2011-2012 Influenza Season: Antiviral Medication Recommendations

Clinician Outreach and Communication Activity (COCA) Conference Call

February 28, 2012

Office of Public Health Preparedness and Response
Division of Emergency Operations

Objectives

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

- List currently recommended influenza antiviral medications
- Understand recommendations for use of influenza antiviral medications for the 2011-2012 influenza season
- Understand the potential benefits of antiviral treatment as outlined by the Advisory Committee on Immunization Practices (ACIP) and CDC

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Today's Presenter

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Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Dr. Tim Uyeki, MD, MPH, MPP

National Center for Immunization & Respiratory Diseases
Influenza Division

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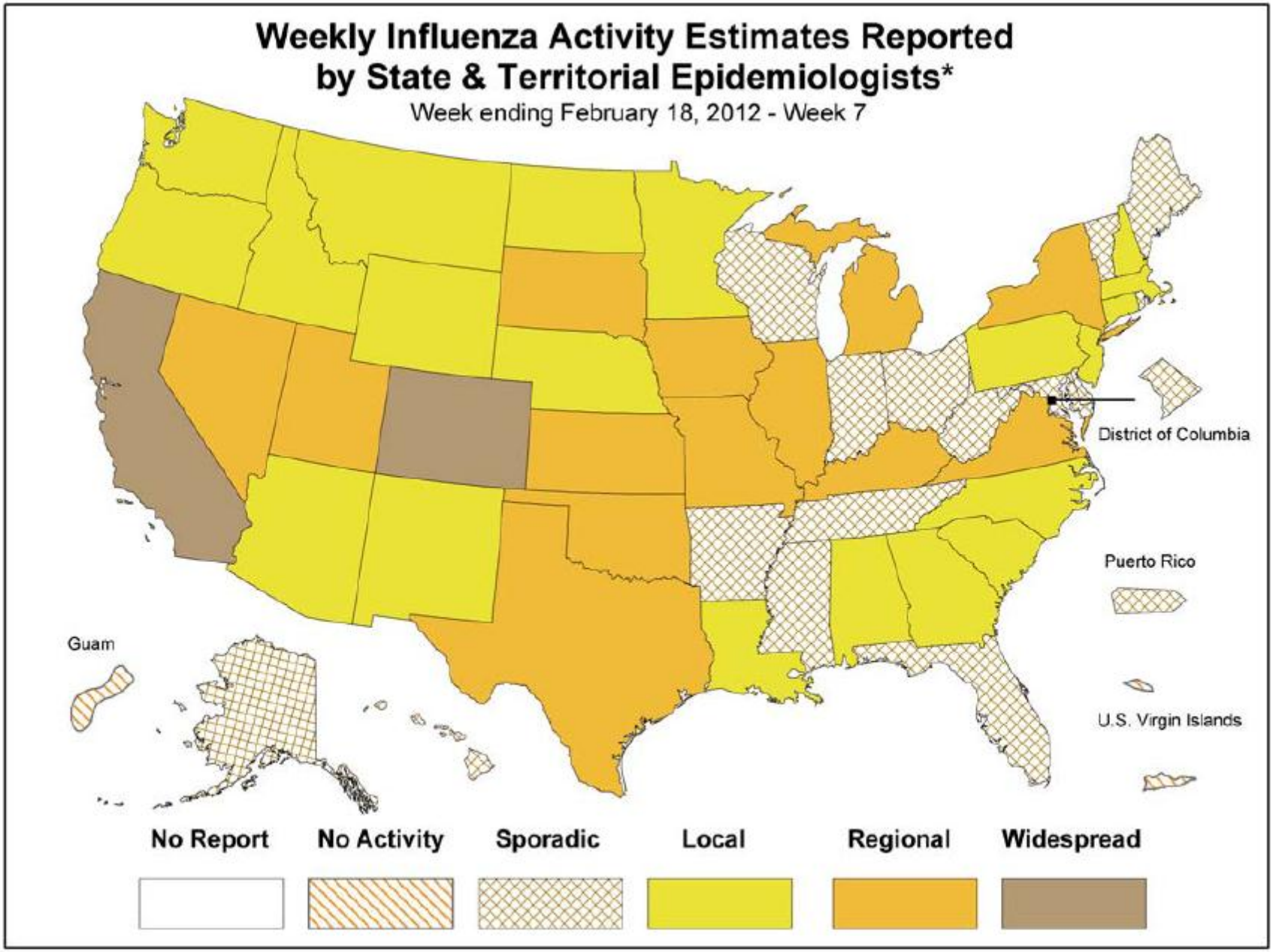
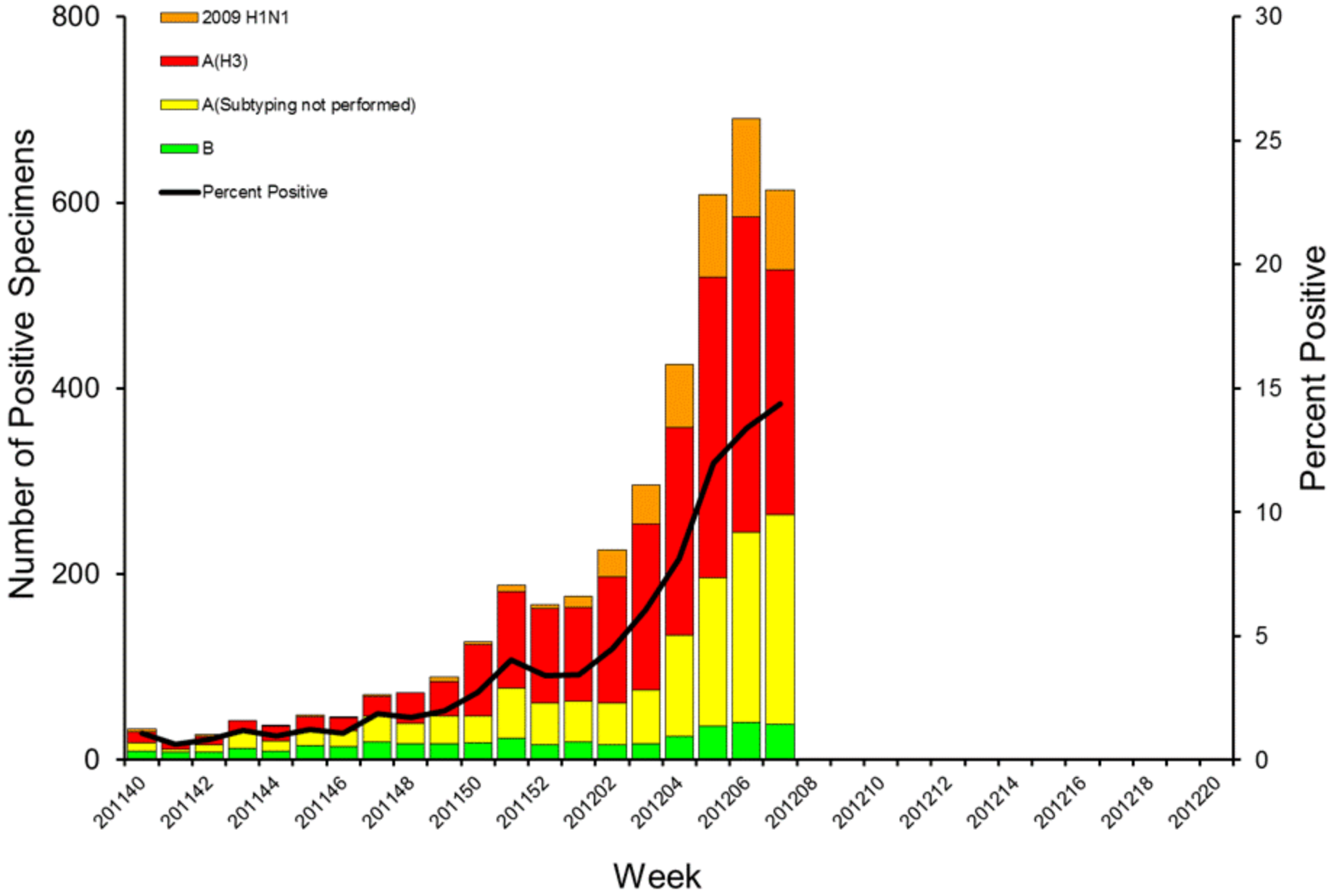


* This map indicates geographic spread & does not measure the severity of influenza activity

Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2011-12



U.S. Virologic Surveillance: WHO and NREVSS collaborating laboratories located in all 50 states report to CDC the number of respiratory specimens tested for influenza and the number positive by influenza type and subtype. The results of tests performed during the current week are summarized in the table below.

	Week 7
No. of specimens tested	4,269
No. of positive specimens (%)	614 (14.4%)
Positive specimens by type/subtype	
Influenza A	576 (93.8%)
2009 H1N1	86 (14.9%)
Subtyping not performed	226 (39.2%)
(H3)	264 (45.8%)
Influenza B	38 (6.2%)

Nationally, a low but increasing number of influenza positive specimens have been reported this season, with influenza A (H3N2) viruses being most common. However, there are regional differences in activity levels and which viruses predominate. Over the past several weeks, the proportion of 2009 H1N1 viruses identified has increased nationally and in several regions, most notably in Regions 6, 8, and 9.

Antigenic Characterization: CDC has antigenically characterized 397 influenza viruses [58 2009 H1N1, 291 influenza A (H3N2) viruses, and 48 influenza B viruses] collected by U.S. laboratories since October 1, 2011.

2009 H1N1 [58]

- Fifty-six (96.6%) of the 58 viruses were characterized as A/California/7/2009-like, the influenza A (H1N1) component of the 2011-2012 influenza vaccine for the Northern Hemisphere.
- Two viruses (3.4%) tested showed reduced titers with antiserum produced against A/California/7/2009.

Influenza A (H3N2) [291]

- Two hundred seventy-seven (95.2%) of the 291 viruses were characterized as A/Perth/16/2009-like, the influenza A (H3N2) component of the 2011-2012 influenza vaccine for the Northern Hemisphere.
- Fourteen viruses (4.8%) tested showed reduced titers with antiserum produced against A/Perth/16/2009.

Influenza B (B/Victoria/02/87 and B/Yamagata/16/88 lineages) [48]:

- **Victoria Lineage [22]**: Twenty-two (45.8%) of the 48 influenza B viruses tested belong to the B/Victoria lineage of viruses and were characterized as B/Brisbane/60/2008-like, the influenza B component of the 2011-2012 Northern Hemisphere influenza vaccine.

- **Yamagata Lineage [26]**: Twenty-six (54.2%) of the 48 influenza B viruses tested belong to the B/Yamagata lineage of viruses.

Introduction

Antiviral Recommendations for 2011-2012

- Antiviral treatment is recommended **as soon as possible** for:
  - Patients with confirmed or suspected influenza who are hospitalized, or have severe, complicated or progressive illness
  - Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications based on their age and/or medical conditions
    - Clinical judgment should be an important component of outpatient treatment decisions
- Recommended antiviral medications are neuraminidase inhibitors (oral oseltamivir and inhaled zanamivir)
  - Based on recent viral surveillance and resistance data indicating that currently circulating influenza virus strains are sensitive to these medications
- Oral oseltamivir should be used for treatment or chemoprophylaxis for infants younger than one year old, when indicated

Introduction

Antiviral Recommendations for 2011-2012 (continued)

- Because antiviral resistance patterns may change over time, clinicians should monitor local influenza antiviral resistance surveillance data
- Antiviral treatment can be considered for any previously healthy, non-high risk, symptomatic outpatient with confirmed or suspected influenza who is not in the recommended groups, based upon clinical judgment, if treatment can be initiated within 48 hours of illness onset

Influenza Virus Transmission

- **Large particle respiratory droplet transmission**
  - Traditionally thought to be the primary mode of person-to-person spread (infected person coughing, sneezing close to a susceptible person)
  - Droplets travel short distances (within about 6 ft) – do not remain suspended in the air – close contact required
- **Relative contribution of different transmission modes is unclear; other possible transmission modalities:**
  - Airborne transmission via small particle aerosols in the vicinity of the infectious individual
  - Indirect contact via hand transfer of influenza virus from virus-contaminated surfaces/objects to mucosal surfaces of the face (e.g., nose, mouth)
- Airborne transmission over longer distances, such as from one patient's room to another has not been documented and is thought *not to occur*

Influenza Virus Transmission

Incubation period: 1-4 days (average: 2 days)

Serial interval: estimated 3-4 days among household contacts

Influenza viral shedding: generally declines after <4 days; detection depends upon testing methods

School-age children and adults: one day before symptoms begin through 5-7 days after illness onset

Young children: a few days before illness onset is possible through 10 or more days after onset of symptoms

Immunocompromised or severely immunosuppressed persons: prolonged influenza viral replication is possible, including weeks to months

Clinical Signs and Symptoms

- **Asymptomatic infection can occur** (contact, household, serological studies)
- **Uncomplicated influenza illness**
  - Abrupt onset of fever, myalgias, headache, malaise, nonproductive cough, sore throat, rhinitis
  - Acute respiratory Illness without fever
  - Young children: less likely to experience typical influenza signs and symptoms (present with dehydration, irritability, poor oral intake)
    - Infants can present with fever only
  - Atypical presentations
    - Elderly may not manifest fever or classic "influenza-like illness"
    - Immunocompromised, severely immunosuppressed patients
- Difficult to identify influenza illness from clinical signs and symptoms alone
  - Multiple etiologies for acute febrile respiratory illness, especially in young children
  - *Diagnosis of influenza should be considered in patients with acute respiratory illness signs and symptoms when influenza viruses are circulating in the community*

Clinical Signs and Symptoms

- **Complications from influenza virus infections:**
  - Moderate complications: sinusitis, otitis media
  - **Exacerbation of underlying conditions** *(e.g., pulmonary or cardiac disease)*
  - **Primary influenza viral pneumonitis and pneumonia**
    - Progressing to respiratory failure and acute respiratory distress syndrome *(can be fulminant)*
    - *Vasopressor dependent shock; acute renal failure*
  - **Coinfections** with other viral or bacterial pathogens
    - Secondary bacterial pneumonia, sepsis

Clinical Signs and Symptoms

- **Complications from influenza virus infections (continued):**
  - **Secondary bacterial pneumonia and/or sepsis** *(can be fulminant)*
    - *Staphylococcus aureus (MSSA, MRSA), Streptococcus pneumoniae, Streptococcus pyogenes*
  - Cardiac: myocarditis, pericarditis *(uncommon)*
  - Neurologic: wide range: febrile seizures to encephalopathy, acute necrotizing encephalitis, transverse myelitis, Reye's syndrome
  - Musculoskeletal: myositis, rhabdomyelitis
  - Young children: initial symptoms can mimic bacterial sepsis (high fever only)
  - ➢ Severe complications can occur even among young and previously healthy persons

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

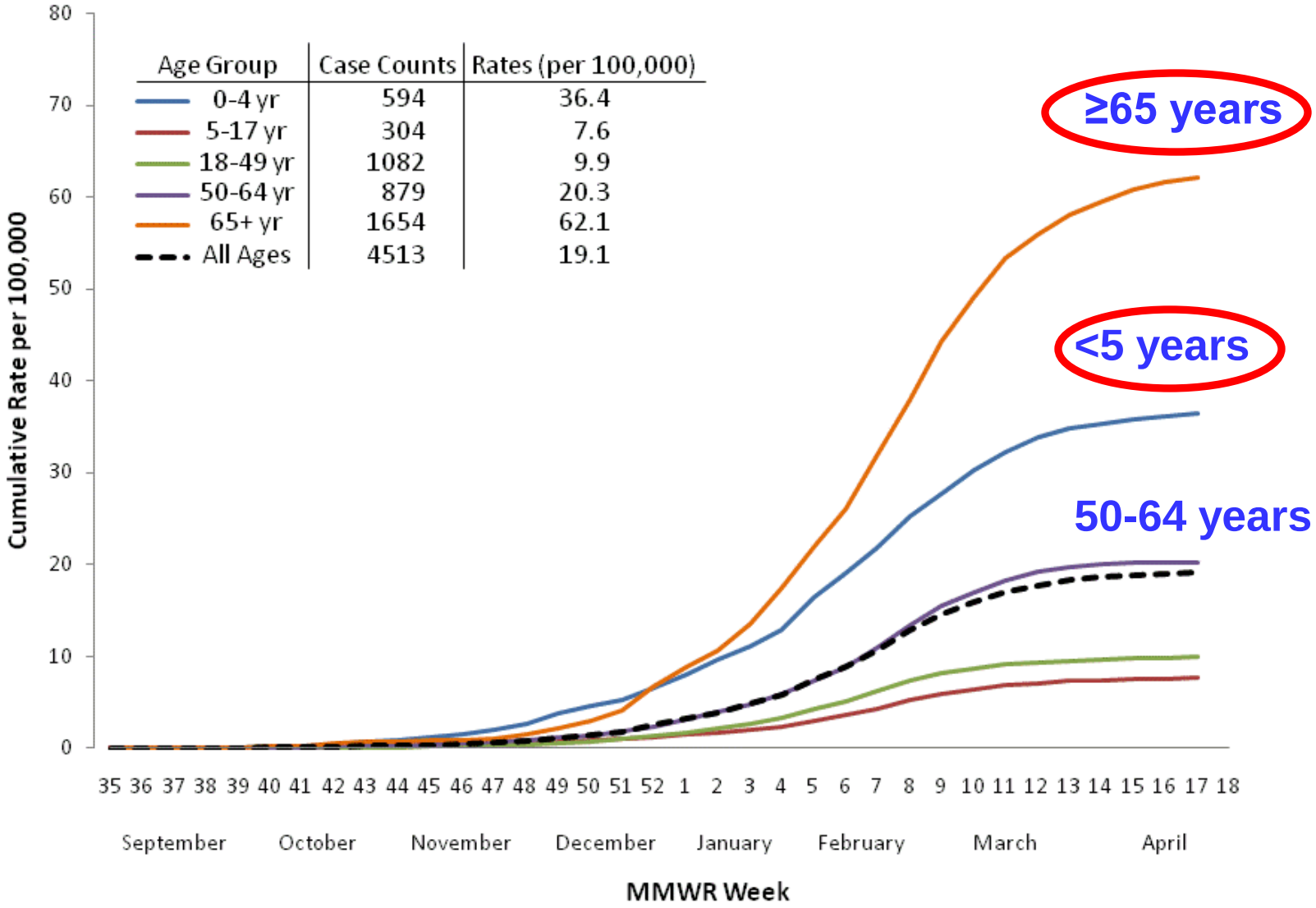
Simonsen L, et al. JID 2000;181:831-837; Izurieta HS et al., NEJM 2000;342:232-239; Neuzil KM et al., NEJM 2000;342:225-231; Thompson WW et al., JAMA 2004;292:1333-1340; Neuzil KM et al. JID 2002;185:147-152

CDC

U.S. 2010-2011 Season

EIP* Laboratory-Confirmed Cumulative Hospitalization Rates (per 100,000), 2010-11 Season

Age Group	Case Counts	Rates (per 100,000)
0-4 yr	594	36.4
5-17 yr	304	7.6
18-49 yr	1082	9.9
50-64 yr	879	20.3
65+ yr	1654	62.1
All Ages	4513	19.1



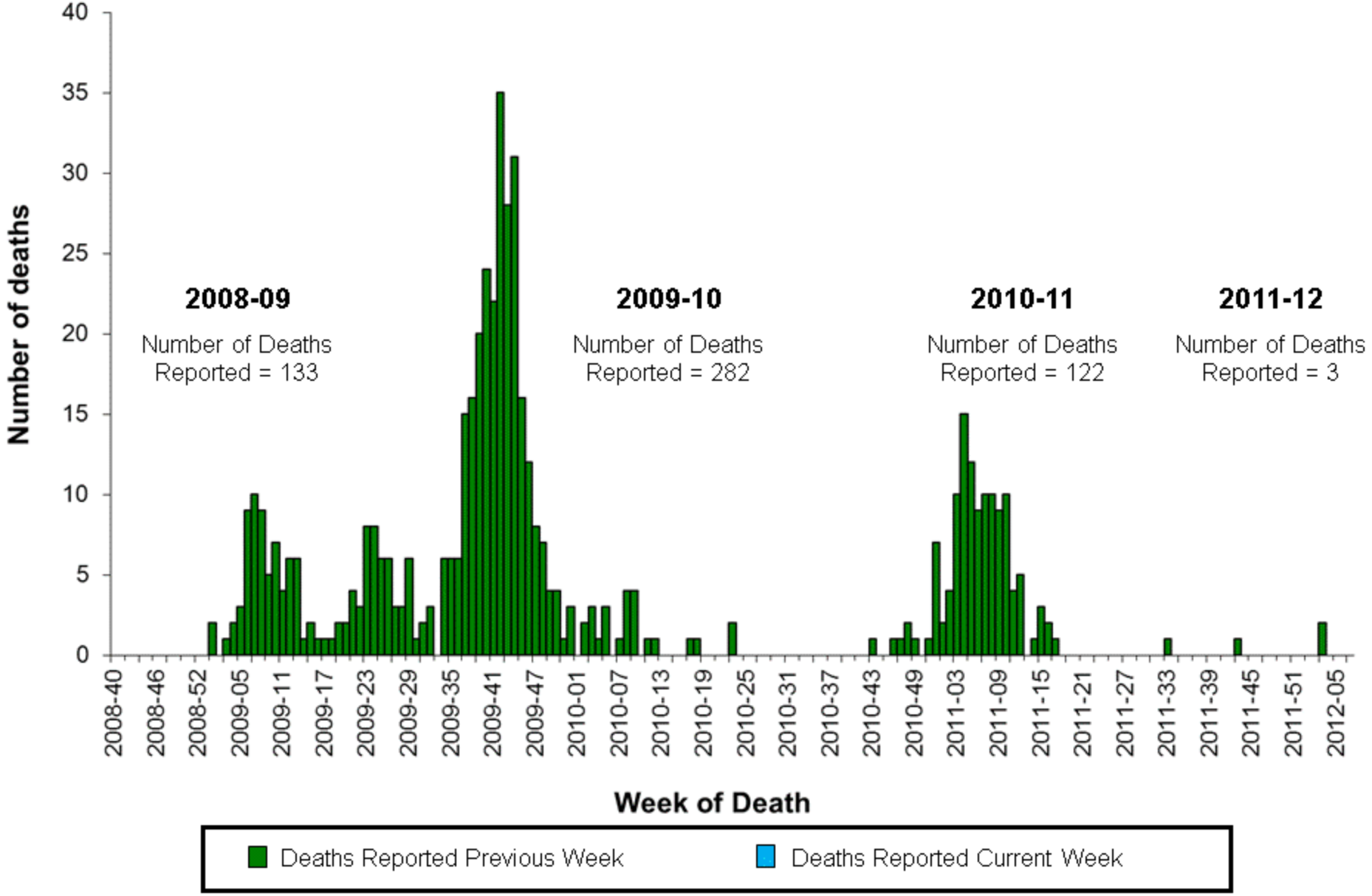
*EIP results represent surveillance in the 10 EIP states (CA, CO, CT, GA, MD, MN, NM, NY, OR, TN)

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**
  - **153 pediatric influenza-associated deaths (2003-04)**
  - **46-88 pediatric deaths/season (2004-08)**

Izurieta NEJM 2000; Neuzil NEJM 2000; Thompson JAMA 2004; Neuzil JID 2002; Thompson JAMA 2003; Viboud PLoS Influenza 2010; Bhat NEJM 2005; Finelli Pediatrics 2008; CDC MMWR 2010.

Number of Influenza-Associated Pediatric Deaths by Week of Death: 2008-09 season to present



Risk Factors for Influenza Complications

- Children younger than 5 years old (especially aged <2 years);
- Adults 65 years of age and older;
- Persons with the following conditions:
  - chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), and neurological and neurodevelopmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury];

Risk Factors for Influenza Complications

- Immunosuppression, including that caused by medications or by HIV infection;
- Women who are pregnant or postpartum (within 2 weeks after delivery);
- Persons younger than 19 years of age who are receiving long-term aspirin therapy;
- American Indians and Alaskan Natives;
- Persons who are morbidly obese (body-mass index equal to or greater than 40);
- Residents of nursing homes and other chronic care facilities

Role of Laboratory Diagnosis

- Diagnosis of influenza based on symptoms alone is limited; illness caused by other pathogens can be similar to influenza virus infection
- Available tests:
  - **Detection of influenza virus antigen**
    - Rapid influenza diagnostic tests [RIDTs] (simple, produce quick result)
    - Immunofluorescence (Direct florescent antibody staining [DFA])
  - **Detection of influenza viral RNA** (not available at every clinical site or hospital)
    - Reverse transcription-polymerase chain reaction [RT-PCR]
  - **Isolation of influenza virus**: tissue cell viral culture (takes 3-10 days)
  - *Serology (not indicated except for research/public health investigations; requires paired sera)*

Role of Laboratory Diagnosis

- **Sensitivity and specificity are test parameters, but can vary by**:
  - Type of test used, type of specimen tested, quality of specimen, timing of specimen collection in relation to illness onset, lab that performs test
- **Prevalence of circulating influenza viruses in the population tested varies during the season and impacts predictive values of influenza tests:**
  - Results should be evaluated in the context of other clinical and epidemiologic information

Role of Laboratory Diagnosis

- Acceptable respiratory specimens vary by test. Specimens should be collected as close to illness onset as possible (<3-4 days after onset)
- Nasopharyngeal and nasal specimens generally have higher yield for detection of influenza viruses than throat swab specimens
- Sensitivities of currently available RIDTs are generally low to moderate 50-70% (range 10-80%) and specificities are high (95-99%)
- **Negative RIDT results do not exclude influenza virus infection and should not be used to make treatment or infection control decisions**
- Only influenza virus isolates can provide detailed information on characteristics of influenza viruses (antigenic, genetic, antiviral resistance)
- RT-PCR is most accurate and sensitive test for detecting influenza viruses; platforms capable of subtyping influenza A viruses are available in state public health laboratories and some reference labs

Uyeki 2003; Chartrand 2012

Antiviral Agents for Influenza

Four licensed influenza antiviral agents in the U.S.:

- **Neuraminidase inhibitors (NIs): oral oseltamivir** (Tamiflu®), **inhaled zanamivir** (Relenza®)
  - **Primary antiviral agents recommended for treatment and chemoprophylaxis**
  - **Active against both influenza A and B viruses**
  - Adverse events:
    - Oseltamivir (nausea, emesis)
    - Zanamivir (bronchospasm, contraindicated in patients with chronic pulmonary disease – asthma, COPD)
    - Both drugs: delirium, abnormal behavior reported in Japanese adolescents
- Adamantanes: amantadine, rimantadine
  - Active only against influenza A viruses, not influenza B viruses
  - **NOT RECOMMENDED** for treatment/chemoprophylaxis of influenza A
    - Widespread resistance among influenza A (H3N2) and 2009 H1N1 virus strains

Antiviral Resistance Among Influenza Viruses

- 2009 H1N1 virus strains, influenza A (H3N2) virus strains
  - Sensitive to oseltamivir and zanamivir
  - Resistant to adamantanes
- Influenza B virus strains
  - Sensitive to oseltamivir and zanamivir
- Sporadic oseltamivir-resistant 2009 H1N1 virus infections identified, with rare episodes of limited transmission, but public health impact has been limited to date
  - Community transmission reported in southeast Australia, 2011
  - Additional sporadic cases of oseltamivir-resistant 2009 H1N1 virus infections expected
  - Ongoing surveillance for oseltamivir-resistance among influenza viruses is essential
- **Currently, no evidence of on-going transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide**

Neuraminidase Inhibitor Resistance Testing Results on Samples Collected Since October 1, 2011.

	Oseltamivir		Zanamivir	
	Virus Samples Tested (n)	Resistant Viruses, Number (%)	Virus Samples tested (n)	Resistant Viruses, Number (%)
Influenza A (H3N2)	339	0 (0.0)	339	0 (0.0)
Influenza B	64	0 (0.0)	64	0 (0.0)
2009 H1N1	88	0 (0.0)	68	0 (0.0)

Use of Antivirals

Treatment efficacy and effectiveness studies

- Oseltamivir or zanamivir can reduce the duration of uncomplicated influenza A or B illness by approximately 1 to 1.5 days when administered within 48 hours of illness onset in randomized placebo-controlled clinical trials
  - Most RCTs conducted in otherwise healthy persons
  - One RCT of oseltamivir treatment of children 1-3 years old with influenza within 24 hours of illness onset reduced the duration of illness by 3.5 days compared to placebo[1]
- One recent systematic review of RCTs reported early oseltamivir treatment reduced influenza illness by 21 hours versus placebo[2]
- Limited data on efficacy or effectiveness of zanamivir or oseltamivir treatment in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases)
  - One meta-analysis of 11 RCTs (unpublished and published) found that oseltamivir treatment reduced the risk of lower respiratory tract complications requiring antibiotic treatment by 37% in patients with laboratory-confirmed influenza[3]
- One observational study indicated that early oseltamivir treatment reduced the progression to CXR-confirmed pneumonia[4]

1) Heinonen 2010; 2) Jefferson 2012; 3) Hernan 2011; 4) Yu 2010

Use of Antivirals

Treatment efficacy and effectiveness studies

- No published RCTs for antiviral treatment of hospitalized patients with severe influenza
- Multiple observational studies of hospitalized patients with seasonal influenza (primarily elderly patients) or 2009 H1N1 (all ages, including pregnant women) indicate that **early** neuraminidase inhibitor treatment (primarily with oseltamivir) is associated with reduced morbidity and mortality, reduced duration of hospitalization
  - Greatest clinical benefit is observed when oseltamivir is started within 2 days after illness onset
  - Starting oseltamivir treatment up to <5 days after illness onset is associated with reduced risk of ICU admission or death
  - A new systematic review concluded that oral oseltamivir treatment of influenza may provide net benefit by reducing mortality, the duration of symptoms and complications of influenza

Jain 2009; Siston 2009; Yu 2011; Lee 2007; Lee 2008; Lee 2010; McGeer 2007; Hsu 2012

Use of Antivirals

Treatment indications

- Benefits of antiviral treatment with neuraminidase inhibitors
  - Greatest if treatment is started as soon as possible after illness onset
  - Evidence for benefit is strongest in studies when treatment was started within 48 hours of illness onset
- However, antiviral treatment of any person with influenza who requires hospitalization is recommended as soon as possible, even if the patient presents more than 48 hours after illness onset

Use of Antivirals

Treatment indications (continued)

- During influenza season:
  - Consider influenza virus infection as the possible cause of any febrile illness requiring hospitalization during influenza season
  - Consider empiric antiviral therapy in patients with suspected influenza as clinically indicated; consider influenza testing if testing will influence treatment decisions, but be aware of limitations of influenza tests and how to interpret test results
  - Monitor local, state and national recommendations during the influenza season to determine the most appropriate treatment practices
  - Receive updates on antiviral resistance profiles of the circulating viruses
- Treatment decisions should be informed by knowledge of influenza activity in the community

Use of Antivirals

Treatment indications (continued)

- Empiric antiviral treatment is recommended
- Treatment initiation should not be delayed while awaiting specimen collection or influenza testing results
- Patients with suspected influenza should continue to receive antiviral treatment regardless of negative initial test results until an alternative diagnosis can be established
- Clinicians who prefer not to treat empirically should:
  - Discuss signs and symptoms of worsening illness with patients
  - Arrange for follow up by telephone or in the clinic

Use of Antivirals

Treatment indications (continued)

- Antiviral treatment is recommended as early as possible for any patient with confirmed of suspected influenza who:
  - Has severe, complicated, or progressive illness; or
  - Is hospitalized; or
  - Is at higher risk for influenza complications
- Clinical judgment, based on the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients. When indicated, antiviral treatment should be started as soon as possible after illness onset.
  - Although all children <2 years are at risk for severe complications from influenza, the risk is highest among young infants <6 months old. Because many children with mild febrile respiratory illness may have other viral infections (e.g. RSV, rhinovirus, parainfluenza, metapneumovirus), knowledge about other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions.

Use of Antivirals

Treatment indications (continued)

- Persons at higher risk for influenza complications who are recommended for antiviral treatment for confirmed or suspected influenza include the following:
  - Children younger than 2 years old (the risk is highest among <6 months old)
  - Adults 65 years of age and older;
  - Persons with the following conditions:

    chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), and neurological and neurodevelopmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury];
  - Immunosuppression, including that caused by medications or by HIV infection;
  - Women who are pregnant or postpartum (within 2 weeks after delivery);
  - Persons younger than 19 years of age who are receiving long-term aspirin therapy;
  - American Indians and Alaskan Natives;
  - Persons who are morbidly obese (body-mass equal to or greater than 40);
  - Residents of nursing homes and other chronic care facilities

Use of Antivirals

Treatment indications (continued)

- **For outpatients, antiviral treatment with a neuraminidase inhibitor is recommended for all persons:**
  - **With confirmed or suspected influenza who are at a higher risk for influenza complications due to age or underlying medical conditions**
- Antibacterial therapy plus antiviral treatment is recommended for patients with community-acquired pneumonia when influenza is also suspected
- Data on effectiveness of antiviral treatment of critically ill patients are very limited
  - Limited observational data suggest that antiviral treatment may reduce duration of hospitalization and mortality

Dominguez-Cherit 2009; Coffin 2011

Use of Antivirals

Treatment indications (continued)

- **Previously healthy, non high-risk, symptomatic outpatients with confirmed or suspected uncomplicated influenza:**
  - Antiviral treatment can be considered based upon clinical judgment if treatment can be initiated within 48 hours of illness onset
  - These patients typically do not require treatment, but early empiric treatment might provide benefit, such as shortened duration of illness or reduced risk of clinical progression
  - These patients are not likely to benefit from treatment if initiated more than 48 hours after illness onset
  - Persons with influenza who are already beginning to recover do not need treatment

Use of Antivirals

Treatment issues for patients hospitalized with confirmed or suspected influenza

- Treatment duration might need to be altered to fit the clinical circumstances
  - For example, clinical judgment should be the guide regarding the need to extend treatment longer than 5 days for patients whose illness is prolonged (e.g. hospitalized patients)
- No published controlled data are available to evaluate the efficacy of higher doses of antivirals to treat severe influenza illness
- Administering oseltamivir via gastric tube can provide systemic absorption in some critically ill patients
  - Gastric stasis or bleeding can make this route problematic
- Parenterally-administered neuraminidase inhibitors are not approved in the U.S.

Use of Antivirals

Treatment issues for patients hospitalized with confirmed or suspected influenza (continued)

- Intravenous zanamivir and intravenous oseltamivir are available for compassionate use via EIND
- Clinical trials are needed to better understand optimal treatment approaches
- www.clinicaltrials.gov (eligibility and enrollment of patients in clinical trials of experimental intravenous antivirals (IV zanamivir, IV peramivir) or combination antiviral treatment

Use of Antivirals

Treatment issues for patients hospitalized with confirmed or suspected influenza (continued)

- Patients receiving antiviral medications who do not respond to antiviral treatment might have infection with an antiviral resistant influenza virus
  - However, patients may worsen or not improve with antiviral treatment due to other complications (e.g. bacterial co-infection, multi-organ failure)
- Infection control measures are important for all hospitalized influenza patients, and especially important for patients who are immunocompromised to reduce the risk of transmission of oseltamivir-resistant influenza virus
- Oseltamivir resistance, sometimes within 1 week of treatment initiation, has been reported particularly among severely immunosuppressed patients with 2009 H1N1 virus infection who were receiving treatment with oseltamivir

Use of Antivirals

Chemoprophylaxis

- Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available
- The likelihood of compliance and adverse events should be considered when determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis
- Failure to complete a course of oseltamivir for chemoprophylaxis due to gastrointestinal adverse events might lead to antiviral resistance if infection has occurred

Use of Antivirals

Post-exposure chemoprophylaxis

- Decisions regarding whether to administer antivirals for chemoprophylaxis should take into account:
  - The exposed person's risk for influenza complications
  - The type and duration of contact
  - Recommendations from local or public health authorities
    - In areas with limited antiviral medication availability, local public health authorities might recommend that antiviral medications be primarily directed at treatment and that antiviral chemoprophylaxis be used only in certain limited situations
  - Clinical judgment
- Generally, post-exposure chemoprophylaxis for individuals should only be used when antivirals can be started within 48 hours of the last exposure

Use of Antivirals

Post-exposure chemoprophylaxis (continued)

- An emphasis on early treatment is an alternative to chemoprophylaxis in managing some persons who have had a suspected exposure to a symptomatic person with influenza virus infection
  - Counsel them about early signs and symptoms of influenza
  - Advise them to immediately contact their health care provider for evaluation and possibly early treatment if clinical signs or symptoms of influenza develop
  - Counsel them about influenza antiviral medication side effects
  - Inform them that they remain susceptible to influenza virus infection after the antiviral medications are stopped
- Health care providers should use clinical judgment regarding situations where early recognition of illness and early antiviral treatment might be an appropriate alternative

Use of Antivirals

Post-exposure chemoprophylaxis (continued)

- Post-exposure chemoprophylaxis with neuraminidase inhibitors should generally be reserved for high-risk patients who have had exposure to a person with symptomatic influenza
- Persons who can be considered for antiviral chemoprophylaxis include:
  - **Residents of institutions during confirmed or suspected influenza outbreaks**
  - Family or other close contacts of suspected or confirmed case
    - Who are at higher risk of influenza complications, and
    - Who have not been vaccinated against the influenza virus strains circulating at the time of exposure
  - Unvaccinated health care workers
    - Who have occupational exposures, and
    - Who did not have adequate personal protective equipment at the time of exposure

Use of Antivirals

Post-exposure chemoprophylaxis (continued)

- Either oral oseltamivir or inhaled zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1, influenza A (H3N2), or influenza B virus infection

- Persons who receive an antiviral medication for chemoprophylaxis might still acquire influenza virus infection and be potentially able to transmit infection, even if clinical illness is prevented

- Antiviral chemoprophylaxis is approximately 70-80% effective in preventing illness, but not necessarily influenza virus infection when exposure to drug sensitive virus occurs

Use of Antivirals

Post-exposure chemoprophylaxis (continued)

- Patients given post-exposure antiviral chemoprophylaxis should:
  - Be informed that chemoprophylaxis lowers but does not eliminate the risk of influenza
  - Be informed that susceptibility to influenza returns once the antiviral medication is stopped
  - Be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness that might indicate influenza (infection can still occur, might be a resistant virus)

- Post-exposure chemoprophylaxis is typically given up to 10 days after last known exposure to a close contact known to have influenza

Use of Antivirals

Pre-exposure chemoprophylaxis

- Pre-exposure chemoprophylaxis should only be used for persons who are:
  - At very high risk of influenza-related complications, and
  - Cannot otherwise be protected during times when there is a high risk for exposure
- Use should be in accordance with current recommendations from CDC or local public health authorities
- When used, pre-exposure chemoprophylaxis must be given for the duration of time when exposure might occur
- To be maximally effective, the drug must be taken each day for the duration of influenza activity in the community
- The adverse events associated with long term use are uncertain, and prolonged use of antivirals might select for resistance to antiviral medications

Use of Antivirals

Pre-exposure chemoprophylaxis (continued)

- In community studies of healthy adults given antiviral medications during times of influenza virus transmission, both oral oseltamivir and inhaled zanamivir had similar efficacy in preventing febrile, lab-confirmed influenza illness
- Studies have also demonstrated effectiveness of antiviral chemoprophylaxis for prevention of influenza among patients in institutional settings
- Data are limited on the efficacy and effectiveness of antiviral agents in preventing influenza among severely immunocompromised persons

Use of Antivirals

Considerations for use if oseltamivir-resistant influenza virus strains are circulating

- Since 2009, 99% of circulating influenza A and B viruses have been susceptible to oseltamivir (i.e., seasonal influenza A (H1N1) viruses have not been detected in the U.S. since 2009)
- CDC provides weekly updates on virus surveillance at the national level (http://www.cdc.gov/flu/weekly/fluactivitysurv.htm)
- If oseltamivir-resistant viruses are not circulating, antiviral treatment for influenza should consist of either oral oseltamivir or inhaled zanamivir
- Continued changes in antiviral resistance are likely among influenza viruses; clinicians should remain attentive to updates in antiviral treatment guidance

Use of Antivirals

Control of influenza outbreaks in institutions

- Antiviral drug treatment and chemoprophylaxis are key to outbreak control in institutions with patients at higher risk for influenza complications
- Neuraminidase inhibitors have been used to successfully control outbreaks when combined with other infection control measures and influenza vaccination
- Inhaled zanamivir should be used when persons require chemoprophylaxis due to exposure to influenza virus strains that are suspected of being oseltamivir-resistant
- Obtain respiratory specimens from ill persons for influenza typing, influenza A virus subtyping (RT-PCR) or viral culture (for antigenic characterization and to assess antiviral resistance) and provide data on the outbreak etiology
- If chemoprophylaxis is indicated, start neuraminidase inhibitors as early as possible
  - Helpful to have preapproved orders from physicians, plans to obtain orders for antiviral medications on short notice

Use of Antivirals

Control of influenza outbreaks in institutions (continued)

- Administer chemoprophylaxis to all eligible residents, regardless of influenza vaccination status
  - Chemoprophylaxis should last for a minimum of 2 weeks
  - If new cases continue to occur, continue until approx.10 days after illness onset in the last patient
- Also offer to unvaccinated staff who care for high-risk persons
- Measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis

Use of Antivirals

Control of influenza outbreaks in institutions (continued)

- Other outbreak-control measures :
  - Institute droplet and contact precautions, establish cohorts of patients with confirmed or suspected influenza
  - Re-offer influenza vaccination (if available) to unvaccinated staff, patients
  - Restrict staff movement between wards or buildings
  - Restrict contact between ill staff or visitors and patients
  - Screen staff and visitors for illness

Recommended Dosage and Duration of Treatment or Chemoprophylaxis for Influenza Antiviral Medications

Antiviral Agent	Use	Children	Adults
Oseltamivir (Tamiflu®)	Treatment	**(Not FDA approved for use in children <1 yr old, but was approved under EUA during the 2009 pandemic)** If <1 yr old, the dose is 3 mg/kg/dose **twice** daily	75 mg **twice** daily
		(Dose varies by child's weight) If ≥1 yr old and weigh 15 kg or less, the dose is 30 mg **twice** a day.	
		If ≥1 yr old and weigh >15 to 23 kg, the dose is 45 mg **twice** a day.	
		If ≥1 yr old and weigh >23 to 40 kg, the dose is 60 mg **twice** a day.	
		If ≥1 yr old and weigh more than 40 kg, the dose is 75 mg **twice** a day.	
	Chemo prophylaxis	**(Not FDA approved for use in children <1 yr old)** If child is <3 months old, chemoprophylactic use is not recommended unless situation is judged critical due to limited data on use in this age group.	75 mg **once** daily
		(Not FDA approved for children <1 yr old, but use in children ≥3 months and <1 yr old was approved under EUA during the 2009 H1N1 pandemic) If child ≥3 months and <1 yr old, dose is 3 mg/kg/dose **once** per day	
		(Dose varies by child's weight) If ≥1 yr old, and weigh 15 kg or less, the dose is 30 mg **once** a day.	
		If ≥1 yr old and weigh >15 to 23 kg, the dose is 45 mg **once** a day.	
		If ≥1 yr old and weigh >23 to 40 kg, the dose is 60 mg **once** a day.	
		If ≥1 yr old and weigh more than 40 kg, the dose is 75 mg **once** a day.	
Zanamivir (Relenza®)	Treatment	10 mg (2 inhalations) **twice** daily **(Not FDA approved for use in children <7 yrs old)**	10 mg (2 inhalations) **twice** daily
	Chemo prophylaxis	10 mg (2 inhalations) **once** daily **(Not FDA approved for use in children <5 yrs old)**	10 mg (2 inhalations) **once** daily

Use of Antivirals

Dosage

TABLE 4. Dosing recommendations for treatment or chemoprophylaxis of children aged <1 year using oseltamivir*

Age	Recommended treatment dose for 5 days†	Recommended chemoprophylaxis dose for 10 days†
<3 mos	3 mg/kg/dose twice daily	Not recommended unless situation judged critical because of limited data on use in this age group
3–11 mos	3 mg/kg/dose twice daily	3 mg/kg/dose once daily

* Oseltamivir is not approved by the Food and Drug Administration (FDA) for use in children aged <1 year. An Emergency Use Authorization (EUA) was issued by the FDA on April 28, 2009, and expired on June 23, 2010 (available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM216494.pdf). This EUA allowed use of oseltamivir for treatment or chemoprophylaxis of 2009 pandemic influenza A (H1N1) virus infection during the pandemic in infants aged <1 year. Currently circulating 2009 H1N1, seasonal influenza A (H3N2), and B viruses have similar sensitivity to oseltamivir.

† Current weight-based dosing recommendations are not appropriate for premature infants. Premature infants might have slower clearance of oseltamivir because of immature renal function, and doses recommended for full-term infants might lead to very high drug concentrations in this age group. Very limited data from a small cohort of premature infants suggested that oseltamivir concentrations among premature infants administered oseltamivir 1 mg/kg twice daily would be similar to those observed with the recommended treatment dose in term infants (3 mg/kg twice daily). Observed drug concentrations were highly variable among premature infants. These data are insufficient to recommend a specific dose of oseltamivir for premature infants (*202*).

For additional information:

- See: Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza. MMWR 2011;Vol.60, No. 1:1-25. Available at: http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf

- See: 2011-2012 Influenza Antiviral Medications: A Summary for Clinicians. Available at: http://www.cdc.gov/flu/pdf/professionals/antivirals/clinician-antivirals2011.pdf

Questions?

For more information please contact Centers for Disease Control and Prevention

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2011-2012 Influenza Season: Antiviral Medication Recommendations

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Presenter(s):

Timothy Uyeki, MD, MPH, MPP
CAPT, U.S. Public Health Service
Deputy Chief for Science
Epidemiology and Prevention Branch
Influenza Division
National Center for Immunization and Respiratory Diseases
CDC

Overview:

CDC estimates that influenza virus infections in the United States result in an average of more than 200,000 related hospitalizations, and between 3,300 to 49,000 deaths each year, depending upon the severity of the influenza season. Annual influenza vaccination is recommended for all persons aged 6 months and older, and is the best way to prevent influenza. However, available evidence consistently indicates that antiviral treatment, when initiated as early as possible in patients with confirmed or suspected influenza, can reduce severe outcomes of influenza. During this COCA conference call, a subject matter expert will review current Advisory Committee on Immunization Practices (ACIP) and CDC guidance on the use of antiviral medications in the prevention and treatment of influenza.

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