

Wisconsin Interim Guidance on Antiviral Recommendations for Patients with Confirmed or Suspected Swine Influenza A (H1N1) Virus Infection and Close Contacts - 4/26/09

Recently the CDC has confirmed cases of swine influenza A (H1N1) infections in residents of California, Texas, Kansas and preliminarily in New York. This is a novel influenza A virus strain and is genetically similar to strains isolated from patients in Mexico where the infections have been more severe. Epidemiologic investigations suggest that human to human transmission has occurred. Although the cases in the US to date have been relatively mild, health care facilities should expect to receive both inpatients and outpatients with potential swine influenza A H1N1 infections and be prepared to manage them with appropriate antiviral treatment and infection control measures to prevent transmission during health care delivery.

The Wisconsin Division of Public Health has developed the following interim influenza antiviral use guidelines based on current information from CDC and will update them as more is learned.

Objective: To provide interim guidance on the use of antiviral agents for treatment and chemoprophylaxis of swine influenza A (H1N1) virus infection. This includes patients with confirmed or suspected swine influenza A (H1N1) virus infection and their close contacts.

Definitions: terms used in the case definitions

Infectious period: The infectious period for a confirmed case of swine influenza A (H1N1) virus infection is defined as 1 day prior to the case's illness onset to 7 days after onset. Persons with swine influenza A virus infections should be considered infectious for at least 7 days after illness onset. Persons who continue to be ill longer than 7 days after illness onset should be considered infectious until symptoms have resolved. Children, especially younger children, may be infectious for longer periods. NOTE: Non-hospitalized ill persons who have a confirmed or suspected case of swine influenza A (H1N1) virus infection are recommended to stay home under voluntary isolation for at least the first 7 days after illness onset except to seek medical care. They should consult their local health departments before returning to work, school, or day care.

Close contact: Exposure within about 6 feet of an ill person (patient) who has a confirmed or suspected case of swine influenza A (H1N1) virus infection during the patient's infectious period.

Acute respiratory illness: recent onset of at least two of the following: rhinorrhea or nasal congestion, sore throat, cough (with or without fever or feverishness).

High-risk group for complications of influenza: persons who is at high-risk for complications of seasonal influenza are listed in the following: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e717a1.htm>. NOTE: it too early to ascertain which persons are at high-risk for complications of swine influenza A (H1N1) virus infection. This guidance will be updated as new information is available.

Case definitions

A patient with a **confirmed case** of swine influenza A (H1N1) virus infection is defined as a person with an acute respiratory illness with laboratory confirmation of swine influenza A (H1N1) virus infection (testing at CDC laboratories) using one or more of the following tests:

- real-time RT-PCR
- viral culture
- four-fold rise in swine influenza A (H1N1) virus-specific neutralizing antibodies

A patient with a **probable case** of swine influenza A (H1N1) virus infection is defined as a person with acute febrile respiratory illness with an influenza test that is positive for influenza A but H1 and H3 negative.

A patient with a **suspected case** of swine influenza A (H1N1) virus infection is defined as a person with acute febrile respiratory illness AND who has any ONE of the following epidemiologic characteristics:

- close contact within 7 days of illness onset with a confirmed case.
- travel within 7 days of illness onset to Mexico or the southwestern region of the US
- close contact with: a person with febrile respiratory illness AND who was in Mexico or the southwestern region of the US in the 7 days preceding onset of illness.

Differential diagnosis considerations: Clinicians should consider swine influenza A (H1N1) virus infection in the differential diagnosis of patients with febrile respiratory disease who:

1. live in areas in the U.S. with confirmed human cases of swine influenza A (H1N1) virus infection, OR,
2. traveled recently to Mexico or were in contact with persons who had febrile respiratory illness and were in the areas of the U.S. with confirmed swine influenza cases or Mexico in the 7 days preceding their illness onsets.

Antiviral treatment and chemoprophylaxis

Antiviral resistance: This **swine** influenza A (H1N1) virus is sensitive (susceptible) to the neuraminidase inhibitor antiviral medications zanamivir and oseltamivir. It is resistant to the adamantane antiviral medications amantadine and rimantadine (Table 1).

NOTE: Seasonal influenza A and B viruses continue to circulate at low levels in the U.S. and in Mexico. Currently circulating **human** influenza A (H1N1) viruses are resistant to oseltamivir

and sensitive (susceptible) to zanamivir, amantadine and rimantadine. Currently circulating **human** influenza A (H3N2) viruses are resistant to amantadine and rimantadine, but sensitive (susceptible) to oseltamivir and zanamivir (Table 1). Therefore, at this time antiviral treatment recommendations for suspected cases of swine influenza A (H1N1) virus infection need to consider potential infection with **swine** influenza A (H1N1) virus as well as **human** influenza viruses, and their different antiviral susceptibilities.

In Wisconsin, influenza infections caused by seasonal influenza viruses are at low levels at this time

Antiviral treatment of patients with suspected cases:

Empiric antiviral treatment is recommended for any ill person ***suspected*** to have swine influenza A (H1N1) virus infection. Antiviral treatment with either zanamivir alone or with a combination of oseltamivir and either amantadine or rimantadine should be initiated as soon as possible after the onset of symptoms. Recommended duration of treatment is five days. Recommendations for use of antivirals may change as data on antiviral susceptibilities become available. NOTE: Antiviral doses and schedules recommended for treatment of swine influenza A (H1N1) virus infection are the same as those recommended for seasonal influenza (Table 2):

<http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm#table>

Antiviral treatment of patients with confirmed cases:

For antiviral treatment of a patient with a confirmed case of swine influenza A (H1N1) virus infection, either oseltamivir or zanamivir may be administered. Recommended duration of treatment is five days. These same antivirals should be considered for treatment of cases that test positive for influenza A but test negative for seasonal influenza viruses H3 and H1 by PCR.

NOTE: Antiviral doses and schedules recommended for treatment of swine influenza A (H1N1) virus infection are the same as those recommended for seasonal influenza (Table 2):

<http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm#table>

Pregnant women: special considerations:

Oseltamivir, zanamivir, amantadine, and rimantadine are all “Pregnancy Category C” medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women. Only two cases of amantadine use for severe influenza illness during the third trimester have been reported. However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at substantially high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs 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 such women.

Antiviral chemoprophylaxis:

For antiviral chemoprophylaxis of swine influenza A (H1N1) virus infection, either oseltamivir or zanamivir are recommended. Duration of antiviral chemoprophylaxis is 7 days after the last known exposure to an ill confirmed case of swine influenza A (H1N1) virus infection. NOTE: Antiviral doses and schedules recommended for treatment of swine influenza A (H1N1) virus infection are the same as those recommended for seasonal influenza (Table 2):

<http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm#table>

Antiviral chemoprophylaxis (pre-exposure or post-exposure) with either oseltamivir or zanamivir is **recommended** for the following individuals:

1. Persons who are at high-risk for complications of influenza (persons with certain chronic medical conditions, elderly) AND who are household close contacts of a person with a confirmed or suspected case
2. School children who are at high-risk for complications of influenza (persons with certain chronic medical conditions) AND who had close contact (face-to-face) with a confirmed or suspected case.
3. Travelers to Mexico who are at high-risk for complications of influenza (persons with certain chronic medical conditions, elderly).
4. Border workers (Mexico) who are at high-risk for complications of influenza (persons with certain chronic medical conditions, elderly).
5. Health care workers or public health workers who had unprotected close contact with an ill individual who has a confirmed case of swine influenza A (H1N1) virus infection during the patient's infectious period.

Antiviral chemoprophylaxis (pre-exposure or post-exposure) with either oseltamivir or zanamivir can be **considered** for the following:

1. Any health care worker who is at high-risk for complications of influenza (persons with certain chronic medical conditions, elderly) who is working in an area where confirmed swine influenza A (H1N1) infections have occurred, and who is caring for patients with any acute febrile respiratory illness.
2. Non-high risk persons who are travelers to Mexico, first responders, or border workers who are working in areas where confirmed cases of swine influenza A (H1N1) virus infection have occurred.

Special considerations for children

Aspirin or aspirin-containing products (e.g. bismuth subsalicylate – Pepto Bismol) should not be administered to any ill individual with a confirmed or suspected case of swine influenza A (H1N1) virus infection who is aged 18 years old and younger due to the risk of Reye syndrome. For relief of fever, other anti-pyretic medications are recommended such as acetaminophen or non steroidal anti-inflammatory drugs.

Adverse events and contraindications

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

<http://www.cdc.gov/flu/professionals/antivirals/side-effects.htm>

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5707a1.htm>

Tables 1 and 2 follow

Table 1: Resistance of swine (new as of April 25, 2009) and seasonal influenza viruses (through March 29, 2009) to antiviral medications for treatment and chemoprophylaxis for the 2008-09 season—United States. Tests conducted at the CDC on isolated detected in the United States.

Swine Influenza					
As of					
April 25, 2009	Isolates tested (n)	Resistant Viruses, Number (%)		Isolates tested (n)	Resistant Viruses, Number (%)
		Oseltamivir	Zanamivir		Adamantanes*
Swine Influenza A (H1N1)	7	0	0	15	15
Data from					
October 1, 2008 -					
March 29, 2009	Isolates tested (n)	Resistant Viruses, Number (%)		Isolates tested (n)	Resistant Viruses, Number (%)
		Oseltamivir	Zanamivir		Adamantanes*
Influenza A (H1N1)	654	649 (99.2%)	0 (0)	605	3 (0.5%)
Influenza A (H3N2)	94	0 (0)	0 (0)	94	94 (100%)
Influenza B	274	0 (0)	0 (0)	N/A*	N/A*

For updated CDC antiviral resistance testing data, see <http://www.cdc.gov/flu/weekly/>.

* The adamantanes (amantadine and rimantadine) are not effective against influenza B viruses.

The table below provides the daily dosage information for the four FDA approved influenza antiviral medications for treatment and chemoprophylaxis of seasonal influenza in the United States for the 2008-09 season. On December 19, 2008, CDC issued [interim recommendations for the use of influenza antiviral medications for the 2008-09 Season](#) based on information about antiviral resistance among circulating influenza viruses.

Table 2: Recommended Daily Dosage of Seasonal Influenza Antiviral Medications for Treatment and Chemoprophylaxis for the 2008-09 Season—United States

Antiviral agent		Age group (yrs)				
		1-6	7-9	10-12	13-64	65 and older
Zanamivir*	Treatment, influenza A and B	N/A†	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
	Chemoprophylaxis, influenza A and B	Ages 1-4 N/A	Ages 5-9 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily
Oseltamivir	Treatment‡, influenza A and B	Dose varies by child's weight§	Dose varies by child's weight§	Dose varies by child's weight§	75 mg twice daily	75 mg twice daily
	Chemoprophylaxis, influenza A and B	Dose varies by child's weight¶	Dose varies by child's weight¶	Dose varies by child's weight¶	75 mg/day	75 mg/day
Amantadine**	Treatment, influenza A	5 mg/kg body weight/day up to 150 mg in 2 divided doses††	5 mg/kg body weight/day up to 150 mg in 2 divided doses††	100 mg twice daily§§	100 mg twice daily	less than or equal to 100 mg/day
	Prophylaxis,	5 mg/kg	5 mg/kg	100 mg	100 mg	less than or

	influenza A	body weight/day up to 150 mg in 2 divided doses††	body weight/day up to 150 mg in 2 divided doses††	twice daily§§	twice daily§	equal to 100 mg/day
Rimantadine¶¶	Treatment#, influenza A	N/A##	N/A	N/A	100 mg twice daily§§§	100 mg/day
	Prophylaxis, influenza A	5 mg/kg body weight/day up to 150 mg in 2 divided doses††	5 mg/kg body weight/day up to 150 mg in 2 divided doses††	100 mg twice daily§§	100 mg twice daily§	100 mg/day\$\$
Duration of Treatment	Treatment	Recommended duration for antiviral treatment is 5 days.				
	Chemoprophylaxis	<p>Recommended duration is 5-7 days after the last known exposure.</p> <p>For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of two weeks, and up to one week after the last known case was identified.</p>				

NOTE: Zanamivir is manufactured by GlaxoSmithKline (Relenza — inhaled powder). Zanamivir is approved for treatment of persons aged 7 years and older and approved for chemoprophylaxis of persons aged 5 years and older. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu® — tablet) Oseltamivir is approved for treatment or chemoprophylaxis of persons aged 1 year and older. Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel® — tablet and syrup); Geneva Pharms Tech (Amantadine HCL — capsule); USL Pharma (Amantadine HCL — capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL — syrup), and Sandoz. Rimantadine is manufactured by Forest Laboratories (Flumadine® — tablet and syrup); Corepharma, Impax Labs (Rimantadine HCL

— tablet), and Amide Pharmaceuticals (Rimantadine HCL — tablet). No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children younger than 1 year of age. This information is based on data published by the [Food and Drug Administration \(FDA\)](#).

* Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease.

† A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance less than 30 mL/min.

§ The treatment dosing recommendation for children who weigh 15 kg or less is 30 mg twice a day. For children who weigh more than 15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh more than 23 kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh more than 40 kg, the dose is 75 mg twice a day.

¶ The chemoprophylaxis dosing recommendation for children who weigh less than 15 kg is 30 mg once a day. For who weigh more than 15 kg and up to 23 kg, the dose is 45 mg once a day. For children who weigh more than 23 kg and up to 40 kg, the dose is 60 mg once a day. For children who weigh more than 40 kg, the dose is 75 mg once a day.

** The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance less than or equal to 50 mL/ min/1.73m².

†† 55 mg/kg body weight of amantadine or rimantadine syrup = 1 tsp/22 lbs.

§§ Children aged 10 years and older who weigh less than 40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg body weight/day.

¶¶ A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance less than 10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

Only approved by FDA for treatment among adults.

Not applicable.

\$Rimantadine is approved by FDA for treatment among adults. However, certain specialists in

the management of influenza consider rimantadine appropriate for treatment among children. Studies evaluating the efficacy of amantadine and rimantadine in children are limited, but they indicate that treatment with either drug diminishes the severity of influenza A infection when administered within 48 hours of illness onset.

\$\$ Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged 65 years and older, if they experience possible side effects when taking 200 mg/day.