The Spectre of a Flu Pandemic – Is it Inevitable?
Dr. Lance Jennings, University of Otago, New Zealand
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Spectre of a Flu Pandemic: is it inevitable?
Lance Jennings
Clinical Virologist, Canterbury Health Laboratories
Senior Clinical Lecturer, CSM&HS, University of Otago

Outline
• The ecology of influenza
• Avian influenza
• Pandemic preparedness
  – Pharmaceutical interventions
  – Non-pharmaceutical interventions
  – Implementation

ABC of Human Influenza
• Acute respiratory viral infection
• Caused by members of the Orthomyxoviridae family

Type A
Type B
Type C
Annual Flu Epidemics
Novel Virus
No Resistance
Human to Human Transmission
Severe Disease
PANDEMIC

Human Influenza
Incubation period
Virus isolation
Fever curve

Time in days
0 1 2 3 4 5 6 7 8 9 10
Sore throat, Headache
Cough
Coryza
Malaise, prostration
Complications

Influenza Virus
Neuraminidase
Haemagglutinin
8 ss RNA segments
The Ecology of Influenza A Viruses

In wild aquatic birds, influenza viruses replicate predominately in the intestinal tract and are shed in the faeces. Transmission is faecal-oral, often through water.

• Influenza viruses in their natural reservoirs are in evolutionary stasis
• Rapid evolution occurs after transfer to new hosts

Factors Influencing the Interspecies Transmission of Influenza A Viruses

- Avian-human species barrier exists
- Factors multigenic

Ecology of Influenza A Viruses

Subtypes based on surface glycoproteins: Haemagglutinin (HA) Neuraminidase (NA)
- The natural reservoir for all HA and NA subtypes is water fowl
- Influenza A viruses infect multiple mammalian species

Factors Influencing the Interspecies Transmission of Influenza A Viruses

- Avian-human species barrier exists
- Factors multigenic

α2-3 Receptors α2-6 Receptors
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Timeline of Emergence of Influenza Viruses in Humans

<table>
<thead>
<tr>
<th>Year</th>
<th>Influenza Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>Spanish Influenza H1</td>
</tr>
<tr>
<td>1957</td>
<td>Asian Influenza H2</td>
</tr>
<tr>
<td>1968</td>
<td>Asian Influenza H3</td>
</tr>
<tr>
<td>1977</td>
<td>Hong Kong Influenza H1</td>
</tr>
<tr>
<td>1997</td>
<td>H1</td>
</tr>
<tr>
<td>2003</td>
<td>No Pandemic for &gt;36 years</td>
</tr>
<tr>
<td>2006</td>
<td>No Pandemic for &gt;36 years</td>
</tr>
</tbody>
</table>

Spanish ‘Flu Symptoms

- “they very rapidly develop the most vicious type of pneumonia that has ever been seen...
- and a few hours later you can begin to see the cyanosis extending from their ears and spreading all over their face, until it is hard to distinguish the coloured men from the white.
- It is only a matter of a few hours until death”
  Grist NR BMJ 1959

1918 ‘Spanish’ Influenza Pandemic - New Zealand

- New Zealand’s greatest public health event
- Two waves July 1918 - mild Oct-Dec 1918 - severe
- Arrived SS Niagara, Auckland, 12th October 1918 (Prime Minister Massey)
- Deaths
  - Auckland 2000 “City of the dead”
  - Canterbury 800
  - New Zealand 8,573 (DR 0.84% /1.4% Maori)
  - Worldwide 20 - 50 million (2-3% Worlds population)

Age Distribution of Deaths of Females in UK 1918-1919

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Population per 1000 deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>200</td>
</tr>
<tr>
<td>6-10</td>
<td>150</td>
</tr>
<tr>
<td>11-15</td>
<td>100</td>
</tr>
<tr>
<td>16-20</td>
<td>50</td>
</tr>
<tr>
<td>21-25</td>
<td>200</td>
</tr>
<tr>
<td>26-30</td>
<td>100</td>
</tr>
<tr>
<td>31-35</td>
<td>50</td>
</tr>
<tr>
<td>36-40</td>
<td>200</td>
</tr>
<tr>
<td>41-45</td>
<td>100</td>
</tr>
<tr>
<td>46-50</td>
<td>50</td>
</tr>
<tr>
<td>51-55</td>
<td>200</td>
</tr>
<tr>
<td>56-60</td>
<td>100</td>
</tr>
<tr>
<td>61-65</td>
<td>50</td>
</tr>
<tr>
<td>66-70</td>
<td>200</td>
</tr>
<tr>
<td>71-75</td>
<td>100</td>
</tr>
<tr>
<td>76-80</td>
<td>50</td>
</tr>
<tr>
<td>81-85</td>
<td>200</td>
</tr>
<tr>
<td>&gt;85</td>
<td>100</td>
</tr>
</tbody>
</table>

Victims of the Great Pandemic-Kansas 1918
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Timeline of Emergence of Influenza Viruses in Humans

N. Cox, 2005

Avian Influenza Viruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Tissue Tropism</th>
<th>Diseases in Chickens</th>
<th>Structure of HA</th>
<th>Responsible Proteases</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPAI</td>
<td>Respiratory &amp; Abdominal Tracts</td>
<td>Subclinical Infection</td>
<td>NA</td>
<td>Specific Secretory Protease</td>
</tr>
<tr>
<td></td>
<td>'Epithelial cells'</td>
<td></td>
<td></td>
<td>Tryptase Clara</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Localized Infection</td>
<td></td>
<td>FXa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fibrin</td>
</tr>
<tr>
<td>HPAI</td>
<td>All tissues and organs</td>
<td>Fowl Plague</td>
<td>HA R RR RR R R</td>
<td>Ubiquitin Protease present in Golgi Body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatal Systemic Infection</td>
<td></td>
<td>Furin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasmin</td>
</tr>
</tbody>
</table>

Avian Influenza A(H5N1) Outbreak Since 2003

WHO, 7 July, 2006
Qinghai Lake May 2004

“An unprecedented event in the history of influenza”

Avian Influenza Viruses

Low Pathogenicity
(H1, H3)

Highly Pathogenic
(H5, H7)

Localised
Respiratory, GI tract

Systemic
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Genesis of H5N1 influenza in Asia

- 1996 A/Goose/Guangdong/1/96 H5N1
- 1997 emergence of H5N1 “bird flu”
  - A reassortant virus
  - Goose x Quail x Duck
  - H5N1, H9N2, H6N1
  - 18 people infected, 6 deaths
- 1997 -2002
  - Goose x multiple mating partners
  - H5N1 x
  - Antigenically conserved
  - Multiple genotypes
  - Pathogenic in chickens

Emergence of a Dominant H5N1 Genotype


Genotypes of H5N1 influenza reassortants in Asia

Chen et al PNAS 2006;103:2845-50

Expanding Host Range of Influenza A (H5N1)

- Tigers and leopards in Thailand 2004
- Domestic cats in Thailand/Indonesia & Experimental transmission
- Infection of pigs in China, Viet Nam & Indonesia
- No Experimental transmission

Confirmed Human cases 2003-20 July 2006

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Viral factors influencing interspecies transmission
A polygenic trait

The H5 HA of Avian Viruses
The H5 HA of avian viruses, with glutamine 226, binds strongly to the avian-like (α2,3-linked sialic acid) receptor, and weakly to the human-like (α2,6-linked sialic acid) receptor

Avian Influenza A/H5N1: Transmission
- Bird to human
  - Implicated in ~80% of patients
  - Handling, plucking/preparing
  - Ingestion of undercooked poultry (duck blood)
- Environment to human
  - ? Exposure to contaminated water (swimming)
  - ? Aerosols of bird droppings
- Human to human
  - Inefficient; no sustained chains of transmission
  - Family clusters in Thailand, Vietnam, Turkey and Indonesia
  - Rare infections in cullers and exposed HCWs

Transmission
Direct exposure to infected birds
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H5N1 Cluster in Indonesia May 2006
Index case

Nature 2006:422 13 July

Pre-requisites for a Human Pandemic
1. Emergence of an antigenically novel strain to which the population has no immunity
2. Transmission to humans in whom the strain can cause severe disease
3. Efficient human to human spread

Pandemic Planning
“having a framework to respond to a pandemic threat, to lessen the impact on a country’s health system, society and its economy ..”

Components:
- Pharmaceutical Interventions: Antivirals, Vaccines, Antibiotics, etc
- Non-pharmaceutical Interventions
- Public health measures
## Influenza Pandemic Preparedness in New Zealand

National Health Emergency Plan: Infectious Diseases

First Published 1999
Revised 2002

Updated in line with WHO Revised Plan 2005;
Now Version 15

### NZ Influenza Pandemic Plan outline

**Plan for it (Current phase)**
- Engage with all relevant agencies

**Keep it out**
- Border management

**Stamp it out**
- Cluster control operations

**Manage it**
- Public health measures,
- Public gatherings, antivirals

**Recover from it**
- Return to normal service delivery

### Antiviral Agents for Influenza

<table>
<thead>
<tr>
<th>Class/Agent</th>
<th>Brand Name</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2 Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>Symmetrel</td>
<td>PO</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>Flumadine</td>
<td>PO</td>
</tr>
<tr>
<td>Neuraminidase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanamivir (GG167)</td>
<td>Relenza</td>
<td>Inhaled</td>
</tr>
<tr>
<td>Oseltamivir (GS4104)</td>
<td>Tamiflu</td>
<td>PO</td>
</tr>
<tr>
<td>Peramivir (RWJ270201)#</td>
<td>Tamiflu</td>
<td>PO</td>
</tr>
</tbody>
</table>

# Investigational

Simonson et al submitted for publication

### Prevalence of adamantane resistance in circulating A(H3N2) viruses

![Graph showing prevalence of adamantane resistance in circulating A(H3N2) viruses from 2002 to 2009 for US, NZ, China, and Japan.](image)

### Aggregation of Influenza Virus by Neuraminidase Inhibitors

![Image of influenza virus aggregation](image)
### Oseltamivir Therapy in H5N1, Thailand and Vietnam, 2004-5

<table>
<thead>
<tr>
<th>Oseltamivir treatment</th>
<th>No. patients</th>
<th>No. (%) survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>25</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>

Writing Committee. NEJM 353:1374, 2005

### Pandemic Influenza Vaccines:
will be different from seasonal vaccines
- Unlikely to be available for for first 6-9 months
- NZ contract with CSL Ltd,
  - 8 million doses pandemic vaccine
  - H5N1 vaccine ??

### Immunogenicity of Candidate H5N1 Vaccines in Healthy Adults

<table>
<thead>
<tr>
<th>Vaccine type (N)</th>
<th>Route</th>
<th>HA dose (µg)</th>
<th>% HI titer &gt; 1:40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-virion, egg-grown (N=451)</td>
<td>IM</td>
<td>7.5</td>
<td>10</td>
</tr>
<tr>
<td>(Treonor, 2006)</td>
<td></td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>(Nolan, 2006)</td>
<td></td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>(Nolan, 2006)</td>
<td></td>
<td>90</td>
<td>54</td>
</tr>
<tr>
<td>Sub-virion, egg-grown (N=400)</td>
<td>IM</td>
<td>7.5</td>
<td>14</td>
</tr>
<tr>
<td>Adjuvant; 2 doses</td>
<td></td>
<td>7.5 + alum</td>
<td>34</td>
</tr>
<tr>
<td>Adjuvant; 2 doses</td>
<td></td>
<td>15 + alum</td>
<td>41</td>
</tr>
</tbody>
</table>

### Immunogenicity of Candidate H5N1 Vaccines in Healthy Adults (18-60 years)

<table>
<thead>
<tr>
<th>Vaccine type (N)</th>
<th>Route</th>
<th>HA dose (µg)</th>
<th>% HI titer &gt; 1:40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-virion, egg-grown; Novel</td>
<td>IM</td>
<td>3.8</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Adjuvant; 2 doses</td>
<td></td>
<td>7.5</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>(N=400 18-60yrs)</td>
<td></td>
<td>15</td>
<td>&gt;70%</td>
</tr>
</tbody>
</table>

(GSK, Media Release 26th July 2006)

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www.webbertraining.com  Page 9
**Major Issue is current Global Influenza Vaccine Production Capacity**

- 65-70% Vaccine manufactured in Europe; ~50% exported

**Non-pharmaceutical Interventions (Public health measures)**

- Effectiveness of measures may depend on the characteristics of the outbreak
- Given the limited availability of vaccines and antivirals, non-pharmaceutical public health interventions are of prime consideration but, as yet, of unquantified value

**Worst Case 1918 Scenario:**

40% attack rate over 8 weeks

- 15% population affected
- 20% available staff

**1° & 2° Healthcare Sector Patient Management**

Separated Streamed Services:

- Green stream
- Red stream

**Principles “Patient focused”**

- Most people with Influenza will be OK with no health service input
- Many will need reassurance
- Some will need antivirals
- Some will need antibiotics
- Some may need fluids (IV or SC)
- Small % will need hospital/intensive Rx
- Others will need treatment related to underlying conditions
  - e.g. COPD, diabetes, asthma, heart failure
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Red Stream
Influenza care pathway

Hospital Care
Community Influenza Care
Community Support
CDHB Draft 2006

Self care at home

- Surveillance
- Message
  - Most people will be OK, if you are worried or if the following occur
  then call phone 0800 - support
  - Continue to self assess - web supported
- What to look out for
  - Trouble breathing
  - Fast breathing
  - Chest pain (other than with cough)
  - Confusion or drowsiness
  - Fever persists longer than 4 days –
  - Flu symptoms go away and then come back
- Outcomes
  - Continue self care at home
  - Call support line
  - Attend CBAC (exception)

Simple Advice for People at Home

- Stay home: If sick keep away from other people --
  avoid visitors and visiting others “Social Distancing”
- Wash and dry your hands: before handling food,
  after coughing, sneezing, using the bathroom, wiping or
  nose blowing (your’s or your child’s), and when looking
  after sick people.
- Keep coughs and sneezes covered: Tissues are
  best. Put the tissue in a rubbish bin.
- Give plenty to drink: to people who have a fever
  and/or diarrhoea.
- Emergency survival kit: Include paracetamol (for
  fever)

www.moh.govt.nz/pandemicinfluenza

- Surge capacity
  exists in the
  community
- Communication
  with the community
  is a priority

Understand how respiratory viruses are transmitted / concept of “social distancing”
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The end of the Spectra: H5N1 the “rule” breaker

- Direct transmission from birds to humans
- High lethality / diversity of pathogenicity for waterfowl
- Transmission of influenza virus genes from domestic poultry to migratory waterfowl
- Transmission of viruses mainly via the respiratory route
- Increased thermal stability
- Transmission to felids

*Is highly pathogenic H5N1 now endemic in waterfowl?*

Continued rapid evolution

How could the next human pandemic virus arise?

It happened with SARS CoV
It happened in 1918 with “Spanish Flu”

A “narrow window of opportunity” exists providing a unique opportunity to intervene.

We Must Prepare Now

South Pacific Teleclass Series 2006

August 27
*The Spectre of a Flu Pandemic – Is it Inevitable* … with Dr. Lance Jennings, University of Otago

September 20
*SARS in Singapore – What Can We Learn?* … with Dr. Chris Wynn, Christchurch Hospital

For registration information www.webbertraining.com/howtoc8.php