Global drug Resistance: The Case of *Streptococcus pneumoniae*

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International Conference on Emerging Infectious Diseases
Atlanta, March 2002
Acute respiratory infections – the leading cause of death in under 5s

 Millions of deaths

- Acute respiratory infections
- AIDS*
- Diarrhoeal diseases
- TB
- Malaria
- Measles

Over age five
Under age five

* HIV-positive people who have died with TB have been included among AIDS deaths

World Health Organization 1999
Global overview of pneumococcal penicillin resistance

UK
3.0% 4.5%

USA
10.7% 22.7%

Mexico
36% 17.5%

Brazil
13.4% 3.0%

France
20.7% 40.0%

Russia
31% 0%

Japan
20.2% 30.9%

Hong Kong
3.6% 71.4%

Saudi Arabia
31.2% 24.7%

Singapore
12.2% 32.6%

South Africa
36.3% 15.4%

Penicillin-intermediate (MIC 0.12 – 1 µg/ml)
Penicillin-resistant (MIC ≥ 2 µg/ml)

Alexander Project data 2000
Prevalence of penicillin- and macrolide-resistant *S. pneumoniae*

**Penicillin-resistant** (defined as penicillin MIC $\geq 2$ µg/ml)

**Macrolide-resistant** (defined as erythromycin MIC $\geq 1$ µg/ml)

<table>
<thead>
<tr>
<th>Country</th>
<th>Penicillin-resistant</th>
<th>Macrolide-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Netherlands</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Brazil</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Italy</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Belgium</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Poland</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Greece</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>Switzerland</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Spain</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>France</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>USA</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Japan</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Singapore</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

Alexander Project data 2000
Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, Regional, Individual
  - Adherence
  - Dose and duration of therapy
  - Therapy with cross – reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
## Risk Factors for Penicillin-Resistant Pneumococcal Infections

- French retrospective study on 10,350 isolates

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 15 years</td>
<td>2.01</td>
</tr>
<tr>
<td>Isolation from URT</td>
<td>2.36</td>
</tr>
<tr>
<td>Isolation from sinus and middle ear</td>
<td>1.63</td>
</tr>
<tr>
<td>HIV infection</td>
<td>2.01</td>
</tr>
<tr>
<td>$\beta$-lactam $R_x$ in prev. 6 months</td>
<td>1.99</td>
</tr>
<tr>
<td>Nosocomial acquisition</td>
<td>2.12</td>
</tr>
</tbody>
</table>

*Bedos et al, CID, 1996*
Fluoroquinolone Use and PRSP
Canada, 1988-1998

Chen et al, NEJM, 1999, 341, 233-9
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Risk Factors for Drug Resistant Pneumococcal Carriage

Multi-resistant type 14 strain in a hospital in Topolcany, Slovakia

- Hospitalization carriage: 33% vs O.P. 0.8%
- Prior hospitalization incidence: 68% vs 23%
- Previous antibiotics incidence: 78% vs 38%
- Hospital stay carriage on admission: 0%
  - Carriage day:
    - 2-7: 13%
    - 8-14: 16%
    - 15-21: 29%
    - >21: 35%

Reichler et al, JID, 1996
Risk factors for Acquisition of Levofloxacin –– Resistant Pneumococci in Hong Kong

- Nosocomial origin – OR 16.2 (95% CI 2.1–122.2)  
  \( P=0.007 \)

- Exposure to a FQ in past 12 months – OR 10.7  
  (95% CI 1.6 – 71.2)  
  \( P=0.01 \)

- Presence of COPD – OR 10.3 (95% CI 1.6 – 66.2)  
  \( P=0.01 \)

- Residence in a nursing home – OR 7.4 (95% CI 1.5 – 35.1)  
  \( P=0.01 \)

Ho et al, CID, 2001, 32, 701-7
Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

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- Site of specimen
- Hospitalization
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  - National, Regional, Individual
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  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
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- Conjugate vaccine
Association of Antibiotic Use with Resistance in the Pneumococcus

The logodds of resistance to penicillin among invasive isolates of *Streptococcus pneumoniae* (PNSP; ln(R/[1-R])) is regressed against outpatient sales of beta-lactam antibiotics in 11 European countries

Association Between Antibiotic – Resistant Pneumococcal Carriage Rate and Regional Antibiotic Consumption: Iceland

Arason, 1996.
Percentages of penicillin-sensitive and penicillin-resistant pneumococci

Weeks since last antimicrobial treatment

Arason et al, BMJ, 1996
# Impact of Azithromycin on Pneumococcal Carriage and Resistance in Aboriginal Children

**Single dose 20 mg/kg**

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carriage rate</strong></td>
<td>54/79 (68%)</td>
<td>11/38 (29%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29/37 (78%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34/39 (87%)</td>
</tr>
<tr>
<td><strong>Azithromycin-</strong></td>
<td>1/54 (1.9%)</td>
<td>6/11 (54.5%)</td>
</tr>
<tr>
<td><strong>resistance</strong></td>
<td></td>
<td>10/29 (34.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/34 (5.9%)</td>
</tr>
<tr>
<td><strong>Azith resistant</strong></td>
<td>1/79 (1.3%)</td>
<td>16/75 (21.3%)</td>
</tr>
<tr>
<td><strong>Serotypes 10F, 23A, 45</strong></td>
<td></td>
<td>2/32 (6%)</td>
</tr>
</tbody>
</table>

*Leach et al. CJD. 1992*

Trachoma Study
## Influence of Antibiotic Class on Pen Resistant Pneumo Carriage

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of cases</th>
<th>Courses in last 12 mos</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>16</td>
<td>-</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>β-lactam</td>
<td>111</td>
<td>1 or 2</td>
<td>6.75</td>
<td>1.8–25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>≥ 3</td>
<td>6.00</td>
<td>1.4–25</td>
<td>0.013</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>54</td>
<td>1 or 2</td>
<td>7.22</td>
<td>1.7–30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>≥ 3</td>
<td>13.14</td>
<td>3.1–55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>11</td>
<td>1 or 2</td>
<td>8.56</td>
<td>1.1–64</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>≥ 3</td>
<td>12.16</td>
<td>1.9–75</td>
<td>0.007</td>
</tr>
</tbody>
</table>

The odds for co-trimoxazole and erythromycin being associated with PRP carriage were twice that for β-lactams in association with 3 or more antimicrobial courses.

Impact of Reduction of Antibiotic Consumption on PRP Carriage

- Incidence of PNSP (penicillin non-susceptible) peaked in 1992 (19.8%): declined to 13% in 1997
- Predominant type 6B multi-resistant clone (Spanish-Icelandic)
- From 1990 β-lactam consumption was not reduced BUT: trimethoprim sulfamethoxazole (TMP/SXT) and erythromycin use was reduced by 30%

Impact of reduction in macrolide and cotrimoxazole Usage on penicillin – resistant pneumococci in Iceland

Austin DJ, Kristinsson KG, Anderson RM
Proc Natl Acad Sci U S A 1999 ;96:1152-6
Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, Regional, Individual
  - Adherence
  - Dose and duration of therapy
  - Therapy with cross – reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
Association of Non – Adherent Antibiotic Use with Resistance in the Pneumococcus

The logodds of resistance of invasive isolates of *Streptococcus pneumoniae* to penicillin (PNSP; \( \ln(R/(1-R)) \)) is regressed against nonadherence rates to antibiotic therapy in four European countries.

Low dose and long duration of β-lactam therapy as risk factors for penicillin-resistant pneumococcal carriage

<table>
<thead>
<tr>
<th></th>
<th>odds ratio</th>
<th>confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral β-lactams in past 30 days</td>
<td>3.0</td>
<td>1.1–8.3</td>
</tr>
<tr>
<td>Dose lower than clinically</td>
<td>5.9</td>
<td>2.1–16.7</td>
</tr>
<tr>
<td>recommended</td>
<td>Treatment &gt; 5 days</td>
<td>3.5</td>
</tr>
</tbody>
</table>

NB Data are based on 16 children carrying PRSP (of 864). Ten of these children had low dose, long duration treatment.

Selection of Resistant Pneumococci by High Dose, Short Duration Amoxicillin Rx

**RELATIVE RISK OF PRSP IN CARRIERS**

<table>
<thead>
<tr>
<th></th>
<th>RELATIVE RISK (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH DOSE vs LOW DOSE</strong></td>
<td>0.78 (0.65 – 0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>DAY 28 vs DAY 0 HIGH DOSE</strong></td>
<td>1.22 (1.02 – 1.48)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>DAY 28 vs DAY 0 LOW DOSE</strong></td>
<td>1.60 (1.36 – 1.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Schrag et al, JAMA, 2001, 286: 49 - 56
Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

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- Site of specimen
- Hospitalization
- Antibiotic use
  - National, Regional, Individual
  - Adherence
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
Therapy for malaria with pyrimethamine-sulfadoxine (fansidar) increases pneumococcal resistance to trimethoprim - sulphamethoxazole

Impact of Fansidar Therapy for Malaria on Cotrimoxazole - Resistance in the Pneumococcus


<table>
<thead>
<tr>
<th>TRANSITION RATE BETWEEN INITIAL VISIT AND 1-WEEK VISIT</th>
<th>K1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>6/50 (12%)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>29/69 (42%)</td>
</tr>
<tr>
<td>SP</td>
<td>29/96 (30%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TRANSITION RATE BETWEEN INITIAL VISIT AND 4-WEEK VISIT</th>
<th>K1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>2/24 (8%)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>9/40 (23%)</td>
</tr>
<tr>
<td>SP</td>
<td>28/73 (38%)</td>
</tr>
</tbody>
</table>
Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, Regional, Individual
  - Adherence
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
### COHORT A

<table>
<thead>
<tr>
<th>Child</th>
<th>1993</th>
<th>1994</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oct</td>
<td>Nov</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

### COHORT B

- Isolation of *S. pneumoniae* 23 F, intermediately susceptible to penicillin and resistant to trimethoprim-sulfamethoxazole
- Siblings

Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, Regional, Individual
  - Adherence
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine
Clonal spread of *S. pneumoniae* 23F
Pneumococcal Molecular Epidemiology Network of the IUMS

Nomenclature

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>SEROTYPE ISOLATED</th>
<th>INTERNATIONAL CLONE NUMBER</th>
<th>SUBSEQUENT SEROTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eg. SPAIN</td>
<td>23F</td>
<td>- 1</td>
<td>- 19F</td>
</tr>
</tbody>
</table>

McGee et al, J Clin Microbiol, July, 2001
Clones of Penicillin – Resistant Pneumococci in the USA

<table>
<thead>
<tr>
<th>Clone Description</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain (23^F) - 1 – 14,19</td>
<td>127/328</td>
<td>38.7%</td>
</tr>
<tr>
<td>Spain (9^V) - 3 – 14,19</td>
<td>40/328</td>
<td>12.2%</td>
</tr>
<tr>
<td>Eight other clones</td>
<td>112/328</td>
<td>34.1%</td>
</tr>
<tr>
<td>The above ten clones</td>
<td>279/328</td>
<td>85.0%</td>
</tr>
</tbody>
</table>

Clonality of Highly Penicillin – Resistant Pneumococci - USA

<table>
<thead>
<tr>
<th>Location</th>
<th>Clones</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain 23F - 1</td>
<td>123/672</td>
<td>18.3%</td>
</tr>
<tr>
<td>Spain 9V - 3</td>
<td>96/672</td>
<td>14.3%</td>
</tr>
<tr>
<td>PFGE type 3</td>
<td>65/672</td>
<td>9.7%</td>
</tr>
<tr>
<td>Spain 6B - 2</td>
<td>44/672</td>
<td>6.5%</td>
</tr>
<tr>
<td>PFGE type 5</td>
<td>42/672</td>
<td>6.3%</td>
</tr>
<tr>
<td>Tennessee 23F - 4</td>
<td>33/672</td>
<td>4.9%</td>
</tr>
<tr>
<td>PFGE type 7</td>
<td>28/672</td>
<td>4.2%</td>
</tr>
<tr>
<td>PFGE type 8</td>
<td>25/672</td>
<td>3.7%</td>
</tr>
<tr>
<td>PFGE type 9</td>
<td>22/672</td>
<td>3.3%</td>
</tr>
<tr>
<td>PFGE type 10</td>
<td>20/672</td>
<td>3.0%</td>
</tr>
<tr>
<td>Taiwan 19F - 14</td>
<td>11/672</td>
<td>1.6%</td>
</tr>
<tr>
<td>PFGE 12</td>
<td>8/672</td>
<td>1.2%</td>
</tr>
<tr>
<td>PFGE 13</td>
<td>7/672</td>
<td>1.0%</td>
</tr>
<tr>
<td>12 Clones</td>
<td>524/672</td>
<td>78.0%</td>
</tr>
</tbody>
</table>

Richter et al, 2002, CID; 34: 330-9
Emergence of FQ Resistance in Global Clones of Pneumococci

- 29 FQ resistant pneumococci with ofloxacin MIC’s ≥ 4 µg/ml were identified from the Alexander project and from Northern Ireland.
- Clonality was determined by BOX – PCR and by pulse field electrophoresis
- 16 types were identified amongst the 29 strains
- 4 strains identical or closely related to SPAIN²³F-1
- These strains came from France and Spain
- 7 strains from France and N. Ireland identical to FRANCE⁹V-3.

Increase in FQ Resistance in the Pneumococcus in Hong Kong

- Two studies of sequential clinical isolates from 6 Hospitals in Hong Kong - 1998 & 2000
- Levo MIC $\geq 4$ µg/ml $\rightarrow$ from 5.5% to 13.3%
- In Pen Resistant strains $\rightarrow$ 9.2% to 27.3%
- Risk factors were:
  - Patients $\geq 65$yrs $-$ 17.1% vs 9.1% (18-64) ($P<0.001$)
  - Adults with COPD $-$ 24.6% vs 9.3% ($P = 0.01$)
- All FQ resistant strains are a clone of SPAIN$^{23F}$ $-$ 1 resistant to penicillin (MIC 2-4 µg/ml) and cefotaxime (MIC 1-4 µg/ml)

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- HIV
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- Conjugate vaccine
Impact of HIV on Penicillin – Resistance in the Pneumococcus

<table>
<thead>
<tr>
<th>Age</th>
<th>HIV + ve</th>
<th>HIV -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>19/100 (19%)</td>
<td>11/259 (4%)</td>
</tr>
<tr>
<td>Children</td>
<td>24/45 (53%)</td>
<td>16/53 (30%)</td>
</tr>
</tbody>
</table>

Crewe-Browne et al, CID, 1997
Emerging Problem

Cotrimoxazole - resistant and multiply resistant pneumococcal infections in HIV – infected patients on prophylaxis with the drug

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- Conjugate vaccine
Single base mutation conferring resistance suggests rapid selection

New Mechanism of Tetracycline Resistance in Pneumococci

tet (O) discovered in 5 strains from Cape Town, South Africa - a single clone in children.

- remains rare, one subsequent report – from Seattle, Washington, USA

- none in 277 tetracycline – resistant strains screened in Europe.

This mechanism will probably will remain rare unless strains acquire genes conferring resistance to commonly prescribed antibiotics in children

Molecular Insights Into Mechanisms of Resistance in the Pneumococcus

A staphylococcal plasmid has linearised, inserted into the pneumococcal genome, and confers chloramphenicol resistance in the pneumococcus.

Could the enterococcal plasmid conferring vancomycin resistance do the same?

Widdowson, Adrian and Klugman, AAC, 2000, 44: 393 - 5.
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- Conjugate vaccine
## Impact of 9 – Valant Conjugate Vaccine on Carriage of Antibiotic – Resistant Pneumococci

<table>
<thead>
<tr>
<th>Antibiotic resistance</th>
<th>Vaccinees (n = 130)</th>
<th>Controls (n = 145)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>27 (21)</td>
<td>60 (41)</td>
<td>.0002</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2 (2)</td>
<td>5 (3)</td>
<td>--</td>
</tr>
<tr>
<td>Tertacycline</td>
<td>14 (11)</td>
<td>13 (9)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Erythromycin</strong></td>
<td>8 (6)</td>
<td>6 (4)</td>
<td>--</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>7 (5)</td>
<td>4 (3)</td>
<td>--</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>--</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>30 (23)</td>
<td>51 (35)</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Any of the above</strong></td>
<td>59 (45)</td>
<td>90 (62)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Mbelle, et al, JID, 1999
Use of Pneumococcal Conjugate Vaccine Reduces Antibiotic Use

Risk of antibiotic use 0.83 (95% CI 0.79 to 0.87; P < 0.001).

Dagan et al, PIDJ, 2001;20:951-958
Interventions

- Education of patients, prescribers and guidelines to reduce inappropriate antibiotic use for viral upper RTI.
- Better diagnostic test to decrease empiric treatment
- Development of new drugs
- Strategies to reduce specific classes of antimicrobial use in order to decrease resistance are complicated by multiple resistance.
- Give antibiotics in short courses at high doses
- Pneumococcal conjugate vaccines interrupt the transmission of multiply resistant strains that belong to vaccine serotypes, and vaccinated children receive less antibiotics.
3rd International Symposium on Pneumococci and Pneumococcal Diseases

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