Respiratory virus associated community-acquired pneumonia in Western Australian Children: case-control study

Mejbah Bhuiyan
PhD Candidate, School of Paediatrics and Child Health
The University of Western Australia
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Background

• Pneumonia - the leading cause of morbidity and mortality among young children worldwide
  – Childhood pneumonia in Australia: 5-8/1000 person years

• Causative agent: Bacteria, virus and both

• Pneumococcal conjugate vaccine – Immunization schedule in 2005

• Influenza vaccine – Low uptake

• Maternal RSV vaccine currently in phase III trials
Asymptomatic carriage of respiratory viruses in Australian children

<table>
<thead>
<tr>
<th>Study</th>
<th>Specimen</th>
<th>% positive</th>
<th>Viruses identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore, H et al. 2010</td>
<td>Nasal aspirate</td>
<td>25% for any virus</td>
<td>HRV (20%), Adenovirus (6%), Coronavirus (4%), RSV (0.5%)</td>
</tr>
<tr>
<td>Wiertsema et al. 2011</td>
<td>Nasopharyngeal swab</td>
<td>71% for any virus</td>
<td>HRV (42%), HBoC (8%), RSV (8%), Coronavirus (5%), HPIV (4%)</td>
</tr>
</tbody>
</table>

Knowledge gap

- Actual contribution of pathogen remains unclear
- Only few case-control studies on childhood viral pneumonia in developed countries in the era of routine Hib and pneumococcal vaccination

- PneumoWA study : May 2015- ongoing
  - **Objective:** To assess contribution of respiratory viruses and bacteria and pathogen-specific population-attributable risk
  - **Rationale:** Accurate knowledge as attributable pathogen-specific burden is essential to develop effective preventive strategies including vaccine development
Methods

• Prospective case-control study: CASE: CONTROL - 1:1 (250 in each arm)
  – CASE- Children with x-ray confirmed pneumonia at PMH of all ages
  – CONTROL- Healthy children at PMH outpatients and Rheola St
    Immunisation Clinic
  – Age and frequency matched controls

• Epidemiological data collection
  – Demographic
  – Medical and immunization record

• Nasopharyngeal swab
  – Both cases and controls
  – STGG (Skim Milk–Tryptone–Glucose–Glycerol)
  – Stored at -80°C

Methods

• Laboratory testing
  – **Duplex real-time polymerase chain reaction** (PCR)- PathWest, QEII
    • Influenza viruses A, B; Parainfluenza viruses 1–4; Human Metapneumovirus;
      RSV A and B; Rhinovirus; Adeno virus; Coronavirus OC43; Coronavirus
      NL63; Coronavirus HKU1; Coronavirus 229E;

  – **Other testing including:**
    • Viral and bacterial load quantification
    • Nasopharyngeal cytokine response

• Statistical analysis
  • Compare distribution of each pathogen in cases and controls
  • Univariate Odds ratio (OR) for each pathogen
  • Logistic regression model adjusting for demographic factors and the
    presence of all pathogens
  • Population attributable risk for each pathogen
Findings

- Enrolment during May 2015-Nov 2016: 168 cases and 168 controls

- Medical information for cases
  - Hospitalization days: median 2 (IQR: 1 – 3)
  - Raised inflammatory markers (WCC ≥20 or CRP ≥40): 43%
  - Empyema: 8%
  - All children were discharged/transferred to other facilities – no death

Distribution of respiratory viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 virus</td>
<td>5.3 (3.1–8.9)</td>
</tr>
<tr>
<td>HMPV</td>
<td>37.3 (4.3–319.0)</td>
</tr>
<tr>
<td>RSV</td>
<td>24.7 (7.8–78.0)</td>
</tr>
<tr>
<td>Influenza (overall)</td>
<td>9.2 (2.2–38.0)</td>
</tr>
<tr>
<td>Coronavirus (overall)</td>
<td>1.5 (0.3–6.67)</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>1.1 (0.5–2.3)</td>
</tr>
</tbody>
</table>

*p<0.05
Population attributable risk (%)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any respiratory virus</td>
<td>47.3</td>
<td>35.6 – 57.0</td>
</tr>
<tr>
<td>RSV</td>
<td>20.8</td>
<td>13.7 – 27.4</td>
</tr>
<tr>
<td>HMPV</td>
<td>8.6</td>
<td>3.8 – 13.1</td>
</tr>
<tr>
<td>Influenza (overall)</td>
<td>8.4</td>
<td>3.1 – 13.5</td>
</tr>
<tr>
<td>Rhino Virus</td>
<td>1.3</td>
<td>-9.1 – 10.8</td>
</tr>
<tr>
<td>Coronavirus (overall)</td>
<td>1.1</td>
<td>-3.7 – 5.8</td>
</tr>
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</table>

Discussion and conclusion

- Respiratory viruses contributed 47% of all x-ray confirmed childhood pneumonia in Western Australia

- RSV - Leading cause of pneumonia in children
  - Effective vaccine targeting RSV could have a significant impact

- Influenza - Another important cause of pneumonia
  - Strengthen efforts to improve uptake of influenza vaccine

- Rhinoviruses - Frequently identified among cases and controls
  - Raises doubt about the significance of rhinovirus as a pneumonia-causing pathogen
Future directions

- Presence of respiratory virus
- Quantitative virology
- Quantitative bacteriology
- Host inflammatory response

Sensitive, specific and prognostic “diagnostic profiles” in children with ALRI

Diagnose and manage pneumonia and ALRI cases more efficiently
Reduce inappropriate use of antibiotics to treat ALRI

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