2011-2012 Influenza Season: Antiviral Medication Recommendations

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Coordinator:

Good afternoon, thank you all parties for standing by. Your lines have been placed on a listen-only mode until the questions and answer session. Today's call is being recorded. If you do object to that, please disconnect at this time. Now I will turn the call over to Ms. Loretta Jackson Brown. Thank you, you may begin.

Loretta Jackson Brown:

Thank you (Suzie). Good afternoon, I'm Loretta Jackson Brown and I'm representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Communication System at the Centers for Disease Control and Prevention. I'm delighted to welcome you to today's COCA webinar, "2011-2012 Influenza Season: Antiviral Medication Recommendations". We are pleased to have with us today Dr. Timothy Uyeki here to review Current Advisory Committee on Immunization Practices (ACIP) and CDC guidance on the use of antiviral medications in the prevention and treatment of influenza. You may participate in today's presentation by audio only, via webinar, or you may download the slides if you are unable to access the webinar. The PowerPoint slide set and the webinar link can be found on our COCA webpage at emergency.cdc.gov/coca. Click on COCA Calls, the webinar link and the slide set can be found under the call end number and call pass code.

At the conclusion of today's session, the participant will be able to list currently recommended influenza antiviral medications, understand recommendations for use of influenza antiviral medications for the 2011-2012 influenza season, and understand the potential benefits of antiviral treatments as outlined by the Advisory Committee on Immunization Practices and CDC.

In compliance with continuing education requirements, all presenters must disclose any financial or other association with the manufacture of commercial products, suppliers of commercial services, or commercial supporters, as well as any use of unlabeled products or products under investigational use. CDC, our planners, and the presenter for this presentation do not have financial or other association with the manufacture of commercial products, supplies of commercial services, or commercial supporters. This presentation does not involve the unlabeled use of a product or a product under investigational use with the exception of oseltamivir which is FDA approved in age one year and older. ACIP and CDC recommend use of oseltamivir in children aged greater than one year. There was no commercial support for this activity.

Free continuing education credits are available for this COCA webinar. Information on how to obtain continuing education credits will be provided at the conclusion of today's COCA webinar.

Today's presenter is Dr. Uyeki. Dr. Uyeki is a Captain with the US Public Health Service and Deputy Chief for Science in the Epidemiology and Prevention Branch, Influenza Division at CDC. Since joining CDC in 1998, he has worked on the epidemiology, prevention, and control of inter-pandemic, zoonotic and

pandemic influenza in the US and worldwide. Dr. Uyeki has served as a consultant to the World Health Organization on clinical epidemiological issues related to seasonal, zoonotic, and pandemic influenza. He is co-author of the World Health Organization review article on avian influenza A H5N1) virus infections in humans, influenza antiviral guidance and the WHO 2009 H1N1 clinical review. He is a co-author of the Annual Advisory Committee on Immunization Practice Influenza Vaccine Recommendations, the ACIP Influenza antiviral recommendations and various influenza articles and book chapters. Board certified in pediatrics, and in preventive medicine and public health, Dr. Uyeki serves as an Associate Clinical Professor in the Department of Pediatrics, University of California, San Francisco and is an Adjunct Associate Professor in the Hubert Department of Global Health at Emory University's Rollins School of Public Health, Atlanta, Georgia. At this time, please welcome Dr. Uyeki.

Dr. Timothy Uyeki:

Thank you Loretta. Today I'm going to be talking about antiviral agents for the treatment and chemoprophylaxis of influenza which reflect the recommendations of the Advisory Committee on Immunization Practices, ACIP. What I'm going to do is start by talking a little bit about recent influenza surveillance. I'll give a little bit of information about transmission of influenza viruses; discuss some of the clinical signs and symptoms of influenza. I'll speak about influenza testing then I'll get into antiviral agents for influenza. I'll also discuss briefly antiviral drug resistance among circulating influenza viruses and then speak about the use of antivirals. In addition, I'll cover some of the antiviral treatment efficacy studies and effectiveness studies, indications for antiviral treatment, and particularly for those who are hospitalized with confirmed or suspected influenza. I'll also cover issues of antiviral chemoprophylaxis. And at the end, I'll cover issues about control of influenza outbreaks in institutions.

So this slide is depicting the latest influenza weekly report on our CDC web pages which is just to show through the week ending February 18 that there is still not that much influenza activity in the US but activity has been increasing over the last several weeks. Only two states have reported widespread influenza activity. A number of others have reported regional activity but quite a few still have reported either local or sporadic activity.

This slide shows the virological data for the US season so far. And normally, during the peak of influenza activity in the US, we see the percent positive for influenza viruses of all specimens tested at least 25% or higher during peak activity. So this is a graph showing where we are through mid-February. We still have some weeks to go before the season peaks. Note that there's been co-circulation of both Influenza A and B viruses in the US.

This slide shows most recent data for Week 7, the week ending February 18. Of the specimens that were tested that week, the majority of these, almost 94% were identified as Influenza A viruses with about 6% Influenza B viruses. There were some variations by region but this reflects national data. And this slide just shows of the viruses that have been antigenically characterized at CDC for the 2009 H1N1 Influenza A virus that there's a very good match between the circulating virus strains and the 2009 H1N1 component of the seasonal influenza vaccine. Similarly for Influenza A H3N2 virus, there's a very high match with circulating H3N2 viruses and the H3N2 vaccine component. For Influenza B viruses, about 46% of the B viruses identified and characterized so far this season were in fact the same as the Influenza B vaccine component. But about 54% were of the different lineage of Influenza B viruses and so not as good as a match.

So what I want to do is first summarize what I'm going to be talking about in terms of antiviral treatment recommendations. And so rather than put this at the end, I'll put it at the beginning that antiviral treatment is recommended this season as soon as possible for any patient with confirmed or suspected influenza, who is hospitalized or has severe complicated or progressive illness. Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications based on their age and/or medical conditions should be also - are recommended also for antiviral treatment. But clinical judgment should be an important component of outpatient treatment decisions, especially for young children.

Recommended antiviral medications for treatment of influenza are the neuraminidase inhibitor drugs which include either oral oseltamivir or inhaled zanamivir. And based upon recent viral surveillance and resistance data, these indicate that currently circulating influenza virus strains are sensitive to these two neuraminidase inhibitors. Oral oseltamivir should be used for chemoprophylaxis for infants younger than one-year old when indicated. Because antiviral resistance patterns may change over time and unpredictably, clinicians should monitor influenza antiviral resistance data at the local level but also consult the CDC web pages for the latest national data. Antiviral treatment can be considered for any previously healthy, non-high risk symptomatic outpatient with confirmed or suspected influenza who is not in the recommended groups based upon clinical judgment if treatment can be started within 48 hours of illness onset.

Now a little background about influenza virus transmission: most influenza virus transmission is thought to be person-to-person through large particle respiratory droplet spread from an infected person who is coughing or sneezing who is in close proximity to a susceptible person. And these large droplets generally travel short distances, within about six feet or two meters, but do not remain suspended in the air for long periods of time at all. Therefore, it's really close contact that is required for transmission. What the relative contribution of different transmission modes is unclear and there are other possible transmission modalities, and these would include airborne transmission via small particle droplet nuclei, aerosols in the vicinity of the infectious individual, and potentially, indirect contact, via hand transfer of influenza virus from virus-contaminated surfaces, objects, fomites, mucosal surfaces of the face. Airborne transmission over longer distances, such as from one patient's room to another, has not been documented and is not thought to occur. The incubation period for influenza virus infection is generally thought to be one to four days with an average of two days. The serial interval between illness onsets particularly in household transmission studies is estimated to be three to four days. Influenza virus shedding in an infected person generally declines after about less than four days. However the detection of virus or virus RNA depends upon the types of influenza testing methods that are used. So that for school-age children and adults, generally influenza virus is detectable one day before symptoms begin. And it is possible to detect viral RNA through five to seven days after illness onset by reverse transcription-polymerase chain reaction that may or may not represent a viable virus. For young children, a few days before illness onset is possible for a detection of an influenza virus through possibly ten or more days after the onset of symptoms. So young children can potentially shed virus for longer periods of time than older children and adults. For immunocompromised or severely immunosuppressed persons, prolonged influenza viral replication is possible including weeks to months.

Asymptomatic infection can occur and this has been identified through contact, household and serological studies. But most people end up having uncomplicated influenza illness. And this is characterized by the abrupt onset of fever, myalgias, headache, malaise, nonproductive cough, sore throat, and rhinitis. However, one can have acute respiratory illness without fever and that is more typical for elderly patients. For young children, they are less likely to experience the typical influenza signs and symptoms such as older children and adults. They may present with dehydration, irritability, poor oral intake. And very young infants may present with fever only. There are atypical presentations. The elderly may not manifest fever or classic influenza-like illness. Immunocompromised persons and the severely immunosuppressed persons also may not manifest the typical influenza-like illness signs and symptoms. It is very difficult to identify influenza illness from clinical signs and symptoms alone because of the multiple etiologies for acute febrile respiratory illness during the winter, during influenza season especially for young children. And the diagnosis of influenza should be considered in patients with acute respiratory illness, signs and symptoms when influenza viruses are circulating in the community, such as right now.

There are many complications from influenza virus infection. Moderate complications can include sinusitis and otitis media. A very common complication is the worsening or exacerbation of underlying chronic medical conditions, for example, a worsening of underlying pulmonary or cardiac disease. Clearly a primary influenza viral pneumonitis and pneumonia can occur. This can progress to respiratory failure and the acute respiratory distress syndrome and this can be very rapid and fulminant. There are other complications such as vasopressor-dependent shock, acute renal failure, and multi organ failure. And

certainly co-infection with other viral or especially bacterial pathogens can cause severe complications such as bacterial sepsis, secondary bacterial pneumonia, and even bacterial meningitis secondary to antecedent influenza virus infection of the upper respiratory tract. In terms of other complications for bacterial pneumonia and/or sepsis, we're particularly concerned about the most common bacteria that are implicated and those include staphylococcus aureus, both methicillin-sensitive and methicillin-resistant, pneumococcus, as well as Group A strep.

In terms of cardiac complications, these are uncommon but myocarditis can occur in adults and children, and pericarditis has also been reported. There is a wide range of neurologic manifestations associated with influenza and these include transient confusion, to febrile seizures, to encephalopathy, to acute necrotizing encephalitis with a fulminant clinical course and death. Transverse myelitis and Reye's syndrome have also been reported. In terms of musculoskeletal complications, myositis and rhabdomyelitis have been reported. For young children, again, not necessarily complications but presenting signs just to reemphasize that they can present – especially very young infants -- can present just with high fever alone with a presentation that mimics bacterial sepsis. And it should be noted that severe complications can occur even among young and previously healthy persons.

So in terms of the epidemiology of influenza in the United States, because of testing limitations there have been modeling studies that have been utilized. And these project an average of more than 200,000 influenza related hospitalizations per year, with the highest hospitalization rates occurring in persons 65 years and older as well as high rates occurring in young children less than two years of age. Hospitalization rates start to increase starting at age 50 and older because of the increasing prevalence of chronic medical conditions.

This is data from last season from the emerging infections program. This is laboratory-confirmed hospitalization rates, population-based surveillance just to show again that the highest hospitalization rates were in persons 65 years and older. The next highest rates were in young children less than five years of age. And note that the lowest rates of hospitalization were in children aged 5 to 17,school-aged children. as well as adults aged 18 to 49.

In terms of mortality, through modeling projections, we estimate an annual average of anywhere from 3,400 to 49,000 influenza-attributable deaths per year. Note the wide range because of mild seasonal epidemics as well as severe epidemics. The highest mortality rates are in persons 65 years and older. And rates are also high for persons who have chronic pulmonary and cardiac disease and other chronic conditions. We have limited data on mortality for children. However, there clearly have been a lot of pediatric influenza associated deaths that have been reported since 2003. In that 03-04 season, we had 153 pediatric influenza associated deaths reported to CDC. And since then we have had at least 46 deaths per year reported to CDC.

This figure shows that last season, 2010-11, there were 122 pediatric influenza associated deaths reported to CDC. During the pandemic we had more than 300 deaths in children due to pandemic influenza reported to CDC. We've only had three deaths in children attributable to influenza reported to CDC to date this season. But the season is early still. Risk factors for influenza complications include young children, especially those aged less than two years of age, older adults, 65 years of age and older, as well as persons with certain chronic, underlying medical conditions that include chronic pulmonary, cardiovascular (but not hypertension) renal hepatic, hematological including sickle cell disease, metabolic disorders including diabetes, myelitis, and neurological and neuro developmental conditions. These include disorders of the brain, spinal cord, peripheral nerve and muscle such as cerebral palsy, epilepsy, seizure disorders, stroke, intellectual disability, mental retardation, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury. Other risk factors for influenza complications include immunosuppression, including that caused by medications or by HIV infection, women who are pregnant or up two weeks post-partum, persons younger than 19 years of age who are receiving long-term aspirin therapy, persons who are American Indian, or Alaskan native, persons who are morbidly obese with a body mass index equal to or greater than 40, and the residents of nursing homes or other chronic care facilities.

In terms of the role of laboratory diagnosis, the diagnosis of influenza based upon symptoms alone is limited. And because illness caused by other pathogens can be very similar clinically to influenza virus infection, the role of laboratory testing for influenza should be considered. And available tests include antigen detection tests, which are rapid influenza diagnostic tests, which are simple and produce quick results generally in ten minutes or immunofluorescence and typically direct fluorescent antibody staining or DFA. And this requires the use of a fluorescent microscope. Another common method of detection which is very accurate is the use of reverse transcription-polymerase chain reaction (RT-PCR) to detect influenza viral RNA. However this is not necessarily available at every clinical site or hospital. And finally, isolation of influenza virus by inoculation of tissue cell viral culture. However, this can take a number of days. There can be shell viral culture which could yield a result in 24 to 48 hours but regular tissue cell viral culture may take at least three days, up to ten days or longer. Serology should not be ordered for influenza diagnostic purposes and should not be used except for research and public health investigations. A single serum specimen is non-diagnostic for seasonal influenza virus infection. You really need paired acute and convalescent sera properly collected and performed in a specialized lab. The sensitivity and specificity are characteristic parameters of a test but can vary by the type of test used, the type of specimen tested, the quality of the specimen, the timing of specimen collection, and relationship to illness onset, and the lab that performs the test. And what's very important is to understand that an important factor in the test results and also for interpretation of test results is the prevalence of circulating influenza viruses in the population tested. And this varies during the season and that definitely impacts the predictive value of influenza tests. So the results of influenza tests should be evaluated in the context of other clinical and epidemiological information.

Acceptable respiratory specimens vary by test. In general, specimens should be collected as close to illness onset as possible, less than three to four days after illness onset is really ideal. Nasopharyngeal and nasal specimens generally have the highest yield for the detection of influenza viruses and are higher in detection than using throat swabbed specimens. Sensitivities of currently available rapid influenza diagnostic tests are generally low to moderate, but specificities are very high. There's a recent review, a meta-analysis of rapid influenza diagnostic tests that was made available yesterday and this does confirm these results. And it does note also that rapid influenza diagnostic tests may have higher sensitivity in younger children. And that may also be due to higher viral load excretion in younger children. It's very, very important to realize that negative results of rapid influenza diagnostic tests do not exclude influenza virus infection and should not be used to make treatment or infection control decisions, especially during influenza season and especially during peak influenza activity in a community. Only influenza isolates can provide detailed information on the characteristics of influenza viruses for antigenic, genetic, and antiviral resistance characteristics and for public health purposes, it's very important to have influenza viruses isolated and characterized. Reverse transcription-polymerase chain reaction is the most accurate and sensitive for detecting influenza viruses in respiratory specimens. And there are platforms capable of subtyping Influenza A viruses that are available in state public health departments and some reference laboratories.

There are four licensed influenza antiviral agents in the United States. There are two classes of agents that are approved by FDA and these include the neuraminidase inhibitors as one class, which include oral oseltamivir as well as inhaled zanamivir. And these two neuraminidase inhibitors are the primary antiviral agents that are recommended for treatment and chemoprophylaxis of influenza in 2011-2012. These drugs are active against both Influenza A and Influenza B viruses. In terms of general adverse events, oseltamivir more commonly can result in nausea and vomiting. Inhaled zanamivir can result in bronchospasm and therefore it is contraindicated in patients with chronic pulmonary disease, asthma, COPD, and those with a history of wheezing. For both drugs there have been reports of delirium and abnormal behavior reported in Japanese adolescents.

The other class of approved antiviral drugs are the Adamantanes, which consist of amantadine and rimantadine. These drugs are only active against Influenza A viruses. They have no activity against Influenza B viruses. These drugs, amantadine and rimantadine, are not recommended for treatment or chemoprophylaxis of Influenza A virus infection in the United States. There is widespread resistance

among Influenza A H3N2 and 2009 H1N1 virus strains to amantadine and rimantadine. Again amantadine and rimantadine are *not* recommended for treatment or chemoprophylaxis of Influenza A.

The 2009 (H1N1) virus strains and the Influenza A (H3N2) virus strains that are circulating are sensitive/ susceptible to oseltamivir and zanamivir. And this is also true for Influenza B virus strains. There has been sporadic cases of oseltamivir resistant 2009 H1N1 virus infections that have been reported. There has been very rare episodes of limited transmission. The public health impact to date has been limited. Persons at highest risk for oseltamivir resistant 2009 (H1N1) virus infection are persons with influenza who are severely immunosuppressed who are treated with oseltamivir. And resistance may emerge during treatment or after treatment. It's important to note that community transmission of oseltamivir resistant 2009 H1N1 viruses has been reported in Southeast Australia during their winter in 2011. We would expect that additional sporadic cases of oseltamivir resistant 2009 H1N1 virus infections will occur. And therefore it's very, very important that there's ongoing surveillance for oseltamivir resistance among circulating influenza viruses and that is happening in conjunction with CDC in the United States. Currently there is no evidence of ongoing transmission of oseltamivir resistant 2009 H1N1 virus strains worldwide.

This table shows that for this season to date, for Influenza A (H3N2), 2009 H1N1 and Influenza B virus strains that have been tested in the United States, none of them, 0% have been identified with resistance to oseltamivir and zanamivir so that is very good new. In terms of treatment efficacy and effectiveness studies for antivirals, oseltamivir or zanamivir can reduce the duration of uncomplicated Influenza A or B illness by approximately one day up to 1.5 days as has been reported when administered within 48 hours of illness onset. This is reported in randomized placebo-controlled clinical trials. It's important to note that most of these RCTs have been conducted among otherwise previously healthy persons. There is one RCT of oseltamivir treatment of children aged one to three years in Finland in which treatment of influenza was started within 24 hours of illness onset so this was very, very early treatment**.** And this was reported to reduce the duration of illness by 3.5 days in the oseltamivir treated arm compared to placebo. One recent systematic review of RCTs reported that early oseltamivir treatment reduced influenza illness by about 21 hours versus placebo. There are limited data on efficacy or effectiveness of inhaled zanamivir or oral oseltamivir treatment in preventing serious influenza complications such as bacterial viral pneumonia or exacerbation of chronic disease. There is one meta-analysis of RCTs including a number of unpublished studies as well as some published studies that found that oseltamivir treatment reduced the risk of lower respiratory tract complications requiring antibiotic treatment by 37% in patients with laboratory confirmed influenza. There is one observational study that indicated that early oseltamivir treatment, a median of three days after illness onset, reduced the progression to chest X-ray confirmed pneumonia from 2009 H1N1 virus infection. There are no published RCTs for antiviral treatment of hospitalized patients with severe influenza. However there are multiple observational studies of hospitalized patients with seasonal influenza, primarily elderly patients or 2009 H1N1 patients of all ages including pregnant women, which indicate early neuraminidase inhibitor treatment primarily with oseltamivir is associated with reduced morbidity and mortality and reduced duration of hospitalization. In general there is a consistent finding among observational studies that the greatest clinical benefit is observed when oseltamivir is started within two days after illness onset. Starting oseltamivir even up to less than five days after illness onset is associated with a reduced risk of ICU admission or death. And a systematic review of observational studies of antiviral treatment concluded that oral oseltamivir treatment of influenza may provide net benefit by reducing mortality, the duration of symptoms and complications of influenza. That systematic review was released yesterday by Annals of Internal Medicine.

The benefits of antiviral treatment with neuraminidase inhibitors are greatest if antiviral treatment is started as soon as possible after illness onset. And observational data consistently show that the evidence for benefit is strongest when treatment was started within 48 hours of illness onset. However, antiviral treatment of any person with influenza who requires hospitalization is recommended as soon as possible even if the patient presents more than 48 hours after illness onset. So during influenza season, influenza virus infection should be considered as a possible cause of any febrile illness requiring hospitalization and clinicians should consider empiric antiviral therapy in patients with suspected influenza as clinically indicated**.** There should also be consideration of influenza testing if influenza testing will influence treatment decisions. But be aware of the limitations of influenza tests and how to interpret test

results. In addition, clinicians should monitor local, state, and national recommendations such as those from ACIP and CDC during the influenza season to determine the most appropriate treatment practices. And also you can check the CDC web pages for the latest information on antiviral resistance profile for circulating influenza viruses. Overall, treatment decisions should be informed by a knowledge of influenza activity in the local community.

Empiric antiviral treatment is recommended for suspected influenza when testing is not done. It's not always possible or necessary to test every patient with suspected influenza. Starting treatment should not be delayed while awaiting specimen collection or influenza testing results. Again, the greatest clinical benefit is when treatment is started as soon as possible and as early as possible. Patients with suspected influenza should continue to receive antiviral treatment regardless of negative initial test results until an alternative diagnosis can be established and that is really pertinent for hospitalized patients. Clinicians who prefer not to treat empirically should discuss signs and symptoms of worsening illness with patients and arrange for follow-up by telephone or in the clinic. Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who has severe, complicated, or progressive illness, or is hospitalized, or is at higher risk for influenza complications. Clinical judgment based upon the patient's disease severity and progression, age, underlying medical conditions, the likelihood of influenza, and time since the onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients. When indicated, antiviral treatment should be started as soon as possible after illness onset.

It should be noted that although children aged less than two years are recognized to be at risk for severe complications from influenza including hospitalization and death, the risk is highest among those infants less than six-months old. In addition, because many children with mild febrile respiratory illness may have other viral infections such as respiratory syncytial virus, rhinoviruses, parainfluenza virus infection, or human metapneumovirus infection, knowledge of other respiratory virus as well as influenza virus strains circulating in the local community is important when making treatment decisions.

Persons with
higher risks for influenza complications are recommended for antiviral treatment for confirmed or suspected influenza include the following: children younger than two years old, the risk is highest among those less than six-months old, adults 65 years of age and older and patients with the following chronic medical conditions: chronic pulmonary, cardiovascular, renal hepatic, hematologic, metabolic disorders, neurological, and neurodevelopmental conditions, immunosuppression, women who are pregnant or within two weeks post-partum, persons younger than 19 years of age receiving long-term aspirin therapy, American Indians and Alaskan natives, persons with morbid obesity, and residents of nursing homes and other chronic care facilities. Treatment for outpatients, antiviral treatment with neuraminidase inhibitor is recommended for all persons with confirmed or suspected influenza who are at higher risk of influenza complications due to age or underlying medical conditions. Antibacterial therapy plus antiviral treatment is recommended for patients with community-acquired pneumonia when influenza is also suspected.
It's important to note that data on the effectiveness of antiviral treatment in critically ill patients are very limited. Limited observational data do suggest that antiviral treatment may reduce the duration of hospitalization and mortality.

For previously healthy, non-high risk symptomatic outpatients with confirmed or suspected uncomplicated influenza, antiviral treatment can be considered for these patients based upon clinical judgment if treatment can be initiated early, within 48 hours of illness onset. These patients typically do not require treatment but early empiric treatment might provide benefit such as shortened duration of illness or reduced risk of clinical progression. These patients are not likely to benefit from treatment if initiated more than 48 hours after illness onset. Persons with influenza who are already beginning to recover do generally not need treatment. In terms of treatment issues for patients hospitalized with confirmed or suspected influenza, treatment duration might need to be altered to fit the clinical circumstances. For example, clinical judgment should be the guide regarding the need to extend antiviral treatment longer than five days for patients whose illness is prolonged particularly for hospitalized patients with severe influenza.

There are no published, available controlled data to evaluate the efficacy of higher doses of antivirals to treat severe influenza at this time. Administering oseltamivir via gastric tube can provide systematic absorption in some critically ill patients. Note that gastric stasis or gastrointestinal bleeding can make this route problematic. Parenterally-administered neuraminidase inhibitors are not approved in the US. However intravenous zanamivir and intravenous oseltamivir are available for compassionate use via emergency investigational new drug application via the manufacturer and approval by the Food and Drug Administration. However, clinical trials are really needed to better understand optimal treatment approaches. For information about eligibility and enrollment of patients in clinical trials of investigational intravenous antivirals such as intravenous zanamivir, or intravenous peramivir, or combination antiviral treatment, please consult www.clinicaltrials.gov for more information.

In terms of patients who are hospitalized with confirmed or suspected influenza, those patients are being treated with antiviral medications who do not respond to antiviral treatment might have infection with an antiviral resistant influenza virus. However, it's also important to realize that patients may worsen or not improve with antiviral treatment due to other complications associated with influenza, including bacterial co-infection or multi organ failure. So when a patient does not improve or experiences clinical deterioration, it may not be the case that there is antiviral resistance to the virus that the patient is infected with. But the issue of antiviral resistance should be considered. Also note that infection control measures are very important for all hospitalized influenza patients and especially are important for patients who are immunocompromised or immunosuppressed to reduce the risk of transmission of oseltamivir resistant influenza viruses. Oseltamivir resistance sometimes within one week of treatment initiation has been reported particularly among severely immunosuppressed patients with 2009 H1N1 virus infection who were receiving oseltamivir treatment. Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. The likelihood of compliance and adverse events should be considered when determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis. Failure to complete a course of oseltamivir for chemoprophylaxis due to gastrointestinal adverse events might lead to antiviral resistance if an infection has occurred and chemoprophylaxis was given post exposure. Regarding post exposure of chemoprophylaxis, decisions regarding whether to administer antivirals for chemoprophylaxis should take into account exposed persons risk for complications, the type and duration of contact, recommendations from local or public health authorities.

In areas with limited antiviral medication availability, local public health authorities might recommend that antiviral medications be primarily directed at treatment and that antiviral chemoprophylaxis be only used in certain limited situations. In addition, clinical judgment really needs to be taken into account. Generally, post exposure chemoprophylaxis for individuals should only be used when antivirals can be started within 48 hours of the last exposure. An emphasis on early treatment is an alternative to post exposure chemoprophylaxis in managing persons who have had an expected exposure to a symptomatic person with influenza. These individuals should be counseled about the early signs and symptoms of influenza and advised to immediately contact their healthcare provider for evaluation and possibly early antiviral treatment if clinical signs or symptoms of influenza develop. They should also be counseled about influenza antiviral medication side effects. And they should be informed that they remain susceptible to influenza virus infection after the antiviral medications are stopped in terms of chemoprophylaxis. Healthcare providers should use clinical judgment regarding situations where early recognition of illness and early antiviral treatment might be a more appropriate alternative. Post exposure chemoprophylaxis with neuraminidase inhibitors should generally be reserved for high risks patients who had exposure to a person with symptomatic influenza. Persons who can be considered for antiviral chemoprophylaxis include residents of institutions during confirmed or suspected influenza outbreaks, families of other close contacts of suspected or confirmed cases who are at higher risk for influenza complications and who have not been vaccinated against the influenza virus strain circulating at the time of exposure.

Also for unvaccinated healthcare workers who have had occupational exposures and who did not have adequate personal protective equipment at the time of the exposure who are not vaccinated. Post

exposure chemoprophylaxis either with oral oseltamivir or inhaled zanamivir is recommended for influenza including for 2009 H1N1, Influenza A (H3N2) or Influenza B virus infection. Persons who receive an antiviral medication for chemoprophylaxis might still acquire influenza virus infection and potentially be able to transmit infection even if clinical illness is prevented because antiviral chemoprophylaxis of influenza is approximately 70% to 80% effective in preventing illness but not necessarily always preventing influenza virus infection when exposure even to drug-sensitive virus occurs. Patients who are administered post exposure chemoprophylaxis should be informed that chemoprophylaxis lowers but does not eliminate the risk of influenza. Be informed that susceptibility to influenza returns once the antiviral medication is stopped and be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness that might indicate influenza because infection can still occur and it could be a resistant virus. Post exposure chemoprophylaxis is typically given up to ten days after the last known exposure to a close contact known to have influenza.

Pre-exposure chemoprophylaxis should only be used for persons who
are at very high risk of influenza risk complications and cannot otherwise be protected during times where there is a high risk for exposure such as those persons for whom influenza vaccination is contraindicated or are not expected to mount a good immune response to influenza vaccination. Use should be in accordance with current recommendations from CDC or local public health authorities. When used, pre-exposure chemoprophylaxis must be given for the duration of time when exposure to influenza viruses might occur. To be maximally effective, the drug must be taken each day for the duration of the influenza activity in the community. And adverse events associated with long-term use are uncertain and prolonged use of antivirals might potentially select for resistance to antiviral medications. In community studies of healthy adults who have been given antiviral medications during times of influenza virus transmission, both oseltamivir and inhaled zanamivir had similar efficacy in preventing febrile lab-confirmed influenza illness. Studies have also demonstrated the effectiveness of antiviral chemoprophylaxis for prevention of influenza and control among patients in institutional settings. But data are limited on the efficacy and effectiveness of antiviral agents in preventing influenza among severely immunocompromised persons. Since 2009, 99% of circulating Influenza A and B viruses have been susceptible to oseltamivir. It should be noted that CDC provides weekly updates on virus surveillance at the national level. And that's available on our web page cited there.

If oseltamivir-resistant viruses are not circulating, antiviral treatment for influenza should consist of either oseltamivir or zanamivir. Continued changes in antiviral resistance are likely among influenza viruses. Clinicians should remain attentive to updates in antiviral treatment guidance based upon any developments regarding the prevalence of circulating antiviral resistance among influenza viruses.

In terms of control of influenza outbreaks in institutions, antiviral drug treatment and antiviral chemoprophylaxis are key to outbreak control in institutions with patients who are at higher risk for influenza complications. Neuraminidase inhibitors have been used to successfully control outbreaks when combined with other infection control measures and influenza vaccination. Inhaled zanamivir should be used when persons require a chemoprophylaxis due to exposure to influenza virus strains that are suspected or confirmed of being oseltamivir resistant. Respiratory specimens should be collected from ill persons for influenza typing and Influenza A virus subtyping by RT-PCR or viral culture for antigenic characterization and to assess antiviral resistance, and to provide data on the outbreak etiology.

If antiviral chemoprophylaxis is indicated, start neuraminidase inhibitors as early as possible. It's very helpful to have pre-approved orders from physicians and plans to obtain orders for antiviral medications on short notice. Antiviral chemoprophylaxis in institutions during influenza outbreaks should be administered to all eligible residents regardless of influenza vaccination status. Chemoprophylaxis should last for a minimum of two weeks. If new cases continue to occur and are detected through surveillance, antiviral chemoprophylaxis should continue until approximately ten days after illness onset in the last patient. Antiviral chemoprophylaxis should also be offered to unvaccinated staff who
care for high risk persons. Measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons including those taking antiviral chemoprophylaxis.

Other outbreak control measures are very, very important to be implemented simultaneously and these include infection control, institution of droplet and contact precautions, and establishing cohorts of patients with confirmed or suspected influenza who are isolated or cohorted. Influenza vaccination should be offered, and re-offered to unvaccinated staff if influenza vaccine is available. Staff movement should be restricted between wards and buildings. There should be restriction of contact between ill staff, ill visitors and patients. And there should be screening for illness among visitors and staff. This table represents dosing recommendations. There's not sufficient time to go over all of this. But for oral oseltamivir it should be noted that this drug, for children, is dosed on the basis of weight. For adults, it's based upon capsule, one capsule twice a day, 75 milligrams twice daily for five days duration is standard. For inhaled zanamivir, for those seven years or older for treatment, it's actually two inhalations, twice daily for five days. There are different chemoprophylaxis doses. But I would note that you can refer to the manufacturer's package insert as well as to CDC web pages for guidance on dosing.

Just to highlight on this page, this shows the recommended dosing for oseltamivir, for treatment and chemoprophylaxis. In children less than one year of age, oseltamivir is approved by FDA for use in children one year and older but is recommended by ACIP and CDC for use in children less than one year of age for treatment or chemoprophylaxis. Treatment is recommended for all ages less than one year of age. However for chemoprophylaxis in general, chemoprophylaxis is not recommended for children less than three months of age unless the situation is judged to be critical and this is because of limited data use in this age group. For additional information, I would just highlight that the ACIP guidance for antivirals for the treatment and chemoprophylaxis of influenza was published last January 2011 in the MMWR Recommendations and Reports. And it is available through the CDC web pages. And also I would highlight the recommendation summary for antiviral medications for clinicians for the 2011-2012 season is also available at this link through our web pages. And I'll stop for questions at this time. Thank you.

Loretta Jackson-Brown:

Thank you Dr. Uyeki. We will now open up the lines for the question and answer session. Also, you may submit questions through the webinar system by clicking on the Q&A tab in the upper left-hand corner of your screen.

Coordinator:

Also for those of you on the phone, you may ask a question by pressing Star-1 on your phone. Please remember to un-mute your phone, record your name clearly so that I may introduce your question. If the question has already been asked, you can withdraw yours by pressing Star-2. Thank you. The first question is from Dr. (Norman Castile), your line is open.

Dr. (Norman Castile):

I have two questions. One is about the use of masks, not N95, for people who are ill to prevent the spread of the illness and for people who are not ill but around those who are. And two, are you recommending a quadrivalent vaccine for next season to cover both strains of B?

Dr. Timothy Uyeki:

Yes, thank you very much for those questions. So regarding measures to prevent transmission of influenza either from healthcare workers to patients or patients to healthcare workers or among those populations, so in terms of droplet precautions, the use of a surgical mask is recommended. For aerosol generating procedures, that's when use of N95 respirator or equivalent, or higher level of respiratory protection is recommended. In terms of the quadrivalent vaccine, so I'm going to defer an answer on that and just say that quadrivalent influenza vaccine,

for those that aren't aware, basically the trivalent seasonal influenza vaccine includes two Influenza A virus strains and one Influenza B virus strains. And as I mentioned at the beginning of this call, there are two lineages of Influenza B viruses circulating. In terms of the two B viruses circulating, the B/Yamagata and the B/Victoria lineages, only one is included in the vaccine. So the use of a quadrivalent vaccine would allow the inclusion of both Influenza B virus lineages, the Yamagata and the Victoria lineages in representative strains. So that would be something that can provide an advantage over current trivalent vaccine in terms of protection against all circulating B viruses of those two lineages. The ACIP will end up actually voting on any quadrivalent influenza vaccine recommendation. And once a vote on that occurs, if it is approved, then that would be the recommendation that goes forward. So I think it's a little bit premature to comment on a vote that hasn't taken place. And there would be other factors that would need to be considered including the supply and availability of whatever manufacturers' quadrivalent influenza vaccine are approved. But thank you for raising that topic.

Dr. (Norman Castile):

Okay thank you.

Coordinator:

I'm not showing any further questions from the phone lines.

Loretta Jackson-Brown:

Hi this is Loretta. Dr. Uyeki I have a question for you through the webinar system. And the question is can we test for influenza if patients do not have fever but other symptoms are present?

Dr. Timothy Uyeki:

So thanks for that question. Absolutely that is something that can be done. Although the classic signs and symptoms of influenza are sort of the abrupt onset of fever, cough, sore throat, muscle aches, potentially headache, et cetera, et cetera of uncomplicated influenza. As I mentioned, there are patients who may not manifest a fever or may have a very low-grade fever that they might not suspect they are feverish. That particularly includes elderly patients. And so a person with acute respiratory illness signs and symptoms except for fever during influenza season could still have influenza, and they could benefit in terms of influenza testing, in terms of clinical management. So especially if there were a high risk patient, especially elderly patients. So the absence of a fever definitely does not preclude influenza.

Loretta Jackson-Brown:

Thank you. Operator, do we have any questions on the phone?

Coordinator:

No further questions.

Loretta Jackson-Brown:

Dr. Uyeki, is there any closing remarks you would like to make?

Dr. Timothy Uyeki:

Thanks. I guess I would say that again, nationally the influenza season has not peaked. We do expect influenza activity to continue and probably increase in the weeks to come. So although it is a late influenza season, we can't predict how much more influenza there's going to be. But there should be a fair amount in the coming weeks. And therefore consideration of antiviral treatment for influenza patients as I mentioned, especially for the recommended groups, I think really needs to be considered by clinicians despite the relatively mild season we have had to date. Thank you very much.

Loretta Jackson-Brown:

Thank you. And on behalf of COCA, I would like to thank everyone for joining us today with a special thank you to our presenter, Dr. Uyeki. If you have additional questions for today's presenter, please email us at coca@cdc.gov. Put Dr. Uyeki in the subject line of your email and we will ensure that your question is forwarded to him for a response. Again that email address is c-o-c-a@cdc.gov .

The recording of this call and the call transcript will be posted to the COCA website at emergency.cdc.gov in the next few days. Free continuing education credits are available for this call. Those who participated in today's COCA conference call and would like to receive continuing education credit should complete the online evaluation by March 28, 2012 using Course Code EC 1648. For those who will complete the online evaluation between March 29, 2012 and February 28, 2013, please use Course Code WD 1648. All continuing education credits and contact hours for COCA conference call are issued online through TCE online. The CDC training and continuing education system at www, the number 2, the letter A, dot CDC.gov, forward slash, TCEonline. To receive information on upcoming COCA calls, subscribe to COCA by sending an email to COCA@CDC.gov and write subscribe in the subject line. Also CDC has a Facebook page for health partners. Like our page at Facebook.com/cdc health partners outreach to receive COCA updates. Thank you again for being apart of today's COCA webinar, have a great day.

Coordinator:

Thank you all for attending. You may disconnect at this time. Thank you.

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