Monitoring Changes in the Influenza Virus at the National Level

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2013 DSHS Influenza Surveillance Workshop
July 16, 2013
OBJECTIVES

- Discuss the World Health Organization’s Global Influenza Surveillance and Response System and the vaccine strain selection process
- Describe the virologic surveillance of influenza
- Describe the methods for monitoring the evolution of influenza viruses by genetic and antigenic characterization
Influenza Surveillance

- **Global:**
  - Global Influenza Surveillance and Response System (GISRS)

- **US**
  - CDC, FluView
WHO Influenza Network

- Six WHO Collaborating Centers (WHO CCs) on Influenza
- Four WHO Essential Regulatory Laboratories
- 141 Institutions that are National Influenza Centers (NICs)
  - Designated by national Ministries of Health and recognized by WHO
  - Collect virus specimens in their country and perform preliminary analysis
  - Ship representative clinical specimens and isolated viruses to WHO CCs for advanced antigenic and genetic analysis
- Ad hoc groups designed to address emerging issues
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Influenza Surveillance and Response System (GISRS), WHO
Map Production: WHO GISRS Team
World Health Organization

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Global Influenza Surveillance and Response System (GISRS)

- Monitors the evolution of influenza viruses and provides recommendations in areas including laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment

- Serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential
Influenza Laboratory Surveillance Information
(by GISRS)
Northern Hemisphere

Southern Hemisphere

Data Source: FluNet (www.who-int/flunet)
U.S. Influenza Surveillance Systems

- Outpatient Illness Surveillance
- Mortality Surveillance
- Hospitalization Surveillance
- Summary of the Geographic Spread of Influenza
- Virologic Surveillance
U.S. Virologic Surveillance

- Approximately 60 NREVSS and 85 WHO collaborating laboratories report:
  - Weekly total of positive influenza tests by type/subtype
  - Percent positive for influenza
- A subset of viruses collected are sent to CDC for further characterization
- Published weekly in FluView
Number of specimens received by CDC

as of 06/25/2013
Influenza Virus

- Negative strand virus
- Three types (A, B, and C)
- Segmented genome
- Influenza A viruses have different subtypes of each:
  - Hemagglutinin (H 1-17)
  - Neuraminidase (N 1-10)
- All known subtypes of Influenza A can infect birds, with the exception of H17N10 which has only been found in bats
Circulation of Influenza Viruses in Humans

Influenza A Viruses
- H1N1
- H1N1pdm09
- H2N2
- H3N2
- H5
- H6
- H7
- H9

Influenza B Viruses
- B Victoria
- B Yamagata
Influenza viruses are capable of reassortment

The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from “reassortment,” a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Experts think multiple reassortment events led to the creation of the H7N9 virus. These events may have occurred in habitats shared by wild and domestic birds and/or in live bird/poultry markets, where different species of birds are bought and sold for food. As the above diagram shows, the H7N9 virus likely obtained its HA (hemagglutinin) gene from domestic ducks, its NA (neuraminidase) gene from wild birds, and its six remaining genes from multiple related H9N2 influenza viruses in domestic poultry.
Specimen pathway: clinical respiratory specimens, and/or tissue culture/egg isolates

- **Diagnosis**
  - PCR
    - Diagnostic PCR Report
    - If PCR +

- **Surveillance**
  - Virus Isolation
    - Culture -
    - Culture +
      - Antigenic Characterization
      - WHO/FDA/VSMs
      - Anti-viral resistance
      - Genetic Characterization
        - Sequences submitted to GISAID/Gen Bank

- **Special Study**
Virus propagation at CDC

- Madin Darby Canine Kidney (MDCK) culture
  - High volume (T75 flask for ~20 ml available for harvest)
    - Permanent storage
    - Antigenic analysis
    - Antiviral analysis
    - Genetic analysis

- Embryonated egg culture
  - Currently licensed influenza vaccine requires egg isolate
  - Original clinical material used as inoculum
  - Egg isolates may be provided to vaccine manufacturers
  - Recovery rate of influenza viruses in egg culture ranges from ~10-50% depending on subtype
Antigenic Analysis by Hemagglutination Inhibition (HI)

- The HI assay is performed on influenza MDCK and egg virus isolates
- The hemagglutinin protein agglutinates red blood cells (RBCs) and is the basis for the HI assay
- The HI assay measures the inhibition of hemagglutination caused by influenza antisera at a standardized concentration of virus and RBCs
- The HI endpoint titer is the reciprocal of the dilution of antisera in the last well with complete inhibition of hemagglutination
# HI reactions of vaccine strain influenza A H3N2 viruses (1968-2009)

<table>
<thead>
<tr>
<th>STRAIN DESIGNATION</th>
<th>Vaccine Strain (years)</th>
<th>HK/08</th>
<th>EN/42</th>
<th>TX/1</th>
<th>BA/01</th>
<th>PH/02</th>
<th>SH/11</th>
<th>BE/35</th>
<th>BE/32</th>
<th>JO/33</th>
<th>NA/933</th>
<th>SY/0</th>
<th>FU/41</th>
<th>BRI/10</th>
<th>PER/1</th>
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<td>1968-1973</td>
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<td>A/BEIJING/32/1992</td>
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<td>A/JOHANNESBURG/33/1994</td>
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<td>A/NANCHANG/933/1995</td>
<td>1996-1998</td>
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<td>20</td>
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<td>1280</td>
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<td>A/FUJIAN/411/2002</td>
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<td>1280</td>
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<tr>
<td>A/BRISBANE/10/2007</td>
<td>2008-2010</td>
<td>5</td>
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<td>5</td>
<td>5</td>
<td>10</td>
<td>320</td>
<td>5</td>
</tr>
</tbody>
</table>

A virus is considered as low to the reference virus if there is an 8-fold or greater reduction in the HI titer when compared to the homologous HI titer (in red) of the reference strain.

U.S. Influenza Isolates Antigenically Characterized (Sept 2012-May 2013)

<table>
<thead>
<tr>
<th>Type/Subtype</th>
<th>Total #</th>
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</thead>
<tbody>
<tr>
<td><strong>H3N2</strong></td>
<td></td>
</tr>
<tr>
<td>A/Victoria/361/2011</td>
<td>1281</td>
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<tr>
<td>A/Victoria/361/2011 (4 fold)</td>
<td>124</td>
</tr>
<tr>
<td>A/Victoria/361/2001 (8 fold) low</td>
<td>5</td>
</tr>
<tr>
<td><strong>H1N1pdm09</strong></td>
<td></td>
</tr>
<tr>
<td>A/California/07/2009</td>
<td>260</td>
</tr>
<tr>
<td>A/California/07/2009 (4 fold)</td>
<td>17</td>
</tr>
<tr>
<td>A/California/07/2009 (8 fold) low</td>
<td>3</td>
</tr>
<tr>
<td><strong>B/Yamagata lineage</strong></td>
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</tr>
<tr>
<td>B/Wisconsin/01/2010</td>
<td>667</td>
</tr>
<tr>
<td>B/Wisconsin/01/2010 (4 fold)</td>
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<tr>
<td>B/Wisconsin/01/2010 (8 fold) low</td>
<td>0</td>
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<tr>
<td><strong>B/Victoria lineage</strong></td>
<td></td>
</tr>
<tr>
<td>B/Brisbane/60/2008</td>
<td>141</td>
</tr>
<tr>
<td>B/Brisbane/60/2008 (4 fold)</td>
<td>197</td>
</tr>
<tr>
<td>B/Brisbane/60/2008 (8 fold) low</td>
<td>33</td>
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</tbody>
</table>
U.S. Viruses Antigenically Characterized by CDC

![Bar chart showing the number of viruses characterized by the CDC from 2009-10 to 2012-13. The chart compares different types of viruses: B Vic, B Yam, H1pdm09, and H3.](image-url)
Genetic Analysis

- Subset (~10%) of cell culture isolates grown at CDC are sequenced. Isolates are chosen for sequencing primarily based on HI results, geographic location, and date of collection.

- Genes sequenced:
  
  **Influenza A**
  - HA
  - NA
  - M

  **Influenza B**
  - HA
  - NA
  - NS
## Anti-Viral Analysis

Neuraminidase Inhibitor Resistance Testing Results on Samples Collected Since Oct. 1, 2012

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Virus Samples tested (n)</td>
<td>Resistant Viruses, Number (%)</td>
</tr>
<tr>
<td>Influenza A (H3N2)</td>
<td>2,123*</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Influenza B</td>
<td>961</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2009 H1N1</td>
<td>542*</td>
<td>2 (0.4)</td>
</tr>
</tbody>
</table>

*Includes specimens tested in national surveillance and additional specimens tested at public health laboratories in 11 states (AZ, DE, HI, ME, MD, MI, MN, NY, PA, WA, and WI) who share testing results with CDC.

Source: FluView, 2012-2013 Influenza Season Week 20 ending May 18, 2013
Continual evolution of influenza viruses may lead to antigenic drift of viruses. When this occurs an update in influenza vaccine viruses is necessary to maintain effectiveness.

<table>
<thead>
<tr>
<th>Season</th>
<th>H3N2</th>
<th>H1N1</th>
<th>B</th>
<th>B lineage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-12</td>
<td>A/Perth/06/2009</td>
<td>A/California/07/2009 H1N1pdm09</td>
<td>B/Brisbane/60/2008</td>
<td>Victoria</td>
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<tr>
<td>2010-11</td>
<td>A/Perth/06/2009</td>
<td>A/California/07/2009 H1N1pdm09</td>
<td>B/Brisbane/60/2008</td>
<td>Victoria</td>
</tr>
<tr>
<td>2009-10</td>
<td>A/Brisbane/10/2007</td>
<td>A/Brisbane/59/2007 H1N1</td>
<td>B/Brisbane/60/2008</td>
<td>Victoria</td>
</tr>
</tbody>
</table>
WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines

• Biannual meeting held in:
  ▪ February for northern hemisphere season
  ▪ September for southern hemisphere season

• Participants include representatives from:
  ▪ WHO CC’s for influenza and WHO H5 Reference Laboratories
  ▪ WHO Essential Regulatory Laboratories
  ▪ National Influenza Centers
  ▪ Experts on antigenic cartography; and representatives from the OIE/FAO Network of expertise on animal influenza (OFFLU)

• Recommendations are based on global influenza virus surveillance data related to epidemiology and antigenic characteristics, serology responses to seasonal vaccines, and availability of candidate strains and reagents.
February 23, 2012: vaccine recommendations announced for 2012-13 season
2013-2014 Northern Hemisphere Vaccine Recommendations

- **Trivalent**
  - A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011*
    - A/Texas/50/2012 H3N2
  - A/California/07/2009 H1N1pdm09
  - B/Massachusetts/02/2012* (Yamagata lineage)

- **Quadrivalent** will be comprised of the three components above and:
  - B/Brisbane/60/2008 (Victoria lineage)

*Updated component from 2012-2013 vaccine*
A/Texas/50/2012 H3N2

- NP wash collected from patient in Fort Worth, April 2012
- Sent to TX DSHS lab in Austin, cell culture isolate grown from NP wash
- Both isolate and NP wash were sent to CA contract lab
- CA contract lab grew high volume MDCK isolate. Both isolate and remaining original specimens were sent from to CDC and antigenically and genetically characterized

- Original clinical specimen (NP wash) inoculated into eggs
- Resulting egg isolate sent to vaccine manufacturers for analysis as a potential vaccine seed

- Recommended as new vaccine component at the February 2013 WHO Vaccine Strain Selection Meeting
Thank You!

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.