The Global Pandemic Mortality Burden project (GLaMOR)

GLaMOR Core Team:

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NIVEL Contract with WHO-Geneva 2011
GlaMOR Objective

To estimate the global mortality burden of the 2009 influenza pandemic
- Based on statistical attributions derived from multiple regression models applied to mortality data from 2009 and prior years
Background

- WHO’s global seasonal influenza mortality estimate: **250,000-500,000 deaths per annum**
- There were 18,209 lab-confirmed pandemic deaths reported to WHO (25 June 2011)
  - severely underestimated burden
- CDC is also working on a global 2009 estimate (using a probabilistic modeling approach)
- GLaMOR started July 2011 – report to WHO August 2012
- A WHO Pandemic Advisory Committee is supporting the work of the GLaMOR project
The GLaMOR Strategy

- Use multiple regression modeling to estimate pandemic mortality in ~20 collaborating countries
  - Weekly mortality and virology data
- Use extrapolation methods to project those single-country results to rest of the world
  - Based on GDP, pop structure, co-morbidities, access to care, more
- Strategy inspired by Murray et al (Lancet’ 06)
  - Estimated the global 1918 pandemic mortality from annual mortality data

Stage 1
- Raw mortality and virology time series
- Stage 1
- ~20 single-country pandemic mortality estimates
- Stage 2
- Global pandemic mortality estimates
Stage 1: Data requirements

- Weekly Time Series for 2005-2009 or longer
- Mortality Data
  - 6 age groups
    - <5, 5-14, 15-44, 45-64, 65-84, 85+
    - Primary analysis breakdown: <>65
  - Underlying Cause (ICD-10 codes)
    - All-cause, cardio-respiratory, respiratory, pneumonia & influenza
    - Mexico supplied “accidents” – a control outcome
- Virology Data
  - Ideally nationally representative, fully subtyped, and RSV
    - We used FluNET-WHO data
      - Influenza virology by type, sub-type (No RSV)
      - A few countries supplied more detailed virology data
- Population data
  - US census bureau international database
GlaMOR Collaborating Countries

19% of world population

Countries collaborating with GlaMOR Stage 1
GlaMOR Collaborating Countries: WHO Euro area

France, Germany, Spain, the Netherlands, Poland, Romania, Slovenia, United Kingdom, Israel, Denmark (all-cause only)

67% EU/EEA pop
38% WHO Region pop

Thank you for this great collaboration
Different types of mortality data

- **All-cause deaths**
  - More likely to be available
  - More sensitive (captures more deaths)
  - Less specific (more related to influenza)

- **Respiratory & Cardiovascular deaths**
  - all “I” and “J” codes
  - Intermediate sensitivity and specificity
  - commonly used to estimate influenza burden

- **Respiratory deaths**
  - all “J” codes
  - Less sensitive (captures fewer deaths)
  - More specific (more related to influenza)

- **Pneumonia and Influenza deaths**
Mild impact country: Mortality Data Time Series
Country X: All 4 causes, <65 years, log scale

Diagram showing mortality data trends over time for all causes, respiratory & cardio causes, respiratory causes, and flu & pneumonia causes. The data is presented on a log scale from 1998 to 2010.
High impact country: Mortality Data Time Series
Country Y: All 4 causes plus diabetes, <65 years, log scale
Mild impact country - Stage 1 Model Results
Age <65years and Outcome=Respiratory, country X
Model nicely captures mortality increase during pandemic wave

R² = 0.84
Pandemic term: p < .0001
High impact country - Stage 1 Model Results

Age=<65 and Outcome=Respiratory, country Y
Pandemic period elevation similar to seasonal 2003 peak levels

R²= 0.86
Pandemic term:
p < .0001
Mild Impact Pandemic Mortality for <65 years, by cause, numbers with 95%CI

<table>
<thead>
<tr>
<th>Age group: &lt;65 years</th>
<th>Number of pandemic deaths</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause</td>
<td>348</td>
<td>50</td>
<td>646</td>
</tr>
<tr>
<td>Resp &amp; Cardio</td>
<td>223</td>
<td>71</td>
<td>375</td>
</tr>
<tr>
<td>Respiratory</td>
<td>152</td>
<td>97</td>
<td>207</td>
</tr>
<tr>
<td>Pneu &amp; Influ</td>
<td>108</td>
<td>83</td>
<td>133</td>
</tr>
</tbody>
</table>
Mild Impact country 2 Pandemic Mortality for <65 years, by cause, numbers with 95%CI

<table>
<thead>
<tr>
<th>Age group: &lt;65 years</th>
<th>Point estimate</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause</td>
<td>-335</td>
<td>-638 -32</td>
</tr>
<tr>
<td>(Adj R²=.65; p=0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resp &amp; Cardio</td>
<td>206</td>
<td>148 264</td>
</tr>
<tr>
<td>(Adj R²=.76; p=0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>138</td>
<td>99 177</td>
</tr>
<tr>
<td>(Adj R²=.79; p&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Low sensitivity combined with low burden produces significant negative pandemic excess mortality in this country for All-Cause. A good argument for modeling a more specific outcome like the lower two, and with tighter 95% CIs.

In high impact country Y - all-cause term highly significant with high $R^2 (0.85)$.
Importance of having good virological data

Virology Data
- Ideally nationally representative, fully subtyped, and RSV
- We used
  - Influenza virology by type, sub-type (no RSV)

FluNET-WHO data has been a fantastic resource
- we have been able to concentrate our efforts on the mortality data and data analysis

For Europe, we noticed some data gaps in FluNet
- In those cases we asked countries to provide their national data
Stage 2: Four distinct strategies

1. Survey sampling (simple projection)
2. Matching (theory-based relations)
3. Multiple Imputation (statistical relations)
Example of Stage 2 Modeled Global Burden pattern

darker color = higher 2009 pandemic mortality rate
Summary: Stage 2

Choice of extrapolation method
- Drop survey method: too simplistic
- “Matching” and “imputation” produce different patterns even when using the same factors
- Initial runs indicate Murray et al. method gives very high estimates (as GDP based)

Final GLaMOR estimates will be based on Respiratory deaths as a confident minimum burden estimate
- Confidence on parameter estimates better
- All-cause and Cardio-Respiratory estimates higher than Respiratory in hardest hit countries, but for countries with low burden, respiratory [and Cardio-resp] is higher
New initiatives for the Glamor Euro network

**WHO Euro project: country specific 2009 pandemic mortality estimates**

- GLaMOR will only publish Regional estimates
- Publication of country-specific mortality estimates for the WHO Euro Region
- We would like to include some more countries (Russia?)
- We would like to produce more detailed estimates (e.g. more age groups)
- We would be able to produce more accurate estimates as the Stage II procedure will be based on WHO Euro countries (53 countries). This would exclude global outliers (e.g. Americas)
**New global initiatives**

- **Global mortality impact for 2010 pandemic**
  - Repeat analysis for 2010 and obtain more complete picture of global pandemic impact (2009 and 2010)

- **Global mortality impact of seasonal influenza**
  - Estimate mortality impact of seasonal influenza (based on data for previous ten seasons)
  - Validation of WHO’s global seasonal mortality estimate of 250,000-500,000 deaths per annum
Acknowledgments -- Country Collaborators

- **Australia**
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- **Argentina**
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- **Canada**
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- **Chile**
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- **Denmark**
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- **Germany**
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- **Hong Kong**
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- **Israel**
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- **Japan**
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- **New Zealand**
  Michael Baker

- **Romania**
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  - Mark Miller

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  - Anne Mazick

- **WHO Geneva**
  - Julia Fitzner

- **WHO Euro, Copenhagen**
  - Caroline Brown
  - Pernille Jorgensen

- **ECDC**
  - Angus Nicoll
Thank you for your attention
Extras
Lab-confirmed H1N1 pandemic deaths reported to WHO

<table>
<thead>
<tr>
<th>Region</th>
<th>Deaths*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Regional Office for Africa (AFRO) ***</td>
<td>168</td>
</tr>
<tr>
<td>WHO Regional Office for the Americas (AMRO)</td>
<td>At least 8450</td>
</tr>
<tr>
<td>WHO Regional Office for the Eastern Mediterranean (EMRO) **</td>
<td>1019</td>
</tr>
<tr>
<td>WHO Regional Office for Europe (EURO)</td>
<td>At least 4879</td>
</tr>
<tr>
<td>WHO Regional Office for South-East Asia (SEARO)</td>
<td>1852</td>
</tr>
<tr>
<td>WHO Regional Office for the Western Pacific (WPRO)</td>
<td>1841</td>
</tr>
<tr>
<td>Total*</td>
<td>At least 18209</td>
</tr>
</tbody>
</table>

*The reported number of fatal cases is an under representation of the actual numbers as many deaths are never tested or recognized as influenza related.

**No update since 7 March 2010

***No update since 23 May 2010

Pros and Cons of GLaMOR approach

### Pros
- Based on actual mortality data
- Comparable between countries (same model, outcomes)
- Comparable to historic pandemic burden estimates
- Comparable to seasonal burden estimates

### Cons
- Need up-to-date weekly mortality data
- Need up-to-date weekly virology data
  - Especially for tropics, sub-tropics, and for 2010-11 due to H1N1 co-circulation with A/H3 and B
  - RSV lab data (or proxy) needed to control for RSV mortality burden
- Must project an ~25 country convenience sample to 170 countries around the world.
**Model Form**

Multiple regression (additive model)

\[ \text{Outcome}_t = \beta_1 t + \beta_2 t^2 + \beta_3 t^3 + \beta_{4-5} \sin(2\pi t/w) + \beta_{6-7} \cos(2\pi t/w) + \beta_7 \text{FluA}_t + \beta_8 \text{FluB}_t + (\beta_{10} \text{RSV}_t) \]

FluA dummy variables,
For each season

This \( \beta_x \text{FluA}_t \) for 2009 yields the pandemic influenza attribution

Pandemic Excess Mortality=

\[ = \sum \beta_x \text{FluA}_t \]

for pandemic period, Apr1 to Dec31 2009

Deaths/100,000 pop
\( t = \) running week number

\( \sin, \cos \) terms for \( \frac{1}{2} \) and 1 year cycles

Virology data = numbers (not %)

Dropped RSV Term due to lack of Virology data

Dropped log link SAS Proc Reg

Sin, cos terms for 1/2 and 1 year cycles

Virology data = numbers (not %)
## Stage 1 Model Fit

and contribution of influenza terms in model (lift)

Lift Table, expanded age groups, all outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No age grouping</th>
<th>0 to 4 years</th>
<th>5 to 14 years</th>
<th>15 to 44 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Rsq</td>
<td>Model Rsq</td>
<td>Lift</td>
<td>F-prob</td>
</tr>
<tr>
<td>All causes</td>
<td>0.7704</td>
<td>0.8325</td>
<td>0.0622</td>
<td>0.9993</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.8229</td>
<td>0.8676</td>
<td>0.0446</td>
<td>0.9983</td>
</tr>
<tr>
<td>Flu &amp; Pneumonia</td>
<td>0.6630</td>
<td>0.8338</td>
<td>0.1708</td>
<td>1.0000</td>
</tr>
<tr>
<td>Resp. &amp; Cardio.</td>
<td>0.8030</td>
<td>0.8650</td>
<td>0.0620</td>
<td>0.9999</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.7444</td>
<td>0.8466</td>
<td>0.1022</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>45 to 64 years</th>
<th>65 to 84 years</th>
<th>85 years or more</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Rsq</td>
<td>Model Rsq</td>
<td>Lift</td>
</tr>
<tr>
<td>All causes</td>
<td>0.7232</td>
<td>0.7939</td>
<td>0.0707</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.7981</td>
<td>0.8400</td>
<td>0.0419</td>
</tr>
<tr>
<td>Flu &amp; Pneumonia</td>
<td>0.3870</td>
<td>0.7820</td>
<td>0.3951</td>
</tr>
<tr>
<td>Resp. &amp; Cardio.</td>
<td>0.7101</td>
<td>0.8166</td>
<td>0.1065</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.5426</td>
<td>0.7948</td>
<td>0.2512</td>
</tr>
</tbody>
</table>

Model also fits well for all age groups, except for diabetes outcomes, with a strong “lift” for respiratory outcomes in age groups 5-64
<table>
<thead>
<tr>
<th>Variable</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t Value</th>
<th>Pr &gt;</th>
<th>t</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cos12</td>
<td>1</td>
<td>0.43480</td>
<td>0.01206</td>
<td>36.06</td>
<td>&lt;.0001</td>
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<tr>
<td>sin6</td>
<td>1</td>
<td>0.00798</td>
<td>0.01056</td>
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<td>0.4502</td>
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<td>1</td>
<td>0.13993</td>
<td>0.01080</td>
<td>12.95</td>
<td>&lt;.0001</td>
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<tr>
<td>z_bl_s</td>
<td>1</td>
<td>-0.00472</td>
<td>0.00210</td>
<td>-2.25</td>
<td>0.0248</td>
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<tr>
<td>z_a_nonpan_y_1_3</td>
<td>1</td>
<td>-0.01253</td>
<td>0.01156</td>
<td>-1.08</td>
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<tr>
<td>z_a_nonpan_y_1_4</td>
<td>1</td>
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<td>0.01129</td>
<td>5.45</td>
<td>&lt;.0001</td>
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<tr>
<td>z_a_nonpan_y_1_5</td>
<td>1</td>
<td>-0.01088</td>
<td>0.00563</td>
<td>-1.93</td>
<td>0.0539</td>
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<td></td>
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<tr>
<td>z_a_nonpan_y_1_6</td>
<td>1</td>
<td>0.01508</td>
<td>0.00186</td>
<td>8.11</td>
<td>&lt;.0001</td>
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<tr>
<td>z_a_nonpan_y_1_7</td>
<td>1</td>
<td>0.00422</td>
<td>0.01902</td>
<td>0.22</td>
<td>0.8245</td>
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<tr>
<td>z_a_nonpan_y_1_8</td>
<td>1</td>
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<td>0.00226</td>
<td>-0.36</td>
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<td>z_hipan_y_1</td>
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<td>0.00001418</td>
<td>21.59</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example of model output

Agegrp: Under 65 years

Outcome: Respiratory

Model Adj R2=.85

Pandemic Flu Term significant (p<0.0001)