The Challenge of Antimicrobial Resistance in Human Health

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R. K. Flamm is an employee of JMI Laboratories, Inc. which has received research and educational grants in 2010-2011 from – Achaogen, Aires, American Proficiency Institute (API), Anacor, Astellas, AstraZeneca, Bayer, bioMerieux, Cempra, Cerexa, Cosmo Technologies, Cubist, Daiichi, Enanta, Furiex, GlaxoSmithKline, Johnson & Johnson (Ortho McNeil), LegoChem Biosciences Inc, Meiji Seika Kaisha, Merck, Mpex, Nabriva, Novartis, Paratek, Pfizer (Wyeth), PPD Therapeutics, Premier Research Group, Seachaid, Shionogi, Shionogi USA, The Medicines Co., Theravance, TREK Diagnostics, Vertex Pharmaceuticals and some other corporations. R. K. Flamm owns stock in Johnson and Johnson.
The Challenge of Antimicrobial Resistance in Human Health
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- Markedly increasing resistance development (novel mechanisms) and rates since 1975
- Reduced interest in anti-infective development by pharmaceutical companies
- Diminished infection control and public health infrastructure
- Limited treatment options
- Urgent need for action (example: ASM Task Force on Antibiotic Resistance, 1995) = SURVEILLANCE
  (also EDUCATION and RESEARCH)
Bad Bugs, No Drugs

- Declining research investments in antimicrobial development

- The Antimicrobial Availability Task Force of the IDSA identified problematic pathogens including gram-negative bacteria

- Problematic pathogens can “escape” the activity of antibacterial drugs

  - “ESKAPE” pathogens include
    - Enterococcus faecium
    - Staphylococcus aureus
    - Klebsiella pneumoniae
    - Acinetobacter baumannii
    - Pseudomonas aeruginosa
    - Enterobacter spp

The Infectious Diseases Society of America’s (IDSA) Efforts

- **2004**
  - IDSA published whitepaper “Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates a Public Health Crisis Brews,” and launched an advocacy campaign to spur government solutions.

- **2009**
  - IDSA published an update on “Bad Bugs, No Drugs…”

- **2010**
  - IDSA statement before the House Committee on Energy and Commerce Subcommittee on Health June 9, 2010
    - “Six years later, the drug pipeline and resistance problems have only grown worse as more companies have withdrawn from antibiotic research and development (R&D) and ever-more resistant “bad bugs” have spread across the United States in health care settings and communities, devastating the lives of the young and the old, the healthy and the frail.”

The Infectious Diseases Society of America’s (IDSA) Statement on Antibiotic Resistance: Promoting Critically Needed Antibiotic Research and Development and the Appropriate Use (“Stewardship”) of these Precious Drugs Before the House Committee on Energy and Commerce Subcommittee on Health June 9, 2010
A Changing Landscape for Approval of Antibacterial Agents: FDA Approvals Over Time

Bars represent number of new antimicrobial agents approved by the FDA during each time frame.

“The number of antibacterials in Phase 2 or 3 of clinical development remains disappointing, and the absence of agents designed to treat infection due to resistant gram-negative bacilli places patients with these infections in danger.”

– Boucher, et al. CID 2009

“We seek a global commitment by the United States Government, particularly the Department of Health and Human Services (HHS), and other governments to create a sustainable antibiotic R&D enterprise, which in the short-term can produce 10 new safe and effective antibiotics by 2020. The antibiotics we seek are those that can treat the most serious and life-threatening pathogens against which most approved antibiotics are not effective.”
A Deadly Germ Unleashed by Antibiotics

For years, health officials have sounded the alarm about overuse of antibiotics and the emergence of so-called “superbugs” that resist treatment. But the spread of a deadly germ linked with antibiotic use shows just how immediate the threat really is.

The culprit is Clostridium difficile, a bacteria that can cause life-threatening infection, diarrhea and stomach pain. What is so frightening about C. difficile is that it is typically triggered by a round of antibiotic use. In addition to killing the targeted infections, antibiotics wipe out beneficial bacteria, which can make a body more vulnerable to C. difficile infection.

To learn more about C. difficile read the full story, “Stomach Bug Crystallizes a Threat From Antibiotics.”

And please, join the discussion below. Have you or any one you know been diagnosed with C. difficile?

Press Release

Moms Across America Uniting to Preserve Effectiveness of Antibiotics

Poll of 800+ Moms Shows More than Three Out of Four Concerned about Use of Antibiotics in Food Animal Production, Support Government Action to Limit Such Use

May 3, 2011

Contact: Josh Wenderoff, 202.540.6842

WASHINGTON -- The Pew Campaign on Human Health and Industrial Farming today launched "Moms for Antibiotic Awareness," a grassroots movement of moms working to preserve the effectiveness of antibiotics for their children and families.

The campaign also released the results of an online poll of 804 American mothers who are registered voters and have children aged 15 or younger. Eighty percent of the respondents were concerned about giving antibiotics to animals that are being produced for meat and poultry, with 42 percent saying they are "very concerned" about this practice.

Each year, tens of thousands Americans die and hundreds of thousands more fall seriously ill from infections resistant to antibiotics. Newborns, children and seniors are particularly vulnerable to these diseases.

"Seven years ago, my one-and-a-half-year-old son, Simon, died from an infection because the antibiotics we relied on had become useless," said Everly Macario, founder of the MRSA Research Center at the University of Chicago and one of the first mothers to join Moms for Antibiotic Awareness. "Simon's death sounded an alarm that my fellow moms across this country need to hear: antibiotics are increasingly ineffective against life-threatening infections, and the lives of our children and loved ones are at stake. I am asking my fellow moms and their family members to honor Mother's Day by visiting www.SaveAntibiotics.org and joining Moms for Antibiotic Awareness."

Last year, the U.S. Food and Drug Administration (FDA), the U.S. Department of Agriculture and the Centers for Disease Control and Prevention testified before Congress that there was a definitive link between the non-therapeutic uses of antibiotics on industrial farms and the crisis of antibiotic resistance in humans. In addition, many medical organizations including the American Medical Association, American...
History of Medicine

2000 B.C.  Here, eat this root.
1000 A.D.   That root is heathen. Here, say this prayer.
1850 A.D.   That prayer is superstition. Here, drink this potion.
1920 A.D.   That potion is snake oil. Here, swallow this pill.
1945 A.D.   That pill is ineffective. Here, take this penicillin.
1955 A.D.   Oops….bugs mutated. Here, take this tetracycline.
1960-2010 A.D. 50 more “oops”…Here, take this powerful antibiotic.
2011 A.D.   The bugs have won! Here, eat this root.

Anonymous
Examples of Antimicrobial Resistance Surveillance Programs

Human pathogens

Global programs
Alexander Project (1992-2001)
MYSTIC Program (1999-2008)
PROTEKT (1999-2008)
SENTRY Program (1997-present)

National/Regional programs
TSN (USA)
EARSS (EUROPE)
CANWARD (CANADA)

Veterinary pathogens

Global programs
WHO GSS (WHO, CDC)

National programs
JVARM (JAPAN)
NARMS (CDC, USDA, FDA)
FoodNet (CDC, USDA, FDA)
SENTRY Program Description

• Global (four regions, 35 countries, 100-140 sites)
  - North America
  - Latin America
  - Europe
  - Asia Pacific (Asia, Australia, South Africa)

• Objectives (prevalence design)
  - Infection site (BSI, CARTI, HAP, UTI, SSSI, etc.)
  - Genus or species
  - Special needs (resistance phenotype, etc)

• Central reference laboratory processing
  - Completely available organism collection

• 35 to 50 antimicrobials each year
  - Investigational agents are selectively monitored
### List of Most Common Pathogens from SENTRY 2010

#### Bloodstream Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Pathogen</th>
<th>Pathogen</th>
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</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em> (approx 23%)</td>
<td><em>Beta-haemolytic streptococci</em></td>
<td><em>Citrobacter</em> spp.</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Haemophilus</em> spp.</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.*</td>
<td><em>Viridans group streptococci</em></td>
<td><em>B. fragilis</em> group</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.*</td>
<td><em>Proteus mirabilis</em></td>
<td><em>Bacillus</em> spp.</td>
</tr>
<tr>
<td><em>Coagulase-negative staphylococci</em></td>
<td><em>Serratia</em> spp.</td>
<td><em>Aeromonas</em> spp.</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.*</td>
<td><em>Salmonella</em> spp. (&lt;1%)</td>
<td><em>Listeria</em> spp.</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.*</td>
<td><em>Stenotrophomonas maltophilia</em></td>
<td><em>Corynebacterium</em> spp.</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.*</td>
<td><em>Indole-positive</em> <em>Proteus</em> spp.</td>
<td></td>
</tr>
</tbody>
</table>

* ESKAPE pathogens; “Bad Bugs, No Drugs”
Trend and Current Status of Resistance

- **Gram-positive pathogens**
  - *S. aureus (MRSA)*
  - Enterococci (VRE)
  - *S. pneumoniae (PenR)*

- **Gram-negative pathogens**
  - Enterobacteriaceae
    - *E. coli (CipR, ESBL)*
    - *Klebsiella* spp. (CipR, ESBL, CarbR)
    - *Enterobacter* spp. (CazR, ESBL)
  - Non-fermentative pathogens
    - *P. aeruginosa (CarbR, MBL)*
    - *Acinetobacter* spp. (CarbR, MDR)

<table>
<thead>
<tr>
<th>Region</th>
<th>MRSA</th>
<th>VRE (E. faecium)</th>
<th>S pneumoniae/penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>34 →58%</td>
<td>17 →30 (73)%</td>
<td>14 →15%</td>
</tr>
<tr>
<td>Europe</td>
<td>26 →28%</td>
<td>1 →8 (22)%</td>
<td>10 →15%</td>
</tr>
<tr>
<td>Latin America</td>
<td>35 →38%</td>
<td>2 →9 (36)%</td>
<td>12 →13%</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>46 →42%</td>
<td>1 →5 (10)%</td>
<td>18 →32%</td>
</tr>
</tbody>
</table>

Trends in MRSA Rates in SENTRY Program Medical Centers (Bacteremias in USA, 1997–2009)

* = MRSA rate declined in 2009

Trends in Erythromycin, Levofloxacin, Clindamycin, Gentamicin, Tetracycline, and TMP/SMX Resistance Rates among 20,049 MRSA in USA (SENTRY Program, 2000-2009)\textsuperscript{a}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{trends_graph.png}
\caption{Trends in Erythromycin, Levofloxacin, Clindamycin, Gentamicin, Tetracycline, and TMP/SMX Resistance Rates among 20,049 MRSA in USA (SENTRY Program, 2000-2009)\textsuperscript{a}}
\end{figure}

\textsuperscript{a} Modified from Jones et al., Diagn. Microbiol. Inf. Disease 71: (in press), 2011.
### Six-year Trends in Linezolid Resistance Rates Observed in the USA LEADER Program (2004 to 2009; 33,378 Isolates)

<table>
<thead>
<tr>
<th>Organism (no. tested)</th>
<th>% of isolates nonsusceptible or resistant to linezolid(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
</tr>
<tr>
<td><strong>S. aureus (18,537)</strong></td>
<td></td>
</tr>
<tr>
<td>CoNS (4,526)</td>
<td>0.20</td>
</tr>
<tr>
<td>Enterococci (4,577)</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>S. pneumoniae (3,292)</strong></td>
<td>0.00</td>
</tr>
<tr>
<td>Other streptococci(^b) (2,446)</td>
<td>NT</td>
</tr>
<tr>
<td><strong>All organisms (33,378)</strong></td>
<td>0.14</td>
</tr>
</tbody>
</table>


\(^b\) Viridans group and β-haemolytic streptococci.
**S. aureus** Indentified as Linezolid-Resistant in the 2009 LEADER Program (MIC, ≥ 8 µg/ml) in the USA, only 5 of 3,257 Isolates or 0.15%

<table>
<thead>
<tr>
<th>Location (State)</th>
<th>Age/Sex</th>
<th>MIC (µg/ml)</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connecticut</td>
<td>68/M</td>
<td>8</td>
<td>L3 (S145 deletion)</td>
</tr>
<tr>
<td>California</td>
<td>14/F</td>
<td>16</td>
<td>G2576T</td>
</tr>
<tr>
<td>Kansas</td>
<td>17/M</td>
<td>16</td>
<td>G2576T</td>
</tr>
<tr>
<td>Ohio</td>
<td>52/M</td>
<td>16</td>
<td>cfr</td>
</tr>
<tr>
<td>Kentucky</td>
<td>52/M</td>
<td>16</td>
<td>cfr</td>
</tr>
</tbody>
</table>

Regional Trends in Blood Culture VRE Rates (SENTRY Program, 1997-2008 [12 years]; >35,000 Isolates)

Progression of Vancomycin Resistance Among *E. faecium* Bacteremias in North America and Europe (1999-2008 SENTRY Program)

*withdrawal of animal growth promoters eg. avoparcin*
Profile of Nonsusceptibility Rates for 3 Commonly Used β-lactams (A/C=amoxicillin/clavulanate, PEN=penicillin, high-dose, and CRO=ceftriaxone) Tested against 14,384 S. pneumoniae isolates from the USA SENTRY Program (1998-2009)

![Graph showing the percentage of non-susceptible isolates over time, with points indicating PCV7 and PCV13 introductions.]

### Trends in Susceptibility for Five Antimicrobial Classes Tested against 14,394 *S. pneumoniae* (1998-2009)\(^a\)

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Susceptibility rate (%)</th>
<th>1998</th>
<th>2009</th>
<th>Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td></td>
<td>82.2</td>
<td>60.8</td>
<td>-21.4</td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td>96.2</td>
<td>79.1</td>
<td>-17.1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>88.8</td>
<td>75.5</td>
<td>-13.3</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td></td>
<td>73.8</td>
<td>65.7</td>
<td>-8.1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td></td>
<td>99.8</td>
<td>99.2</td>
<td>-0.6</td>
</tr>
<tr>
<td>(Ciproflaxacin)(^b)</td>
<td></td>
<td>(2.2)(^b)</td>
<td>(3.3)(^b)</td>
<td>-</td>
</tr>
</tbody>
</table>


\(^b\) Ciproflaxacin MICs at ≥ 4 µg/ml = % with mutational events in QRDR (Chen et al., 1999).

<table>
<thead>
<tr>
<th>Region</th>
<th>Enterobacter / Ceftazidime</th>
<th>E. coli / ESBL phenotype</th>
<th>E. coli / Ciprofloxacin</th>
<th>Klebsiella / ESBL phenotype</th>
<th>Klebsiella / Ciprofloxacin</th>
<th>Klebsiella / Imipenem (≥2 μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>21→19%</td>
<td>3→5%</td>
<td>4→19%</td>
<td>6→15%</td>
<td>4→13%</td>
<td>&lt;1→5 (3.7)</td>
</tr>
<tr>
<td>Europe</td>
<td>33→26%</td>
<td>5→8%</td>
<td>12→21%</td>
<td>23→24%</td>
<td>6→13%</td>
<td>&lt;3→3 (0.4)</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>31→36%</td>
<td>9→51%</td>
<td>20→61%</td>
<td>22→49%</td>
<td>8→27%</td>
<td>&lt;2→1 (0.6)</td>
</tr>
<tr>
<td>Latin America</td>
<td>32→30%</td>
<td>7→16%</td>
<td>19→28%</td>
<td>40→47%</td>
<td>8→27%</td>
<td>&lt;1→1 (0.6)</td>
</tr>
</tbody>
</table>

ESBL, extended spectrum β-lactamases
Regional Trends in *Enterobacter* Derepressed AmpC Resistances (SENTRY Program, 1997-2006)

![Graph showing regional trends in Enterobacter derepressed AmpC resistances](image)

- **% resistance**
- **Europe**
- **Latin America**
- **North America**

- **Legend**:
  - 1997
  - 1998
  - 1999
  - 2000
  - 2001
  - 2002
  - 2003
  - 2004
  - 2005
  - 2006

a. Ceftazidime resistance rates

% of strains

<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>APAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Colors: Derepressed AmpC - Red, Other (ESBL, KPC, etc.) - Blue*

### United States
- **P. aeruginosa / Imipenem**: 9→8%
- **P. aeruginosa / Piperacillin-tazobactam**: 11→12%
- **P. aeruginosa / Ciprofloxacin**: 17→19%
- **Acinetobacters / Amikacin**: 11→16%
- **Acinetobacters / Ceftazidime**: 23→45%
- **Acinetobacters / Imipenem**: 3→7%

### Europe
- **P. aeruginosa / Imipenem**: 16→16%
- **P. aeruginosa / Piperacillin-tazobactam**: 16→17%
- **P. aeruginosa / Ciprofloxacin**: 26→23%
- **Acinetobacters / Amikacin**: 47→51%
- **Acinetobacters / Ceftazidime**: 48→55%
- **Acinetobacters / Imipenem**: 22→27%

### Latin America
- **P. aeruginosa / Imipenem**: 18→21%
- **P. aeruginosa / Piperacillin-tazobactam**: 25→20%
- **P. aeruginosa / Ciprofloxacin**: 35→36%
- **Acinetobacters / Amikacin**: 66→65%
- **Acinetobacters / Ceftazidime**: 67→71%
- **Acinetobacters / Imipenem**: 11→25%

### Asia Pacific
- **P. aeruginosa / Imipenem**: 9→24%
- **P. aeruginosa / Piperacillin-tazobactam**: 11→28%
- **P. aeruginosa / Ciprofloxacin**: 12→38%
- **Acinetobacters / Amikacin**: 22→54%
- **Acinetobacters / Ceftazidime**: 30→61%
- **Acinetobacters / Imipenem**: 5→37%

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Resistance Mechanisms Occurring in 50 Meropenem-Resistant *P. aeruginosa* Isolates

Mechanism patterns

<table>
<thead>
<tr>
<th>AmpC hyperproduction</th>
<th>OprD reduction</th>
<th>Efflux upregulation</th>
<th>No. isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>25</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10</td>
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<td>+</td>
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<td>+</td>
<td>5</td>
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<td>+</td>
<td>5</td>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>2</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>1</td>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1</td>
</tr>
</tbody>
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IMP-15

**Acinetobacter**

- *Acinetobacter* stands out in NNIS survey since 2003
- Rapidly increasing in prevalence (especially pneumonia)
- At ICAAC 2006, carbapenem resistance rates reported as high as 40% \(^2\)
- *A. baumannii* Resistant to Carbapenems (USA MYSTIC Program, 2007)
  - Nine of 15 centers had epidemic clusters (60%)
  - Five centers had OXA-type carbapenemases
    - OXA-23 (10) and OXA-24 (5)
    - Arkansas, Colorado, Kentucky, New Jersey and New York
    - 30% of carbapenem-resistant isolates
- Multidrug-resistant phenotypes were routine, 2 to 5 organism clonal occurrences

---

Conclusions

- Resistance to antimicrobials continues to evolve
- Resistance mechanisms are diverse and often multiple
  - MRSA
  - VRE
  - DRSP
  - Target alterations (OMP, porins)
- Therapeutic options may vary
  - More acceptable for Gram-positive cocci
  - Limited for MDR Gram-negative bacilli
  - Major pharmaceutical industry is generally disinterested (recent excitement!)
  - Regulatory approval intervals have actually increased
Conclusions

• Management of AMR requires a multi-disciplinary approach
  - Formulary controls
  - Infection control
  - Microbiology laboratory resistance detection systems and epidemiologic typing methods
  - Interested medical staff with institutional commitment of resources
  - Local and global surveillance systems are needed
  - Public education
  - Increased drug development
Social Context

- Concern about resistance is used as ammunition for other agendas, most obviously including marketing by the pharmaceutical industry and cost containment within managed or socialized health care.
- This argument assumes a vacuum in which no new drugs are developed.
- Concerns about resistance have led to the banning of most agricultural growth promoters in Europe.
- Less is said on the other aspects of modern life that potential exacerbate resistance: Large hospitals; the concentration of the very young and very old in socialized care; and increasing travel. Action on these would be socially and politically impossible, even if they are more pertinent to the sum total of resistance than the use of zinc bacitracin as a agricultural growth promoter!!!
## Acknowledgements

<table>
<thead>
<tr>
<th>JMI Laboratories</th>
<th>Consultants</th>
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<tr>
<td>M. Castanheira, Ph.D.</td>
<td>A. Fuhrmeister</td>
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<td>J. Turnidge, M.D.</td>
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