ANTIBIOTIC RESISTANCE

John G. Bartlett
Johns Hopkins University
School of Medicine

Conflicts – None
ANTIBIOTIC RESISTANCE

The issue: “Bad bugs, No drugs”
The magnitude: Global crisis
Contributing factors:
• Antibiotic abuse – farm and patients
• Dry pipeline
• Paucity of data
Solution: Coordinated plan
MRSA: USA 300 STRAIN
<table>
<thead>
<tr>
<th>Similarity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Isolate</th>
</tr>
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<tbody>
<tr>
<td>St. Louis Rams professional football team, Missouri</td>
</tr>
<tr>
<td>Professional football team A</td>
</tr>
<tr>
<td>College football team, California</td>
</tr>
<tr>
<td>College football team, Pennsylvania</td>
</tr>
<tr>
<td>Fencers, Colorado</td>
</tr>
<tr>
<td>Prison inmates, Mississippi</td>
</tr>
<tr>
<td>Prison inmates, Georgia</td>
</tr>
<tr>
<td>Prison inmates, Texas</td>
</tr>
<tr>
<td>Children, Tennessee</td>
</tr>
<tr>
<td>Children, California</td>
</tr>
<tr>
<td>Men who have sex with men, California</td>
</tr>
<tr>
<td>Hospital Strain USA100</td>
</tr>
<tr>
<td>Hospital Strain USA200</td>
</tr>
</tbody>
</table>
TRENDS IN ESTIMATED NOSOCOMIAL BACTEREMIA IN EUROPE
Distribution of NDM-1 producing Enterobacteriaceae strains in Bangladesh, India, Pakistan and the UK
Emergence of new antibiotic resistance mechanism: New Delhi metallo betalactamase 1

(Kumarasamy K. Lancet ID 2010;10:597)

Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency’s national reference laboratory from 2003 to 2009
Method: Enterobacteraceae isolates in Reference Labs (UK and India) → carbapenem resistance → Hodge test, etc. → PCR for bla NDM-1 gene

Results: UK-37, India-70

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>107</th>
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<tbody>
<tr>
<td>Pip-tazo</td>
<td>0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>3%</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>0</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8%</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>67%</td>
</tr>
<tr>
<td>Colistin</td>
<td>100%</td>
</tr>
</tbody>
</table>
**Issue:** Epidemiology of outbreak of KPC K. pneumoniae

**Methods:**

**Patient #1:** Transferred from NYC ICU with KPC 6/13 → 7/13/11 (enhanced precautions)

**Patient #2:** Tracheal aspirate 8/5/11 – positive – but never on same ward

**Patients #3-18** with 6 attributable deaths (7/13/11 – 1/1/12)
Patient location and time line to first positive culture (black line) ICU=blue
<table>
<thead>
<tr>
<th>Year</th>
<th>Pts.</th>
<th>Courses</th>
</tr>
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<tbody>
<tr>
<td>2002</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2003</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2004</td>
<td>6</td>
<td>6</td>
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<td>2005</td>
<td>4</td>
<td>4</td>
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<td>2006</td>
<td>20</td>
<td>22</td>
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<td>2007</td>
<td>40</td>
<td>47</td>
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<td>2008</td>
<td>43</td>
<td>64</td>
</tr>
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<td>2009</td>
<td>68</td>
<td>96</td>
</tr>
<tr>
<td>2014</td>
<td>1156</td>
<td>1632</td>
</tr>
</tbody>
</table>
COLISTIN

**FDA approval:** 1961

**Recommendation dose (PI):** 2.5-5.0 mg/kg/d in 2-4 doses (max – 350 mg/d)

**Correct dose (Nation AAC 2011;55:3284):**

Target serum level 3.4 ug/mL

Maximum dose: 475 mg/d

**Toxicity renal:** 6-55%

**Combine:** Rif, Mero, Mino, Carb

**Efficacy:** Maybe
Meta-analysis of “Comparative” Trials with Colistin
(Eur J Clin Micro & ID 2011;18:18)
COST OF ANTIBIOTIC RESISTANCE

Cook County Hospital: Review 1,392 charts
- Average cost: $23,700
- LOS increase: 9.5 days
- Mortality: 6.5%

Extrapolated for US hospitals
- Total cost: $23 billion/yr
- Hospital days: ↑ 17,000,000 hospital days
NO ANTIBACTERIALS – WHY?

Duration of use:
Antibiotics: 1-2 weeks
Chronic disease: yrs (Lipitor)

Alternative markets: (London School of Economics – 2010)
Neuromuscular drug: +$1.5 billion/yr
New antibiotic: -$50 million/yr

Market Forces: IDSA

Only Drugs (except narcotics) that loose potency with more use

Pricing: Antibiotics: $150/day
Advocacy: Best for chronic disease
HUMBLING US DATA

• 80% of antibiotic use in US is for agriculture (growth promotion and infection prevention)

• Risk of MRSA bacteremia is 49 x more likely in a US hospital compared to The Netherlands

• US accounts for 4.6% of the global population and 46% of the global antibiotic market

• The EU has country-specific data for antibiotic use and resistance for 26 countries x 15 yrs. US has no clue.
Method: Review 1000 Twitter updates that mention antibiotics

Results: Abx + flu (345) or cold (302)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Followers</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Finally over my cold thank you Z pack”</td>
<td>850,375</td>
</tr>
<tr>
<td>“Starting to feel better from flu. One antibiotic to go”</td>
<td>172,571</td>
</tr>
<tr>
<td>“Need antibiotic. If you have any left over, I will pay u”</td>
<td>6,216</td>
</tr>
</tbody>
</table>
Per Capita Antibiotic Use in 26 European Countries in 2002

DDD=defined daily dose.
Significant Reduction of Antibiotic Use in the Community after a Nationwide Campaign in France, 2002–2007

Elifsu Sabuncu¹,², Julie David¹,², Claire Bernède-Bauduin¹,², Sophie Pépin³, Michel Leroy⁴, Pierre-Yves Boëlle⁵,⁶, Laurence Watier⁷,⁸, Didier Guillemerot¹,²,⁹,¹⁰*


Abstract

Background: Overuse of antibiotics is the main force driving the emergence and dissemination of bacterial resistance in the community. France consumes more antibiotics and has the highest rate of beta-lactam resistance in Streptococcus pneumoniae than any other European country. In 2001, the government initiated “Keep Antibiotics Working”; the program’s main component was a campaign entitled “Les antibiotiques c’est pas automatique” (“Antibiotics are not automatic”) launched in 2002. We report the evaluation of this campaign by analyzing the evolution of outpatient antibiotic use in France 2000–2007, according to therapeutic class and geographic and age-group patterns.

Methods and Findings: This evaluation is based on 2000–2007 data, including 453,407,458 individual reimbursement data records and incidence of flu-like syndromes (FLSs). Data were obtained from the computerized French National Health Insurance database and provided by the French Sentinel Network. As compared to the preintervention period (2000–2002), the total number of antibiotic prescriptions per 100 inhabitants, adjusted for FLS frequency during the winter season, changed by −26.5% (95% confidence interval [CI] −33.5% to −19.6%) over 5 years. The decline occurred in all 22 regions of France and affected all antibiotic therapeutic classes except quinolones. The greatest decrease, −35.8% (95% CI −48.3% to −23.2%), was observed among young children aged 6–15 years. A significant change of −45% in the relationship between the incidence of flu-like syndromes and antibiotic prescriptions was observed.

Conclusions: The French national campaign was associated with a marked reduction of unnecessary antibiotic prescriptions, particularly in children. This study provides a useful method for assessing public-health strategies designed to reduce antibiotic use.

Please see later in the article for the Editors’ Summary.
Issue: France consumes most antibiotics and has most penicillin resistant S. pneumoniae

Method: National campaign including detailing

Data: reimbursement data especially for ILI

Results: 26% decline in Abx prescriptions and reduced S. pneumoniae resistance

Global antibiotics market 2011: France has greatest decrease in Abx use (21% decrease)
## DOES ANTIBIOTIC USE CORRELATE WITH RESISTANCE

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Country</th>
<th>Abx use (DDD/1000)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella*</td>
<td>Greece</td>
<td>38</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>The Netherlands</td>
<td>11</td>
<td>0.2%</td>
</tr>
<tr>
<td>MRSA**</td>
<td>Greece</td>
<td>38</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>The Netherlands</td>
<td>11</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

*Bacteremic Klebsiella-carbapenemase positive**

**MRSA as % of S. aureus isolates**
Europe launches 12 point plan to tackle resistance to antibiotics as 25,000 die from resistant bacteria

Rory Watson BRUSSELS

The European Commission presented its first action plan to tackle antimicrobial resistance to drugs on 17 November, as new research that was based on Europe-wide surveillance data confirmed that Klebsiella pneumoniae that is resistant to carbapenems is on the rise.

Several European countries say that between 15% and 50% of K pneumoniae are resistant to carbapenems.
PROPOSED DRUG DEVELOPMENT MODEL (LPAD)  
(Alemayehu D. CID 2012;15:562)  
Red: PK/PD; Blue: Intervention;  
Green: observational; Yellow: “real world”
RESISTANCE: NEW THREATS

GNB – Carbabenems, etc
MRSA – Vancomycin
N. Gonorrhoeae – Cefixime, FQ
Influenza – Oseltamivir
M. Tuberculosis – Rif, INH
Malaria – Artemisinin
Cholera – ESBL, FQ
ANTIBIOTIC RESISTANCE: PLAYERS

- Pharma
- Diagnostics
- IDSA (ACP, AMA)
- SHEA
- Payors
- Press

- FDA
- CMS
- HCR
- CDC
- NIAID
- Congress
Thanks to:

Dave Gilbert – Oregon
≈
Brad Spellberg – UCLA
≈
Vance Fowler – Duke
≈
Bob Guidos – IDSA
≈
Otto Cars – Sweden
≈
Jan Klutmans – The Netherlands