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Interim Guidance on Antiviral Recommendations for Novel Influenza A (H1N1) Virus Infection

Objective: To provide interim guidance on the use of antiviral agents for treatment and chemoprophylaxis of novel influenza A (H1N1) virus infections in individuals, nursing homes and non-medical institutions.

Summary: CDPH recommends the limited use of treatment and prophylaxis with either oseltamivir or zanamivir to reduce the level of severe disease and mortality that may be caused by novel influenza A (H1N1) virus infection.

Antiviral treatment *for five days* is recommended for:

- Hospitalized patients:

  Confirmed, probable and highly suspected cases: Treatment recommended

  Suspected cases: Treatment recommended until PCR testing for influenza is negative or any testing for non-influenza causes of primary respiratory infection is positive.

- Non-hospitalized patients at higher risk for severe influenza:

  Confirmed, probable and highly suspected cases: Treatment recommended

  Suspected cases: Use clinical judgment and frequent reassessment regarding the severity and progression of illness and the fragility of the patient. For nearly all suspected cases of novel influenza A (H1N1) virus infection, the benefits of antiviral treatment will be modest and disease will not become severe if antiviral therapy is delayed or not given. Available testing for other causes of primary respiratory infection (seasonal influenza viruses and non-influenza causes) may be helpful in guiding treatment decisions. Local inventory may be insufficient to treat suspected cases.

Antiviral chemoprophylaxis *for ten days after last exposure* can be considered for:

- Persons who are at high-risk for severe influenza and have been household close contacts of a confirmed, probable or highly suspected case.
- Health care workers or public health workers who were not using appropriate personal protective equipment during close contact with an infectious case that is confirmed, probable, or highly suspected.
- Patients at high-risk for severe influenza who have had close contact with an infectious health care worker or patient who is a confirmed or probable case.

These recommendations also apply to educational, residential and correctional facilities.

Antiviral treatment and prophylaxis of residents and employees are recommended during outbreaks of confirmed novel influenza A (H1N1) virus infection in nursing homes and related medical facilities.

In localities of California where seasonal influenza caused by oseltamivir-resistant human A (H1N1) viruses is still occurring, consider using zanamvir monotherapy or a combination of oseltamivir and either rimantadine or amantadine.

Prevention of the spread of novel influenza A (H1N1) virus infection relies on non-pharmacologic infection control measures. Therefore, persons with mild influenza should be directed to remain at home rather than visit health care facilities. Medical care providers can be contacted by telephone or email for questions about treatment.

Patients should seek medical care for symptoms of more severe influenza, such as:

- difficulty breathing
- unable to take adequate fluids
- confusion or altered mental status; severe headache or other pain that is clearly not controlled by usual medications; sudden weakness, or change in vision
- rapid worsening of symptoms

These interim recommendations are currently more restrictive than those of the federal Centers for Disease Control and Prevention. Recommendations may change as additional data on antiviral effectiveness, clinical spectrum of illness, adverse events from antiviral use, and antiviral susceptibility become available.

Principles: As novel influenza A (H1N1) virus infection currently appears to be no more severe than seasonal influenza, this guidance on the use of antiviral medications reflects the current

- Policies on antiviral medications for seasonal influenza viruses.
- Possibility that the novel influenza A (H1N1) virus might become increasingly resistant to antiviral medications, especially if the medications are heavily used.
- Possibility that the novel influenza A (H1N1) virus may become increasingly virulent in the future.
- Absence of a vaccine for the novel influenza A (H1N1) virus.

The priority for the use of available supplies of antiviral medications is to reduce the level of severe disease and mortality that may be caused by novel influenza A (H1N1) virus infection.

The need to protect individuals from infection with novel influenza A (H1N1) virus must be weighed with existing information on disease severity, treatment efficacy, current and future antiviral resistance, current and future supplies of medications, and other factors.

Case Definitions for Infection with Novel Influenza A (H1N1) Virus

A ***confirmed case*** is defined as a person with influenza-like illness who has novel influenza A (H1N1) virus infection confirmed by real-time RT-PCR or viral culture.

A ***probable case*** is defined as a person with influenza-like illness who is positive for influenza A, but negative for H1 and H3 by influenza RT-PCR.

For the purposes of this guidance, a ***highly suspected case*** is defined as a person with influenza-like illness with onset within 7 days of close contact with a person who is a confirmed or probable case.

For the purposes of this guidance, a ***suspected case*** is defined as a person with influenza-like illness who does not meet the other case categories and who does not have laboratory evidence of a primary infection other than influenza (e.g., parainfluenza virus, respiratory syncytial virus, etc.).

The ***infectious period*** is defined as 1 day prior to illness onset to 7 days after onset.

Close contact is defined as having cared for or lived with a confirmed, probable or suspected case of novel influenza A (H1N1) infection, 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 kissing or embracing, 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.

An ***influenza-like illness*** is defined as fever greater or equal to 37.8°C (100°F) and either cough or sore throat.

High-risk groups: Persons who are at high-risk for severe complications infection with novel influenza A (H1N1) virus are defined as:

- Children younger than 2 years old
- Adults 65 years of age and older
- Residents of nursing homes and other chronic-care facilities.

Persons with the following conditions:

- Chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), or metabolic disorders (including diabetes mellitus);
- Immunosuppression, including that caused by medications or by HIV;
- Pregnant women;
- Persons younger than 19 years of age and receiving long-term aspirin therapy;
- Any condition (e.g., cognitive dysfunction, spinal cord injuries, severe seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration.

See MMWR: Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008.

Antiviral Treatment of Novel Influenza A (H1N1) Virus Infection

Recommendations for use of antiviral medications may change as additional data on antiviral effectiveness, clinical spectrum of illness, adverse events from antiviral use, and antiviral susceptibility data become available.

Antiviral Treatment *for five days* is recommended for:

- Hospitalized patients:

  Confirmed, probable and highly suspected cases: Treatment recommended

  Suspected cases: Treatment recommended until PCR testing for influenza is negative or any testing for non-influenza causes of primary respiratory infection is positive.

- Non-hospitalized patients at higher risk for severe influenza:

  Confirmed, probable and highly suspected cases: Treatment recommended

  Suspected cases: Use clinical judgment and frequent reassessment regarding the severity and progression of illness and the fragility of the patient. For nearly all suspected cases of novel influenza A (H1N1) virus infection, the benefits of antiviral treatment will be modest and disease will not become severe if antiviral therapy is delayed or not given. Available testing for other causes of primary respiratory infection (seasonal influenza viruses and non-influenza causes) may be helpful in guiding treatment decisions. Local inventory may be insufficient to treat suspected cases.

Once the decision to administer antiviral treatment is made, treatment with zanamivir or oseltamivir should be initiated as soon as possible after the onset of symptoms. Evidence for benefits from treatment in studies of seasonal influenza is strongest when treatment is started within 48 hours of illness onset. However, some studies of treatment of seasonal influenza have indicated benefit, including reductions in mortality or duration of hospitalization even for patients whose treatment was started more than 48 hours after illness onset.

Antiviral doses recommended for treatment of novel influenza A (H1N1) virus infection in adults or children 1 year of age or older are the same as those recommended for seasonal influenza (Table 1). Oseltamivir use for children < 1 year old was recently approved by the U.S. Food and Drug Administration (FDA) under an Emergency Use Authorization (EUA), and dosing for these children is age-based (Table 2).

Note: Providers in areas that continue to have seasonal influenza activity, especially those with circulation of oseltamivir-resistant human A (H1N1) viruses, might prefer to use either zanamivir monotherapy or a combination of oseltamivir and rimantadine or amantadine to provide adequate empiric treatment or chemoprophylaxis for patients who might have seasonal human influenza A (H1N1) infection.

Antiviral Chemoprophylaxis

Antiviral chemoprophylaxis with either oseltamivir or zanamivir (Table 1) can be considered for:

- Persons who are at high-risk for severe influenza and have been household close contacts of a confirmed, probable or highly suspected case.
- Health care workers or public health workers who were not using appropriate personal protective equipment during close contact with an infectious case that is confirmed, probable, or highly suspected.
- Patients at high-risk for severe influenza who have had close contact with an infectious health care worker or patient who is a confirmed or probable case.

Antiviral chemoprophylaxis typically should be given for 10 days. If additional exposure occurs after chemoprophylaxis has started, continue until 10 days after last confirmed exposure with an infectious case. Chemoprophylaxis is not necessary if contact with an ill case occurred more than 7 days after the onset of illness.

Oseltamivir can also be used for chemoprophylaxis in children <1 year of age under the EUA (Table 3).

Antiviral Use for Control of Novel H1N1 Influenza Outbreaks in Nursing Homes

The use of antiviral medications has been a cornerstone for the control of seasonal influenza outbreaks in nursing homes and other long term care facilities. For outbreaks of confirmed novel influenza A (H1N1) infection in these settings, prompt initiation of zanamivir or oseltamivir are recommended for:

- Treatment of ill patients
- Chemoprophylaxis of employees and well residents for a minimum of two weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 7 days after illness onset in the last patient.

In addition to antiviral medications, other outbreak-control measures include appropriate infection control, establishing cohorts of patients with confirmed or suspected influenza, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients, and active surveillance for new cases. Medical directors of long-term care facilities should review their plans for outbreak control of influenza. Additional guidance for infection control measures in long-term care facilities can be found at http://www.cdc.gov/flu/professionals/infectioncontrol/institutions.htm.

See MMWR: Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008.

Non-medical Institutions

The following recommendations apply to persons working, residing in or attending non-medical institutions, including educational, residential and correctional facilities:

Confirmed, probable or highly suspected cases of novel influenza A (H1N1) virus infection associated with these settings should be considered for treatment, especially if at higher risk for influenza complications.

Contacts who have shared the same bedroom or cell of a confirmed or probable case and who are at high-risk for complications of influenza (e.g., persons with certain chronic medical conditions, persons 65 or older, children younger than 2 years of age, and pregnant women) can be considered for antiviral chemoprophylaxis.

Additional institutional contacts of a confirmed or probable case can be considered for treatment once symptomatic, especially if at high risk for severe influenza.

Children Under 1 Year of Age

Children under one year of age are at high risk for complications from seasonal human influenza virus infections. The characteristics of human infections with novel H1N1 viruses are still being studied, and it is not known whether infants are at higher risk for complications associated with novel H1N1 infection compared to older children and adults. Limited safety data on the use of oseltamivir (or zanamivir) are available from children less than one year of age. Oseltamivir is not licensed for use in children less than 1 year of age (although use for children < 1 year of age was recently approved by the FDA under an EUA (Table 2). Available data come from use of oseltamivir for treatment of seasonal influenza. These data suggest that severe adverse events are rare, and the Infectious Diseases Society of America recently noted, with regard to use of oseltamivir in children younger than 1 year old with seasonal influenza, that "…limited retrospective data on the safety and efficacy of oseltamivir in this young age group have not demonstrated age-specific drug-attributable toxicities to date." (See http://www.idsociety.org/content.aspx?id=9202#flu for IDSA guidelines for seasonal influenza).

Because infants typically have high rates of morbidity and mortality from influenza, infants with novel influenza A (H1N1) infections may benefit from treatment using oseltamivir (Tables 2 and 3, http://www.cdc.gov/h1n1flu/eua/tamiflu.htm).

Healthcare providers should be aware of the lack of data on safety and dosing when considering oseltamivir use in a seriously ill young infant with confirmed novel H1N1

influenza or who has been exposed to a confirmed case novel influenza A (H1N1) virus infection and carefully monitor infants for adverse events when oseltamivir is used. See http://www.cdc.gov/h1n1flu/eua/ for additional information on oseltamivir for this age group.

Pregnant Women

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. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, oseltamivir or zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus; the manufacturers' package inserts should be consulted. However, no adverse effects have been reported among women who received oseltamivir or zanamivir during pregnancy or among infants born to women who have received oseltamivir or zanamivir. Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use. Because of its systemic activity, oseltamivir is preferred for treatment of pregnant women. The drug of choice for prophylaxis is less clear. Zanamivir may be preferable 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.

Adverse Events and Contraindications

For further information about influenza antiviral medications, including contraindications and adverse effects, please see the following:

- Antiviral Agents for Seasonal Influenza: Side Effects and Adverse Reactions
- MMWR: Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008
  MMWR August 8, 2008 / 57(RR07);1-60
- Harper SA, Bradley JS, Englund JA, et al. Infectious Diseases Society of America Guidelines. Seasonal Influenza in Adults and Children—Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America: at http://www.idsociety.org/content.aspx?id=9202#flu

Adverse events from influenza antiviral medications should be reported through the U.S. FDA Medwatch website.

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Tables

Table 1. Antiviral medication (oseltamivir and zanamivir) dosing recommendations for treatment or chemoprophylaxis of novel influenza A (H1N1) infection.
(Table extracted from IDSA guidelines for seasonal influenza.)

Agent, group		Treatment – 5 day Course	Chemoprophylaxis –
Oseltamivir			
Adults		75-mg capsule twice per day for 5 days	75-mg capsule once per day
Children (age, 12 months or older), weight:	< 15 kg	60 mg per day divided into 2 doses	30 mg once per day
	15-23 kg	90 mg per day divided into 2 doses	45 mg once per day
	24-40 kg	120 mg per day divided into 2 doses	60 mg once per day
	>40 kg	150 mg per day divided into 2 doses	75 mg once per day
Zanamivir			
Adults		Two 5-mg inhalations (10 mg total) twice per day	Two 5-mg inhalations (10 mg total) once per day
Children		Two 5-mg inhalations (10 mg total) twice per day (age, 7 years or older)	Two 5-mg inhalations (10 mg total) once per day (age, 5 years or older)

Table 2. Dosing recommendations for antiviral treatment of children younger than 1 year using oseltamivir

Age	Recommended dose for 5 days
<3 months	12 mg twice daily
3-5 months	20 mg twice daily
6-11 months	25 mg twice daily

Table 3. Dosing recommendations for antiviral chemoprophylaxis of children younger than 1 year using oseltamivir

Age	Recommended prophylaxis dose for 10 days
<3 months	Not recommended unless situation judged critical due to limited data on use in this age group
3-5 months	20 mg once daily
6-11 months	25 mg once daily