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HEALTH ADVISORY #228 JANUARY 9, 2009
UPDATED INTERIM CDC RECOMMENDATIONS FOR THE USE OF INFLUENZA ANTIVIRAL MEDICATIONS

Please distribute immediately to all Emergency Departments, Family Medicine, Infection Control, Pediatrics, Laboratory Medicine, Internal Medicine, Infectious Disease, Pulmonary Medicine, and all Community-based providers.

SUMMARY

• The Centers for Disease Control and Prevention (CDC) has reported high levels of antiviral resistance to the antiviral drug oseltamivir (Tamiflu) among influenza A(H1N1) isolates tested so far in the 2008-09 influenza season.

• Thus far in New York State, two patient specimens from New York City residents with influenza A(H1N1) have shown resistance to oseltamivir. Based on this limited information, oseltamivir-resistant influenza A(H1N1) virus may be circulating in New York State.

• CDC has issued interim recommendations for this season, attached to this advisory:
  o Interim antiviral treatment and prophylaxis recommendations should be based on patient testing data or local resistance activity.
  o Clinicians should strongly consider using testing that can distinguish influenza A from influenza B.
  o For areas with circulating oseltamivir resistant influenza A(H1N1), use of zanamivir (Relenza®) alone or combination therapy with oseltamivir and rimantidine is recommended in the absence of or prior to results of testing of the patient's viral isolate.

• The New York State Department of Health (NYSDOH) asks hospital laboratories to submit influenza A(H1N1) or A(unspecified) patient specimens to Wadsworth Center Laboratory for antiviral resistance testing for purposes of monitoring resistance and guiding treatment decisions.

• The NYSDOH strongly recommends that influenza vaccination efforts continue throughout the influenza season. THE BEST PROTECTION AGAINST INFLUENZA REMAINS VACCINATION.

BACKGROUND

On December 19, 2008, CDC issued a report outlining high levels of resistance to oseltamivir (Tamiflu®) among influenza A(H1N1) isolates tested so far this season; 49 out of 50 (98%) isolates tested by CDC from 15 states were oseltamivir resistant (http://www.cdc.gov/flu/weekly/). None of the isolates tested were from New York State (NYS) or New York City (NYC). However, NYSDOH Wadsworth Center Laboratory has tested two additional influenza A(H1N1) patient specimens from NYC residents; both were resistant to oseltamivir.

Among the virus isolates characterized antigenically, CDC has reported good matching with this season's influenza vaccine for all influenza A(H1N1) and A(H3N2) isolates and about one third of influenza B isolates tested.

RECOMMENDATIONS

VACCINATION

The best means of prevention for influenza this season remains vaccination. The NYSDOH recommends that vaccination efforts continue throughout the influenza season because the duration of the season varies and influenza might not appear in certain communities until February or March. Influenza vaccine, including thimerosal-free vaccine, continues to be available in sufficient supply and can still be purchased. Information on where to obtain influenza vaccine can be found at the National Influenza Vaccine Summit website at: http://www.preventinfluenza.org/ivats/.

TREATMENT AND PROPHYLAXIS

CDC has distributed interim guidance for patients for whom antiviral treatment or prophylaxis is indicated (attached). Ultimately, the recommendation for choice of antiviral medication relies on patient testing results, local circulating viruses, and patient vulnerability.

Influenza surveillance data for NYS is updated weekly and posted on the NYSDOH website (http://www.health.state.ny.us/diseases/communicable/influenza). Data is reported in aggregate and results of subtyping and antiviral resistance testing often lags behind true influenza activity. The NYSDOH will provide the most up-to-date information available regarding local and statewide influenza activity. Clinicians are urged to review the CDC guidance carefully and to use all available local data to make appropriate clinical decisions about treatment and prophylaxis of patients.

For persons at a higher priority for chemoprophylaxis according to CDC (high risk persons within 2 weeks of vaccination, high risk persons for whom influenza vaccine is contraindicated, unvaccinated family members or care providers with ongoing exposure to high risk persons, persons with immune deficiencies, and staff and persons during response to an outbreak in a closed institutional setting with residents at high risk), special attention should be paid to local activity and choice of antiviral prophylaxis. Nursing homes identifying influenza among a resident or residents are asked to consult by telephone with the NYSDOH Regional Epidemiologist so that specific and appropriate recommendations can be made. Nursing homes in New York City should contact the New York City Department of Health and Mental Hygiene per routine procedures. Specific guidance from NYSDOH for management of influenza in nursing homes will be forthcoming.

LABORATORY TESTING

To better assess influenza viruses circulating in New York State, until further notice, NYSDOH is asking clinical diagnostic laboratories to submit all primary patient specimens positive for influenza A(H1N1) or influenza A(unspecified). Laboratories should not submit specimens positive for influenza A(H3N2), influenza B, or unknown viral isolates unless special requests or arrangements are made through the NYSDOH Regional Epidemiologist. Laboratories should complete all appropriate submission forms including the Virus Detection History Form (DOH-1795) noting testing is for current state surveillance effort. Specimens should be shipped refrigerated overnight (or on dry ice if previously frozen) to Griffin Laboratory. Specific instructions and contact information for labs are available at: http://www.wadsworth.org/divisions/infdis/virology/collectsubmit.htm.

The NYSDOH will continue to monitor influenza activity and antiviral resistance in NYS and nationally. Should any significant findings become available or recommendations change, NYSDOH will issue updated guidance.

Thank you for your attention to this important matter. If you have questions about influenza surveillance or reporting, please contact the Erie County Department of Health at (716) 858-7697, Monday thru Friday, 9:00am to 5:00pm or the NYSDOH Regional epidemiologist. Contact information is available online at: http://www.health.state.ny.us/professionals/diseases/reporting/communicable/infection/regional_epi_staff.htm

This is an official

CDC Health Advisory

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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.

Health Category Definitions:

Health Alert FLASH: conveys the highest level of importance due to a large-scale, catastrophic public health emergency; warrants immediate action or attention

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