CDC Recommendations for Influenza Antiviral Medications Remain Unchanged

April 10, 2014 – CDC continues to recommend the use of the neuraminidase inhibitor antiviral drugs (oral oseltamivir and inhaled zanamivir) as an important adjunct to influenza vaccination in the treatment of influenza. CDC's current influenza antiviral recommendations are available on the CDC website and are based on all available data, including the most recent Cochrane report, about the benefits of antiviral drugs in treating influenza.

CDC considers all of the published evidence available from Randomized Control Trials (RCT) conducted among outpatients and observational studies conducted among hospitalized patients, including benefits and risks from safety data, when issuing recommendations on antiviral treatment of influenza. These CDC recommendations emphasize early antiviral treatment as soon as possible for patients who are severely ill and for those who are at greatest risk for complications from influenza. This includes hospitalized patients with suspected or confirmed influenza, those with severe or progressive illness, and outpatients who are at high risk for influenza complications (for example, young children, people aged 65 years and older, pregnant women, and persons with certain underlying chronic medical conditions). In addition, because other reviews of RCTs and observational studies have found consistent clinical benefit of early oseltamivir treatment in reducing the risk of lower respiratory tract complications such as those requiring antibiotics, persons with uncomplicated influenza who are not in a high risk group and who present within 48 hours of illness onset can be treated with antiviral medications based upon clinical judgment.

One large study that was published recently, "Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A(H1N1pdm09) virus infection: a meta-analysis of individual participant data", adds to the growing body of evidence which supports that neuraminidase inhibitor treatment can reduce the risk of death in hospitalized patients with influenza. In this meta-analysis of published studies, researchers compiled individual-level data from 78 observational studies across 38 countries on more than 29,000 patients who were hospitalized with 2009 H1N1 influenza virus infection during the 2009-10 pandemic. In this study among patients aged ≥16 years, treatment with a neuraminidase inhibitor antiviral drug was associated with a 25% reduction in the likelihood of death compared to no antiviral treatment. Early treatment with neuraminidase inhibitor antiviral drugs (i.e., within 48 hours of development of influenza illness) halved the risk of death compared to no antiviral treatment. This confirms findings from previous observational studies in hospitalized influenza patients that the clinical benefit of neuraminidase inhibitor antiviral treatment is greatest when started within two days of influenza illness onset.

A review of RCT data for the influenza neuraminidase inhibitor antiviral medications published by the Cochrane Collaboration updates a previous Cochrane review published in 2012, and raises questions about the value of antiviral medications for the prevention and treatment of influenza. The updated Cochrane review assessed full internal clinical study reports from manufacturers containing published and unpublished data from 46 randomized controlled trials (RCTs) of oral oseltamivir or inhaled zanamivir versus placebo for preventing and

treating outpatients with mild illness who were 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. This finding is similar to results in previously published RCTs which reported a reduction of approximately one day of laboratory-confirmed uncomplicated influenza illness in outpatients by early oral oseltamivir treatment verus placebo. One RCT in outpatients who were aged 1 to 3 years with uncomplicated influenza found a reduction of 3.5 days when oral oseltamivir treatment was started within 24 hours after illness onset. The Cochrane review concluded that inhaled zanamivir reduced symptoms in adults by approximately half a day compared to placebo, but had no significant effect in children. The Cochrane review reported no significant effect of oral oseltamivir treatment of outpatients on hospitalizations for adults or children, and the authors conclude that the treatment trials do not settle the question of whether the complications of influenza are reduced by treatment in outpatients because of a lack of diagnostic definitions.

Systematic reviews of RCTs should include published and unpublished data, and researchers should have full access to these data. CDC welcomes the inclusion of data from previously unpublished RCTs among outpatients in the Cochrane review. However, such a review of data on outpatients with clinically mild influenza-like illness is unlikely to answer the question of whether antiviral treatment reduces severe influenza complications, such as those resulting in hospitalization in generally healthy persons, because much larger numbers of participants would be needed. The studies in the recent Cochrane review were statistically underpowered and not designed to assess the effects of the medications on more severe influenza illness outcomes, such as hospitalizations, intensive care unit admissions, or deaths. Notably, no RCT data are available for antiviral treatment of hospitalized patients with severe influenza illness. Furthermore, the burden of influenza disease is greatest among the elderly, young children, pregnant women, and persons with underlying medical conditions such as chronic obstructive pulmonary disease (COPD), asthma, congestive heart failure and diabetes. These groups are at highest risk for developing severe complications from influenza resulting in hospitalization or death, and generally have not been studied in RCTs.

Importantly, the Cochrane review did not consider any data from an abundance of observational studies of oral oseltamivir or inhaled zanamivir treatment. While such studies have inherent design limitations and potential biases, they can inform clinical practice and public health. Observational studies are especially important when data from RCTs are unavailable to address questions relevant to specific outcomes (like severe disease) or to certain high-risk groups, or because having a placebo group would be unethical since antiviral treatment is recommended for these groups. Indeed, many observational studies of antiviral treatment of seasonal influenza or influenza A (H1N1) pdm09 (2009 H1N1) have been conducted among hospitalized patients, including critically ill children and adults. These observational studies from many countries have consistently found that early oseltamivir treatment of influenza patients reduces the duration of hospitalization and risk of severe outcomes such as intensive care unit admission or death. These studies have reported that clinical benefit is greatest when oseltamivir treatment is started within 48 hours of illness onset; however, clinical benefit has still been observed when oseltamivir treatment is started up to less than 5 days after illness onset.

CDC estimates that influenza virus infections in the United States result in an average of more than 200,000 related hospitalizations, and between 3,000 to 49,000 deaths each year, depending upon the severity of the influenza season. CDC continues to emphasize that annual influenza vaccination of all persons aged 6 months

and older is recommended, and is the best way to prevent influenza. However, available evidence for seasonal influenza and 2009 pandemic H1N1 virus infections consistently indicates that antiviral treatment, when initiated as soon as possible, can have clinical and public health benefit in reducing severe outcomes of influenza. Therefore, neuraminidase inhibitor antiviral medications continue to be recommended for treatment of influenza.

For a summary of CDC antiviral guidance for the 2013-2014 influenza season, see: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

For an outline of ACIP and CDC recommendations and references supporting the statements in this "Have You Heard," see Recommendations of the Advisory Committee on Immunization Practices (ACIP): Information for Health Care Professionals. This information has been updated from the original "Recommendations of the Advisory Committee on Immunization Practices (ACIP)" available at http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf.