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CDPH Advisory

Severe influenza due to influenza A (H1N1) pdm09 (pH1N1) virus

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Last week, the CDC issued a Health Alert Network (HAN) discussing recent reports from several states of severe infection associated with pH1N1 virus infection (http://emergency.cdc.gov/HAN/han00359.asp.) The HAN described critically-ill young and middle-aged adults infected with influenza, with complications of severe pneumonia requiring hospitalization, intensive care unit (ICU) admission, need for mechanical ventilation, extra corporeal membrane oxygenation (ECMO) and death. CDPH maintains a statewide surveillance system monitoring children and adults under age 65 years with laboratory-confirmed influenza who require ICU hospitalization or who die. In the last week, many counties statewide have reported an increase in severe influenza cases. While many of these people with severe illness have had risk factors for influenza-associated complications, including pregnancy and morbid obesity, others have not. The influenza vaccination status of these severe cases is not known, however, the 2013-2014 influenza vaccines include protection against pH1N1.

Since its emergence in 2009, pH1N1 has been observed to cause more illness in children and young adults compared to older adults, although severe illness has been seen in all age groups. While it is still early in the 2013-14 influenza season, pH1N1 has been the predominant circulating virus so far both nationwide and in California. The severe flu outcomes reported in the HAN are a reminder that flu can be a very serious disease for anyone, including young, healthy adults.

CDC and CDPH recommend annual influenza vaccination for everyone 6 months and older. Anyone who has not yet been vaccinated this season should get an influenza vaccine now; particularly persons at higher risk for severe influenza such as pregnant women and obese persons.

While annual vaccination is the best tool for prevention of influenza and its complications, treatment with antiviral drugs called neuraminidase inhibitors (oral oseltamivir and inhaled zanamivir) is an important second line of defense for those who become ill to reduce morbidity and mortality. Oseltamivir is an oral medication approved for treatment of persons aged 2 weeks and older. Zanamivir is administered through oral inhalation and is approved for treatment of persons aged 7 years and older. Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications.

General Recommendations for Influenza Antiviral Medications

- Clinicians should encourage all persons with influenza-like illness who are at high risk for influenza complications (see list below) to seek care promptly to determine if treatment with influenza antiviral medications is warranted.
    - Antiviral treatment [oseltamivir 75 mg orally twice a day for 5 days for adults and adolescents (13 years and older), pediatric patients (1 year and older) should be dosed by weight; or zanamivir powder for inhalation twice daily for 5 days for patients 7 years and older] is recommended as early as possible, ideally within 48 hours of symptom onset, for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications. This list includes:
        - children aged younger than 2 years and adults aged 65 years and older;
        - persons with chronic pulmonary, cardiovascular (except hypertension alone), renal, hepatic, hematological, metabolic disorders, or neurologic and neurodevelopment conditions;
        - persons with immunosuppression, including that caused by medications or by HIV infection;
        - women who are pregnant or postpartum (within 2 weeks after delivery);
        - persons aged younger than 19 years who are receiving long-term aspirin therapy;
        - American Indians/Alaska Natives;
        - persons who are morbidly obese (i.e., body-mass index is equal to or greater than 40); and
        - residents of nursing homes and other chronic-care facilities.
- Antiviral treatment may also be beneficial in patients with severe, complicated, or progressive illness, when started after 48 hours of illness onset, as indicated by clinical and observational studies.

- Antiviral treatment can also be considered for suspected or confirmed influenza in previously healthy, symptomatic outpatients not at high risk on the basis of clinical judgment, especially if treatment can be initiated within 48 hours of illness onset.

- Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza.

- Polymerase chain reaction (PCR) is the most sensitive test for influenza and is preferred. Rapid influenza diagnostic tests (RIDTs) have limited sensitivities and predictive values; negative results of RIDTs do not exclude influenza virus infection in patients with signs and symptoms suggestive of influenza. Therefore, antiviral treatment should not be withheld from patients with suspected influenza, even if the RIDT test is negative.

- While influenza vaccination is the best way to prevent influenza, a history of influenza vaccination does not rule out influenza virus infection in an ill patient with clinical signs and symptoms compatible with influenza.

Recommendations for Use of Influenza Antiviral Medications in the Hospital or ICU Setting

- Initiation of antiviral treatment as early as possible is recommended for hospitalized patients. Antiviral treatment may be effective in reducing morbidity and mortality in hospitalized patients even if treatment is not started until more than 48 hours after onset of illness.

- Critically ill patients with influenza may be treated with higher doses of oseltamivir (e.g. 150 mg orally every 12 hours for 10 days in patients with normal renal function). Limited data indicate that administering oseltamivir via a gastric tube can provide systemic absorption in some critically ill patients.

- Gastric stasis or bleeding can make the gastric tube administration route problematic because of the potential for reduced absorption of medication. For these patients, parenteral medications might be preferable, but no clinical trials have demonstrated increased benefit, and none are FDA-approved. If patients continue to do poorly on oral oseltamivir, investigational intravenous zanamivir is available under an emergency investigational new drug (EIND) request to the Food and Drug Administration (FDA). To request an EIND, contact:

  (8:00AM - 4:30PM EST): 301-796-1500

After business hours (4:30 pm – 8:00 am EST): Call FDA Emergency Coordinator at (866) 300-4374 or (301) 796-8240 or Call CDER Emergency Coordinator at (301) 796-9900

- CDPH has recently received requests for the unapproved antiviral drug peramivir IV to treat hospitalized patients with influenza. During H1N1, peramivir was potentially available under an FDA issued Emergency Use Authorization (EUA) on a case by case basis when request by a treating physician for a particular hospitalized patient. The EUA for distribution and use of peramivir expired on June 23, 2010. According to CDC guidance, any leftover or unused peramivir is to be destroyed and not kept for future use. Peramivir is currently not available from either the CDC or from the manufacturer.

- For patients who are intubated, use of the zanamivir disc inhaler is not possible. Suboptimal delivery to sites of infection in patients with pneumonic or extrapulmonary disease is of concern for patients with severe respiratory illness. Use of the nebulized preparation of the licensed powder formulation contained in the disc inhaler is not recommended because it has been demonstrated to clog ventilator tubing.

- Patients receiving antiviral medications who do not respond to treatment might have an infection with an antiviral-resistant influenza virus. Oseltamivir resistance, sometimes within 1 week of treatment initiation, has been reported particularly among immunocompromised patients with 2009 H1N1 virus infection who were receiving treatment with oseltamivir. Oseltamivir resistance should be suspected in patients who are persistently positive with repeated PCR testing, particularly if they are immunocompromised. Specimens from these patients can be sent to the CDPH VRDL and CDC for testing for antiviral resistance.

Additionally, in critically ill influenza-infected patients:

- Clinicians should also be vigilant for secondary bacterial infections (e.g., *Staphylococcus aureus* or *Streptococcus pneumoniae*), which may follow influenza infection.

- All specimens collected on critically ill or fatal cases with suspected or laboratory-confirmed influenza should be referred to a public health lab for further PCR confirmation and subtyping. The CDPH Viral and Rickettsial Disease Laboratory is also available for surge capacity testing as needed.

- LHJs are asked to promptly report laboratory-confirmed influenza in cases requiring intensive care and fatal cases age 0-64 years. Cases should be reported to CDPH using CalREDIE or faxing the Severe Influenza Case History Form to 916-440-5984.

References:

1. Centers for Disease Control and Prevention (CDC) Health Advisory. CDCHAN-00359. Notice to Clinicians: Early Reports of pH1N1-Associated Illnesses for the 2013-14 Influenza Season December 24, 2013, 14:30 ET (2:30 PM ET). Available at URL: http://www.bt.cdc.gov/HAN/han00359.asp

2. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention (CDC)Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011 Jan 21;60(1):1-24