Influenza-Related Mortality and Encephalopathy among Children in the United States

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Influenza Morbidity and Mortality

• Influenza causes annual epidemics
  – Major cause of morbidity & mortality: children aged <24 months, those aged >65, and those with underlying pulmonary, cardiac, etc. disease
• Nationally available data has limitations
  – Relatively few respiratory illness cases tested
  – Influenza generally not a reportable disease
• Estimates of U.S. deaths & hospitalizations made with statistical models for decades
  – With retrospective death certificate, hospital discharge data, and viral surveillance data
Hospitalizations & Deaths from Influenza

- Modeling studies estimate an average of
  - >200,000 influenza-associated hospitalizations/year
  - ~36,000 influenza-associated deaths/year
  - Average numbers ‘hide’ considerable variability
- Highest rates of complications are in:
  - Persons with pulmonary and cardiac disease
  - Persons ≥65 years
  - Children <5 years
- Mortality data for children limited
  - Estimated average of ~92 influenza-related deaths among children aged <5 years annually


Pertinent Features of the 2003-04 Influenza Season

- Began as early as October in some states
- Influenza A (H3N2) predominant subtype
  - Historically associated with more severe seasons
- Vaccine mismatch for H3N2 strain
- CDC began receiving reports of influenza-related deaths in children in November 2003
  - No comparable historical data available
  - Public concern; spot vaccine shortages
- On December 12, 2003, request to state, territorial, and local health departments for reports of pediatric influenza-associated deaths
Enhanced Surveillance Methods

- **Surveillance period**
  - September 28, 2003 - May 22, 2004
- **Case definition**
  - U.S. resident
  - <18 years old
  - Death during surveillance period
  - Evidence of influenza virus infection by at least one laboratory test: rapid test, IFA, culture, RT-PCR, or immunohistochemistry on autopsy specimens

Results 2003-04 Season

- 153 deaths reported from 40 states
- Median age 3 years; range 2 weeks - 17 years
- 76 (50%) male
- **Race (n=146)**
  - White 67%
  - Black 22%
  - Asian 6%
- **Ethnicity (n=134)**
  - Hispanic 24%
### Method of Diagnosis (n=153)

<table>
<thead>
<tr>
<th>Sole method</th>
<th>Number (%)</th>
<th>Total Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid antigen/EIA</td>
<td>58 (38)</td>
<td>117</td>
</tr>
<tr>
<td>Viral Culture</td>
<td>17 (11)</td>
<td>54</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>5 (3)</td>
<td>11</td>
</tr>
<tr>
<td>Fluorescent antibody (DFA, IFA)</td>
<td>5 (3)</td>
<td>25</td>
</tr>
<tr>
<td>Immunohistochemical staining</td>
<td>5 (3)</td>
<td>27</td>
</tr>
<tr>
<td>Multiple methods</td>
<td></td>
<td>63 (41)</td>
</tr>
</tbody>
</table>

### Epidemic Curve and Virologic Activity

![Epidemic Curve and Virologic Activity Graph](image)
### Age Distribution (n=153)

![Bar chart showing age distribution](chart.png)

### Age-specific Mortality Rates

<table>
<thead>
<tr>
<th>Age group</th>
<th>N (%)</th>
<th>Deaths/100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>18 (12)</td>
<td>0.88 (0.52-1.39)</td>
</tr>
<tr>
<td>6 - 23 months</td>
<td>43 (28)</td>
<td>0.71 (0.51-0.96)</td>
</tr>
<tr>
<td>2 - 4 years</td>
<td>35 (23)</td>
<td>0.30 (0.20-0.42)</td>
</tr>
<tr>
<td>5 - 17 years</td>
<td>57 (37)</td>
<td>0.11 (0.08-0.14)</td>
</tr>
<tr>
<td>All ages</td>
<td>153 (100)</td>
<td>0.21 (0.18-0.24)</td>
</tr>
</tbody>
</table>
Underlying Health Status

- Healthy, 70, 45%
- ACIP + non-ACIP, 34, 22%
- ACIP only, 15, 10%
- Non-ACIP only, 30, 20%
- Unknown, 4, 3%

Figure 2. Influenza-Associated Mortality Rates According to Age Group — United States, 2003–2004 Season.

**Location at Time of Death (n=153)**

- **Home/Transit, 47, 31%**
- **ER, 16, 10%**
- **Inpt/ICU, 90, 59%**

**Reported Clinical & Autopsy Diagnoses - 1**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical only</th>
<th>Autopsy only</th>
<th>Both</th>
<th>Total (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>26</td>
<td>29</td>
<td>16</td>
<td>71</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>1</td>
<td>10</td>
<td>--</td>
<td>11</td>
</tr>
<tr>
<td>ARDS</td>
<td>9</td>
<td>1</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>Croup</td>
<td>6</td>
<td>--</td>
<td>--</td>
<td>6</td>
</tr>
<tr>
<td>Tracheitis/bronchitis</td>
<td>--</td>
<td>27</td>
<td>--</td>
<td>27</td>
</tr>
<tr>
<td>Sepsis</td>
<td>32</td>
<td>6</td>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>Shock</td>
<td>30</td>
<td>1</td>
<td>2</td>
<td>33</td>
</tr>
</tbody>
</table>
# Reported Clinical and Autopsy Diagnoses - 2

<table>
<thead>
<tr>
<th>diagnosis</th>
<th>Clinical only</th>
<th>Autopsy only</th>
<th>Both</th>
<th>Total (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy/encephalitis</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Seizures</td>
<td>14</td>
<td>--</td>
<td>--</td>
<td>14</td>
</tr>
<tr>
<td>Myo/pericarditis</td>
<td>1</td>
<td>5</td>
<td>--</td>
<td>6</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>--</td>
<td>2</td>
<td>--</td>
<td>2</td>
</tr>
<tr>
<td>Myositis/rhabdomyolysis</td>
<td>4</td>
<td>1</td>
<td>--</td>
<td>5</td>
</tr>
<tr>
<td>DIC</td>
<td>15</td>
<td>2</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Hemophagocytosis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*On review, 9 met the case definition for probable or suspected influenza-associated encephalopathy*
Antiviral Medication Use

Total Deaths
N=153

Antiviral status unknown
38 (25%)

Antiviral status known
115 (75%)

Median 1 day
Mean 2.6 days

Antivirals received
26 (23%)

No antivirals received
89 (77%)

- Amantidine 12 (46%)
- Rimantadine 2 (8%)
- Oseltamivir 12 (46%)
- Zanamivir 0 (0%)

Limitations

- Request for case reports was made near the peak of the season in December
- Passive surveillance
- Variations in testing practices, clinical, and pathologic diagnoses
- Incomplete medical records
- Limited information for non-hospitalized cases
- Lack of comparable data, from prior and subsequent seasons
Pediatric Influenza Mortality Reporting System

• Lab-confirmed pediatric influenza-associated death became a nationally notifiable condition in June 2004
  - Reporting began October 2004
  - Data reported weekly in MMWR Table 1 and weekly influenza update
• Fewer data elements collected in 2-page reporting form

Pediatric Influenza Mortality Reporting System

• 47 cases reported from 18 states during the 2004-05 season
  - 1 received oseltamivir
• 45 cases from 14 states during 2005-06
  - 3 received oseltamivir, 1 rimantadine
• 71 cases from 26 states during 2006-07
  - 3 received oseltamivir, 1 unknown antiviral
Influenza-Associated Acute Encephalopathy in Children - United States, 2003-04 Influenza Season

Background

- Influenza-associated encephalopathy (IAE) is an uncommon complication of influenza
- Can result in serious neurologic sequelae
- IAE most commonly reported in young Japanese children
  - 148 Japanese cases reported during 1998-99
  - 25 U.S. cases identified during 1999-2003
Enhanced Surveillance Methods

• Surveillance period
  - September 28, 2003 - May 22, 2004

• Case definition
  - U.S. resident
  - <18 years of age
  - Febrile illness
  - Laboratory-confirmed Influenza virus infection
  - Altered mental status

Case Classification

Probable
  - Altered mental status >24 hours
And
  - Onset of altered mental status within 5 days of fever onset
And
  - No other cause for altered mental status identified
Case Classification

**Suspect**
- Duration of altered mental status unknown

Or
- Altered mental status ≥ 24 hours, but unable to rule out another cause

Or
- Altered mental status < 24 hours, or other cause for altered mental status identified

And **Status Epilepticus**

Or **Objective findings of cerebral inflammation (CT, MRI, EEG, CSF)**

Results 2003-04 Season

- 42 IAE cases reported from 22 states
  - 22 Probable
  - 20 Suspect

- 20 Males (48%)
  - Probable: 54% Male
  - Suspect: 40% Male
Results 2003-04 Season

• White
  - Probable: 9 (50%)
  - Suspect: 12 (67%)
• Black
  - Probable: 6 (33%)
  - Suspect: 6 (33%)
• Asian
  - Probable: 3 (17%)
  - Suspect: 0

• Ethnicity information available for some probable and suspect cases
  - 6 Hispanic (23%)
• Probable: N=13
  - 1 Hispanic (8%)
• Suspect: N=13
  - 5 Hispanic (38%)
Age Distribution (N=42)

- Median: 5 years
- Mean: 6.9 years
- Range: 6 months - 17 years

Underlying High Risk Medical Conditions

- 42 Suspect and Probable Cases
  - 27 had no prior medical conditions
  - 15 had at least 1 chronic medical conditions
    - 7 Probable
    - 8 Suspect
    - 5 had a condition for which ACIP recommended influenza immunization for the 2003-04 influenza season
Specific High Risk Medical Conditions

- Chronic GI: 1
- Arthritis: 1
- Chronic lung disease: 1
- Cerebral palsy: 2
- Seizure disorder: 2
- ENT abnormality: 2
- Asthma: 3
- Developmental delay: 6

Time from fever to onset of encephalopathy

<table>
<thead>
<tr>
<th>Days</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

[Graph showing the number of cases by days, with bars for suspect and probable cases]
Clinical Presentation - 1

• 33 (78%) presented with altered mental status
  - Duration: median 3 days (range 1-31) among 28 patients with available data
• 20 (48%) Seizures: 9 Probable & 11 Suspect
  8 Status Epilepticus: 3 Probable & 5 Suspect
  16 Multiple seizures: 8 Probable & 8 Suspect

Clinical Presentation - 2

• 17 (40%) Movement Disorder/Ataxia
  - 8 Probable
  - 9 Suspect
• Decreased strength/Flaccid weakness
• Hypotonicity/Hypertonicity
• Slow movements
• Unable to hold trunk/head properly
Neuroimaging Studies - 1

- 26 children had an MRI
  - 17 (65%) Abnormal
  - 17 Probable
    - 11 Abnormal
  - 9 Suspect
    - 6 Abnormal

Abnormalities included
- Cerebral edema (most common)
- Evidence of infarct
- Tonsilar herniation
- Focal cerebritis

Neuroimaging Studies - 2

- 11 Children only had CT scan
  - 3 Probable
    - 1 Abnormal
  - 8 Suspect
    - 3 Abnormal

- All 4 abnormal CTs showed cerebral edema
  - 2 with herniation
Diagnostic Testing

• 31 (71%) Cerebrospinal Fluid Studies
  • 18 Probable cases
    • 7 with > 5 WBCs/mm³
    • Range 8-69 cells
  • 13 Suspect cases
    • 1 with > 5 WBCs/mm³ (13 cells)
• Influenza CSF Cultures (N=17)
  • 1 positive (Suspect case)

Antiviral Treatment

• 20 Received antivirals
  • 10 Probable
    • 10 Oseltamivir
    • 1 Rimantadine
  • 10 Suspect
    • 4 Oseltamivir
    • 5 Amantadine
    • 1 Rimantadine
Antiviral Treatment: Timing

- Before neurological symptoms
  - 0 probable, and 1 suspect case
- Day of development of neurological symptoms
  - 2 probable, and 5 suspect cases
- After development of neurological symptoms
  - 8 probable, and 4 suspect cases

Outcomes

- 19 recovered without neurologic sequelae: 10 Probable and 8 Suspect cases
- 13 recovered with chronic neurologic sequelae: 8 Probable and 5 Suspect cases
- 7 died: 4 Probable and 3 Suspect cases
- Status unknown for 3 Suspect cases
Outcomes by Age

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>1 - 4</td>
<td>16</td>
</tr>
<tr>
<td>5 - 9</td>
<td>10</td>
</tr>
<tr>
<td>10 - 17</td>
<td>12</td>
</tr>
</tbody>
</table>

- Died
- With Neuro Sequelae
- Recovered

Limitations

- Passive surveillance
- May have missed cases
- Selection or referral bias
- Differential reporting by states
- Timing of surveillance
- Limited clinical data
- No national system to collect data on laboratory-confirmed cases
Summary

• At least 42 IAE cases occurred
  - 22 Probable
  - 20 Suspect

• Asian-Americans were not prominent

• 50% were <5 years old, but older children also affected

• 20 had severe outcomes, including death or chronic neurologic sequelae

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