

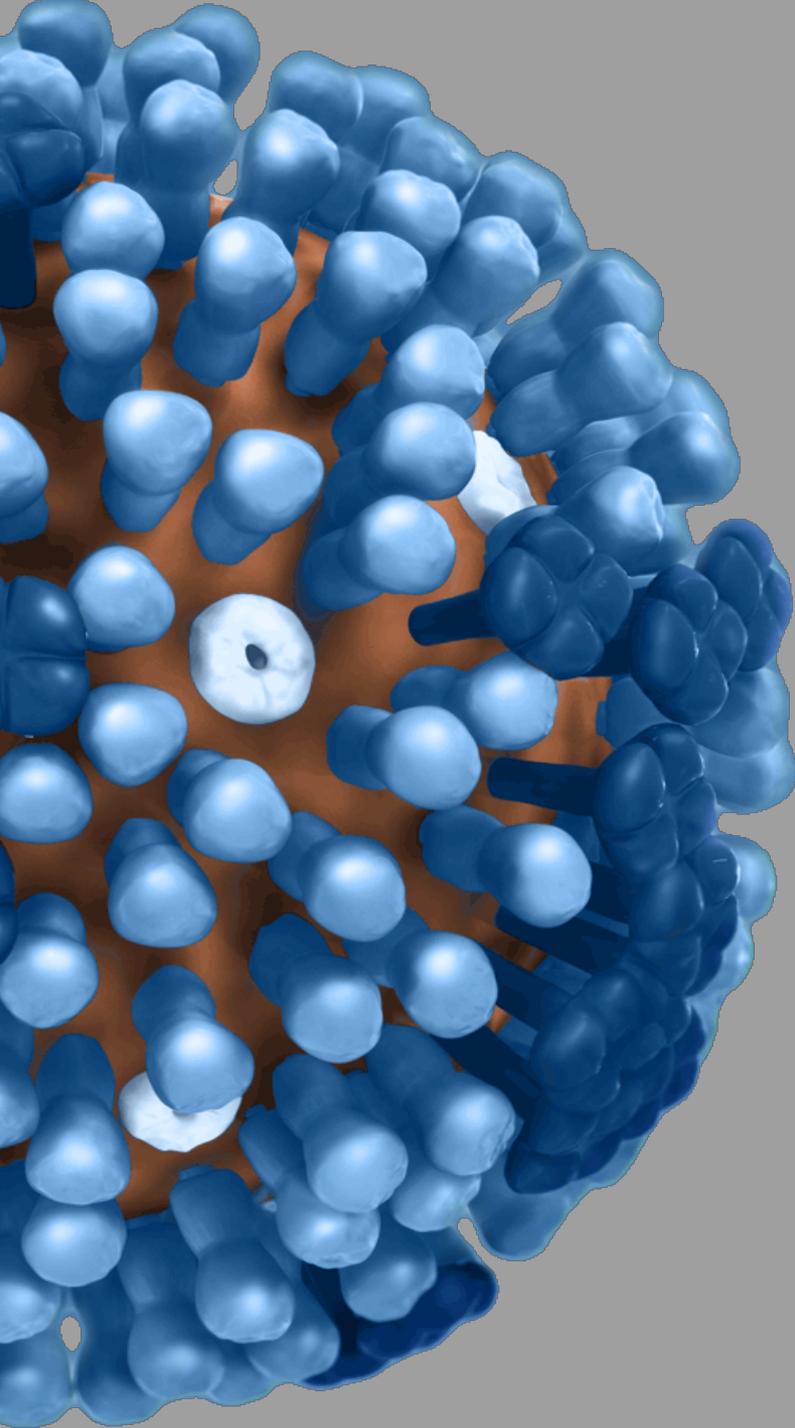
# Public Health Perspective on Potential Benefits and Risks of OTC Influenza Diagnostics

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Centers for Disease Control and Prevention  
August 16, 2016



# Overview

- ❑ Influenza - Burden of disease
  - Estimating burden based on diagnostic test results
- ❑ Treatment of Influenza
  - Guidance vs practice
- ❑ Diagnostic tests
  - RIDTs – Pros and Cons
  - Improving diagnostic tests
- ❑ Potential benefits and risks of OTC influenza diagnostic tests



# Influenza Burden of Disease

# Hospitalizations Attributable to Influenza (U.S.)

- ❑ Average of >200,000 influenza-related hospitalizations/year
  - Estimated by modeling studies using retrospective data and influenza surveillance data
- ❑ Children
  - High rates in young children <2 years
  - Children 2-5 years next highest
  - High rates for children with chronic high-risk conditions
- ❑ Adults
  - Highest rates in persons >65 years
  - High rates in persons with chronic illness

# Seasonal Influenza-associated Mortality (U.S.)

## ❑ Estimated average of severity is variable

- 3,349 to 48,614 influenza-attributable deaths/year (1976-2007)

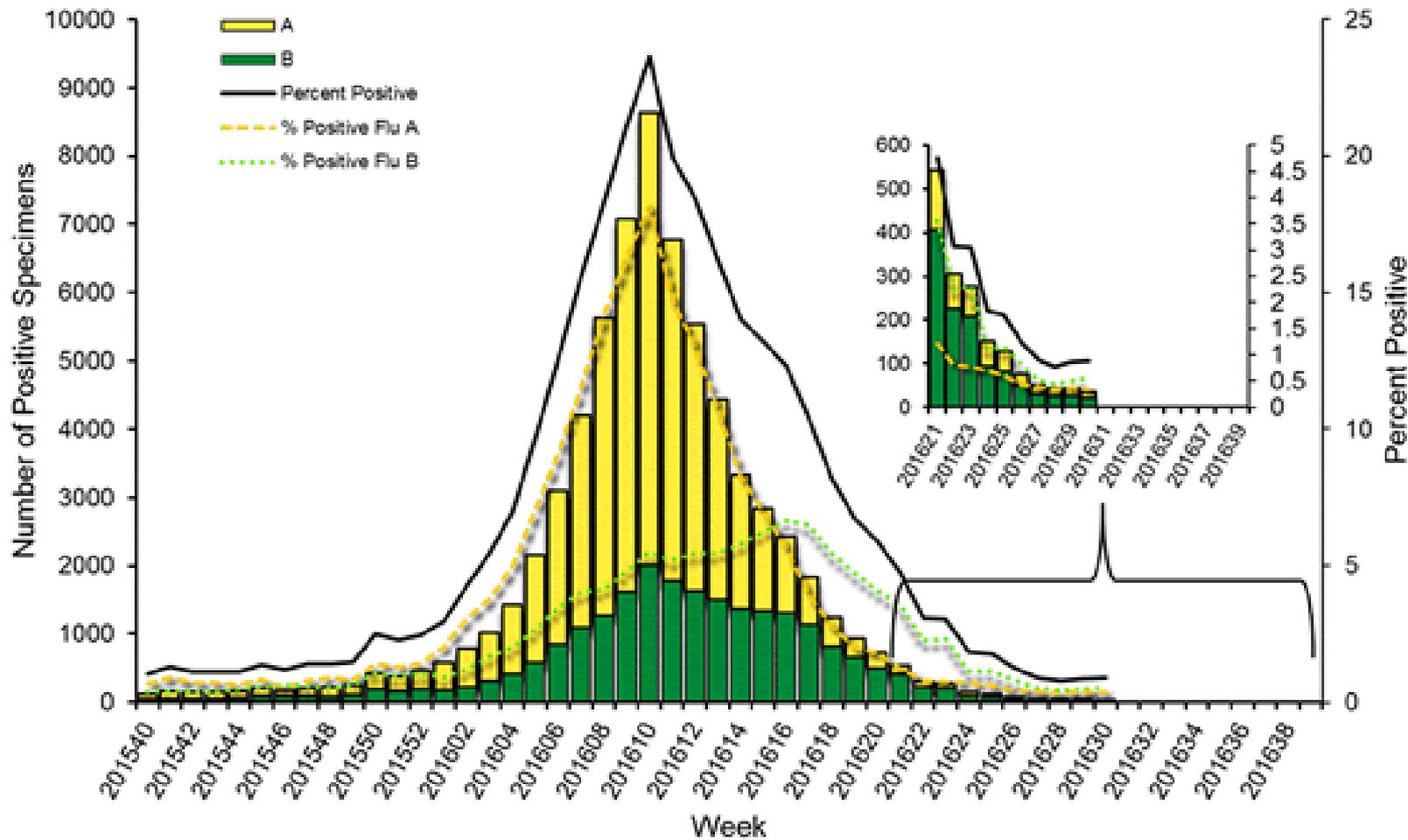
## ❑ Highest mortality rates

- Persons >65 years
- Persons with chronic pulmonary and cardiac disease; other chronic conditions

## ❑ Mortality data limited for children

- Estimated average of 92 influenza-related deaths among children aged <5 years annually
- 148 deaths during 2014-2015 season; 85 during 2015-2016 to date

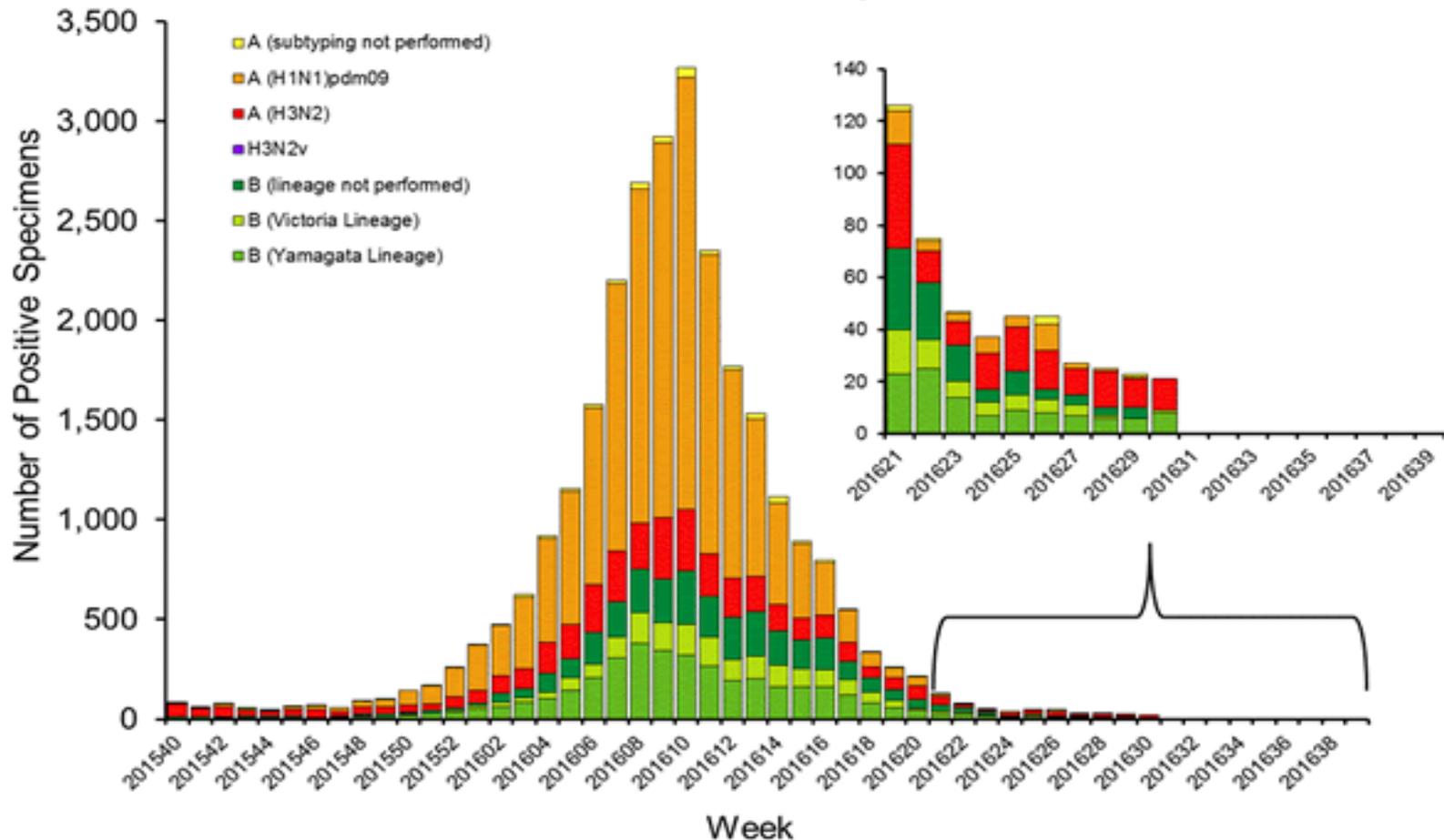
# Influenza Positive Tests Reported to CDC by U.S. Clinical Laboratories, National Summary, 2015-2016 Season



<http://www.cdc.gov/flu/weekly/>



# Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2015-2016 Season



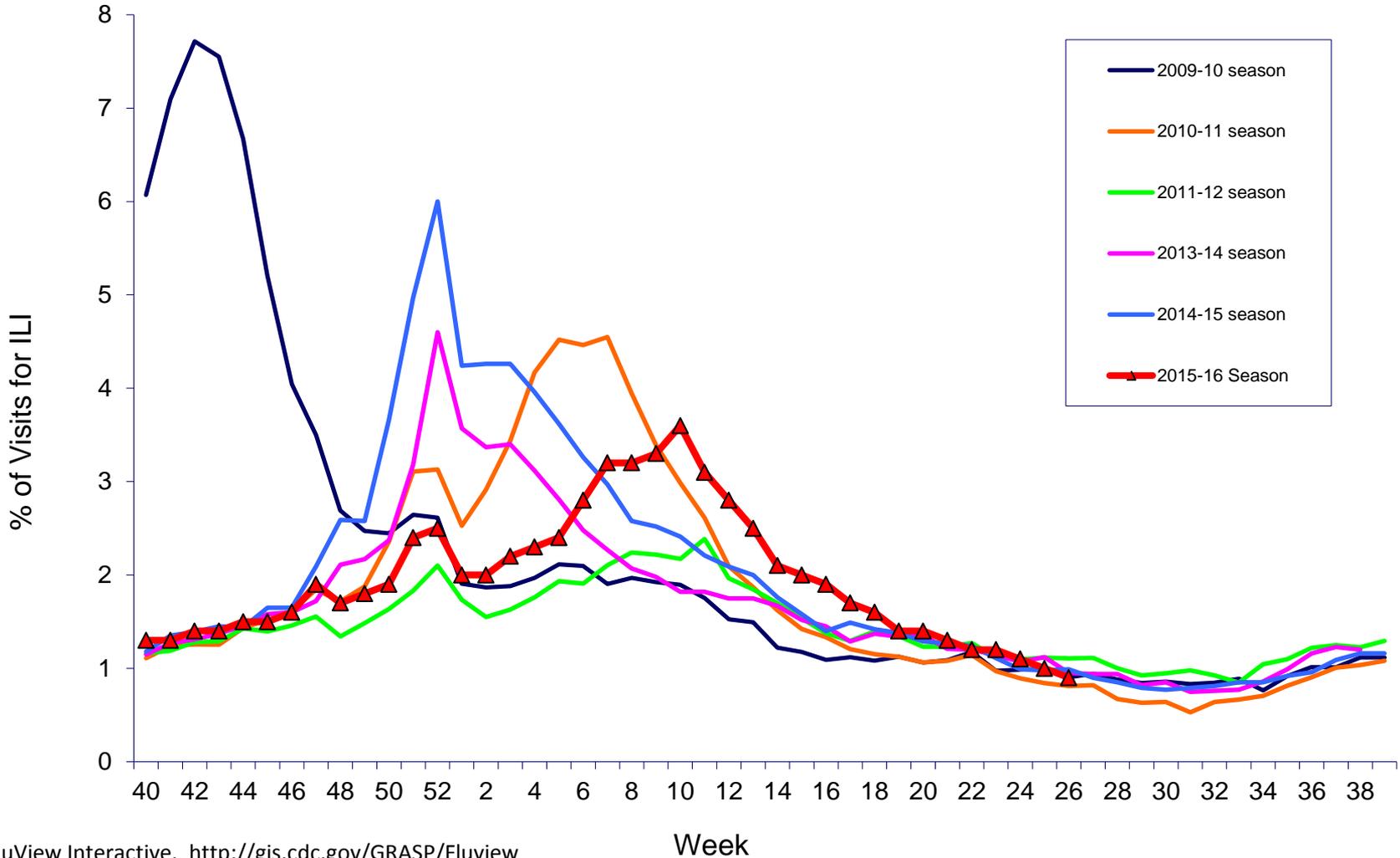
<http://www.cdc.gov/flu/weekly/>



# Variability in Season Onset

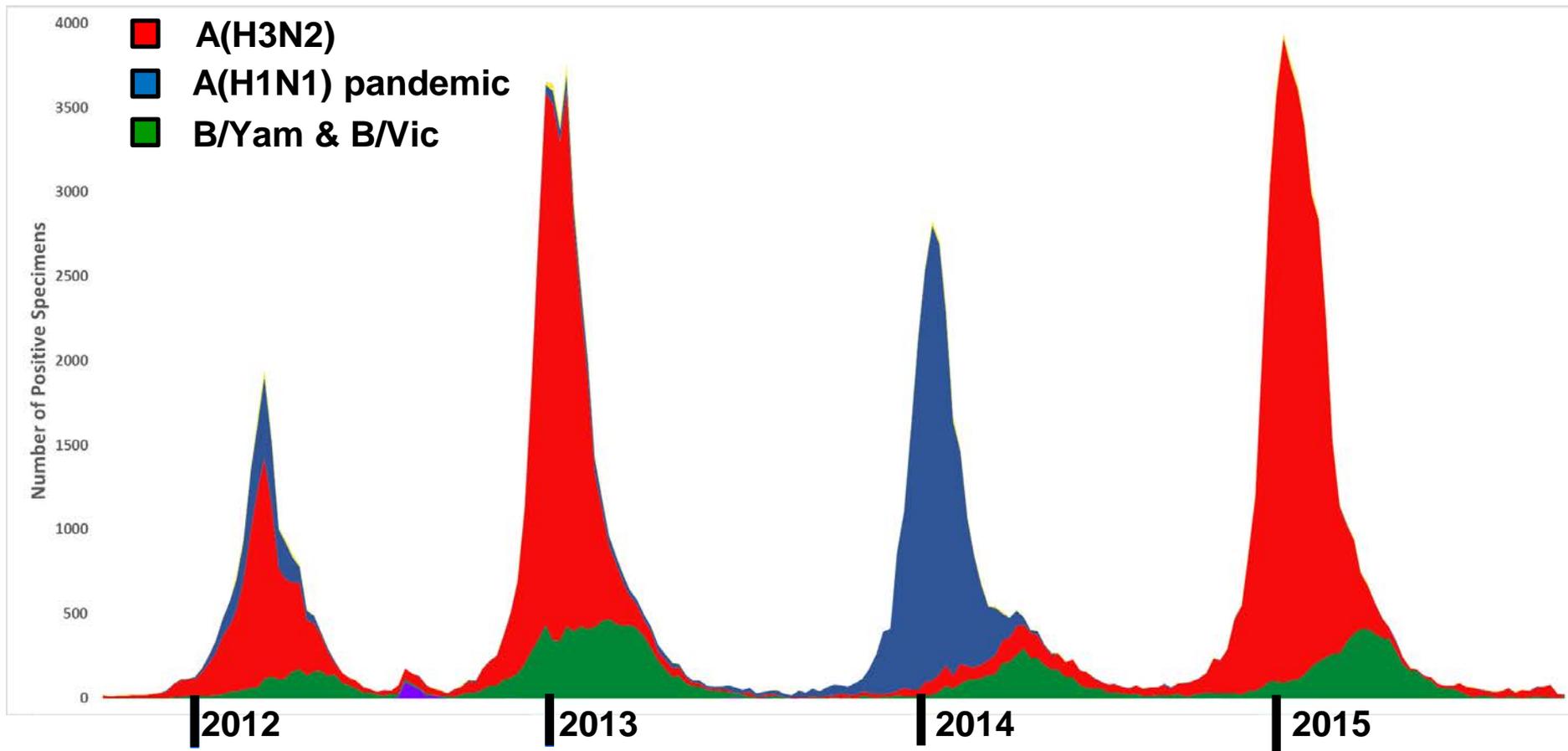


Percentage of Visits for Influenza-like Illness (ILI) Reported to CDC ILINet For Selected Previous Seasons from all U.S. States

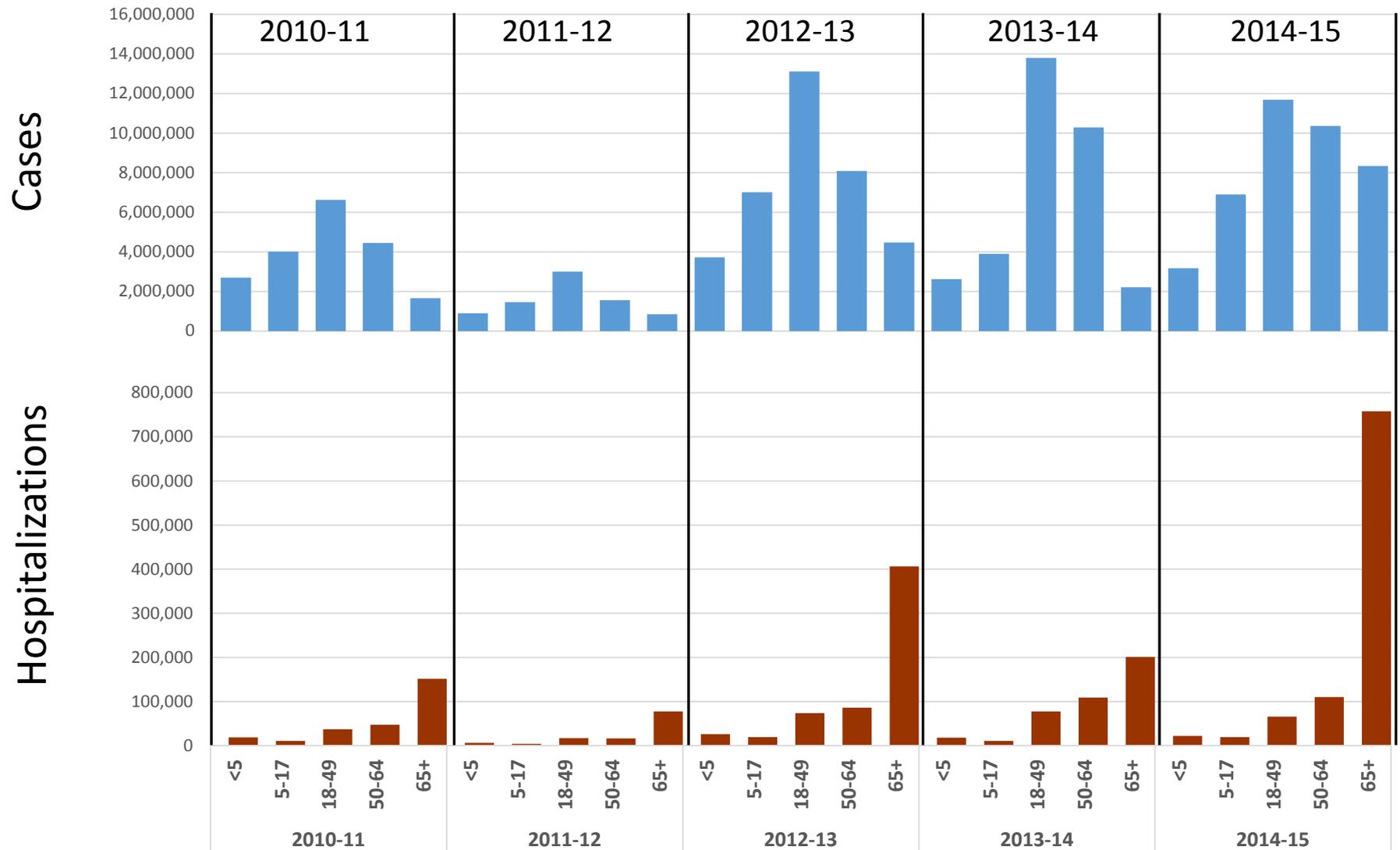


# Influenza Virus Surveillance 2011 – 2015

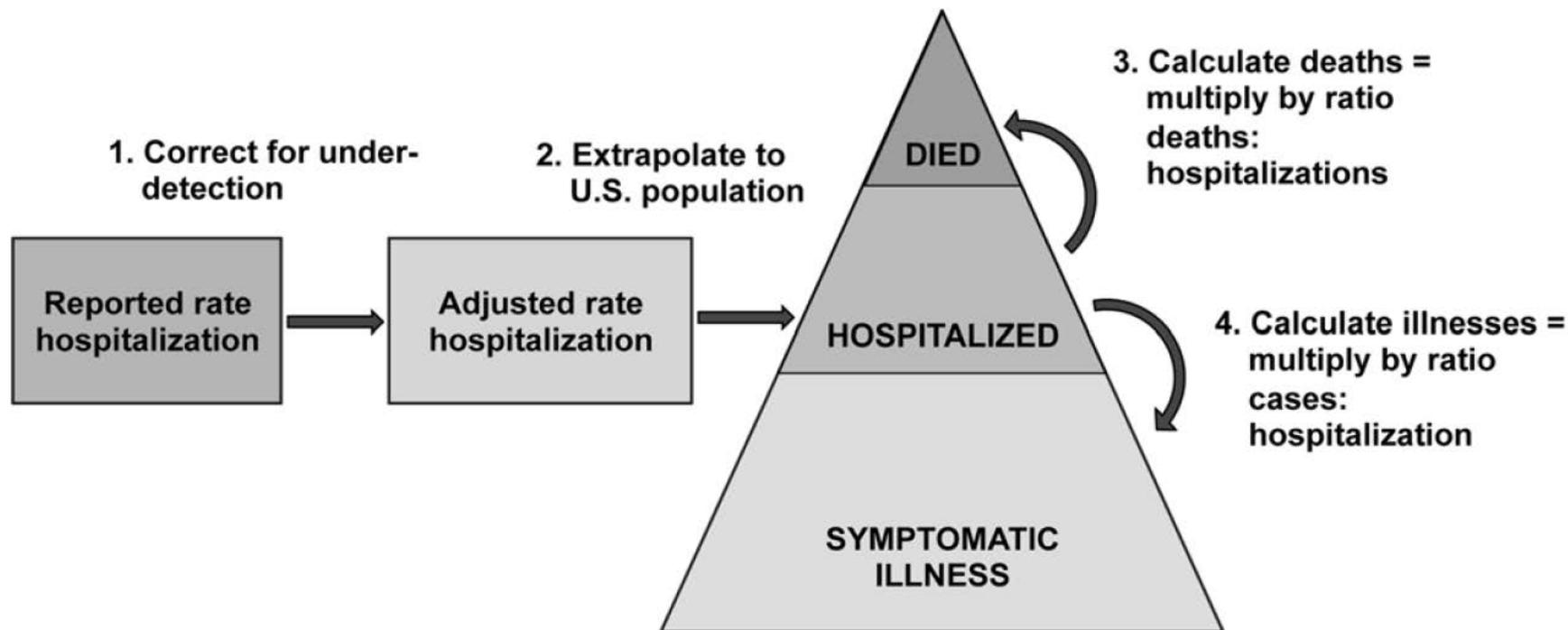
U.S. Public Health Laboratories



# Annual Influenza Impact Varies by Age Group

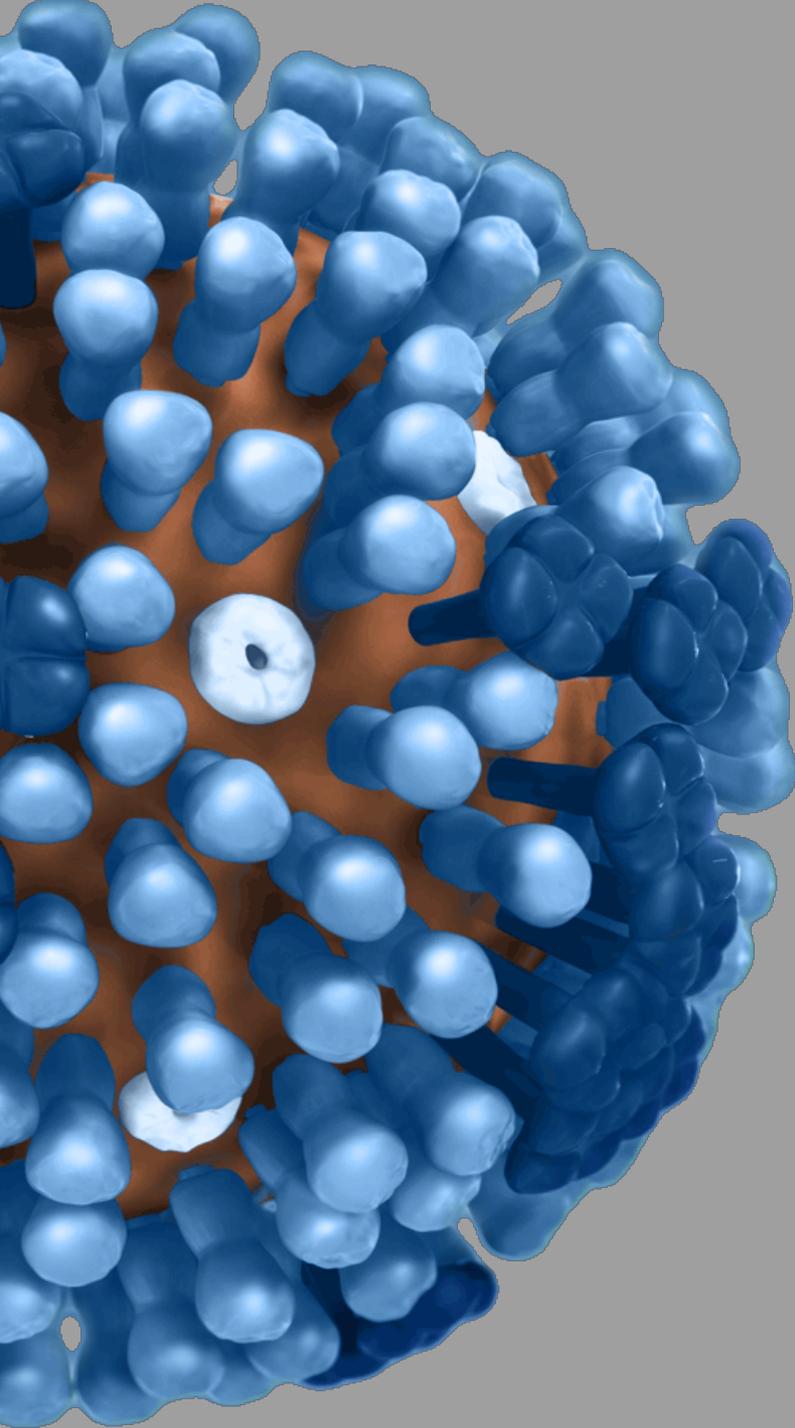


# Estimating Influenza Disease Burden



General framework for estimating influenza disease burden in the U.S. population using FluSurv-NET hospital-based influenza surveillance data.





# Influenza Treatment: Antivirals

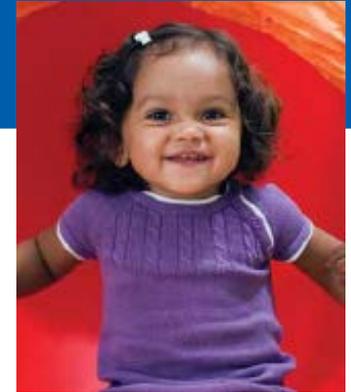
# CDC Antiviral Recommendations

- ❑ **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)



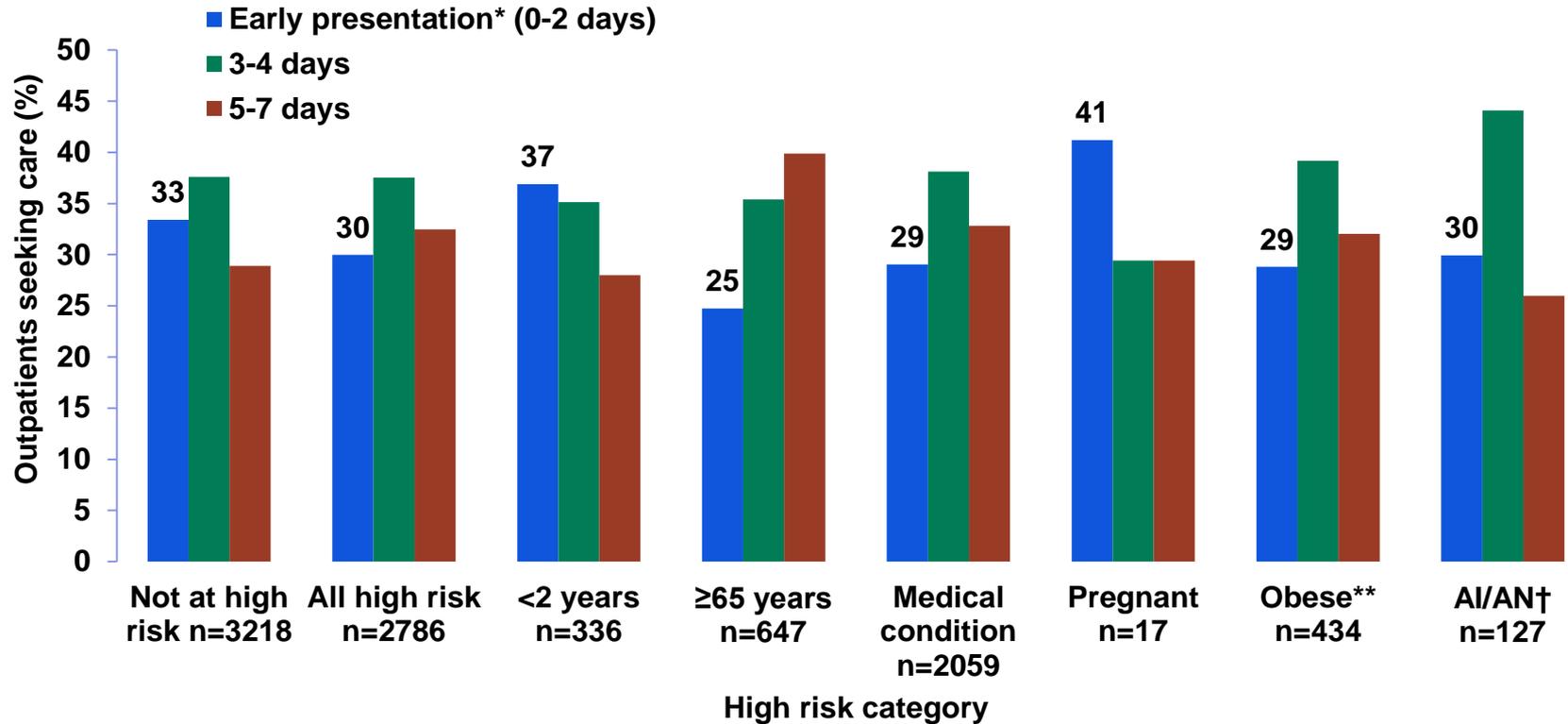
# Persons at High Risk for Influenza Complications

- ❑ Children <2 years
- ❑ Adults >65 years
- ❑ Pregnant and postpartum (within 2 weeks after delivery)
- ❑ American Indians and Alaska Natives
- ❑ Persons who are morbidly obese (BMI >40)
- ❑ Residents of long-term care facilities
- ❑ Persons with certain underlying medical conditions or who are immunosuppressed



\* Havers, et. al. *Clin. Infect. Dis.* 15 Sept 2014.

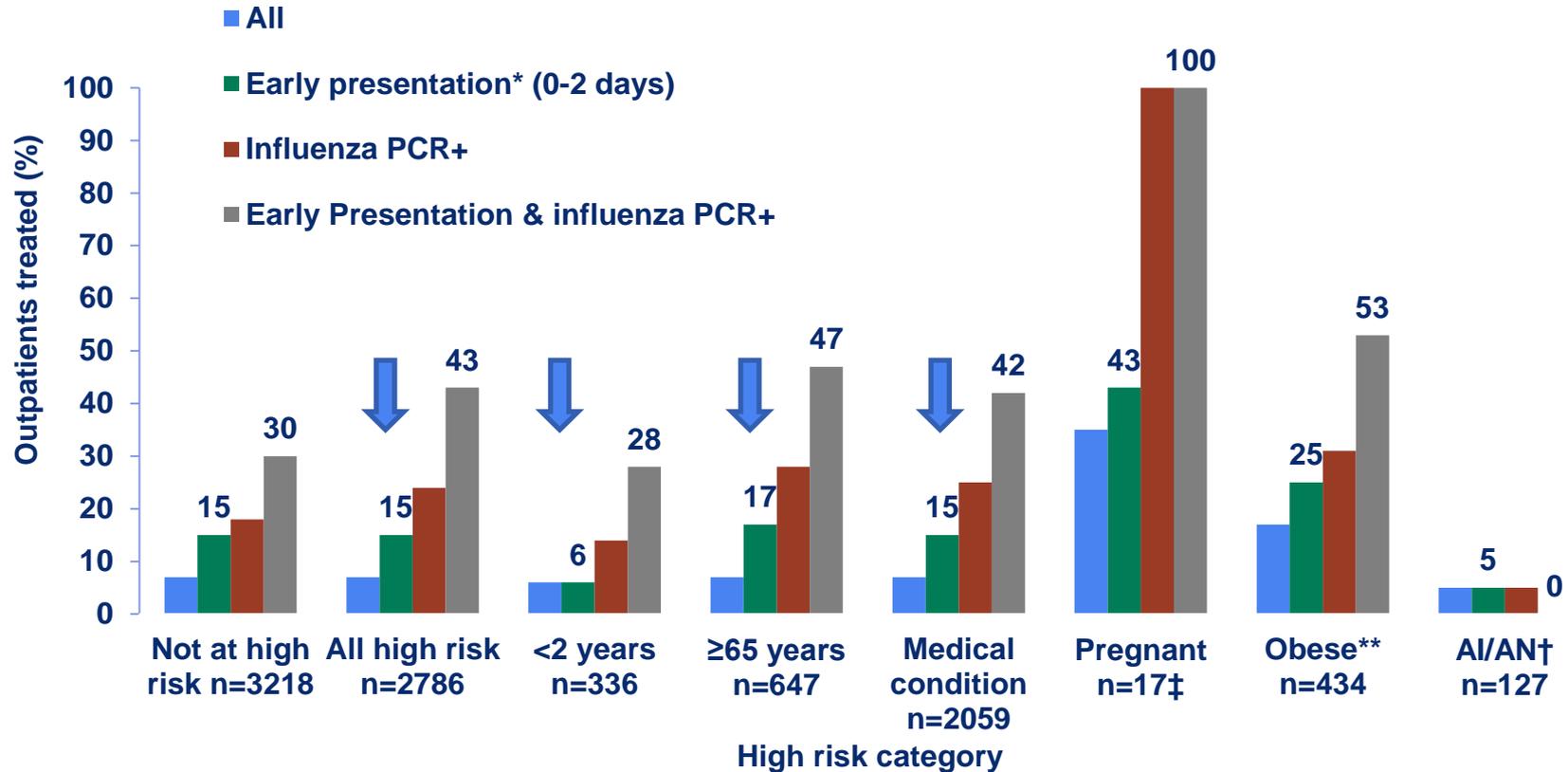
# Time from symptom onset to presentation, US Flu Vaccine Effectiveness Network, 2013-14 season



\*Early Presentation: Sought care from their outpatient provider  $\leq 2$  days after symptom onset \*\*Body Mass Index  $\geq 40$  kg/m<sup>2</sup>. †American Indian, Alaska Native, Native Hawaiian, or Pacific Islander. There was a small number of pregnant patients with PCR-confirmed influenza (6), among whom 3 presented early. NOTE: Clinicians one of five sites had access to study-related influenza PCR testing results. Havers, et. al. *Clin. Infect. Dis.* 15 Sept 2014.



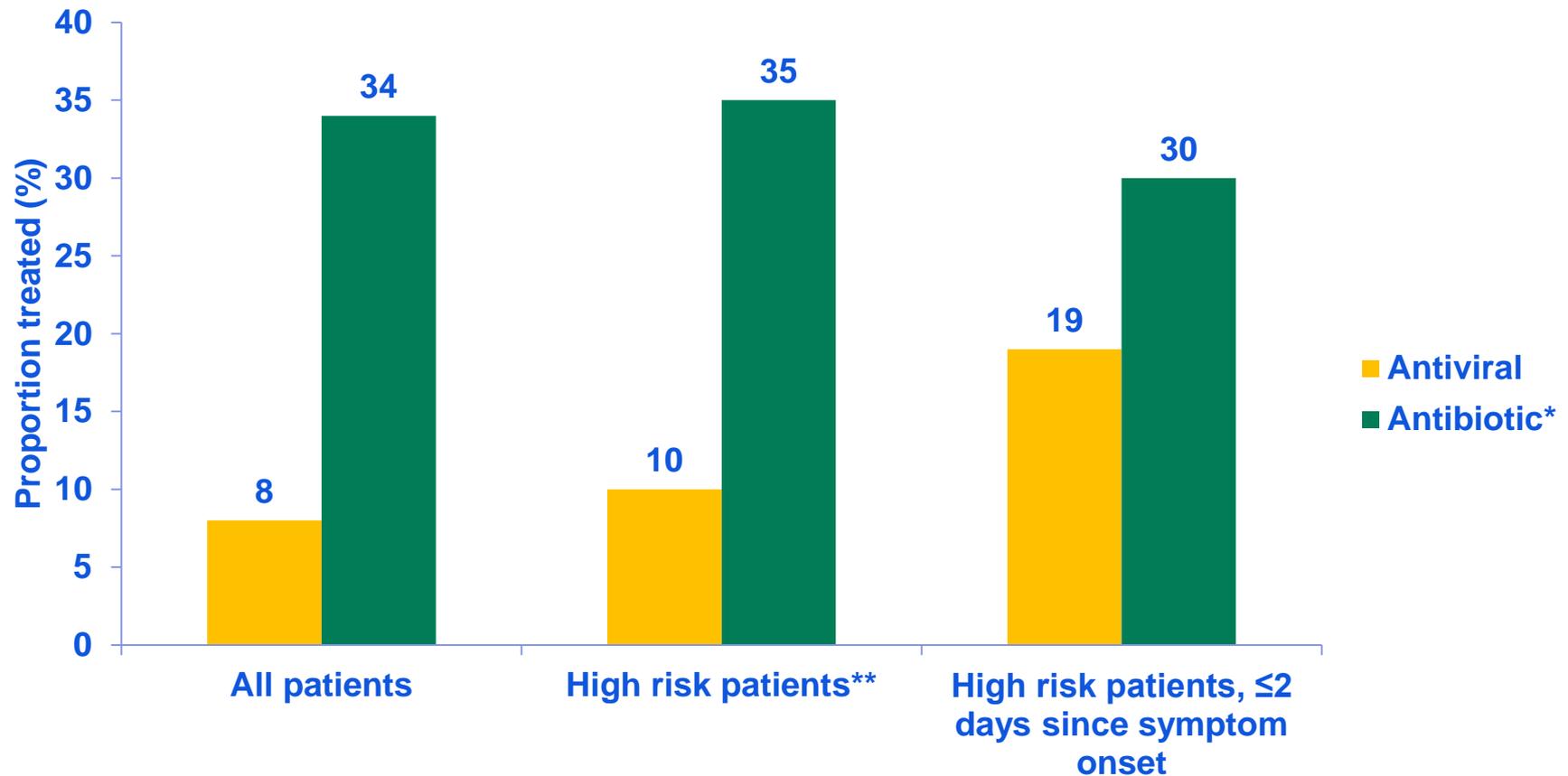
# Proportion of outpatients with ARI prescribed influenza antiviral medications, US Flu Vaccine Effectiveness Network, 2013-14 season



\*Early Presentation: Sought care from their outpatient provider ≤2 days after symptom onset \*\*Body Mass Index ≥40 kg/m<sup>2</sup>. †American Indian, Alaska Native, Native Hawaiian, or Pacific Islander. There was a small number of pregnant patients with PCR-confirmed influenza (6), of whom 3 presented early. NOTE: Clinicians one of five sites had access to study-related influenza PCR testing results. Havers, et. al. *Clin. Infect. Dis.* 15 Sept 2014.



# Outpatients with Acute Respiratory Illness Treated with an Antiviral Medication or Antibiotics, 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 Treatment Analysis, 2013-14 Season

- ❑ Fewer than half of the influenza-infected high risk outpatients seeking care for an ARI presented to care early enough for optimal neuraminidase-inhibitor treatment
- ❑ Among high-risk patients who presented early, 15% prescribed an antiviral medication
- ❑ Higher among those high-risk patients who presented early AND who also had laboratory-confirmed influenza (43%) or who presented during peak of influenza season (31%)
- ❑ At the influenza season's peak, 42% of high-risk patients who presented early and had laboratory-confirmed influenza did not receive antiviral treatment.



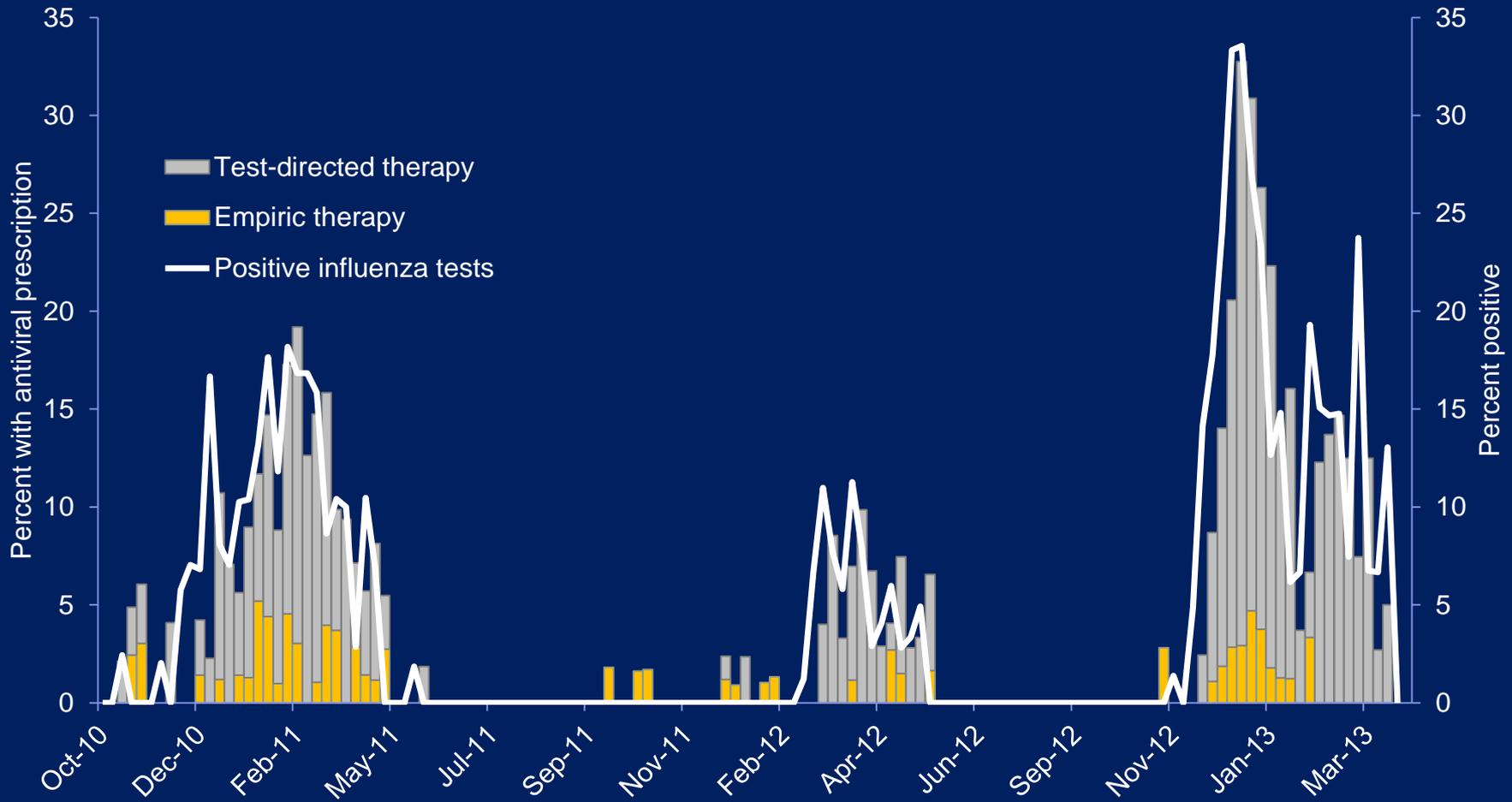
*Open Forum Infectious Diseases*

BRIEF REPORT

# Respiratory Viral Testing and Influenza Antiviral Prescriptions During Hospitalization for Acute Respiratory Illnesses

Melissa A. Rolfes,<sup>1,2</sup> Kimberly M. Yousey-Hindes,<sup>3</sup> James I. Meek,<sup>3</sup> Alicia M. Fry,<sup>2</sup> and Sandra S. Chaves<sup>2</sup>

# Rate of antiviral prescriptions among ARI hospitalizations — CT, October 2010–April 2013



Rolfes et al., Open Forum Infect. Dis. 2015



# Respiratory Viral Testing and Influenza Antiviral Prescriptions During Hospitalization for ARI

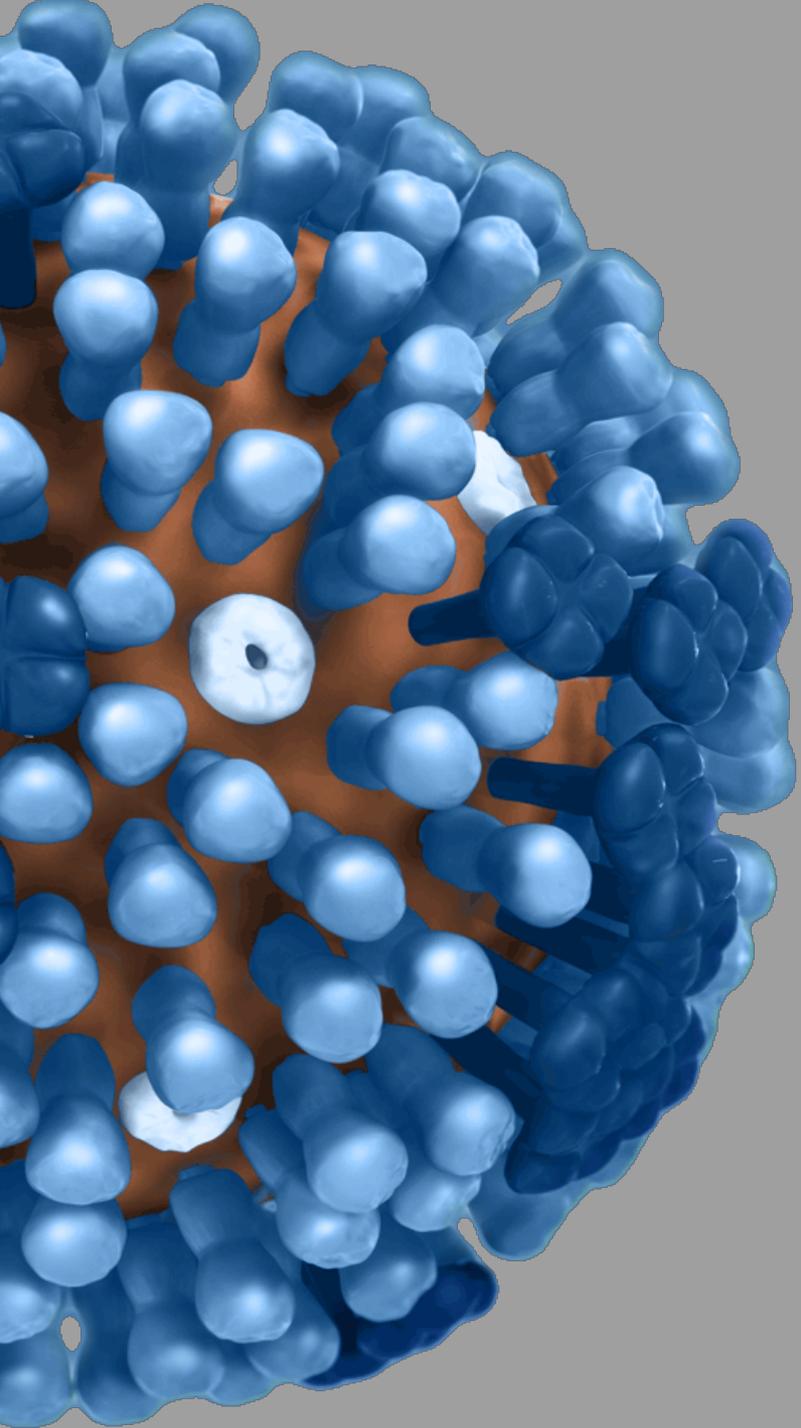
- ❑ Almost all influenza antiviral prescriptions were test-directed.
- ❑ Dependence on test results led to low rates of empiric prescription.
- ❑ Only 3.4% of inpatients were ordered an antiviral prescription empirically,
- ❑ Suggesting that opportunities for influenza treatment may have been missed.
- ❑ Healthcare providers are encouraged to start influenza antiviral treatment as soon as possible for patients hospitalized with suspected influenza, often on an empiric basis, especially during periods of high influenza prevalence

# Antiviral Treatment - Summary



- ❑ During 2012–2013, antiviral medications were under-prescribed and antibiotics may have been inappropriately prescribed to a large proportion of outpatients with influenza;
- ❑ Continuing education on appropriate antibiotic and antiviral use is essential to improve healthcare quality.
- ❑ Few ambulatory care providers appeared to follow current antiviral guidance recommending antiviral treatment for persons at high risk for influenza-associated complications.
- ❑ Additional efforts are needed to understand the barriers to the use of antiviral treatment in ambulatory care settings and to better communicate the benefits of prompt antiviral therapy, especially for those at high risk for influenza-associated complications.



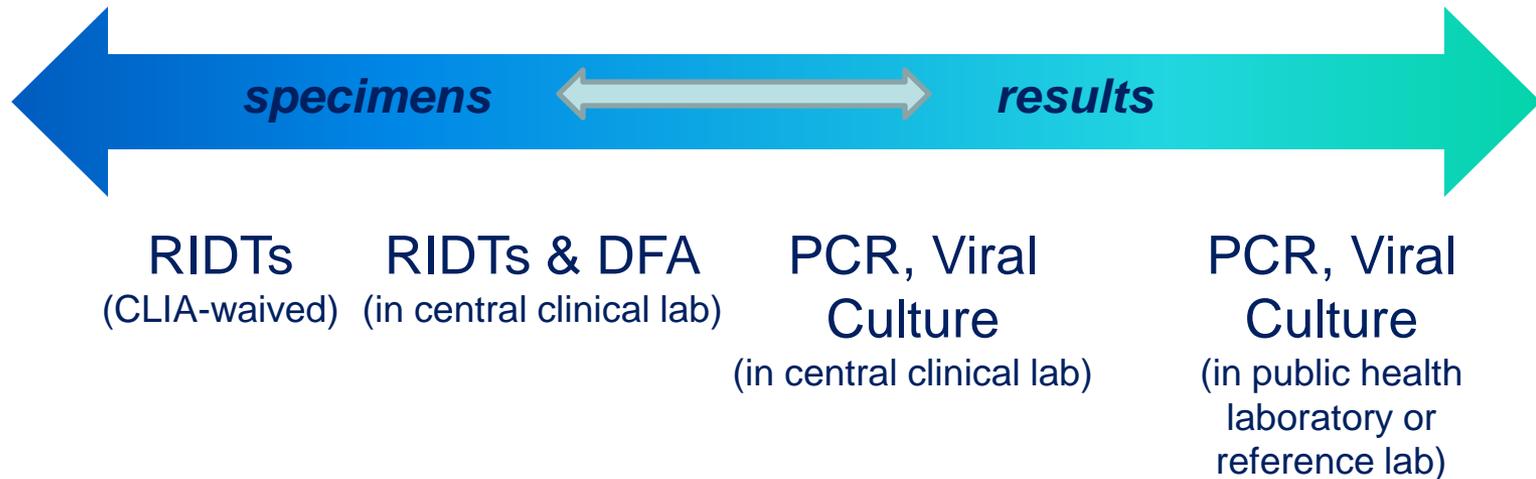


# Diagnostic Tests

# Influenza Diagnostic Dilemma

Clinical assessment & preliminary clinical diagnosis of ILI

Lab-confirmed diagnosis at public health lab or CDC

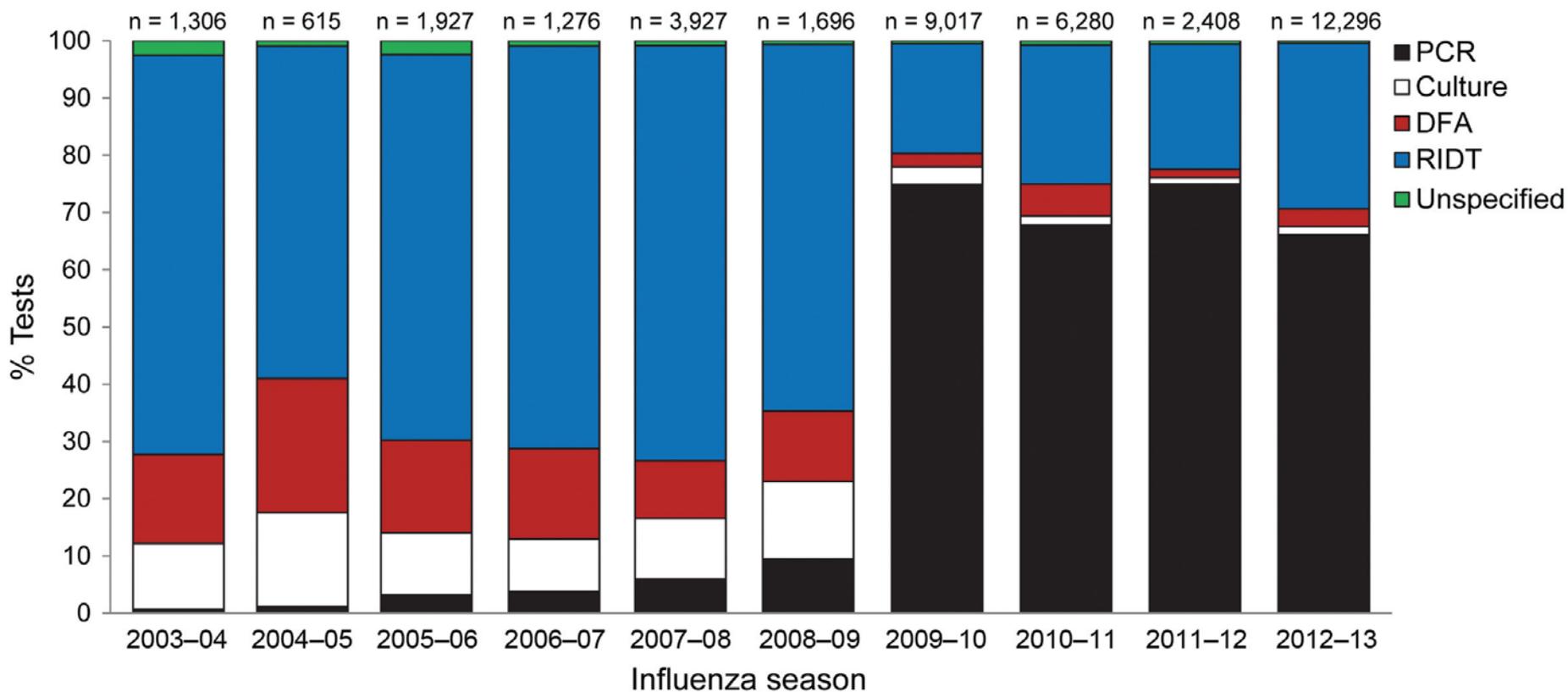


# Improving Accuracy of Influenza-Associated Hospitalization Rate Estimates

Alexander J. Millman, Carrie Reed, Pam Daily Kirley, Deborah Aragon, James Meek, Monica M. Farley, Patricia Ryan, Jim Collins, Ruth Lynfield, Joan Baumbach, Shelley Zansky, Nancy M. Bennett, Brian Fowler, Ann Thomas, Mary L. Lindegren, Annette Atkinson, Lyn Finelli, Sandra S. Chaves

□ FluServ Net – CDC Influenza Hospital Surveillance Network

# Distribution of influenza diagnostic tests among identified cases in the FluSurv-NET, 2003–2013

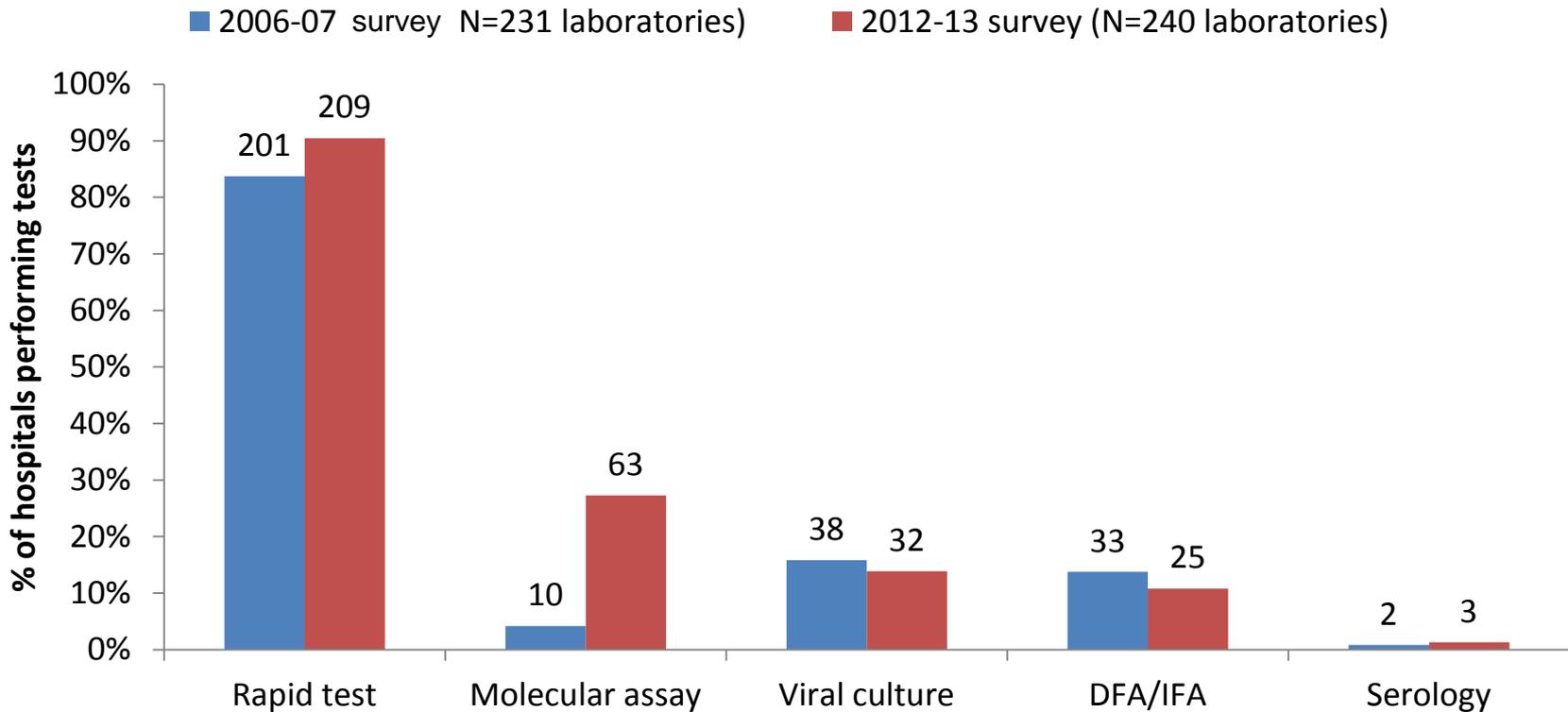


# Influenza diagnostic test sensitivity range, by patient age group (years), 2003–2013

| Diagnostic test | Patient age group | Range from literature review, % |
|-----------------|-------------------|---------------------------------|
| RT-PCR          | 0-17              | 79.2-100                        |
|                 | 18-64             | 79.2-100                        |
|                 | ≥65               | 79.2-93                         |
| Culture         | 0-17              | 45-100                          |
|                 | 18-64             | 45-100                          |
|                 | ≥65               | 19.4-53.8                       |
| DFA             | 0-17              | 45-90                           |
|                 | 18-64             | 53-84.2                         |
|                 | ≥65               | 53-84.2                         |
| RIDT            | 0-17              | 61.6-71.7                       |
|                 | 18-64             | 47.7-59.8                       |
|                 | ≥65               | 8-43                            |

FluSurv-NET, Centers for Disease Control and Prevention Influenza Hospital Surveillance Network;  
DFA, direct fluorescent antibody; RIDT, rapid influenza diagnostic test; RT-PCR, reverse transcription PCR

# Influenza diagnostic tests performed in hospital laboratories, FluSurv-NET



# Rapid Influenza Diagnostic Test Characteristics

- ❑ Detection of influenza nucleoprotein (NP) using specific antibodies
- ❑ Can obtain results within 15 min. and are available to clinicians during the time of a patient's office or clinic visit.
- ❑ Extremely variable performance reported
  - Sub-optimal sensitivity reports in previous years
  - 2012 Meta-analysis of 159 studies that compared RIDTs to a reference standard (RT-PCR or culture)
    - Sensitivity 62.3% - highly heterogeneous
    - Specificity 98.2%
    - More sensitive for influenza A than influenza B
    - Lower sensitivity in adults than in children

# What can be done to achieve improved patient diagnosis and test performance?

- Changes in the devices?
  - Improved antibodies, new methods, readers?
- Changes in clinician behaviors and knowledge?
  - Quality and timing of specimen collection? Use of local flu data for improved predictive value?
- Tools for manufacturers, clinicians, regulators?
  - Reagents? Evaluation standards? Diagnostic tools?

# 2010 Public Health Initiatives to improve patient diagnosis and test performance

Goal: To improve the use of RIDTS for clinical management and public health practice

## □ Better practices

- Facilitate optimal use of RIDTs

## □ Better guidance

- Dissemination of relevant information for clinicians and laboratories

## □ Better tests available to clinicians and laboratories

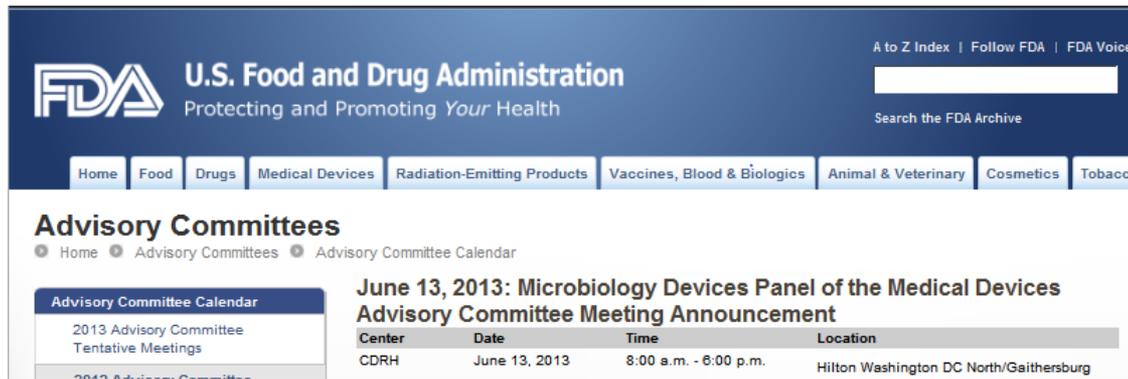
- Identify factors which can lead to improved RIDTs.
- Incentives and support needed from CDC, BARDA, FDA, professional societies, manufacturers, and others



# Better Tests

## *Proposed New Device Regulations*

- Inputs from studies and surveys informed new proposed U.S. Food and Drug Administration regulation to reclassify RIDTs from Class 1 devices to Class 2 devices with Special Controls
- June 13, 2013 public meeting of Microbiology Devices Panel



The screenshot shows the FDA website's "Advisory Committees" section. The main heading is "June 13, 2013: Microbiology Devices Panel of the Medical Devices Advisory Committee Meeting Announcement". Below this is a table with the following data:

| Center | Date          | Time                  | Location                                |
|--------|---------------|-----------------------|---|
| CDRH   | June 13, 2013 | 8:00 a.m. - 6:00 p.m. | Hilton Washington DC North/Gaithersburg |

<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm351035.htm>



# Benefits of Reclassification of RIDTs

- ❑ Enable FDA to enforce higher performance criteria and monitoring of annual reactivity testing and analytical performance validation by the manufacturers of influenza virus antigen detection systems
  
- ❑ Provide mechanisms for annual post-market evaluation
  - Provide panels of characterized virus reference standards
  - Annual performance monitoring against seasonal influenza
  - Evaluation against emerging novel influenza viruses

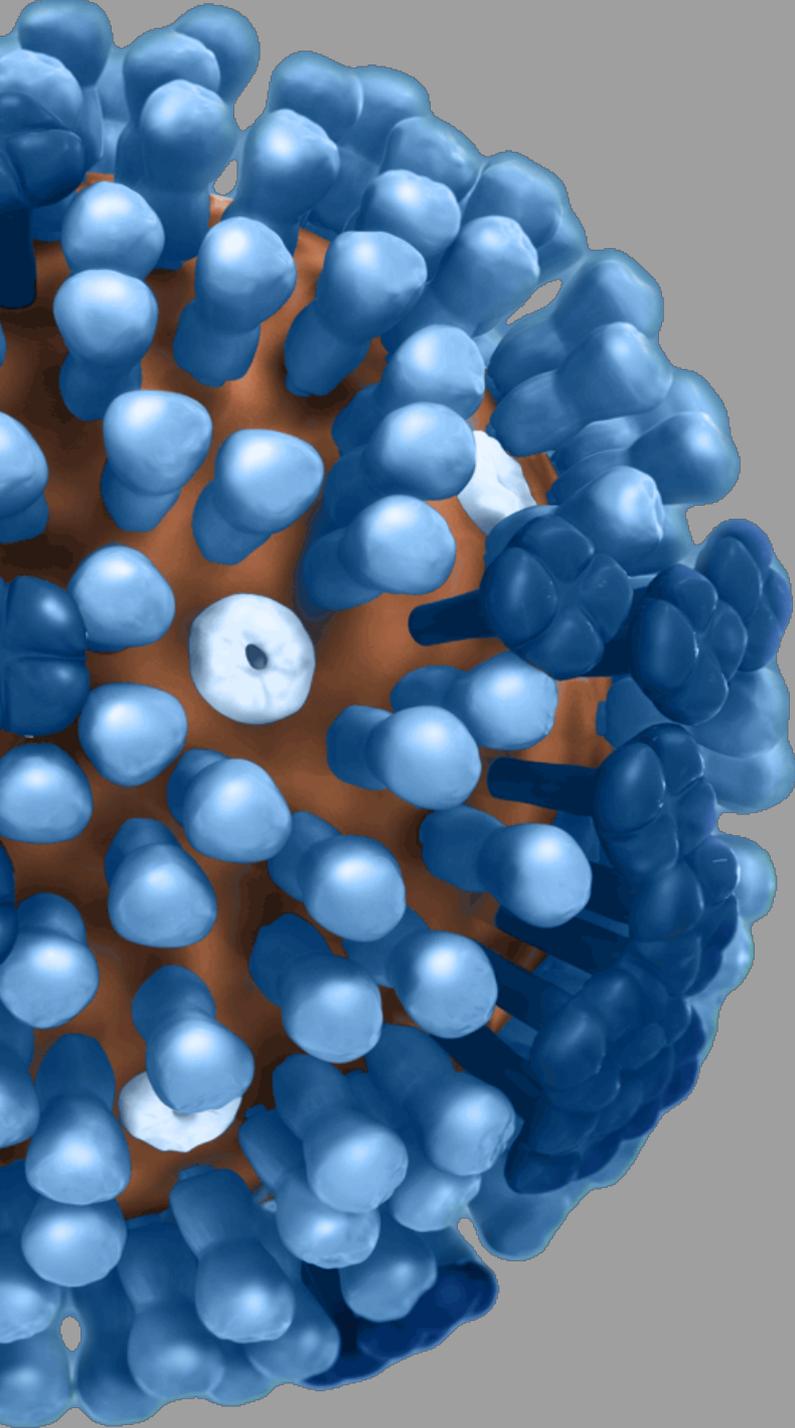
# Benefits of Reclassification to Public Health

## ❑ Heightened performance

- Minimum performance criteria to reduce sensitivity issues

## ❑ Introduction of advanced technologies

- Encourage manufacturers to develop new methods and techniques to assist the clinician in making an informed decision regarding patient management



# Benefits and Risks of OTC Influenza Diagnostic Tests

# Benefits of an OTC Influenza Test

- ❑ Earlier testing = Earlier treatment
  - Potential for patients seeking earlier treatment – especially high risk populations
  - Lower prescription of antibiotics
  
- ❑ Home testing may decrease healthcare visits for:
  - Worried well (negative results)
  - Lower risk patients with positive results
  - Self-quarantine - Possibly reduced community spread

**Assuming OTC tests with high sensitivity/specificity!**

# Benefits of an OTC Influenza Test

- ❑ Labeling/packaging gives an opportunity for improved education/guidance:
  - The lack of need for antibiotics for positive viral results
  - The importance of avoiding spread of infection
  - The importance for high-risk populations to seek medical care and potential treatment regardless of result
  
- ❑ Potential for improved surveillance data collection for public health

# Risks Associated with OTC Diagnostic Tests

- ❑ Primary risks of an inaccurate OTC diagnostic test result, due to either false positive or false negative results
- ❑ Respiratory specimen collection
  - Variability of specimen quality by untrained users
  - Safety considerations of self-sampling
- ❑ Reporting of results
  - possible loss of data
- ❑ Patient treatment/management

# Risks of an OTC Influenza Test:

## ❑ False Negative Result:

- Potential loss of treatment benefit
- Untreated influenza
- Increased community spread of infection
- Underestimation of burden

## ❑ False Positive Result:

- Unnecessary anti-viral medications
- Patient may not seek treatment for true cause of illness

# Risks of an OTC Influenza Test:

- ❑ Less testing in health care facilities and public health labs could negatively impact surveillance activities:
  - Fewer specimens submitted to public health labs for virus surveillance, (antigenic characterization, antiviral resistance testing and/or detection of novel influenza viruses)
  - Missing data on prevalence of influenza-like illness visits
  
- ❑ Poor Positive Predictive Value when influenza has low prevalence:
  - Patients who test when influenza is not active in their area have a higher risk of a false positive result

# Risks of an OTC Influenza Test:

- ❑ Potential for inaccurate results may increase if circulating flu strains change, most significantly if new strains emerge
- ❑ Requirements similar to those proposed for reclassification special controls on RIDTs may be necessary:
  - Standard reference method
  - Annual performance monitoring against seasonal influenza
  - Evaluation against emerging novel influenza viruses

# Questions OTC Influenza Test

## ❑ Performance?

- Highly performing tests critical to mitigate risks due to false positive/negative results.

## ❑ Reporting?

- Requirement for communication of results with clinicians necessary for proper patient management.
- Reporting mechanism of OTC test results important for public health surveillance.

## ❑ Challenges remain regarding performance of current point-of-care tests (RIDTs)

## ❑ Other considerations

- Ease of use
- Cost



# Thank you

