Influenza and other Respiratory Viruses Update--2015

Pete Shult, PhD
CDD Director & Emergency Laboratory Response

and

Erik Reisdorf, MPH, M(ASCP)^{CM}
Surveillance and Virology Lab-Team Lead

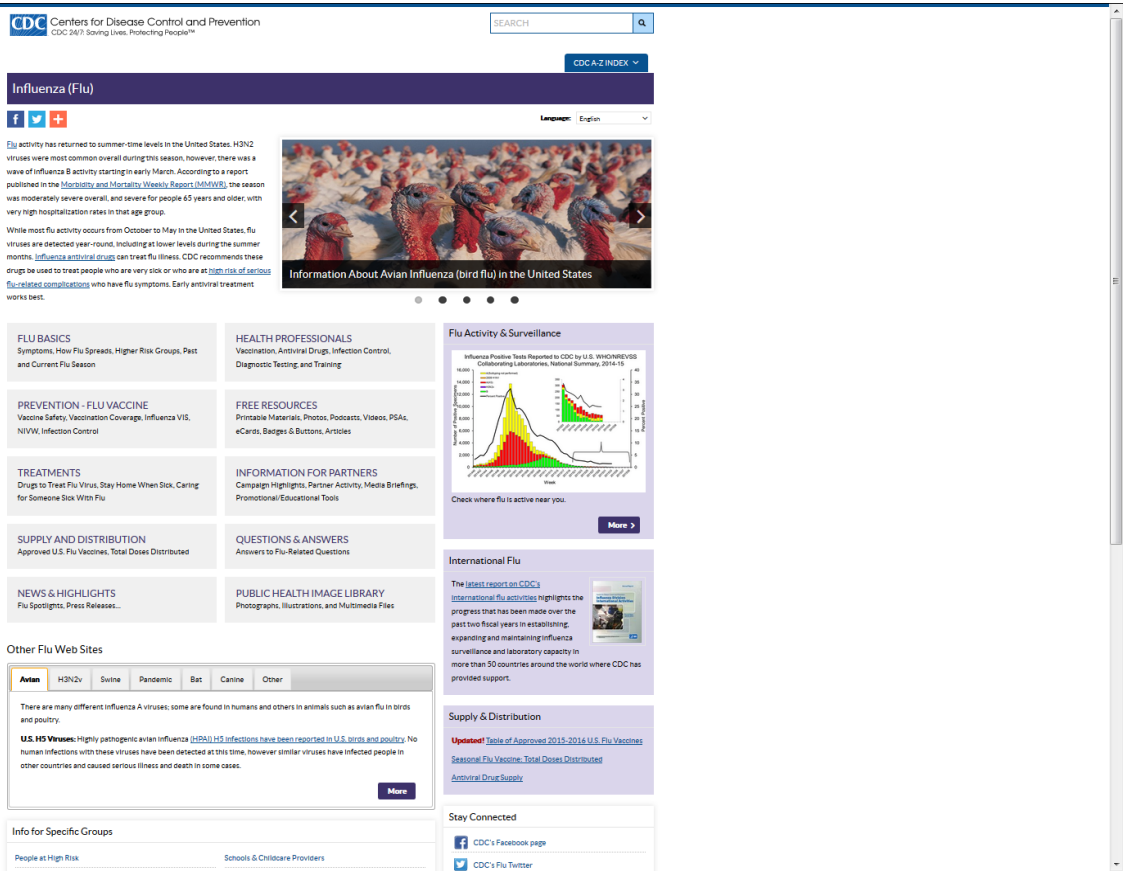
Learning Objectives

- 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

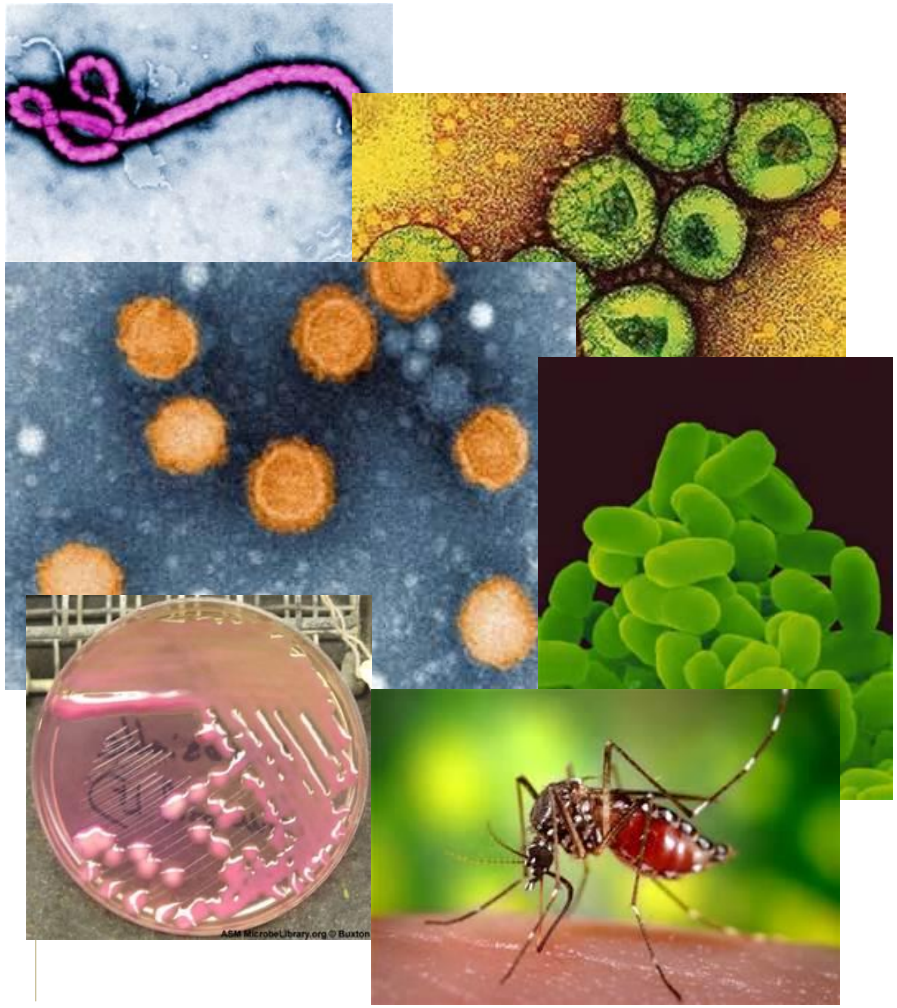
www.cdc.gov/flu/index.htm



What We're Dealing with Now

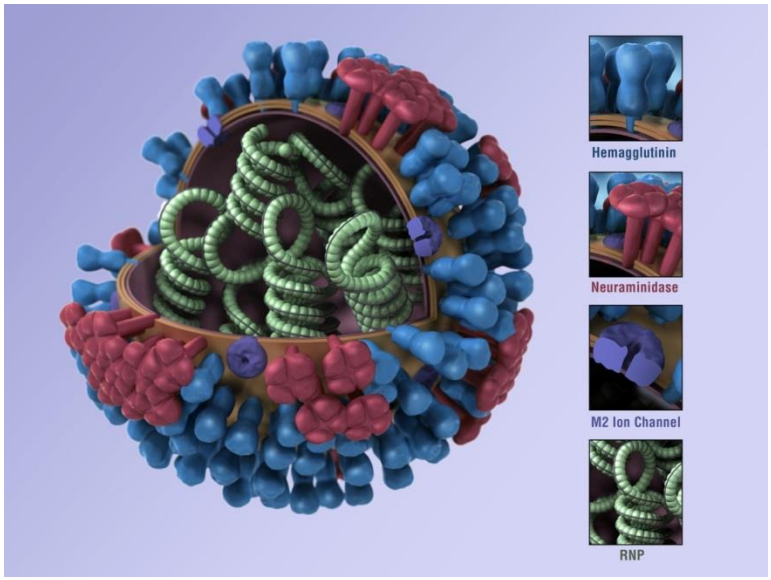
- Ebola virus
- EV-D68
- MERS CoV
- Dengue fever
- Chikungunya
- Anthrax
- Measles/mumps

… So what's the big deal with influenza?



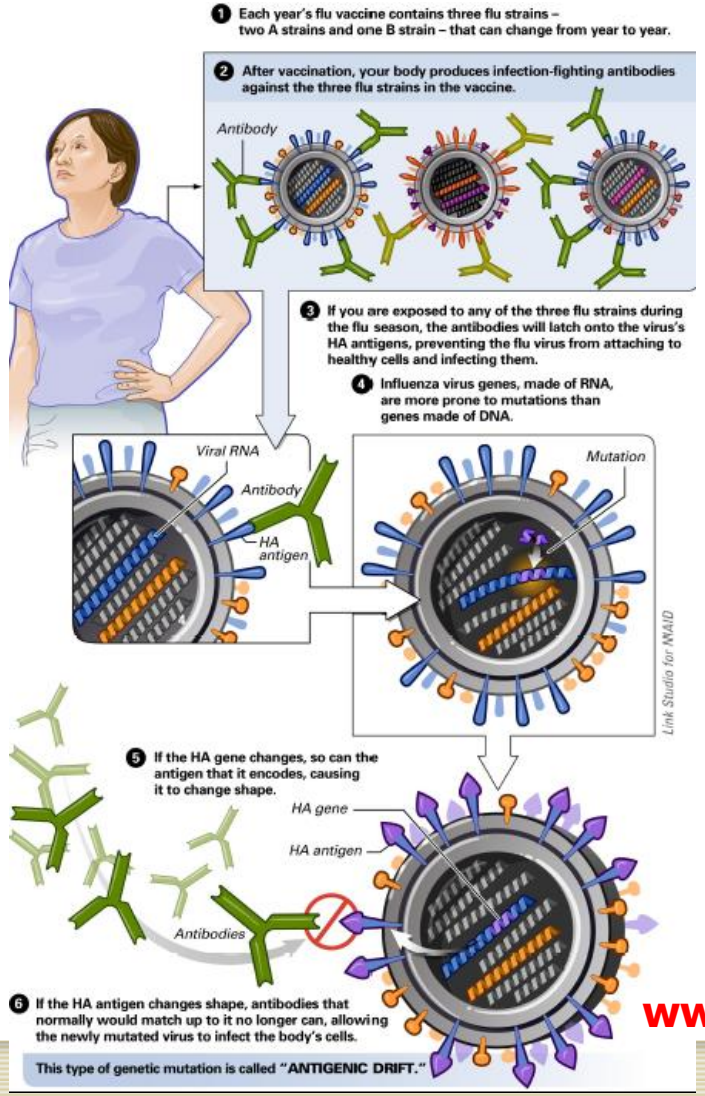
The Changeability of Influenza

Antigenic Drift →Seasonal Influenza



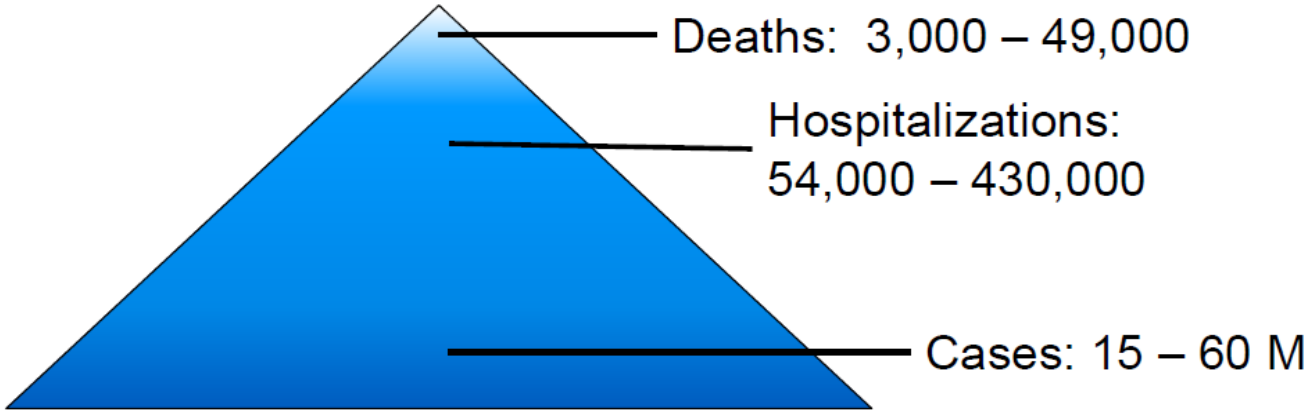
<u>Antigenic Drift</u>

Manifests in HA and NA as a result of continuous and gradual accumulation of point mutations in the HA and NA genes



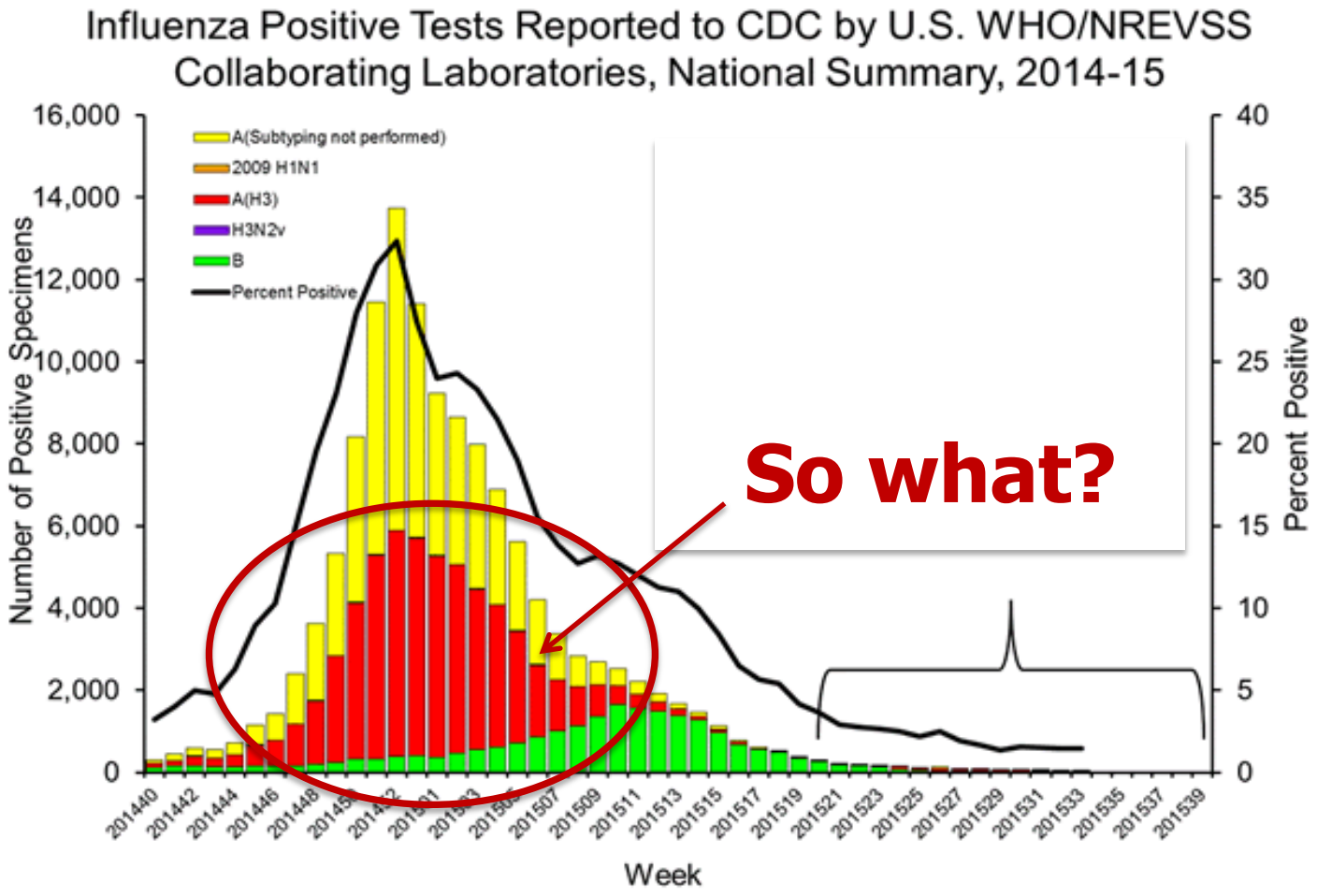
www.flu.gov

Estimated Annual Burden of Seasonal Influenza in the United States

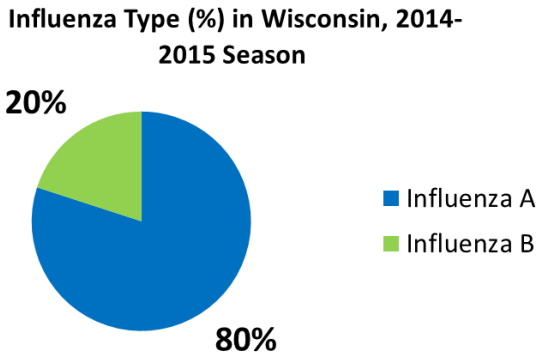


Direct medical costs: $10.4 billion

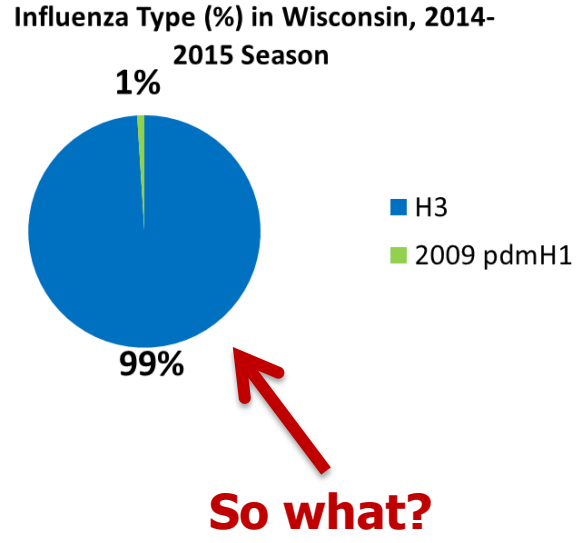
Influenza in the U.S. 2014-15

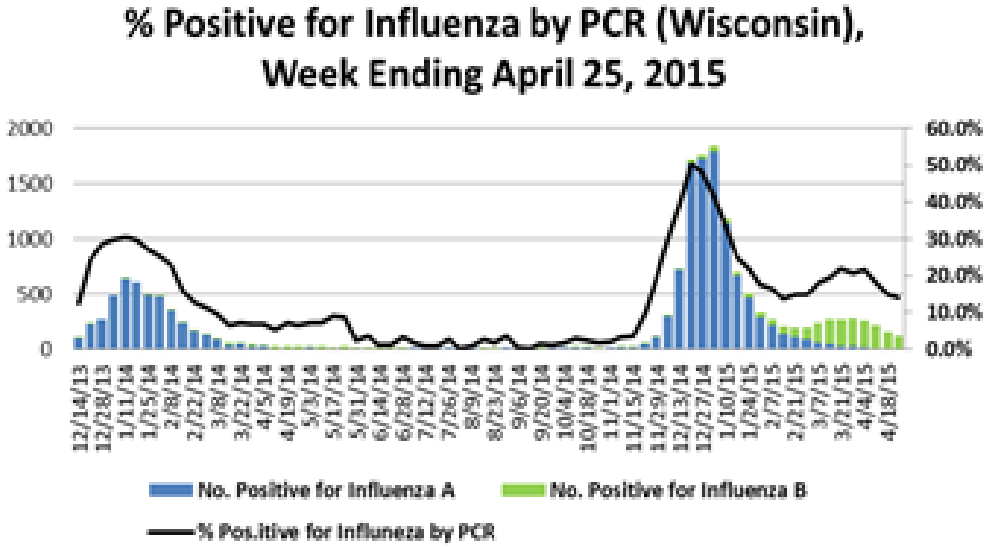


Influenza in WI, 2014-2015



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





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

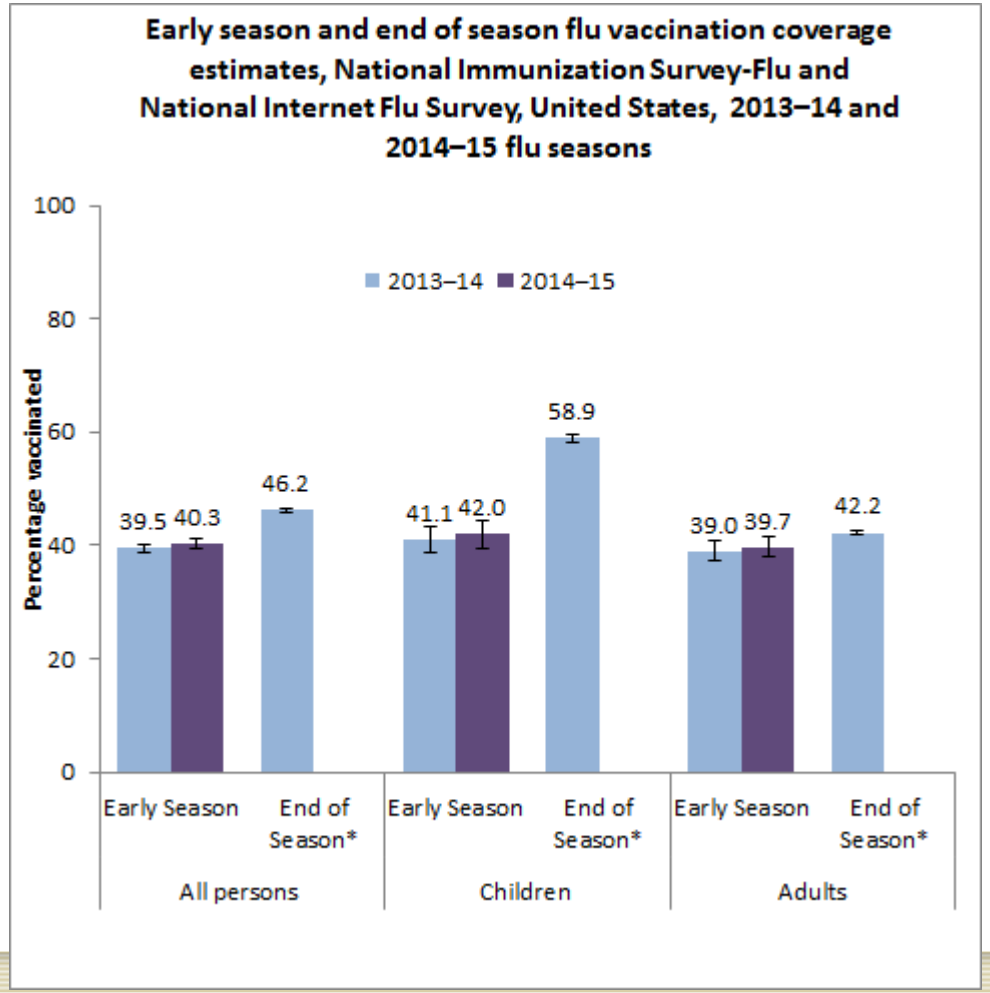
Table. Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2015

Influenza Season†	Reference	Study Site(s)	No. of Patients‡	Adjusted Overall VE (%)	95% CI
2004-05	Belongia 2009	WI	762	10	-36, 40
2005-06	Belongia 2009	WI	346	21	-52, 59
2006-07	Belongia 2009	WI	871	52	22 ,70
2007-08	Belongia 2011	WI	1914	37	22, 49
2009-10	Griffin 2011	WI, MI, NY, TN	6757	56	23, 75
2010-11	Treanor 2011	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Unpublished	WI, MI, PA, TX, WA	5990	51	43, 58
2014-15	ACIP presentation, Flannery	WI, MI, PA, TX, WA	9329	23	7, 29

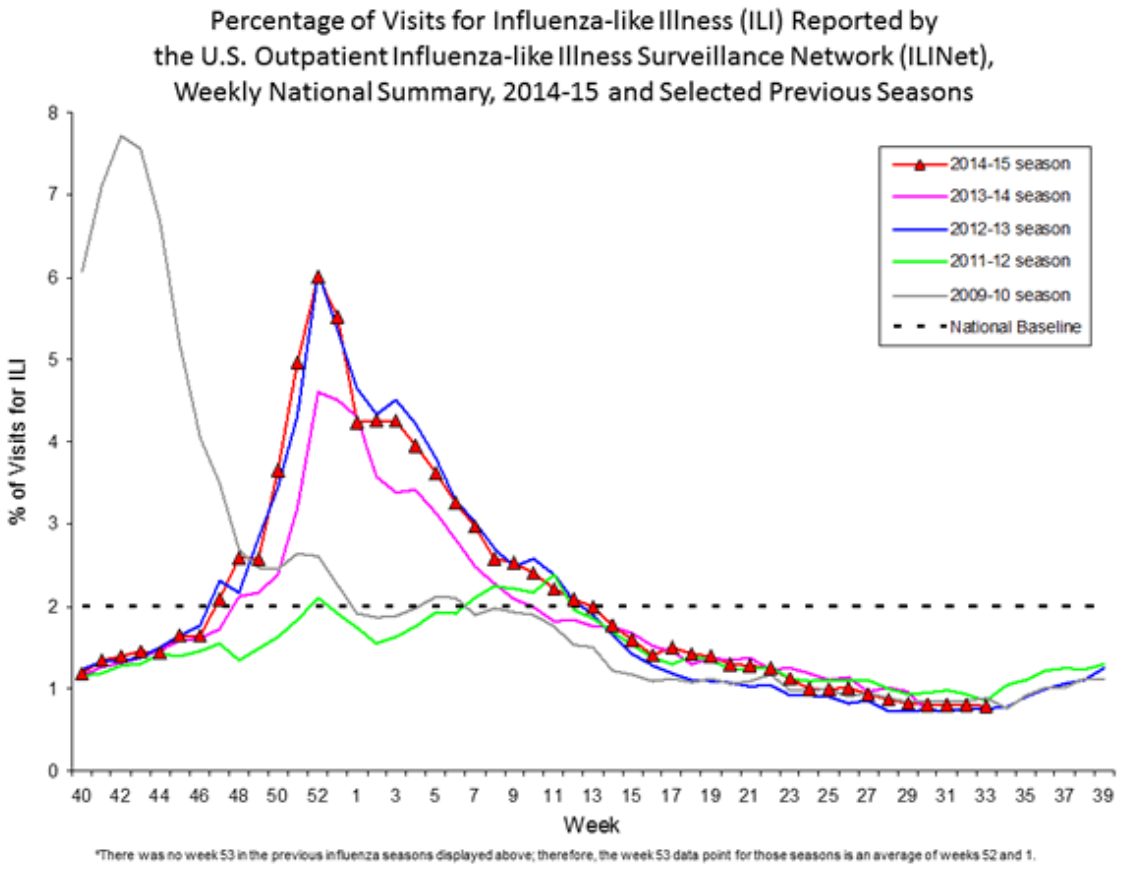
Vaccination Rates---2013-14 and 2014-15

General Population

http://www.cdc.gov/flu/professionals/vaccination/

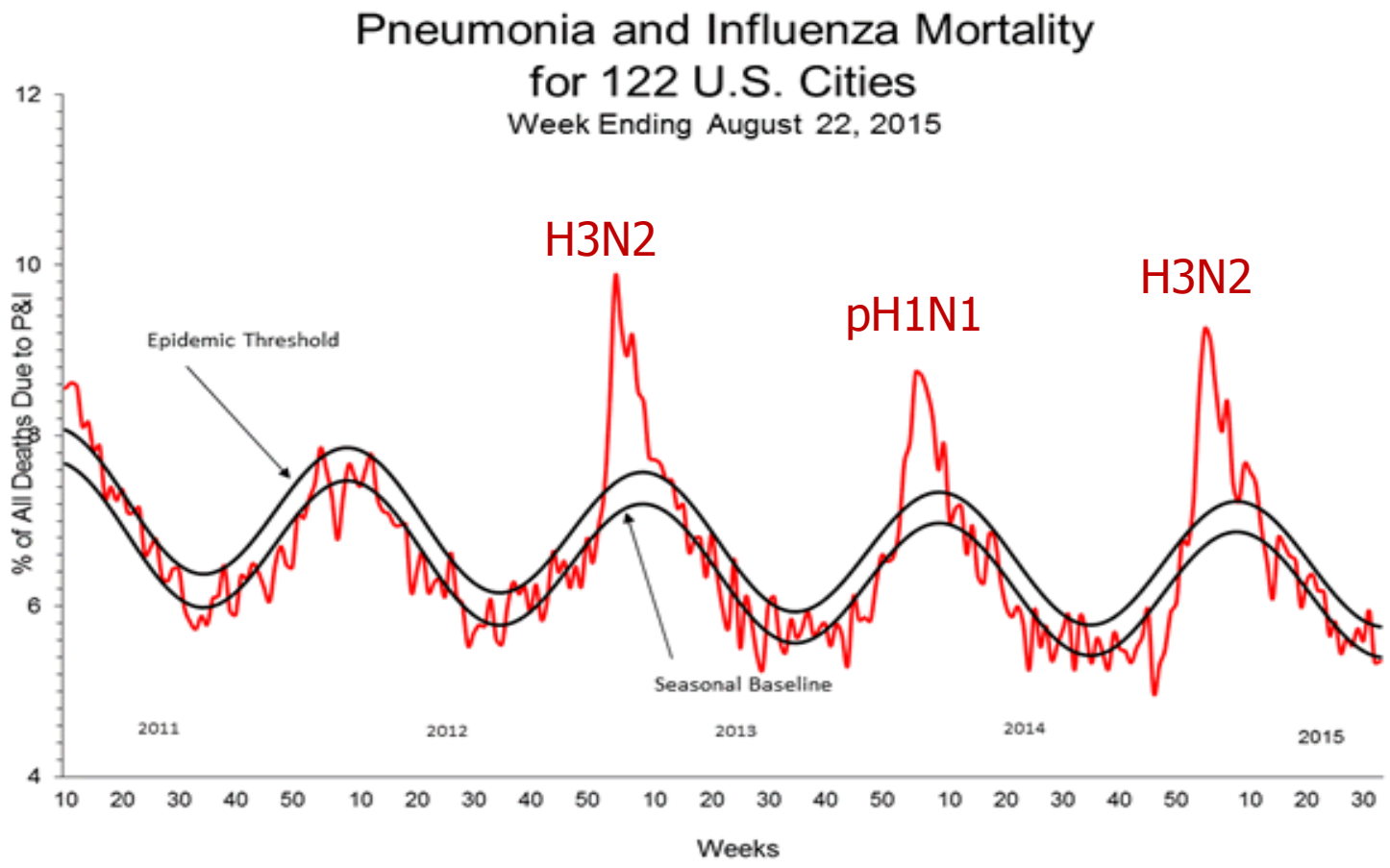


Influenza in the U.S. 2014-15



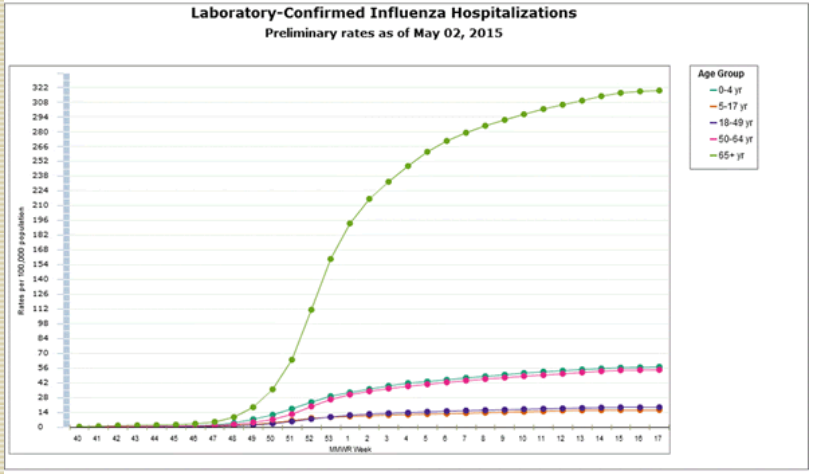
*There was no week 53 in the previous influenza seasons displayed above; therefore, the week 53 data point for those seasons is an average of weeks 52 and 1.

Influenza in the U.S. 2014-15

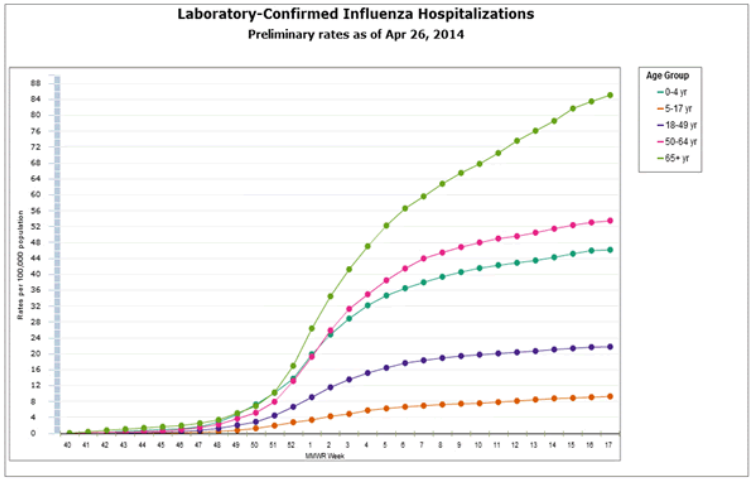


Influenza Hospitalizations

2014-15

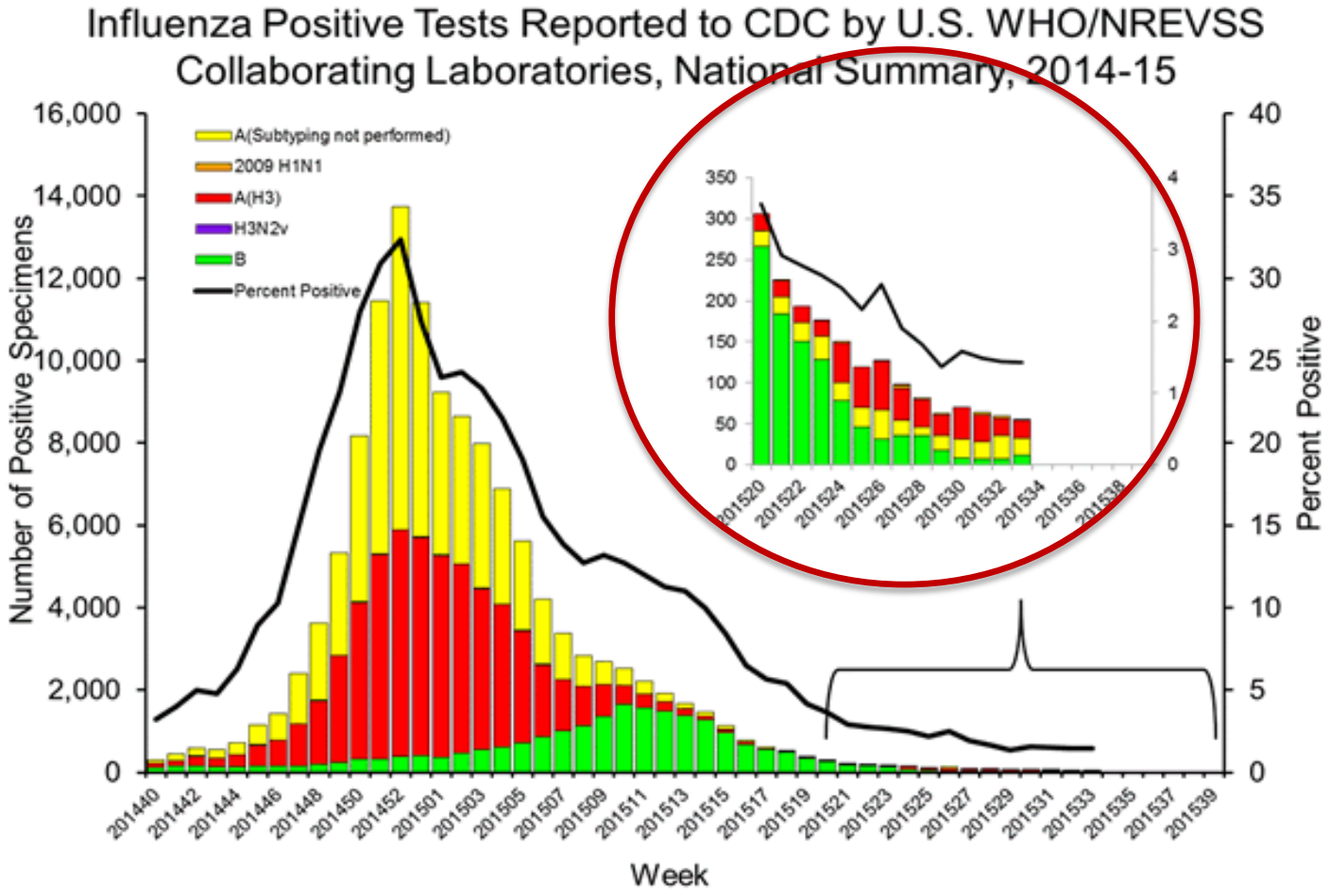


In contrast, 2013-14

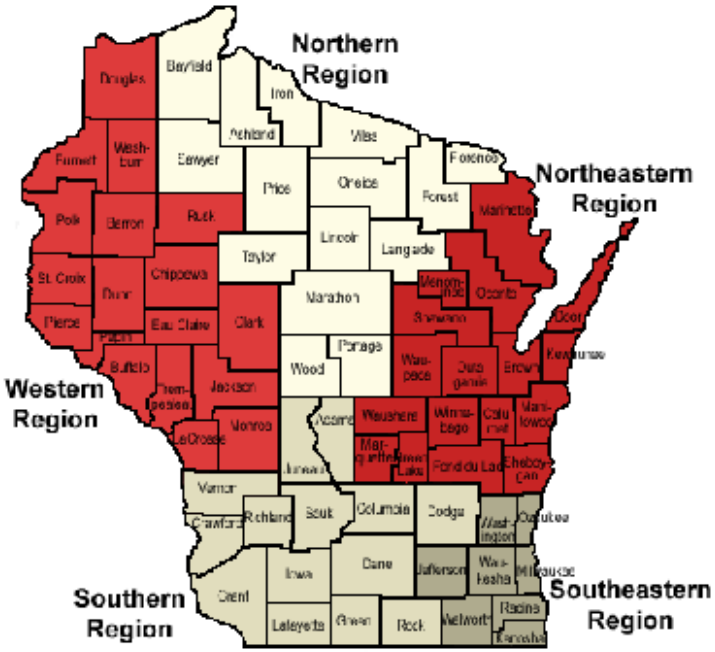


Data from the Influenza Hospitalization Surveillance Network (FluSurv-NET), a population-based surveillance for influenza related hospitalizations in children and adults in 13 US states. Incidence rates are calculated using the National Center for Health Statistics' (NCHS) population estimates for the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

Influenza in the U.S. Early 2015-16



Early 2015-2016 Season….

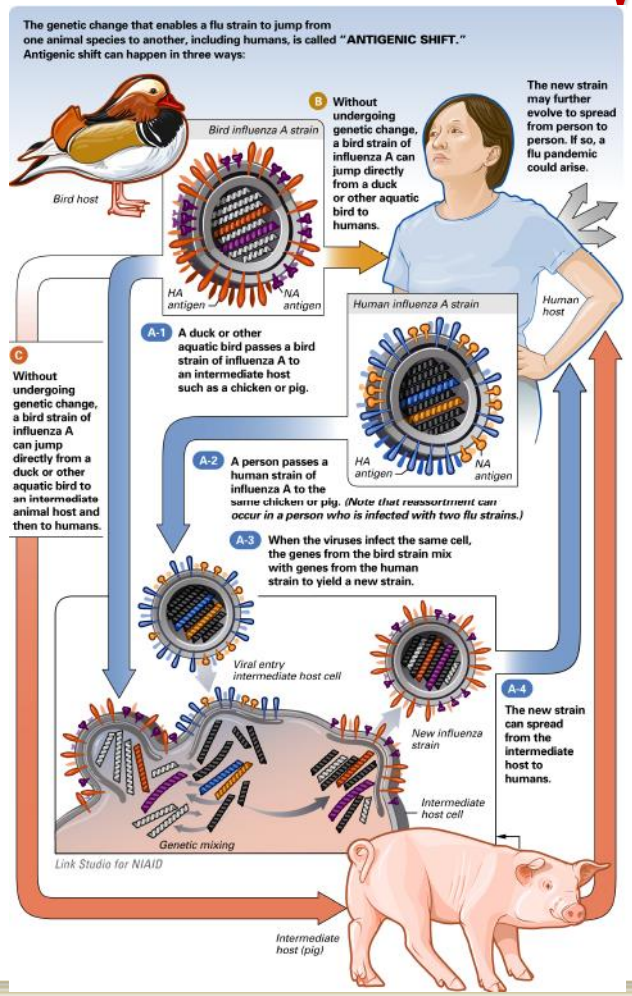


PH Region	Date Received	Influenza type
S	8/7/2015	Flu A (H3)
S	8/18/2015	Flu A (H3)
NE	8/25/2015	Flu A (H3), Flu B
S	8/28/2015	Flu A (H3)
S	9/2/2015	Flu A (H3)

… 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

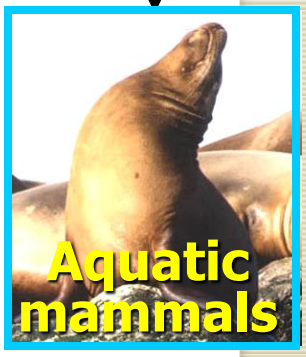


<u>Antigenic Shift</u>
When a new subtype (a novel HA and/or NA) of influenza A emerges in the host (humans)

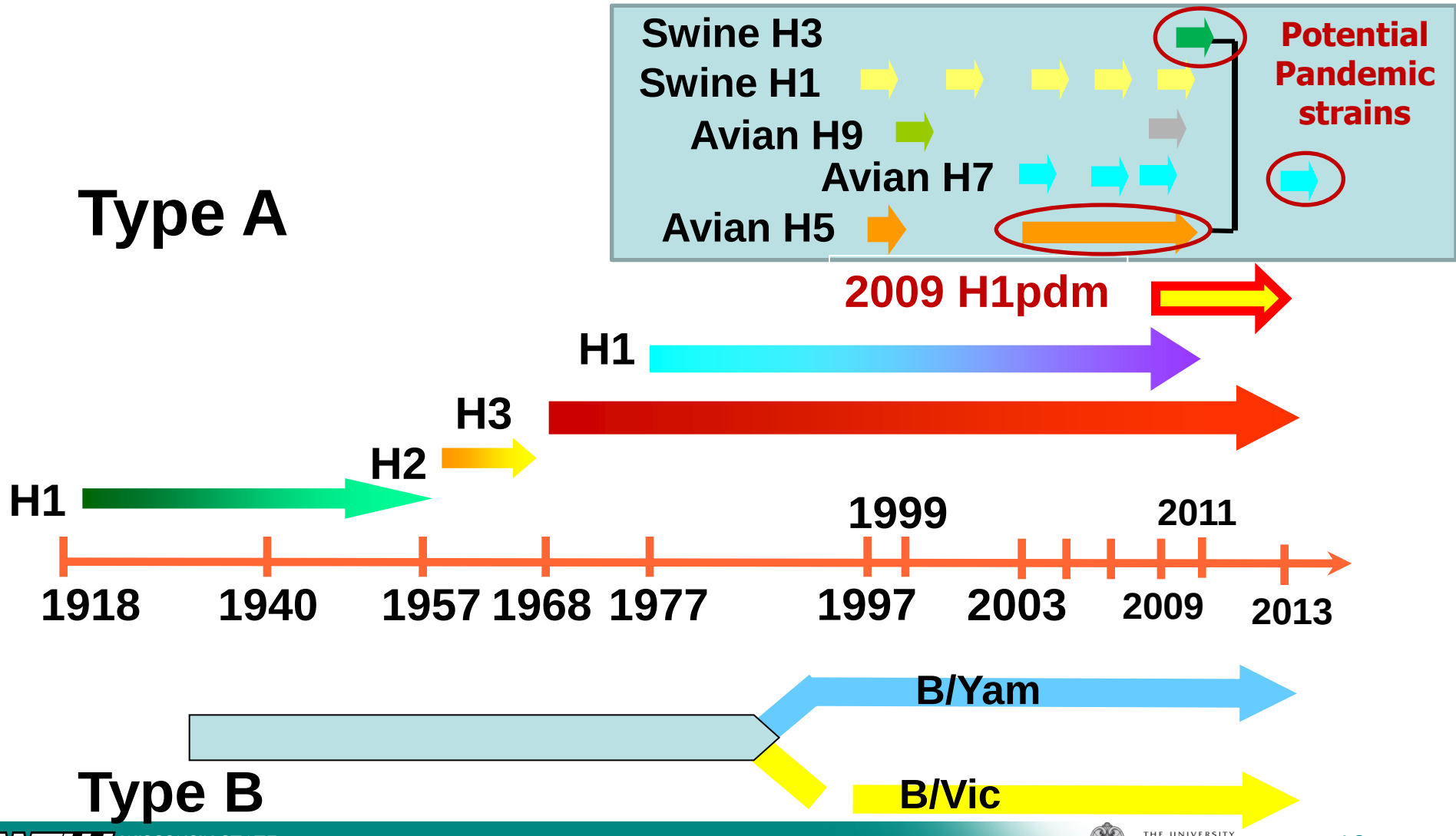
Influenza at the Human-Animal Interface

Influenza A

- **H1 - H17**
- **N1 – N10**



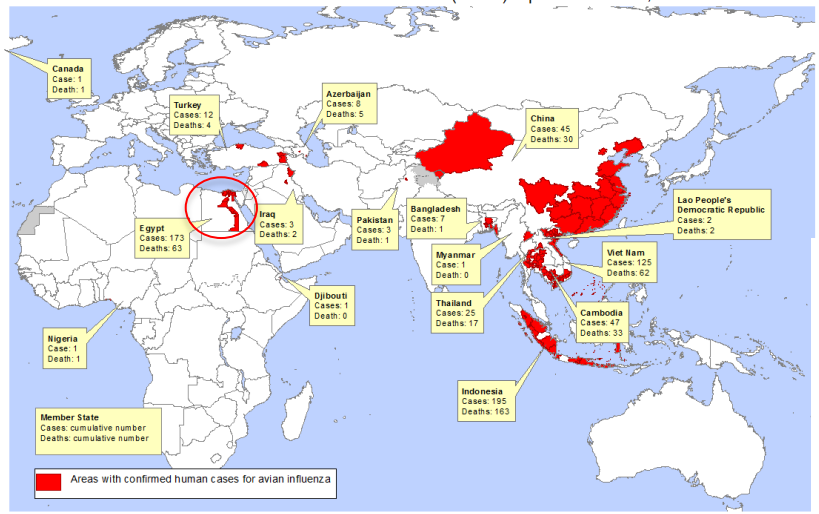
Timeline of Influenza Viruses in Humans



Global Influenza Concerns:
A(H5N1) and A(H7N9)

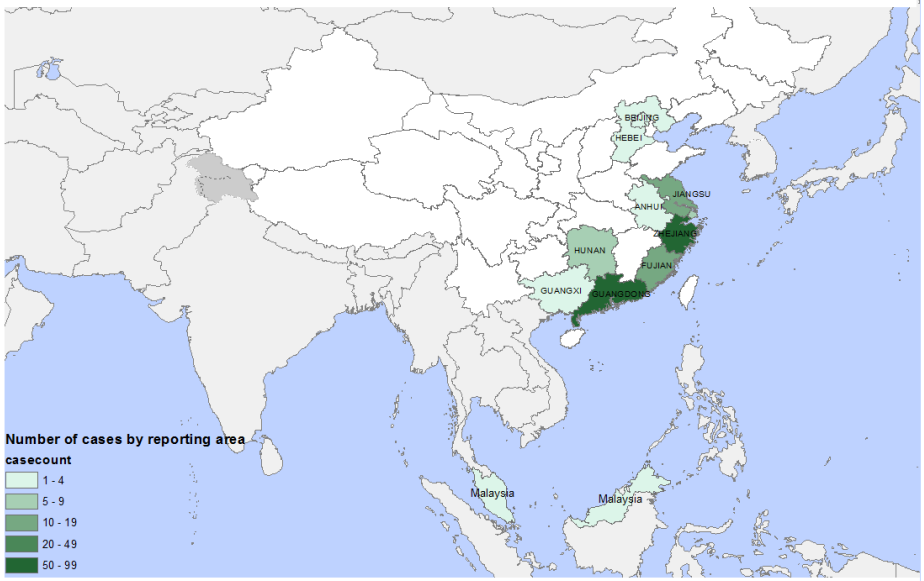
http://www.who.int/csr/disease/avian_influenza/en/

Areas with confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013*



*All dates refer to onset of illness
Data as of 24 January 2014
Source: WHO/GIP

Areas reporting confirmed human cases for influenza A(H7N9) to WHO from 2013-06-01 *



*All dates refer to onset of illness
Data as of 14/02/2014
Source: WHO

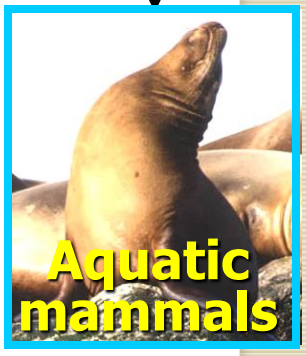
World Health Organization

Influenza: Emergence of Novel Flu A Subtypes

Chickens and turkeys take center stage

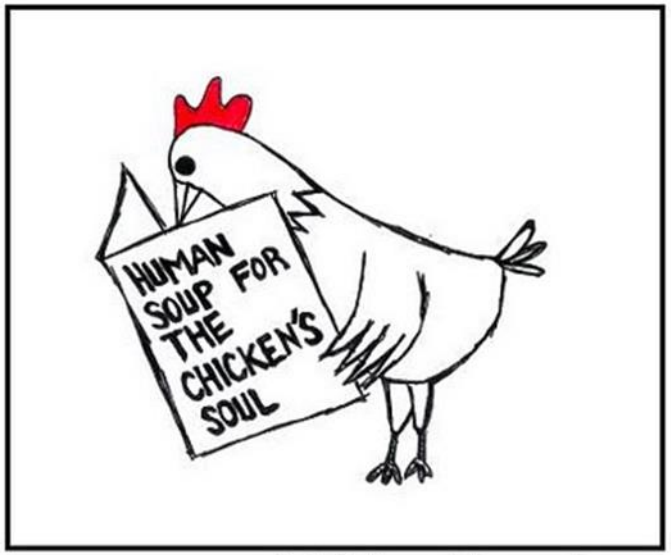
Influenza A

- **H1 - H17**
- **N1 – N10**



Avian Influenza Terminology

- **H**ighly **P**athogenic **A**vian **I**nfluenza
- 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

USDA APHIS | Animal Hea

www.aphis.usda.gov/wps/portal/aphis/ourfocus/animalhealth/sa_animal_disease_information/sa_avian_health/ct_avian_influenza_disease/!ut/p/a1/lVFNc4IwEP0tHnpkEgH5OPrRCla0U6cquWTWAJIpBAaCjv31DWo79

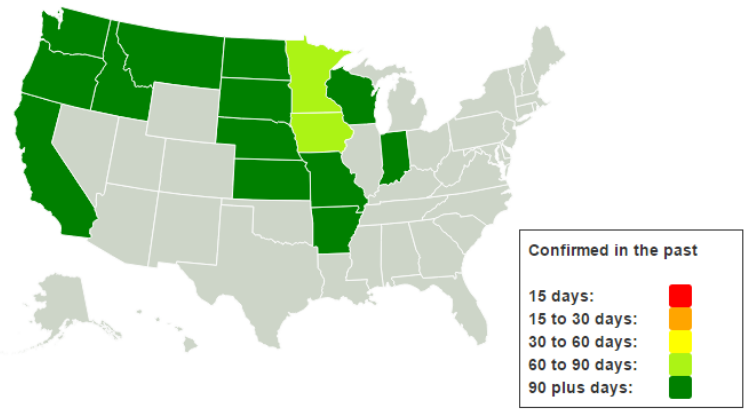
Home | Our Focus | Resources | Newsroom | Blog

Animal Health / Animal Disease Information / Avian Health / Detection by State

- Animal Health
- Contact Us
- Program Overview
- Animal Disease Information
  - Biosecurity for Birds
- Emergency Management
- Export from the U.S.
- Import into the U.S.
- Laboratory Information Services
- Monitoring and Surveillance
- One Health
- OIE International Standards
- Traceability
- Training and Development
- Veterinary Accreditation
- Veterinary Biologics

ALL Findings

Update on Avian Influenza Findings
Poultry Findings Confirmed by USDA's National Veterinary Services Laboratories



223 Detections Reported	**48,091,293** Birds Affected
12/19/14 First Detection Reported	**6/17/15** Last Detection Reported

View detailed list of detections

Download list of detections

9:55 AM 9/2/2015

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.

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

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 Distribution

www.aphis.usda.gov/animal_health/downloads/animal_diseases/ai/hpai-incident-map.pdf

USDA, APHIS, VS
Center for Epidemiology and Animal Health
2150 Centre Ave.
Fort Collins, CO 80526

Data Source: Provided by Requestor

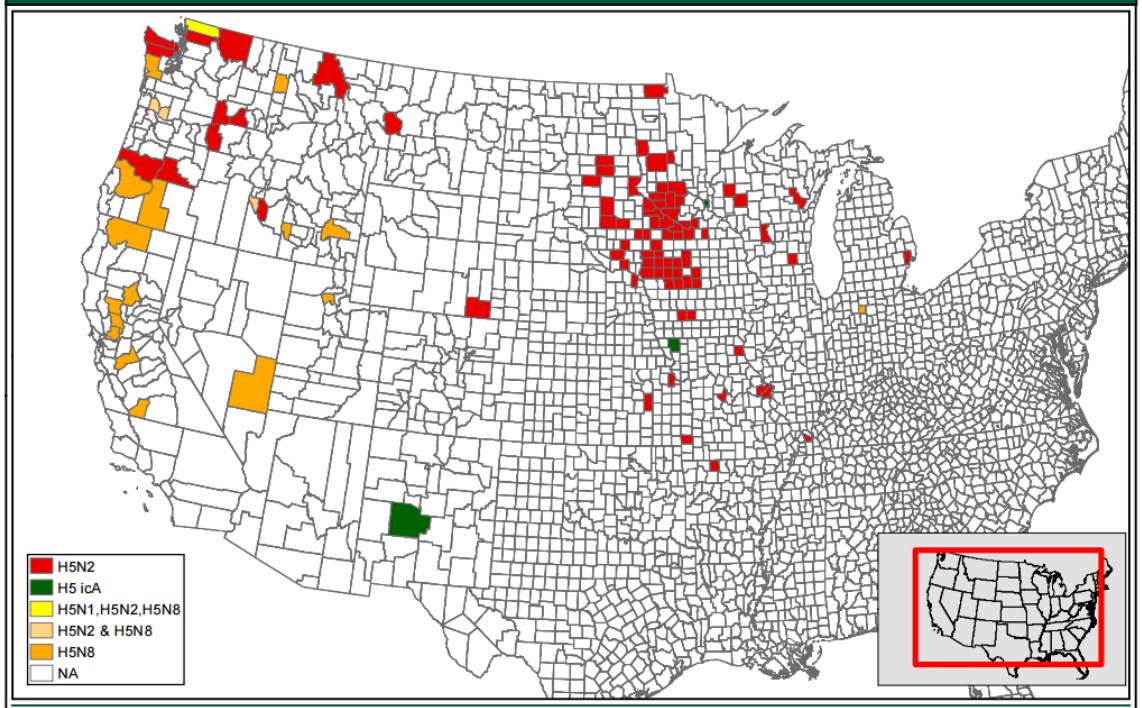
N

0 130 260 390 520 Miles

Date Created: August 27, 2015
Time Created: 11:32:51 AM MST
Coordinate System: North America Albers Equal Area Conic

USDA United States Department of Agriculture

Figure 9. HPAI Detections by Subtype in All Birds, as of 8/27/2015
(as reported on ww.aphis.usda.gov) *one or more detections may have occurred in county



USDA, APHIS, VS
Center for Epidemiology and Animal Health
2150 Centre Ave.
Fort Collins, CO 80526

Data Source: Provided by Requestor

N

0 130 260 390 520 Miles

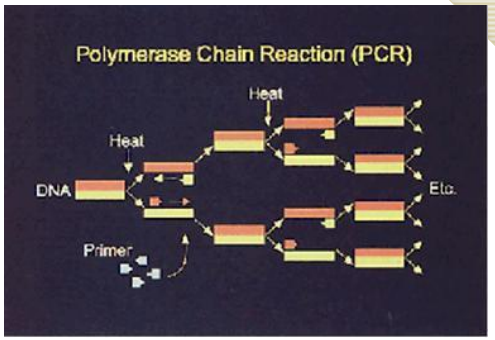
Date Created: August 27, 2015
Time Created: 11:33:42 AM MST
Coordinate System: North America Albers Equal Area Conic

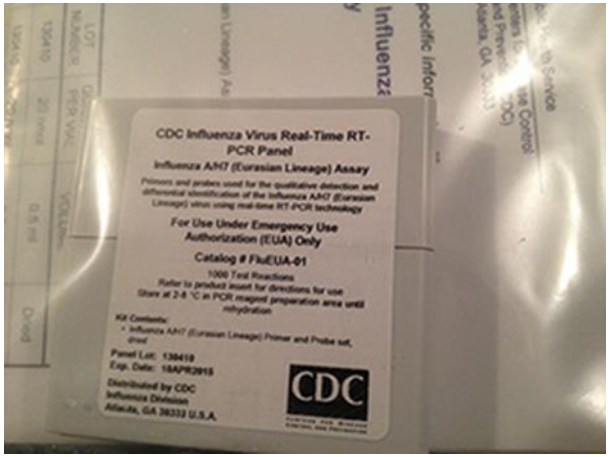
These data, and all the information contained therein, have been collected by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS), or by its cooperators on APHIS' behalf, for restricted government purposes only and is the sole property of APHIS. Data may be disseminated on a need-to-know basis only and must be used for their intended government purpose(s). All information contained within these data are subject to required Federal safeguards and shall only be shared and/or used consistent with the Trade Secrets Act [18 U.S.C. 1905], the Privacy Act of 1974, as amended [5 U.S.C. 552a], the Freedom of Information Act [5 U.S.C. 552], the confidentiality provisions of the Food Security Act of 1985 [7 U.S.C. 2276], Section 1619 of the Food, Conservation, and Energy Act of 2008 [7 U.S.C. 8791], and other applicable Federal laws and implementing regulations, as well as with the confidentiality or non-disclosure provisions of any other agreement entered into between APHIS and a cooperator.

10:18 AM
9/2/2015

H5Nx Diagnostic Testing

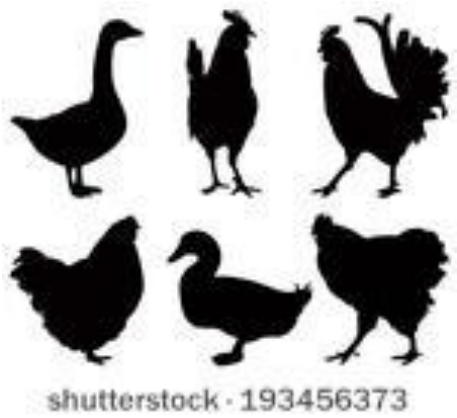
- Most commercial assays will **NOT** be able to differentiate seasonal viruses from novel strains.
- The WSLH and MHDL have PCR tests that **can** identify H5Nx strains.
- Preferred specimen are **combined NP/OP swab** in virus transport medium.
- Testing is performed on WDPH approved specimens.





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.



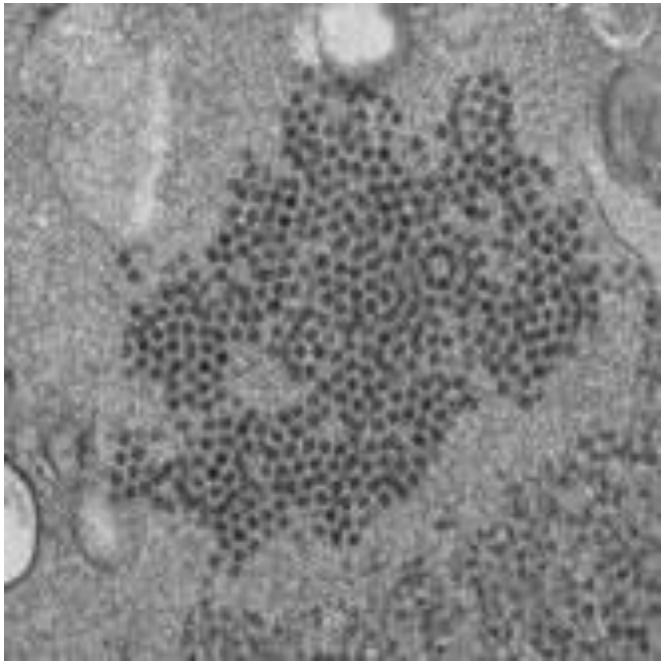
Patients with illness and close contact should contact their LHD or WDPH epidemiologist for follow-up evaluation.

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)

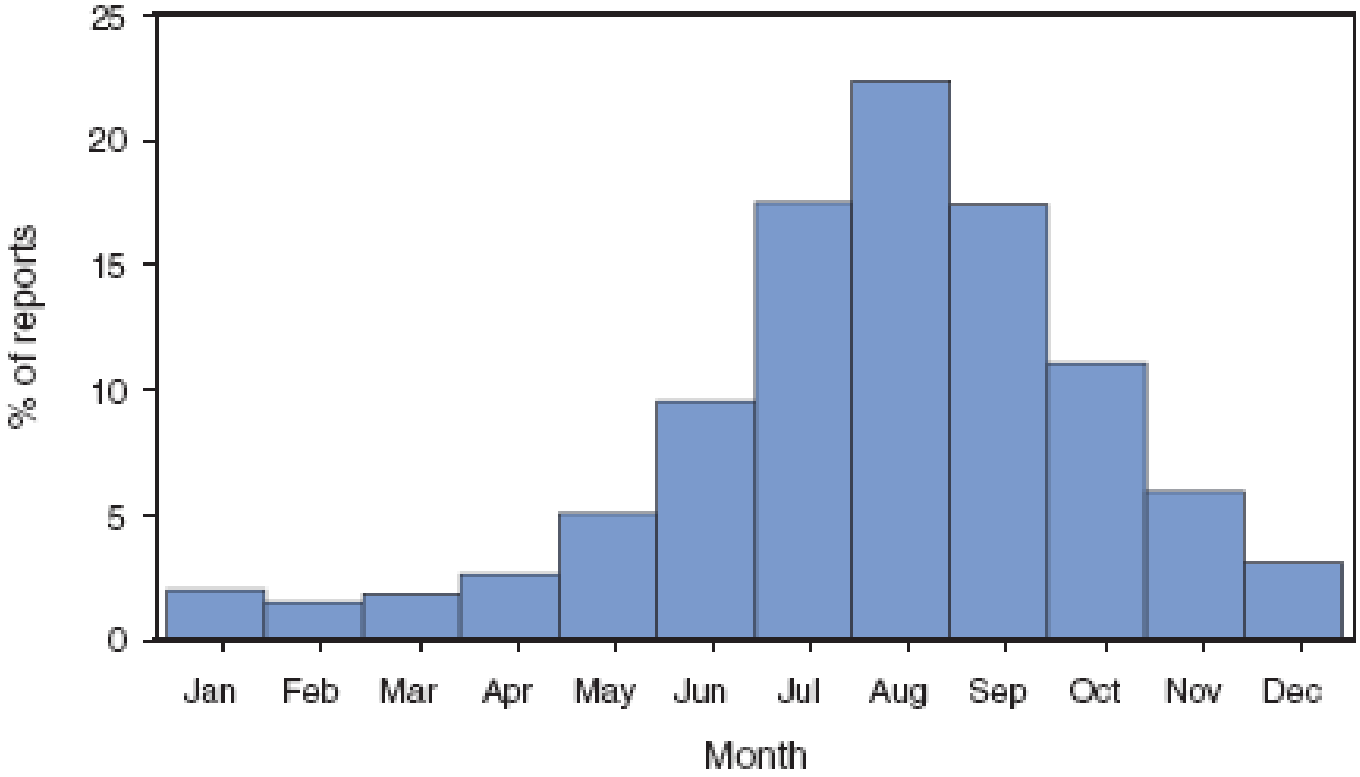
Enterovirus D68

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



MMWR (2006) Enterovirus Surveillance—US, 1983-2005. 55(SS08) 1-20.

Enterovirus D68

TABLE 2. Frequencies, ranks, and number of years reported for individual enterovirus serotypes — National Enterovirus Surveillance System, United States, 1970–2005*

Serotype	Overall rank	Reports with known serotype (N = 49,637) No.	%	Rank 1970–1979	1980–1989	1990–1999	2000–2005	Highest rank	No. of years the serotype was Reported	Among the 15 most common	Among the five most common
Echovirus 9	**1**	**5,868**	**11.8**	1	2	4	1	1	36	35	22
Echovirus 11	**2**	**5,638**	**11.4**	2	1	2	10	1	36	35	22
Echovirus 30	**3**	**5,021**	**10.1**	12	3	1	2	1	36	30	18
Coxsackievirus B5	**4**	**4,313**	**8.7**	3	4	9	5	1	36	28	12
Echovirus 6	**5**	**3,023**	**6.1**	5	5	4	6	1	36	34	7
Coxsackievirus B2	**6**	**2,596**	**5.2**	6	6	5	12	1	36	35	14
Coxsackievirus A9	**7**	**2,399**	**4.8**	8	8	6	7	2	36	35	17
Echovirus 4	**8**	**2,304**	**4.6**	4	11	19	14	1	36	27	8
Coxsackievirus B4	**9**	**2,089**	**4.2**	7	9	10	11	2	36	33	10
Echovirus 7	**10**	**2,010**	**4.0**	9	10	7	9	1	35	22	20
Coxsackievirus B3	**11**	**1,945**	**3.9**	10	7	11	13	2	36	32	6
Echovirus 18	**12**	**1,341**	**2.7**	18	13	15	3	2	36	18	6
Coxsackievirus B1	**13**	**1,143**	**2.3**	14	8	8	8	2	35	17	6
Echovirus 3	**14**	**958**	**1.9**	11	16	20	20	1	32	9	8
Echovirus 5	**15**	**916**	**1.8**	22	12	13	18	4	34	21	18
Human Parechovirus 1	16	890	1.8	15	14	14	19	8	35	26	—
Echovirus 14	17	713	1.4	13	19	18	22	4	34	19	1
Coxsackievirus A16	18	615	1.2	17	17	22	21	6	34	11	—
Echovirus 13	19	578	1.2	36	35–36	39	4	1	28	6	2
Echovirus 25	20	547	1.1	19	23	12	16	5	36	16	1
Echovirus 24	21	537	1.1	23	15	26–27	29	5	31	5	1
Echovirus 16	22	501	1.0	16	24	17	25	1	33	6	2
Echovirus 21	23	458	0.9	26	21	25	24	2	31	7	1
Echovirus 20	24	349	0.7	40	20	21	30–34	3	24	2	1
Echovirus 31	25	337	0.7	25	22	24	30–34	9	30	4	—
Echovirus 17	26	286	0.6	27	17	23	46–47	2	27	4	1
Enterovirus 71	27	270	0.5	—	30	16	15	5	23	11	1
Echovirus 2	28	211	0.4	21	28	28	44–45	12	29	2	—
Coxsackievirus A4	29–30	180	0.4	24	31	33	30–34	14	25	2	—
Echovirus 1	29–30	180	0.4	29	26	29	35	17	28	—	—
Echovirus 33	31	146	0.3	20	46–47	42	36	3	18	1	1
Coxsackievirus A10	32–33	138	0.3	30	29	30	37–39	14	27	2	—
Echovirus 27	32–33	138	0.3	35	27	26–27	30–34	16	30	—	—
Echovirus 15	34–35	120	0.2	33	32	31–32	27–28	18	31	—	—
Echovirus 19	34–35	120	0.2	28	44	36	27–28	12	24	1	—
Coxsackievirus A2	36	87	0.2	31	35–36	40–41	44–45	18	19	—	—
Coxsackievirus A5	37	72	0.1	32	38–39	48–51	37–39	12	20	1	—
Coxsackievirus B6	38	68	0.1	48	33	31–32	37–39	18	24	—	—
Human Parechovirus 2	39	60	0.1	39	37	34	40	17	22	—	—
Coxsackievirus A6	40	58	0.1	38	34	43–45	—	17	15	—	—
Coxsackievirus A24	41	55	0.1	49	53–54	52–56	17	6	8	1	—
Echovirus 12	42	53	0.1	37	40	35	41–43	20	23	—	—
Coxsackievirus A7	43	46	0.1	34	41	52–56	41–43	20	15	—	—
Coxsackievirus A21	44	42	0.1	44–47	38–39	37–38	30–34	17	17	—	—
Coxsackievirus A13	45	32	0.1	41	42–43	43–45	—	19	11	—	—
Echovirus 29	46	27	0.1	44–47	45	37–38	—	26	14	—	—
Enterovirus 68	47	26	0.1	[illegible]							
Echovirus 32	48	25	0.1	42	46–47	48–51	—	27	14	—	—
Coxsackievirus A1	49	24	<0.1	44–47	55–57	48–51	26	11	7	1	—
Coxsackievirus A14	50	21	<0.1	54	42–43	48–51	41–43	21	8	—	—
Coxsackievirus A8	51	17	<0.1	43	49	52–56	—	24	10	—	—
Echovirus 26	52	16	<0.1	52	48	43–45	—	33	9	—	—
Coxsackievirus A3	53	13	<0.1	44–47	50–52	46–47	—	31	9	—	—
Coxsackievirus A11	54	10	<0.1	51	50–52	46–47	—	31	8	—	—
Coxsackievirus A17	55	8	<0.1	50	53–54	52–56	—	36	7	—	—
Coxsackievirus A20	56	5	<0.1	—	50–52	—	46–47	27	3	—	—
Coxsackievirus A12	57	3	<0.1	53	55–57	—	—	37	2	—	—
Enterovirus 70	58	1	<0.1	—	—	52–56	—	26	1	—	—

* The 15 most common serotypes are shown in bold. Coxsackieviruses A19 and A22, enterovirus 69, and recently identified enteroviruses numbered 73 and higher have not been reported during the study period.

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

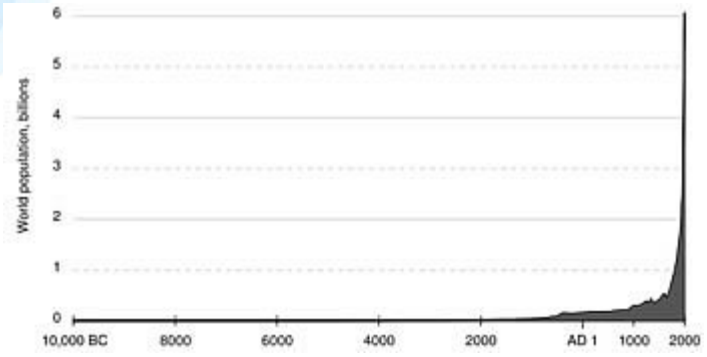
Enterovirus D68

Diagnostic Testing

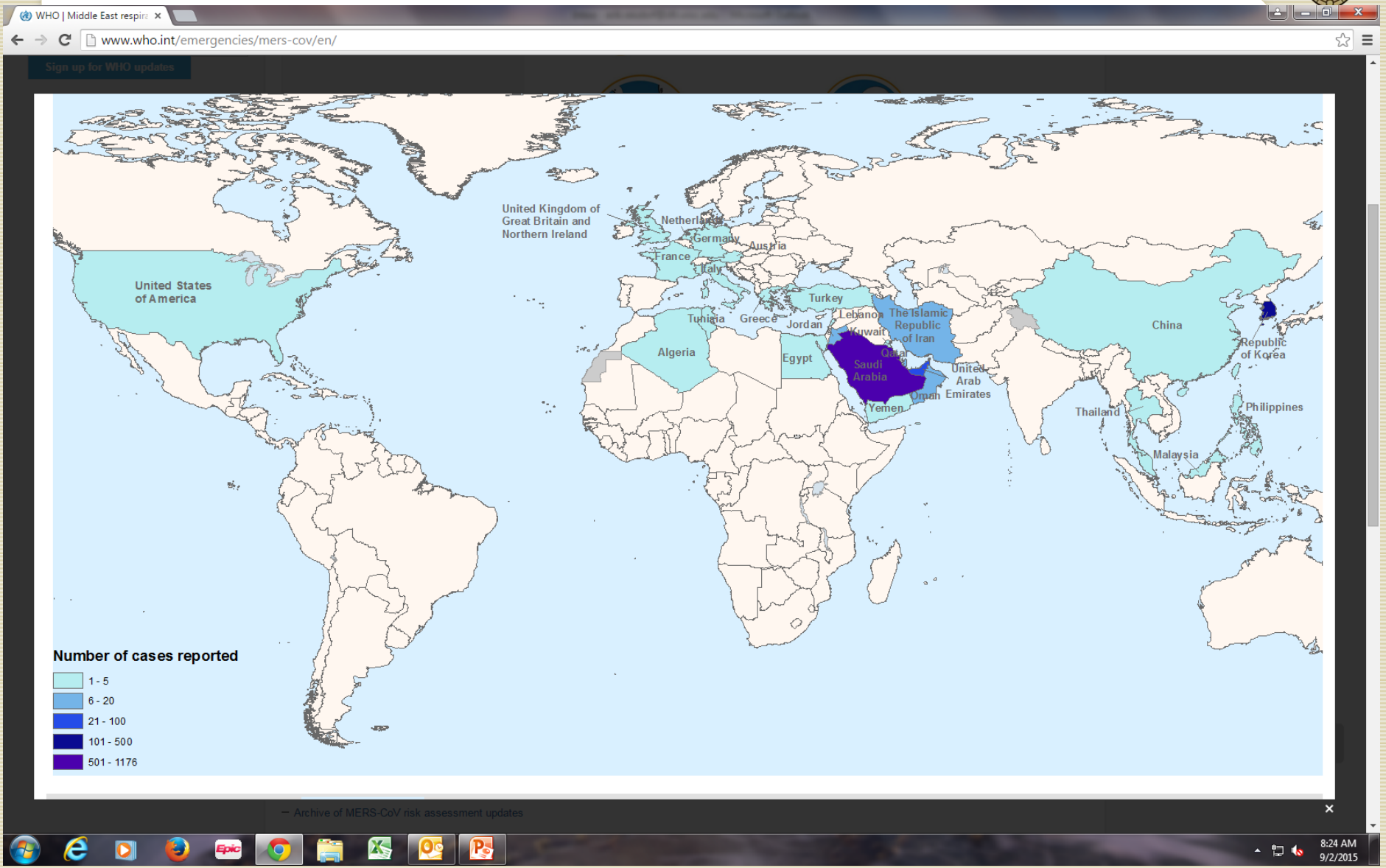
- Genetically very similar to rhinoviruses.
- Most PCR assays cannot accurately discriminate!
- Some commercial PCR assays may have variable sensitivities for EV D68.
- Testing is limited to cases that are WDPH approved.
- Combined NP/OP is the preferred specimen.
- WSLH is performing Enterovirus PCR 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/

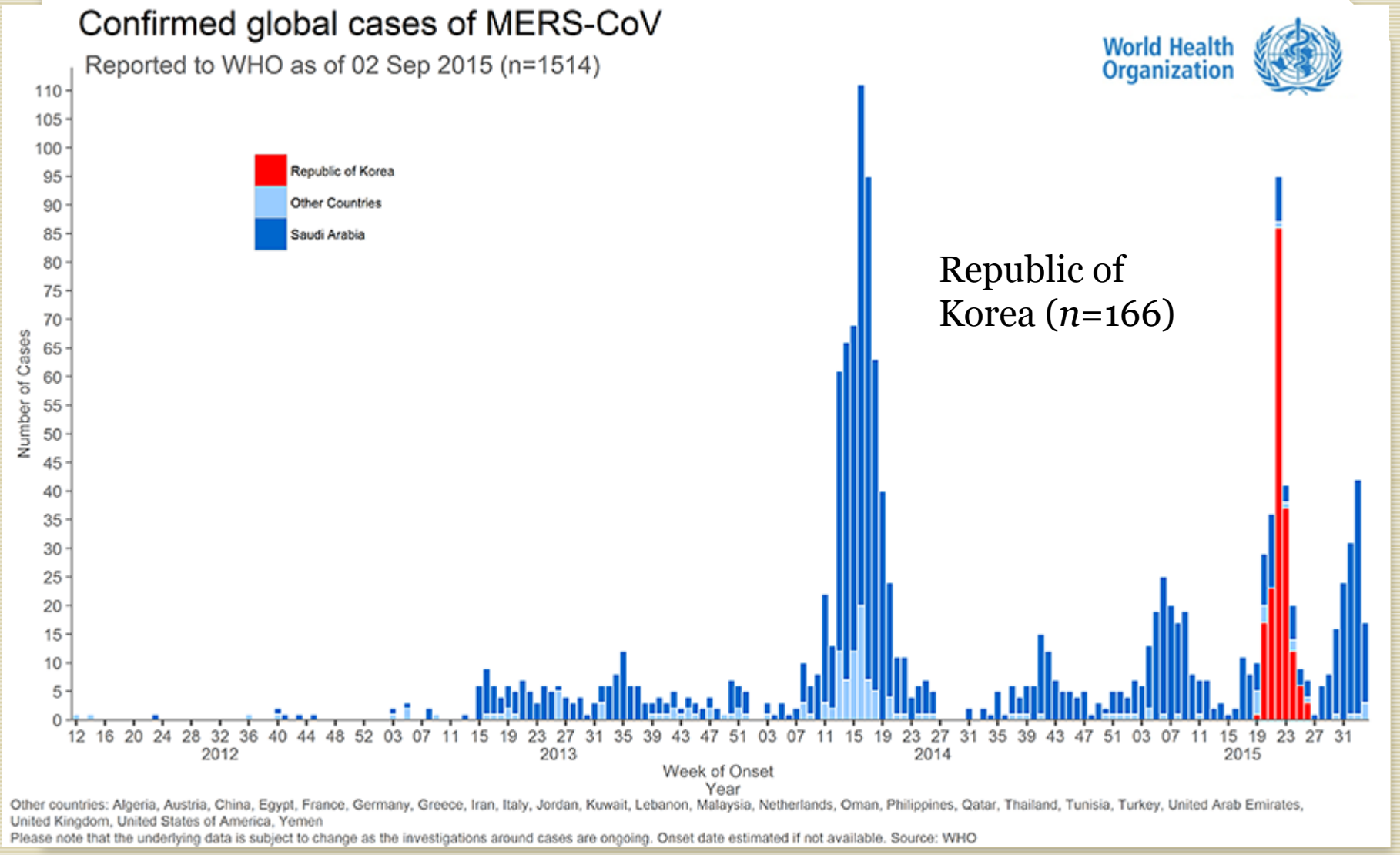
Emerging Disease Threats



MERS-Coronavirus



MERS-Coronavirus



Republic of Korea (*n*=166)

MERS-CoV
What we know!

- Virus is ***different*** than SARS-Coronavirus and seasonal coronavirues.
- 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

NGS

Automation

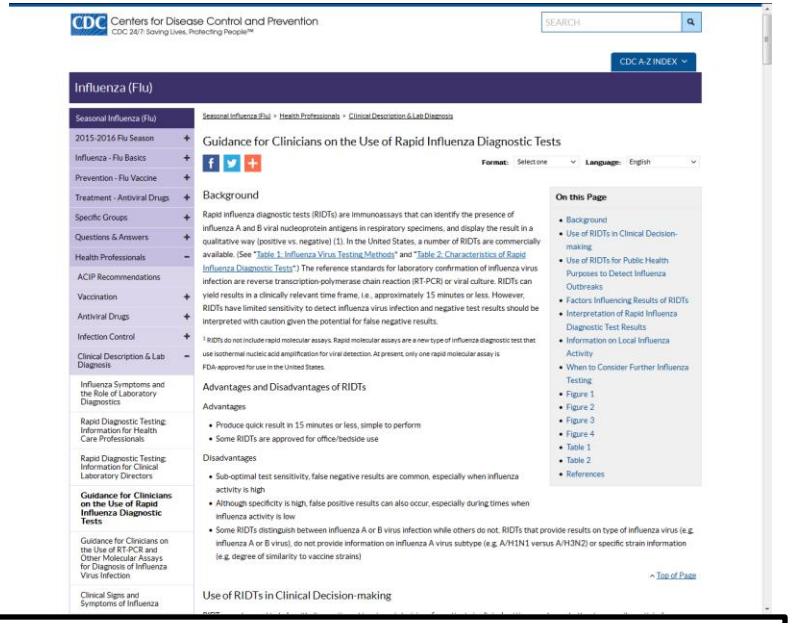
Multiplex PCRs

REGULATIONS

Rapid Molecular

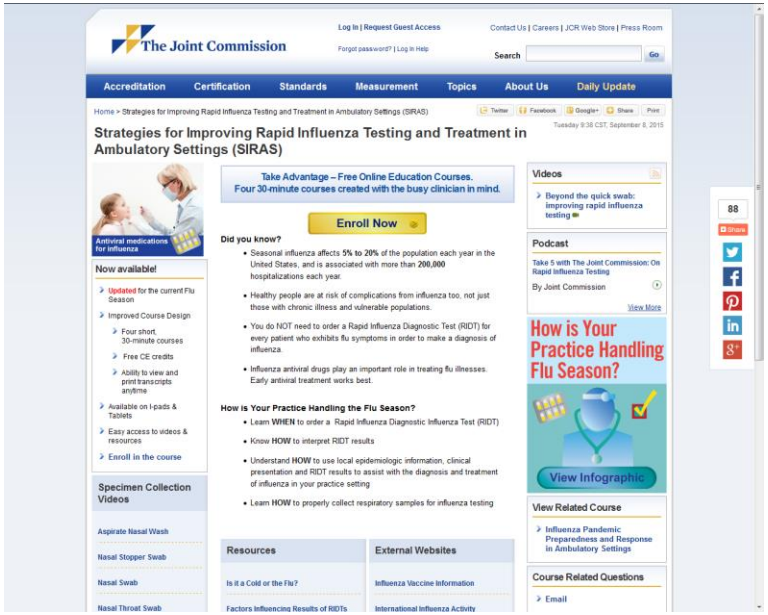
Rapid Influenza Diagnostic Tests (RIDTs)

A perennial discussion



www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm

www.jointcommission.org/siras.aspx



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 **V**irus **A**ntigen **D**etection test

Federal Register / Vol. 79, No. 99 / Thursday, May 22, 2014 / Proposed Rules 29387

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA–2014–N–0440]

Microbiology Devices; Reclassification of Influenza Virus Antigen Detection Test Systems Intended for Use Directly With Clinical Specimens

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify antigen based rapid influenza virus antigen detection test systems intended to detect influenza virus directly from clinical specimens that are currently regulated as influenza virus serological reagents from class I into class II with special controls and into a new device classification regulation.

DATES: Submit either electronic or written comments on the proposed order by August 20, 2014. See section XI for the proposed effective date of any final order that may publish based on this proposed order.

ADDRESSES: You may submit comments, identified by Docket No. FDA–2014–N–0440, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/*Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA–2014–N–0440 for this rulemaking. All comments received may be posted without change to *http://www.regulations.gov*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section.

Docket: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Stephanie Akselrod, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5517, Silver Spring, MD 20993–0002, 301–796–6188.

SUPPLEMENTARY INFORMATION:

I. Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94–295), the Safe Medical Devices Act of 1990 (Pub. L. 101–629), and the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107–250), the Medical Devices Technical Corrections Act (Pub. L. 108–214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110–85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112–144), among other amendments, established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under the FD&C Act, FDA clears or approves the three classes of medical devices for commercial distribution in the United States through three regulatory processes: Premarket approval (PMA), product development protocol, and premarket notification (a premarket notification is generally referred to as a "510(k)" after the section of the FD&C Act where the requirement is found). The purpose of a premarket notification is to demonstrate that the new device is substantially equivalent to a legally marketed predicate device. Under section 513(i) of the FD&C Act, a device is substantially equivalent if it has the same intended use and technological characteristics as a predicate device, or has different technological characteristics but data demonstrate that the new device is as safe and effective as the predicate device and does not raise different issues of safety or effectiveness.

FDA determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 of the regulations (21 CFR part 807). Section 510(k) of the FD&C Act and the implementing regulations in part 807, subpart E, require a person who intends to market a medical device to submit a premarket notification submission to FDA before proposing to begin the introduction, or delivery for introduction into interstate commerce, for commercial distribution of a device intended for human use.

In accordance with section 513(f)(1) of the FD&C Act, devices that were not in commercial distribution before May 28, 1976, the date of enactment of the 1976 amendments, generally referred to as postamendment devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless FDA classifies the device into class I or class II by issuing an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval or the device is reclassified into class I or class II. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act and part 807 of FDA's regulations.

Section 513(f)(2) of the FD&C Act establishes procedures for "de novo" risk-based review and classification of postamendment devices automatically classified into class III by section

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?

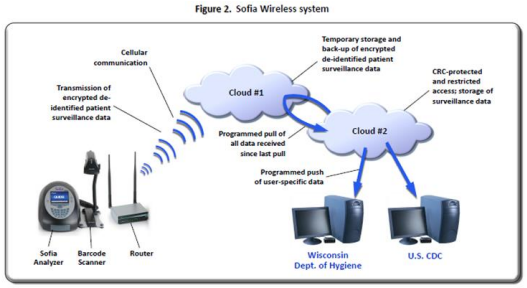
Rapid Influenza Diagnostic Tests
The Next Generation

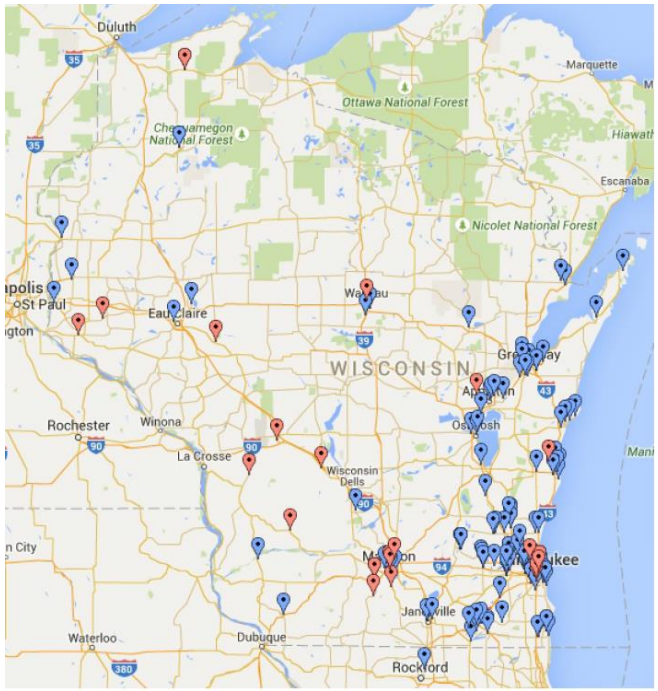
- Incorporates reader instrument
- Reduces subjectivity
- Improved sensitivity
- CLIA-waved
- Data transmission capabilities
- A step in the right direction

Quidel Sofia Influenza A & B

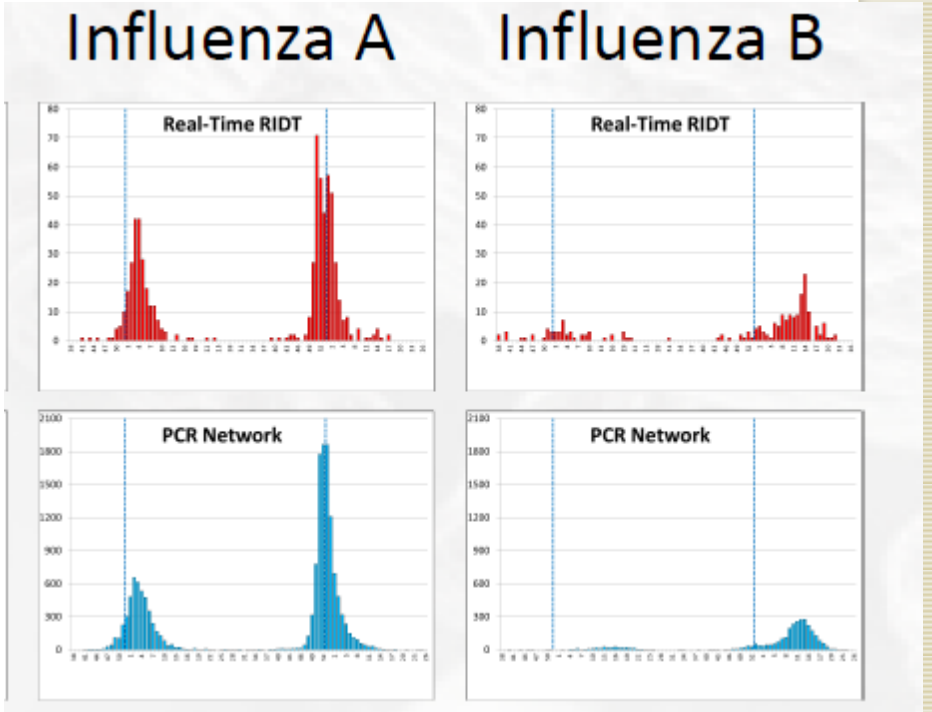
B-D Veritor Influenza A & B

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

http://www.alere.com/us/en.html

Influenza Molecular Tests - PCR

Commercially Available - FDA Cleared

Table 1. FDA-cleared RT-PCR Assays and Other Molecular Assays for Influenza Viruses

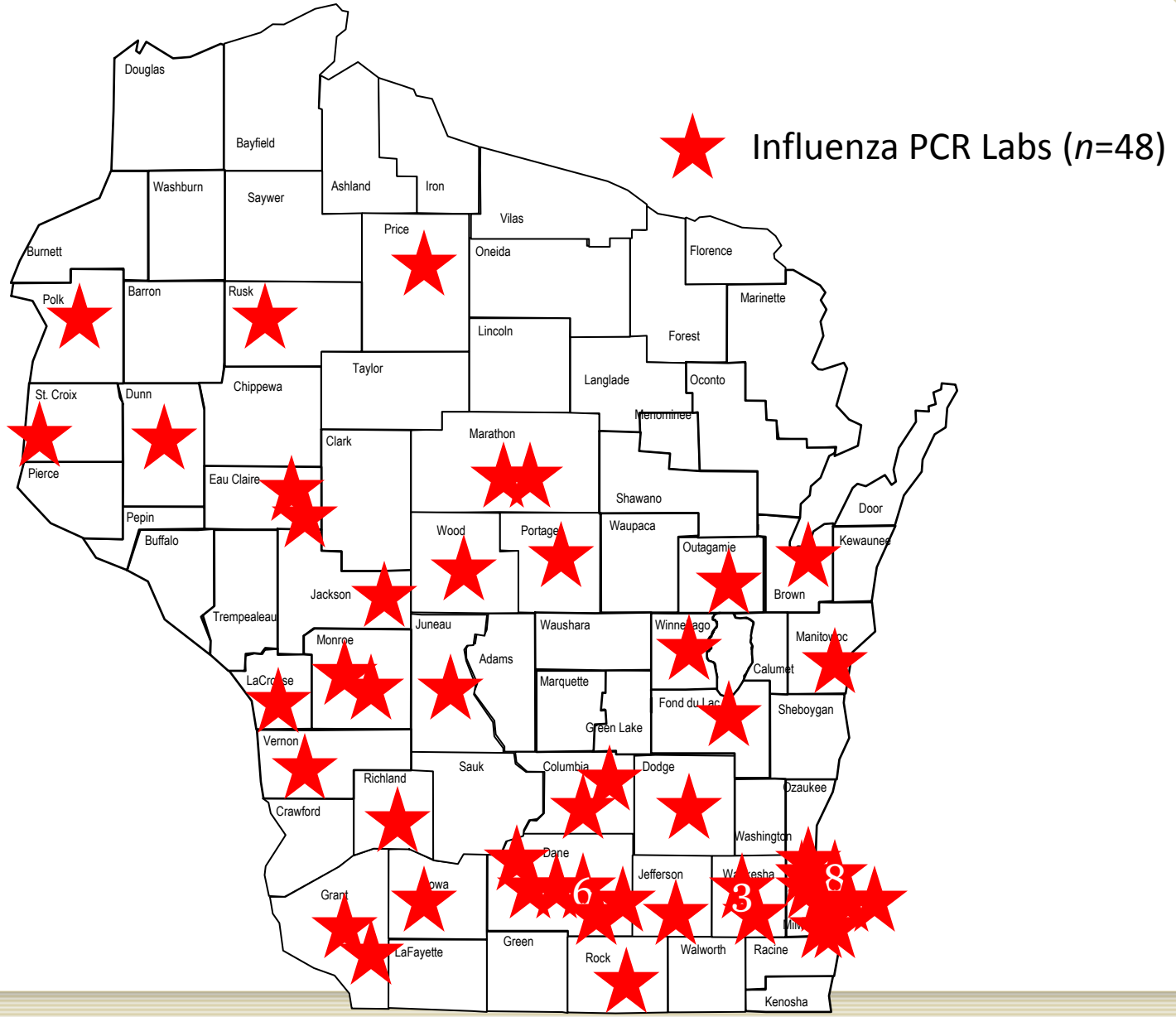
Products	Manufacturer(s)	Influenza Virus Type Detected	Influenza A Virus Subtype(s) Differentiated	Other Respiratory Viruses Differentiated	Acceptable Specimens[1]	Test Time[2], Complexity[3]
CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel[4]	CDC Influenza Division	Influenza A and B	H1, H3, 2009 H1, H5N1 (Asian lineage)	None	Nasopharyngeal swabs, nasal swabs, nasal aspirates, nasal washes, dual nasopharyngeal/ throat swabs, bronchoalveolar lavages, tracheal aspirates, bronchial washes, and viral culture	~4 h/ High
Cepheid Xpert Flu Assay	Cepheid	Influenza A and B	2009 H1	None	Nasopharyngeal swabs, nasal aspirates, and nasal washes.	1.0 h/ Moderate
eSensor® Respiratory Viral Panel (RVP)	Clinical Micro Sensors, Inc. dba GenMark Diagnostics, Inc.	Influenza A and B	H1, H3, 2009 H1	Respiratory Syncytial Virus subtype A, Respiratory Syncytial Virus subtype B, Parainfluenza 1, 2, and 3 virus, Human Metapneumovirus, Adenovirus Species B/E, Adenovirus Species C, and Human Rhinovirus	Nasopharyngeal swabs	~8 h/ High
FilmArray Respiratory Panel	Idaho Technologies	Influenza A and B	H1, H3, 2009 H1	Respiratory Syncytial Virus, Parainfluenza 1, 2, 3 and 4 virus, Human Metapneumovirus, Rhinovirus/Enterovirus, Adenovirus, Coronavirus HKU1, Coronavirus NL63	Nasopharyngeal swabs	1.0 h/ Moderate
Ibis PLEX-ID Flu	Ibis/Abbott	Influenza A and B	H1, H3, 2009 H1	None	Nasopharyngeal swabs	~8 h/ High
iQuum Liat Influenza A/B Assay	iQuum	Influenza A and B	None	None	Nasopharyngeal swabs	0.5 h/ Moderate
Prodesse PROFLU™+	GenProbe	Influenza A and B	None	Respiratory Syncytial Virus	Nasopharyngeal swabs	<4h/ High
Prodesse ProFAST™+	GenProbe	Influenza A	H1, H3, 2009 H1	None	Nasopharyngeal swabs	<4h/ High
Quidel Molecular Influenza A+B Assay	Quidel	Influenza A and B	None	None	Nasopharyngeal swabs and nasal swabs	~4 h/ High
Qiagen Artus Influenza A/B Rotor-gene RT-PCR kit	Qiagen	Influenza A and B	None	None	Nasopharyngeal swabs	~4 h/ High
Simplexa™ Flu A/B & RSV	Focus Diagnostics, 3M	Influenza A and B	None	RSV	Nasopharyngeal swabs	<4h/ High
Simplexa™ Flu A/B & RSV Direct	Focus Diagnostics, 3M	Influenza A and B	None	RSV	Nasopharyngeal swabs	<2h/ Moderate
Simplexa™ Influenza A H1N1 (2009)	Focus Diagnostics, 3M	Influenza A	2009 H1	None	Nasopharyngeal swabs, nasal swabs, and nasopharyngeal aspirates	<4h/ High
U.S. Army JBAIDS Influenza A/H5[5]	Idaho Technologies	Influenza A	H5N1 (Asian Lineage)	None	Nasopharyngeal and throat swabs	~4 h/ High
U.S. Army JBAIDS Influenza A&B Detection Kit[5]	Idaho Technologies	Influenza A and B	None	None	Nasopharyngeal swabs and Nasopharyngeal washes	~4 h/ High
U.S. Army JBAIDS Influenza A Subtyping Kit[5]	Idaho Technologies	Influenza A	H1, H3, 2009 H1	None	Nasopharyngeal swabs and Nasopharyngeal washes	~4 h/ High
Verigene® Respiratory Virus Nucleic Acid Test	Nanosphere, Inc	Influenza A and B	None	Respiratory Syncytial Virus subtype A, Respiratory Syncytial Virus subtype B	Nasopharyngeal swabs	3.5 h/ Moderate
Verigene® Respiratory Virus Plus Nucleic Acid Test (RV+)	Nanosphere, Inc	Influenza A and B	H1, H3, 2009 H1	Respiratory Syncytial Virus subtype A, Respiratory Syncytial Virus subtype B	Nasopharyngeal swabs	3.5 h/ Moderate
xTAG® Respiratory Viral Panel (RVP)	Luminex Molecular Diagnostics Inc.	Influenza A and B	H1, H3	Respiratory Syncytial Virus subtype A, Respiratory Syncytial Virus subtype B, Parainfluenza 1, 2, and 3 virus, Human Metapneumovirus, Rhinovirus, and Adenovirus	Nasopharyngeal swabs	~8 h/ High
xTAG® Respiratory Viral Panel Fast (RVP FAST))	Luminex Molecular Diagnostics Inc.	Influenza A and B	H1, H3	Respiratory Syncytial Virus Human Metapneumovirus, Rhinovirus, and Adenovirus	Nasopharyngeal swabs	~6 h/ High

[1] These specimen types are specified in product package inserts cleared by the U.S. Food and Drug Administration (FDA)
[2] Test Time is inclusive of actual test time and is exclusive of transport, handling, laboratory run schedules, and generating results. Timing may vary depending on extraction process used. Contact laboratory for expected turn-around time.
[3] Clinical Laboratory Improvement Amendments require categorization of tests as waived, moderate or high complexity.
[4] Available only to qualified DoD laboratories, U.S. public health laboratories, and NREVSS collaborating laboratories.

- 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

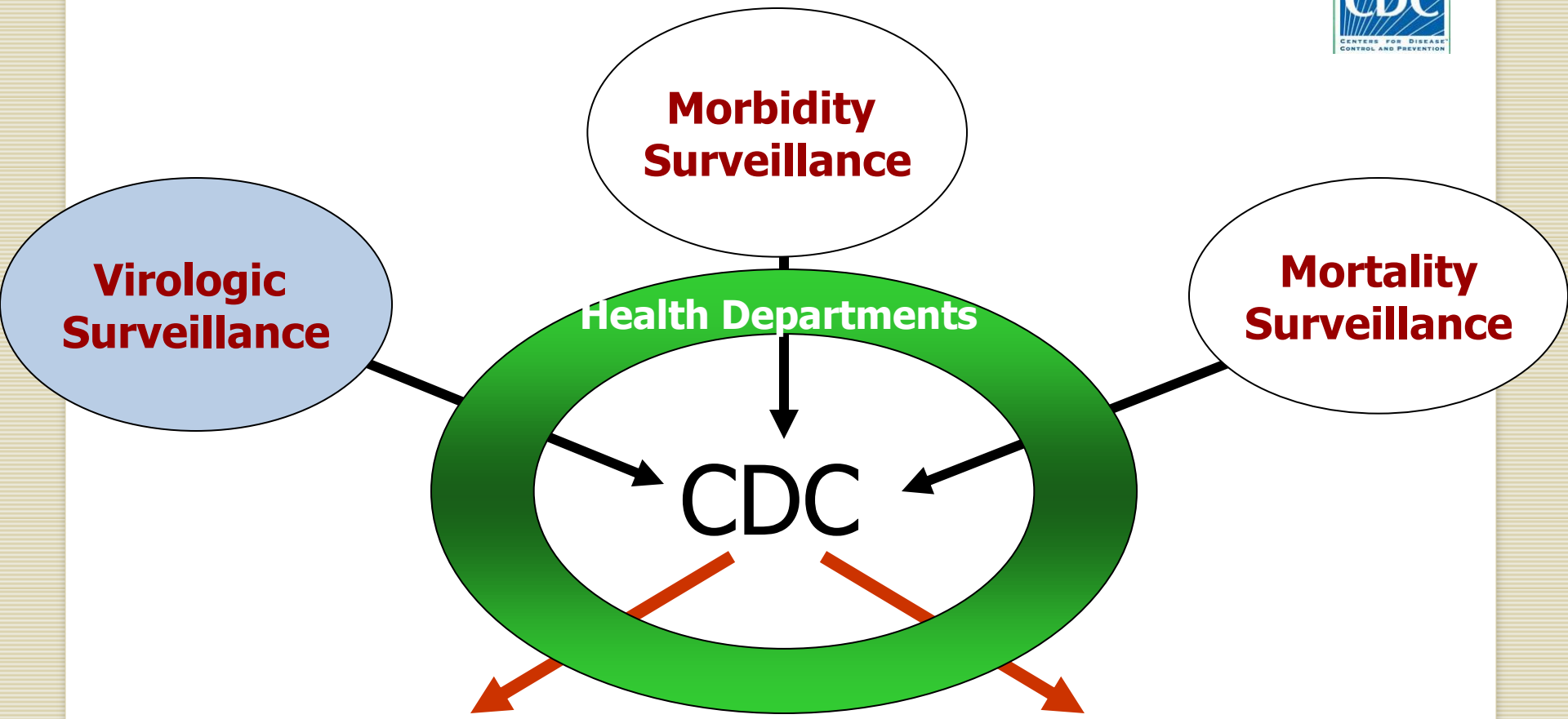
http://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm

Wisconsin Labs with Flu PCR Capacity, 2015



U.S. Influenza Surveillance

www.cdc.gov/flu/weekly

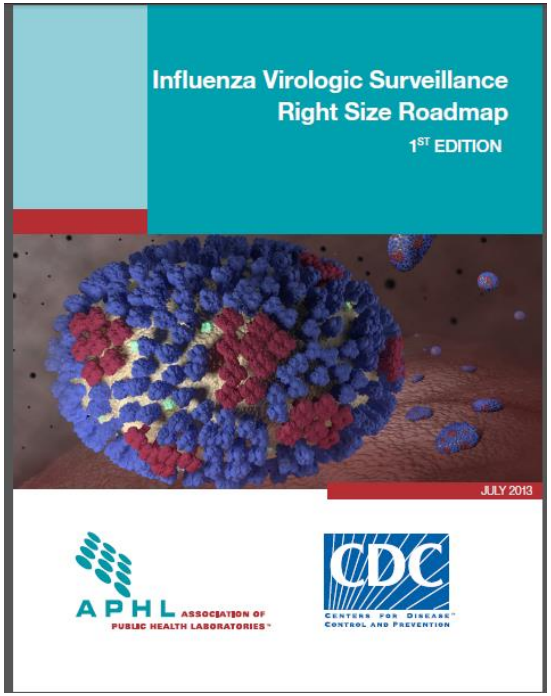


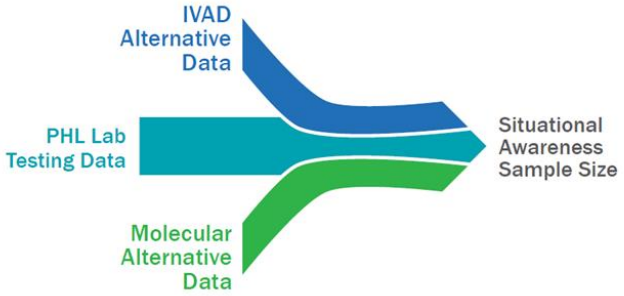
FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

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

http://www.aphl.org/aphlprograms/infectious/influenza/Pages/Influenza-Virologic-Surveillance-Right-Size-Roadmap.aspx

Influenza Virologic Surveillance

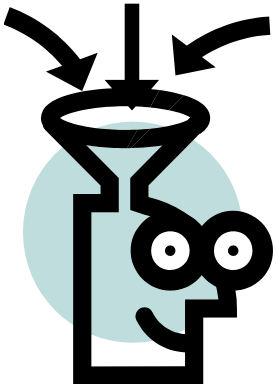
Increasing Role for the Clinical Lab

- Provide situational awareness
  - **Clinical lab testing data** → (Via WSLH or directly) **CDC**

- Detect novel or reassortant viruses
- Inform vaccine strain selection
- Detect and monitor antiviral resistance
  - **Specimens/isolates from clinical labs** → **WSLH** → **CDC**

Laboratory Surveillance Plan, 2015-2016

What YOU need to know!



Influenza Surveillance in Wisconsin

Multi-element approach

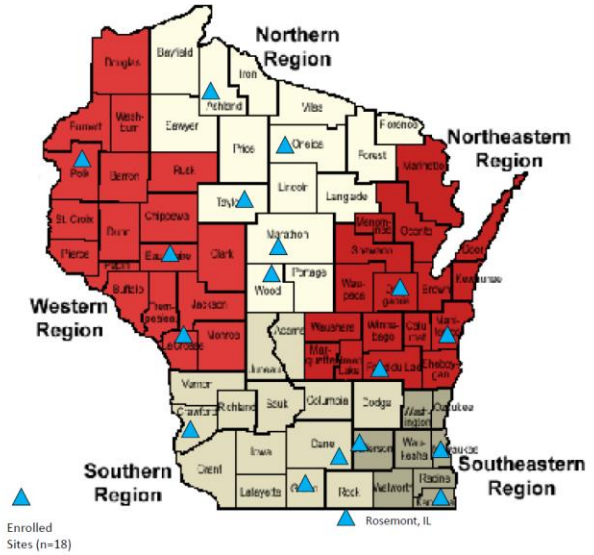
1. Rapid Influenza Diagnostic Testing (RIDT) Sites
   - >50% of Influenza testing in WI.
   - Confirmatory testing during periods of low prevalence!

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.

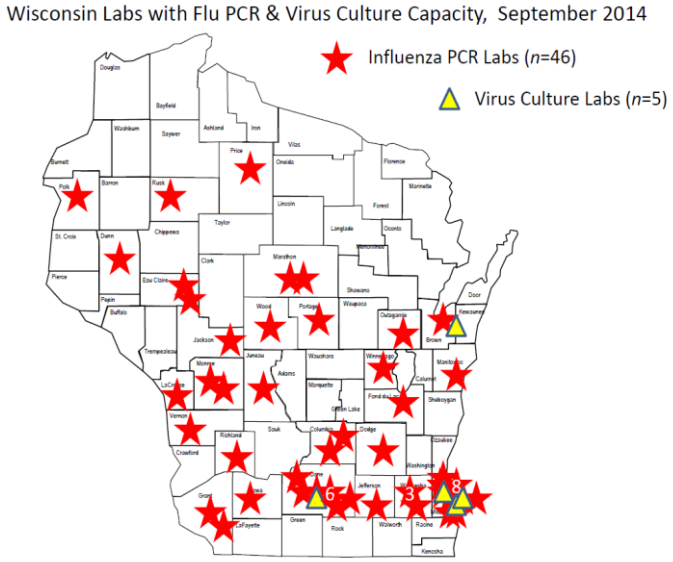


Request to continue to submit the first 3 specimens per week with influenza test requests to WSLH.

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

Gastrointestinal Pathogens PCR Testing

Please report the number of specimens tested and the number positive.

	Number Tested	Number Positive
Aeromonas		
Campylobacter		
Clostridium difficile (Toxin A/B)		
E. coli O157		
Enteroaggregative E. coli (EAEC)		
Enteropathogenic E. coli (EPEC)		
Enterotoxigenic E. coli (ETEC)		
Plesiomonas shigelloides		
Salmonella		
Shiga-like toxin-producing E. coli (STEC)		
Shigella		
Shigella/Enteroinvasive E. coli (EIEC)		
Vibrio		
Vibrio cholerae		
Yersinia enterocolitica		
Adenovirus 40/41		
Astrovirus		
Norovirus GI/GII		
Rotavirus A		
Sapovirus		
Cryptosporidium		
Cyclospora cayetanensis		
Entamoeba histolytica		
Giardia lamblia		

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

Back Next

75%

2. FAX reporting

Please FAX by **noon Wednesday** of each week to:
Erik Reisdorf or Mary Wedig, Wisconsin State Laboratory of Hygiene at 608-265-9091

Contact Mary Wedig (608-890-0353) or Erik Reisdorf (608-262-1021) 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.**

WISCONSIN TESTING FAX REPORT

Identification Number: **Your Institution's Name, Address & Telephone Number:**

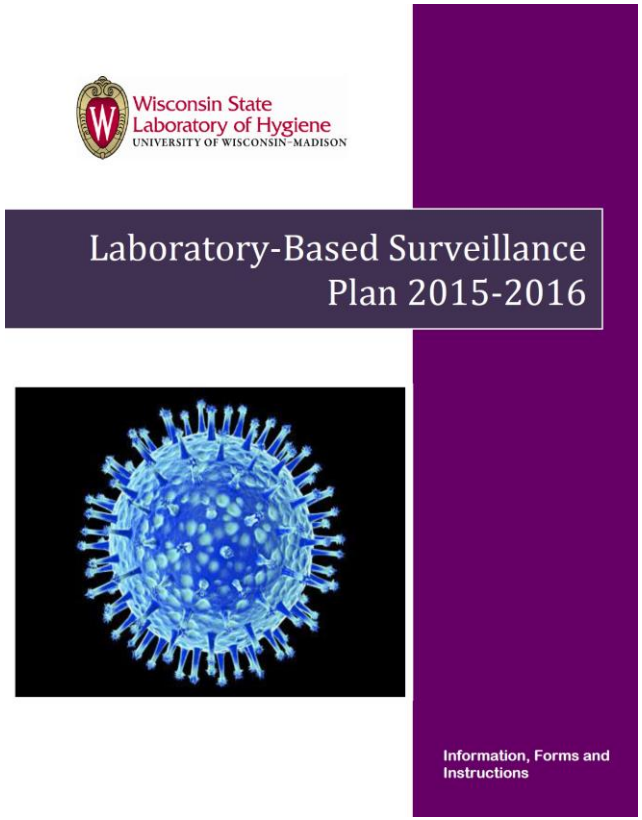
Change of Institution Address: _____

Report For Week (Sunday through Saturday) Ending: _____

Rapid Testing - Virus / Bacteria	Number Tested	Number Positive					
		Influenza			RSV	Rota	Strep
		A	B	A & B			
Influenza A and B (Differentiated) *Testing provides 2 results – 1 result for A & 1 result for B*							
Influenza (Type Not Known) *Testing provides 1 result; could be A or B*				Unknown			
RSV							
Rotavirus							
Rapid Strep (Streptococcus Group A)							

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