Lessons Learned from the 2009 H1N1 Influenza Pandemic

Ruben Donis
Influenza Division, CDC, DHHS

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Verona, April 27-29, 2010

“Those who do not remember the past are condemned to repeat it.”
George Santayana (1863-1952)

- 1918 H1N1 Pandemic
- 1957 H2N2 Pandemic
- 1968 H3N2 Pandemic
- 1976 Swine flu USA
- 1977 H1N1 re-entry
- 1997 H5N1 Outbreak
Other Zoonotic Influenza Infections

- Swine
  - ~ 60 zoonotic H1N1 swine influenza cases reported since 1958
    - Classical swine lineage viruses
    - Eurasian swine lineage viruses
    - "triple reassortant" North American viruses
- Swine influenza lacked human-to-human transmissibility
- Seals and poultry
  - H7N7 and H7Nx in Europe and North America

Pandemic Preparedness Plans: Assumptions
Main Assumptions for Pandemic Planning

- H5N1 greatest concern, H2 and H9 possible
- Population immunity to H1N1 and H3N2 preclude subtype H1 and H3 emergence
- Avian virus genes to reassort with human virus
- Asia leading epicenter for emergence
- Naïve population require two doses of vaccine
- Slow initial spread of avian-origin virus
- Preparedness for H5N1 would be “portable” to other subtypes

Predictions

- The assumption that antibodies to human influenza viruses of the H1 and H3 subtypes are cross-reactive towards contemporary avian H1 and H3 viruses of Eurasian lineage is incorrect.

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CDC Pandemic Preparedness: Before April 2009

- **Diagnostics**
  - Rapid, Point of care
  - Differentiate human seasonal from other influenza viruses
  - Laboratory Dx capacity
  - Clinical trials: FDA approval

- **Surveillance**
  - Focus on Asia
  - Strengthened public health lab capacity (atypical flu)

- **Vaccines**
  - H5N1, H7N7, H9N2, etc.
    - Antigenic drift monitoring
    - Vaccine candidate development
    - Vaccine stockpiles

- **Antiviral drugs**
  - Detect resistant strains
  - Stockpile

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**First Detection of 2009 H1N1 in the U.S.**

- **24 April**
- **22 May**
U.S. declares National Public Health Emergency

Response to 2009 H1N1 by CDC

- **Detection**
  - Surveillance: Epidemiology, diagnostics, etc.
  - Domestic and global

- **Intervention**
  - Pharmacologic
    - Antiviral drugs and Vaccines
  - Non-pharmacologic
    - Community mitigation (e.g. school closure)
    - Travel restrictions, border controls, etc.
    - Hospital infection control, laboratory biosafety, etc.
ORIGIN OF THE 2009 PANDEMIC H1N1 VIRUS

Lesson #1

Gaps in Surveillance

Lesson #1

- No recent ancestors known
- ~9-17 years evolving without detection
- Escaped virologic surveillance
Lesson #1 2009 Pandemic H1N1 Virus Broke the Rules

- Pre-existing immunity to seasonal H1N1 in humans did not preclude emergence of 2009 H1N1 virus
- Household secondary attack rates are lower than previous pandemics: 2009 H1N1 is less transmissible
- No recent avian or human virus reassortment
- 2009 H1N1 virus probably emerged with pandemic properties in Mexico
  - Ressortment time, place, host remain unknown

Secondary Attack Rates: 10-13%

Table 2. Baseline Characteristics of the Household Contacts, According to Age Group.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=600)</th>
<th>0-4 Yr (N=40)</th>
<th>5-18 Yr (N=164)</th>
<th>19-50 Yr (N=120)</th>
<th>&gt;51 Yr (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever or feverishness</td>
<td>75 (13)</td>
<td>11 (28)</td>
<td>32 (20)</td>
<td>31 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Cough</td>
<td>95 (16)</td>
<td>10 (25)</td>
<td>36 (22)</td>
<td>48 (15)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>50 (8)</td>
<td>5 (12)</td>
<td>15 (9)</td>
<td>28 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>47 (7)</td>
<td>7 (18)</td>
<td>16 (10)</td>
<td>17 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (3)</td>
<td>3 (9)</td>
<td>8 (5)</td>
<td>7 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like illness:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected contacts — no. (%)</td>
<td>62 (10)</td>
<td>9 (23)</td>
<td>27 (17)</td>
<td>21 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>3.18 (1.66-6.10)</td>
<td>2.20 (1.35-3.53)</td>
<td>1.55 (0.84-2.89)</td>
<td>1.03 (0.50-1.89)</td>
<td>0.22</td>
</tr>
<tr>
<td>P-value for relative risk</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory illness:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected contacts — no. (%)</td>
<td>7 (1.2)</td>
<td>2 (5)</td>
<td>21 (13)</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>2.13 (1.10-4.43)</td>
<td>1.65 (1.12-2.43)</td>
<td>1.07 (0.36-3.60)</td>
<td>1.00 (0.29-3.60)</td>
<td>0.16</td>
</tr>
<tr>
<td>P-value for relative risk</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* The data are for household contacts from the 256 households with two to six members in which the index patient was the first case patient in the household, and information on symptoms and age was complete for all household members. The median age of the household contacts was 26 years. CI denotes confidence interval.
† Influenza-like illness was defined as fever or feverishness plus cough, sore throat, or both.
‡ Acute respiratory illness was defined as the presence of at least two of the following signs: fever or feverishness, cough, sore throat, and runny nose.

Lesson #2  Diagnostic Preparedness

- Global pandemic preparedness for a H5N1 facilitated rapid an effective response to 2009 H1N1
- Additional networks and institutional partnerships allowed a more coordinated and measured global response
- Rapid publication of CDC sequence data allowed rapid development of molecular tests
- More sensitive and inexpensive tests are needed
- Diagnostics tests that inform on subtype in clinical settings may detect pandemic viruses earlier

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CDC Virologic Surveillance – 2008-10 Influenza Seasons

As of April 3, 2010

>600,000 Specimens Tested
2.5 fold increase over prior season

Week Number

- B
- A(H3)
- A(H1)
- A(Unable to Subtype)
- A(2009 H1N1)

Percent Positive

www.cdc.gov/H1N1flu
Timeline From Virus Seed to Vaccine

**APRIL**
- Prepare high growth reassortant
- Prepare monovalent pilot lot
- Production monovalent vaccine
- FDA release
- Formulate & Fill
- Potency testing
- Distribution

**MAY**
- 25 April: Working seed
- 26 May: Production monovalent vaccine

**JUNE**

**JULY**

**AUG**

**SEPT**

**OCT**
- 5 October: Distribution

Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2008-09

- **Decision to Place Order For Vaccines for US population**
- **July: Spring Wave H1N1 Down in US**

Jan 1, 2009, May, Jun, Jul
Lesson #3

2009 Pandemic H1N1 Vaccine

- Vaccine purchase decisions have to be made before needed knowledge is available
- Future course of the 2009 H1N1 outbreak uncertain
  - Transmissibility
  - Virulence in various age groups

“I am sure that what any of us do, we will be criticized either for doing too much or for doing too little…. If an epidemic does not occur, we will be glad. If it does, then I hope we can say… that we have done everything and made every preparation possible to do the best job within the limits of available scientific knowledge and administrative procedure.” —US Surgeon General Leroy Burney, Meeting of the Association of State and Territorial Health Officers, August 28, 1957

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From Seed to Vaccine

Vaccine manufacturing need firm orders

<table>
<thead>
<tr>
<th>APRIL</th>
<th>MAY</th>
<th>JUNE</th>
<th>JULY</th>
<th>AUG</th>
<th>SEPT</th>
<th>OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

- Prepare high growth reassortant
- Working seed
- Prepare monovalent pilot lot
- Production monovalent vaccine
- Potency testing
- FDA release
- Formulate & Fill
- US Gov’t Places Orders
- Distribution
- For Vaccines for US population
- Shown for Inactivated Vaccine (Live Vaccine Available Earlier)
The Fall Wave of 2009 H1N1

Lesson #4 2009 Pandemic H1N1 Vaccine

- Pandemic vaccine delivery started within 6 months of emergence –per Pandemic Plan
  - Despite production being slower than expected
- Second wave spread through the US in early Fall
  - ~ 3 months earlier than normal “flu season”
- A 4-month timeline for vaccine availability is necessary for future pandemics
Revisit Pandemic Planning Assumptions

- H5N1 greatest concern, H2 and H9 possible
- Population immunity to H1N1 and H3N2 preclude subtype H1 and H3 emergence
- Avian virus genes to reassort with human virus
- Asia leading epicenter for pandemic emergence
- Naïve population require two doses of vaccine
- Slow initial spread of avian-origin virus
- All of the above: not this time
- Preparedness for H5N1 would be “portable” to other subtypes

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- Michael Persue, BARDA

Forever Unprepared — The Predictable Unpredictability of Pathogens

Kurt A. Sepkowitz, M.D.
Virus of the Year:
The Novel H1N1 Influenza

• “Scientists characterized the new virus and distributed tests to detect it at record speed, sharing findings nearly in real time.”

• SCIENCE VOL 326 18 DECEMBER 2009

THANK YOU!

QUESTIONS?
Consultation Questions

- 1. What are the knowledge gaps we should address to further define drivers of emergence and predict emergence?
- 2. What are the surveillance strategies that we need to develop and that can be implemented where these diseases occur?
- 3. What control and prevention measures are applicable in different scenarios, particularly different economic situations?
- 4. For which diseases is research into reservoir(s) or disease ecology critical to develop prevention and control measures?
- 5. Which tools do we have to differentiate between the occurrence of opportunistic and evolutionary or (co-evolutionary) events?
- 6. How do we decide when to respond?

2009 H1N1 Vaccine Coverage, U.S.

- January 2010
- U.S. Median:
  - 33% among ACIP Priority groups
  - 24% all persons > 6 months of age