Clinical Issues
Pandemic Influenza A (H1N1) Virus Infection

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www.pandemicflu.gov  www.cdc.gov/flu
U.S. Cases Reported to CDC

- **Confirmed/Probable**: 27,717
  - Median age: 12 years
- **Hospitalizations***: 3,065
  - Median age: 20 years
- **Deaths**: 127
  - Median age: 37 years

*Current priority for testing
Pandemic H1N1 Case Rate/100,000 population by age group

Pandemic H1N1 Hospitalization Rates* by Age Group (n=3,065)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hospitalizations per 100,000 Population</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 Yrs</td>
<td>3.0</td>
<td>639</td>
</tr>
<tr>
<td>5-24 Yrs</td>
<td>1.4</td>
<td>1168</td>
</tr>
<tr>
<td>25-64 Yrs</td>
<td>0.7</td>
<td>1057</td>
</tr>
<tr>
<td>65 Yrs</td>
<td>0.3</td>
<td>122</td>
</tr>
</tbody>
</table>

*Hospitalizations with unknown ages are not included (n=79)
Pandemic H1N1 Deaths by Age Group
As of 25 JUN 2009 (n=127)

Number of Deaths

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 Yrs</td>
<td>7</td>
<td>6%</td>
</tr>
<tr>
<td>5-24 Yrs</td>
<td>26</td>
<td>22%</td>
</tr>
<tr>
<td>25-64 Yrs</td>
<td>80</td>
<td>63%</td>
</tr>
<tr>
<td>≥ 65 Yrs</td>
<td>9</td>
<td>6%</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>3%</td>
</tr>
</tbody>
</table>
Pandemic H1N1 Case Fatality Proportion by Age Group
Data reported as of 18 JUN 2009 (n=87)

Case Fatality Ratio

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Case Fatality Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 Yrs</td>
<td>0.26%</td>
</tr>
<tr>
<td>5-24 Yrs</td>
<td>0.19%</td>
</tr>
<tr>
<td>25-64 Yrs</td>
<td>1.54%</td>
</tr>
<tr>
<td>≥65 Yrs</td>
<td>3.38%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.09%</td>
</tr>
</tbody>
</table>
Serologic Investigations

• Pre and Post vaccination sera evaluated
• Microneutralization (MN) and hemagglutination inhibition (HI) assays performed at CDC
  • Among 79 children (6 months to 9 years), little evidence of preexisting cross-reactive antibodies to novel A/California/04/2009 (H1N1) virus
  • Sera from persons >60 years old had some cross-reactive antibodies against novel H1N1
  ➢ Suggests some immunity for infection/illness in older persons, but not <60 years

Katz J et al MMWR May 21, 2009
Transmission Dynamics (U.S.)

- Secondary attack rate in household contacts:
  - Acute respiratory illness: 19%
  - Influenza-like illness: 8-12%
  - Higher attack rates observed in schools

- Serial interval:
  - Acute respiratory illness: 2.0-3.1 days
  - Influenza-like illness: 2.4-3.1 days

- Estimated Ro = 1.4-1.7
Pandemic H1N1 Diagnostic Testing of Respiratory Specimens

- Best respiratory specimen to detect pandemic H1N1 virus infection: not yet known
  - Nasopharyngeal (swab, aspirate)
  - Nasal swab
  - Throat swab
  - Combined specimens
  - Lower respiratory tract specimens (intubated patients)
Pandemic H1N1 Diagnostic Testing of Respiratory Specimens

• **Antigen Detection**
  • **Rapid influenza diagnostic tests**
    • Sensitivity: 51% (compared to rRT-PCR, QuickVue Influenza A+B)*
    • Sensitivity: 10-40% (compared to Luminex PCR, Binax NOW, 3MA+B)**
    • Cannot distinguish between seasonal influenza or pandemic H1N1 virus infection
  ➢ Positive and Negative results need interpretation

• **Immunoflorescence**
  • Sensitivity: 47%** (compared to Luminex PCR Resp Viral Panel)
  • Cannot distinguish between seasonal influenza or pandemic H1N1 virus infection
  ➢ Positive and Negative results need interpretation

*Faix et al., NEJM 2009; **Ginocchio JC Virol 2009
Pandemic H1N1 Diagnostic Testing
Respiratory Specimens

➢ Detection of viral RNA (preferred method)
   • Real-time reverse transcription polymerase chain reaction (rRT-PCR)
     • Highest sensitivity, highly specific
     • CDC primer-probes for specific detection of pandemic H1N1 distributed throughout the U.S and worldwide
       • Use of seasonal influenza primer-probes will be positive for influenza A, but negative for seasonal H1, H3 subtypes
   • Isolation of virus
     • Viral tissue cell culture
       • High sensitivity, highly specific
Clinical Spectrum of Influenza Virus Infection

- Asymptomatic infection:
  - Occurs with seasonal influenza virus infection
  - Serological investigations pending

- Uncomplicated mild-moderate illness
  - Upper respiratory tract symptoms without fever
  - Influenza-like illness (ILI)
    - Fever, headache, non productive cough, rhinorrhea, sore throat, myalgias
    - ILI with vomiting, diarrhea
      - More frequent than with seasonal influenza
Clinical Spectrum of Influenza Virus Infection
Seasonal Influenza - Expect with Pandemic H1N1

• Mild to moderate complications:
  • Otitis media, sinusitis, bronchitis

• Moderate to severe complications:
  • Exacerbation of chronic illness (e.g. cardiac, pulmonary)
  • Lower respiratory tract disease
    • Pneumonia (viral, bacterial co-infection)
    • Bronchiolitis, croup
  • Cardiac: myocarditis
  • Musculoskeletal: myositis, rhabdomyolysis
  • Neurologic: encephalopathy, encephalitis
  • Toxic shock syndrome
  • Severe dehydration
CRX Findings at Admission

- Evidence of pneumonia in 40-50% cases
- Bilateral or unilateral infiltrates
- Patchy, diffuse, alveolar, interstitial infiltrates
- Multilobar or single lobe involved
Hospitalized Pandemic H1N1 Cases, U.S.  
(N = 268)

- Median time from onset to admission
  - 3 days (range 1-14 days)
- Median length of stay
  - 3 days (range 1-59)
- Median age
  - 22 years (range 21 days-86 years)
- 128 female (48%), 140 male (52%)
  - 71% with underlying co-morbidities
  - 21% admitted to ICU
  - 13% required mechanical ventilation
  - 17 deaths (6.3%)
Clinical Characteristics at Admission (n=268)

- Fever*: 93%
- Cough: 83%
- SOB: 54%
- Fatigue/weakness: 40%
- Chills: 31%
- Myalgias: 36%
- Rhinorrhea: 31%
- Sore throat: 31%
- Headache: 29%
- Vomiting: 24%
- Wheezing: 24%
- Diarrhea: 24%

* as of 19 JUN 2009
**Novel Influenza A (H1N1) Hospitalizations, U.S. (n=268)**

- **Median age:** 22 years (range 21 days-86 years)

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Hospitalized No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-23 months</td>
<td>24 (9)</td>
</tr>
<tr>
<td>2-4 years</td>
<td>20 (8)</td>
</tr>
<tr>
<td>5-9 years</td>
<td>28 (10)</td>
</tr>
<tr>
<td>10-17 years</td>
<td>55 (20)</td>
</tr>
<tr>
<td>18-49 years</td>
<td>95 (35)</td>
</tr>
<tr>
<td>50-64 years</td>
<td>31 (12)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>15 (6)</td>
</tr>
</tbody>
</table>
# Underlying Conditions among 268 Hospitalized Patients With Novel Influenza A (H1N1) Reported to CDC Compared to US Prevalence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence, hospitalized H1N1 patients</th>
<th>Prevalence, General US Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma or COPD</strong></td>
<td>32%</td>
<td>8% (asthma)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Immunocompromised</strong></td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic cardiovascular disease</strong>*</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Current Smoker</strong></td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Chronic Renal Disease</strong></td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Neurocognitive disorder</strong></td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td><strong>Neuromuscular disorder</strong></td>
<td>7%</td>
<td>0.03%</td>
</tr>
<tr>
<td><strong>Pregnant</strong></td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Seizure disorder</strong></td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>8%</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Excludes hypertension
Pandemic (H1N1) Deaths Reported to CDC by States as of 25 JUN 2009

- Limited data available on 99/111 deaths in 20 states

- 49 Female (53%), 44 Male (47%)

- Median time from illness onset to death
  - 7.5 days (range 0 - 40 days)
Pandemic (H1N1) Deaths Reported to CDC by States (24 JUN 2009)

- N=87
- Median age: 37 years (range 2 months-72 years)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-23 months</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>2-4 Yrs</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>5-9 Yrs</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>10-17 Yrs</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>18-29 Yrs</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>30-49 Yrs</td>
<td>35 (40%)</td>
</tr>
<tr>
<td>50-64 Yrs</td>
<td>18 (21%)</td>
</tr>
<tr>
<td>≥65 Yrs</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
Pandemic (H1N1) Deaths Reported to CDC by States as of 25 JUN 2009 (n=99)

- 12 (12%) persons with **no** underlying conditions
- **82% with underlying conditions** - may overlap for individual cases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent Deceased Cases with Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>11%</td>
</tr>
<tr>
<td>Other Pulmonary disease</td>
<td>24%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13%</td>
</tr>
<tr>
<td>Chronic cardiovascular disease</td>
<td>14%</td>
</tr>
<tr>
<td>Neurocognitive disorder</td>
<td>15%</td>
</tr>
<tr>
<td>Neuromuscular disorder</td>
<td>11%</td>
</tr>
<tr>
<td>Pregnant</td>
<td>8%</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>7%</td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>11%</td>
</tr>
<tr>
<td>Obesity</td>
<td>34%</td>
</tr>
<tr>
<td>Other serious (hepatic, cancer, immunosuppressed)</td>
<td>13%</td>
</tr>
</tbody>
</table>
Possible Pathogenesis in Severe Disease

- Unknown to date - data needed
- Fulminant pneumonia
  - Suggests viral infection of lower respiratory tract
    - Possible high viral replication triggering cytokine dysregulation (similar to highly pathogenic avian influenza H5N1 virus infection?)
    - Acute lung injury, rapid progression to ARDS
      - Refractory ARDS
- Invasive bacterial co-infection
- Multi-organ failure, septic shock
- Muscle inflammation
- Potential for extrapulmonary dissemination
  - Viremia, fecal shedding, etc.
Clinical Management*

- Early antiviral treatment with neuraminidase inhibitors (Oseltamivir, Zanamivir)
- Oxygen therapy - ensure adequate oxygenation
- Advanced respiratory support - mechanical ventilation - follow guidelines for sepsis-associated ARDS
- Antibiotic treatment following evidence-based guidance for community-acquired pneumonia
- Corticosteroids: no routine use
  - Low dose for septic shock requiring vasopressors and have adrenal insufficiency
- No aspirin or aspirin-containing products for <18 years

*WHO Clinical Management Guidance May 2009
Infection Control

- **WHO Guidance**
  - Isolation of patients
  - Standard, Droplet precautions
  - Aerosol-generating procedures
    - N95 or FFP2 respirator, eye protection, gowns, gloves, airborne precaution room with natural or mechanically ventilated ventilation per WHO guidance

- **CDC Guidance**
  - Isolation of patients
  - Standard, Droplet, Eye precautions, fit-tested N95 respirator, gowns, gloves, when providing care
  - Aerosol-generating procedures - negative pressure room
Summary

- Most pandemic H1N1 disease is mild-to-moderate self-limited influenza-like illness
- Severe and fatal disease has occurred, and will continue to occur
  - Expect a wide range of clinical syndromes, not just pneumonia cases
- Hospitalizations and deaths have occurred in children and adults <65 years old
  - Most have had underlying co-morbidities
- Data on severe disease pathogenesis are needed
  - Clinical and virological data are needed to inform clinical guidance {we need to learn together!}
Thank you for your attention!