CDC Influenza Division Key Points
April 10, 2014

In this document:

Publication of a new Cochrane review of previously published and unpublished randomized controlled trials on NAI antiviral medications

- On April 10, 2014, the Cochrane Collaboration published a review entitled "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review) by Thomas Jefferson et al. This review is available online.
    - This review assessed full internal clinical study reports from manufacturers containing previously published along with unpublished data from 46 randomized controlled trials (RCTs) of oral oseltamivir or inhaled zanamivir versus placebo for preventing and treating influenza in otherwise healthy adults and children.
    - The review concluded that in adults and children with influenza-like illness, early oral oseltamivir treatment shortens the duration of symptoms by approximately 17 hours and 29 hours, respectively, compared to placebo.
    - The review also concluded that zanamivir reduced symptoms in adults by approximately half a day, but the review reported no significant effect in children.
    - The Cochrane review reported no significant effect of oseltamivir on hospitalizations for adults or children, although the authors conclude that the included treatment trials do not settle the question of whether the complications of influenza are reduced.
    - The review did not analyze the effect of treatment with neuraminidase inhibitors on deaths because there were too few events.
    - The review also reports increased risk of nausea and vomiting with oseltamivir treatment, and of headaches, psychiatric disturbances, and renal events with oseltamivir chemoprophylaxis.
- Several accompanying articles, commentaries and features were published in the British Medical Journal (BMJ).
    - Two of the articles break down information from the larger review on oseltamivir (trade name Tamiflu, manufactured by Roche Pharmaceuticals) and zanamivir (trade name Relenza, manufactured by GlaxoSmith Kline). Links are provided below:
        - Jefferson Tamiflu study
        - Heneghan Zanamivir study

    - The remaining articles are commentaries, features and editorials related to this review from the BMJ website.

- CDC has posted a "Have You Heard" article discussing the Cochrane review and CDC's antiviral recommendations and considerations online at http://www.cdc.gov/media/haveyouheard/stories/Influenza_antiviral2.html.

CDC Overview: Influenza (Flu) Antiviral Drugs

- The Centers for Disease Control and Prevention (CDC) continues to recommend the use of the neuraminidase inhibitor antiviral drugs (oral oseltamivir and inhaled zanamivir) as an important adjunct to vaccination in the prevention and control of influenza.
- CDC's antiviral recommendations are available online here: http://www.cdc.gov/flu/professionals/antivirals/index.htm.
- CDC and the Advisory Committee on Immunization Practices (ACIP) consider all of the published evidence available when issuing recommendations on antiviral treatment of influenza. This includes safety data as well as data from randomized controlled trials (RCTs) and observational studies.
- CDC and ACIP have reviewed a considerable and ever growing number of observational studies conducted in hospitalized influenza patients that show the benefits of antiviral medications in not only reducing and shortening symptoms of influenza, but also preventing deaths and severe outcomes, including in hospitalized high risk children, adults and pregnant women.
- Observational studies can inform clinical practice and public health. However, there are limitations and possible biases that must be considered and controlled in observational studies. RCTs are generally preferable because they are not subject to many of these biases, but they are often difficult to conduct due to ethical considerations. There have been no RCTs conducted in high risk patients evaluating the ability of these drugs to prevent severe influenza illness, including hospitalization. There are no RCTs of oral oseltamivir or inhaled zanamivir treatment in hospitalized influenza patients.
    - Data from observational studies are especially useful when data from RCTs are unavailable or have not been conducted among high-risk groups or hospitalized influenza patients, and when having a placebo group would be unethical since antiviral treatment is recommended as soon as possible for these groups.
- CDC has compiled a list of influenza antiviral publications with links that is available on the CDC website: http://www.cdc.gov/flu/professionals/antivirals/antiviral-mmwr-references.htm. (Note: this list is not comprehensive, but it is regularly updated.)
- Seasonal influenza epidemics are associated with an estimated average of more than 200,000 hospitalizations per year in the United States, and a range of from about 3,000 to 49,000 influenza-associated deaths per year.
- Vaccination is the best way to prevent influenza, but it won't prevent all illness from influenza. This is why influenza antiviral drugs are an important second line of defense against influenza.
- The neuraminidase inhibitor class of antiviral drugs is the only CDC-recommended treatment option available against influenza.

- CDC actively supports efforts aimed at developing new and better drugs for the treatment of influenza. In the meantime, CDC is committed to making the best use of the tools at its disposal to protect public health.

The Benefits of Antiviral Treatment

- The benefits of antiviral drugs for treatment of influenza have been documented for some time.
- In randomized clinical trial studies of previously healthy patients with uncomplicated influenza, early treatment (within 48 hours of illness onset) with neuraminidase inhibitor antiviral drugs (oral oseltamivir or inhaled zanamivir) reduced illness by 1-2 days and lessened illness severity.
- Prior to the 2009 H1N1 pandemic, little information was available on the benefits of antiviral treatment among the severely ill (for example, hospitalized patients with influenza) or among people at high risk for influenza complications, including pregnant women and people with certain underlying medical conditions. However, a few observational studies suggested that oseltamivir treatment of hospitalized adults with complications of influenza virus infection reduced duration of hospitalization and mortality.
- During and since the 2009 H1N1 pandemic, several observational studies demonstrated a reduction in serious influenza-related complications, such as pneumonia, respiratory failure necessitating intensive care unit (ICU) admission, and death, and a reduction in the length of hospitalization and duration of influenza virus detection, with early antiviral treatment of hospitalized patients compared to no treatment or delayed treatment. Many of these studies included hospitalized patients, patients with underlying medical conditions and pregnant women.
- A recent meta-analysis of patient-level data from more than 29,000 hospitalized patients published in *The Lancet Respiratory Medicine*, which included of 78 observational studies across 38 countries, found that use of the neuraminidase inhibitor class of antiviral drugs (which includes oral oseltamivir and inhaled zanamivir) reduced the risk of death in patients hospitalized with 2009 H1N1 virus infection during the 2009 pandemic.
    - Among key findings of this study:
        - Among adult patients (defined in this study as people aged 16 years and older) infected with 2009 H1N1 virus (the pandemic virus) who were admitted to a hospital, treatment with a neuraminidase inhibitor (NAI) antiviral drug was associated with a 25% (95% CI: 13%-36%) reduction in the likelihood of death compared to no antiviral treatment.
        - Starting early treatment with NAI antiviral drugs (i.e., within 48 hours of development of illness onset) halved the risk of death compared to no antiviral treatment. This supports existing evidence that the clinical benefit provided by NAI antiviral treatment is greatest when administered within 2 days of illness onset.
        - A significant reduction in the risk of death also was observed for pregnant women at 54% (95% CI: 11%-77%). Early NAI antiviral treatment in pregnant

women (within 48 hours of development of illness onset) reduced the women's likelihood of death by around 80% compared to no antiviral treatment.

- Among adult patients in the ICU, NAI treatment reduced the risk of death by 28% (95% CI: 6%-44%).

- This study is available at http://www.thelancet.com/journals/lancet/article/PIIS2213-2600(14)70041-4/fulltext.

- In addition, several observational studies suggested that antiviral treatment among severely ill persons with influenza still had clinical benefit even if started more than 2 days after symptom onset, including studies with large cohorts (~10,000 patients) under observation.
- Pregnant women are at greater risk for hospitalization and death from 2009 H1N1 virus infection. Several studies showed that treatment with antiviral drugs reduced the risk for ICU admission and death among pregnant women, especially when given within 2 days of symptom onset. However, benefits from NAI treatment were observed even when given up to 4 days after symptom onset.
- While clinical judgment based on the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since symptom onset is important to consider when making antiviral treatment decisions -- the body of evidence available at this time has led CDC to continue recommending that empiric antiviral treatment with the neuraminidase inhibitors oral oseltamivir (Tamiflu®) or inhaled zanamivir (Relenza®) be considered for a patient with suspected influenza who:
  - Has severe, complicated, or progressive illness;
  - Is hospitalized; or
  - Is at high risk for influenza complications, including pregnant women and people with certain underlying medical conditions.
- When clinically indicated for patients with suspected influenza who are hospitalized, have severe, complicated or progressive illness, or in outpatients who are at higher risk for influenza complications, antiviral treatment with an NAI should be started as soon as possible, ideally (but not limited to) within 48 hours of symptom onset.
- Starting NAI treatment in a suspected influenza patient should not wait for laboratory confirmation of influenza virus infection.
- Antiviral treatment with an NAI can also be considered for any previously healthy, non-high-risk, symptomatic outpatient with confirmed or suspected influenza based upon clinical judgment, if treatment can be initiated within 48 hours of illness onset.
- Influenza vaccination to prevent influenza virus infection and prompt antiviral therapy to treat influenza illness in high risk patients are the two most important medical countermeasures against influenza viruses. Their application by health care professionals can provide lifesaving benefits to patients.
- For additional information about influenza antiviral drug recommendations influenza season, please visit http://www.cdc.gov/flu/professionals/antivirals/index.htm.

Influenza Antiviral Side Effects/Safety

- All of the licensed influenza antiviral drugs have reported side effects. Most of these side effects are not serious and are different for each antiviral drug.
- Serious side effects from antiviral drugs are uncommon, but have been reported.
- Oseltamivir (Tamiflu®) has been in use since 1999. The most common side effects are nausea or vomiting which usually happen in the first 2 days of treatment. Taking Tamiflu® with food can reduce the chance of having these side effects.
- Zanamivir (Relenza®) has been in use since 1999. The most common side effects are dizziness, runny or stuffy nose, cough, diarrhea, nausea, or headache. Relenza® may also cause wheezing and trouble breathing in people with lung disease, which is why this drug is not recommended for use in people with underlying respiratory diseases.
- Neuropsychiatric behaviors, including confusion and abnormal behavior leading to serious injury, have also been reported rarely in people with influenza who were treated with Tamiflu® or Relenza®; most such effects occurred in Japanese adolescents with influenza after one dose of drug. Since some neuropsychiatric and neurologic manifestations can be associated with influenza virus infection itself, it is not possible at this time to conclude that these behaviors were due to the drug versus influenza virus infection.
- Neuropsychiatric events have also been reported in oseltamivir chemoprophylaxis trials, although oral oseltamivir has overall been well-tolerated. CDC and FDA consider review of the clinical trial data submitted for Tamiflu® and Relenza® to be adequate to support their approval to prevent influenza in the populations studied.
- Information about side effects also is available in the general influenza antiviral guidance http://www.cdc.gov/flu/professionals/antivirals/antiviral-adverse-events.htm.
- Oseltamivir (brand name Tamiflu®) package insert is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021087s056_021246s039lbl.pdf.
- Zanamivir (brand name Relenza®) is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021036s025lbl.pdf.

CDC Antiviral Treatment Recommendations

- Clinical benefit is greatest when antiviral treatment is administered early. When indicated, antiviral treatment should be started as soon as possible after illness onset, ideally within 48 hours of symptom onset. However, antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness and in hospitalized patients when started after 48 hours of illness onset, as indicated by observational studies.
- 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.

- Treatment of persons with suspected influenza should not wait for laboratory confirmation of influenza.
    - When there is clinical suspicion of influenza and antiviral treatment is indicated, antiviral treatment should be started as soon as possible, along with use of appropriate infection control measures.
- Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza based on clinical judgment, if treatment can be initiated within 48 hours of illness onset.
- The antiviral medications that are currently recommended for treatment of influenza are oral oseltamivir and inhaled zanamivir.
- More information is available at http://www.cdc.gov/flu/professionals/antivirals/index.htm.

Antiviral Stockpiling Considerations:

Note: Information provided by Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) and CDC's Division of Strategic National Stockpile (SNS)

HHS ASPR Statement on U.S. Influenza Antiviral Stockpiling:

- Decisions regarding the purchase of influenza antiviral drugs for use in the U.S. Strategic National Stockpile are made by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR).
- Based on all available data about the benefits of antiviral drugs in treating influenza versus the risks associated with previous influenza pandemics and pending threats, HHS purchased antiviral drugs for distribution to states as part of response efforts prior to and during the 2009 H1N1 pandemic.
- There is a substantial and growing number of observational studies that show the clinical benefit of antiviral treatment of seasonal and pandemic influenza.
- In addition, as part of the federal government's ongoing pandemic preparedness efforts, HHS continues to support research and development of new antiviral drugs, vaccines, diagnostics, and medical devices.
- In future pandemic responses, HHS purchases of antiviral drugs and vaccines will be based on risk-benefit analyses using all product safety and efficacy and disease severity and transmission data available at that time.

CDC SNS Information on U.S. Influenza Antiviral Stockpiling:

- To date, the U.S. government has spent approximately $1.3 billion on Tamiflu and Relenza for the Strategic National Stockpile.
- The decision for the United States to stockpile influenza antiviral drugs was a part of the national pandemic preparedness strategy.
- Antiviral drugs are the only FDA-approved countermeasure for the treatment of influenza.

Background on Antiviral Drugs

- Antiviral drugs are prescription medicines (pills, liquid or an inhaled powder) that fight against influenza viruses in the respiratory tract. Antiviral drugs are not sold over-the-counter. You can only get them if you have a prescription from your doctor or health care provider. Antiviral drugs are different from antibiotics, which fight against bacterial infections.
- Antiviral drugs are a second line of defense to treat influenza if you get sick. Annual influenza vaccination is the first and best way to prevent influenza.
- Two FDA-approved influenza antiviral medications are recommended for use in the United States during the 2013-2014 influenza season: oral oseltamivir (Tamiflu®) and inhaled zanamivir (Relenza®).
- Oseltamivir and zanamivir are known as neuraminidase inhibitors and have activity against both influenza A and B viruses.
- Antiviral treatment with oral oseltamivir or inhaled zanamivir is recommended as early as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness; who require hospitalization; or who are at greater risk for serious influenza-related complications, including young children, pregnant women, and persons with certain chronic medical conditions.
- Influenza vaccination to prevent influenza and prompt antiviral therapy to treat influenza illness are the two most important medical countermeasures against the influenza viruses. Their correct application by health care professionals can provide life-saving benefits to patients.
- CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis so as to limit the possibilities that antiviral resistant viruses could emerge. Indiscriminate use of antiviral chemoprophylaxis might promote resistance to antiviral medications, or reduce antiviral medication availability for treatment of persons at higher risk for influenza complications or those who are severely ill.
- In general, CDC does not recommend seasonal or pre-exposure antiviral chemoprophylaxis, but antiviral medications can be considered for chemoprophylaxis in certain situations such as one of many interventions to control institutional influenza outbreaks.
- For more information about antiviral medications, visit http://www.cdc.gov/flu/antivirals/index.