Health Update:

2009 H1N1 Influenza Update 11: Antiviral Medication and Influenza Testing Issues

September 25, 2009

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September 25, 2009

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SUBJECT: **2009 H1N1 Influenza Update 11: Antiviral Medication and Influenza Testing Issues**

This Health Update provides: 1) information on potential confusion associated with use of the oral dosing dispenser provided with Tamiflu suspension; 2) reports of limited supplies of Tamiflu suspension; 3) updated guidance on the use of antiviral drugs; 4) updated antiviral medication recommendations for obstetric care providers; and 5) information on possible positive rapid influenza diagnostic test results in persons who have recently received live, attenuated influenza vaccine.

Potential Confusion Associated With Use of the Oral Dosing Dispenser Provided With Tamiflu Oral Suspension

An issue that physicians and pharmacists may face is the need to ensure that the units of measure on the dosing dispenser and the dosing instructions match. An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations of Tamiflu is provided in the packaging for the manufacturer's product rather than graduations in milliliters (mL) or teaspoons (tsp). This can lead to patient or caregiver confusion and dosing errors. When dispensing commercially manufactured Tamiflu oral suspension, pharmacists should ensure the units of measure on the dosing instructions match the dosing device provided. If prescription instructions specify administration using mL or tsp, then the device included in the Tamiflu product package should be removed and replaced with an appropriate measuring device, such as an oral syringe if the prescribed dose is in milliliters (mL). When dispensing Tamiflu oral suspension for children younger than 1 year of age, the oral dosing dispenser that is included in the product package should always be removed. Pharmacists and health care providers should provide an oral syringe that is capable of accurately measuring the prescribed milliliter (mL) dose, and counsel the caregiver how to administer the prescribed dose. Oseltamivir is authorized for emergency use in children younger than 1 year of age under an Emergency Use Authorization (EUA) issued by the Food and Drug Administration (FDA). For the EUA, see http://www.cdc.gov/h1n1flu/eua/pdf/tamiflu-hcp.pdf.

Limited Supplies of Tamiflu Oral Suspension

The Food and Drug Administration (FDA) and Roche (maker of Tamiflu) have acknowledged that commercial and stockpiled supplies of Tamiflu oral suspension are limited. **Limited supplies** of Tamiflu oral suspension made available to Missouri from the Strategic National Stockpile (SNS) and included in local public health agencies' antiviral medication planning can be used **for treatment** when other community resources have been exhausted.

If pediatric formulations of Tamiflu are not available, pharmacists may compound Tamiflu 75 mg capsules into an oral suspension onsite. For the FDA -approved instructions for the emergency compounding of an oral suspension from Tamiflu 75mg capsules, see the FDA approved manufacturer package insert for oseltamivir (Tamiflu) at: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM147992.pdf.

Compounding an oral suspension from Tamiflu 75mg capsules provides an alternative when commercially manufactured oral suspension formulation is not readily available. Tamiflu capsules 75 mg may be compounded using either of two vehicles: Cherry Syrup (Humco®) or Ora-Sweet® SF (sugar-free) (Paddock Laboratories). Other supplies needed to

compound include mortar and pestle and amber glass or amber polyethyleneterephthalate (PET) bottle.

In addition, for children who may not be able to swallow capsules, Tamiflu (30mg, 45mg, and 75mg) capsules may be opened and mixed with sweetened liquids, such as regular or sugar-free chocolate syrup, if oral suspension is not available.

Updated Guidance on the Use of Antiviral Drugs for Treatment and Prophylaxis of Influenza

On September 22, 2009, CDC updated its recommendations for the use of antiviral drugs for treatment and prophylaxis of 2009 H1N1 influenza and seasonal influenza. The updated recommendations are available at http://www.cdc.gov/h1n1flu/recommendations.htm, and are intended to help clinicians prioritize the use of antiviral medications for treatment and prevention.

As in earlier recommendations, the priority for use of antiviral medications continues to be in people with more severe illness, such as people hospitalized with influenza, and people at increased risk of influenza-related complications. CDC notes that as with any medical decision making, clinical judgment is an essential factor in making decisions about treatment with antiviral medications.

DHSS strongly emphasizes the importance of a judicial use of antiviral medications in order to prevent emergence of antiviral resistance, and to ensure that the existing limited supplies of antiviral medications are being used in the most effective way possible.

Key points from the guidance include the following. All clinicians who provide care for influenza patients and their contacts are strongly encouraged to read the complete document (http://www.cdc.gov/h1n1flu/recommendations.htm).

Treatment

- Most healthy persons who develop an illness consistent with influenza, or persons who appear to be recovering from influenza, do not need antiviral medications for treatment. However, persons presenting with suspected influenza and more severe symptoms such as evidence of lower respiratory tract infection or clinical deterioration should receive prompt empiric antiviral therapy, regardless of previous health or age.
- Treatment with oseltamivir (Tamiflu) or zanamivir (Relenza) is recommended for all persons with suspected or confirmed influenza requiring hospitalization.
- Early empiric treatment with oseltamivir or zanamivir should be considered for persons with suspected or confirmed influenza who are at higher risk for complications including:
    - **Children younger than 2 years old;**
    - **Persons aged 65 years or older;**
    - **Pregnant women;**
    - **Persons of any age with certain chronic medical or immunosuppressive conditions (see http://www.cdc.gov/h1n1flu/recommendations.htm); and,**
    - **Persons younger than 19 years of age who are receiving long-term aspirin therapy**

  Clinical judgment should be used in deciding whether outpatients with risk factors for influenza-related complications require treatment.
- Children 2 years to 4 years old are more likely to require hospitalization or urgent medical evaluation for influenza compared with older children, although the risk is much lower than for children younger than 2 years old. Children aged 2 years to 4 years without high risk conditions and with mild illness do not necessarily require antiviral treatment.
- Treatment, when indicated, should be initiated as early as possible (and should not wait on laboratory results) because studies show that treatment initiated early (i.e., within 48 hours of illness onset) is more likely to provide benefit. However, some studies of hospitalized patients with seasonal influenza treated with oseltamivir have suggested benefit, including reductions in mortality or duration of hospitalization, even for patients whose treatment was started more than 48 hours after illness onset.
- The recommended duration of treatment is five days. Hospitalized patients with severe infections (such as those with prolonged infection or who require intensive care unit admission) might require longer treatment courses. Some experts have advocated use of increased (doubled) doses of oseltamivir for

some severely ill patients, although there are no published data demonstrating that higher doses are more effective.

- Oseltamivir use for children younger than 1 year old was recently authorized by FDA under an EUA (see http://www.cdc.gov/h1n1flu/eua/tamiflu.htm). These EUA provisions apply only when the product is provided in accordance with the local public health authority's response plans. Dosing for children younger than 1 year old is age-based in the EUA guidance (see the dosing recommendations at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM153546.pdf). However, some experts who are currently conducting studies on oseltamivir use in this age group prefer weight based dosing for this age group, particularly for premature or underweight infants.

Chemoprophylaxis

- Consideration for chemoprophylaxis should generally be reserved for persons at higher risk for influenza-related complications who have had contact with someone likely to have been infected with influenza. However, early treatment is an emphasized alternative to chemoprophylaxis after a suspected exposure. Household or close contacts (with risk factors for influenza complications) of confirmed or suspected cases can be counseled about the early signs and symptoms of influenza, and advised to immediately contact their health care provider for evaluation and possible early treatment if clinical signs or symptoms develop.

  Close contact, for the purposes of this guidance, is defined as having cared for or lived with a person who is a confirmed, probable, or suspected case of influenza, or having been in a setting where there was a high likelihood of contact with respiratory droplets and/or body fluids of such a person. Examples of close contact include sharing eating or drinking utensils, physical examination, or any other contact between persons likely to result in exposure to respiratory droplets. Close contact typically does not include activities such as walking by an infected person or sitting across from a symptomatic patient in a waiting room or office.

- Post-exposure chemoprophylaxis with either oseltamivir or zanamivir can also be considered for health care personnel, public health workers, or first responders who have had a recognized, unprotected close contact exposure to a person with known or suspected 2009 H1N1 or seasonal influenza.
- For antiviral chemoprophylaxis of 2009 H1N1 influenza virus infection, either oseltamivir or zanamivir is recommended. Duration of post-exposure chemoprophylaxis is 10 days after the last known exposure to 2009 H1N1 influenza.
- Antiviral agents should not be used for post-exposure chemoprophylaxis in healthy children or adults based on potential exposures in the community, school, camp, or other settings. Chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the last contact with an infectious person. Chemoprophylaxis is not indicated when contact occurred before or after, but not during, the ill person's infectious period.

  For the purposes of this guidance, the infectious period for influenza is defined as one day before until 24 hours after fever ends.

- Patients receiving chemoprophylaxis should be encouraged to promptly seek medical evaluation if they develop a febrile respiratory illness that might indicate influenza.
- Oseltamivir was authorized for use for chemoprophylaxis under the EUA for children younger than 1 year of age, subject to the terms and conditions of the EUA. Age-based dosing recommendations are provided in the fact sheets included with the EUA letter of authorization (available at http://www.cdc.gov/h1n1flu/eua/); dosing recommendations are also available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM153546.pdf. Note that weight-based dosing is an alternative preferred by some experts who are currently conducting studies of oseltamivir use in this age group.
- Oseltamivir-resistant 2009 H1N1 viruses have been identified, typically among persons who develop illness while receiving oseltamivir for chemoprophylaxis or immunocompromised patients with influenza who are being treated. These findings underscore the importance of careful and limited use of antiviral medications for chemoprophylaxis and the need for persons taking antiviral medications to continue to follow recommendations for hand and respiratory hygiene to prevent the spread of antiviral-resistant viruses.

Patients receiving treatment should be advised that they remain potentially infectious to others while on treatment. Despite treatment with antiviral agents, including treatment with the neuraminidase inhibitors, patients may continue to shed influenza virus for up to four or more days after beginning therapy. Therefore, patients should continue good hand washing and respiratory hygiene practices during the entire period on therapy to prevent the transmission of virus to close contacts. See *Taking Care of a Sick Person in Your Home* at http://www.cdc.gov/h1n1flu/guidance_homecare.htm, and *Home Care Guidance: Physician Directions to Patient/Parent* at http://www.cdc.gov/h1n1flu/guidance_homecare_directions.htm.

Recommendations for Obstetric Health Care Providers Related to Use of Influenza Antiviral Medications

Pregnant women are at higher risk for severe complications and death from influenza, including both 2009 H1N1 influenza and seasonal influenza. CDC has recently issued updated recommendations for obstetric health care providers on the use of antiviral medications (http://www.cdc.gov/H1N1flu/pregnancy/antiviral_messages.htm). Key points from the recommendations include the following. All clinicians who provide care for pregnant women are strongly encouraged to read the complete document.

Treatment

- Treatment with oseltamivir (Tamiflu) or zanamivir (Relenza) is recommended for pregnant women with suspected or confirmed influenza and can be taken during any trimester of pregnancy.
- Oseltamivir and zanamivir are "Pregnancy Category C" medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women. However, CDC states the available risk-benefit data indicate pregnant women with suspected or confirmed influenza should receive prompt antiviral therapy. Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use.
- For treatment of pregnant women with suspected or confirmed influenza, oseltamivir is currently preferred because of its systemic absorption.
- Fever in pregnant women should be treated because of the risk that it appears to pose to the fetus. Acetaminophen appears to be the best option for treatment of fever during pregnancy.

Chemoprophylaxis

- Post-exposure chemoprophylaxis can be considered for pregnant women who have had contact with someone likely to have been infectious with influenza. The drug of choice for chemoprophylaxis of pregnant women is less clear. Zanamivir may be the preferable antiviral for chemoprophylaxis of pregnant women because of its limited systemic absorption. However, respiratory complications that may be associated with zanamivir because of its inhaled route of administration need to be considered, especially in women at risk for respiratory problems. For these women, oseltamivir is a reasonable alternative.
- Early treatment is an alternative to chemoprophylaxis for some pregnant women who have had contact with someone likely to have been infectious with influenza. Clinical judgment is an important factor in treatment decisions.

Rapid Influenza Diagnostic Tests and Live, Attenuated Influenza Vaccine

Rapid influenza diagnostic tests (RIDTs) are widely used, and last month CDC issued guidance for the detection of 2009 H1N1 virus using these tests (http://www.cdc.gov/h1n1flu/guidance/rapid_testing.htm). Clinicians should be aware that if a person receives live, attenuated influenza vaccine (LAIV) and then, within the next few days, develops an influenza-like illness and has a rapid influenza test, this test may be positive because it is detecting the presence of vaccine virus or, alternatively, it could be detecting a wild-type influenza virus. In studies that have looked at vaccine virus shedding in LAIV recipients (using RIDTs and other, more sensitive, tests such as culture and PCR), none of the participants had detectable virus beyond 10 days after receipt of the vaccine. (*MMWR* 2008;57[RR-7]:17-18.)

Links to comprehensive information and guidance on 2009 H1N1 influenza for medical professionals is available at http://www.dhss.mo.gov/BT_Response/_MedProfs.html.

Questions on 2009 H1N1 influenza can be directed to your local public health agency, or to DHSS' Bureau of Communicable Disease Control and Prevention at 573-751-6113 or 866-628-9891.