRs)**
  - Found close to 3’ conserved sequences of class 1 integrons
  - Resemble an atypical class of insertion sequences, IS91-like
  - Closely associated with many antimicrobial resistance genes (CTXs)
General Structure of a Class 1 Integron

Insertion of antibiotic resistance genes

NDSU Animal Sciences
Insertion/Excision of Gene Cassettes into Integrons

Integration

Excision

Gene cassette (Str\(^R\))

P\(_c\)

P\(_{\text{ant}}\)

**intI**

Gene cassette

\[5'\text{-CS} \quad q\text{ac}\Delta E \quad sulI \quad 3'\text{-CS}\]
Insertion/Excision of Gene Cassettes into Integrons

\[ \text{intI} \quad \text{qac} \Delta E \quad \text{sulI} \]

Integration

\[ \text{3'}-\text{CS} \]

\[ \text{intI} \quad \text{qac} \Delta E \quad \text{sulI} \]

Gene cassette (Amp^R)

Gene cassette
Transposon Tn21
The Biological Matryoshka effect

**Gene Cassette:** encodes streptomycin resistance

**Integron, In2:** encodes resistance to streptomycin and sulfa antimicrobials

**Tn21:** encodes Mercury resistance

**Plasmid:** encodes resistance to streptomycin, sulfas, mercury, chloramphenicol and ampicillin
Matryoshka (Russian doll) effect
Transferable Drug Resistances

- Beta-lactams
- Chloramphenicol; (Florfenicol)
- Tetracycline
- Macrolides; Lincosamides
- Sulfa drugs
- Aminoglycosides
- Quinolones?
First plasmid-mediated quinolone resistance determinant, Qnr (later termed QnrA), was described in a *K. pneumoniae* strain from the U.S. in 1998

Three major groups, QnrA, QnrB, and QnrS, have been identified in various enterobacteriaceae
- At least five *qnrB* and two *qnrS* variants have been described
- *qnrA* can be located in complex *sul1*-type class 1 integrons

May protect DNA gyrase directly from quinolone inhibition, leading to an 8- to 32-fold increase in MICs

Aquatic environment the reservoir???
Widespread *Salmonella* MDR-AmpC Plasmid Present in MDR *Yersinia pestis*

- *Y. pestis* plasmid pIP1202 has an IncA/C plasmid backbone that is shared by MDR plasmids isolated from *S. Newport* and the fish pathogen *Y. ruckeri*.

- This plasmid backbone was detected in numerous MDR enteric bacteria from retail meats collected between 2002 and 2005 in the US.

- The high degree of sequence identity and gene synteny of this shared plasmid backbone suggests recent acquisition of these plasmids from a common ancestor.

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**Welch et al. Multiple antimicrobial resistance in plague: an emerging public health risk.**

Gene Synteny

The condition of two or more genes being located on the same chromosome whether or not there is demonstrable linkage between them.

Commensal Bacteria as a Reservoir?

Resistance gene reservoir hypothesis

Possible resistance gene transfers

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th>Gram-negative</th>
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<tbody>
<tr>
<td>Bacillus spp.</td>
<td>ermG Bacteroides spp.</td>
</tr>
<tr>
<td>Clostridium spp.</td>
<td>ermB Bacteroides spp.</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>Campylobacter spp.</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>Fusobacterium nucleatum</td>
</tr>
<tr>
<td>Clostridium spp.</td>
<td>Gardenella vaginalis</td>
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<tr>
<td>Enterococcus spp.</td>
<td>Haemophilus spp.</td>
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<tr>
<td>Staphylococcus spp.</td>
<td>Neisseria spp.</td>
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<tr>
<td>Streptococcus spp.</td>
<td>Veillonella spp.</td>
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<tr>
<td>Actinomyces spp.</td>
<td>Firmicute Statistical</td>
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<tr>
<td>Bifidobacterium spp.</td>
<td>Eubacterium Statistical</td>
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<tr>
<td>Clostridia spp.</td>
<td>ermF Bacteroides spp.</td>
</tr>
<tr>
<td>ErM Bacteroides spp.</td>
<td>tetQ Bacteroides spp.</td>
</tr>
<tr>
<td>ErN Bacteroides spp.</td>
<td>Bacteroides spp.</td>
</tr>
<tr>
<td>Porphorymonas spp.</td>
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</table>
Soil as a Reservoir of Resistance

- Screened 480 soil bacteria against a panel of 21 antimicrobials
- Multidrug resistance was extensive
- No evidence of direct transfer of resistance elements to pathogens
- However, shows the environmental resistome is much more significant than previously thought
The Antimicrobial Resistome

The resistome comprises all the antimicrobial resistance genes and their precursors in pathogenic and non-pathogenic bacteria (including antibiotic-producing bacteria).

The Enemy Among Us

- Chromosomal resistance factors (DNA) found in contaminated antibiotics
- Produced from source antibiotic-producing organism
- Possible explanation for rapid rise in resistance factor dissemination

The Global Village and Antimicrobial Resistance

- The rapid globalization of food production and trade has increased the potential for international incidents involving food contamination with microbial or chemical hazards.

- Information on the magnitude of the public health burden due to resistant foodborne pathogens shows that the circumstances are complex and differ by region and country.

- Can be influenced by a number of variables:
  - Human and veterinary antimicrobial use practices
  - Process controls at animal slaughter
  - Food storage and distribution systems
  - Availability of clean water
  - Proper cooking and home hygiene methods, among others
An International Outbreak Strain?

- Imported food studies revealed a multidrug resistant (including CipR) *S. Schwarzengrund* isolate from dehydrated chili’s from Thailand.

- Its PFGE pattern was indistinguishable from that observed among three CipR resistant *S. Schwarzengrund* isolates recovered from human clinical illness in both Denmark and Thailand.

- This data indicates that global food trade could transmit foodborne pathogens from one country to another.
  - No illness linked to this strain in the U.S.

Hurry, Sale ends today!!!
Sulfamethoxazole/trimethoprim 800/600 mg

500 mg Cephalexin

Antihistamine

Vitamin

Vitamin C

Tetracycline HCL 500 mg

Also cephalexin and the 3 mystery tablets
Resistance patterns for *Escherichia coli* isolates from large animal panels for the year 2001, NDSU VDL, March 2002.

<table>
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<tr>
<th>Antibiotic</th>
<th>n</th>
<th>Percent Sensitive</th>
<th>Percent Intermediate</th>
<th>Percent Resistant</th>
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<td>489</td>
<td>99</td>
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<tr>
<td>Ampicillin</td>
<td>503</td>
<td>36</td>
<td>-</td>
<td>63</td>
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<td>Ceftiofur</td>
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<td>16</td>
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<td>Florfenicol</td>
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## NDSU VDL Antibiotic Resistance Patterns for E. coli, 2006

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<th>% Susceptible</th>
<th>% Intermediate</th>
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n=298
Food for Thought

- Macovei and Zurek, AEM, 2006, 72:4028-4035

- Showed that houseflies in food-handling and -serving facilities carry antibiotic-resistant and potentially virulent enterococci
We still need to improve our understanding of -

- The contribution of the normal flora to antimicrobial resistance
- Factors that contribute to the selection of resistant microbes (dose, frequency of dose, duration, organism exposure)
- The frequency of selection for antimicrobial resistance bacteria
- Adaptation of resistance mechanisms
- Mechanisms of linkage and transmissibility of resistance determinants
Cycle of Antimicrobial Development and Emergence of Resistance

Sisyphus is best known for being punished in the **Underworld** by rolling a stone with his hands and head in an effort to heave it over the top of a hill; but regardless of how much he pushes, the stone always rolled down again and again.
Antimicrobial Resistance = Complex Phenomenon

- Antimicrobial resistance is a broad-based problem that involves not just patients and doctors/veterinarians in clinical settings, but industry, public health officials, farmers, producers and consumers.

- The solutions involve a range of federal and state agencies, international governments and organizations, consumer, scientific and professional groups and individuals.
Antimicrobial Resistance = Complex Phenomenon

- It is most likely impossible to stop antimicrobial resistance from emerging
- Resistance is a natural consequence of biological adaptation, which is an inherent factor in the adaptation of organisms
- Therefore, efforts to tackle antimicrobial resistance should focus primarily on how we can better mitigate resistance development and transfer
NARMS Annual Reports

More details and data are available on the FDA-CVM webpage and links to CDC, USDA and CVM annual reports

http://www.fda.gov/cvm/narms_pg.html
Salmonella - NARMS

- Sentinel organism
- ~ 51,000 isolates tested since 1997
- Serotypes
  - Vary over time
  - Vary by source
Summary reports and interactive feature on website

Percent Resistance Trends - Top Serotypes
*Cattle at Slaughter*

**Antimicrobials**
- Amikacin
- Gentamicin
- Kanamycin
- Streptomycin
- Ampicillin
- Amoxicillin/Clavulanic Acid
- Ceftiofur
- Ceftriaxone
- Cephalothin
- Cefoxitin
- Sulfonamides
- Trimethoprim/Sulfamethoxazole
- Chloramphenicol
- Ciprofloxacin
- Nalidixic Acid
- Tetracycline

**Serotypes**
- Montevideo
- Anatum
- Newport
- Muenster
- Typhimurium
- Typhimurium var. 5-
- Kentucky
- Mbundaka
- Cerro
- Agona
- Meleagridis
- Reading
- Senftenberg
- Infantis
- Dublin

**Number of Isolates Tested**

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</table>
Percentage of Isolates of S. Typhimurium resistant to at least ACSSuT and percentage confirmed DT104, 1997-2006* (Slaughter isolates)

<table>
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<th>Year</th>
<th>Typhimurium - Human (includes var. 5-)</th>
<th>Typhimurium, Animal</th>
<th>Typhimurium var. 5, Animal</th>
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* 2006 preliminary data
Distribution of DT104 isolates from slaughter by source, 1997-2006

No. of isolates

* 2006 preliminary data
Antimicrobial resistance is a multi-factorial problem that requires a multi-disciplinary and multi-agency approach.
March 22, 1954, Sir Alexander Fleming was asked about a cure for colds.

"A good gulp of hot whisky at bedtime -- it's not very scientific, but it helps."
APATHY

If we don’t take care of the customer, maybe they’ll stop bugging us.