Pandemic Influenza and Mortality: Past Evidence and Projections for the Future

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Contributors

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  – National Institute of Allergy and Infectious Diseases
What are we planning for? 1918 or 1957-like? Will there be enough time for vaccine?

In the case of pandemics, we are planning for the equivalent of a tornado… rare and completely unpredictable until the last minute, when a “weather watch” (e.g., pandemic alert) appears on the TV screen.

Ed Kilbourne, JID 1997
Excess mortality associated with influenza
-Best available measure of mortality impact

Observed Deaths
Epidemic Threshold

Weekly P&I Deaths

Year and Week
Mortality impact of Pandemic influenza
1918 pandemic an order of magnitude apart

<table>
<thead>
<tr>
<th>US</th>
<th>Antigenic shift</th>
<th>Excess Deaths</th>
<th>Excess Mortality Rate/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918-19</td>
<td>All novel?</td>
<td>~ 500,000</td>
<td>530</td>
</tr>
<tr>
<td>A(H1N1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1957-58</td>
<td>H + N</td>
<td>~ 60,000</td>
<td>40</td>
</tr>
<tr>
<td>A(H2N2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1968/69</td>
<td>H only</td>
<td>~ 40,000</td>
<td>18</td>
</tr>
<tr>
<td>A(H3N2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What makes pandemic impact different from epidemic impact?

Number of deaths may be similar, but mortality burden shifts to younger people.

<table>
<thead>
<tr>
<th>Year</th>
<th>Excess all-cause deaths/100,000 pop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ages</td>
</tr>
<tr>
<td>1968</td>
<td>15</td>
</tr>
<tr>
<td>1967/68 A/H2N2 epidemic</td>
<td>18</td>
</tr>
<tr>
<td>1968/69 A/H3N2 Pandemic</td>
<td>22</td>
</tr>
</tbody>
</table>
Age-shift: ~50% pandemic deaths in persons < 65 years
After ~1 decade “epidemic” pattern is restored

Simonsen et al, JID 1998
1968 pandemic and the following A/H3N2 epidemics: Increase in mortality risk during the first decade in younger population

Excess Mortality rate in A/H3N2-dominated epidemics in persons aged 45-64 years, 1968-1999, US
VIRTUES OF ORIGINAL ANTIGENIC SIN:
1968 pandemic - when it was a good thing to be very old

- Did childhood exposure to H3-like antigens ("Original Sin") before 1892 provide protection during the 1968 pandemic when H3 was recycled?

- predicted by Marine & Workman 1969
Sero-archeology:
% prevalence of H3 antibodies by birth year

Persons born before 1890 have high titers of serum antibody against the 1968 pandemic virus.

These people were 77+ years old in the 1968/69 pandemic.

Data from Dowdle, Bull WHO 1999
Age-specific mortality rate of 1968 pandemic and severe A/H3N2 epidemic

Log_{10}(P&I excess deaths/100,000)

1000

100

10

1

0.1

Born before 1892 (in 1968)

Viboud, and Simonsen, Reichert and Miller, in press
Those 80+ years of age were protected, relative to surrounding severe epidemics.

Evidence that H3-like antibodies carried since childhood in most elderly born before 1892 provided protection in the 1968 A/H3N2 pandemic.

Simonsen, Reichert and Miller, in press
The 1968 pandemic: MISMS

2/3 of pandemic mortality in UK occurred in 2nd year
Also true for France, Australia and Japan, but not Canada

P&I death rate /100,000

USA

UK

First wave (1968/69)
Second wave (1969/70)
Baseline

Viboud et al, unpublished
1918 pandemic revisited

Age-specific P&I Mortality Rates in U.S. for the entire Calendar Year

Annual mortality rate (/100,000)

Age group

<1 1 to 4 5 to 14 15 to 24 25 to 34 35 to 44 45 to 54 55 to 64 65 to 74 75 to 84 85 +

1918

Average 1911-15
### Deaths according to age groups, October, 1918

<table>
<thead>
<tr>
<th>Boroughs</th>
<th>All Ages</th>
<th>Under 1 Year</th>
<th>Under 2 Years</th>
<th>1-5 Years</th>
<th>5-15 Years</th>
<th>15-25 Years</th>
<th>25-45 Years</th>
<th>45-65 Years</th>
<th>65 Years and over</th>
<th>Colored</th>
<th>Chinese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manhattan</td>
<td>9,961</td>
<td>722</td>
<td>348</td>
<td>1,484</td>
<td>433</td>
<td>1,314</td>
<td>3,899</td>
<td>1,267</td>
<td>664</td>
<td>454</td>
<td>45</td>
</tr>
<tr>
<td>The Bronx</td>
<td>2,700</td>
<td>166</td>
<td>79</td>
<td>334</td>
<td>173</td>
<td>498</td>
<td>1,226</td>
<td>308</td>
<td>161</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Brooklyn</td>
<td>7,427</td>
<td>532</td>
<td>305</td>
<td>1,249</td>
<td>537</td>
<td>1,227</td>
<td>3,120</td>
<td>938</td>
<td>556</td>
<td>133</td>
<td>8</td>
</tr>
<tr>
<td>Queens</td>
<td>1,551</td>
<td>117</td>
<td>54</td>
<td>254</td>
<td>117</td>
<td>217</td>
<td>711</td>
<td>171</td>
<td>81</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Richmond</td>
<td>609</td>
<td>45</td>
<td>21</td>
<td>102</td>
<td>35</td>
<td>104</td>
<td>252</td>
<td>71</td>
<td>45</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>City of N.Y</td>
<td>21,548</td>
<td>1,582</td>
<td>807</td>
<td>3,423</td>
<td>1,295</td>
<td>3,360</td>
<td>9,208</td>
<td>2,755</td>
<td>1,507</td>
<td>653</td>
<td>60</td>
</tr>
</tbody>
</table>

*Don Olson*
Classical 1918 “W”-shaped curve revisited

Don Olson et al, to-be-published
Monthly Age-specific All-cause Deaths in NY City, 1911-1920

Little or no impact among persons 45 years of age and older

Don Olson et al, To-be-published
Evidence of a Severe Herald Wave
Early spring 1918, New York City
Age-specific Excess Mortality Rates show “pandemic pattern”

1918/19 pandemic
1918 herald wave
Feb-April 1918
1915/16 epidemic

Don Olson et al, to-be-published
Origin of the 1918 Influenza Pandemic?

....we are not in Kansas anymore...

Map modified from Patterson & Pyle, 1991
1957 A/H2N2 Pandemic:
Better described as a series of twisters

1957/58 A/H2N2 emergence
1959/60 A/H2N2
1962/63 A/H2N2
Later A/H2N2 Epidemics up to 1968
1957 A/H2N2 Pandemic and first 5 years
Sustained mortality impact in first 3 “waves”

PNEUMONIA-INFLUENZA DEATH RATES
BY MONTH, UNITED STATES

Serfling et al, AJE 1967
### 1957 Pandemic:

% influenza-related deaths in first 3 waves

<table>
<thead>
<tr>
<th>P&amp;I excess mortality for first 3 H2N2 seasons</th>
<th>All Ages</th>
<th>YOUNG 15-19 years of age</th>
<th>ELDERLY 75+ years of age</th>
</tr>
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<tbody>
<tr>
<td>1957/58</td>
<td>44%</td>
<td>71%</td>
<td>33%</td>
</tr>
<tr>
<td>1959/60</td>
<td>30%</td>
<td>18%</td>
<td>35%</td>
</tr>
<tr>
<td>1962/63</td>
<td>26%</td>
<td>11%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Total Impact 3 seasons</strong></td>
<td><strong>100%</strong></td>
<td><strong>100%</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
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Data from Serfling et al, JID 1967
# 1957 A/H2N2 Pandemic: First 3 waves, 1957-63

<table>
<thead>
<tr>
<th>Pandemic</th>
<th>Proportion P&amp;I deaths All Ages</th>
<th>YOUNG 15-19 years of age</th>
<th>ELDERLY 75+ years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957/58 Attack rate *</td>
<td>44% ~40%</td>
<td>71% 73%</td>
<td>33% 16-32%</td>
</tr>
<tr>
<td>1959/60</td>
<td>30%</td>
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* Age-specific attack rates from the Cleveland Family Study

Bill Jordan et al, 1958
Projections for the Future
- if past is prologue (and n=3!)

• 1918: A “herald wave” 6 months before
  • We may get a warning

• 1957: Continued severe impact in first 3 H2N2 “waves” of 1959/60 and 1962/63

• 1968: “Smoldering” pandemic in Europe
  • Not all the action occurs in the first season

• All 3 pandemics: Age shift in mortality
  • Mortality impact is difficult to predict but age shift to younger ages is expected
Implications for Future Pandemics: Should younger people have higher priority?

• 1918: Highest mortality risk among young adults
  – Elderly were at lower risk! Prior exposure to recycled virus?

• 1957: 70% of all pandemic deaths in children and young adults occurred early – in 1957/58
  – Only 1/3 of elderly deaths during 1957/58, the rest followed

• 1968: Elderly 77+ years of age were protected by Ab from childhood (recycling)
  – Relative to epidemics, elderly were not at increased risk
  – However, elderly were at higher risk than younger age groups