The Severity of Pandemic H1N1 Influenza in the US, from April to July 2009: A Bayesian Analysis

A.M. Presanis et al. (2009)
PLoS Medicine, 6, e1000207

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Biostatistics Journal Club
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Outline

1. Motivation
2. Data
3. Methods
4. Results
5. Discussion
6. Conclusion
Motivation: Background

- every winter millions of people catch influenza and half a million die
- seasonal epidemics occur because small but frequent changes in the virus occur
- March 2009 new virus called "pandemic H1N1/09" ("Swine flu") occurred at first in Mexico and spread rapidly
- risk for global epidemics (pandemics) that kill millions of people (e.g. the "Spanish flu" 1918)
Why was the study done?

- autumn and return of children to school after summer break help to spread influenza
- H1N1 cases, hospitalizations and deaths in the Northern Hemisphere have greatly increased
- the impact on human health is unknown
- accurate measurements are needed to estimate the severity of the infection and the impact in an upcoming autumn-winter pandemic wave
Measures of severity of infections

- many people are infected but do not show symptoms
- many people who get an ILI (influenza-like illness) are not going to see any medical professional
- serological surveys were not available
Measures of severity of infections

- many people are infected but do not show symptoms
- many people who get an ILI (influenza-like illness) are not going to see any medical professional
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-> it is not that easy to estimate case-severity ratios
Measures of severity of infections

- many people are infected but do not show symptoms
- many people who get an ILI (influenza-like illness) are not going to see any medical professional
- serological surveys were not available

-> it is not that easy to estimate case-severity ratios

-> instead: focus on symptomatic cases
Symptomatic case severity ratios

- **sCHR** symptomatic case-hospitalization ratio (the proportion of symptomatic cases that result in hospitalization)

- **sCIR** symptomatic case-intensive care ratio (the proportion of symptomatic cases that require treatment in an ICU (intensive care unit))

- **sCFR** symptomatic case-fatality ratio (the proportion of symptomatic cases that result in death)
Data

Milwaukee

- April 27 - May 20 testing persons with influenza symptoms by using a RT-PCR (reverse transcriptase polymerase chain reaction) test specific for H1N1
  -> medically attended, hospitalized, ICU-admitted and death data

- May 21 - June 14 reduced testing of mild cases
  -> only hospitalized, ICU-admitted and death data were used
Data

Milwaukee

- April 27 - May 20 testing persons with influenza symptoms by using a RT-PCR (reverse transcriptase polymerase chain reaction) test specific for H1N1
  -> medically attended, hospitalized, ICU-admitted and death data

- May 21 - June 14 reduced testing of mild cases
  -> hospitalized, ICU-admitted and death data were used

New York

- April 26 - July 7 testing hospitalized patients with ILI by using a rapid influenza antigen test

- patients who were tested positive and all ICU patients were tested by RT-PCR
Telephone Survey Data

New York

- May 20 - May 27 1.006 surveys
- June 15 - June 19 1.010 surveys
- random-digit dialing
- non-randomized individual was interviewed
- provided information about ILI of all household members
Telephone Survey Data

New York

- May 20 - May 27 1.006 surveys
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- non-randomized individual was interviewed
- provided information about ILI of all household members

CDC - Center for Disease Control and Prevention

- May 2009 in 11 US states
- Survey from 2007 was used as a template to conduct a survey about ILI [Reed et al., 2009]
<table>
<thead>
<tr>
<th>Location</th>
<th>Age Group</th>
<th>Severity</th>
<th>Medically Attended</th>
<th>Hospitalized to May 20</th>
<th>Hospitalized to June 14</th>
<th>ICU-Admitted to June 14</th>
<th>Dead to June 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milwaukee</td>
<td>0-4</td>
<td>126</td>
<td>7</td>
<td>27</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-17</td>
<td>470</td>
<td>6</td>
<td>29</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18-64</td>
<td>189</td>
<td>12</td>
<td>87</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>788</td>
<td>25</td>
<td>147</td>
<td>27</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>New York</td>
<td>0-4</td>
<td>—</td>
<td>225</td>
<td></td>
<td>44</td>
<td>2 / 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-17</td>
<td>—</td>
<td>197</td>
<td></td>
<td>51</td>
<td>2 / 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18-64</td>
<td>—</td>
<td>518</td>
<td></td>
<td>147</td>
<td>46 / 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>—</td>
<td>56</td>
<td></td>
<td>15</td>
<td>3 / 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>—</td>
<td>996</td>
<td></td>
<td>257</td>
<td>53 / 9</td>
<td></td>
</tr>
</tbody>
</table>

**Table:** Cases at each level of severity
Methods

- Bayesian evidence synthesis framework: to combine information and uncertainty about each level of severity into a single estimate
- two different approaches
- each provides estimates for the general population and for age groups 0-4, 5-17, 18-64, 65+
Model

**APPROACH 1**
- New York
- Milwaukee
- CDC surveys
  - Medically attended
  - Symptomatic
  - Serologically infected

**APPROACH 2**
- New York deaths
- sCFR
- New York ILI self-reports

**Figure**: Diagram of two approaches to estimating the sCFR
Model(II)

Figure: Bayesian model to synthesise severity data
Observation model

- the observations are related to the true numbers $N$ and the detection probabilities

- $O_{iM} \sim Binomial(N_{iM}, d_M)$
- $O_{iHk} \sim Binomial(N_{iHk}, d_{Hk})$
- $O_{iIk} \sim Binomial(N_{iIk}, d_{Ik})$
- $O_{iDk} \sim Binomial(N_{iDk}, d_{Dk})$

$i$: age group
$M$: medically attended
$H$: hospitalized
$I$: ICU
$D$: death
$k$: Milwaukee or New York
Case-severity ratios

Conditional probabilities

Number of cases by severity

Detection probabilities

Observed cases
Detection probabilities

- probability of performing a test \( \times \) sensitivity of the test
- \( d_{MW}, d_{Hk}, d_{Ik}, d_{Dk} \)

Example: detection probability for medically attended in Milwaukee

\[ d_{MW} = d_{MW1} \times d_{MW2} \]

\( d_{MW1} = \) the probability of performing a test \( \sim \) Uniform(0.2, 0.35)

\( \rightarrow \) CDC Data

\( d_{MW2} = \) sensitivity of the RT-PCR-test \( \sim \) Uniform(0.95, 1)

\( \rightarrow \) Assumption
Case-severity ratios

Conditional probabilities

Number of cases by severity

Detection probabilities

Observed cases
True number of persons at each level of severity

**Approach 1**

\[ N_{iMk} \sim \text{Binomial}(N_{iSk}, c_{iM}|S) \]
\[ N_{iHk} \sim \text{Binomial}(N_{iMk}, c_{iH}|M) \]
\[ N_{iIk} \sim \text{Binomial}(N_{iHk}, c_{iI}|H) \]
\[ N_{iD,Hk} \sim \text{Binomial}(N_{iHk}, c_{iD}|H) \]
\[ N_{iD,Hk} \sim \text{Binomial}(N_{iMk}, c_{iD,H}|M) \]
\[ N_{iSW} \sim \text{Uniform}(O_{iMW}, 0.25 \times \text{popn}_{iW}) \]
\[ N_{iSN} \sim \text{Uniform}(0, \text{upper}_{iN} \times \text{popn}_{iN}) \]
\[ \text{upper}_{iN} \sim \text{Beta}(\cdot) \]

**Approach 2**

- 
\[ N_{iH} \sim \text{Binomial}(N_{iS}, c_{iH}|S) \]
\[ N_{iI} \sim \text{Binomial}(N_{iH}, c_{iI}|H) \]
\[ N_{iD,H} \sim \text{Binomial}(N_{iH}, c_{iD}|H) \]
\[ N_{iD,H} \sim \text{Binomial}(N_{iS}, c_{iD,H}|S) \]
- 
\[ N_{iS} \sim \text{Binomial}(\text{popn}_{iN}, c_{iS}|P) \]
\[ c_{iS}|P \sim \text{Beta}(\cdot) \]
Case-severity ratios

Conditional probabilities

Number of cases by severity

Detection probabilities

Observed cases
Conditional probabilities - Approach 1

\[ c_D|S = P\{\text{death} \mid \text{symptoms}\} \]
\[ = P\{\text{death among hospitalized, death among medically attended but not hospitalized} \mid \text{symptoms}\} \]
\[ = c_D|H \cdot c_H|M \cdot c_M|S + c_D, \overline{H}|M \cdot c_M|S \]

- similar \( c_I|S, c_H|S \)
- \( c_D|H, c_I|H, c_H|M, c_D, \overline{H}|M \sim Beta() \), very shallow Beta distributions (probabilities of true H1N1 deaths, ICU and hospitalizations given the previous severity)
- \( c_M|S \sim Beta(51.5, 48.5) \) (prior from CDC-Data)
Conditional probabilities - Approach 2

- medically attended level is not considered

- \( c_D|S = c_D|H \cdot c_H|S + c_D, \overline{H}|S \)

- \( c_I|S = c_I|H \cdot c_H|S \)
Case-severity ratios

Conditional probabilities

Number of cases by severity

Detection probabilities

Observed cases
unknown parameters $\theta = (c_{ij}, d_{ij}, N_{ijk}, s\text{CHR}, s\text{CIR}, s\text{CFR})$

known $O = O_{ij}$

$P(\theta | O) \propto P(\theta) L(O | \theta)$

OpenBUGS

MCMC was used to obtain samples from the posterior distribution

three chains of 1,000,000 iterations including 800,000 burn-ins
Results: Estimates for the sCFR, sCIR, sCHR - Approach 1

<table>
<thead>
<tr>
<th>Age</th>
<th>sCFR</th>
<th>sCIR</th>
<th>sCHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>0.026% (0.006%–0.092%)</td>
<td>0.321% (0.133%–0.776%)</td>
<td>2.45% (1.10%–5.56%)</td>
</tr>
<tr>
<td>5–17</td>
<td>0.010% (0.003%–0.031%)</td>
<td>0.106% (0.043%–0.244%)</td>
<td>0.61% (0.27%–1.34%)</td>
</tr>
<tr>
<td>18–64</td>
<td>0.159% (0.066%–0.333%)</td>
<td>0.542% (0.230%–1.090%)</td>
<td>3.00% (1.35%–5.92%)</td>
</tr>
<tr>
<td>65+</td>
<td>0.090% (0.008%–1.471%)</td>
<td>0.327% (0.035%–4.711%)</td>
<td>1.84% (0.21%–25.38%)</td>
</tr>
<tr>
<td>Total</td>
<td><strong>0.048% (0.026%–0.096%)</strong></td>
<td><strong>0.239% (0.134%–0.458%)</strong></td>
<td><strong>1.44% (0.83%–2.64%)</strong></td>
</tr>
</tbody>
</table>

Table: Posterior median (95% CI) estimates of the sCFR, sCIR, and sCHR, by age group, based on a combination of data from New York City and Milwaukee, and survey data on the frequency of medical attendance for symptomatic cases.
Estimates for the sCFR, sCIR, sCHR - Approach 2

<table>
<thead>
<tr>
<th>Age</th>
<th>sCFR</th>
<th>sCIR</th>
<th>sCHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>0.004%</td>
<td>0.044%</td>
<td>0.33%</td>
</tr>
<tr>
<td></td>
<td>(0.001%–0.011%)</td>
<td>(0.026%–0.078%)</td>
<td>(0.21%–0.63%)</td>
</tr>
<tr>
<td>5–17</td>
<td>0.002%</td>
<td>0.019%</td>
<td>0.11%</td>
</tr>
<tr>
<td></td>
<td>(0.000%–0.004%)</td>
<td>(0.013%–0.027%)</td>
<td>(0.08%–0.18%)</td>
</tr>
<tr>
<td>18–64</td>
<td>0.010%</td>
<td>0.029%</td>
<td>0.15%</td>
</tr>
<tr>
<td></td>
<td>(0.007%–0.016%)</td>
<td>(0.021%–0.040%)</td>
<td>(0.11%–0.25%)</td>
</tr>
<tr>
<td>65+</td>
<td>0.010%</td>
<td>0.030%</td>
<td>0.16%</td>
</tr>
<tr>
<td></td>
<td>(0.003%–0.025%)</td>
<td>(0.016%–0.055%)</td>
<td>(0.10%–0.30%)</td>
</tr>
<tr>
<td>Total</td>
<td>0.007%</td>
<td>0.028%</td>
<td>0.16%</td>
</tr>
<tr>
<td></td>
<td>(0.005%–0.009%)</td>
<td>(0.022%–0.035%)</td>
<td>(0.12%–0.26%)</td>
</tr>
</tbody>
</table>

Table: Posterior median (95% CI) estimates of the sCFR, sCIR, and sCHR, by age group, using self-reported ILI as the denominator of symptomatic cases.
Discussion: Limitations

- imperfect detection and reporting cases
- small sample size in some age groups (in particular the 65+ age group)
- detection probabilities are time dependent
- assumption that for each level of severity case reporting was equal across age groups
- \( \text{sCFR, sCIR and sCHR are dependent on the true number of symptomatic cases } N_{iSk} \), prior assumptions and the detection probabilities
- there could be a shift from the younger to older groups in whom infection is more severe
Estimates for the June 2009 - February 2010 H1N1 wave in England

- same author A.M. Presanis did similar study in England about changes in severity of 2009 pandemic H1N1 influenza [Presanis et al., 2011]
- the symptomatic cases of the data were used to compare it with the estimates in the US
Estimates for the June 2009 - February 2010 H1N1 wave in England (II)

<table>
<thead>
<tr>
<th></th>
<th>Appr 1</th>
<th>Appr 2</th>
<th>UK Jun-Aug</th>
<th>UK Sep-Feb</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCHR</td>
<td>1.44</td>
<td>0.16</td>
<td>0.54</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>(0.83-2.64)</td>
<td>(0.12-0.26)</td>
<td>(0.33-0.82)</td>
<td>(0.28-0.89)</td>
</tr>
<tr>
<td>sCIR</td>
<td>0.239</td>
<td>0.028</td>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>(0.134-0.458)</td>
<td>(0.022-0.035)</td>
<td>(0.03-0.08)</td>
<td>(0.05-0.16)</td>
</tr>
<tr>
<td>sCFR</td>
<td>0.048</td>
<td>0.007</td>
<td>0.015</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>(0.026-0.096)</td>
<td>(0.005-0.009)</td>
<td>(0.010-0.022)</td>
<td>(0.013-0.040)</td>
</tr>
</tbody>
</table>

*Table*: Posterior median (95% CI) estimates of the sCFR, sCIR, and sCHR for both approaches and the two waves of H1N1 in England.
estimations of an autumn-winter pandemic wave in the US compared to seasonal influenza:

- less or equal death toll
- possible more deaths in younger persons (18-64)

Approach 1:
- increase of ill individuals
  -> the burden on hospitals could be large

Approach 2:
- estimates of hospitalizations and ICU admissions are possible lower
estimations of an autumn-winter pandemic wave in the US compared to seasonal influenza:

- less or equal death toll
- possible more deaths in younger persons
- Approach 1: increase of ill individuals
  -> the burden on hospitals could be large
- Approach 2: estimates of hospitalizations and ICU admissions are possible lower

experienced and established frameworks are necessary:

- for robust estimates of severities
- to interpret data as quickly as possible
Thank you for your attention


Changes in severity of 2009 pandemic a/h1n1 influenza in england: a bayesian evidence synthesis.

*BMJ*, 343:d5408.


The Severity of Pandemic H1N1 Influenza in the United States, from April to July 2009: A Bayesian Analysis.


Estimates of the Prevalence of Pandemic (H1N1) 2009, United States, April-July 2009.