Health Update:

2009 H1N1 Influenza Update 12: Use of H1N1 Influenza Vaccine Containing Thimerosal, Missouri's H1N1 InfoLine, Antiviral Drug Use, Clinical Features of Severe Cases, Triage Algorithms, H1N1 Influenza Vaccine

October 23, 2009

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Health Update
October 23, 2009

FROM: **MARGARET T. DONNELLY**
DIRECTOR

SUBJECT: **2009 H1N1 Influenza Update 12: Use of H1N1 Influenza Vaccine Containing Thimerosal, Missouri's H1N1 InfoLine, Antiviral Drug Use, Clinical Features of Severe Cases, Triage Algorithms, H1N1 Influenza Vaccine**

This Health Update provides: 1) information on the use of H1N1 influenza vaccine containing thimerosal in pregnant women and young children; 2) announcement of Missouri's H1N1 InfoLine; 3) updated information on the use of antiviral drugs for influenza treatment and prophylaxis; 4) information on the clinical features of severe cases of 2009 H1N1 influenza; 5) links to triage algorithms for adults and children with influenza-like illness; and 6) information and guidance on 2009 H1N1 influenza vaccine.

Use of 2009 H1N1 Influenza Vaccine Containing Thimerosal in Pregnant Women and Young Children

Margaret Donnelly, director of the Department of Health and Senior Services (DHSS), granted an exemption Thursday, October 22, 2009, to the requirements of 191.235, RSMo. This exemption allows pregnant women and parents of children less than three years old to choose whether to receive 2009 H1N1 influenza vaccine containing thimerosal. Director Donnelly determined that a shortage of preservative-free vaccine was preventing pregnant women and young children from obtaining the new H1N1 vaccine.

Donnelly's action temporarily sets aside the statute that prohibited pregnant women and children under three from receiving vaccine with this preservative. The waiver will remain in effect until the shortage no longer exists.

Under the exemption, pregnant women and families of children younger than three years old will be able to decide whether to receive 2009 H1N1 influenza vaccine that contains small traces of mercury-based preservative.

Information on thimerosal in influenza vaccine is available from the Centers for Disease Control and Prevention (CDC) at http://www.cdc.gov/flu/about/qa/thimerosal.htm.

Missouri's H1N1 InfoLine

Missourians, including Missouri medical professionals, now have access to a toll-free H1N1 influenza information line. Named the **H1N1 InfoLine**, and sponsored by DHSS, it can provide information and guidance on 2009 H1N1 influenza and H1N1 vaccine to both the public and medical providers. This service is available 24 hours a day, seven days a week at 1-877-FLU-4141 (1-877-358-4141).

Use of Antiviral Drugs for Treatment and Prophylaxis of Influenza

DHSS and the Board of Registration for the Healing Arts have recently sent a letter to medical providers reminding them of the importance of the appropriate use of antiviral medications for the treatment and prophylaxis of influenza. Proper use of these drugs is necessary in order to ensure that adequate amounts will remain available for persons who

will benefit most from their use, and so that the potential development of widespread antiviral resistance to these medications can be avoided. The medical providers' letter, and an accompanying summary of updated antiviral guidance from CDC, are shown in the Appendix to this document, and are also available at http://www.dhss.mo.gov/BT_Response/SwineFlu/PhysicianLetterandGuidanceSummary.pdf. The CDC guidance (which applies to the treatment and prophylaxis of both 2009 H1N1 and seasonal influenza virus infections) is found at http://www.cdc.gov/h1n1flu/recommendations.htm.

Regarding treatment, the CDC guidance states that most healthy persons who develop an illness consistent with uncomplicated 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. Antiviral treatment is also recommended for all persons with suspected or confirmed influenza requiring hospitalization. In addition, early empiric antiviral treatment should be considered for persons with suspected or confirmed influenza who are at higher risk for complications (these are listed in the guidance document). For antiviral treatment of 2009 H1N1 virus infection, either oseltamivir or zanamivir is recommended. Both the CDC guidance document and a more recent CDC statement (http://www.cdc.gov/H1N1flu/HAN/101909.htm) emphasize that when treatment is indicated in a patient with suspected influenza, health care providers should initiate empiric antiviral treatment as soon as possible. Waiting for laboratory confirmation of influenza to begin treatment with antiviral drugs is not necessary. Patients with a negative rapid influenza diagnostic test should be considered for treatment if clinically indicated because a negative rapid influenza test result does not rule out influenza virus infection. The sensitivity of rapid influenza diagnostic tests for 2009 H1N1 virus can range from 10% to 70%, indicating that false negative results occur frequently.

The CDC guidance additionally states that consideration for antiviral chemoprophylaxis (with either oseltamivir or zanamivir) 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. 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. Also, chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the last contact with an infectious person.

In addition to the updated antiviral guidance, CDC has recently issued supplemental recommendations for health care providers of children and adolescents on the use of antiviral medications for treatment and chemoprophylaxis. These recommendations are available at http://www.cdc.gov/h1n1flu/recommendations_pediatric_supplement.htm. CDC has also issued guidance on influenza antiviral treatment of pregnant women, which is available at http://www.cdc.gov/h1n1flu/clinician_pregnant.htm.

CDC has recently developed a new website which provides safety information on antiviral drugs; it can be accessed at http://www.cdc.gov/H1N1flu/antivirals/safety_info.htm.

Links to more information on antiviral drugs are available at http://www.dhss.mo.gov/BT_Response/_MedProfs.html (see the Antiviral Drugs section).

Clinical Features of Severe Cases of Pandemic Influenza

On October 14-16, the World Health Organization (WHO) hosted a three-day meeting in Washington, DC, to gather information about the clinical features and management of patients with 2009 H1N1 influenza. A brief report is found at http://www.who.int/csr/disease/swineflu/notes/h1n1_clinical_features_20091016/en/index.html. Key points include the following:

- The meeting confirmed that the overwhelming majority of persons worldwide infected with the new H1N1 virus continue to experience uncomplicated influenza-like illness, with full recovery within a week, even without medical treatment.

- Concern is now focused on the clinical course and management of small subsets of patients who rapidly develop very severe progressive pneumonia. In these patients, severe pneumonia is often associated with failure of other organs, or marked worsening of underlying asthma or chronic obstructive airway disease.

- Treatment of these patients is difficult and demanding, strongly suggesting that emergency rooms and intensive care units will experience the heaviest burden of patient care during the pandemic.

- Primary viral pneumonia is the most common finding in severe cases and a frequent cause of death. Secondary bacterial infections have been found in approximately 30% of fatal cases. Respiratory failure and refractory shock have been the most common causes of death.

- The clinical picture in severe cases is strikingly different from the disease pattern seen during epidemics of seasonal influenza. While people with certain underlying medical conditions, including pregnancy, are known to be at increased risk, many severe cases occur in previously healthy young people. In these patients, predisposing factors that increase the risk of severe illness are not presently understood.

- In severe cases, patients generally begin to deteriorate around 3 to 5 days after symptom onset. Deterioration is rapid, with many patients progressing to respiratory failure within 24 hours, requiring immediate admission to an intensive care unit. Upon admission, most patients need immediate respiratory support with mechanical ventilation. However, some patients do not respond well to conventional ventilatory support, further complicating the treatment.

- There is a growing body of evidence that prompt treatment with the antiviral drugs, oseltamivir or zanamivir, reduces the severity of illness and improves the chances of survival. These findings strengthen previous WHO recommendations for early treatment with these drugs for patients who meet treatment criteria, even in the absence of a positive confirmatory test.

- In addition to pneumonia directly caused by replication of the virus, evidence shows that pneumonia caused by co-infection with bacteria can also contribute to a severe, rapidly progressive illness. Bacteria frequently reported include *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin-resistant strains in some cases. As these bacterial co-infections are more frequent than initially recognized, clinicians stressed the need to consider empiric antimicrobial therapy for community-acquired pneumonia as an early treatment.

- Participants agreed that the risk of severe or fatal illness is highest in three groups: pregnant women, especially during the third trimester of pregnancy, children younger than 2 years of age, and people with chronic lung disease, including asthma. Neurological disorders can increase the risk of severe disease in children.

- Evidence presented during the meeting further shows that disadvantaged populations, such as minority groups and indigenous populations, are disproportionately affected by severe disease.

- Although the exact role of obesity is poorly understood at present, obesity and especially morbid obesity have been present in a large portion of severe and fatal cases. Obesity has not been recognized as a risk factor in either past pandemics or seasonal influenza.

Triage Algorithms For Adults and Children With Influenza-Like Illness

CDC, in collaboration with Emory University School of Medicine, has developed a triage algorithm for adults (>18 years of age) with influenza-like illness (ILI). This algorithm was designed to assist physicians and those under their supervision in identifying indicators of and responses to symptoms of flu-like illness. It is available at http://www.cdc.gov/h1n1flu/clinicians/pdf/adultalgorithm.pdf.

CDC and the American Academy of Pediatrics (AAP) have developed a triage algorithm for children (≤18 years of age) with ILI. This algorithm is intended for use by physicians and those under their direct supervision to help in discussions and providing advice to parents or other caregivers of ill children regarding seeking medical care for an ILI. It is available at http://www.cdc.gov/h1n1flu/clinicians/pdf/childalgorithm.pdf.

2009 H1N1 Influenza Vaccine

Four influenza vaccine manufacturers have received approval from the Food and Drug Administration (FDA) for their 2009 H1N1 monovalent influenza vaccines. Both live, attenuated and inactivated influenza vaccine formulations have been approved. Initial supplies of these vaccines are now coming into Missouri, and more will become available in the coming weeks. See http://www.dhss.mo.gov/BT_Response/_provider_listing.html for current information on 2009 H1N1 and seasonal influenza vaccines in Missouri.

Because the initially available quantities of these vaccines are limited, they should, at this time, be given to persons in the following priority groups (note that the order of the target groups does not indicate priority):

- **Pregnant women,**
- **Persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers),**
- **Health-care and emergency medical services personnel who have direct contact with patients or infectious material,**
- **Children aged 6 months - 4 years, and**
- **Children and adolescents aged 5 - 18 years who have medical conditions that put them at higher risk for influenza-related complications. These conditions include chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus); or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus).**

Once vaccine availability increases (hopefully within the next few weeks), the following five groups will then be prioritized to receive the vaccine (note that the order of the target groups does not indicate priority):

- Pregnant women,
- People who live with or provide care for infants younger than 6 months of age (e.g., parents, siblings, and day care providers),
- Health care and emergency medical services personnel,
- People 6 months through 24 years of age, and,
- People 25 years through 64 years of age who have certain medical conditions that put them at higher risk for influenza-related complications.

Then, when vaccination programs and providers are meeting the demand for vaccine among persons in these target groups, vaccination should be expanded to all persons aged 25-64 years.

Finally, once demand for vaccine among younger age groups is being met, vaccination should be expanded to all persons aged ≥65 years.

Information and guidance on 2009 H1N1 influenza vaccine is available from CDC and FDA, and includes:

- Update on Influenza A (H1N1) 2009 Monovalent Vaccines (CDC)
  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5839a3.htm
- Vaccine Information Statements: 2009 H1N1 Influenza Vaccine (CDC)
  http://www.cdc.gov/vaccines/pubs/vis/default.htm#h1n1live

- H1N1 Clinicians Questions and Answers (CDC)
  http://www.cdc.gov/h1n1flu/vaccination/clinicians_qa.htm
- 10 FAQs for Immunization Programs and Providers (CDC)
  http://www.cdc.gov/H1N1flu/vaccination/top10_faq.htm
- 2009 H1N1 Influenza Vaccine and Pregnant Women: Information for Healthcare Providers (CDC)
  http://www.cdc.gov/h1n1flu/vaccination/providers_qa.htm
- Influenza A (H1N1) 2009 Monovalent (FDA) (Includes links to the package insert for each vaccine.)
  http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm181950.htm

More information on 2009 H1N1 vaccine is available at http://www.dhss.mo.gov/BT_Response/_MedProfs.html (see the Vaccine section).

APPENDIX

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Margaret T. Donnelly
Director

Jeremiah W. (Jay) Nixon
Governor

October 21, 2009

To All Missouri Medical Physicians:

The Missouri Department of Health and Senior Services (DHSS) and the Board of Registration for the Healing Arts wish to emphasize the importance of the appropriate use of antiviral medications for the treatment and prophylaxis of influenza in order to prevent emergence of antiviral resistance, and to ensure that the existing limited supplies of antiviral drugs are being used in the most effective way possible.

2009 H1N1 influenza virus infections are spreading widely throughout the United States, including Missouri. Most infected persons have uncomplicated, typical influenza-like illness and do not require medical care. However serious illnesses and deaths have occurred, and certain groups of persons appear to be at increased risk of complications. Antiviral medications are available for influenza treatment and prophylaxis, but proper use of these drugs is important in order to ensure that adequate amounts will remain available for persons who will most benefit from their use, and so that the widespread occurrence of antiviral resistance can be avoided.

Shortages of oseltamivir (Tamiflu) oral suspension have recently been reported, and there are ongoing concerns that the widespread resistance to oseltamivir currently seen with seasonal H1N1 influenza viruses could also emerge in 2009 H1N1 influenza viruses. A relatively small number of 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 events particularly underscore the importance of the appropriate use of antiviral medications for treating individuals with known or suspected influenza, and the careful and limited use of these drugs for chemoprophylaxis.

The Centers for Disease Control and Prevention (CDC) has issued guidance for the use of antiviral medications for treatment and prophylaxis of influenza. Physicians are strongly encouraged to become familiar with these recommendations, and to incorporate them into their clinical decision-making. This guidance will likely be updated periodically, and the current version can be found at http://www.cdc.gov/h1n1flu/recommendations.htm. Also note that this guidance applies to the treatment and prophylaxis of both 2009 H1N1 and seasonal influenza virus infections. A summary of the guidance is attached.

Sincerely,

Margaret T. Donnelly

Margaret T. Donnelly
Director

Summary of Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza

Centers for Disease Control and Prevention (CDC)
October 16, 2009

See http://www.cdc.gov/h1n1flu/recommendations.htm for the complete set of recommendations. In addition, supplemental recommendations for health care providers of children and adolescents have also been issued and are found at http://www.cdc.gov/h1n1flu/recommendations_pediatric_supplement.htm.

Treatment

- Influenza antiviral medications can reduce the severity and duration of influenza illness and can reduce the risk of influenza-related complications, including severe illness and death.
- Most healthy persons who develop an illness consistent with uncomplicated influenza, or persons who appear to be recovering from influenza, do not need antiviral medications for treatment or prophylaxis.
- 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 or zanamivir 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 and women up to 2 weeks postpartum (including following pregnancy loss);
  - Persons of any age with certain chronic medical or immunosuppressive conditions
    - ✓ Chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), or metabolic disorders (including diabetes mellitus);
    - ✓ Disorders that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders)
    - ✓ Immunosuppression, including that caused by medications or by HIV; and
  - Persons younger than 19 years of age who are receiving long-term aspirin therapy.
- Children 2 years to 4 years old are more likely to require hospitalization or urgent medical evaluation for influenza compared with older children and adults, 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. [For more information on antiviral treatment of children and adolescents, see the supplementary guidance available at http://www.cdc.gov/h1n1flu/recommendations_pediatric_supplement.htm.]
- Treatment, when indicated, should be initiated as early as possible because the benefits are greatest when started within the first 2 days of illness. However, some studies of hospitalized patients with seasonal and 2009 H1N1 influenza have suggested benefit of antiviral treatment even when treatment was started more than 48 hours after illness onset.
- To reduce delays in treatment initiation, consider:

    - Informing persons at higher risk for influenza complications of signs and symptoms of influenza and need for early treatment after onset of symptoms of influenza (i.e., fever, respiratory symptoms);
    - Ensuring rapid access to telephone consultation and clinical evaluation for these patients as well as patients who report severe illness;
    - Considering empiric treatment of patients at higher risk for influenza complications based on telephone contact if hospitalization is not indicated and if this will substantially reduce delay before treatment is initiated.
- Treatment should not wait for laboratory confirmation of influenza because lab testing can delay treatment and because a negative rapid test for influenza does not rule out influenza. The sensitivity of rapid tests in detecting 2009 H1N1 has ranged from 10% to 70%. Information on the use of rapid influenza diagnostic tests (RIDTs) is found at http://www.cdc.gov/h1n1flu/guidance/rapid_testing.htm.
- Testing for 2009 H1N1 influenza infection with real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) should be prioritized for persons with suspected or confirmed influenza requiring hospitalization and based on guidelines from local and state health departments. [See page 3 of the Missouri Department of Health and Senior Services (DHSS) Health Update found at http://www.dhss.mo.gov/BT_Response/HAds/HU10SwineFlu9-11-09.pdf.]

Chemoprophylaxis

- Consideration for antiviral chemoprophylaxis should generally be reserved for persons at higher risk for influenza-related complications who have had close 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 healthcare provider for evaluation and possible early treatment if clinical signs or symptoms develop. Early recognition of illness and treatment when indicated is preferred to chemoprophylaxis for vaccinated persons after a suspected exposure.
- 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.
- 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.
- 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.
- [For important additional information on antiviral prophylaxis of children and adolescents, see the supplementary guidance at http://www.cdc.gov/h1n1flu/recommendations_pediatric_supplement.htm. Included in this guidance is the statement that oseltamivir chemoprophylaxis for influenza virus infection in children younger than 1 year old is age-based; however, chemoprophylaxis for asymptomatic infants less than 3 months old is not recommended due to lack of safety data.]
- 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 these recommendations, the infectious period for influenza is defined as one day before illness onset until 24 hours after fever ends [without the use of fever reducing medications].

- Close contact, for the purposes of this document, 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.

Additional Information

- Based on global experience to date, 2009 H1N1 influenza viruses likely will be the most common influenza viruses among those circulating in the coming season, particularly those causing influenza among younger age groups. Circulation of seasonal influenza viruses during the 2009-10 season is also expected. Influenza seasons are unpredictable, however, and the timing and intensity of seasonal influenza virus activity versus 2009 H1N1 circulation cannot be predicted in advance.
- Currently circulating 2009 H1N1 viruses are susceptible to oseltamivir and zanamivir, but resistant to amantadine and rimantadine; however, antiviral treatment regimens might change according to new antiviral resistance or viral surveillance information.
- Information on the dose and dosing schedule for oseltamivir and zanamivir is provided in the document (http://www.cdc.gov/h1n1flu/recommendations.htm). An April 2009 Emergency Use Authorization authorizes the emergency use of oseltamivir in children younger than 1 year old (http://www.cdc.gov/h1n1flu/eua/) subject to the terms and conditions of the EUA.

Note that this CDC guidance should be considered interim, and will be updated as needed. The current version will be available at http://www.cdc.gov/h1n1flu/recommendations.htm.

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

Links to comprehensive information and guidance on seasonal influenza are found at http://www.dhss.mo.gov/PandemicInfluenza/MedSeasonalFlu.html.