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% Penicillin-sensitive, 4.5% Penicillin-resistant
- **France**: 20.7% Penicillin-sensitive, 40.0% Penicillin-resistant
- **Russia**: 31% Penicillin-sensitive, 0% Penicillin-resistant
- **Japan**: 20.2% Penicillin-sensitive, 30.9% Penicillin-resistant
- **Saudi Arabia**: 31.2% Penicillin-sensitive, 17.5% Penicillin-resistant
- **Singapore**: 12.2% Penicillin-sensitive, 32.6% Penicillin-resistant
- **Brazil**: 13.4% Penicillin-sensitive, 3.0% Penicillin-resistant
- **Mexico**: 36% Penicillin-sensitive, 17.5% Penicillin-resistant
- **USA**: 10.7% Penicillin-sensitive, 22.7% Penicillin-resistant
- **Hong Kong**: 3.6% Penicillin-sensitive, 71.4% Penicillin-resistant
- **South Africa**: 36.3% Penicillin-sensitive, 15.4% Penicillin-resistant

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

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

- **Penicillin-resistant** (defined as penicillin MIC $\geq 2 \, \mu g/ml$)
- **Macrolide-resistant** (defined as erythromycin MIC $\geq 1 \, \mu g/ml$)

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
Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

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- Conjugate vaccine
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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  - Adherence
  - Dose and duration of therapy
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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

- % Penicillin-resistant pneumococci vs. No. of treatment courses
- Yearly courses of antibiotic per child vs. % Penicillin-resistant pneumococci

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

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>Carriage rate</td>
<td>54/79 (68%)</td>
<td>2-3 weeks 11/38 (29%), 2 months 29/37 (78%), 6 months 34/39 (87%)</td>
</tr>
<tr>
<td>Azithromycin-resistant</td>
<td>1/54 (1.9%)</td>
<td>6/11 (54.5%), 10/29 (34.5%), 2/34 (5.9%)</td>
</tr>
<tr>
<td>Azith resistant Serotypes l0F, 23A,45</td>
<td>1/79 (1.3%)</td>
<td>16/75 (21.3%), 2/32 (6%)</td>
</tr>
</tbody>
</table>
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
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- 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
The logodds of resistance of invasive isolates of *Streptococcus pneumoniae* to penicillin (PNSP; In(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</td>
<td>3.0</td>
<td>1.1–8.3</td>
</tr>
<tr>
<td>in past 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose lower than</td>
<td>5.9</td>
<td>2.1–16.7</td>
</tr>
<tr>
<td>clinically recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment &gt; 5 days</td>
<td>3.5</td>
<td>1.3–9.8</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>Comparison</th>
<th>Relative Risk</th>
<th>P-value</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
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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
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  - Therapy with cross – reacting molecule
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- Conjugate vaccine
Isolation of *S. pneumoniae* 23 F, intermediately susceptible to penicillin and resistant to trimethoprim-sulfamethoxazole

Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

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- 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>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</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain $^{23F}$ - 1 – 14,19</td>
<td>127/328</td>
<td>38.7%</td>
</tr>
<tr>
<td>Spain $^{9V}$ - 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>

<table>
<thead>
<tr>
<th>Region</th>
<th>Type</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>23F - 1</td>
<td>123/672</td>
<td>18.3%</td>
</tr>
<tr>
<td>Spain</td>
<td>9V - 3</td>
<td>96/672</td>
<td>14.3%</td>
</tr>
<tr>
<td>PFGE type 3</td>
<td></td>
<td>65/672</td>
<td>9.7%</td>
</tr>
<tr>
<td>Spain</td>
<td>6B - 2</td>
<td>44/672</td>
<td>6.5%</td>
</tr>
<tr>
<td>PFGE type 5</td>
<td></td>
<td>42/672</td>
<td>6.3%</td>
</tr>
<tr>
<td>Tennessee</td>
<td>23F - 4</td>
<td>33/672</td>
<td>4.9%</td>
</tr>
<tr>
<td>PFGE type 7</td>
<td></td>
<td>28/672</td>
<td>4.2%</td>
</tr>
<tr>
<td>PFGE type 8</td>
<td></td>
<td>25/672</td>
<td>3.7%</td>
</tr>
<tr>
<td>PFGE type 9</td>
<td></td>
<td>22/672</td>
<td>3.3%</td>
</tr>
<tr>
<td>PFGE type 10</td>
<td></td>
<td>20/672</td>
<td>3.0%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>19F - 14</td>
<td>11/672</td>
<td>1.6%</td>
</tr>
<tr>
<td>PFGE 12</td>
<td></td>
<td>8/672</td>
<td>1.2%</td>
</tr>
<tr>
<td>PFGE 13</td>
<td></td>
<td>7/672</td>
<td>1.0%</td>
</tr>
<tr>
<td>12 Clones</td>
<td></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 INCLUDING
- 4 strains identical or closely related to SPAIN\(^23\)F-1
- These strains came from France and Spain.
- 7 strains from France and N. Ireland identical to FRANCE\(^9\)V-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 $\geq 4 \, \mu g/ml$ - → from 5.5% to 13.3%
- In Pen Resistant strains - → 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 $\mu g/ml$) and cefotaxime (MIC 1-4 $\mu g/ml$)

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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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## Impact of 9 – Valent 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>Any of the above</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

May 5 - 9, 2002
Anchorage, Alaska
The Hotel Captain Cook

http://www.asmusa.org/mtgsrc/isppd02.htm

Hosted by the Centers for Disease Control and Prevention’s Arctic Investigations Program, John Hopkins University Center for American Indian and Alaska Native Health, and managed by the American Society for Microbiology.