Reducing disease and antibiotic use in one shot: the use of vaccines to prevent antibiotic resistance

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Combating antimicrobial resistance

New antibiotic development

Appropriate use of antibiotics

Vaccines
Vaccines that reduce antibiotic use

- **Bacterial**
  - Pneumococcal
  - Hib
  - Pertussis

- **Viral**
  - Influenza
  - Varicella
  - MMR
Hypothesized mechanisms by which antecedent viral infections increase risk of bacterial co-infection

- Virus destruction of respiratory epithelium may increase bacterial adhesion
- Inflammatory response to viral infection may facilitate expression of molecules used as bacterial receptors
- Virus induced immunosuppression may increase risk of bacterial superinfection
Epidemiology of influenza - *Staphylococcus aureus* co-infection
Influenza-**S. aureus** co-infection

- Synergistic interaction recognized since the 1930s†

- 1957 influenza pandemic – 2 distinct co-infection syndromes described‡
  - Early in course with overwhelming pneumonia
  - Late in course after period of clinical improvement

- Co-infection speculated to be cause of “Plague of Athens” 427-430 BC¥

Severe Methicillin-Resistant *Staphylococcus aureus* Community-Acquired Pneumonia Associated with Influenza — Louisiana and Georgia, December 2006–January 2007

*Staphylococcus aureus* infection has been reported infrequently as a cause of community-acquired pneumonia (CAP) and typically has been associated with influenza virus infection or influenza-like illness (ILI). During the 2003–04 influenza season, meticillin-resistant *S. aureus* (MRSA) gained attention as a cause of 15 cases of influenza-associated CAP† (1). No formal surveillance has been conducted, and few additional cases of MRSA CAP were reported to CDC during the

Case Reports

**Louisiana case 1.** A previously healthy boy aged 10 years (Table) became ill with fever, cough, sore throat, and bilateral earache on December 6, 2006, and was treated with acetaminophen at home. The next day, his symptoms worsened and he was taken to a local ED in respiratory distress with a fever of 104°F (40°C). A chest radiograph was performed and revealed multilobar pneumonia. The patient was transferred
### Characteristics of pediatric influenza-associated death by season, 2004-2008

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Season</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>04-05 (N=47)</td>
</tr>
<tr>
<td>Invasive bacterial infection</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Bacterial cx non sterile site¹</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>S. aureus sterile OR non-sterile site</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

¹ includes ET tube, post mortem lung biopsy
Influenza vaccine: room for improvement

- Influenza vaccination coverage is low among children even though they may have an indication for vaccination.

- Co-infection with *S. aureus* increased dramatically over 3-4 years.
  - Factors that may have contributed to the increase:
    - Predominance of USA 300 strain in community which is an effective colonizer.
    - MRSA colonization rates increasing especially in school-aged children.
Benefits of influenza vaccine on antibiotic use

- Reduces inappropriate antibiotic use for treatment of viral respiratory infection
- Reduces secondary bacterial infections that may be resistant and require antibiotic therapy
Pneumococcal Conjugate Vaccine (PCV7)

- Includes poly- / oligosaccharides of 7 of 90 known pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, 23F)
- Conjugated to a non-toxic variant of diphtheria toxin
- Introduced into routine childhood immunization program in U.S. in 2000
Conjugate Vaccine Effect on Carriage
## Clinical trials of pneumococcal conjugate vaccines

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCKP (7v)</td>
<td>Invasive disease, VT</td>
<td>97.4 (82.7-99.9)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia, X-ray confirmed</td>
<td>20.5 (4.4-34.0)</td>
</tr>
<tr>
<td></td>
<td>Otitis media episodes</td>
<td>7.0 (4.1-9.7)</td>
</tr>
<tr>
<td>Navajo (7v)</td>
<td>Invasive disease, VT</td>
<td>82.6 (21.4-96.1)</td>
</tr>
<tr>
<td>S Africa (9v)</td>
<td>Invasive disease, VT HIV -</td>
<td>83 (39-97)</td>
</tr>
<tr>
<td></td>
<td>Invasive disease, VT HIV +</td>
<td>65 (24-86)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia, consolidation, HIV-</td>
<td>20 (2-35)</td>
</tr>
<tr>
<td></td>
<td>Invasive disease, pen resistant</td>
<td>67 (19-88)</td>
</tr>
<tr>
<td>Gambia (9v)</td>
<td>Invasive disease, VT</td>
<td>77 (51-90)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia, X-ray confirmed</td>
<td>37 (27-45)</td>
</tr>
<tr>
<td></td>
<td>All-cause hospital admission</td>
<td>15 (7-21)</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>16 (3-28)</td>
</tr>
</tbody>
</table>

Active Bacterial Core surveillance (ABCs) & invasive pneumococcal disease

- Case Definition: *Streptococcus pneumoniae* isolated from a normally sterile site (e.g. blood, CSF)

- Review of clinical chart for each case
  - Confirm residency status (population-based surveillance)
  - Confirm isolation from sterile site (laboratory-based surveillance)

- Isolates sent to reference laboratories:
  - Serotyping
  - Genotyping
  - Antimicrobial susceptibility testing
## ABCs surveillance population

<table>
<thead>
<tr>
<th>State</th>
<th>Counties</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>3</td>
<td>920,695</td>
</tr>
<tr>
<td>CO</td>
<td>5</td>
<td>2,224,779</td>
</tr>
<tr>
<td>CT</td>
<td>All</td>
<td>3,483,375</td>
</tr>
<tr>
<td>GA</td>
<td>20</td>
<td>4,464,200</td>
</tr>
<tr>
<td>MD</td>
<td>6</td>
<td>2,572,121</td>
</tr>
<tr>
<td>MN</td>
<td>All</td>
<td>5,059,375</td>
</tr>
<tr>
<td>NM</td>
<td>All</td>
<td>1,874,614</td>
</tr>
<tr>
<td>NY</td>
<td>15</td>
<td>2,186,060</td>
</tr>
<tr>
<td>OR</td>
<td>3</td>
<td>1,514,744</td>
</tr>
<tr>
<td>TN</td>
<td>11</td>
<td>2,896,734</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>27,196,697</strong></td>
</tr>
</tbody>
</table>

9.1% of U.S. population of >298 million
Figure 3. Annual Incidence of Invasive Disease Caused by Penicillin-Nonsusceptible Pneumococci in Persons Two Years of Age or Older, 1996 to 2004

Rates of IPD among children aged <5 years, 1998/99-2006

Pilishvili, IDSA 2007
Rates of antibiotic nonsusceptible invasive disease among children aged <5 years, 1998/99-2005
Rates of serotype 19A IPD among children aged <5 years, by penicillin susceptibility, 1998/99-2006

ABCs, Unpublished
Why has serotype 19A increased?

Cause of invasive disease
(Robinson et al, JAMA 2001)

Common in carriage
(Bluengemann et al, JID 2003)

Associated with antibiotic resistance
(Pai et al, JID 2005)

New clones emerging in the absence of vaccination
(Dagan et al. ICAAC 2007)
(Choi et al. EID 2008)

Evidence of capsular switching
(Bluengemann et al, PLoS Pathogen In press)

PCV7 not effective against type 19A IPD
(Whitney et al. Lancet 2006)

Key point: Multiple factors are contributing to observed increases in serotype 19A disease

Pilishvili, IDSA 2007
The advantages of pneumococcal vaccines

- Relationship between antimicrobial use and antimicrobial resistance clearly established
- Reducing disease incidence decreases need for antibiotics
- Targeting resistant serotypes reduces incidence of resistant disease
- Herd immunity effects of the vaccine prevent disease and resistance among unvaccinated persons
Goals for decreasing antibiotic use and resistance through vaccination

- Identify missed opportunities for vaccination (increase vaccine coverage)
- Develop and introduce new vaccines, such as the expanded-valent pneumococcal conjugate vaccines
Acknowledgements

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The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.
ACIP Influenza Vaccination Recommendations

- High risk children ≥ 6 mos
- Healthy 6-23 mos ‘encouraged’ in 2002-03
- All 6-23 mos recommended in 2004-05
- All 24-59 mos recommended in 2006-07
- Priming dose and 2nd dose required for children <9 yrs old

The CDC’s Advisory Committee has recommended that the age group for influenza immunization be expanded to include all children between 6 months and 18 years of age by the 2009-2010 influenza season.
Pencillin breakpoints for S. pneumoniae

In June 2007, the U.S. Clinical & Laboratory Standards Institute (CLSI, formerly NCCLS) voted to change pencillin breakpoints for non-meningitis cases of pneumococcal disease effective January 1, 2008.

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>MICs, mcg/ml</th>
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<tbody>
<tr>
<td>Susceptible</td>
<td>≤0.06</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.12-1</td>
</tr>
<tr>
<td>Resistant</td>
<td>≥2</td>
</tr>
</tbody>
</table>

...and conundrums

How will the breakpoint change influence proportions of pneumococcal infections considered susceptible, intermediate, & resistant?

How should surveillance programs manage this change, especially if MICs are not reported to them?
How vaccines decrease resistance

- Decrease in antibiotic use for bacterial infections
- Decrease in inappropriate antibiotic use for viral illness
- Decrease in bacterial co-infection
- Decrease in circulation of antibiotic resistant strains