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CDC Health Advisory

Distributed via Health Alert Network

December 19, 2008, 11:50 EST (11:50 AM EST)
CDCHAN-00279-08-12-19-ADV-N

CDC Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008-09 Influenza Season

Although influenza activity is low in the United States to date, preliminary data from a limited number of states indicate that the prevalence of influenza A (H1N1) virus strains resistant to the antiviral medication oseltamivir is high. Therefore, CDC is issuing interim recommendations for antiviral treatment and chemoprophylaxis of influenza during the 2008-09 influenza season. When influenza A (H1N1) virus infection or exposure is suspected, zanamivir or a combination of oseltamivir and rimantadine are more appropriate options than oseltamivir alone. Local influenza surveillance data and laboratory testing can help with physician decision-making regarding the choice of antiviral agents for their patients. The 2008-09 influenza vaccine is expected to be effective in preventing or reducing the severity of illness with currently circulating influenza viruses, including oseltamivir-resistant influenza A (H1N1) virus strains. Since influenza activity remains low and is expected to increase in the weeks and months to come, CDC recommends that influenza vaccination efforts continue.

Background

Influenza A viruses, including two subtypes (H1N1) and (H3N2), and influenza B viruses, currently circulate worldwide, but the prevalence of each can vary among communities and within a single community over the course of an influenza season. In the United States, four prescription antiviral medications (oseltamivir, zanamivir, amantadine and rimantadine) are approved for treatment and chemoprophylaxis of influenza. Since January 2006, the neuraminidase inhibitors (oseltamivir, zanamivir) have been the only recommended influenza antiviral drugs because of widespread resistance to the adamantanes (amantadine, rimantadine) among influenza A (H3N2) virus strains. The neuraminidase inhibitors have activity against influenza A and B viruses while the adamantanes have activity only against influenza A viruses. In 2007-08, a significant increase in the prevalence of oseltamivir resistance was reported among influenza A (H1N1) viruses worldwide. During the 2007-08 influenza season, 10.9% of H1N1 viruses tested in the U.S. were resistant to oseltamivir.

Influenza activity has been low thus far this season in the United States. As of December 19, 2008, a limited number of influenza viruses isolated in the U.S. since October 1 have been available for antiviral resistance testing at CDC. Of the 50 H1N1 viruses tested to date from 12 states, 98% were resistant to oseltamivir, and all were susceptible to zanamivir, amantadine and rimantadine. Preliminary data indicate that oseltamivir-resistant influenza A (H1N1) viruses do not cause different or more severe symptoms compared to oseltamivir sensitive influenza A (H1N1) viruses. Influenza A (H3N2) and B viruses remain susceptible to oseltamivir. The proportion of influenza A (H1N1) viruses among all influenza A and B viruses that will circulate during the 2008-09 season cannot be predicted, and will likely vary over the course of the season and among communities. Oseltamivir-resistant influenza A (H1N1) viruses are antigenically similar to the influenza A (H1N1) virus strain represented in 2008-09 influenza vaccine, and CDC recommends that influenza vaccination efforts continue as the primary method to prevent influenza.

Oseltamivir resistance among circulating influenza A (H1N1) virus strains presents challenges for the selection of antiviral medications for treatment and chemoprophylaxis of influenza, and provides additional reasons for clinicians to test patients for influenza virus infection and to consult surveillance data when evaluating persons with acute respiratory illnesses during influenza season. These interim guidelines provide options for treatment or

chemoprophylaxis of influenza in the United States if oseltamivir-resistant H1N1 viruses are circulating widely in a community or if the prevalence of oseltamivir resistant H1N1 viruses is uncertain.

Interim Recommendations

Persons providing medical care for patients with suspected influenza or persons who are candidates for chemoprophylaxis against influenza should consider the following guidance for assessing and treating patients during the 2008-09 influenza season (see attached Antiviral Guidance Table):

- 1) Review local or state influenza virus surveillance data weekly during influenza season, to determine which types (A or B) and subtypes of influenza A virus (H3N2 or H1N1) are currently circulating in the area. For some communities, surveillance data might not be available or timely enough to provide information useful to clinicians.
- 2) Consider use of influenza tests that can distinguish influenza A from influenza B.
 - a. Patients testing positive for influenza B may be given either oseltamivir or zanamivir (no preference) if treatment is indicated.
 - b. At this time, if a patient tests positive for influenza A, use of zanamivir should be considered if treatment is indicated. Oseltamivir should be used alone only if recent local surveillance data indicate that circulating viruses are likely to be influenza A (H3N2) or influenza B viruses. Combination treatment with oseltamivir and rimantadine is an acceptable alternative, and might be necessary for patients that cannot receive zanamivir, (e.g., patient is <7 years old, has chronic underlying airways disease, or cannot use the zanamivir inhalation device), or zanamivir is unavailable. Amantadine can be substituted for rimantadine if rimantadine is unavailable.
 - c. If a patient tests negative for influenza, consider treatment options based on local influenza activity and clinical impression of the likelihood of influenza. Because rapid antigen tests may have low sensitivity, treatment should still be considered during periods of high influenza activity for persons with respiratory symptoms consistent with influenza who test negative and have no alternative diagnosis. Use of zanamivir should be considered if treatment is indicated. Combination treatment with oseltamivir and rimantadine (substitute amantadine if rimantadine unavailable) is an acceptable alternative. Oseltamivir should be used alone only if recent local surveillance data indicates that circulating viruses are likely to be influenza A(H3N2) or influenza B viruses.
 - d. If available, confirmatory testing with a diagnostic test capable of distinguishing influenza caused by influenza A (H1N1) virus from influenza caused by influenza A (H3N2) or influenza B virus can also be used to guide treatment. When treatment is indicated, influenza A (H3N2) and influenza B virus infections should be treated with oseltamivir or zanamivir (no preference). Influenza A (H1N1) virus infections should be treated with zanamivir or combination treatment with oseltamivir and rimantadine is an acceptable alternative.
- 3) Persons who are candidates for chemoprophylaxis (e.g., residents in an assisted living facility during an influenza outbreak, or persons who are at higher risk for influenza-related complications and have had recent household or other close contact with a person with laboratory confirmed influenza) should be provided with medications most likely to be effective against the influenza virus that is the cause of the outbreak, if known. Respiratory specimens from ill persons during institutional outbreaks should be obtained and sent for testing to determine the type and subtype of influenza A viruses associated with the outbreak and to guide antiviral therapy decisions. Persons whose need for chemoprophylaxis is due to potential exposure to a person with laboratory-confirmed influenza A (H3N2) or influenza B should receive oseltamivir or zanamivir (no preference). Zanamivir should be used when persons require chemoprophylaxis due to exposure to influenza A (H1N1) virus. Rimantadine can be used if zanamivir use is contraindicated.

Enhanced surveillance for influenza antiviral resistance is ongoing at CDC in collaboration with local and state health departments. Clinicians should remain alert for additional changes in recommendations that might occur as the 2008--09 influenza season progresses. Oseltamivir resistant influenza A (H1N1) viruses are antigenically similar to the influenza A(H1N1) viruses represented in the vaccine, and vaccination should continue to be considered the primary prevention strategy regardless of oseltamivir sensitivity. Information on antiviral resistance will be updated in weekly surveillance reports (available at <http://www.cdc.gov/flu/weekly/fluactivity.htm>).

For more information on antiviral medications and additional considerations related to antiviral use during the 2008-09 influenza season, visit <http://www.cdc.gov/flu/professionals/antivirals/index.htm>.

TABLE

Interim recommendations for the selection of antiviral treatment using laboratory test results and viral surveillance data, United States, 2008-09 season‡

This table is an attachment to HAN issued 12/19/2008, "CDC Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008-09 Influenza Season"

Rapid antigen or other laboratory test	Predominant virus(es) in community	Preferred medication(s)	Alternative (combination antiviral treatment)
Not done or negative, but clinical suspicion for influenza	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Not done or negative, but clinical suspicion for influenza	H3N2 or B	Oseltamivir or Zanamivir	None
Positive A	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Positive A	H3N2 or B	Oseltamivir or Zanamivir	None
Positive B	Any	Oseltamivir or Zanamivir	None
Positive A+B**	H1N1 or unknown	Zanamivir	Oseltamivir + Rimantadine*
Positive A+B**	H3N2 or B	Oseltamivir or Zanamivir	None

*Amantadine can be substituted for rimantadine but has increased risk of adverse events. Human data are lacking to support the benefits of combination antiviral treatment of influenza; however, these interim recommendations are intended to assist clinicians treating patients who might be infected with oseltamivir-resistant influenza A (H1N1) virus.

**Positive A+B indicates a rapid antigen test that cannot distinguish between influenza and influenza B viruses

‡ Influenza antiviral medications used for treatment are most beneficial when initiated within the first two days of illness. Clinicians should consult the package insert of each antiviral medication for specific dosing information, approved indications and ages, contraindications/warnings/precautions, and adverse effects.

Influenza Antiviral Resistance: Issues for Consideration December 19, 2008 Background

- CDC recommends annual influenza vaccination as the first and most important step in preventing the flu.
- Antiviral medications with activity against influenza viruses are a second line of defense against influenza.
- Antiviral medications are important to consider especially for treatment of patients with severe influenza or patients at higher risk for influenza-related complications.
- There are four antiviral medications approved for use in the United States: oseltamivir, zanamivir, amantadine and rimantadine.
 - Oseltamivir and zanamivir have activity against influenza A and B viruses.
 - Amantadine and rimantadine have activity against influenza A viruses, but not against influenza B viruses.
- Influenza viruses can develop resistance to antiviral medications.
- Since 2006, CDC has recommended the use of oseltamivir and zanamivir against seasonal influenza because of a high resistance to amantadine and rimantadine among influenza A (H3N2) viruses.
- In the last two years, CDC has enhanced surveillance efforts for the detection of viruses resistant to oseltamivir (Tamiflu®) and zanamivir (Relenza®).
- These enhanced efforts have provided CDC with the capability to detect resistant strains more quickly, and enabled CDC to monitor for changing trends over time.
- During the 2007-08 influenza season, a small increase in the number of influenza viruses resistant to oseltamivir was observed.
- CDC's influenza season summary for 2007-2008 reported that 10.9% of tested influenza A (H1N1) viruses were resistant to oseltamivir.
- Last season, CDC tested 1,769 viruses for antiviral resistance.
- During the 2007-08 influenza season in the Northern Hemisphere, oseltamivir resistance of H1N1 viruses varied in different countries: from 0% to 70% in some European countries.
- During the 2008 Southern Hemisphere season, oseltamivir resistance of H1N1 viruses continued to be reported, with some Southern Hemisphere countries reporting that a majority of tested A (H1N1) viruses were resistant to oseltamivir.

Current Situation

- At this point in the season, a low level of influenza activity has been reported in the United States. As a result, very few viruses have been available for testing thus far.

- Early and limited data from this season has detected a significant increase in the proportion of influenza A (H1N1) viruses that are resistant to oseltamivir.
- In the latest CDC FluView report published on December 19, 2008, 78 influenza viruses from 15 states had been tested for antiviral resistance.
- This includes 50 influenza A (H1N1) viruses, 8 influenza A (H3N2 viruses) and 20 influenza B viruses.
- Preliminary data show:
 - 49 of the 50 influenza A (H1N1) viruses tested were resistant to oseltamivir (98%).
 - These oseltamivir resistant viruses have been detected in 12 states, but the majority of samples have come from two states.
 - All 50 influenza A (H1N1) viruses were sensitive to zanamivir and amantadine and rimantadine.
 - All 8 influenza A (H3N2) viruses remain sensitive to oseltamivir and zanamivir.
 - All 20 influenza B viruses remain sensitive to oseltamivir and zanamivir.
 - All influenza A(H3N2) viruses tested were resistant to amantadine and rimantadine.
- Weekly reports summarizing U.S. surveillance activity are published every Friday from October through mid-May at <http://www.cdc.gov/flu/weekly/fluactivity.htm>
- The fact that oseltamivir-resistance is significantly higher among H1N1 viruses compared to last season in the U.S. is not surprising. Worldwide, the proportion of H1N1 viruses that are resistant to oseltamivir has been increasing.
- Influenza viruses change constantly through changes in their genetic makeup, and one of such mutations conferred resistance to oseltamivir.
- There is no evidence that the resistant viruses are causing more severe illness than other influenza viruses or that they are transmitted differently.
- At this time, it's not possible to predict how common H1N1 viruses will be during the rest of the 2008–09 season, as every influenza season is different.
- CDC is monitoring this situation very closely and will continue to test influenza viruses and update information on resistance throughout the influenza season.
- Recommendations regarding the use of antiviral medications have been reviewed and updated guidance will be issued given surveillance data indicating an increase in the number of oseltamivir-resistant influenza H1N1 viruses in the United States.
- Different options for antiviral treatment in the setting of increased circulation of oseltamivir-resistant H1N1 viruses have been considered. These options, such as use of zanamivir or combination therapy with oseltamivir and rimantadine, were outlined in the 2008 influenza recommendations.

- CDC's interim guidance on the use of influenza antiviral medications in the United States for the 2008-09 season will be issued in a Health Alert Advisory on December 19. This revised guidance will be available at www.cdc.gov/flu.
- Clinicians should be aware that revised interim guidance on the use of antiviral medications is being provided by CDC for the current influenza season and will be available at www.cdc.gov/flu.
- Information from local or state virus surveillance data and laboratory testing can help clinicians in selecting appropriate antiviral medications for their patients.
- When influenza A (H1N1) virus infection or exposure is suspected, zanamivir or a combination of oseltamivir and rimantadine are more appropriate options than oseltamivir alone.
- CDC is working to communicate this new guidance broadly through a clinician communications campaign to alert health care providers to the change in recommendations for antiviral medications this season.
- **Influenza vaccines are expected to be effective in preventing or reducing the severity of infection with currently circulating influenza viruses, including oseltamivir-resistant influenza A (H1N1)**