Influenza Vaccine – what are the challenges?

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Asia-Pacific Alliance for the Control of Influenza (APACI)

Outline of presentation

• Virus characteristics and evolution
• Epidemiology and transmission of influenza
• Genomic changes – antigenic shift and drift
• Seasonality of influenza epidemics
• Clinical spectrum of influenza (H3N2 in 2016-2017)
• Zoonotic infections with avian A(H7N9) in China
• Current influenza vaccines
Seasonal Influenza: Ongoing Public Health Threat

- Current influenza vaccines are moderately effective (approx. 60% effective in seasons with a good antigenic match)
- Impacts millions of people globally
  - 10-20% population; 250,000-500,000 deaths
- $80 B / yr. loss attributed to influenza disease in the USA
- Unpredictable changes in HA and NA lead to epidemics and global pandemics
  - Due to antigenic shift and antigenic drift
- Two types of influenza that affect humans: Type A and Type B
  - Type A: H1N1 and H3N2
  - Type B: Victoria and Yamagata lineages
- Emerging strains present pandemic risk to humans
  - e.g. H5N1, H7N9, H9N2, H6N1 & H10N8

Influenza virus

<table>
<thead>
<tr>
<th>Human</th>
<th>Pig</th>
<th>Horse</th>
<th>Bird</th>
<th>Bats</th>
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<tr>
<td>H types</td>
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<td>H1</td>
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<td>H11-H18</td>
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<td>M2e</td>
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<td>M protein</td>
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<td>Haemagglutinin (A,B &amp; C subtypes)</td>
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<td>RNA (8 segments)</td>
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<td>Nucleoprotein</td>
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<td>M2e</td>
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<tr>
<td>Neuraminidase (N)</td>
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<tr>
<td>Envelope</td>
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<td>M protein</td>
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| N types |
| N1    | ✓   | ✓     | ✓    |
| N2    | ✓   | ✓     | ✓    |
| N3    | ✓   | ✓     | ✓    |
| N4    | ✓   | ✓     | ✓    |
| N5    | ✓   | ✓     | ✓    |
| N6    | ✓   | ✓     | ✓    |
| N7    | ✓   | ✓     | ✓    |
| N8    | ✓   | ✓     | ✓    |
| N9    | ✓   | ✓     | ✓    |
| N10-N11 | ✓    |
Evolution of Influenza A Virus Pandemic Strains

1889 H2N2    1900 H3N8    1918 H1N1 Spanish    1957 H2N2 Asian    1968 H3N2 Hong Kong    1977 H1N1 Russian    2009 A(H1N1)pdm09 & A(H1N1)pdm09

Currently circulating H5N2 & H3N2

Adapted and modified from: BR Murphy & RG Webster “Orthomyxoviruses” in Fields Virology, 3rd Edition Lippincott-Raven Publishers

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Transmission of avian influenza to pigs

Viral genes reassortment

Transmission of human influenza to pigs

New flu virus

Spread by aerosol

- cross infection of human & avian influenza in pigs
- leading to reassortment of genes and new strains (antigenic shift)

Evolution of Novel Influenza A Virus Strains (antigenic shift)

Infection of both viruses into the same cell

Genomic exchange

Progeny reassortants

256 different combinations

Avian

H5N1

H3N2

Human

Cell cytoplasm

Reassortment of Influenza Virus Genes (antigenic shift)
Influenza A Virus Evolution (antigenic drifts)

- **Antigenic Drift**
  - minor change, same subtype
  - caused by point mutations in gene
  - may result in epidemic

- **Example of antigenic drift**
  - in 2002-2003, A/Panama/2007/99 (H3N2) virus was dominant
  - A/Fujian/411/2002 (H3N2) appeared in late 2003 and caused widespread illness in 2003-2004

Replication of the RNA genome of influenza viruses is associated with a relatively high mutation rate ($2.3 \times 10^{-3}$) because the viral RNA-dependent RNA polymerase lacks 3'→5'-exonuclease activity and therefore has no proof-reading function.

Antigenic drift is shown in terms of change of location in the first antigenic dimension through time.

**Antigenic drift of A/H3N2, A/H1N1, B/Vic and B/Yam viruses**

Antigenic drift is shown in terms of change of location in the first antigenic dimension through time.

Trevor Bedford et al. eLife Sciences 2014;3:e01914
Consequences of Mutations in Influenza Virus Genes

- Changes in receptor binding characteristics
  - changes viral tropism - avian (α2-3 linkage SA) to human (α2-6 linkage SA)
  - increase risk of non-human subtypes to infect human
  - enhance human-human transmission

- Alteration in pathogenesis
  - aerosol transmission to airborne transmission (H5N1 lab mutation)
  - changes in targeted organs (disease clinical presentations)

- Antigenic changes in neutralizing epitopes on HA protein
  - escape-mutations leading to vaccine failure
  - reduction of vaccine efficacy and effectiveness

- Antiviral resistance
  - treatment failure in using antiviral drugs

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Seasonality of influenza by geographic zone (n = 77 locations)

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Influenza – what are the challenges?
Age-specific mortality rate of influenza & pneumonia, USA 2013

Source: CDC, Wonder On-line Database, 2013 data.

Age-specific incidence rate of influenza-associated acute lower respiratory infection hospitalizations in Thailand 2009 - 2010

Influenza-associated hospital admission & deaths in Hong Kong 2013-2017

Number of severe complicated influenza cases reported by week of onset, Taiwan 2015 - 2017
Number of respiratory specimens positive for influenza reported by public health laboratories, by influenza virus type, subtype/lineage, and surveillance week — United States, October 2, 2016–May 20, 2017

Number of respiratory specimens positive for influenza reported by the Swiss Federal Office of Public Health laboratories, by influenza virus type, subtype/lineage, and surveillance week — Switzerland, October, 2016 – April, 2017
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The 5th H7N9 Epidemic season: 732 cases/ 274 fatal (as of 2017-Jun-15)

Human cases reach 1,507 and 595 fatal (CFR 39%) in 26 provinces, since 2013

<table>
<thead>
<tr>
<th>No. of provinces</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>134</td>
<td>304</td>
<td>219</td>
<td>118</td>
<td>732</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>44</td>
<td>127</td>
<td>100</td>
<td>48</td>
<td>272</td>
</tr>
<tr>
<td>Case-fatality rate</td>
<td>33</td>
<td>42</td>
<td>46</td>
<td>41</td>
<td>37</td>
</tr>
</tbody>
</table>
Summary on H7N9 infections in China

- The wave in 2017 occurred earlier, higher and longer
- Wider geographic distribution
- Increase in rural cases, due to mobile poultry vendors in some provinces
- HPAI H7N9 cases occurred
- No significant in age, sex and clinical severity, and no sustained H to H transmission

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Unique characteristics of influenza vaccines

- Influenza vaccine is unique among other vaccines:
  - Include all ages and recommendations for specific groups
  - Seasonal applications (Northern vs. Southern formulations)
  - Repeated annual vaccination (changing of circulating viruses)

- Prediction of variant viruses for vaccine production:
  - Requires an extensive global surveillance system
  - Tight manufacturing schedule (2 formulations)
  - Unable to match new viruses within the manufacturing cycle

- Vaccine performance
  - Main vaccine target – severe illness
  - Approved primarily on immune correlate – ≥1:40 HI; ≥70% subjects responding to that level and ≥40% seroconversion rate, which correspond to 50% efficacy in healthy adults
  - Effectiveness varies from year to year and for different groups
  - Vaccine viruses may not correspond to circulation viruses

- Manufacturing capacity unable to match timing and volume required for PANDEMIC control