Topics

• **Interpandemic influenza**
  – Illness characteristics
  – Who is affected

• **Influenza virus**
  – Classification
  – Changes

• **How a pandemic virus originates**
Topics (Cont’d)

• **Influenza vaccine**
  – Time line for production
  – Vaccine efficacy and effectiveness

• **Antivirals for influenza**
  – Adamantanes
  – Neuraminidase inhibitors

• **Vaccines and antivirals for future pandemics**
Influenza A: Frequency of Signs and Symptoms in Adults

- Cough, fever, prostration
- Headache
- Sudden onset nasal discharge, pharyngeal injection
- Myalgia, conjunctival injection
- Sore throat
- Substernal pain
- Productive cough (sputum)

From Kilbourne ED. *Influenza*. 1987:159, with permission.
Signs and Symptoms in Young Children

- Fever, rhinitis
- Pharyngitis
- Vomiting, diarrhea
- Bronchiolar-pulmonary signs

From Kilbourne ED. *Influenza*. 1987:161, with permission.
Clinical Influenza Attack Rates (Kansas City, 1957) and Annual Mortality Rate Pneumonia and Influenza (U.S. 1957)
The Virus

- Influenza types A & B
- Spread by aerosol, contact
- Year on year antigenic ‘drift’
- Rare antigenic ‘shift’
Influenza type B does not occur as subtypes.
Antigenic Drift: A Modest Change in the Influenza Virus
Antigenic Shift = Pandemic Potential

- Profound variation in hemagglutinin or neuraminidase
  - reassortment of genomic material
- Influenza type A only
- New virus with novel antigenic profile
- Influenza virus transmitted from aquatic birds (center) directly (solid lines) to fowl and pigs, who transmit to humans

Diagram courtesy of Robert G. Webster, PhD.
Antigenic Shift
Genetic reassortment hypothesis (influenza A virus)

Avian influenza

Mixed infection in pig

Reassortant strain capable of infecting man but containing new gene for HA to which man has no immunity

Human influenza
Mortality Rates in Different Influenza Epidemics

The 1918 Pandemic in Asia and Africa Influenza-Associated Deaths

• Asia
  – India: 12.5 million deaths (higher than bubonic plague).
  – Japan: 257,000 deaths.
  – Rest of Asia: 3,000,000 deaths.

• Africa
  – Union of South Africa: 139,471 deaths out of 6,100,000 population.
  – Madagascar: 114,000 deaths out of 3,250,000 population.

Jordan, ED. Epidemic Influenza, AMA, Chicago, 1927.
Influenza A Pandemics

1918    H1N1
1957    H2N2
1968    H3N2
1977*    H1N1

*Affected mainly young people born after 1957.
Now H3N2 and H1N1 co-circulate with influenza B.
Inactivated Influenza Vaccines

- Contains 3 strains: type A(H3N2), type A(H1N1) & type B
- Updated annually based on strains submitted to WHO
- In recent years, close relationship between circulating strains & those in the vaccine
- The more strains that are submitted to WHO, the more likely that the proper strains will be chosen
- Now 2 formulations: Northern Hemisphere (selected in previous February) & Southern Hemisphere (selected in previous September)
- Selection of new strains based on evidence of potential for spread. Ideal situation is when antibodies to new strain protect against old strain.
The characteristics of the strains circulating the previous season provide the basis for selecting virus strains for the next year’s vaccine. Courtesy of the Centers for Disease Control and Prevention.
Development of Vaccines: History

- Early 1930s: first human influenza viruses isolated
- Prophylaxis of influenza
  - Inactivated vaccine developed in the 1940s
  - Developed to guarantee troop readiness in World War II
  - Method of production very similar to that used today

Protective Efficacy of Inactivated Influenza Vaccines 1943-1969

Percent Protection

Year, Type of Virus

A(H1N1) 1943  B 1945  A(H1N1) 1950  A(H1N1) 1951  A(H1N1) 1953  B 1955  A(H1N1) 1957  A(H2N2) 1957  A(H3N2) 1958  B 1958  A(H2N2) 1960  A(H3N2) 1968  A(H3N2) 1969
Epidemiologic Concepts

• Determined the use of vaccine as policy adopted by many countries
• Key element: recognition that influenza occurs every year, and that morbidity/mortality is expressed in different population groups
• Mortality highest elderly and those with risk conditions - traditional vaccine targets
• Morbidity highest in children and young adults - not usually vaccine targets
Live FluMist Vaccine

• Trivalent - similar to inactivated vaccines
• Licensed for 5-49 year olds without high risk conditions (individuals who should receive inactivated vaccine)
• Transmission issues not settled – at present should not be given to healthcare workers with close contact with immunosuppressed individuals.
• Ease of administration - theoretical superiority.
Efficacy of Cold-Adapted (US) Influenza Vaccine in Preventing Influenza and Complications in 15-71 Month Old Children, 1996-1997

*Adapted from Belshe et al., 1998.
Influenza Virus Structure

- Neuraminidase
- Hemagglutinin
- RNA
- M₂ protein (only on type A)
Role of M2 Inhibitors in Influenza Control

- Efficacious both in prophylaxis and therapy of type A influenza.
- Effect limited to type A viruses.
- Extended to all type A viruses, whatever their antigenic composition.
- No evidence in therapy of prevention of complication.
### Protective Efficacy of M2 Inhibitors Against Laboratory-Confirmed Clinical Influenza

<table>
<thead>
<tr>
<th>Site and Subtype</th>
<th>Efficacy</th>
<th>Significance</th>
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<tbody>
<tr>
<td><strong>Michigan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A(H1N1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>71%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Vermont</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types A(H3N2) &amp; A(H1N1)</td>
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<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>91%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>85%</td>
<td></td>
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</tbody>
</table>
### Withdrawal Rates in Two Prophylactic Studies

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Group</th>
<th>No. of Withdrawals</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan</td>
<td>Amantadine</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>N=144</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>N=142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vermont</td>
<td>Amantadine</td>
<td>32</td>
<td>22</td>
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<tr>
<td></td>
<td>N=145</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rimantadine</td>
<td>14</td>
<td>10</td>
</tr>
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<td></td>
<td>N=147</td>
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<td>Placebo</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>N=148</td>
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</tr>
</tbody>
</table>
Limitations of Amantadine and Rimantadine

- Ineffective in prophylaxis/therapy of type B
- No information on value in severe infections
- No information in prevention of complications
- May result in transmissible antiviral resistance
- Amantadine produces significant adverse events—related in part to renal excretion
Neuraminidase and Viral Dissemination

- Permits release of progeny virus from infected host cells
- Prevents aggregation of newly formed viral particles
- Allows penetration of mucus and respiratory tract
Neuraminidase Inhibitors (NIs)

- Active *in vitro* and in animal models against both influenza A and B viruses
- Active against neuraminidases of all influenza A viruses tested (N1-N9)
- Zanamivir (GG167) *Relenza*  
  - topically applied sialic acid analog
- Oseltamivir (GS4104, Ro 04-0796) *Tamiflu*  
  - oral prodrug of GS4071, transition state analog
Percentage of Patients with a Positive Influenza Test Result by Baseline Cough and Temperature Score

**Reduction in Events Following Oseltamivir Treatment of Children 1-12 Years of Age**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Reductions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness Duration until Alleviation</td>
<td>1.5 days</td>
</tr>
<tr>
<td>Duration of Fever</td>
<td>1.1 days</td>
</tr>
<tr>
<td>Physician Diagnosed Complications Requiring Antibiotics</td>
<td>40%</td>
</tr>
<tr>
<td>Physician Diagnosed Otitis Media</td>
<td>44%</td>
</tr>
<tr>
<td>Tympanometric Confirmed Otitis Media</td>
<td>50%</td>
</tr>
</tbody>
</table>
Efficacy of Seasonal Prophylaxis of Influenza with Zanamivir (4 weeks) and Oseltamivir (6 weeks)

<table>
<thead>
<tr>
<th>Prevention of Symptomatic Laboratory Confirmed Influenza</th>
<th>Zanamivir</th>
<th>67%</th>
<th>Oseltamivir</th>
<th>74%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of Influenza with Fever</td>
<td>Zanamivir</td>
<td>84%</td>
<td>Oseltamivir</td>
<td>82%</td>
</tr>
</tbody>
</table>

Use of Antivirals in Pandemics

- **Treatment**
  - Should assume at least 5-day course – twice daily. May need to be longer based on recent animal studies.
  - May reduce shedding, but this cannot be relied on to reduce transmission (quantitative data, family studies).

- **Prophylaxis**
  - Dose of adamantane (if useful) could probably be reduced to 100 mg.
  - Dose of oseltamivir 75 mg once daily.
  - 10 days of prophylaxis of contact of a single case adequate. Longer duration in health care workers and if there are multiple generations.
Goals

- Global stockpile to be used for early intervention, and would be used primarily as transmission from human to human begins.
- Stockpiling for the pandemic itself a national consideration – WHO provides guidelines for consideration.
Problems in Producing a Specific A (H5N1) Vaccine

• There are always delays of 6-8 months in producing a vaccine containing a new antigen.
• The A (H5N1) virus must be handled in containment and kills chick embryos without.
• Preparation of seed virus requires reverse genetics - regulating and intellectual property concerns.
• Dosing and need for adjuvants undetermined.
Eight-Plasmid Pol I-Pol II System for Generation of Influenza A Virus

Summary

• Pandemic viruses are always Type A. Derive from avian viruses by mutation or reassortment.
• Avian virus can transmit directly to humans. Pigs or other “mixing” vessels not necessary.
• Vaccines for avian influenza viruses take extra steps to prepare – lag time unpredictable.
• Antivirals, particularly oseltamivir, are effective against current A (H5N1) strain. Logistic and other issues remain.