Influenza and other Respiratory Viruses Update--2015

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and

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Learning Objectives

- Review of the 2013-2014 influenza season.
- Avian influenza
- Emerging diseases impacting community health.
- Review of new point-of-care nucleic acid amplification assays.
- Discuss surveillance strategy for 2015-2016
Influenza

The latest information

www.cdc.gov/flu/index.htm
What We’re Dealing with Now

- Ebola virus
- EV-D68
- MERS CoV
- Dengue fever
- Chikungunya
- Anthrax
- Measles/mumps

... So what’s the big deal with influenza?
The Changeability of Influenza

**Antigenic Drift → Seasonal Influenza**

Antigenic Drift manifests in HA and NA as a result of continuous and gradual accumulation of point mutations in the HA and NA genes.

1. Each year’s flu vaccine contains three flu strains – two A strains and one B strain – that can change from year to year.
2. After vaccination, your body produces infection-fighting antibodies against the three flu strains in the vaccine.
3. If you are exposed to any of the three flu strains during the flu season, the antibodies will latch onto the virus’s HA antigens, preventing the flu virus from attaching to healthy cells and infecting them.
4. Influenza virus genes, made of RNA, are more prone to mutations than genes made of DNA.
5. If the HA gene changes, so can the antigen that it encodes, causing it to change shape.
6. The HA antigen normally binds to sialic acid on the surface of cells, but if it changes shape, it may not bind as well, allowing the newly mutated virus to infect the body’s cells.

This type of genetic mutation is called "ANTIGENIC DRIFT."

www.flu.gov
Estimated Annual Burden of Seasonal Influenza in the United States

- Deaths: 3,000 – 49,000
- Hospitalizations: 54,000 – 430,000
- Cases: 15 – 60 M

Direct medical costs: $10.4 billion
Influenza in the U.S. 2014-15

Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2014-15

So what?
Influenza in WI, 2014-2015

A Peak (%) was 12/20/14
A Peak (# positives) was 1/3/15

So what?
Influenza 2014-15

What was expected...
- A/Texas/50/2012(H3N2), the vaccine strain

What we got instead...
- A/Switzerland/9715293/2013(H3N2)

... a significant antigenic drift!

What were the consequences...
- Vaccine ineffectiveness
- Difficult virus to work with and characterize
Seasonal Influenza Vaccines

How effective?

http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm
http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

Table. Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2015

<table>
<thead>
<tr>
<th>Influenza Season</th>
<th>Reference</th>
<th>Study Site(s)</th>
<th>No. of Patients</th>
<th>Adjusted Overall VE (%)</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>2004-05</td>
<td>Belongia 2009</td>
<td>WI</td>
<td>762</td>
<td>10</td>
<td>-36, 40</td>
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<td>2005-06</td>
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<td>346</td>
<td>21</td>
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<td>2006-07</td>
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<td>WI</td>
<td>671</td>
<td>52</td>
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<td>2009-10</td>
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<td>WI, MI, NY, TN</td>
<td>6757</td>
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<td>2010-11</td>
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<td>WI, MI, NY, TN</td>
<td>4757</td>
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<td>2011-12</td>
<td>Ohmit 2014</td>
<td>WI, MI, PA, TX, WA</td>
<td>6771</td>
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<td>2012-13</td>
<td>McLean 2014</td>
<td>WI, MI, PA, TX, WA</td>
<td>6452</td>
<td>49</td>
<td>43, 55</td>
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<tr>
<td>2013-14</td>
<td>Unpublished</td>
<td>WI, MI, PA, TX, WA</td>
<td>5990</td>
<td>51</td>
<td>43, 58</td>
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<tr>
<td>2014-15</td>
<td>ACIP presentation, Flannery</td>
<td>WI, MI, PA, TX, WA</td>
<td>9329</td>
<td>23</td>
<td>7, 29</td>
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</tbody>
</table>
Vaccination Rates---2013-14 and 2014-15

General Population

http://www.cdc.gov/flu/professionals/vaccination/
Influenza in the U.S. 2014-15

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2014-15 and Selected Previous Seasons

*There was no week 53 in the previous influenza seasons displayed above; therefore, the week 53 data point for those seasons is an average of weeks 52 and 1.*
Influenza in the U.S. 2014-15
Influenza Hospitalizations

2014-15

In contrast, 2013-14

Data from the Influenza Hospitalization Surveillance Network (Influenza-NET), a population-based surveillance for influenza-related hospitalizations in children and adults in 13 US states. Incidence rates are calculated using the National Center for Health Statistics (NCHS) population estimates for the counties included in the surveillance catchment area.
Influenza in the U.S. Early 2015-16
**Early 2015-2016 Season...**

<table>
<thead>
<tr>
<th>PH Region</th>
<th>Date Received</th>
<th>Influenza type</th>
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<tbody>
<tr>
<td>S</td>
<td>8/7/2015</td>
<td>Flu A (H3)</td>
</tr>
<tr>
<td>S</td>
<td>8/18/2015</td>
<td>Flu A (H3)</td>
</tr>
<tr>
<td>NE</td>
<td>8/25/2015</td>
<td>Flu A (H3), Flu B</td>
</tr>
<tr>
<td>S</td>
<td>8/28/2015</td>
<td>Flu A (H3)</td>
</tr>
<tr>
<td>S</td>
<td>9/2/2015</td>
<td>Flu A (H3)</td>
</tr>
</tbody>
</table>

... plus several other **Flu A (H3)** reported by clinical labs, not confirmed by WSLH, in **S** and **SE** Regions.
The Changeability of Influenza Antigenic Shift

www.flu.gov

Antigenic Shift

When a new subtype (a novel HA and/or NA) of influenza A emerges in the host (humans)
Influenza at the Human-Animal Interface

**Influenza A**
- H1 - H17
- N1 – N10

Aquatic birds

Poultry
Humans
Pigs
Horses
Aquatic mammals
Cats
Dogs
Timeline of Influenza Viruses in Humans

Type A


H1 H2 H3

Swine H3
Swine H1
Avian H9
Avian H7
Avian H5

2009 H1pdm

Type B

1940

B/Yam

B/Vic
Global Influenza Concerns: A(H5N1) and A(H7N9)

http://www.who.int/csr/disease/avian_influenza/en/
Influenza: Emergence of Novel Flu A Subtypes

Chickens and turkeys take center stage

Influenza A
- H1 - H17
- N1 – N10

Aquatic birds

Poultry → Humans → Pigs → Horses → Aquatic mammals

Cats
Avian Influenza Terminology

- **Highly Pathogenic Avian Influenza**
- Bird flu
- Pathogenicity refers to avian NOT human
- H5N1, H5N2 and H5N8 are collectively referred to as H5Nx
- H5N2 and H5N8 have both been detected in the US in 2015.
Emergence of Avian Flu (H5)

- Avian Influenza (H5) emerged in North America (November 2014).
- Many flocks in the area were infected by December including those in the US.

Data and image courtesy of Hon Ip, USGS, National Wildlife Health Research Center, Madison, WI
Current Situation

Webpage from the USDA Animal Health website showing findings related to Avian Influenza. The image displays a map of the United States with states highlighted in different colors to indicate the time frame of detections. Key details include:

- **223** detections reported
- **48,091,293** birds affected

The first detection was reported on **12/19/14**, and the last detection was reported on **6/17/15**.
### Detections by State

Since December 2014, the United States Department of Agriculture has confirmed several cases of highly pathogenic avian influenza (HPAI) H5 in the Pacific, Central, and Mississippi flyways (or migratory bird paths). The disease has been found in wild birds, as well as in a few backyard and commercial poultry flocks. The Centers for Disease Control and Prevention (CDC) considers the risk to people from these HPAI H5 infections to be low. No human cases of these HPAI H5 viruses have been detected in the United States, Canada, or internationally.

<table>
<thead>
<tr>
<th>State</th>
<th>Flyway</th>
<th>Confirmed Detections</th>
<th>Last Detection Reported</th>
<th>Total Birds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arkansas</td>
<td>Mississippi</td>
<td>1</td>
<td>March 11, 2015</td>
<td>40,020</td>
</tr>
<tr>
<td>California</td>
<td>Pacific</td>
<td>2</td>
<td>February 12, 2015</td>
<td>247,300</td>
</tr>
<tr>
<td>Idaho</td>
<td>Pacific</td>
<td>1</td>
<td>January 16, 2015</td>
<td>30</td>
</tr>
<tr>
<td>Indiana</td>
<td>Mississippi</td>
<td>1</td>
<td>May 10, 2015</td>
<td>pending</td>
</tr>
<tr>
<td>Iowa</td>
<td>Mississippi</td>
<td>75</td>
<td>June 17, 2015</td>
<td>31,723,300</td>
</tr>
<tr>
<td>Kansas</td>
<td>Central</td>
<td>1</td>
<td>March 13, 2015</td>
<td>10</td>
</tr>
<tr>
<td>Minnesota</td>
<td>Mississippi</td>
<td>105</td>
<td>June 5, 2015</td>
<td>8,996,050</td>
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<tr>
<td>Missouri</td>
<td>Mississippi</td>
<td>3</td>
<td>May 5, 2015</td>
<td>53,100</td>
</tr>
<tr>
<td>Montana</td>
<td>Central</td>
<td>1</td>
<td>April 2, 2015</td>
<td>40</td>
</tr>
<tr>
<td>Nebraska</td>
<td>Central</td>
<td>4</td>
<td>June 4, 2015</td>
<td>3,794,100</td>
</tr>
<tr>
<td>North Dakota</td>
<td>Central</td>
<td>2</td>
<td>April 24, 2015</td>
<td>111,500</td>
</tr>
<tr>
<td>Oregon</td>
<td>Pacific</td>
<td>2</td>
<td>February 17, 2015</td>
<td>200</td>
</tr>
<tr>
<td>South Dakota</td>
<td>Central</td>
<td>10</td>
<td>June 1, 2015</td>
<td>1,168,200</td>
</tr>
<tr>
<td>Washington</td>
<td>Pacific</td>
<td>5</td>
<td>February 3, 2015</td>
<td>6,710</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>Mississippi</td>
<td>10</td>
<td>May 6, 2015</td>
<td>1,950,733</td>
</tr>
</tbody>
</table>

**Wisconsin:**
- 10 flocks infected
- Almost 2 million infected
- Last detection in May 2015

Data source: USDA, Animal and Plant Health Inspection Service (Sept. 2, 2015)
H5Nx Diagnostic Testing

- Most commercial assays will **NOT** be able to differentiate seasonal viruses from novel strains.
- The WSLH and MHDL have PCR tests that **can** identify H5Nx strains.
- Preferred specimen are **combined NP/OP swab** in virus transport medium.
- Testing is performed on WDPH approved specimens.
Key Points

- There have been NO human cases.
- CDC considers general risk is low.
- Risk for people handling sick/dead poultry.
- No risk for eating cooked poultry products.
- Symptoms may be atypical.

Patients with illness and close contact should contact their LHD or WDPH epidemiologist for follow-up evaluation.
It’s **NOT** all about influenza.... other diseases of public health importance.....
Enterovirus D68

Current Situation

- August 2014 to Jan. 2015 >1,100 EV D68 cases.
- Majority of cases in children with asthma or a history of wheezing.
- 33% tested positive for rhinovirus or another enterovirus.
- Many experienced severe disease.
- No cases reported this season

EV Image source: CDC (2015)
Enterovirus D68

**Background**

- Enteroviruses are very common respiratory viruses (10-15M/year).
- Transmission respiratory route (person-to-person)
- Cause a wide variety of illnesses.
- Sometimes disease can be severe.
- There are no vaccines or antiviral therapeutics.
- Children with asthma are more vulnerable.
Enterovirus D68

FIGURE 2. Percentage of enterovirus reports, by month of specimen collection — United States, 1983–2005

Enterovirus D68

- Large diversity of enteroviruses circulate seasonally.
- EV D68 has been rare

### Table 2: Frequencies, ranks, and number of years reported for individual enterovirus serotypes — National Enterovirus Surveillance System, United States, 1970–2005

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Reports with known serotype (N = 49,567)</th>
<th>Rank</th>
<th>Highest rank</th>
<th>Among the 15 most frequent</th>
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<tbody>
<tr>
<td>Echovirus 9</td>
<td>1,588</td>
<td>11.8</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Echovirus 11</td>
<td>5,539</td>
<td>11.4</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Echovirus 16</td>
<td>5,521</td>
<td>10.4</td>
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<td>2</td>
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<tr>
<td>Coxsackievirus B5</td>
<td>4,213</td>
<td>9.7</td>
<td>3</td>
<td>3</td>
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<td>Echovirus 6</td>
<td>5,303</td>
<td>6.4</td>
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<td>5</td>
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<td>3,596</td>
<td>5.2</td>
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<td>7,399</td>
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<td>Echovirus 4</td>
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<td>4.6</td>
<td>4</td>
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<td>Coxsackievirus B4</td>
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<td>4.3</td>
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<td>Echovirus 7</td>
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</tbody>
</table>

*The 15 most common serotypes are shown in bold. Coxsackieviruses A19 and 22, echovirus 69, and recently identified enteroviruses numbered 73 and higher have not been reported during the study period.*
**Enterovirus D68**

**Diagnostic Testing**

- Genetically very similar to rhinoviruses.
- Most PCR assays cannot accurately discriminate!
- Some commercial PCR assays may have variable sensitivities for EV D68.
- Testing is limited to cases that are WDPH approved.
- Combined NP/OP is the preferred specimen.
- WSLH is performing Enterovirus PCR on approved specimens.
- Specific EV D68 typing at CDC.
- EUA test will be available should the situation warrant.

http://www.slh.wisc.edu/enterovirus-d68-confirmed-in-wisconsin/
Emerging Disease Threats
MERS-Coronavirus

Confirmed global cases of MERS-CoV
Reported to WHO as of 02 Sep 2015 (n=1514)

Republic of Korea (n=166)
MERS-CoV
What we know!

- Virus is *different* than SARS-Coronavirus and seasonal coronaviruses.
- First cases in 2012.
- All cases linked to the Arabian Peninsula.
- Virus does not easily transmit from person-to-person.
- Requires close personal contact.
- Genetically stable.
- Bats and camels play a role in host transmission; dynamics not well understood.
- Healthcare workers at higher risk.
Influenza Diagnostic Technology Update

RIDTs Automation NGS

Multiplex REGULATIONS Rapid Molecular PCR
Rapid Influenza Diagnostic Tests (RIDTs)

A perennial discussion
Improving RIDT Performance

There are new regulations in our future

https://www.federalregister.gov/articles/2014/05/22#food-and-drug-administration

- New nomenclature proposed: Influenza Virus Antigen Detection test
If you are an RIDT(IVAD) user...

- What would the new regulations entail?
  - Reclassifying RIDTs from Class I to Class II
  - Add “special controls” to ensure device safety and effectiveness
    - Set minimum clinical performance criteria for sensitivity and specificity
    - Identify appropriate comparator tests for new assays
    - Accuracy assessed by manufacturers each year and when novel strain emerges

- When will this happen?

- Possible impacts:
  Better tests? Fewer tests?
Rapid Influenza Diagnostic Tests

The Next Generation

- Incorporates reader instrument
- Reduces subjectivity
- Improved sensitivity
- CLIA-waved
- Data transmission capabilities
- A step in the right direction

Quidel Sofia Influenza A & B

B-D Veritor Influenza A & B
Quidel Sofia sites within WI
Summer 2014-15

Temte, et al study, 2015
The power of rapid real-time reporting

ICEID meeting, Atlanta, GA
Rapid Influenza Diagnostic Tests

Molecular Results in Minutes!

https://usdiagnostics.roche.com/en/cobas-liat-lab.html#overview

Influenza Molecular Tests - PCR

Commercially Available - FDA Cleared

- CDC periodically updates list
- More and more clinical labs using these
- Literature in general indicates high level of performance
- Concerns:
  - Detection of novel influenza A’s
  - Variable subtyping capabilities

U.S. Influenza Surveillance

www.cdc.gov/flu/weekly

Morbidity Surveillance

Virologic Surveillance

Mortality Surveillance

State-level data to state surveillance coordinators
"Right-Sizing" Influenza Virologic Surveillance

The Importance of "Alternative Data"

Alternative data is existing virologic data from non-PHL sources that can be used to supplement PHL data for improved situational awareness.

Right Size Roadmap

Influenza Virologic Surveillance

*Increasing Role for the Clinical Lab*

- Provide situational awareness
  - Clinical lab testing data → CDC

Detect novel or reassortant viruses

Inform vaccine strain selection

Detect and monitor antiviral resistance

- Specimens/isolates → WSLH → CDC
  
  from clinical labs
Laboratory Surveillance Plan, 2015-2016

What YOU need to know!
Influenza Surveillance in Wisconsin

Multi-element approach

1. Rapid Influenza Diagnostic Testing (RIDT) Sites
   - >50% of Influenza testing in WI.
   - Confirmatory testing during periods of low prevalence!

   WSLH can provide confirmatory testing for out-of-season positives and the first two positive influenza A and influenza B specimens.
Influenza Surveillance in Wisconsin

Multi-element approach

2. Enrolled Surveillance Sites
   - 18 labs in 5 public health regions.
   - Provide randomized specimens weekly.

Request to continue to submit the first 3 specimens per week with influenza test requests to WSLH.
Influenza Surveillance in Wisconsin

Multi-element approach

3. PCR Labs
   - “Gold Standard” testing.
   - Provide weekly testing data summary reports.
   - 48 WI PCR labs!

Request to report both the *number positive* and the *number tested* weekly.
**Send Flu A unsubtypable specimens when subtyping for both 2009 H1N1 and seasonal H3 were attempted (Ct<35).**
Laboratory-based Surveillance

All Clinical Laboratories performing influenza diagnostic testing

**All Labs:**
- Send those with international travel histories
- *Sampling* of influenza-related hospitalizations
- Unusual presentations/results
- Contact with swine/ sick or dead poultry
- Antiviral treatment failure
Other Pathogens of Public Health Importance to Report

- B. pertussis/parapertussis
- RSV
- Non-influenza respiratory viruses
- Grp A Strep
- VZV
- Rotavirus

NEW! Gastropathogen PCR
Reporting Lab Results

There are two options.....

1. Web-based reporting

   Select the method below to enter data; you must also select "Next".

   - Antigen Detection
   - PCR
   - Culture

   [Image]

2. FAX reporting

   Please FAX by noon Wednesday of each week to:
   - Erik Reisdorf or Mary Wedig, Wisconsin State Laboratory of Hygiene at 608-266-3291
   - Contact Mary Wedig (608-265-0355) or Erik Reisdorf (608-265-1021) with questions.
   - Please report the number of specimens tested and the number of specimens positive for each Sunday through Saturday week throughout the year even if no specimens were tested.

   [Image]
What is the WSLH able to provide to support participating labs?

- Specimen collection supplies.
- Specimen shippers & packaging supplies.
- NO cost specimen transport.
- Influenza confirmatory testing.
- Influenza PCR validation specimen panel.
- Weekly updated surveillance data (*B. pertussis*, *Influenza*, RSV & others).
- Laboratory Surveillance Reports
Educational Opportunities

WCLN Regional Meeting (2015)
- Laboratory preparedness and biosafety
- P.A.C.E® approved.

Locations          Date
- Rice Lake, WI    Oct. 13
- Kimberly, WI     Oct. 14
- Wisconsin Dells, WI Oct. 16
Your participation in the Wisconsin surveillance system is **vital** to monitor for emerging novel strains with pandemic potential and other pathogens that impact community health.
WSLH Surveillance Coordinators
1. Erik Reisdorf
   Virology Lab-Team Lead
   Ph: 608-262-1021
   erik.reisdorf@slh.wisc.edu

2. Mary Wedig
   Electronic Reporting Coordinator
   Ph: 608-890-0353
   mary.wedig@slh.wisc.edu