Modeling Mortality Shock
An overview of the Swiss Re pandemic influenza model

Stephen Kramer  - 10 June 2012
SCOR pandemic conference
Agenda

History of influenza pandemics – the modelling problem
Model principles & methodology
Some model details
Results & sensitivities
History of influenza pandemics

- 1918 unique event with high mortality
  - unusually, impacted young adults most heavily
  - high incidence of viral pneumonia / cytokine storm

- 1957 / 1968 pandemics – return to typical mortality intensity and pattern: most excess deaths confined to infants and elderly; use of antibiotics; better knowledge; behavioural changes etc

- 2009 pandemic – infection risk highly skewed to young; low infectivity; low lethality; still uncertainty about serological attack rate by age

<table>
<thead>
<tr>
<th>Pandemic Year</th>
<th>USA Excess Mortality / 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>5.30</td>
</tr>
<tr>
<td>1957</td>
<td>0.41</td>
</tr>
<tr>
<td>1968</td>
<td>0.17</td>
</tr>
</tbody>
</table>
Factors that complicate comparison of pandemics

<table>
<thead>
<tr>
<th>Date</th>
<th>Understanding of viruses</th>
<th>Social distancing (available, even if not used)</th>
<th>Antibiotics</th>
<th>Pandemic Vaccines</th>
<th>Antivirals</th>
<th>R₀ value (spread capability)</th>
<th>Lethality (death per infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>X</td>
<td>√</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>2.1</td>
<td>1.1%</td>
</tr>
<tr>
<td>1957</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√ but too late</td>
<td>X</td>
<td>1.6</td>
<td>0.275%</td>
</tr>
<tr>
<td>1968</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√ but too late</td>
<td>X</td>
<td>1.89</td>
<td>0.054%</td>
</tr>
<tr>
<td>2009</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>small effect</td>
<td>√</td>
<td>1.45??</td>
<td>unknown – very low</td>
</tr>
<tr>
<td>today</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√ often too late</td>
<td>√</td>
<td>??</td>
<td>??</td>
</tr>
</tbody>
</table>

- Inferring current risk based on past total mortality is inappropriate.
- Model must reliably imitate spread dynamics & changes that have occurred.
The modeling problem

- Pandemics are:
  - RARE
  - have been recorded over a time span covering large MEDICAL ADVANCES

Our modeling solution

- Generate some basic variables that describe the outcome of a pandemic
  - $R_0$, lethality, antivirals on/off, susceptibility profile

- Apply interventions on top of this appropriate to the time
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Some model details

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Model principles

- attempts to identify baseline variables and understand their importance and interaction (e.g. lethality, spread characteristics, age profile, proportion bacterial/viral, age-specific susceptibility)

- incorporates most of these factors into an SIR model (susceptible, infected, recovered individuals, with defined rates of flow between groups)

- ‘event based’ modelling which randomly selects certain key factors from a range of defined possibilities based on history and current conditions, e.g. basic reproduction number ($R_0$), lethality, antiviral success
Key factors considered in model

- demographically useful quinquennial age groups
- individually modelling 37 territories globally
- taking account of a wide range of factors present in the three pandemics of the last century
  - e.g. differences in mortality and susceptibility to infection by age
- many of the widely-recognised non-pharmaceutical and pharmaceutical interventions that may slow or mitigate the effects of a pandemic
- imitating the capacities of the public and institutions to respond to a pandemic, and to maintain these responses
**R₀ and lethality**

- **R₀** is a measure of the ability of a virus to spread.

- Lethality is the risk of death per infection with the virus, in the absence of medical intervention.

- Using modelling and analysis, we can establish the values of these parameters for past pandemics:
  - The values are used to generate distributions for these parameters.
  - The distributions in turn are used to generate random simulations.
  - The small sample of past pandemics means substantial uncertainty in deriving the distributions.
Fit to historic events

- frequency of pandemics: approximately 1/30 years on average
- 1918 – using $R_0 = 2.1$, and death-per-infection of 0.011 for USA
  - Fit numbers of deaths, lethals, date of peak, etc
- 1957/1968 – much less data, so tested lethality curves mainly, and used published data on $R_0$ values
- algorithm developed to produce age profile of lethality:
  - model automatically produces age profile depending on lethality level
- in generating event set use 2009 demographic equivalent:
  - $R_0 : 1918 = 2.1 ; 1957 = 1.6 ; 1968 = 1.89 ; (2009 = ??)$
  - Baseline lethality: 1889=0.00375; 1918=0.011; 1957=0.002753; 1968=0.00054
Randomise using historical events

Two main uncertainties in generating distributions of $R_0$ and lethality

- distribution type: tested log normal, gamma, extreme value (generalised Pareto), Weibull and normal distributions
  - sensitivity to distribution shape is low (5% max change)

- small sample of past events - parameters uncertain
  - sensitivity to parameter variability is high
Overview of methodology

**INPUTS**
Key factors accounted for by Swiss Re’s model

- Ability to cause death
- Simulated pandemic
- Ability to spread
- Inception variables and calibrations, eg
  - Age profile of deaths, rates of clinical infection, contagiousness

**OUTPUT**
Estimated excess mortality

- Simulations sorted to examine the excess mortality that would be expected from a pandemic of a specific severity probability

**Key result**

- Demographic characteristics, eg
  - Global population data
  - Daily contacts by age
  - Travel patterns

- Interventions, eg
  - Antibiotics, antivirals, vaccines
  - Contact modification, travel restrictions
Spread model – calculation process

- model begins with infected people in any one of the 37 territorial entities

- population cells: 5yr age groups, 37 countries, disease state (susceptible, infected by duration, recovered, dead, vaccinated)

- model is based on daily iterations: cells change incrementally on a daily basis (i.e. gradually changing new infections, deaths)

- specified within each population cell:
  - mixing between ages, mixing rates, mortality per infection, viral/bacterial disease progression, travel propensity, share of meds

- at each time, number of infections in each cell dependent on previous day’s:
  - susceptibles; no. contacts (of both uninfected and infected); number infected in groups with which contact occurs; transmission prob. (affected by stage, antivirals, vaccines)

- intervention affects one/some of the above, slowing infection and/or reducing mortality
### Calculating spread

(process day by day)

- using Susceptible/Infected/Recovered (SIR) cells the model calculates spread at discrete time intervals, each lasting 24 hours

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Model run begins with a number of people infected in any chosen country, and in any chosen age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>Number infected by Day 2 is a mathematical function based on underlying contagiousness of those already infected on Day 1 and the number of contacts they have with susceptible people</td>
</tr>
<tr>
<td>Day 3</td>
<td>As the days go by, more people become infected, fewer remain susceptible, and the proportion of contacts with people who have recovered becomes increasingly large</td>
</tr>
<tr>
<td>etc...</td>
<td>Eventually the pool of susceptible people is sufficiently depleted (and the pool of recovered people sufficiently large) that the number of new infections starts to decrease</td>
</tr>
<tr>
<td>etc...</td>
<td>Pandemic has peaked; number of new infections drops rapidly</td>
</tr>
<tr>
<td>etc...</td>
<td></td>
</tr>
</tbody>
</table>
Calculating spread

few infected, but driven by large pool of Susceptible’s (i.e. high reproduction)

increasing numbers Infected (and infectious) balances out reduced numbers Susceptible

reduced numbers Susceptible (and increased non-transmitting contacts with Recovered’s) eventually slows the rate of new infections, and the numbers currently Infected peak

reduced Susceptible’s result in reduced numbers Infected, causing a gradual decline in deaths and ultimately an end to the pandemic
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Inception variables and calibrations

Contagiousness

- Proportion of total
  - 70%
  - 60%
  - 50%
  - 40%
  - 30%
  - 20%
  - 10%
  - 0%

- Duration since infection (in days)
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8

Swiss Re
One key parameter, for example:

**Age profile of lethality**

- **Low lethality pandemics** (1957 and 1968) are assumed to be entirely due to bacterial pneumonia (U-shaped).

- **Mortality in high lethality pandemics** (1918) is a combination of the two causes (W-shaped).

- **Impact of each of the two causes changes proportionally as lethality increases.**

Chart sources: see Pandemic influenza: A 21st century model for mortality shocks.
Demographic characteristics

Number of contacts by age group and age profile of those contacts

- Young adults have more than 3x as many contacts with other people as the elderly.

- Ageing populations tend to have lower spread values, especially as mixing rates peak among young adults.

Chart source: see Pandemic influenza: A 21st Century model for mortality shocks
Other key parameters

- age profile of lethality
- contagiousness (by age & duration since infection)
- behavioural factors (by age & clinical status)
- susceptibility to infection (by age)
- population age structure (for each geographical entity)
- daily contacts (by age)
Non-pharmaceutical interventions

- Contact modification
  - the first, and most widely used, of the non-pharmaceutical intervention assumptions in the model
  - the model features varying intensities of contact modification, which are triggered in each country when deaths reach a certain level
  - applies, fades over time, but is re-applied after resurgence (with hysteresis)

- Travel restrictions
  - this intervention has virtually no impact on the total number of deaths produced by each simulation, although it can slow down the rate of spread
  - 99% reduction delays by about 2 weeks on average
Pharmaceutical interventions

- antibiotics
  - assumed to reduce bacterial pneumonia mortality by 70%, but no effect on transmission of the virus itself
  - assumed to be used by most of those needing them in most developed countries and around 13.5% in poorest developing countries

- antiviral treatment
  - antivirals are assumed not to work at all in 1 in 4 simulated pandemics
  - assumed to reduce infectiousness, as well as sickness and mortality; will therefore slow the spread of the simulated pandemic
  - antivirals need to reach people within 48 hours of becoming sick to be most effective
  - likely to be a challenge even for strong healthcare systems; assumed to be achieved in only 65% of sick people in highly developed countries

- vaccines
  - because a pandemic is generated by a novel virus, a new vaccine needs to be produced
  - currently largely ineffective in reducing mortality in pandemic’s first year given today’s production technology and capacity (but changing !!) – currently production after 154 days
understanding the risk is best achieved by creating a representative set of plausible events

- ‘event set’ modelling consists of a number of randomly generated simulations of the level of excess mortality (to be statistically significant, this can run to many thousands of events)
- necessary because the precise nature of a future pandemic is unknown

each event within the set is defined by variables based on distributions reflecting historical evidence

- e.g. the ability of a virus to spread, the likelihood that an infected person will die (i.e. its lethality), or the probability that antivirals will to some degree be effective in reducing the impact of a new virus

each simulation produces an estimate of mortality in the global population over the first year
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Simulated 1918 pandemic, then & now...

The graph shows the cumulative effect on mortality rates of selected changes between 1918 (the “Base”) and 2006.

1. 2006 population structure (spread rate and age profile of mortality)
2. ... plus underlying health changes relative to US (US assumed unchanged)
3. ... plus antibiotics
4. ... plus antiviral treatment
5. ... plus vaccines
Canada is among the countries appearing to be least impacted, with estimated 1-in-200-year excess mortality at around 0.7% in an insurance-age population.
Countries expected to experience higher levels of mortality include India, Pakistan and Indonesia, due to high population density, along with a weak capacity to reduce contact rates (India shown).

The healthcare systems of these countries are also weaker than in developed countries & almost no antivirals are available.
Modelling results: Sensitivity analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0$ and lethality fit of historical data: parameter error</td>
<td></td>
</tr>
<tr>
<td>Pre-pandemic partially effective vaccine</td>
<td></td>
</tr>
<tr>
<td>Contact modification</td>
<td></td>
</tr>
<tr>
<td>Proportion of deaths <code>bacterial pneumonia</code>/<code>viral pneumonia and cytokine storm</code> causes</td>
<td></td>
</tr>
<tr>
<td>Lower underlying mortality – health improvements in the United States</td>
<td></td>
</tr>
<tr>
<td>Probability of pandemic occurring</td>
<td></td>
</tr>
<tr>
<td>Population density effects</td>
<td></td>
</tr>
</tbody>
</table>

Weighted excess mortality (per 1 000)
Updates & Conclusions

- over time the model will need to be reviewed and updated
  - a review in early 2009 that considered high antiviral stocks and faster vaccine development
  - further updates may include:
    - 2009 as a data point for $R_0$ and lethality
    - wastage of antivirals
    - updates on vaccine production capacity
    - demographic changes, etc

Conclusions

- in most developed countries the 1/200 mortality shock is between 0.8 and 1.5 per mille
- in most developing countries this is between 1.5 and 3 per mille
- the outcomes are highly uncertain and this uncertainty must be kept in mind (but we need a best estimate!!)
Thank you

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