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CDC HEALTH ADVISORY

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Influenza Season Continues with an Increase in Influenza A(H3N2) Activity

CDC reminds clinicians to have a high suspicion for influenza and recommends rapid antiviral treatment of high-risk patients with suspected influenza.

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this health advisory to notify clinicians that influenza activity remains high in the United States, with an increasing proportion of activity due to influenza A(H3N2) viruses, continued circulation of influenza A(H1N1) viruses, and low levels of influenza B viruses. Influenza should be considered as a possible diagnosis for patients with respiratory illness while local influenza activity remains elevated. Because influenza A(H3N2) viruses may be associated with severe disease in older adults, this health advisory serves as a reminder that early empiric treatment with influenza antiviral medications is recommended for hospitalized and high-risk patients, especially those 65 years and older. Antiviral treatment should be started as soon as possible after illness onset and should not wait for laboratory confirmation.

Background

In the United States, influenza activity remains elevated and widespread, and the season is likely to last several more weeks (see CDC FluView report for details: https://www.cdc.gov/flu/weekly/index.htm). Earlier in the season, influenza A(H1N1) viruses were predominant in most of the country. Although A(H1N1) viruses continue to circulate and remain predominant for the season overall, during the three weeks ending March 16, influenza A(H3N2) viruses have been identified more frequently than A(H1N1) viruses in most of the country. In the past, A(H3N2) virus-predominant influenza seasons have been associated with more hospitalizations and deaths in people 65 years and older than A(H1N1) virus-predominant seasons. Influenza vaccine effectiveness is generally lower against influenza A(H3N2) viruses than against A(H1N1) or B viruses [1]. In addition, one genetic clade of A(H3N2) viruses, the 3C.3a clade, has recently become predominant among circulating A(H3N2) viruses and according to laboratory testing these viruses are antigenically distinct from the A(H3N2) virus included in this season's vaccine.

CDC recommends antiviral medications for treatment of influenza, regardless of a patient's influenza vaccination status. Antiviral treatment 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 [2–9]. Influenza antiviral medications are most effective in treating influenza and reducing complications when treatment is started early (within 48 hours of illness onset). However, some studies suggest clinical benefit among hospitalized patients and young children with febrile illness even when treatment starts three to five days after illness onset [10–16].

Recommendations

1. **All Hospitalized, Severely Ill, and High-Risk Patients with Suspected or Confirmed Influenza Should Be Treated with Antivirals**
   Antiviral treatment is recommended as early as possible for any patient with suspected or confirmed influenza who:
   1) Is hospitalized—treatment is recommended for all hospitalized patients;
   2) Has severe, complicated, or progressive illness—this may include outpatients with severe or prolonged progressive symptoms or patients who develop complications such as pneumonia but who are not hospitalized;
   3) Is at high risk for influenza complications but not hospitalized—this includes
      a. Adults 65 years and older.

      b. Children younger than two years. Although all children younger than five years are considered at higher risk for complications from influenza, the highest risk is for those younger than two years.

      c. People with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), and metabolic disorders (including diabetes mellitus).

      d. People with 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, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury).

      e. People with immunosuppression, including that caused by medications or by HIV infection.

      f. Women who are pregnant or postpartum (within two weeks after delivery).

      g. People younger than 19 years who are receiving long-term aspirin therapy.

      h. American Indians and Alaska Natives.

      i. People with extreme obesity (i.e., body-mass index is equal to or greater than 40).

      j. Residents of nursing homes and other chronic-care facilities.

2. **Antivirals in Non-High Risk Patients with Uncomplicated Influenza**
   Antiviral treatment can benefit other individuals with influenza. While current guidance focuses on antiviral treatment of those with severe illness or at high risk of complications, antiviral treatment may be prescribed for any previously healthy (non-high risk) outpatient with suspected or confirmed influenza who presents within two days after illness onset. Clinical judgment—considering the patient's disease severity and progression, age, likelihood of influenza, and time since onset of symptoms—is important when making antiviral treatment decisions for outpatients who are not at increased risk for influenza complications.

3. **Choice of Antiviral Medication**
   Four influenza antiviral medications approved by the U.S. Food and Drug Administration (FDA) are recommended for use in the United States during the 2018-2019 influenza season. Three drugs are chemically related antiviral medications known as neuraminidase inhibitors that block the viral neuraminidase enzyme and have activity against both influenza A and B viruses: oral **oseltamivir phosphate** (available as a generic version or under the trade name Tamiflu®), inhaled **zanamivir** (trade name Relenza®), and intravenous **peramivir** (trade name Rapivab®). The fourth drug is oral **baloxavir marboxil** (trade name Xofluza®), which is active against both influenza A and B viruses but has a different mechanism of action. Baloxavir is a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication. Recommended ages for treatment

and prevention with antiviral medications are summarized in the table below. Dosing and more detailed treatment considerations can be found in the Summary of Influenza Antiviral Treatment Recommendations for Clinicians (http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm).

Antiviral	Route	Treatment (Recommended Age)	Chemoprophylaxis (Recommended Age)	Most Common Adverse Events
Oseltamivir	oral and enteric	any age	≥3 months	nausea, vomiting, headache*
Zanamivir	inhaled	≥7 years	≥5 years	bronchospasm
Peramivir	intravenous	≥2 years	n/a	diarrhea
Baloxavir	oral	≥12 years	n/a	none more common than placebo

*Nausea and vomiting are generally transient and can be mitigated if oseltamivir is taken with food
n/a = not applicable

For outpatients with acute uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for treatment.
The recommended treatment course for uncomplicated influenza is

- Two doses per day of oral oseltamivir for five days, or
- Two doses per day of inhaled zanamivir for five days, or
- One dose per day of intravenous peramivir for one day, or
- One dose per day of oral baloxavir for one day.

Oral or enterically-administered oseltamivir is the only recommended antiviral medication for treatment of hospitalized patients with suspected or confirmed influenza and patients with severe or complicated illness with suspected or confirmed influenza (e.g., pneumonia, exacerbation of underlying chronic medical condition) who are not hospitalized. There are insufficient data for inhaled zanamivir, intravenous peramivir, and oral baloxavir in patients with severe influenza disease.

Oral oseltamivir is preferred for treatment of pregnant women. Pregnant women are recommended to receive the same antiviral dosing as non-pregnant people. Baloxavir is not recommended for the treatment of pregnant women or breastfeeding mothers, as there are no available efficacy or safety data.

4. **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.

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 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. High-risk patients should be advised to call their provider promptly if they have symptoms of influenza.

References

1. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis 2016; 16:942–951. https://www.sciencedirect.com/science/article/pii/S1473309916001298?via%3Dihub

2. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med 2018; 379:913–923. https://www.nejm.org/doi/full/10.1056/NEJMoa1716197

3. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. Clin Infect Dis 2018; 68:e1–e47. https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciy866

4. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. The Lancet 2015; 385:1729–1737. https://www.sciencedirect.com/science/article/pii/S0140673614624491?via%3Dihub

5. Malosh RE, Martin ET, Heikkinen T, Monto AS, Brooks WA, Whitley RJ. Efficacy and Safety of Oseltamivir in Children: Systematic Review and Individual Patient Data Meta-analysis of Randomized Controlled Trials. Clin Infect Dis 2018; 66:1492–1500. https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cix1040

6. Hsu J, Santesso N, Brozek J, et al. Antivirals for influenza: a summary of a systematic review and meta-analysis of observational studies. Influenza Other Respir Viruses 2013; 7 Suppl 2:76–81. https://onlinelibrary.wiley.com/doi/full/10.1111/irv.12085

7. Doll MK, Winters N, Kraicer-Melamed H, Boikos C, Quach C, Gore G. Safety and effectiveness of neuraminidase inhibitors for influenza treatment, prophylaxis, and outbreak control: a systematic review of systematic reviews and/or meta-analyses. J Antimicrob Chemother 2017; 72:2990–3007. https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkx271

8. Venkatesan S, Myles PR, Leonardi-Bee J, et al. Impact of Outpatient Neuraminidase Inhibitor Treatment in Patients Infected With Influenza A(H1N1)pdm09 at High Risk of Hospitalization: An Individual Participant Data Metaanalysis. Clin Infect Dis 2017; 64:1328–1334. https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cix127

9. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med 2014; 2:395–404. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(14)70041-4/fulltext

10. Lee N, Choi KW, Chan PKS, et al. Outcomes of adults hospitalised with severe influenza. Thorax 2010; 65:510–515. https://thorax.bmj.com/content/65/6/510

11. Lee N, Cockram CS, Chan PKS, Hui DSC, Sung JJY, Choi KW. Antiviral Treatment for Patients Hospitalized with Severe Influenza Infection May Affect Clinical Outcomes. Clin Infect Dis 2008; 46:1323–1324. https://academic.oup.com/cid/article/46/8/1323/364997

12. Lee EH, Wu C, Lee EU, et al. Fatalities Associated with the 2009 H1N1 Influenza A Virus in New York City. Clin Infect Dis 2010; 50:1498–1504. https://academic.oup.com/cid/article/50/11/1498/507049

13. Louie JK, Yang S, Acosta M, et al. Treatment With Neuraminidase Inhibitors for Critically Ill Patients With Influenza A (H1N1)pdm09. Clin Infect Dis 2012; 55:1198–1204. https://academic.oup.com/cid/article/55/9/1198/435273

14. McGeer A, Green KA, Plevneshi A, et al. Antiviral Therapy and Outcomes of Influenza Requiring Hospitalization in Ontario, Canada. Clin Infect Dis 2007; 45:1568–1575. https://academic.oup.com/cid/article/45/12/1568/303324

15. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 Influenza A(H1N1) Virus Illness Among Pregnant Women in the United States. JAMA 2010; 303:1517–1525. https://jamanetwork.com/journals/jama/fullarticle/185713

16. Fry AM, Goswami D, Nahar K, et al. Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial. Lancet Infect Dis 2014; 14:109–118. https://www.ncbi.nlm.nih.gov/pubmed/24268590

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