2015-16 Influenza Activity and Clinical Recommendations

Clinician Outreach and Communication Activity (COCA) Conference Call

February 16, 2016

National Center for Immunization & Respiratory Diseases
Influenza Division

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Objectives

At the conclusion of this session, the participant will be able to:

- Describe the current status of influenza activity in the United States
- Discuss the circulating influenza strains seen this season and the implications for clinicians
- Discuss the use of influenza diagnostic tests and their role in clinical care
- Discuss antiviral treatment and implications for patient evaluation, treatment and testing

Today's Presenter

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Medical Officer

Epidemiology and Prevention Branch, Influenza Division

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Influenza Season Timing

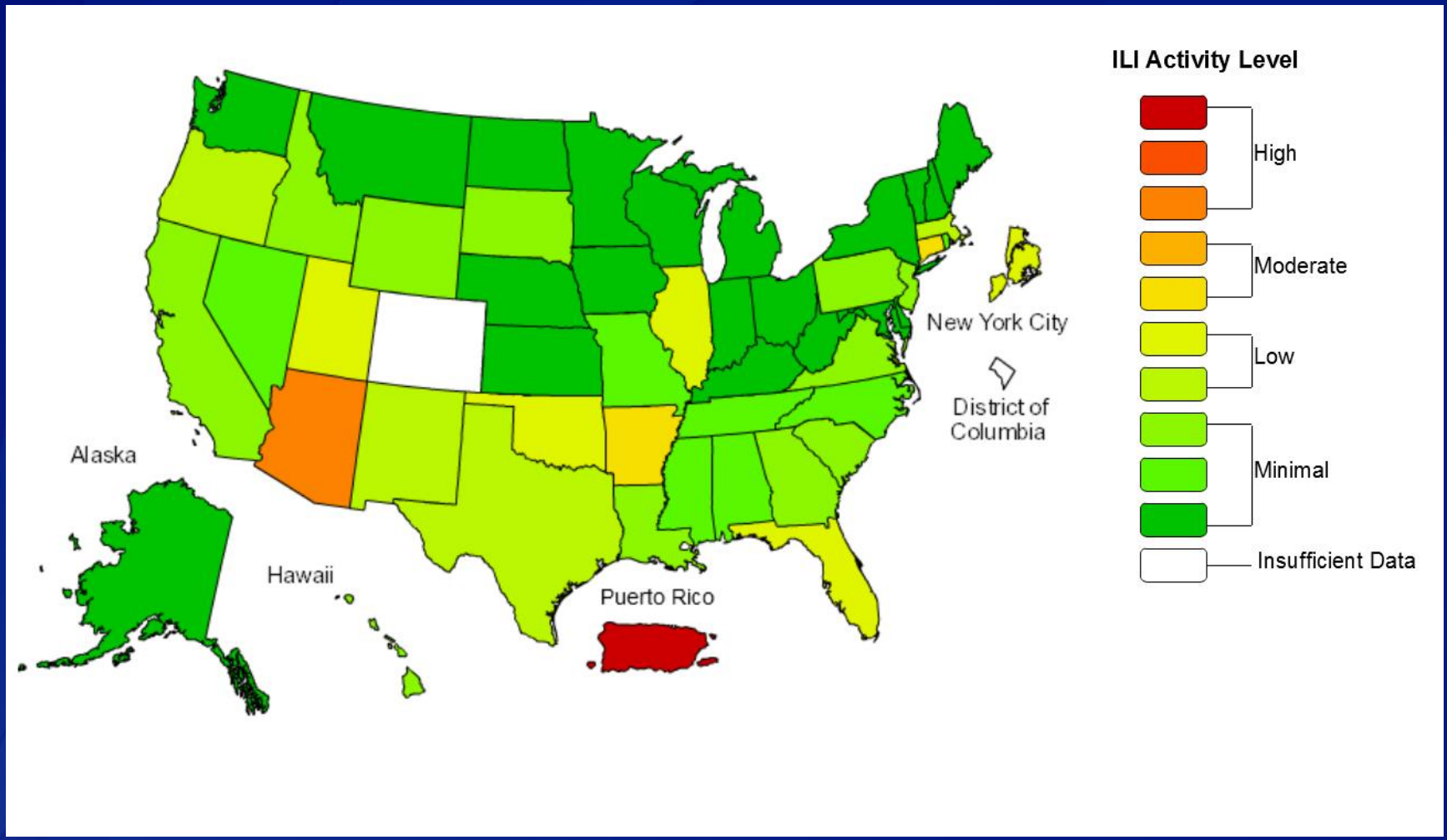
- Timing of influenza activity in the United States can be variable
- Most often peaks between January and March
- During the three most recent influenza seasons, activity began relatively early, and peaked in late December and early January.
- The current season activity began to increase in mid-December, a more typical influenza activity pattern.

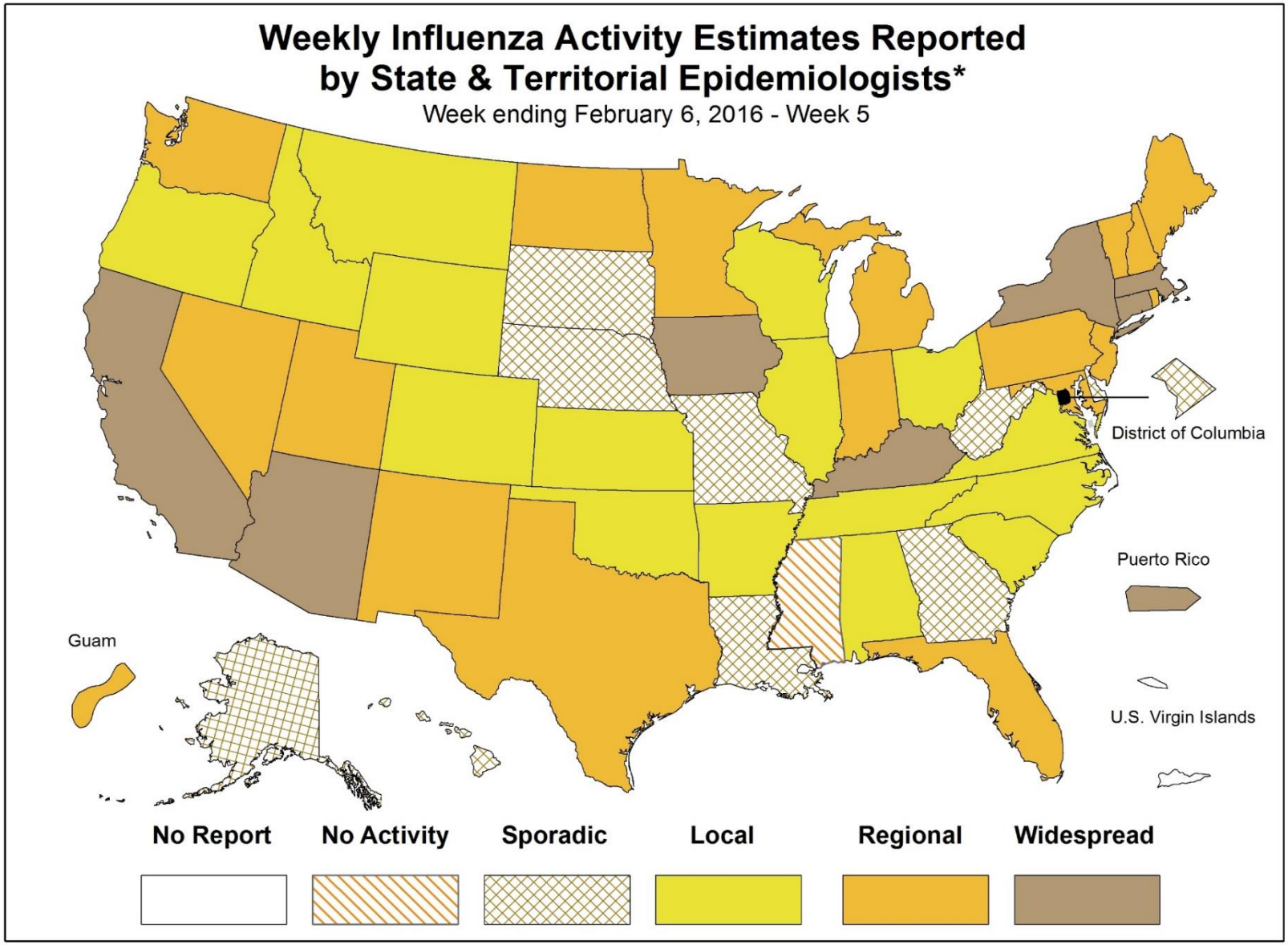
SUMMARY OF 2015-16 INFLUENZA ACTIVITY

National Surveillance

http://www.cdc.gov/flu/weekly/fluactivitysurv.htm

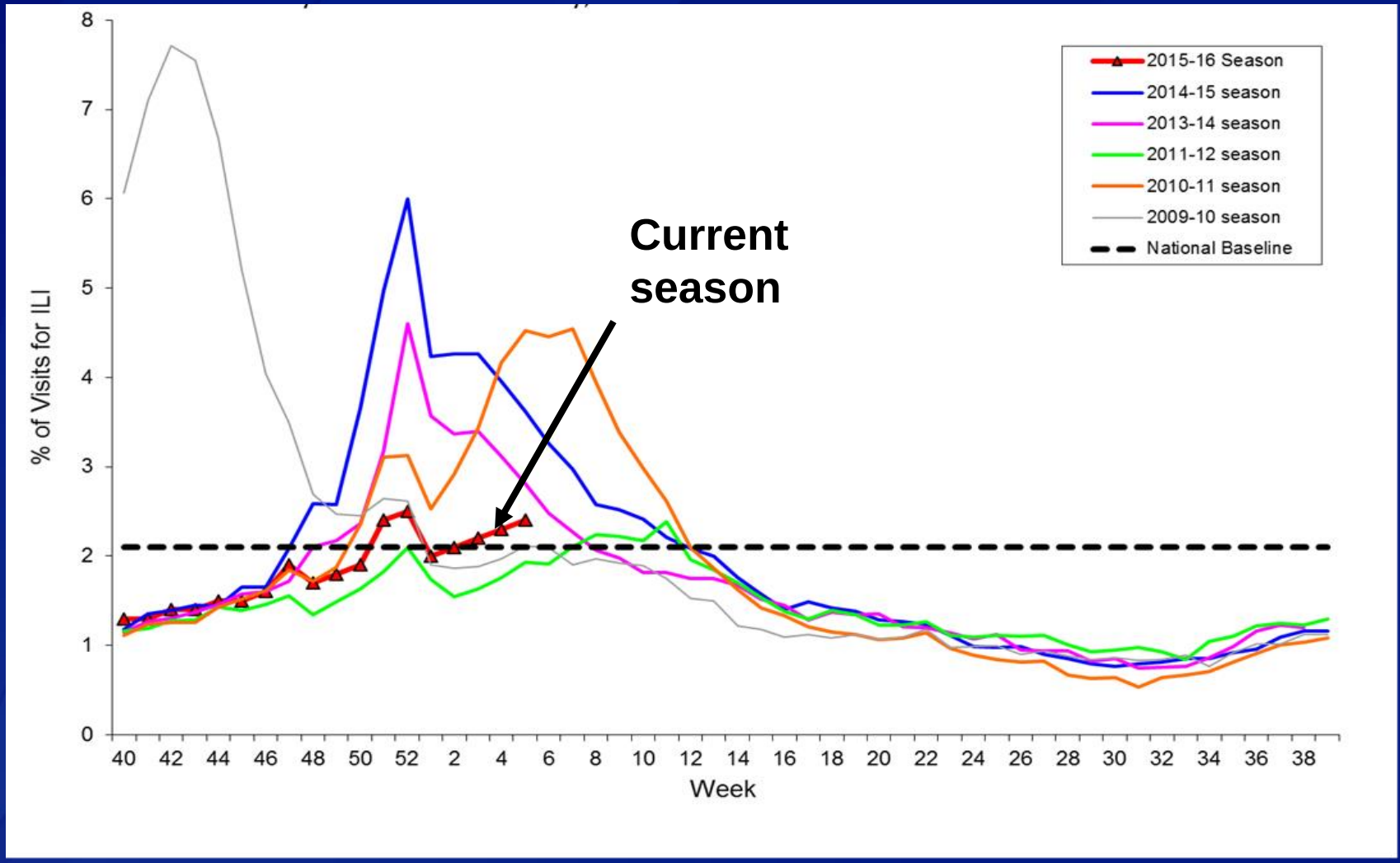
Influenza-Like Illness (ILI) Activity Level Indicator Determined by Data Reported to ILINET, week ending February 6,2016



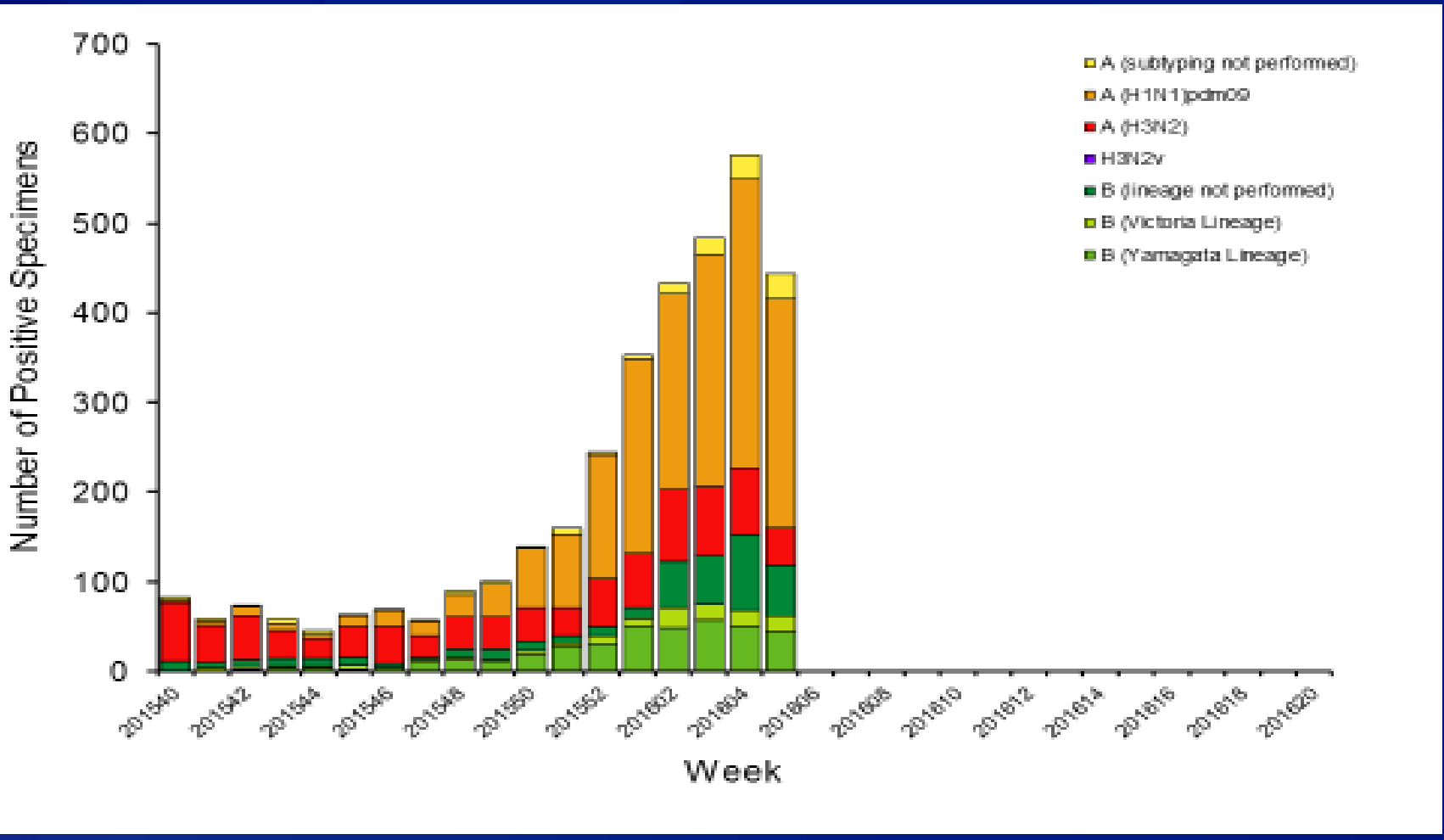


* This map indicates geographic spread & does not measure the severity of influenza activity

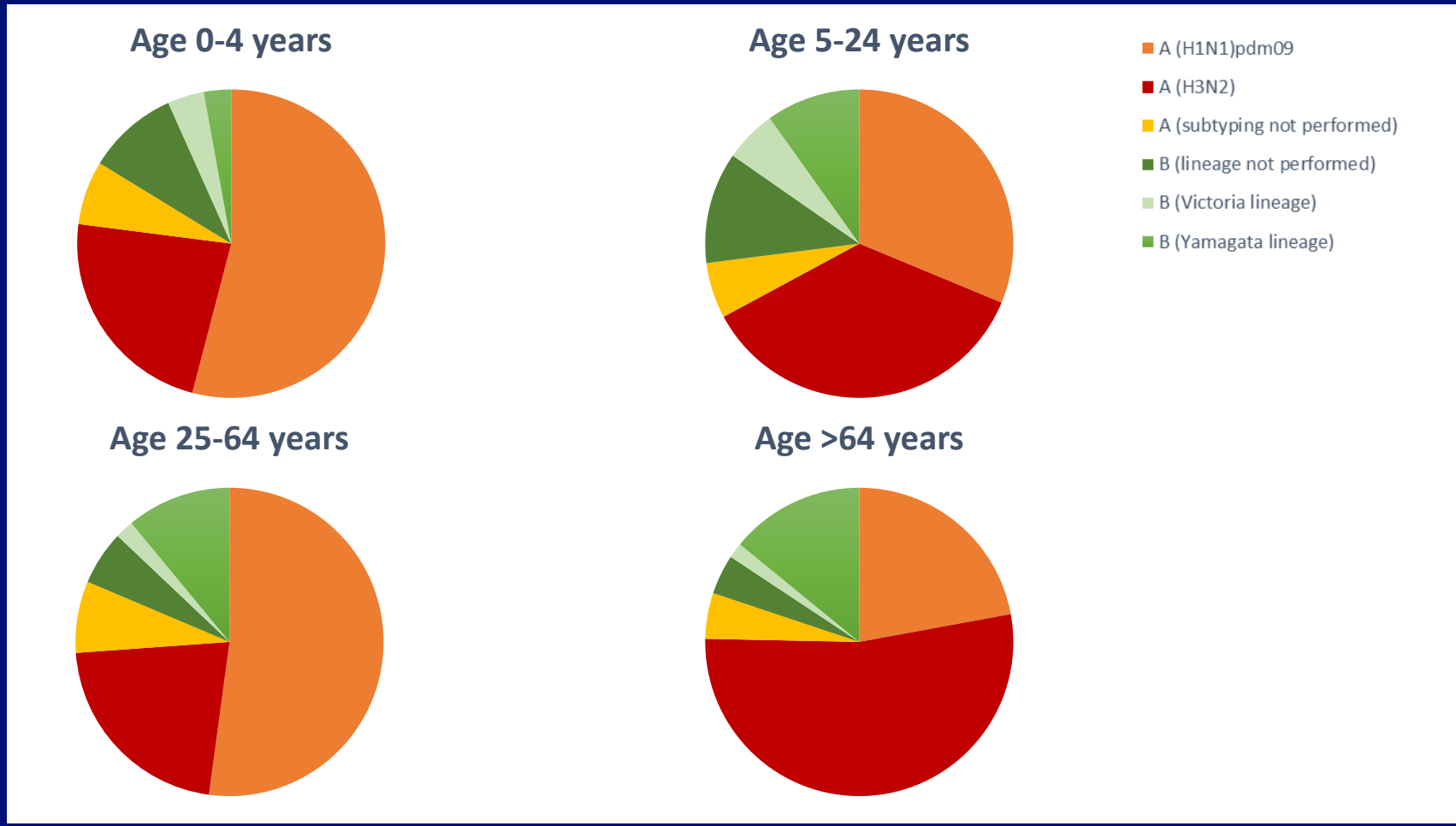
Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient ILI Surveillance Network (ILINet), 2015-2016 and Selected Previous Seasons



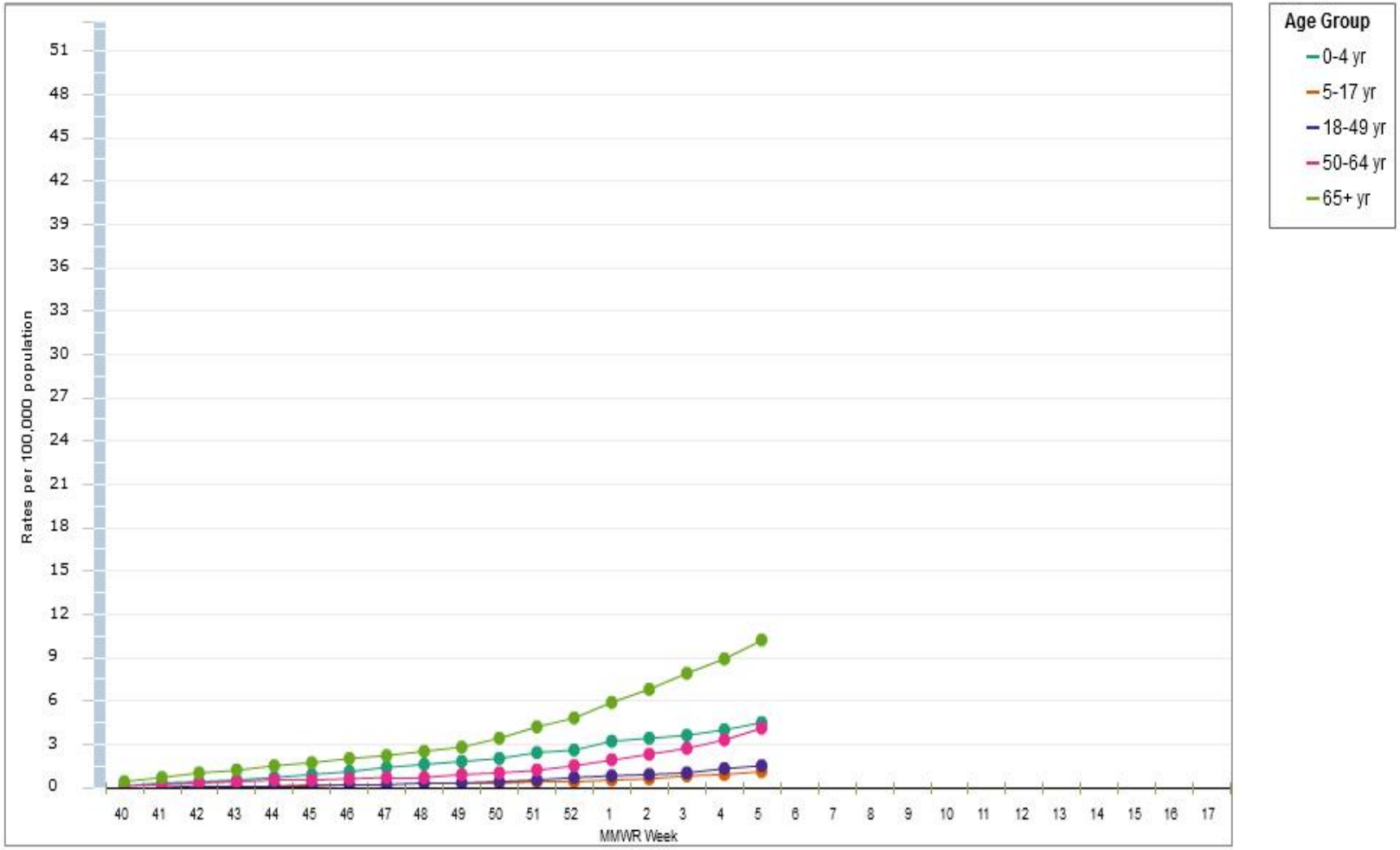
Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, 2015–2016 Season



Age group distribution of influenza positive specimens* reported by public health laboratories — October 4, 2015 to February 6, 2016

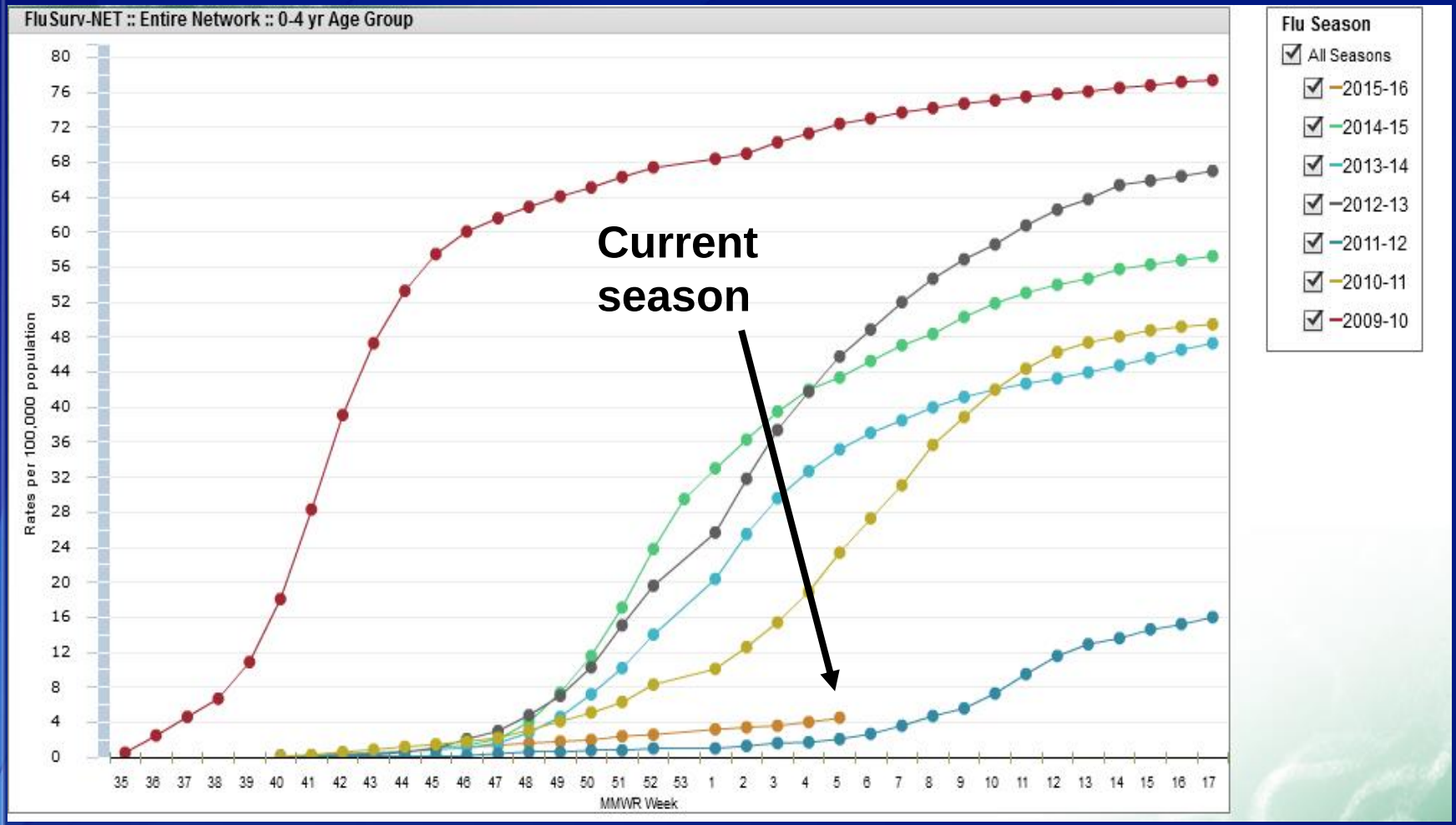


Laboratory-Confirmed Influenza Hospitalizations
Preliminary cumulative rates as of Feb 6, 2016



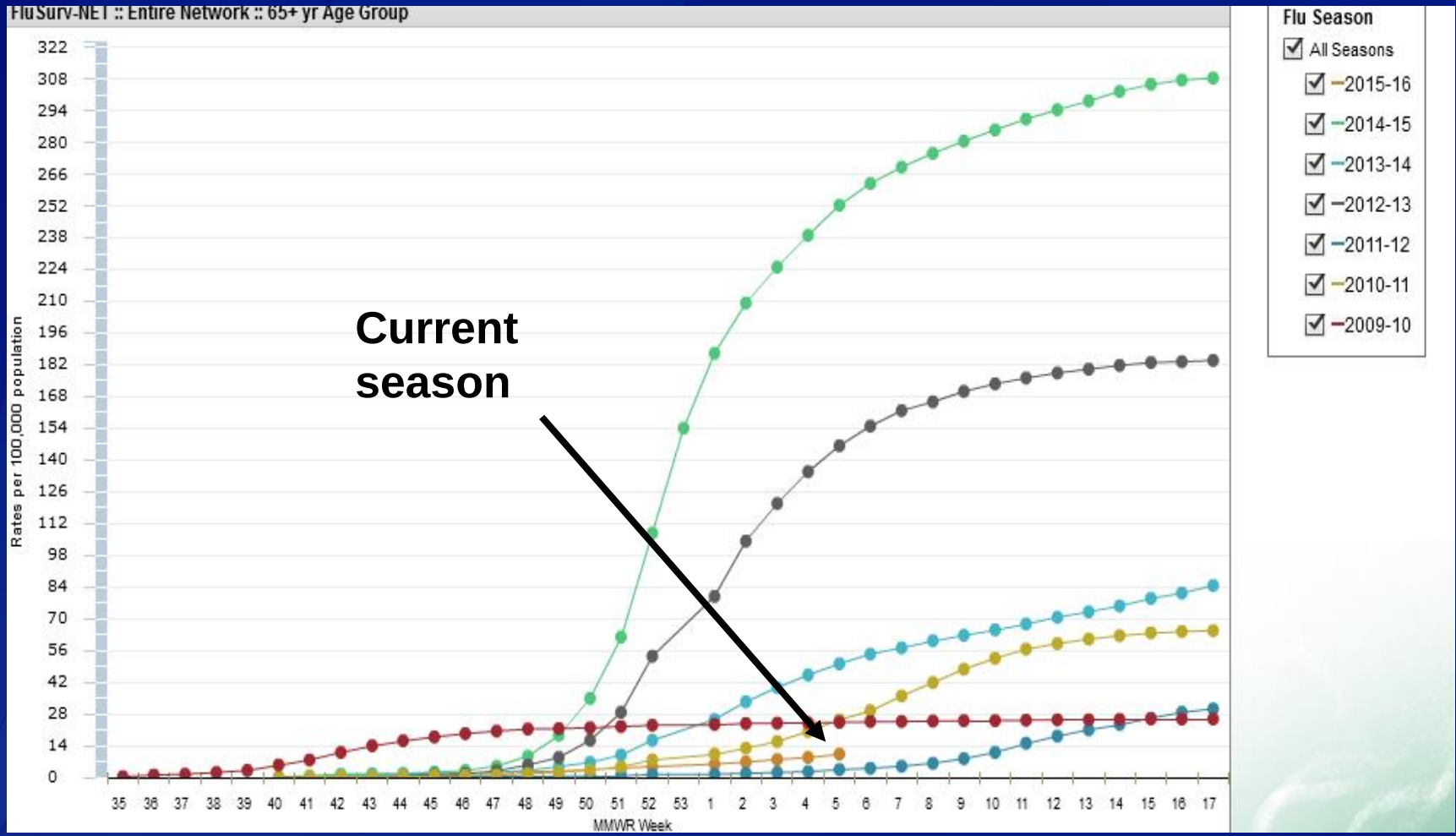
Laboratory-Confirmed Influenza Hospitalizations, Children 0 to 4 years

Preliminary cumulative rates as of Feb 6, 2016

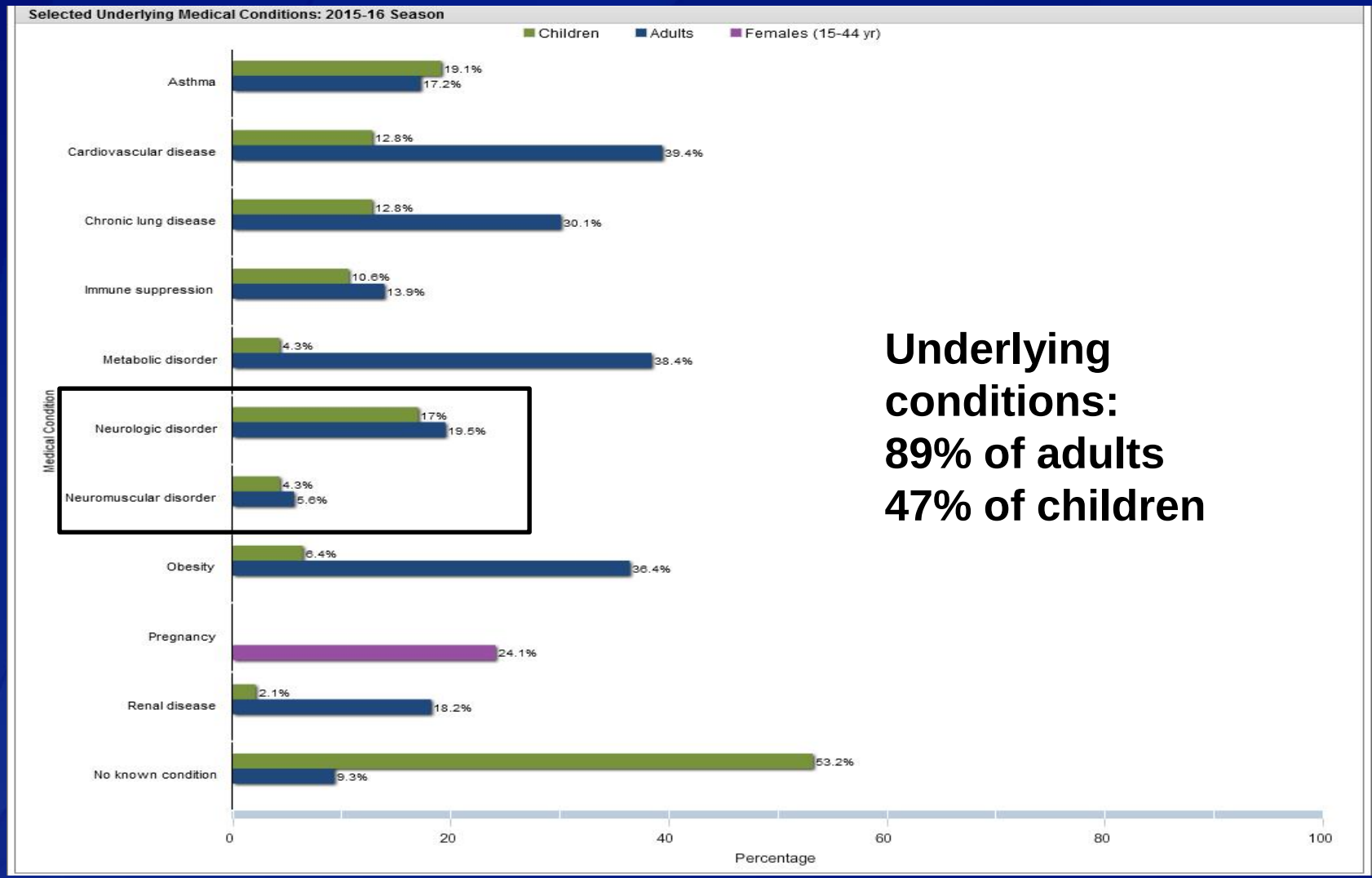


Laboratory-Confirmed Influenza Hospitalizations, Adults ≥65 years

Preliminary cumulative rates as of Feb 6, 2016



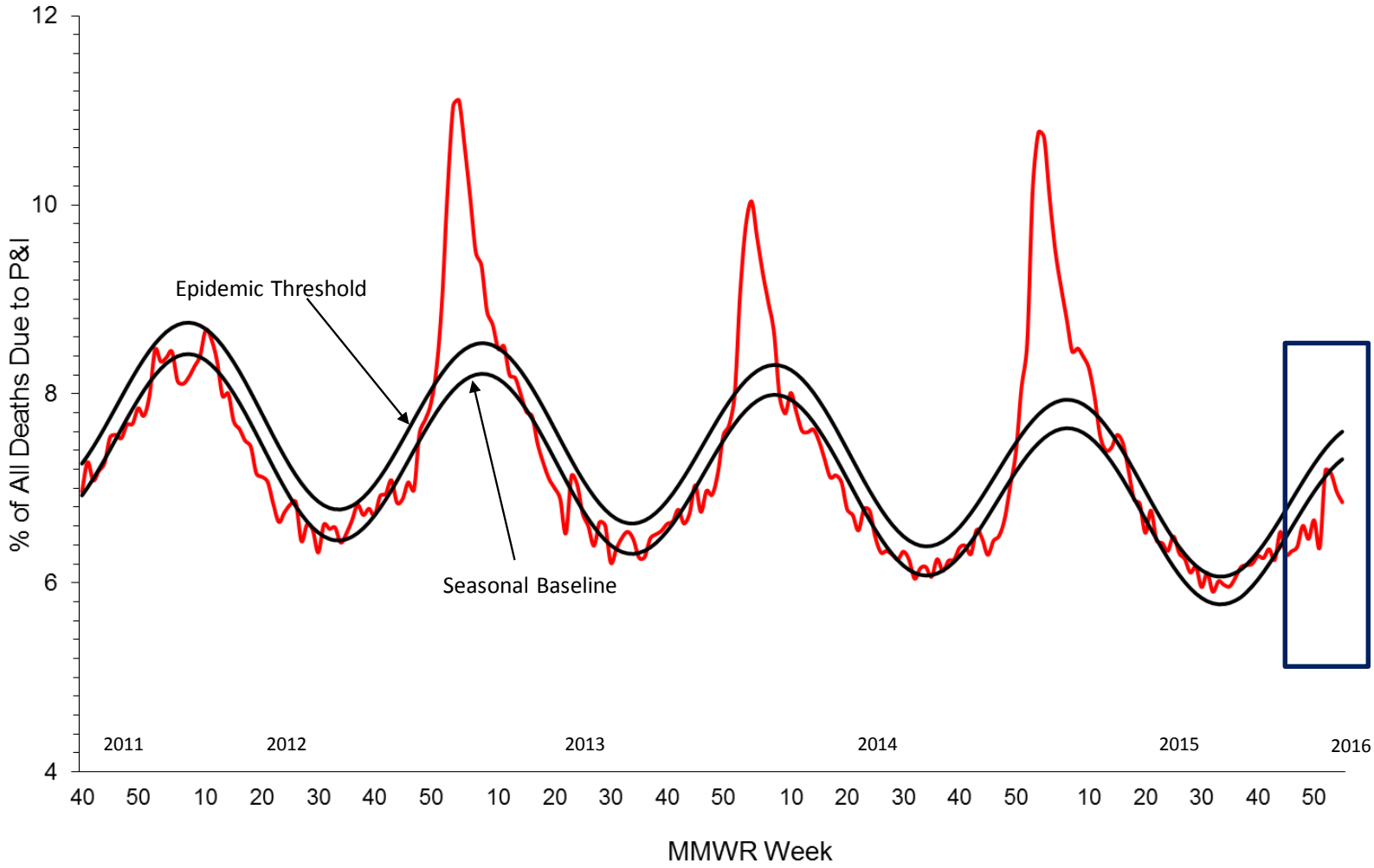
Laboratory-Confirmed Influenza Hospitalizations
Preliminary data as of Feb 6



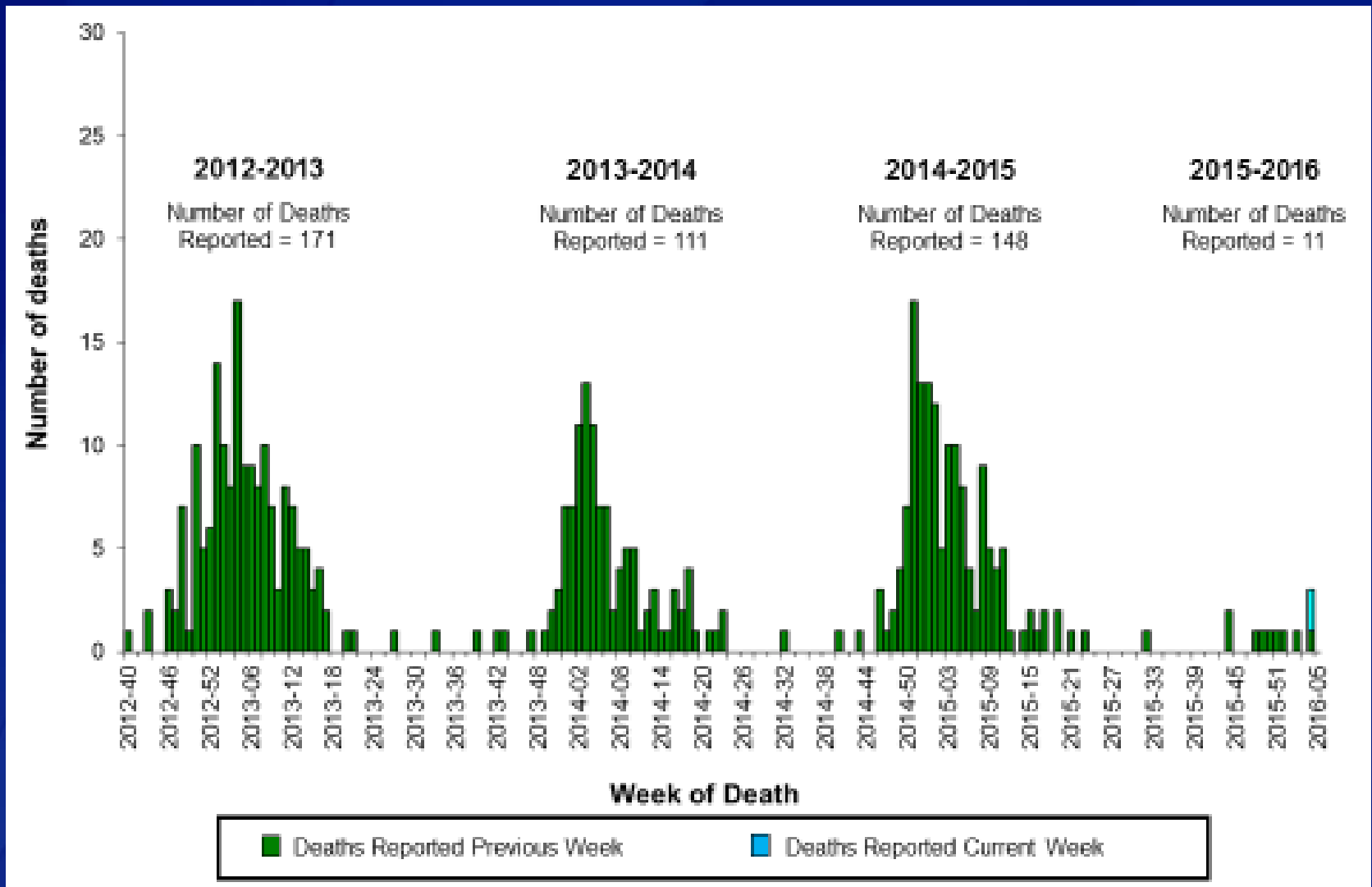
Underlying conditions:
89% of adults
47% of children

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending January 23, 2016, as of February 11, 2016



Number of Influenza-Associated Pediatric Deaths by Week of Death: 2012-2013 season to present



Reports of severe disease

- **In recent weeks, CDC has received reports from several states of severe respiratory illnesses among young- to middle-aged adults**
  - Patients requiring intubation
  - Fatalities
- **Infected with influenza A(H1N1)pdm09 viruses**

Reports of severe disease (cont.)

- **Some of these patients reportedly tested negative for influenza by rapid influenza diagnostic tests (RIDTs)**
  - Influenza diagnosis was made later with molecular assays
- **Most of these patients were reportedly unvaccinated.**

This is an official
CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
Monday, February 01, 2016, 08:50 EST (8:50 AM EST)
CDCHAN-00387

Flu Season Begins: Severe Influenza Illness Reported

CDC urges rapid antiviral treatment of very ill and high risk suspect influenza patients without waiting for testing

Reminders to clinicians

- **H1N1 virus infection in the past has caused severe illness in some children and young- and middle-aged adults.**
- **Promptly start antiviral treatment of severely ill and high-risk patients if influenza is suspected or confirmed.**
- **A negative rapid influenza antigen diagnostic test does not exclude a diagnosis of influenza**
  - Treatment should not be delayed even for a few hours to wait for the results of testing

Influenza Vaccinations

- Most of the influenza viruses characterized from October to February are antigenically similar to vaccine viruses strains recommended for inclusion in the 2015-16 Northern Hemisphere vaccines.
- No interim vaccine effectiveness (VE) estimates available yet.
- Clinicians should continue to vaccinate patients this season for as long as influenza viruses are circulating.
- Annual vaccination recommended for all persons ≥6 months

Summary: Influenza season to date

- **Activity began to increase in late December 2015**
- **Continues to increase slowly through early February 2016**
- **Influenza A(H1N1) viruses are currently the most frequently identified viruses**
  - Reports of severe disease in some children and young and middle-aged adults

Testing Guidance

IDSA GUIDELINES

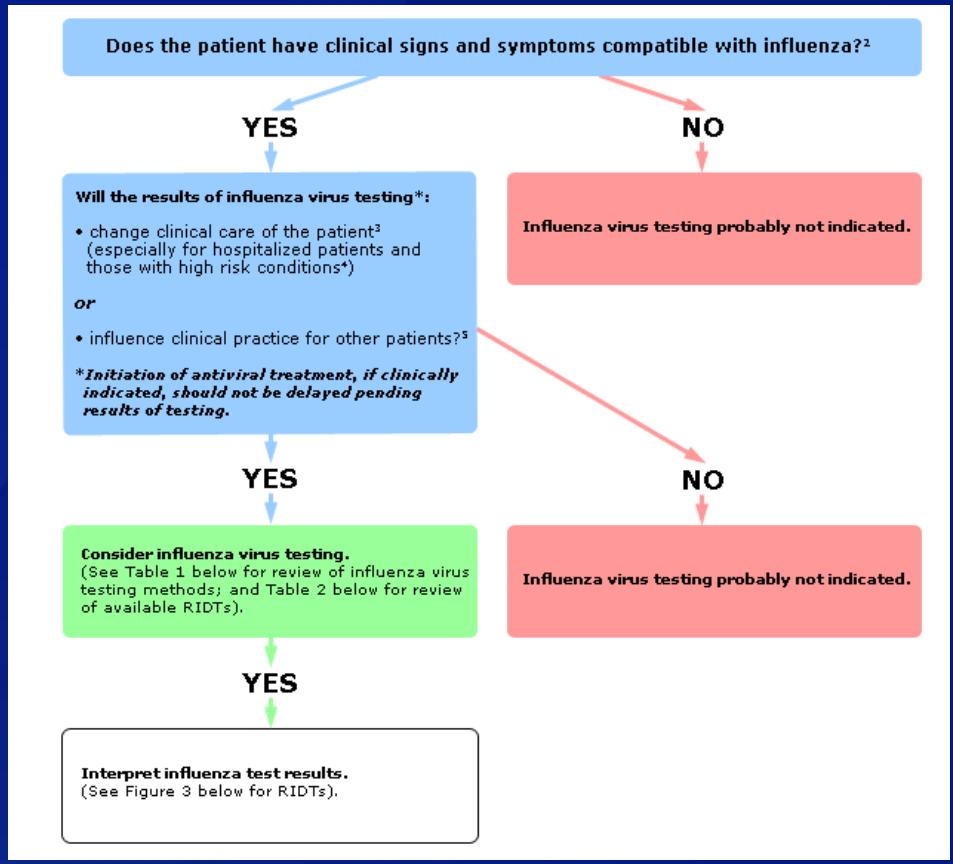
Seasonal Influenza in Adults and Children—Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America

Persons who should be tested during the flu season:

- **High risk outpatients with ARI, 5 days from illness onset**
- **Hospitalized patients with fever and ARI any time from illness onset**
- **Elderly and infants with sepsis**
- **Immunocompromised patients with ARI**

Harper SA et al CID March 2009

CDC testing guidance: Will result change clinical care?



http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm#figure1

Influenza Diagnostic Tests

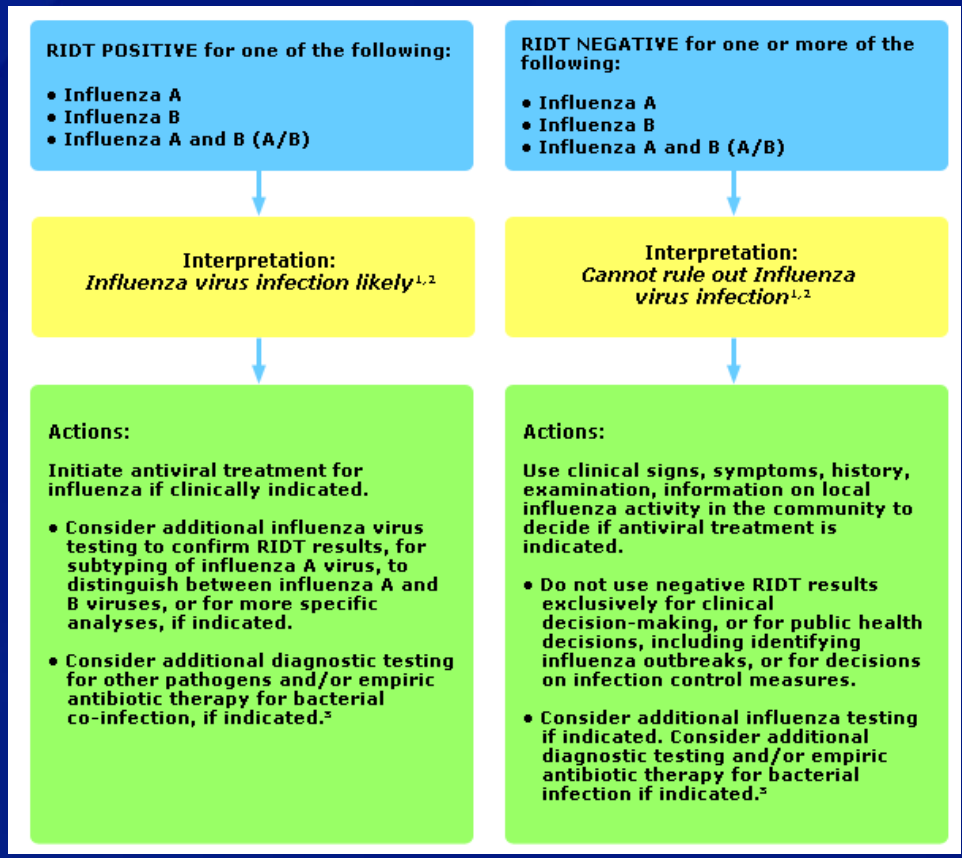
Table 1: Influenza Virus Testing Methods

Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Viral cell culture (conventional)	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	No
Rapid cell culture (shell vials; cell mixtures)	A and B	As above	1-3 days	No
Immunofluorescence, Direct (DFA) or Indirect (IFA) Antibody Staining	A and B	NP[4] swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[5] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	Varied (Generally 1-6 hours)	No
Rapid Influenza Diagnostic Tests[6] (antigen)	A and B	NP[4] swab, (throat swab), nasal wash, nasal aspirate	<30 min.	Yes/No

http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table

Rapid Influenza Diagnostic Tests ("Rapid Tests")

- Results available ~15-20 min
- Point of care (POC)
- Insensitive (~40-70% c/w PCR)
- When prevalence low, specificity reduced
- False negatives frequent



What do we know about antiviral use and diagnostic testing for influenza?

- Survey of outpatient providers: Use of Rapid Influenza Diagnostic Tests, 2010
- 80-90% reported use of RIDTs to confirm influenza before antivirals prescribed

Williams, et al, J Clin Vir 2014

Testing in high-risk outpatients with acute respiratory illness

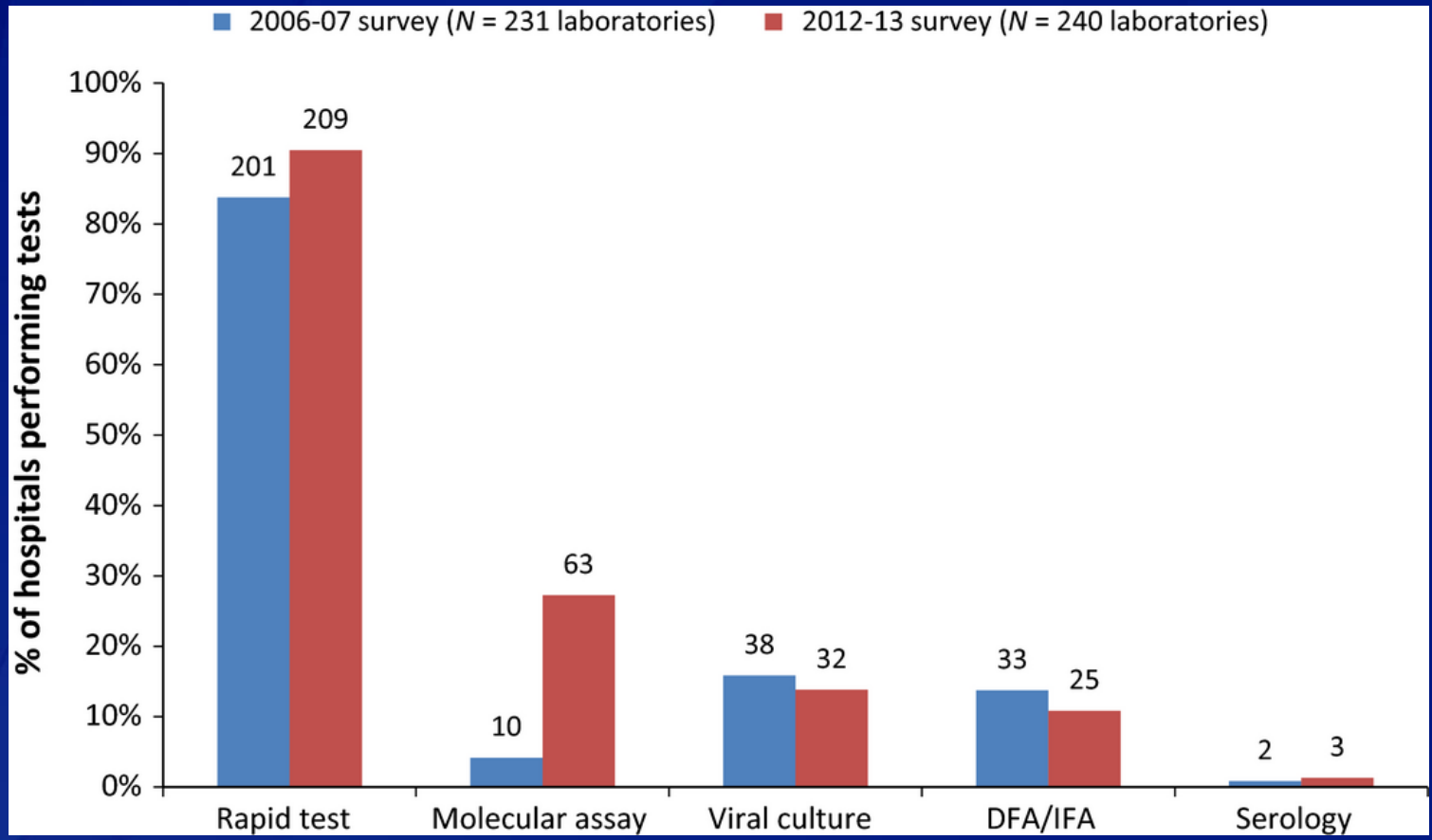
- Many come to clinic >2 days after illness onset
- Antiviral drugs are used less commonly prescribed than antibiotics
- RIDT is preferred diagnostic, clinicians treat based on test result
- RIDTs often give false negatives

Diagnostic Tests Performed in Hospital Laboratories, FluSurv-NET (n=240)

- 67% relied ONLY on RIDT to diagnose influenza
- 26% reported the availability of molecular diagnostic assays for detection of influenza
- Testing for other viruses less common

Su Su, et al, Influenza and Other Respiratory Viruses, March 2016.

Survey of influenza and other respiratory viruses diagnostic testing in US hospitals, 2012–2013



Su Su, et al, Influenza and Other Respiratory Viruses, March 2016.

Testing in Hospitalized ARI patients

- **In recent seasons, most hospitalized patients with positive influenza test were treated in US**
- **Testing for influenza not common**
- **Tests with results available quickly were used more**
  - RIDT still used by most hospital laboratories in 2012/13
- **Antiviral treatment strongly associated with influenza testing**
  - Empiric treatment was uncommon

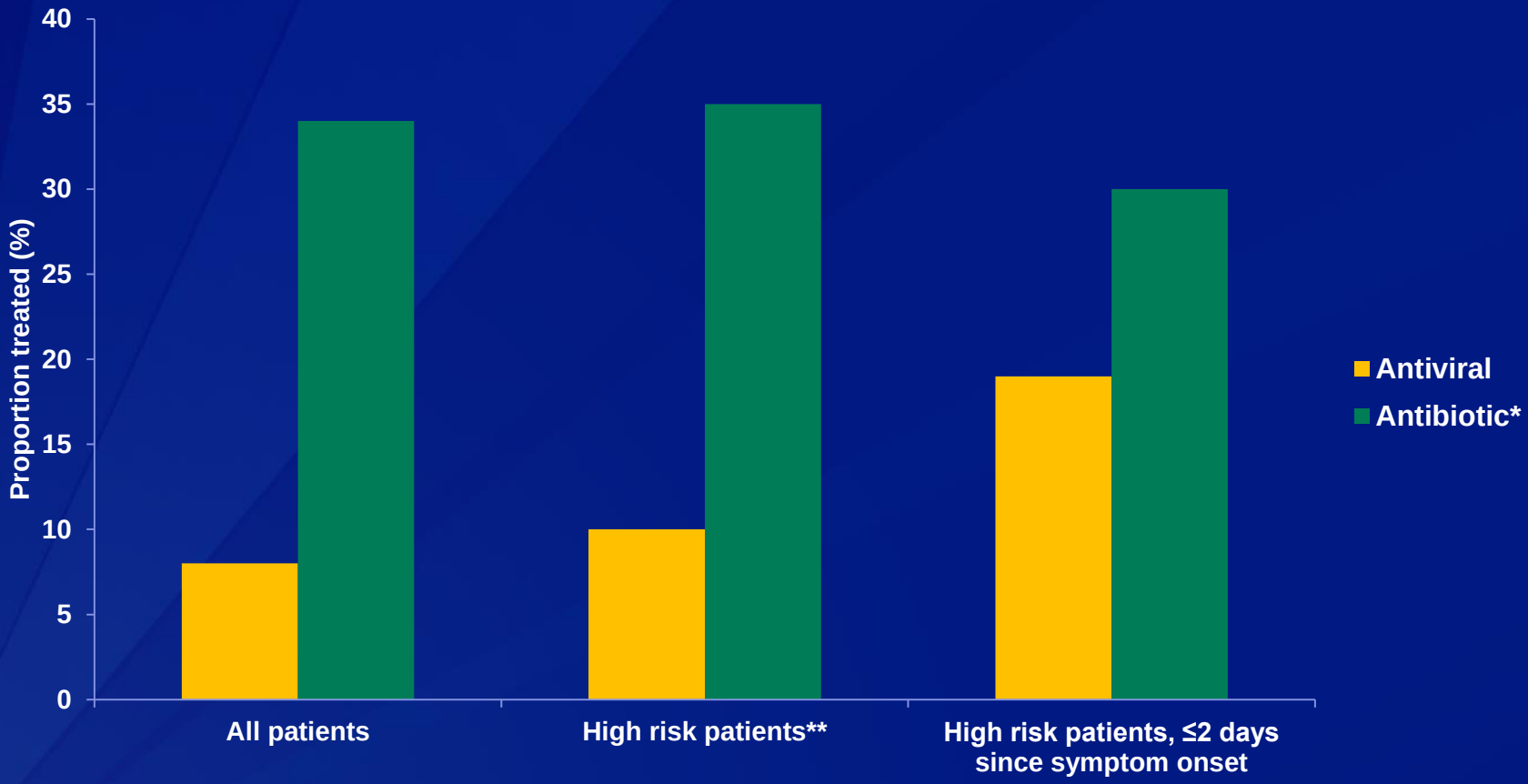
Reminders to Clinicians (2)

- Influenza should be high on the list of possible diagnoses for ill patients
- A negative rapid influenza antigen diagnostic test (RIDT) does not exclude a diagnosis of influenza
- All hospitalized and all high-risk patients with suspected or confirmed influenza should be treated as soon as possible without waiting for confirmatory testing

Antiviral Use

- **Evidence from current and previous influenza seasons suggests that antiviral drugs are underutilized**
  - Low awareness of antiviral recommendations
  - Wide range in perception about antiviral effectiveness
  - Many clinicians may require a positive diagnostic test before prescribing; results of rapid influenza diagnostic tests (not molecular) may not be accurate
  - Some clinicians may not prescribe after the 48-hour window that is optimal for treatment

Outpatients with Acute Respiratory Illness Treated with an Influenza Antiviral Medication or Antibiotics During Influenza Season, US Flu VE Network, 2012-13



* Antibiotics limited to amoxicillin, amoxicillin-clavulanate, and azithromycin

Data from Havers, et al. CID 2014;59(6):774-82

Antiviral Medications

- **Oral oseltamivir (Tamiflu®)**
  - Recommended for treatment of all ages, chemoprophylaxis for age ≥3 months
- **Inhaled zanamivir (Relenza®)**
  - Recommended for treatment for age ≥7 years, chemoprophylaxis for age ≥5 years
- **Intravenous peramivir (Rapivab®)**
  - Approved on December 19, 2014, for treatment of acute uncomplicated influenza in persons ≥18 years
  - 600 mg dose infused over 15-30 min

Adverse Events

- **Oral oseltamivir: Slightly increased risk of nausea, vomiting over placebo**
  - Mild, transient
  - Improved when taken with food
- **Inhaled zanamivir: Cases of bronchospasm reported during postmarketing – not recommended for persons with underlying airways disease such as asthma, COPD**
- **Intravenous peramivir: Slightly increased risk of diarrhea, neutropenia over placebo**

CDC Influenza Treatment Guidelines

- **Focus is on prevention of severe outcomes**
  - Treatment of those with severe disease and persons at highest risk of severe influenza complications
  - No RCTs available
- **Include observational studies and meta-analyses of antiviral effectiveness**
- **Antiviral recommendations are common to ACIP, IDSA, AAP**

CDC Antiviral Recommendations

- **All patients in the following categories with suspected or confirmed influenza should be treated as soon as possible, without waiting for confirmatory influenza testing**
  - Hospitalized patients
  - Patients with severe, complicated, or progressive illness
  - Patients at high risk for complications from influenza (either outpatient or hospitalized)

CDC Antiviral Recommendations (2)

- Antiviral treatment may be prescribed on the basis of clinical judgment for any previously healthy (non-high risk) outpatient with suspected or confirmed influenza

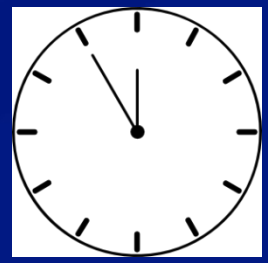
Persons at High Risk for Influenza Complications

- Children <2 years
- Adults ≥65 years
- Pregnant and postpartum women (within 2 weeks after delivery)
- American Indians and Alaska Natives
- Persons who are morbidly obese (BMI ≥40)
- Residents of long-term care facilities

Persons at High Risk for Influenza Complications (continued)

- Persons with immunosuppression
- Persons <19 years who are receiving long-term aspirin therapy
- Persons with underlying medical conditions: chronic pulmonary, cardiovascular (except hypertension alone), renal, hepatic, hematologic, and metabolic disorders (incl. diabetes), or neurologic and neurodevelopment conditions

Timing of Treatment



- **When indicated, antiviral treatment should be started as soon as possible after illness onset**
- **Ideally, treatment should be initiated within 48 hours of symptom onset**
- **Treatment should not be delayed even for a few hours to wait for the results of testing**
  - A negative rapid influenza antigen diagnostic test does **not** exclude a diagnosis of influenza

High-Risk Outpatients and Early Treatment

- During influenza season, providers should advise high-risk patients to call promptly if they have symptoms of influenza
- Phone triage lines may be useful to enable high risk patients to discuss symptoms over the phone
- To facilitate early initiation of treatment, when feasible, an antiviral prescription can be provided without testing and before an office visit

Antiviral Treatment Initiated after 48 Hours Can Still be Beneficial in Some Patients

- Observational studies of hospitalized patients suggest that treatment might still be beneficial when initiated 4 or 5 days after symptom onset
- Observational data in pregnant women has shown antiviral treatment to provide benefit when started 3-4 days after onset
- A randomized placebo controlled study suggested clinical benefit when oseltamivir was initiated 72 hours after illness onset among febrile children with uncomplicated influenza

Louie, CID 2012;55:1198-204; Yu, CID 2011;52:457-65;
Siston, JAMA 2010;303:1517-25; Fry Lancet ID 2014;14:109-18

Outpatient Treatment

- **Any neuraminidase inhibitor may be used for treatment of outpatients**
  - 5-day course of oseltamivir or inhaled zanamivir
  - 1-day of IV peramivir
- **Oral oseltamivir is preferentially recommended for pregnant women**

Treatment for Hospitalized Patients

- **Treatment with oral or enterically administered oseltamivir is recommended**
  - Limited data suggest that oseltamivir administered by oro/naso gastric tube is well absorbed in critically ill influenza patients, including those in the intensive care unit, on continuous renal replacement therapy, and/or on extracorporeal membrane oxygenation
- **Inhaled zanamivir is not recommended because of lack of data for use in patients with severe influenza disease**
- **Insufficient data regarding efficacy of intravenous peramivir for hospitalized patients**
- **For patients who remain severely ill after 5 days of treatment, longer treatment courses may be considered**

Treatment for Hospitalized Patients:
Concern Regarding Oseltamivir Absorption

- **For patients who cannot tolerate or absorb oral oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding, the use of IV peramivir or investigational IV zanamivir should be considered**
  - If peramivir used in severely ill patients, single dose should not be given
  - For severely ill patients, adult dose of 600 mg IV once daily for 5 days is recommended (dose for children >6 years: 10 mg/kg once daily [up to 600 mg] for 5 days); minimum of 5 days duration

de Jong, et al. CID 2014; 59:172-85

Treatment for Hospitalized Patients:
Concern Regarding Oseltamivir Resistance

- **Some influenza viruses may become resistant to oseltamivir and peramivir during antiviral treatment with one of these agents and remain susceptible to zanamivir**
  - Investigational use of intravenous zanamivir should be considered for treatment of severely ill patients with oseltamivir-resistant virus infection

Additional Information: Antibiotics and Bacterial Infections

- Antibiotics are not effective against influenza
- Several reports suggest inappropriate use of antibiotics for patients with influenza
- Bacterial infections can occur as a complication of influenza, so should be considered and appropriately treated if suspected

Institutional Outbreaks
(Long-Term Care Facilities, Nursing Homes, other Living Facilities that House High-Risk Persons)

- **Use of antiviral chemoprophylaxis to control outbreaks among high-risk persons in institutional settings is recommended**
  - For all residents (regardless of vaccination status)
  - For unvaccinated healthcare personnel
  - For a minimum of 2 weeks, continuing at least 7 days after last known case identified

Summary of Antiviral Recommendations

- **Early empiric antiviral treatment is recommended for suspected or confirmed influenza among the following:**
  - Hospitalized patients
  - Patients with severe or progressive illness
  - Patients at high risk for complications
- **Decisions about antiviral treatment should not wait for laboratory confirmation of influenza**
- **Clinical benefit is greatest when antiviral treatment is initiated early, but treatment initiated later than 48 hours after onset can still be beneficial for some patients**

Summary

- Influenza activity is increasing
- Vaccination still possible
- H1N1 viruses now most frequently detected, but H3N2 and influenza B viruses also seen
- Can expect to see some severe disease in children and young and middle-aged adults
- Decisions regarding treatment should not be made on the basis of a negative RIDT

For Additional Information

- Summary of Influenza Antiviral Treatment Recs for Clinicians: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
- Guidance for Clinicians on the Use Rapid Influenza Diagnostic Tests: http://http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm
- Interim Guidance for Influenza Outbreak Management in Long-Term Care Facilities: http://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm
- Prevention Strategies for Seasonal Influenza in Healthcare Settings http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm
- FDA Influenza (Flu) Antiviral Drugs and Related Information (including package inserts): http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm
- American Academy of Pediatrics (AAP) Information on Influenza in Children: www.aap.org/disasters/flu

Acknowledgements

- **Influenza Division CDC**
  - Angela Campbell
  - Alicia Fry
  - Communications team

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- **Using the Webinar System**
  - “Click” the Q&A tab at the top left of the webinar tool bar
  - “Click” in the white space
  - “Type” your question
  - “Click” ask

- **On the Phone**
  - Press Star (*) 1 to enter the queue
  - State your name
  - Listen for the operator to call your name
  - State your organization and then ask your question

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Please email us questions at coca@cdc.gov

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