Influenza and Bacterial Superinfection

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Flu In Children: Background Data

• Annual incidence of seasonal influenza: 2 – 10%
• Annual burden of disease in children difficult to establish and often underestimated
• Attack rates highest in children <5 years
• Average annual hospitalization rate in children ± 0.9:10.000
  but higher in infants: up to 1:1.000
• Rapid dissemination of influenza in school children
• Mortality due to influenza is very low but highest < 6 months (0.88:100.000)
• Pre-existing medical conditions increase risk of complications;
• Vaccination of children prevents morbidity and mortality in the elderly
• Two types of vaccines are available:
  - trivalent influenza vaccine (TIV)
  - live attenuated influenza vaccine (LAIV)
• No vaccines are available for children < 6 months
• Vaccination of pregnant women in 3rd trimester may protect young infants
Role for viral-bacterial synergy

- Synergism observed during influenza A virus pandemics and epidemics
- Viral infection increases risk of developing severe secondary bacterial infection
- Observed for many viruses and bacteria (e.g. RSV, *Staphylococcus aureus*)
Not only influenza, but also secondary bacterial infections!

Morens et al. 2008 JID
Influenza virus and mortality

- Rapid! Mortality sometimes within 24h of first symptoms: due to ARDS (10-15%) or slower due to bronchopneumonia (85-95%)
- Seasonal local epidemics and global pandemics

Excess deaths:

1918 Spanish flu  (50x10^6)
1957 Asian influenza  (675,000)
1968 Hong Kong influenza  (86,000)
2009 Swine flu  (56,300)

Influenza and bacterial superinfection resulting in deaths

• Causative agents:
  • S. pneumoniae
  • S. aureus
  • S. pyogenes
  • H. influenzae

• Differences in etiology, age range and mortality rates due to:
  • Strain related differences in virus or bacteria
  • Vaccination status
  • Pre-existing immunity

Morens; J Infect Dis 2008
Taubenberger; Ann Rev Pathol 2008
Mc Cullers; Nat Rev Microbiol 2014
Is Flu in Children Associated with High Mortality Rates?

Only 5 (6%) of risk groups were fully vaccinated. Bacterial co-infection in 6, 15 and 34%
Population of the USA 313.7 million; Netherlands: 17 million → mortality 10/year
CONCLUSION: mortality due to flu is rare. Bacterial superinfection is common and likely underestimated. Risk is highest in infants below 6 months

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age group, n (%)</td>
<td>8 (17)</td>
<td>8 (17)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>0-5 mo</td>
<td>4 (8)</td>
<td>13 (28)</td>
<td>10 (14)</td>
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<tr>
<td>6-23 mo</td>
<td>9 (20)</td>
<td>5 (10)</td>
<td>10 (14)</td>
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<tr>
<td>5-8 y</td>
<td>10 (22)</td>
<td>9 (19)</td>
<td>15 (21)</td>
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<tr>
<td>9-12 y</td>
<td>7 (15)</td>
<td>6 (13)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>13-17 y</td>
<td>8 (17)</td>
<td>5 (10)</td>
<td>12 (16)</td>
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2003-2004 Bacterial co-infection: 25%
underlying conditions: 50%
Defense mechanisms of the respiratory tract

Physical
- Turbulence
- Ciliated cells
- Epithelial barrier
- Surfactant

Innate
- Mucus
- Complement system
- Natural IgA
- Type I IFNs
- Innate cells: Neutrophils, Macrophages

Adaptive
- Cellular
- Antibodies
Schematic representation of the epithelial-endothelial barrier in the human respiratory tract

Short KR, Lancet ID 2014
Temporal associations between viral titre, bacterial load and the availability of immune effectors in a model of viral-bacterial co-infection

Influenza and Bacterial Superinfection: Immunologic mechanisms of disease

• Dysfunction of lung physiology, oxygen exchange, airway hyperreactivity, decreased clearance of bacteria
• Epithelial cell barrier damage
• Endothelial cell activation
• Neutrophil induced damage
• Destruction of alveolar macrophages
• Virus effects on immunity of bacteria: Type I interferons
• Increased inflammation
• Bacterial interference with anti-viral immunity
• Strain-specific differences
The interplay between virus, host and bacteria in co-infections

Increased pneumococcal load precipitates disease

** Mann-Whitney p<0.01
Influenza vaccination with LAIV, but not PCV prevents pneumococcal outgrowth in the URT
Increased pneumococcal load in the nasopharynx is associated with viral co-infection.
Increased pneumococcal load in the nasopharynx is associated with RCP.
Viral coinfections and invasive pneumococcal disease

Ref: PIDJ 2010; Techasaensiri
Excess Rates of Hospitalization for Acute Respiratory Disease Attributable to Influenza Virus Among Children without High-Risk Conditions during Periods in Which Influenza virus Predominated

<table>
<thead>
<tr>
<th>Study Site and Age Group</th>
<th>Rate in Period When Influenzavirus Predominated</th>
<th>Rate in Summer Base-Line Period</th>
<th>Excess Rate Attributable to Influenzavirus (95% CI)†</th>
<th>P Value</th>
<th>Rate in Peri-Seasonal Base-Line Period</th>
<th>Rate Attributable to Influenzavirus (95% CI)‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rate/100,000 person-months</td>
<td>rate/100,000 person-months</td>
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<tr>
<td>Northern California Kaiser</td>
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</tr>
<tr>
<td>0–1 yr</td>
<td>231</td>
<td>81</td>
<td>151 (113 to 188)</td>
<td>&lt;0.001</td>
<td>120</td>
<td>112 (73 to 150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2–4 yr</td>
<td>53</td>
<td>27</td>
<td>26 (9 to 42)</td>
<td>&lt;0.002</td>
<td>38</td>
<td>15 (−2 to 33)</td>
<td>&lt;0.081</td>
</tr>
<tr>
<td>5–17 yr</td>
<td>19</td>
<td>19</td>
<td>0 (−5 to 5)</td>
<td>0.951</td>
<td>14</td>
<td>5 (1 to 10)</td>
<td>&lt;0.026</td>
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<tr>
<td>Group Health Cooperative</td>
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<tr>
<td>0–1 yr</td>
<td>193</td>
<td>66</td>
<td>127 (82 to 171)</td>
<td>&lt;0.001</td>
<td>107</td>
<td>86 (39 to 132)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2–4 yr</td>
<td>21</td>
<td>16</td>
<td>5 (−9 to 20)</td>
<td>0.468</td>
<td>24</td>
<td>−3 (−19 to 13)</td>
<td>0.727</td>
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<tr>
<td>5–17 yr</td>
<td>17</td>
<td>12</td>
<td>5 (−3 to 10)</td>
<td>0.066</td>
<td>10</td>
<td>7 (1 to 12)</td>
<td>&lt;0.012</td>
</tr>
</tbody>
</table>

Conclusions

1. Infants and young children without underlying diseases are at increased risk for hospitalization
2. Flu causes considerable disease burden in children
H1N1 infections in the Netherlands in hospitalized children (N=940)

Ahout et al: submitted
H1N1 infections: number of hospitalizations per week
Number of hospitalizations per week in relation to start vaccination campaign

Ahout et al: submitted
Risk groups * for hospitalization by influenza: 50% of all cases

Young age
Pre-existing heart and lung disease
Prematurity
Hematological disorders
Neuromuscular and psychomotor disorders

* Down syndrome, diabetes, cystic fibrosis and metabolic disorders were not confirmed
Control and prevention of influenza-associated pneumonia

- Influenza vaccination
  - Risk group based?
  - Age-related: young children?
  - All children?
  - Choice of vaccine: TIV or LAIV?
- Vaccination of pregnant women?
- During pandemic seasons or also seasonal flu?
- Vaccination against pneumococcus
- Vaccination against H. influenzae
- Neuraminidase inhibitors: selection of patients? Timing?
- Antimicrobial therapy: selection? When to start?
Childhood influenza: number needed to vaccinate to prevent 1 hospitalization

No. of children needed to be vaccinated

Vaccine efficacy


25% 50% 75%

1031-3050 4255-6897
Summary

- Bacterial-viral co-infection is common during severe ALRI
- Viral infections modulate the antibacterial response in multiple ways and lead to increased pneumococcal replication in the URT
- Increases in URT load are associated with increased severity of pneumococcal disease and with inter-individual spread
- Vaccination against influenza virus may offer an attractive strategy to limit the development of secondary bacterial disease