2009 Ian Constable Lecture

The 21st Century Pandemic

Anne Kelso
A viral disease eradicated

Following an intense vaccination campaign, the last known case of naturally acquired smallpox was contracted in Somalia in October 1977.

Frank Fenner announced the eradication of smallpox to the World Health Assembly on 8 May 1980.
The first influenza pandemic of the 21st century

Dr Margaret Chan and Dr Keiji Fukuda at the press conference to announce the start of the 2009 influenza pandemic, 11 June 2009
• How do influenza pandemics start?
• Why do they spread?
• Why can't we eradicate influenza?
• What have we learned in 2009?
• What can we expect now?
Influenza

• Highly contagious respiratory illness caused by influenza virus
• Spread by droplets from coughing and sneezing and by hands
• Fever, chills, headaches, muscle aches, weakness, cough
• Can cause serious illness and death from viral pneumonia and secondary bacterial infection
Seasonal influenza

Human-adapted influenza viruses circulate continuously in the world and cause epidemics each winter in temperate climates, infecting 5-10% of the population.

In Australia:

Australian Influenza Surveillance Report, Dept Health & Ageing (May 2009)
Human deaths from influenza in the 20th century

<table>
<thead>
<tr>
<th></th>
<th>Each year</th>
<th>250,000 – 500,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seasonal influenza</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1918 – 1919</td>
<td>~50 million</td>
</tr>
<tr>
<td>Pandemic influenza</td>
<td>1957 – 1958</td>
<td>~2 million</td>
</tr>
<tr>
<td></td>
<td>1968 – 1969</td>
<td>~1 million</td>
</tr>
</tbody>
</table>
Pandemic influenza

New influenza viruses, not previously adapted to humans, emerge at irregular intervals, causing global epidemics. People are not protected by their immunity to other influenza viruses.

Taubenberger & Morens, Rev Sci Tech (2009)
Pandemic influenza

New influenza viruses, not previously adapted to humans, emerge at irregular intervals, causing global epidemics. People are not protected by their immunity to other influenza viruses.
### Three types of influenza virus infect humans

<table>
<thead>
<tr>
<th>Type</th>
<th>Natural host</th>
<th>Variability</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Avian (others)</td>
<td>High</td>
<td>Most epidemics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All pandemics</td>
</tr>
<tr>
<td>B</td>
<td>Human only</td>
<td>Moderate</td>
<td>Some epidemics</td>
</tr>
<tr>
<td>C</td>
<td>Human (pig)</td>
<td>None</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Seasonal influenza vaccines currently contain two subtypes of influenza A and one influenza B virus.
Influenza A virus

- HA (haemagglutinin)
- NA (neuraminidase)
- M1 (membrane protein)
- M2 (ion channel)
- PB1
- PB2
- PA
- NP
- NS1 infected cell protein

8 RNA strands

Polymerase complex: NS2

Lipid bilayer

Adapted from De Jong et al, J Infect (2000)
All influenza A viruses come from birds

- Subtypes are named according to their HA and NA, eg H1N1.
- 16 HA and 9 NA subtypes have been identified in birds.
All influenza A viruses come from birds

- Subtypes are named according to their HA and NA, eg H1N1.
- 16 HA and 9 NA subtypes have been identified in birds.
Development of new influenza A viruses

Mutation

Reassortment

Drift
Random genetic changes, immune selected

Shift
Genome shuffling when two viruses infect one cell
The problem with influenza

• Because of mutation and reassortment, influenza viruses are highly variable.

• The driving force for emergence of mutated variants is human population immunity.

• Avian and other animal reservoirs provide a perpetual supply of influenza A viruses.

• Reassortment allows invention of new influenza viruses.
Origins of previous pandemic influenza A viruses

1918
avian/swine/human reassortment?

1957
avian/human reassortment

1968
avian/human reassortment

H1N1 PB1
re-emerged 1977

H2N2 PB1
extinct

H3N2 PB1
circulating
Origin of 2009 pandemic H1N1 virus

- Swine
- Avian
- Human

1998 North American swine H1N1

Eurasian swine H1N1

2009 human H1N1

HA
NA
Subtype replacement in pandemic influenza

Adapted from a slide of Dr Masato Tashiro, NIID, Japan
Subtype replacement in pandemic influenza

Components of trivalent seasonal vaccine

1900 1920 1940 1960 1980 2000

Adapted from a slide of Dr Masato Tashiro, NIID, Japan
Subtype replacement in pandemic influenza

Adapted from a slide of Dr Masato Tashiro, NIID, Japan
The 1918 - 1919 pandemic

http://1918.pandemicflu.gov/
Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918-1919

Reproduced from Taubenberger & Morens, EID 12:15 (2006)
Number of deaths per week during the 1919 influenza pandemic in NSW
Comparison of male death rates for the 1891 and 1919 influenza pandemics in NSW

Source: NSW Department of Public Health – Influenza Report 1920
Mortality in the 1918 pandemic

Children in a remote Alaskan village survived the 1918–19 pandemic while most of their parents and grandparents succumbed.

## Rates of infection and death in the three pandemics of the 20th century

<table>
<thead>
<tr>
<th>Pandemic</th>
<th>Symptomatic infection (%)</th>
<th>Deaths (number)</th>
<th>Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish Flu 1918</td>
<td>20-40</td>
<td>50 million</td>
<td>2.5</td>
</tr>
<tr>
<td>USA</td>
<td>~25</td>
<td>675,000</td>
<td>0.6</td>
</tr>
<tr>
<td>New Zealand</td>
<td>~40</td>
<td>&gt;8,600</td>
<td>0.7</td>
</tr>
<tr>
<td>Western Samoa</td>
<td>&gt;60</td>
<td>8,500</td>
<td>20</td>
</tr>
<tr>
<td>American Samoa</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td>&gt;12,000</td>
<td>0.24</td>
</tr>
<tr>
<td>NSW</td>
<td>37</td>
<td>6,000</td>
<td>0.3</td>
</tr>
<tr>
<td>Tasmania</td>
<td></td>
<td>225</td>
<td>0.1</td>
</tr>
<tr>
<td>Asian Flu 1957</td>
<td>10-60</td>
<td>2 million</td>
<td>0.07</td>
</tr>
<tr>
<td>Hong Kong Flu 1968</td>
<td>25-30</td>
<td>1 million</td>
<td>0.03</td>
</tr>
</tbody>
</table>
What worked in the 1918 pandemic?

- Strong leadership and coordination
- Maritime quarantine (Australia, Tasmania, American Samoa) (October – December 1918)
- Border quarantine (QLD, WA)
- International sharing of knowledge
- Social isolation (self-imposed, limits to public gathering)
- Bacterial vaccines?

Adapted from K. Horsley in Lessons from the Past for Today’s Pandemic Planners and Officers, 2007
Characteristics of the 1918 pandemic

- Extreme pathogenicity
- Unusual impact on young adults
- Multiple waves of infection, in and out of season

Multiple waves were also seen in the 1957 and 1968 pandemics.
The 2009 pandemic
Mexico, May 2009
The Australian
12 April: Mexico reports outbreaks of influenza-like illness to WHO

15-17 April: new swine H1N1 virus identified in two cases from California

23 April: new H1N1 virus confirmed in several patients in Mexico

25 April: WHO announces a public health emergency of international concern
24 February: first known case of pandemic H1N1 in Mexico
26 April: Melbourne WHO CC alerted to Auckland influenza cases

27 April: Melbourne WHO CC receives Auckland samples; H1N1 confirmed 28 April

Victorian Premier John Brumby (L) inspects a laboratory researching influenza for the World Health Organisation in Melbourne. Picture: AFP
**WHO’s pandemic influenza phases (2009)**

- **Phase 3**: sporadic cases of infection with non-seasonal influenza virus
- **Phase 4**: community-level outbreaks = significant increase in risk of pandemic
- **Phase 5**: human-to-human spread in at least 2 countries in one region
- **Phase 6**: community-level outbreaks in at least one other region = Pandemic
<table>
<thead>
<tr>
<th>JANUARY</th>
<th>FEBRUARY</th>
<th>MARCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 April: WHO raises the influenza pandemic alert from phase 3 to phase 4</td>
<td>29 April: WHO raises the influenza pandemic alert from phase 4 to phase 5</td>
<td>26 May: WHO recommends virus for H1N1 vaccines</td>
</tr>
<tr>
<td>3 June: pandemic virus reported in all 6 WHO regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 June: WHO raises the pandemic alert from phase 5 to phase 6</td>
<td></td>
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</tbody>
</table>
Characteristics of the 2009 pandemic virus

• H1N1 subtype is a reassortant of North American swine and Eurasian swine influenza viruses with additional mutations.

• Virus lacks several features of highly pathogenic 1918 pandemic and avian H5N1 viruses.

• Virus is sensitive to antiviral drugs Tamiflu and Relenza.

• Antibodies induced by seasonal H1N1 vaccination do not recognise the pandemic H1N1 virus.

• Some older people have antibodies that recognise the pandemic H1N1 virus.
People wait at a flu clinic set up at the Cairns Base Hospital to cope with testing. Picture: Chris Hyde

Stephen Till, at his Oxenford home, after his wife, Vicky, was taken to hospital with suspected swine flu. Picture: Luke Marsden

Olympic diver Matthew Mitcham, wearing a face mask around his neck, arrives at Sydney Airport after returning from Mexico. Picture: Jeremy Piper
Pandemic H1N1 influenza in Australia

• 9 May: First case reported in Brisbane, returned from US, already recovered

• 20 May: First case detected in Melbourne, returned from US

• 22 May: Case detected through Victorian GP sentinel surveillance, no travel or known contact

• 25 May: Outbreak on Pacific Dawn cruise ship, index case from Melbourne

• Cases exported from Melbourne to WA, China and elsewhere

5 of first 100 Victorian cases reported travel to US or Mexico; 54 of first WA cases reported links to Victoria (Heath Kelly, VIDRL).
Melbourne: swine flu capital of the world
Pandemic H1N1 influenza in Australia

Confirmed cases of pandemic (H1N1) 2009

Week 30 = 20 July

Week 38 = 14 Sep

Source: NetEPI database

Australian Influenza Surveillance Report (18 September 2009)
Pandemic H1N1 influenza in Australia

Hospitalisations

Deaths

Australian Influenza Surveillance Report (18 September 2009)
# Pandemic H1N1 in Australia, May - October 2009

<table>
<thead>
<tr>
<th></th>
<th>Confirmed cases</th>
<th>Hospitalised cases</th>
<th>ICU cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>36,670</td>
<td>4,806</td>
<td>732</td>
<td>183</td>
</tr>
<tr>
<td>Total in WA</td>
<td>844</td>
<td>79</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>21 yr</td>
<td>31 yr</td>
<td>46 yr</td>
<td>51 yr</td>
</tr>
<tr>
<td>Female</td>
<td>51%</td>
<td>50%</td>
<td>52%</td>
<td>44%</td>
</tr>
<tr>
<td>Indigenous</td>
<td>10%</td>
<td>20%</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Pregnant</td>
<td>-</td>
<td>11%</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- An average of 1,925 people with influenza were admitted to hospital each year between 2001 and 2007. The median age of deaths from seasonal flu is 83 yr.

- Pregnant women account for 32% of 20-39 yr-old women hospitalised for pandemic H1N1.

- Indigenous Australians are ~10 times more likely to be hospitalised for pandemic H1N1 than non-indigenous Australians.
Characteristics of pandemic H1N1 infection

- Preferentially infects the young
- Mild disease in most people, many probably asymptomatic
- Severe disease in some people, eg, those with diabetes, asthma, cancer, obesity, indigenous people, pregnant women (especially trimesters 2 and 3), young and healthy
- Acute respiratory distress and long stays in ICU for some people
- Low case fatality rate (case number denominator uncertain)
Objectives of public health intervention

- Delay and flatten epidemic peak
- Reduce peak burden on healthcare system
- Reduce total number of cases
- Buy time for vaccine production

Adapted from slide of Angus Nicoll, ECDC
What worked in the 1918 pandemic?

• Strong leadership and coordination

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• Bacterial vaccines?

Adapted from K. Horsley in Lessons from the Past for Today’s Pandemic Planners and Officers, 2007
What is different today?

- Higher population number and density
- Higher numbers and proportion of elderly people
- More immune-compromised people (HIV, immunosuppressive drugs)
- Rapid global travel
- Globalised economy
- High-density farming
- Faster global communication
- Antiviral drugs, antibiotics, better vaccines
- Better understanding of the influenza virus

Adapted from K. Horsley in Lessons from the Past for Today's Pandemic Planners and Officers, 2007
Global aviation network

What worked in 2009?

• Strong planning, leadership and coordination
• International sharing of knowledge, viruses and reagents
• Antiviral drugs for slowing spread and reducing disease
• Advanced clinical care
• Border control? Quarantine? School closures?
• Vaccines...
Models tell us that a pandemic looks like this:

8 Weeks

Adapted from a slide of Dr Hitoshi Oshitani, Japan
Pandemic H1N1 influenza in the USA

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

http://www.cdc.gov/flu/weekly/
Seasonal and pandemic H1N1 influenza in the southern hemisphere

New Zealand

South Africa

- Each country's experience is unique.
- Regardless of timing, seasonal viruses were largely displaced.

Dr Sue Huang, ESR, New Zealand; Dr Barry Schoub, NICD, South Africa
The real H1N1 pandemic

Adapted from a slide of Dr Hitoshi Oshitani, Japan
The real H1N1 pandemic

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The real H1N1 pandemic

Adapted from a slide of Dr Hitoshi Oshitani, Japan
The real H1N1 pandemic

Adapted from a slide of Dr Hitoshi Oshitani, Japan
So we're all agreed, the sky is falling, what's next?...
What's next?

• Will the pandemic virus mutate?

• Will it become more virulent?

• Will there be a second wave?

• Will it replace previous seasonal influenza A viruses?

• What are the implications for next year's flu vaccine?
What's next?

• Will the pandemic virus mutate? Yes

• Will it become more virulent?

• Will there be a second wave?

• Will it replace previous seasonal influenza A viruses?

• What are the implications for next year’s flu vaccine?
What’s next?

• Will the pandemic virus mutate? Yes

• Will it become more virulent? Unpredictable

• Will there be a second wave?

• Will it replace previous seasonal influenza A viruses?

• What are the implications for next year’s flu vaccine?
What’s next?

• Will the pandemic virus mutate? Yes

• Will it become more virulent? Unpredictable

• Will there be a second wave? Yes, in at least some countries

• Will it replace previous seasonal influenza A viruses?

• What are the implications for next year’s flu vaccine?
What's next?

• Will the pandemic virus mutate? Yes

• Will it become more virulent? Unpredictable

• Will there be a second wave? Yes, in at least some countries

• Will it replace previous seasonal influenza A viruses? Probably

• What are the implications for next year's flu vaccine?
Next year’s vaccine in Australia

On 2 October, the Australian Influenza Vaccine Committee adopted WHO’s recommendation for the composition of influenza vaccines for the southern hemisphere in 2010.

<table>
<thead>
<tr>
<th>Southern hemisphere 2009</th>
<th>Northern hemisphere 2009/2010</th>
<th>Southern hemisphere 2010</th>
</tr>
</thead>
</table>
In conclusion

• Even in the 21st century, influenza viruses are unpredictable.

• Each pandemic is unique.

• In a globalised world, effective responses depend on:
  
  - international cooperation and sharing of resources
  - enhanced surveillance of human and animal viruses
  - understanding the virus and its spread
  - vaccines: better, sooner, for everyone.
Acknowledgements

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WHO National Influenza Centres and Collaborating Centres

Australian Government Department of Health and Ageing

Many colleagues in VIDRL, UM and elsewhere

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Thank you