11 January 2018
Influenza Alert – CDC Health ALERT (see attached pdf)

From our past studies, the positive predictive value (PPV) of fever plus (cough and/or sore throat) for influenza in ambulatory patients aged 5 years and older is about 80%

Wisconsin:
Wisconsin influenza activity is widespread and increasing. Influenza A[H3N2] has been the dominant strain so far in Wisconsin, comprising 95% of all tested viruses. As of December 30, 2017, there had been 1,328 influenza-related hospitalizations since September 1, 2017; 68% of hospitalizations have been in individuals aged ≥65 years. There have been 157 admissions to ICUs, 54% were aged ≥65 years; and there have been 29 cases requiring mechanical ventilation, 48% aged ≥65 years.

The prevalence of influenza-like illness [fever of 100°F or higher and either cough or sore throat] in Wisconsin's primary care patients is at 3.9% and is increasing.

13.8% of last week's primary care patients had all-cause respiratory infections.
The prevalence of acute diarrheal illness (ADI) in Wisconsin's primary care patients is at 1.7%

Primary Care Snapshot:
The most commonly identified viral cause of Acute Respiratory infections (ARI) in Wisconsin is **Influenza A**. Over the past 4 weeks the typical ARI case presenting for primary care has been 34.0 years old and 54% of patients have been female. 63% of patients identified a sick contact 1-to-3 days before illness onset and typically present to the clinic 4.5 days after illness onset. 29% of illnesses are characterized as mild, with 63% having moderate symptoms and 5% having severe symptoms.

Typical Symptoms	Percent
fever	**56**
cough	**80**
sore throat	**67**
nasal congestion	**58**
nasal discharge	**58**
headache	46
malaise	**62**
myalgia	43

Viruses in Circulation	Percent
Influenza A	**42**
Influenza B	0
Coronavirus	19
RSV	2
Parainfluenza	9
hMPV	2
Rhino/Enterovirus	**23**
Adenovirus	2
Bocavirus	0

Symptoms in Patients with PCR-Confirmed Influenza	Percent
fever	**81**
cough	**85**
sore throat	**62**

nasal congestion	**54**
nasal discharge	**73**
headache	**50**
malaise	**50**
myalgia	27

CLINICAL NOTES:

See Attached CDC Guidance:

Seasonal Influenza A(H3N2) Activity and Antiviral Treatment of Patients with Influenza (pdf)

Prophylaxis

- Influenza vaccine is recommended universally – keep vaccinating everyone over the age of 6 months, including pregnant women
- there is a good match of vaccine to the currently circulating viruses, but the current vaccine had low overall efficacy during the 2017 Australian influenza outbreak
- Pneumococcal vaccine PPSV23 is indicated for smokers, people with asthma and other chronic lung conditions as well as a number of other chronic conditions
- ACIP routinely recommends PCV13 for individuals 65 years and older PPSV23 should be given 12 months after PCV13

Diagnosis

Performance of Rapid Influenza Diagnostic Tests (RIDTs) depends on age and time from symptom onset

Higher sensitivities are attained at younger ages and within the first 3 days of symptoms

Clinical judgment is essential in diagnosis

- influenza infections are at low to moderate levels at this time
- PPV of rapid antigen tests at this time is high
- NPV of rapid antigen tests at this time is moderately high

Treatment – see attached guidance

Antivirals need to be started with 48 hours of symptom onset to be effective against influenza
Antivirals started after 48 hours may be effective for hospitalized patients with confirmed influenza

Resistance Patterns:

- 462 influenza A[H3N2], 111 influenza A[H1N1] and 127 influenza B viruses have been tested since 10/01/17.
  - one influenza A[H1N1] (0.9%) was resistant to oseltamivir and peramivir
- all influenza A[H3N2] and influenza B viruses have been sensitive to oseltamivir, zanamivir and peramivir
- high levels of adamantane antiviral resistance exist in influenza A isolates from around the world

Adamantanes include amantadine and rimantadine; they are ineffective for influenza B

Other

- Rhinoviruses and coronaviruses are co-circulating in Wisconsin.
- RSV activity is increasing

Across the U.S.:
9,228 (25.5%) respiratory specimens during week 52 (December 24-30) were positive for influenza.

For the 2017-2018 season to date (last week):
-83.0% (86.6%) of subtyped isolates have been type A
91.6% (91.9%) of A viruses have been H3N2
8.4% (8.1%) of all sub-typed A viruses have been 2009 H1N1
-17.0% (13.4%) of isolates have been type B
90.7% (90.0%) were of the Yamagata lineage
(Yamagata lineage is not included in this year's trivalent vaccines, such as high-dose IIV)
9.3% (10.0%) were of the Victoria lineage

-6.7% of deaths during week 50 (December 10-16, 2017) were due to pneumonia or influenza [below the seasonally-adjusted epidemic threshold of 6.9%]

-Thirteen pediatric deaths due to influenza have been reported this season: 3 deaths were due to A[H3N12], 3 deaths were due to A[H1N1], 4 deaths were due to an A virus for which no subtyping was performed, and 3 deaths were due to influenza B.

Global News [from the WHO/CDC]:

Zika: 5,613 cases have been reported in the U.S. with 2,364 cases in pregnant women. Wisconsin has had 4 cases in 2017 – all associated with travel. See: https://www.cdc.gov/zika/ for up-to-date information.

Other Observations:

January 11th Phenology: Today' photoperiod is 9 hours, 15 minutes and 45 seconds, and daylength is increasing by 1 minute and 26 seconds per day.

Wisdom: Last month, Wisdom—the world's oldest known wild bird—laid an egg at the age of 67. Since 2006, the Laysan albatross has raised and fledged at least nine chicks with her life mate Akeakamai, according to the U.S. Fish & Wildlife Service. Together, they return each year to Midway Atoll in the Papahānaumokuākea Marine National Monument to nest and raise their young. It's believed that over her lifetime Wisdom has likely raised 30 to 35 albatross chicks, outliving several of her mates. See: https://www.smithsonianmag.com/smart-news/wisdom-worlds-oldest-wild-bird-expecting-age-67-180967718/

And a good south wind sprung up behind;
The Albatross did follow,
And every day, for food or play,
Came to the mariner's hollo!

From: The Rime of the Ancient Mariner
- Samuel Taylor Coleridge (1834)

Close to Home: In general, Bald Eagles begin courtship in October, productive mating in late January or early February, and egg-laying in mid to late February. Hatching usually begins in late March to early April, and the eaglets fledge in mid-to-late June. While young usually disperse between August and October, the adults remain on territory year round. They eat live and dead fish, squirrels, other birds, rabbit, muskrat, deer, possum and anything else they can catch or find.
http://www.ustream.tv/decoraheagles

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CDC HEALTH ADVISORY

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Seasonal Influenza A(H3N2) Activity and Antiviral Treatment of Patients with Influenza

Summary
The Centers for Disease Control and Prevention (CDC) is providing: 1) a notice about increased influenza A(H3N2) activity and its clinical implications; 2) a summary of influenza antiviral drug treatment recommendations; 3) an update about approved treatment drugs and supply this season; and 4) background information for patients about influenza treatment.

Background
In the United States (U.S.), influenza activity has increased significantly over recent weeks with influenza A(H3N2) viruses predominating so far this season. In the past, A(H3N2) virus-predominant influenza seasons have been associated with more hospitalizations and deaths in persons aged 65 years and older and young children compared to other age groups. In addition, influenza vaccine effectiveness (VE) in general has been lower against A(H3N2) viruses than against influenza A(H1N1)pdm09 or influenza B viruses. Last season, VE against circulating influenza A(H3N2) viruses was estimated to be 32% in the U.S. CDC expects that VE could be similar this season, should the same A(H3N2) viruses continue to predominate. For this reason, in addition to influenza vaccination for prevention of influenza, the use of antiviral medications for treatment of influenza becomes even more important than usual. The neuraminidase inhibitor (NAI) antiviral medications are most effective in treating influenza and reducing complications when treatment is started early. Evidence from previous influenza seasons suggests that NAI antivirals are underutilized in outpatients and hospitalized patients with influenza who are recommended for treatment.

This CDC Health Advisory is being issued to—

1) Remind clinicians that influenza should be high on their list of possible diagnoses for ill patients because influenza activity is increasing nationwide, and
2) Advise clinicians that all hospitalized patients and all high-risk patients (either hospitalized or outpatient) with suspected influenza should be treated as soon as possible with a neuraminidase inhibitor antiviral. While antiviral drugs work best when treatment is started within 2 days of illness onset, clinical benefit has been observed even when treatment is initiated later.

Recommendations

1. CDC Antiviral Recommendations for the 2017–2018 Season

CDC recommends antiviral medications for treatment of influenza as an important adjunct to annual influenza vaccination. Treatment with neuraminidase inhibitors has been shown to have clinical and public health benefit in reducing illness and severe outcomes of influenza based on evidence from randomized controlled trials, meta-analyses of randomized controlled trials, and observational studies during past influenza seasons and during the 2009 H1N1 pandemic.[1,2,3,4,5,6]

2. All Hospitalized, Severely Ill, and High-Risk Patients with Suspected or Confirmed Influenza Should Be Treated with Antivirals

Any patient with suspected or confirmed influenza in the following categories should be treated as soon as possible with a neuraminidase inhibitor:

1) Any patient who is hospitalized—treatment is recommended for all hospitalized patients;

2) Any patient who has severe, complicated, or progressive illness—this may include outpatients with severe or prolonged progressive symptoms or who develop complications such as pneumonia but who are not hospitalized;

3) Any patient who is at higher risk for influenza complications but not hospitalized. Patients in this group include—

- children younger than 2 years (although all children younger than 5 years are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 years)
- adults aged 65 years and older
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), and metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment 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)
- people with immunosuppression, including that caused by medications or by HIV infection
- women who are pregnant or postpartum (within 2 weeks after delivery)
- people aged younger than 19 years who are receiving long-term aspirin therapy
- American Indians/Alaska Natives
- people with extreme obesity (i.e., body-mass index is equal to or greater than 40)
- residents of nursing homes and other chronic-care facilities

3. Timing of Treatment and Implications for Patient Evaluation, Treatment, and Testing

Clinical benefit is greatest when antiviral treatment is administered as early as possible after illness onset. Therefore, antiviral treatment should be started as soon as possible after illness onset and **should not be delayed** even for a few hours to wait for the results of testing. Ideally, treatment should be initiated within 48 hours of symptom onset. **However, antiviral treatment initiated later than 48 hours after illness onset can still be beneficial for some patients.**

A very large observational study of more than 29,000 hospitalized influenza patients reported that while the greatest clinical benefit was found when antiviral treatment was initiated within 48 hours of illness onset, starting antiviral treatment more than 2 days after onset had survival benefit in adults versus no treatment.[6] Also, a randomized, placebo-controlled study suggested clinical benefit when oseltamivir was initiated 72 hours after illness onset among febrile children with uncomplicated influenza.[7] Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for outpatients, particularly those who are not at increased risk for influenza complications.

Because of the importance of early treatment, **decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza**. Therefore, empiric antiviral treatment should generally be initiated as soon as possible when there is known influenza activity in the community. A history of current season influenza vaccination does not exclude a diagnosis of influenza in an ill child or adult. During influenza season especially, high-risk patients should be advised to call their provider promptly if they have symptoms of influenza. It may be useful for providers to implement phone triage lines 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.

4. Influenza Testing

Information to assist clinicians about influenza testing decisions is available at https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm. The most accurate influenza tests are molecular assays. Rapid molecular assays are available in clinical settings that can detect influenza virus nucleic acids in respiratory specimens in 15-30 minutes with high sensitivity and specificity. Other approved molecular assays can yield results in 60-80 minutes or in several hours with very high sensitivity and specificity.

For hospitalized patients with suspected influenza, molecular assays are recommended. Information on influenza molecular assays is available at https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm. Rapid influenza diagnostic tests (RIDTs) with an analyzer device can detect influenza A and B viral nucleoprotein antigens in respiratory specimens in 10-15 minutes with moderate sensitivity, and RIDTs without an analyzer device have low to moderate sensitivity compared with reverse transcription-polymerase chain reaction (RT-PCR).

Proper interpretation of influenza testing results is important to guide optimal management of influenza patients. An algorithm to assist clinicians in interpreting the results of influenza testing when influenza viruses ARE circulating in the community is available at https://www.cdc.gov/flu/professionals/diagnosis/algorithm-results-circulating.htm. **Clinicians should be aware that a negative RIDT result does not exclude a diagnosis of influenza in a patient with suspected influenza when there is influenza activity in the community.** Other factors such as the quality of the specimen, the source of the specimen in the respiratory tract, and the timing of specimen collection in relationship to illness onset, may also affect test results.

5. Antivirals in Non-High Risk Patients with Uncomplicated Influenza

Neuraminidase inhibitors can benefit other individuals with influenza. While current guidance focuses on antiviral treatment of those with severe illness or at high risk of complications from influenza, antiviral treatment may be prescribed on the basis of clinical judgment for any previously healthy (non-high risk) outpatient with suspected or confirmed influenza who presents within 2 days after illness onset. Neuraminidase inhibitors can reduce the duration of uncomplicated influenza illness by approximately 1 day when started within 2 days after illness onset in otherwise healthy persons. It is possible that antiviral treatment started after 48 hours may offer some benefit. [7]

6. Antiviral Medications

Three prescription neuraminidase inhibitor antiviral medications are approved by the U.S. Food and Drug Administration (FDA) and are recommended for use in the U.S. during the 2017–2018 influenza season: oseltamivir (available as a generic version or under the trade name Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab®).

- Oral oseltamivir is FDA-approved for treatment of uncomplicated influenza within 2 days of illness onset in persons aged 2 weeks and older, and for chemoprophylaxis to prevent influenza in people 1 year of age and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants younger than 14 days old, and for chemoprophylaxis in infants 3 months to 1 year of age, is recommended by CDC and the

American Academy of Pediatrics. Due to limited data, use of oseltamivir for chemoprophylaxis is not recommended in children younger than 3 months unless the situation is judged critical. CDC recommends oseltamivir treatment as soon as possible for hospitalized patients with suspected or confirmed influenza, high-risk outpatients with suspected or confirmed influenza, and those with progressive disease.

- Inhaled zanamivir is FDA-approved for treatment of uncomplicated influenza within 2 days of illness onset in persons 7 years and older and for prevention of influenza in persons 5 years and older. Inhaled zanamivir is not recommended for treatment of influenza in hospitalized patients due to limited data.

- Intravenous peramivir is FDA-approved for the treatment of acute uncomplicated influenza within 2 days of illness onset in persons aged 2 years and older.

Adamantanes (rimantadine and amantadine) are not currently recommended for antiviral treatment or chemoprophylaxis of influenza A because of high levels of resistance among circulating influenza A viruses.

There are no current national shortages of neuraminidase inhibitors (i.e., oseltamivir, zanamivir and peramivir), and manufacturers report they expect to meet projected seasonal demands. If there is difficulty locating oseltamivir for oral suspension, as there has been in some previous seasons, oral suspension can be compounded by a pharmacy from oseltamivir capsules. However, this compounded suspension should not be used for convenience or when oseltamivir oral suspension is commercially available.

More information about compounding an oral suspension from oseltamivir 75 mg capsules can be found at https://www.gene.com/download/pdf/tamiflu_prescribing.pdf

Additional Considerations for Clinicians

- **Bacterial Infections:** Antibiotics are not effective against influenza virus infection, and early diagnosis of influenza can reduce the inappropriate use of antibiotics if bacterial co-infection is not suspected. However, because certain bacterial infections can produce symptoms similar to influenza and bacterial infections can occur as a complication of influenza, bacterial infections should be considered and appropriately treated, if suspected. In addition, because pneumococcal infections are a serious complication of influenza infection, current pneumococcal vaccine recommendations for adults 65 years of age or older, as well as adults and children at increased risk for invasive pneumococcal disease due to chronic underlying medical conditions, should be followed (see http://www.cdc.gov/vaccines/vpd-vac/pneumo/vac-PCV13-adults.htm and http://www.cdc.gov/vaccines/vpd-vac/pneumo/vacc-in-short.htm for further information).

- **Adverse Events and Antiviral Use**: The most common adverse events associated with oral oseltamivir include a slightly increased risk of nausea and vomiting as compared to placebo, with nausea occurring in 10% of adults with influenza who received oseltamivir and 6% of people who received placebo in controlled clinical trials (3% and 4%, respectively, in children), and vomiting occurring in 9% of adults with influenza who received oseltamivir and 3% of people who received placebo in controlled clinical trials (15% and 9%, respectively, in children). These symptoms are generally transient and can be mitigated if oseltamivir is taken with food. Adverse events for inhaled zanamivir were not increased as compared to placebo in clinical trials, but cases of bronchospasm have been reported during post marketing; inhaled zanamivir is not recommended for persons with underlying airways disease (e.g., asthma or chronic obstructive pulmonary diseases). For people who received peramivir intravenously or intramuscularly in clinical trials, the most common adverse event was diarrhea, occurring in 8% versus 7% in people who received placebo.

Resources for Patient Education

Results from unpublished CDC qualitative research shows that most people interviewed were not aware that drugs to treat influenza illness are available. A fact sheet for patients is available at http://www.cdc.gov/flu/antivirals/whatyoushould.htm.

Note the following important background information for patients:

- If you get the flu, antiviral drugs are a treatment option.
- It is very important that antiviral drugs are used early to treat hospitalized patients, people with severe flu illness, and people who are at high risk for flu complications because of their age, severity of illness, or underlying medical conditions.
- If you have severe illness or are at high risk of serious flu complications, you may be treated with flu antiviral drugs if you get the flu.
- If you have a high-risk condition, treatment with an antiviral drug can mean the difference between having milder illness instead of very serious illness that could result in a hospital stay.
- Other people also may be treated with antiviral drugs by their doctor this season. Most otherwise-healthy people who get the flu, however, do not need to be treated with antiviral drugs.
- Studies show that flu antiviral drugs work best for treatment when they are started within 2 days of getting sick. However, starting antivirals later can still be helpful for some people.
- If your health care provider thinks you have the flu, your health care provider may prescribe antiviral drugs. A test for flu is not necessary.
- Antibiotics are not effective against the flu. Using antibiotics inappropriately can lead to antibiotic resistance and may expose patients to unwanted side effects of the drug.
- Other practices that may help decrease the spread of influenza include respiratory hygiene, cough etiquette, social distancing (e.g., staying home from work and school when ill, staying away from people who are sick) and hand washing.

Additional Resources

- Summary of Influenza Antiviral Treatment Recommendations for Clinicians: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
- Clinical Description and Lab Diagnosis of Influenza: http://www.cdc.gov/flu/professionals/diagnosis/index.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
- Influenza Virus Testing in Investigational Outbreaks in Institutional or Other Closed Settings: https://www.cdc.gov/flu/professionals/diagnosis/guide-virus-diagnostic-tests.htm

- FDA Influenza (Flu) Antiviral Drugs and Related Information (including package inserts): http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm

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Categories of Health Alert Network messages:

Health Alert	Requires immediate action or attention; highest level of importance
Health Advisory	May not require immediate action; provides important information for a specific incident or situation
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HAN Info Service	Does not require immediate action; provides general public health information

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