

2014-2015 Influenza Activity and CDC Antiviral Recommendations for Treatment of Patients with Influenza

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Objectives

- ❑ Provide an update of the 2014-2015 influenza season
- ❑ Review CDC influenza antiviral recommendations
- ❑ Discuss data that support the appropriate use of neuraminidase inhibitor (NAI) antiviral medications for treatment of influenza

Influenza Impact in U.S.

❑ Annual epidemics

- 5% - 20% of US population infected
 - highest illness rates in school age children
 - highest complication rates in elderly
- Annual average of 220,000 hospitalizations
 - About 50% in persons >65 yrs

❑ Estimated average of **3,349 to 48,614** influenza-attributable deaths/year (subtype and susceptibility dependent)

❑ >90% deaths are in persons >65 yrs (1976-2007)

SUMMARY OF 2014-15 INFLUENZA ACTIVITY

National Surveillance



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

U.S. Virologic Surveillance

	Week 1 (ending Jan 10, 2015)
No. of specimens tested	26,204
No. of positive specimens (%)	5,284 (20.2%)
Positive specimens by type/subtype	
Influenza A	5,051 (95.6%)
2009 H1N1	7 (0.1%)
H3	1,868 (37.0%)
Subtyping not performed	3,176 (62.9%)
Influenza B	233 (4.4%)

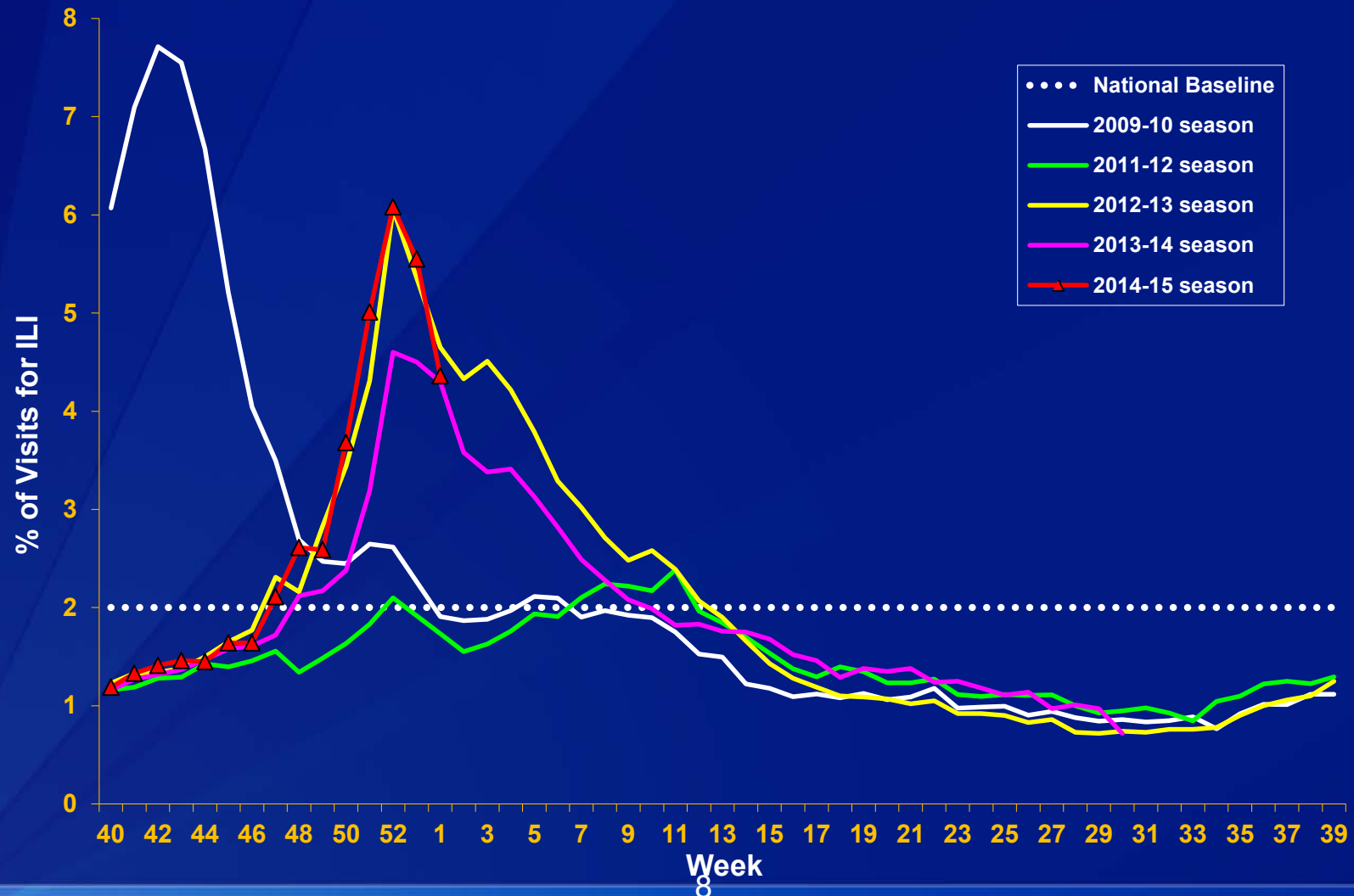
U.S. Virologic Surveillance

**Of 349 viruses tested, 227 (65.0%)
were antigenically or genetically
different from the H3N2 vaccine
virus.**

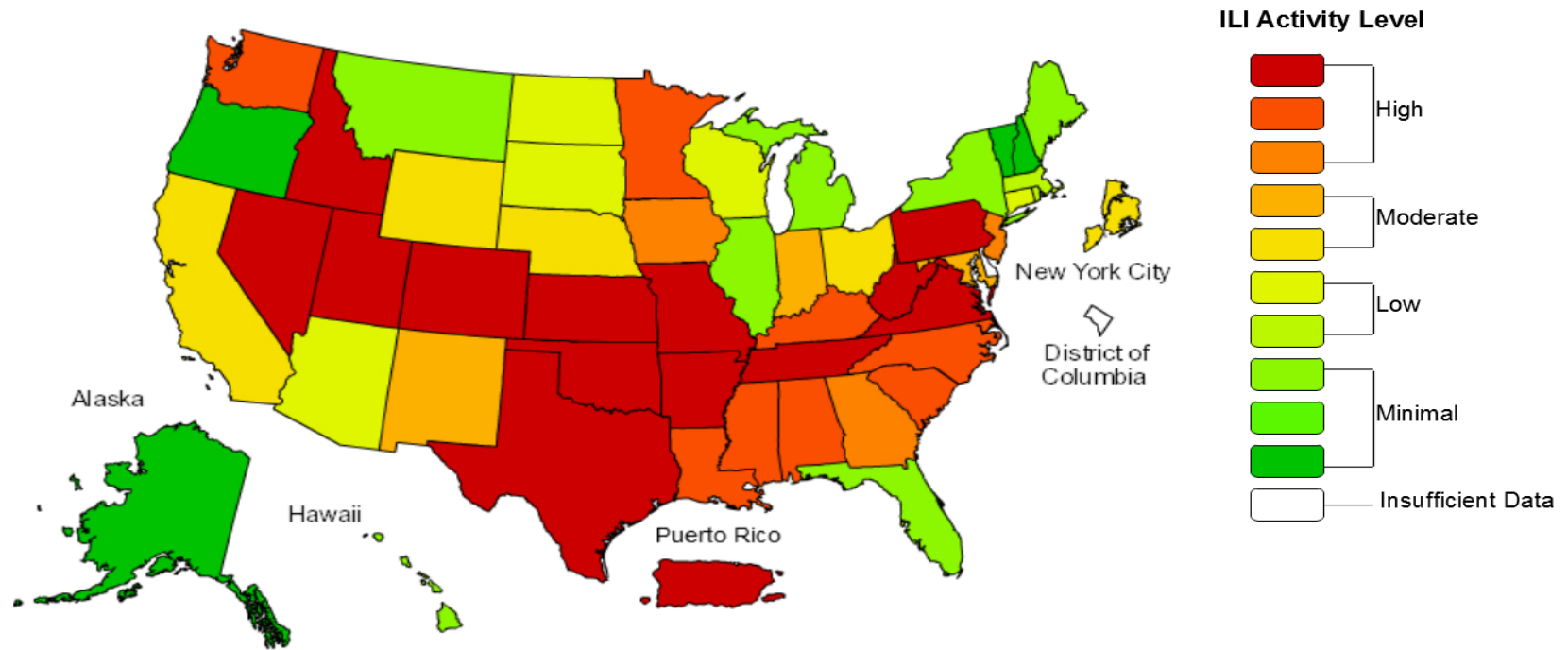
**Most were similar to
A/Switzerland/9715293/2013.**

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



Influenza-Like Illness (ILI) Activity Level Indicator Determined by Data Reported to ILINet
2014-15 Influenza Season Week 1 ending Jan 10, 2015



- **High / moderate ILI activity** – 31 states, PR, and NYC
- **Low / minimal activity** – 18 states
- **Insufficient Data** – 1 state and DC

Weekly Influenza Activity Estimates Reported by State & Territorial Epidemiologists*

Week ending January 10, 2015 - Week 1

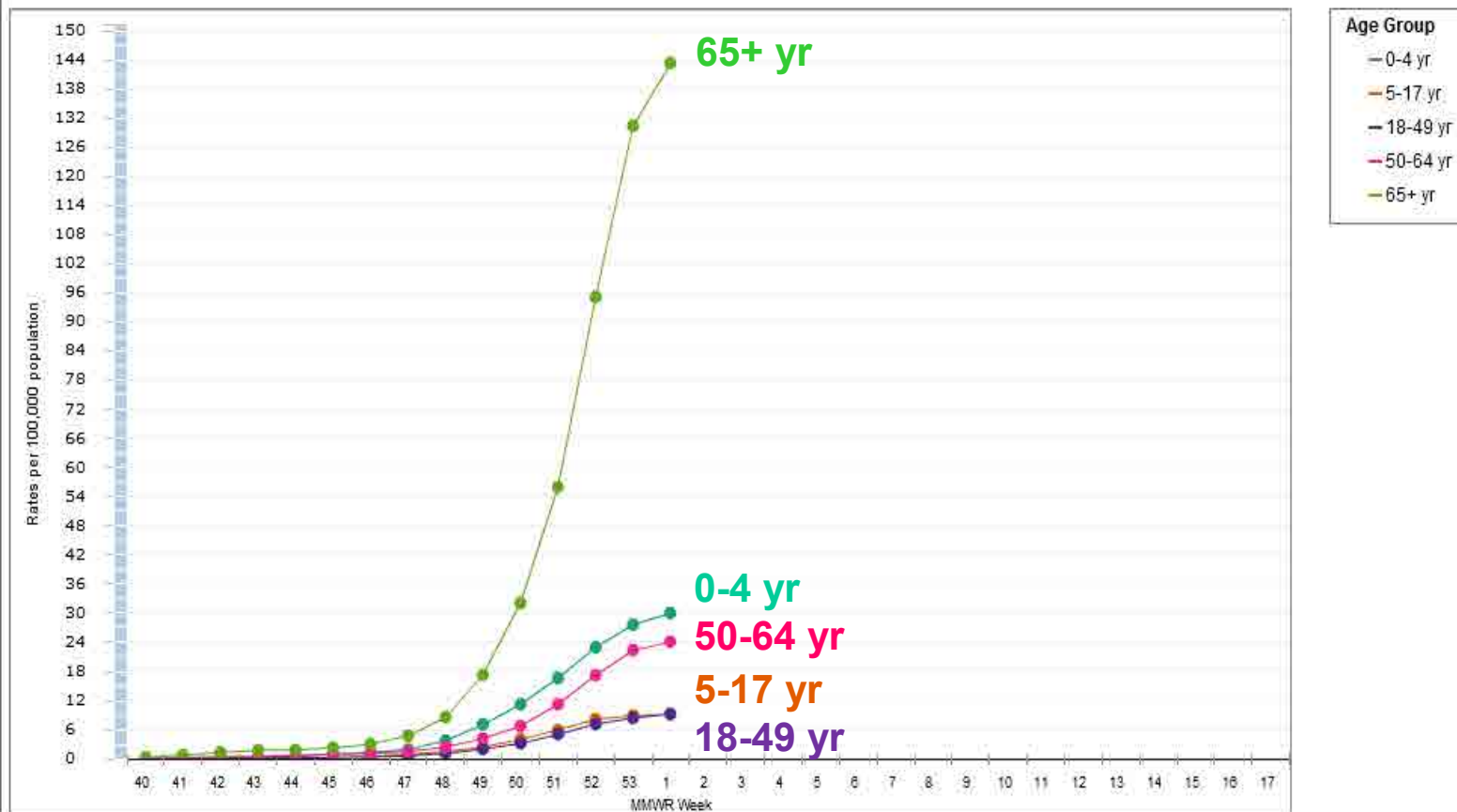


* This map indicates geographic spread & does not measure the severity of influenza activity

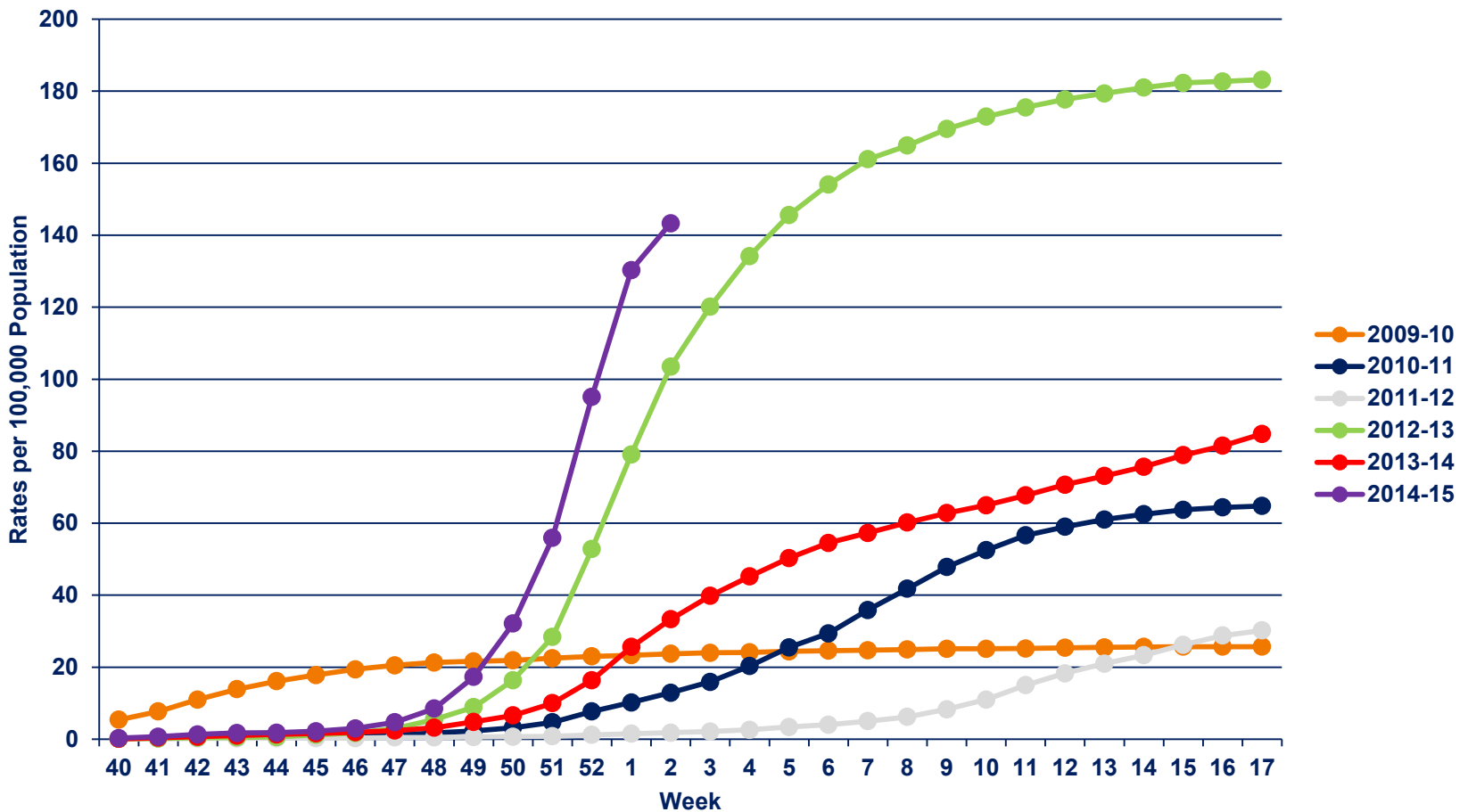
- **Widespread** – 46 states, Guam
- **Regional / local activity** – 4 states, DC, PR, USVI

Laboratory-Confirmed Influenza Hospitalizations

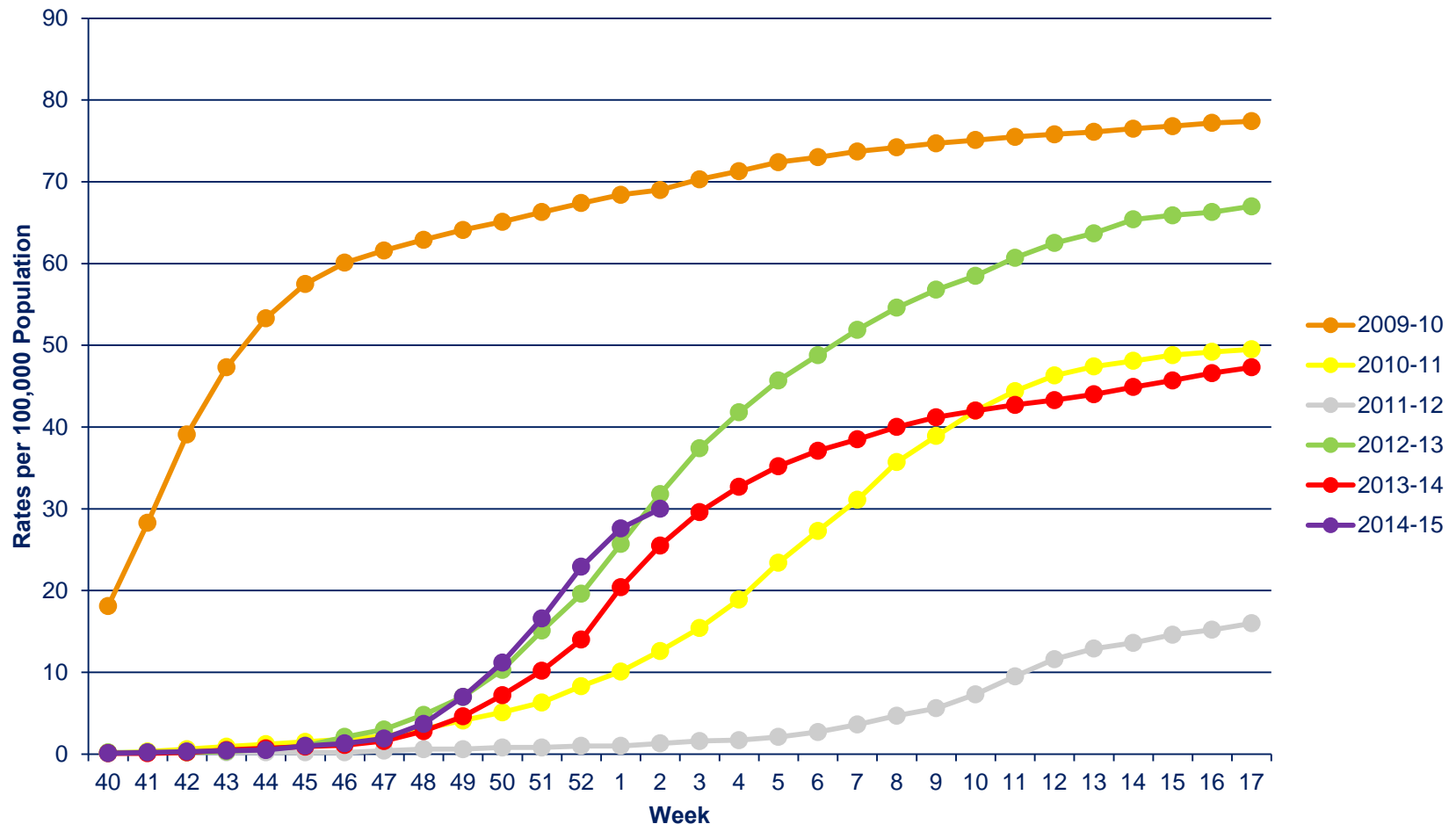
Preliminary rates as of Jan 10, 2015



Hospitalization Rates in People 65 and Older, by Season

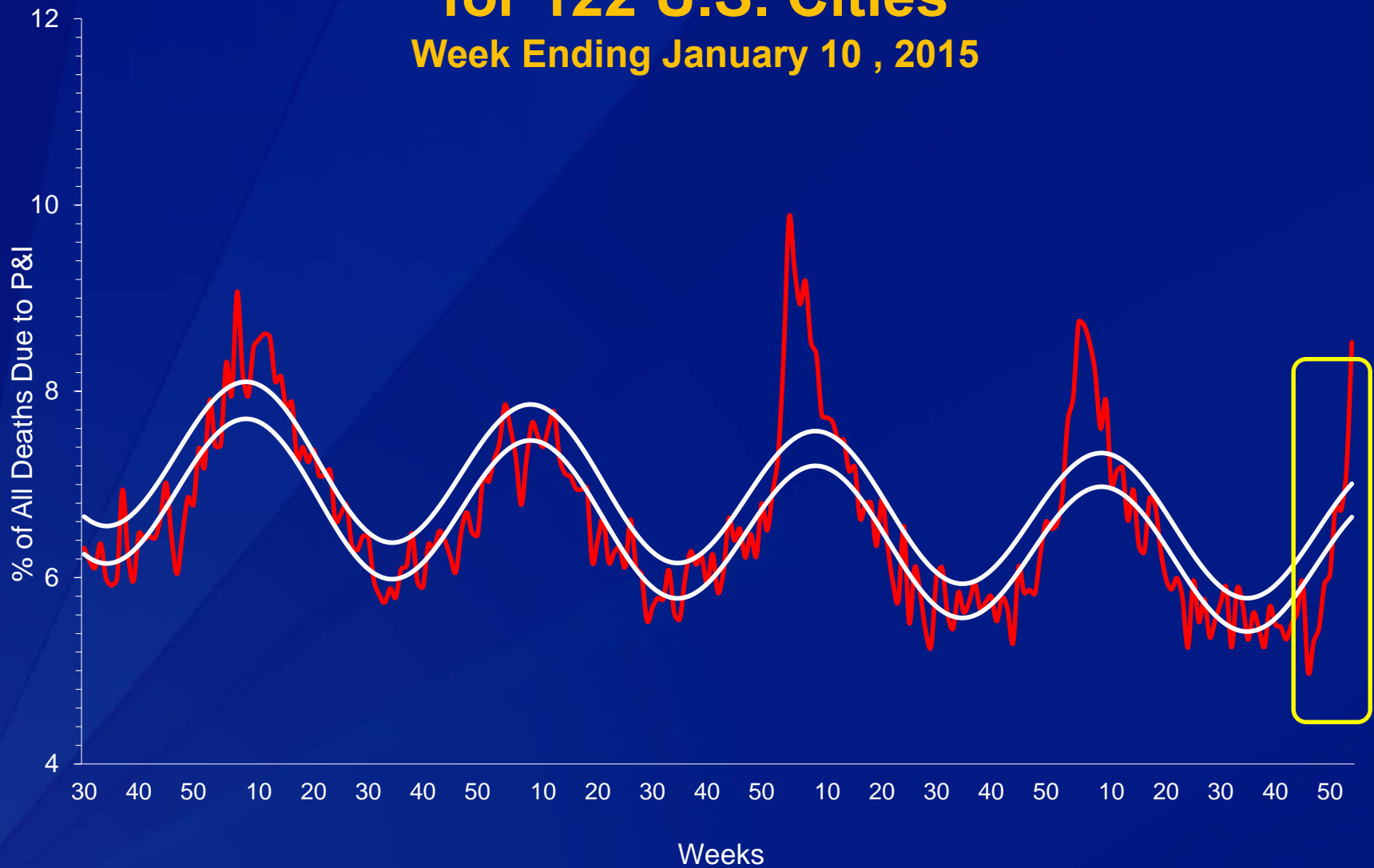


Hospitalization Rates in Children <5, by Season



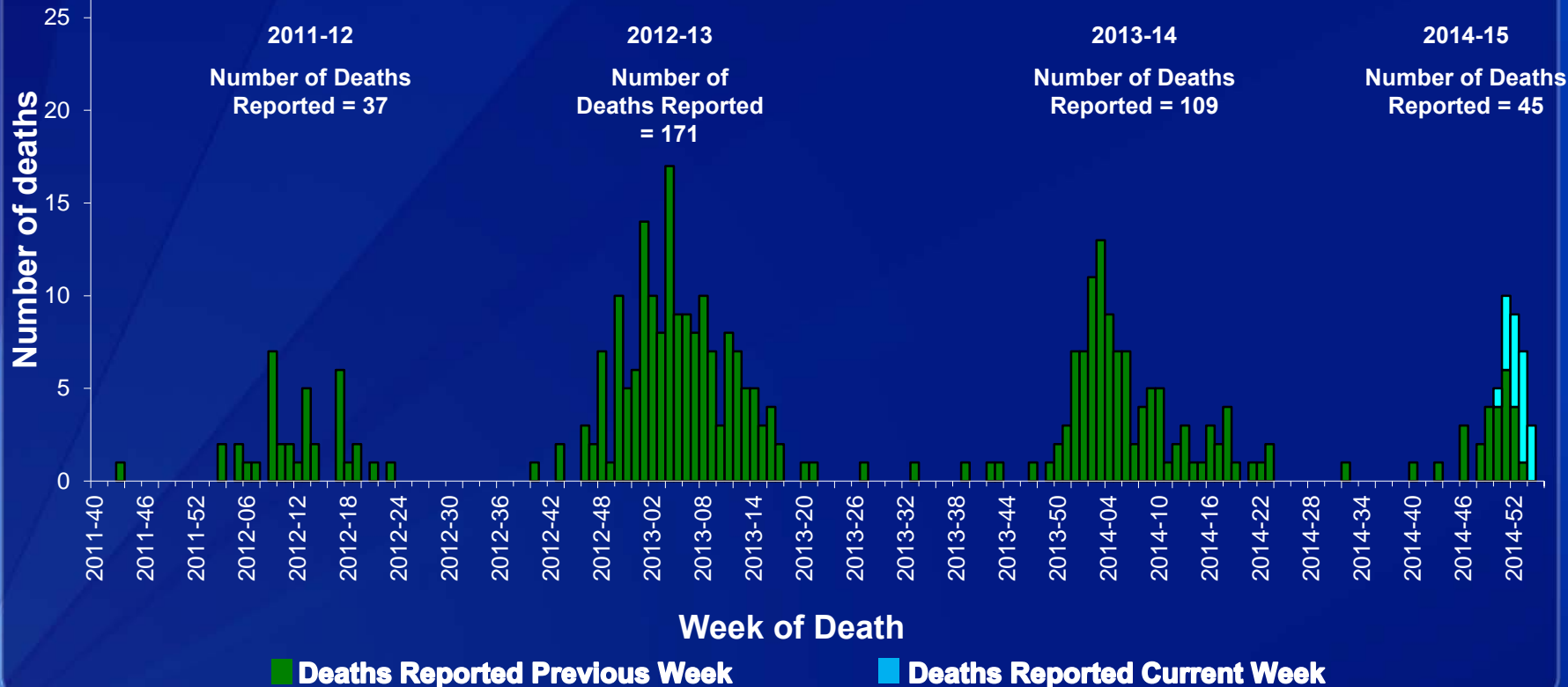
Week Ending January 10 , 2015

Week Ending January 10 , 2015



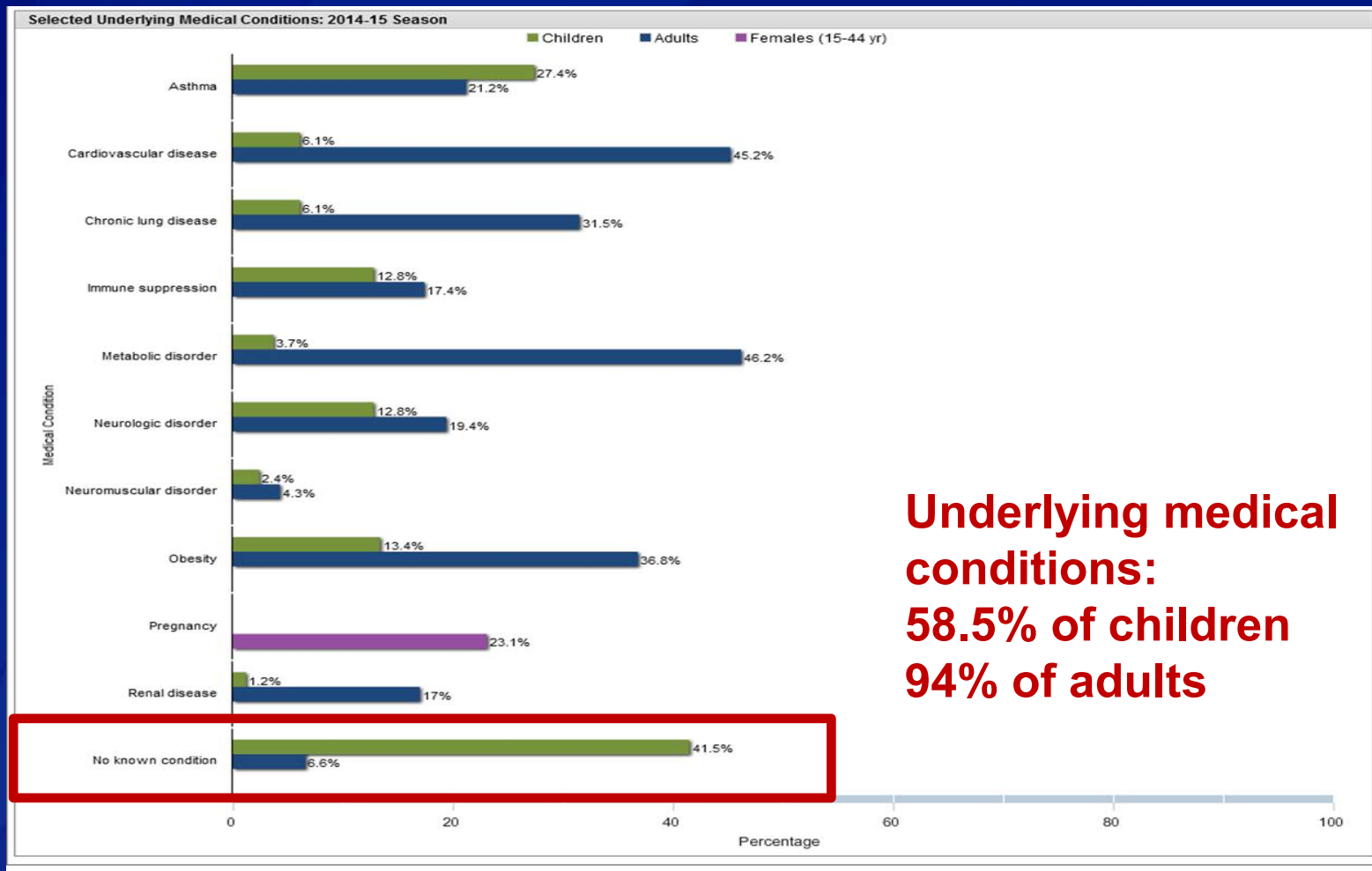
Number of Influenza-Associated Pediatric Deaths by Week of Death: 2011-12 Season to Present

	Influenza A (2009 H1N1)	Influenza A (H3N2)	Influenza A (Subtype not Determined)	Influenza B	Influenza A and B Co-infection	Type not Determined	Total
# Deaths Reported Current Week – 13	0	8	9	1	0	1	19
# Deaths Since September 28, 2014	0	20	19	4	0	2	45



Laboratory-Confirmed Influenza Hospitalizations

Preliminary rates as of Jan 10, 2015



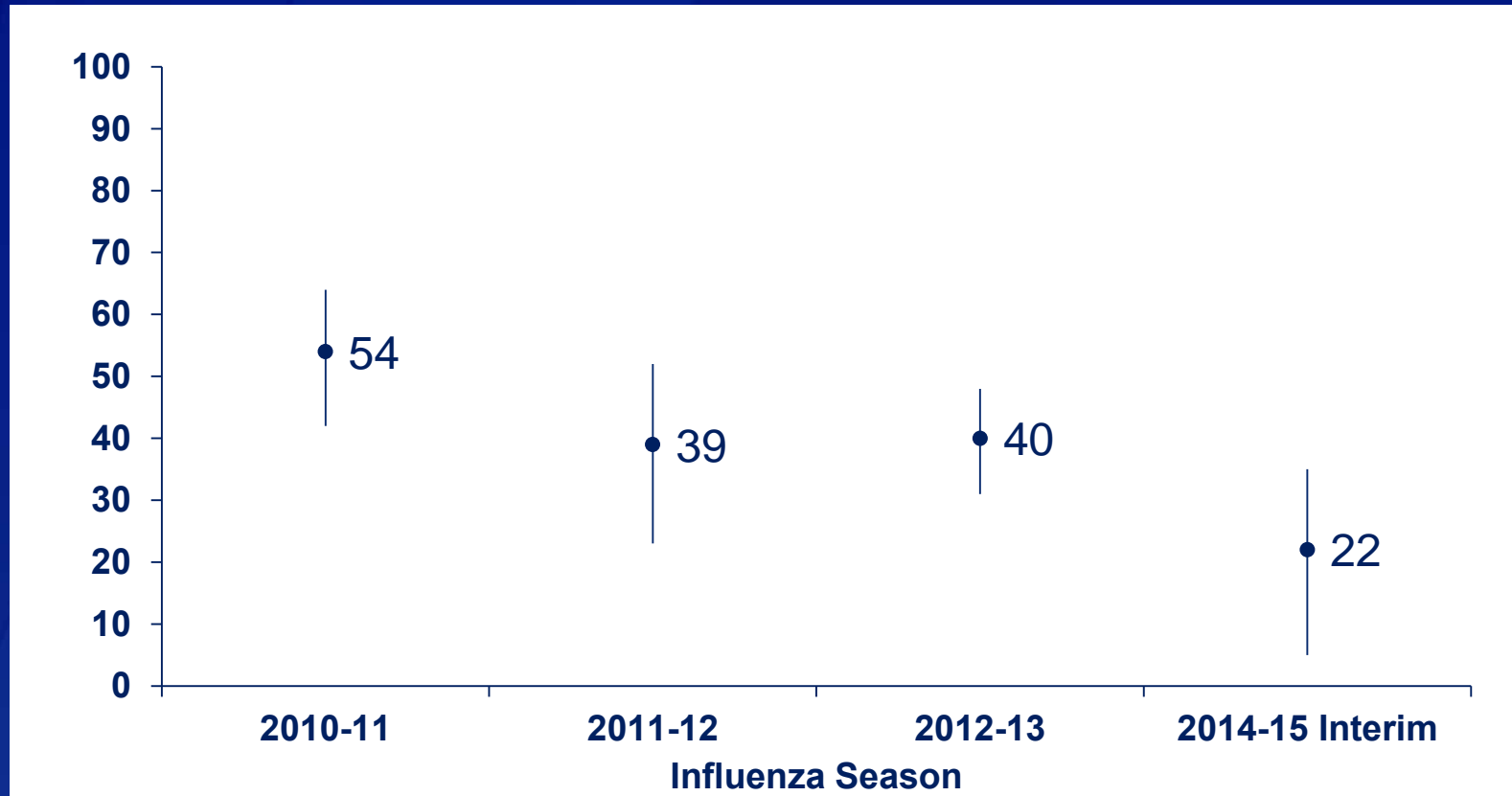
**Underlying medical conditions:
58.5% of children
94% of adults**

Interim adjusted VE estimates for ≥1 dose of 2014-15 seasonal influenza vaccine

	Flu pos	% vaccinated	Flu neg	% vaccinated	Adjusted VE	(95% CI)
Influenza A and B						
All ages	950	49%	1371	56%	23%	(8 to 36)
Age group (yrs)						
6 mos–17	410	39%	583	49%	24%	(0 to 43)
18–49	268	43%	400	48%	16%	(-18 to 41)
≥50	272	71%	388	76%	23%	(-14 to 47)
Influenza A (H3N2))						
All ages	841	48%	1371	56%	22%	(5 to 35)
Age group (yrs)						
6 mos–17	375	38%	583	49%	26%	(2 to 45)
18–49	235	43%	400	48%	12%	(-26 to 39)
≥50	231	71%	388	76%	14%	(-31 to 43)

* Vaccine effectiveness was estimated as 100% X (1 – odds ratio [ratio of odds of vaccination among flu-positive cases to odds of vaccination among flu-negative controls]) using logistic regression. Multivariate models adjusted for study site, age, sex, race/Hispanic ethnicity, self-rated health status, and days from illness onset to enrollment. Models for “all ages” include age as a categorical variable; age-specific models include age in years as a continuous variable.

Adjusted VE against Influenza A(H3N2), US Flu VE Network



Notes: Includes all ages. 2010-11 network sites included New York, Tennessee, Michigan, Wisconsin. In subsequent seasons, network sites included Michigan, Wisconsin, Pennsylvania, Washington, Texas.

1. Treanor (2012) CID 2. Ohmit (2013) CID 3. McLean et al. (2014) JID

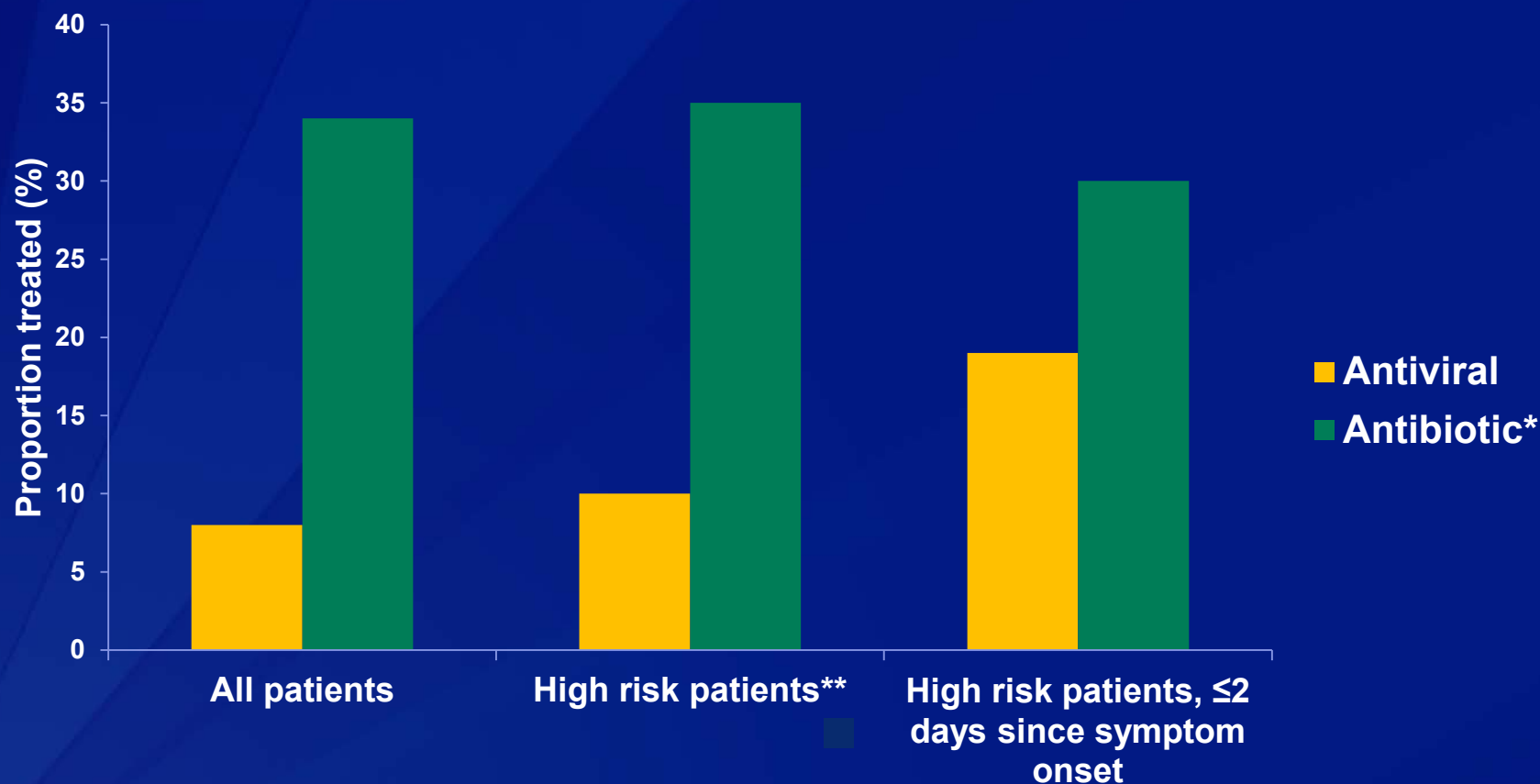
Season Overview

- ❑ **Influenza A(H3N2) viruses continue to be the most common so far in the United States**
 - H3N2 predominant years are often associated with higher mortality and hospitalization rates among older adults and young children
- ❑ **Activity so far this season is similar to the 2012-2013 season, the last season when H3N2 viruses predominated**
- ❑ **So far ~2/3 of H3 viruses analyzed are antigenically or genetically different from the H3N2 component in the 2014-15 vaccine**

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 2-day window that is optimal for treatment

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

RESPONSE TO THE 2014-15 INFLUENZA SEASON

This is an official
CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
December 03, 2014, 16:00 ET (4:00 PM ET)
CDCHAN-00374

**CDC Health Advisory Regarding the Potential for Circulation of Drifted
Influenza A (H3N2) Viruses**

- ❑ **Vaccination should still be the most important first step in protecting against flu**
 - Even a vaccine with low vaccine effectiveness can prevent some infection
 - Protection against other viruses (e.g., H1N1 & B) that may circulate this season
- ❑ **This season, the use of neuraminidase inhibitor (NAI) antiviral medications is especially important when indicated for treatment and prevention of influenza**

CDC Health Update – Take Two

This is an official
CDC HEALTH UPDATE

Distributed via the CDC Health Alert Network
January 9, 2015, 11:00 ET
CDCHAN-00375

CDC Health Update Regarding Treatment of Patients with Influenza with Antiviral Medications

As a follow-up to HAN 00374 (<http://emergency.cdc.gov/han/han00374.asp>, Dec. 3, 2014), CDC is providing 1) a summary of influenza antiviral drug treatment recommendations, 2) an update about approved treatment drugs and supply this season, and 3) background information for patients regarding anti-influenza treatment.

CDC Health Update: Jan 9, 2015

Reminders to Clinicians

- ❑ Influenza should be high on the list of possible diagnoses for ill patients**
- ❑ All hospitalized patients and all high-risk outpatients with suspected or confirmed influenza should be treated as soon as possible without waiting for confirmatory testing**

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

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

Influenza Antiviral Medications: The Data Behind the Recommendations

Clinical trials and observational data show that early antiviral treatment can:

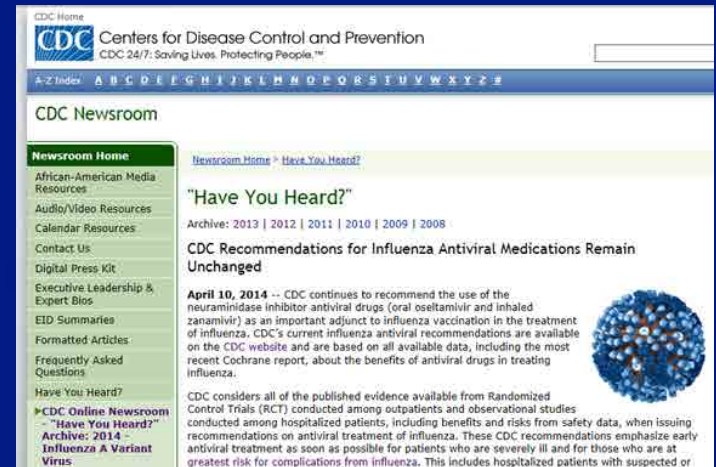
- ❑ Shorten the duration of fever and illness symptoms**
- ❑ Reduce the risk of complications (such as otitis media in children and pneumonia requiring antibiotics in adults)**
- ❑ Reduce the risk of death among hospitalized patients**

Data for Uncomplicated Influenza: Cochrane Review 2014

- ❑ **Analyzed treatment RCTs evaluating outcomes in the intention-to-treat (ITT) population (with and without flu): 15 oral oseltamivir and 16 inhaled zanamivir trials**
 - Most among otherwise healthy persons with influenza-like illness (ILI) during seasonal epidemics
- ❑ **NAIs reduced time to symptom alleviation**
 - Oseltamivir vs placebo in adults by ~17 hr, in children by ~29 hr
 - Zanamivir vs placebo in adults by ~14 hr
- ❑ **Reduced investigator-mediated unverified pneumonia by 45%; no benefits in studies that recorded pneumonia in more detail**
- ❑ **No evidence to support reduction in other flu-related complications (sinusitis, bronchitis, OM) or hospitalizations**
- ❑ **4-5% increased N/V in adults; 5% increased vomiting in children**

Assessment and Limitations of Cochrane Review

- ❑ Findings similar to previously published RCTs
 - All showed 1-2 day reduction in illness duration for early NAI treatment
- ❑ Analyzed only ITT results – because neuraminidase inhibitors are active against influenza, one analysis should have evaluated outcomes in the Intention-to-Treat-Infected (ITTI) patients
- ❑ Placebo controlled RCTs evaluated effect of treatment in healthy, non high-risk outpatients
 - None designed or powered to assess severe outcomes (hospitalization, ICU, death) or outcomes in high-risk persons
 - Persons at high-risk of influenza complications generally not in RCTs
- ❑ No published RCTs evaluating hospitalized patients



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**
 - Cochrane review did not consider data from observational studies
- ❑ **Antiviral recommendations are common to ACIP, IDSA, AAP**

Data Regarding Oseltamivir Effectiveness: Hospitalized Patients

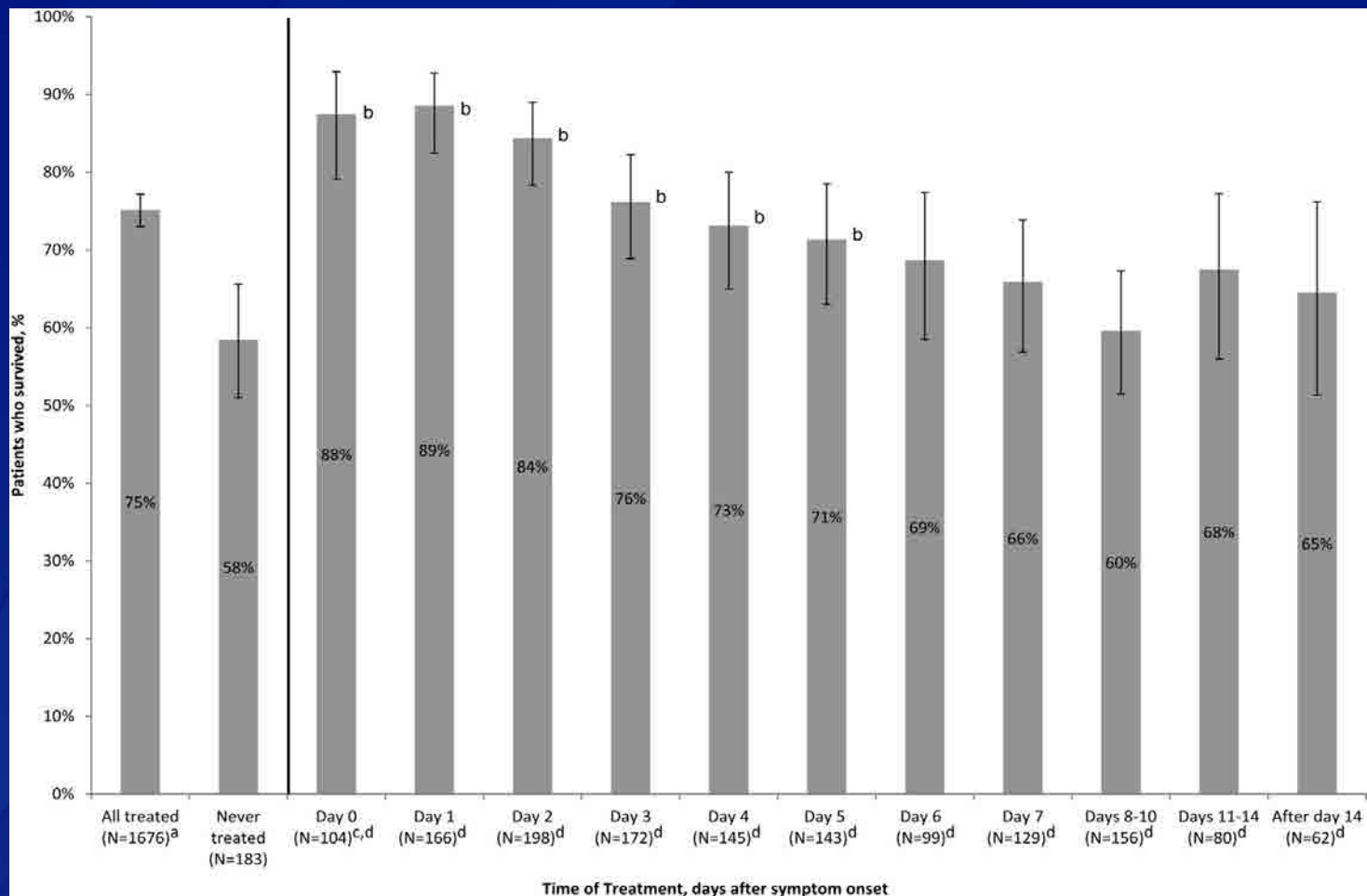
Study	Med. age (yr)	Setting; % Treated	Antiviral Effect (against death unless specified)
McGeer* 2007	77	Hosp; 32%	Treated vs untreated: aOR 0.21 (0.06-0.80)
Lee* 2010	70	Hosp; 52%	Treated vs untreated: aHR 0.27 (0.13-0.55) Treated vs untreated <2d: aHR 0.29 (0.14-0.61) Treated vs untreated <4d aHR 0.34 (0.17-0.70)
Hiba 2011	39-48	Hosp; 100%	Late vs early treatment: aOR 3.28 (1.56-6.89), for severe complications (death, ICU, MV)
Louie* 2012	37	ICU; 90%	No treatment: 58% survival Early treatment (day 0): 88% survival Treatment ≤ 4 d: 73% survival
Louie 2013	6	ICU; 83%	Treated vs untreated: aOR 0.36 (0.16-0.83)

p for trend
<0.0001

*Studies suggesting that treatment initiation >48 hours may be beneficial

McGeer CID 2007;45:1568-75; Lee Thorax 2010;65:510-5; Hiba JAC 2011;66:1150-55;
Louie CID 2012;55:1198-204; Louie CID 2013;132:e1539-45

Survival by Timing of Treatment in Critically Ill Patients with 2009 H1N1



Data Regarding NAIs Effectiveness: Hospitalized Patients

- Recent large meta-analysis of individual patient-level data from 78 observational studies on >29,000 patients hospitalized during 2009-10 H1N1 pandemic
 - Adults: treatment associated with a 25% reduction in likelihood of death compared to no antiviral treatment; aOR **0.75** (0.64-0.87)
 - Pregnant women: aOR **0.46** (0.23-0.89)
 - Children: aOR 0.82 (0.58-1.17)
 - Treatment within 48 hr of symptom onset halved the risk of death compared to no antiviral treatment; aOR **0.51** (0.45-0.58)

Effectiveness of Oseltamivir to Prevent Complications: Outpatients – Children

Study	Method	Outcome	Antiviral Effect among Influenza + (Intent to Treat Infected; ITTI)
Whitley 2001	RCT secondary outcome; Children 1-12 yrs	Otitis media	44% reduction
Heinonen 2010	RCT; Children 1-3 yrs	Otitis media	Initiate ≤ 12 hr: 85% reduction; Initiate > 24 hr: no reduction

Whitley PIDJ 2001;20:127-33; Heinonen 2010 CID;51:887-94

Effectiveness of NAI Treatment to Prevent Complications: Outpatients

Study	Method	Outcome	Antiviral Effect among Influenza + (ITTI)
Hernan 2011	Meta-analysis, 11 pub & unpub RCTs	LRTC requiring antibiotics	37% (18-52%) reduction
Lipsitch 2013	Re-analysis 2011 data: excl. serology +	LRTC requiring antibiotics	33% (3-54%) reduction
Hsu 2012	Meta-analysis, 74 pub & unpub obs. studies	Hospitalization	OR 0.75 (0.66-0.89); <48 hr: OR 0.52 (0.33-0.81)
Ebell 2013	Meta-analysis, 11 pub & unpub RCTs	Pneumonia All complications* Hospitalization	Pneumonia ITTI: -0.9% ; All comps ITTI: -2.8% ; Hosp ITT: no diff
Cochrane Rev. 2014	Meta-analysis, 31 pub & unpub RCTs	Pneumonia**	ITT: RR 0.55 (0.33-0.90)

LRTC = lower respiratory tract complications;

* All complications = otitis media, sinusitis, pneumonia, bronchitis

** Investigator-mediated unverified

Summary of Data Evaluating Reduction in Complications after Outpatient Treatment

- ❑ Not enough hospitalizations to evaluate
- ❑ Persons at highest risk of developing severe complications generally not studied in RCTs
- ❑ Pooled data from RCTs consistently show a reduction in pneumonia requiring antibiotics among adults; reduction in otitis media shown for children
- ❑ *Pending* – Individual patient data meta-analysis of RCTs comparing oseltamivir with placebo for treatment of outpatients with influenza (Multiparty Group for Advice on Science)

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 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

- ❑ 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

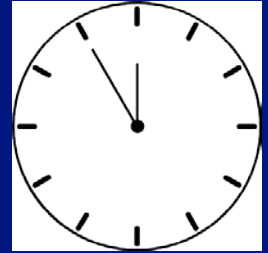
- ❑ Children <2 years
- ❑ Adults ≥ 65 years
- ❑ Pregnant and postpartum women (within 2 weeks after delivery)
- ❑ American Indians and Alaska Natives
- ❑ Persons who are morbidly obese (BMI ≥ 40)
- ❑ Residents of long-term care facilities



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**

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

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 is recommended (dose for children >6 years: 10 mg/kg once daily [up to 600 mg]); minimum of 5 days duration*

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**

Additional Information: Pneumococcal Vaccine Recommendations

- ❑ **Pneumococcal infections are a serious complication of influenza infection**
- ❑ **New pneumococcal vaccine recommendations for adults ≥ 65 years, and adults and children at increased risk for invasive pneumococcal disease due to chronic underlying medical conditions should be followed:**
 - <http://www.cdc.gov/vaccines/vpd-vac/pneumo/vac-PCV13-adults.htm>
 - <http://www.cdc.gov/vaccines/vpd-vac/pneumo/vacc-in-short.htm>

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
 - Consider for all, regardless of vaccination status, if outbreak is caused by a virus that is not well matched to the vaccine
 - For a minimum of 2 weeks, continuing at least 7 days after last known case identified

Antiviral Supply

- ❑ **No current national shortages**
 - Manufacturers have stated they have sufficient product on hand to meet the projected high demand
- ❑ **Local spot shortages have been reported, specifically for Tamiflu formulations**
- ❑ **It may be necessary to contact more than one pharmacy to fill a prescription for an antiviral medication**
- ❑ **Pharmacies that are having difficulties getting orders filled should contact their distributor or the manufacturer directly**

CDC Antiviral Call Center – 1

- ❑ For long-term care facilities or institutions experiencing difficulty accessing antiviral supplies in outbreak settings**
- ❑ CDC will coordinate with commercial partners to facilitate the rapid resolution of large orders of antiviral drugs**

CDC Antiviral Call Center – 2

- ❑ **As of Jan. 12, the Division of Strategic National Stockpile (DSNS) is available from 7:00 AM to 7:00 PM EST, Mon – Fri, to assist public health officials and health care facilities by coordinating with supply chain partners to rapidly redirect supply to the identified location**
- ❑ **Contact DSNS at dsns-Request@cdc.gov for assistance with facility specific unmet antiviral drug supply needs**

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**

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 of RT-PCR and Other Molecular Assays for Diagnosis of Influenza Virus Infection:**
<http://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm>
- ❑ **Interim Guidance for Influenza Outbreak Management in Long-Term Care Facilities:**
<http://www.cdc.gov/flu/professionals/infectioncontrol/ltc-facility-guidance.htm>
- ❑ **FDA Influenza (Flu) Antiviral Drugs and Related Information (including package inserts):**
<http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm>

Thank You

<http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>



Questions?

- Don't forget to MUTE your phones if possible. If you don't... we all get to hear you and your conversations.
- Don't ever put our call on hold as everyone on the call will then hear your VAMC music!
- This program will be repeated, LIVE, on Mon., Jan 26th. VANTS code: 76901# at 3 pm EASTERN. Slides are posted at <https://vaww.vha.vaco.portal.va.gov/sites/PublicHealth/handhygiene/Teleconference%20Slides/Forms/AllItems.aspx>

GET A FLU SHOT



Flu is **STILL** spreading
Flu season can last into springtime

FLU SHOTS ARE AVAILABLE HERE

Protect yourself and your loved ones from flu & other germs by:

1. Getting a flu shot 
2. Covering your sneezes & coughs 
3. Keeping your hands clean 

 www.publichealth.va.gov/infectionDontPassItOn  **VA** DEFINING EXCELLENCE in the 21st Century FIG 10-101