COCA Call: Antiviral Agents for the Prevention and Control of Influenza.
[*Note: Call title was recorded as Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza]*

Date/Time: November 23, 2010 (2:00 PM- 3:00 PM ET)
Speaker: Dr. Tim Uyeki, Deputy Chief for Science Epidemiology and Prevention Branch (CDC)

Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen-only mode. During the question and answer session today please press star 1 on your touch-tone phone.

Today's call is being recorded. If you have any objections you may disconnect at this time. I would now like to turn the meeting over to Loretta Jackson Brown. You may begin.

Loretta Jackson Brown: Thank you (Barb). Good afternoon. I'm Loretta Jackson Brown and I am representing the Clinician Outreach and Communication Activity, COCA with the Emergency Communication System at the Centers for Disease Control and Prevention.

I am delighted to welcome you to today's COCA conference call, Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza.

We are pleased to have with us today Dr. Tim Uyeki, Deputy Chief for Science Epidemiology and Prevention Branch at Centers for Disease Control

and Prevention here to discuss effectiveness and safety of antiviral treatment medications.

During today's call you will hear the presenter referring to Slides in his PowerPoint presentation. The PowerPoint slides that is available from our COCA Web site at emergency.cdc.gov/coca. Click on COCA calls. The slide set can be found under the call in number and call pass code.

The objectives for today's call are the participants will be able to list currently recommended influenza antiviral medications, describe the effectiveness and safety of influenza antiviral medications, and understand current recommendations for the use of antiviral medications to treat and prevent influenza during the current season.

Following the presentation you will have an opportunity to ask our presenter questions. Dialing star 1 will put you into the queue for questions.

In compliance with continuing education requirements all presenters must disclose any financial or other relationship with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters as well as any use of an unlabeled product or products under investigational use.

This presentation will not include the discussion of the unlabeled use of a product or products under investigational use with the exceptions of Oseltamivir which is FDA approved for use in age one year and older.

During the influenza pandemic CDC distributed the drug to birth under an EUA Emergency Use Authorization protocol.

Although the EUA has expired CDC recommends Oseltamivir to birth. There is no commercial support for this presentation.

Today's presenter Dr. Tim Uyeki is a Captain with the US Public Health Service and the Deputy Chief for Science in the Epidemiology and Prevention Branch Influenza Division at CDC.

Dr. Uyeki served as a consultant to the World Health Organization on clinical and epidemiological issues related to seasonal, zoonotic, and pandemic influenza.

A frequent contributor to WHO publications, Dr. Uyeki is a co-author of the Annual Advisory Committee on immunization practices, influenza recommendations and numerous influence articles and book chapters.

Board certified in pediatrics, preventive medicine and public health, Dr. Uyeki serves as an Associate Clinical Professor in the Pediatric Department of the University of California San Francisco.

He is also an Adjunct Associate Professor in the Hubert Department of Global Health at Emory's University Rollins School of Public Health Atlanta, Georgia.

If you're following along on the slides you should be on Slide 6. Again the PowerPoint slide set is available from our COCA Web

site@emergency.cdc.gov.coca. At this time please welcome today's presenter Dr. Uyeki.

Tim Uyeki: Thank you. Today I'll be talking about antiviral agents for the treatment and chemoprophylaxis of influenza.

So these are the recommendations of the Advisory Committee on Immunization Practices ACIP and will be published in the near future.

Slide 7 is an overview of what I'll be discussing. I'll start with an update and go over some changes to the recommendations for antiviral treatment in chemoprophylaxis for the 2010-2011 influenza season.

I'll briefly talk about influenza virus transmission, clinical signs and symptoms of influenza, the role of laboratory diagnosis, and talk about the recommended antiviral medications for influenza.

I'll briefly speak about antiviral drug resistance among circulating influenza viruses and then get into the use of antivirals including summarizing some of the data on treatment efficacy and effectiveness studies, treatment indications, treatment issues for patients who are hospitalized with confirmed or suspected influenza, chemoprophylaxis indications, considerations for use if there are antiviral resistant influenza virus strains in circulation, and speak a little bit about the control of influenza outbreaks in institutions and the use of antivirals.

Slide 8, so the first thing I want to do is go over some of the changes and updates in the recommendations for the 2010-2011 influenza season.

First we are prioritizing and so antiviral treatment is recommended as soon as possible for patients with confirmed or suspected influenza who are hospitalized or those who have severe, complicated, or progressive illness.

This includes out-patients with confirmed or suspected influenza who are at higher risk for influenza complications based upon their age and/or medical conditions.

Clinical judgment should be an important component of making antiviral treatment decisions for outpatients.

The recommended antiviral medications for treatment and chemoprophylaxis of influenza are Oseltamivir and Zanamivir. Both are neuraminidase inhibitor medications.

And this is based upon influenza virus surveillance data and antiviral resistance testing susceptibility, testing indicating that the overwhelmingly vast majority of circulating influenza virus strains are sensitive to Oseltamivir and Zanamivir.

In addition another point is that Oseltamivir should be used to provide treatment or chemoprophylaxis for infants younger than 1 year old when indicated.

And as was noted Oseltamivir is FDA approved for use in persons one year of age or older and so that this represents an off- label use. But Oseltamivir was

used down to birth during the 2009 H1N1 pandemic under an emergency use authorization.

Although this EUA has expired we do recommend that when use of antivirals for treatment or chemoprophylaxis is indicated for infants younger than 1 year old Oseltamivir is recommended.

Slide 9, because antiviral resistance patterns can change over time, clinicians should monitor influenza antiviral resistance surveillance data either at the local or state levels and also view the weekly CDC Influenza Surveillance Report which is available on our Web pages, which provides the latest information about antiviral susceptibility and resistance data among circulating influenza viruses.

And finally we do want to note that antiviral treatment can be considered for any previously healthy non-high risk symptomatic outpatient with confirmed or suspected influenza who is not in one of the recommended groups as mentioned previously, based upon clinical judgment, if antiviral treatment can be initiated within 48 hours of illness onset.

In other words, we are not saying do not treat previously healthy non-high risk symptomatic outpatients with uncomplicated either confirmed or suspected influenza.

But we are saying that this can be considered based upon clinical judgment if early treatment can be initiated.

So Slide 10, influenza virus transmission. Large particle respiratory droplet transmission is thought to be the traditional primary mode of person to person spread.

And this occurs when an infected person who is symptomatic is coughing or sneezing close to a susceptible person.

Large droplets travel short distances within about 6 feet or about 2 meters but do not remain suspended in the air. And therefore close contact between a symptomatic infected person and a susceptible person is required for transmission to occur.

The relative contribution of different transmission modes is unclear and other possible transmission modalities can include airborne transmission via small particle aerosols in the vicinity of the infectious individual that are expelled also during coughing or sneezing.

Indirect contact might occur via hand transfer of influenza virus contaminated surfaces for - or objects to mucosal surfaces of the face such as the nose or mouth. However we really do not have good data on the relative contributions of these modalities.

It’s important to note that airborne transmission over longer distances beyond 2 meters such as from one patient - one patient’s room to another has not been documented and is not thought to occur.

Slide 11, in terms of other influenza virus transmission issues, the incubation period from the time of exposure and infection to the onset of symptoms is typically one to four days, but more characteristically about two days.

The serial interval or the time from illness onset of an index case to a secondary case is approximately three to four days among household contact studies.

Regarding influenza viral shedding, adults generally can have virus detected one day before symptoms begin. And viral shedding can be detected through about five to seven days after illness onset. It can be a bit longer, but typically five to seven days.

In terms of young children however, young children may have viral shedding a few days before illness onset. In very young infants it's been documented longer than that, not typically, but it can occur.

And viral shedding can persist for longer periods the younger the child is, including ten or more days after the onset of symptoms.

For immunocompromised or severely immunosuppressed patients of any age influenza viral shedding for weeks up to many months has been documented.

And so this is an important issue for healthcare personnel caring for immunocompromised or severely immunosuppressed patients. And prolonged viral replication in such patients can occur even while asymptomatic.

On Slide 12 regarding the clinical signs and symptoms it's first important to note that asymptomatic infection can occur. This has been documented in contacts and household studies and in serological studies where persons either had been followed closely after exposure to an asymptomatic case and actually had virus detected in upper respiratory tracts specimens but never developed symptoms in follow-up, or similarly had a rise in antibody detected in serological studies, but were never symptomatic.

But in terms of many people who have uncomplicated influenza illness, the classic signs and symptoms are the abrupt onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.

It's important to realize that not all persons will manifest fever with acute respiratory illness symptoms however.

Young children are less likely to experience typical influenza signs and symptoms. They can present with dehydration, irritability, or oral intake. Infants can also present with fever only.

Other atypical presentations may be more commonly seen among elderly. Elderly may not always manifest fever or the classic influenza like illness symptoms.

Immunocompromised and severely immunosuppressed patients may also have atypical presentations and also may not always have fever.

Therefore it's difficult to identify influenza illness based upon clinical signs and symptoms alone. There are multiple etiologies for acute febrile respiratory illness especially in very young children.

However the diagnosis of influenza should be considered in patients with acute respiratory illness signs and symptoms when influenza viruses are circulating in the community.

Now on Slide 13 regarding complications from influenza virus infection, moderate complications can include sinusitis or otitis media in very young children.

However the most common complications of influenza virus infection particularly in older children and adults is exacerbation of underlying medical conditions, particularly pulmonary or cardiac disease.

This could include an exacerbation of COPD or asthma or worsening of congestive heart failure with influenza virus infection.

Primary influenza viral pneumonitis and pneumonia can develop. This was observed particularly among young previously healthy adults and those with chronic illness during the pandemic of 2009 H1N1.

There can be progression to respiratory failure and the acute respiratory distress syndrome. Progression can be very fulminant. Complications in such patients and others can include vasopressor-dependent shock as well as acute renal dysfunction or acute renal failure.

There can be co-infections with other viral or bacterial pathogens including secondary bacterial pneumonia and/or sepsis.

This can also be very fulminant, can occur within two to three days or less of the onset of influenza signs and symptoms.

And some of the most common bacterial pathogens implicated in secondary bacterial pneumonia with influenza are *Staphylococcus aureus*, both methicillin sensitive and methicillin resistant, *Streptococcus pneumoniae* and *Streptococcus pyogenes* (Group A *Streptococcus*).

In terms of cardiac manifestations, uncommon manifestations that can occur both in children young children and adults are myocarditis and pericarditis.

Neurologic complications are a bit more common although still somewhat uncommon. They can occur more commonly in children but have occurred in adults of all ages.

There's a wide clinical spectrum of neurological complications ranging from febrile seizures to encephalopathy to fulminant acute necrotizing encephalitis resulting in either neurologic sequelae or death.

There can be transverse myelitis, Reye's Syndrome especially associated with Influenza B or Influenza A or B with co-administration of aspirin particularly in children, is a devastating complication. And therefore aspirin is not recommended for children aged <18 years old unless medically indicated for chronic conditions in children.

Musculoskeletal complications include myositis. A classic complication in children of school age is bilateral gastrocnemius myositis, or severe pain in the calves bilaterally causing the child not to walk. Rhabdomyolysis can occur in any age.

Young children can have signs and symptoms that mimic bacterial sepsis. They may present with very high fever.

But it's important to note that severe complications, including very fulminant complications, can occur even among young and previously healthy persons.

So on Slide 14 - risk factors for influenza complications include children younger than five years old, especially those age less than two years, adults 65 years of age and older, and persons with the following chronic medical conditions.

Those include chronic pulmonary conditions, chronic cardiovascular with the exception of hypertension, renal, chronic renal, chronic hepatic, hematological disorders including sickle cell disease, metabolic disorders including diabetes mellitus, neurological and neuro-developmental conditions including 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 immunosuppression including that caused by medications or by HIV infections, women who are pregnant or postpartum within two weeks after delivery, persons younger than 19 years of age who are receiving long term aspirin therapy, persons who are American Indians or Alaska natives, persons who are morbidly obese, that is a body mass index equal to or greater than 40, residents of nursing homes and other chronic care facilities.

These are all risk factors for severe influenza complications that may result in hospitalization or admission to the intensive care unit or death.

And these are associated with seasonal influenza and also with pandemic influenza. And some of these were observed during the past year with 2009 H1N1.

On Slide 15 regarding the role of laboratory diagnosis, because the diagnosis of influenza just based on signs and symptoms alone may be limited , illness caused - because illness caused by other pathogens can be similar to influenza virus infection, it's important to realize there are influenza tests that are available.

For clinicians most of the tests that are utilized are the rapid diagnostic or antigen detection tests which include both rapid influenza diagnostic tests which can produce very quick results really less than 15 minutes. They're very simple to perform. Some of them are approved for use at the bedside.

The other is immunofluorescence, direct fluorescent antibody staining or DFA. However that requires a fluorescent microscope and may take up to two to four hours after the lab receives the specimen to produce results. And it's not available widely.

Detection of viral RNA through reverse transcription polymerase chain reaction (RT-PCR), either conventional or real-time, is highly accurate; however it's not available at every clinical site or hospital and also may require time anywhere from four to eight hours to perform this and it may not be performed right away.

Isolation of influenza virus by tissue cell viral culture requires three to ten days and may not inform direct clinical management.

However it's the most important for public health to characterize viruses to assess antiviral, full antiviral resistance testing including functional assays, and especially to look at antigenic characteristics.

Serology - it's very important to understand that serology is not recommended, it's not indicated except for research or public health investigations.

Serological testing will not be readily available and will not be timely enough to inform clinical management.

And the sensitivity and specificity of influenza tests are parameters that can vary. They're fixed test parameters but they can vary by study because of the type of test used, the type of specimen that's tested, the site of the upper versus lower respiratory tract, the quality of the specimen, the timing of specimen collection in terms of relationship to illness onset, the lab that performs the test.

There are many factors that can influence the ability of a test to produce accurate results, especially the sensitivity.

And it's very important for clinicians to realize that the prevalence of circulating influenza viruses in the population tested varies throughout the

season, low season, high season. And this impacts interpretation and the predictive values of influenza tests.

And so all results of influenza tests should be evaluated in the context of other clinical and epidemiological information.

So on Slide 16 it's important to understand the specimen should be collected as close to illness onset as possible, if possible less than four days after illness onset because viral shedding in general will decline thereafter and virus may not be detected.

Naso pharyngeal and nasal specimens generally have higher yield for detection of influenza viruses than throat swab specimens.

The sensitivities of available rapid influenza diagnostic tests are generally low to moderate of (50% to 70%) but there's a very, very wide range and some tests have performed very poorly.

However specificities are high. So overall clinicians need to understand that negative rapid influenza diagnostic test results do not exclude influenza virus infection and should not be used to make treatment or infection control decisions.

If influenza is clinically suspected and treatment is indicated then empiric treatment should be given or other testing should be considered.

The reverse transcription polymerase chain reaction for influenza is the most accurate, the most sensitive test to detect influenza viruses.

These platforms are capable of sub typing Influenza A viruses and are available in state public health laboratories and some reference laboratories.

On Slide 17 there, regarding the antiviral agents that are approved in the United States. There are two classes of antiviral drugs and two in each class that are approved.

But I want to really emphasize the neuraminidase inhibitors. These are Oseltamivir (trade name is Tamiflu) or Zanamivir (the trade name is Relenza).
These are the primary antiviral agents that are recommended for treatment or chemoprophylaxis of influenza in the US for 2010-2011. These drugs are active against both Influenza A and Influenza B virus strains.

It’s important to note some of the adverse events which for the most part are not very significant except for one that I'll mention.

Oseltamivir has been associated in clinical trials and post marketing surveillance with nausea and emesis.

Zanamivir, this is important, that it’s been associated with bronchospasm. It is contraindicated in patients with chronic pulmonary disease such as asthma or COPD.

Rarely it’s important to know that both drugs, there have been reports of delirium and abnormal behavior resulting in injury reported among Japanese

adolescents with influenza who were treated with Oseltamivir or Zanamivir -- but very few reports in the US.

The Adamantanes or Amantadine or Rimantadine are active only against Influenza A viruses. They have no activity Influenza B viruses.

I'm not going to really talk about them further because these drugs again Adamantanes or Amantadine and Rimantadine are not recommended for treatment or chemoprophylaxis of Influenza A virus infection in the United States for 2010-2011 due to widespread resistance among circulating influenza A (H3N2) and 2009 H1N1 virus strains.

Slide 18 - 2009 H1N1 virus strains and Influenza A (H3N2) virus strains are sensitive to Oseltamivir and Zanamivir. They are resistant to the Adamantanes, Amantadine and Rimantadine.

Circulating Influenza B virus strains are sensitive to Oseltamivir and Zanamivir. And in the United States this season and also in the Northern Hemisphere, although it’s early in the season, what we have seen is a mixed season so far.

So there has been detection of 2009 H1N1 virus strains, Influenza A (H3N2) virus strains and Influenza B virus strains. And this has also been observed in the Southern Hemisphere and in the tropics and subtropics.

Although we cannot predict what is going to happen with this upcoming influenza season it is quite possible that we will continue to see co-circulation of influenza A (H3N2), 2009 H1N1, and Influenza B virus strains.

Now regarding Oseltamivir resistance, there have been sporadic Oseltamivir resistant 2009 H1N1 virus strains identified infections of persons in the US. This has also been reported sporadically worldwide.

There have been very rare episodes of limited transmission but the public health impact has been very limited to date.

We do expect that there may be additional sporadic cases of Oseltamivir resistant 2009 H1N1 virus infections during the season. And therefore ongoing surveillance for Oseltamivir resistance and other antiviral resistance among circulating influenza virus strains is really essential.

We need to monitor this to help inform clinical use of antiviral drugs. But currently there is no evidence of ongoing transmission of Oseltamivir-resistant 2009 H1N1 virus strains worldwide or H3N2 virus strains worldwide. So that's good news.

So what we're seeing is for the most part is circulating influenza virus strains this season are so far susceptible to Oseltamivir and Zanamivir.

Slide 19 just summarizes this. I'll just say that the row for Adamantanes just they're not recommended. So the good news is that for Oseltamivir and Zanamivir both for H3N2 2009 H1N1 as well as Influenza B strains circulating, these are susceptible.

So Slide 20 is a summary of the treatment efficacy and effectiveness studies. So Oseltamivir or Zanamivir can reduce the duration of uncomplicated

Influenza A or Influenza B illness by approximately 1 to 1.5 days when administered within 48 hours of illness onset and this has been shown in randomized placebo-controlled clinical trials predominantly among previously healthy outpatients.

There is one observational study of 2009 H1N1 which indicated that early Oseltamivir treatment reduced the progression to chest x-ray confirmed pneumonia.

There are no published randomized clinical trials for antiviral treatment of hospitalized patients with severe influenza.

However there are observational studies of hospitalized patients with either seasonal influenza, although these are primarily have been conducted among elderly patients, or 2009 H1N1 conducted among all ages including pregnant women.

And these all indicate that early neuraminidase inhibitor treatment primarily with Oseltamivir is associated with reduced morbidity and mortality.

And initiation of Oseltamivir treatment up to less than five days from illness onset is associated with reduced risk of admission to the intensive care unit or death.

It’s important to realize that these are uncontrolled studies. They are observational but they all do point to the same direction of benefit with early treatment.

But treatment up to about five days, less than five days from illness onset can have some effectiveness in reducing the risk of severe morbidity or mortality in patients who were hospitalized with complications of influenza.

There are limited data on the effectiveness of Zanamivir or Oseltamivir treatment in preventing serious influenza related complications such as those with bacterial or viral pneumonia or exacerbation of chronic diseases.

Slide 21, the benefits of antiviral treatment clearly are when greatest if treatment is initiated as soon as possible after illness onset especially within the first 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.

Slide 22, during the influenza season clinicians should consider influenza virus infection as a possible cause of any febrile illness requiring hospitalization during influenza season, and consider empiric antiviral therapy in patients with suspected influenza as clinically known as indicated. Consider influenza testing if testing will influence clinical treatment decisions, but be aware of the limitations of influenza tests and how to correctly interpret test results.

Clinicians should monitor local state and national recommendations and data during the influenza season to determine the most appropriate treatment practices.

This is available on the CDC Web site throughout the season. And clinicians can also consult influenza surveillance data regarding updates on influenza resistant profiles of circulating influenza virus strains also can be found in the CDC Web pages Weekly Influenza Surveillance Report.

And overall, treatment decisions should be informed by knowledge of influenza activity in the local patient's community population.

So to summarize again on Slide 23 empiric antiviral treatment is recommended for certain patients with suspected influenza.

Treatment initiation should not be delayed while awaiting specimen collection or influenza testing results.

If treatment is indicated patients should continue to receive antiviral treatment regardless of initial test results if negative until an alternative diagnosis can be established.

And clinicians who prefer not to treat empirically should discuss the signs and symptoms of worsening influenza illness with patients and arrange for follow-up by telephone or in the clinic in person.

So on Slide 24 just to go over the treatment recommendations for 2010-2011, 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 on the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, are 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. Although all children less than two years old are at risk for severe complications from influenza, the risk is highest among young infants aged less than six months old because many children with mild febrile respiratory illness may have other viral infections - for example RSV, rhinovirus, para-influenza virus infection, human metapneumo virus infection.

Knowledge about other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions by pediatricians, and family practitioners and emergency physicians.

Slide 25, persons at higher risk for influenza complications who are recommended for antiviral treatment for suspected or confirmed influenza include the following.

These are essentially all the high risk groups that I mentioned previously with the exception of children.

Instead of less than 5 years old, we're emphasizing children younger than 2 years old and also know that the risk is highest among those less than 6 months old.

The rest are the same high risk groups which include adults 65 years of age and older, persons with certain chronic medical conditions, persons with immunosuppression, pregnant women or postpartum women up to two weeks after delivery, persons less than 19 years of age receiving long term aspirin therapy, American Indians and Alaska natives, morbidly obese persons and residents of nursing homes and other chronic care facilities.

Slide 26, we also want to emphasize that for outpatients, antiviral treatment with a neuraminidase inhibitor is recommended for all persons with confirmed or suspected influenza who are at higher risk for influenza complications due to age or underlying conditions as just noted.

Antibacterial therapy plus antiviral treatment is recommended for patients with community acquired pneumonia when influenza is also suspected. Note that data on the effectiveness of antiviral treatment of critically ill patients are very limited.

So on Slide 27 another important point to emphasize is that previously healthy non-high risk symptomatic outpatients with confirmed or suspected uncomplicated influenza, these patients can be considered for antiviral treatment based upon clinical judgment if treatment can be initiated within 48 hours of illness onset.

In other words, we are not saying do not treat these individuals who were previously healthy (non-high risk) persons, if they have uncomplicated influenza - either confirmed or suspected.

We’re saying that if they present and can be treated early within 48 hours of illness onset, clinical judgment can be used to base treatment decisions.

In general, these kinds of patients, previously healthy, non-high risk outpatients with suspected or confirmed uncomplicated influenza, typically do not require treatment.

They'll generally resolve their illness without antiviral treatment. But early empiric treatment my provide benefits such as shortened duration of illness or reduced risk of clinical progression.

And again these patients are not likely to benefit from treatment if antiviral treatment is initiated greater than 48 hours after illness onset.

Persons with influenza who are already beginning to recover do not need antiviral treatment.

So on Slide 28 this is basically a summary of various testing results and the preferred medication. But in general the best simplest summary is to say that Oseltamivir or Zanamivir are the recommended antiviral medications for treatment.

Slide 29, there are some concerns or special treatment issues for patients who are hospitalized with confirmed or suspected influenza, and these patients by definition have more severe complications of influenza requiring hospitalization.

Antiviral treatment regimens might need to be altered in certain clinical circumstances. For example, clinical judgment should be utilized regarding whether to extend treatment duration longer than five days (which is standard duration of therapy) for patients who have prolonged illness.

There are no controlled data at the moment, at least not published that are available to evaluate the effectiveness of higher doses of antivirals to treat severe influenza illness, in other words standard versus higher dose.

Some data have been presented but not published. And some clinicians have utilized higher doses, particularly of Oseltamivir, in more severely ill patients. Some clinicians have also utilized twice the duration - up to ten days or even longer for patients in the intensive care unit.

Some clinicians have administered Oseltamivir via nasogastric or oral gastric tube. Studies, limited studies have documented that this can provide systemic absorption in some critically ill patients. And this has been done particularly in patients with suspected or documented mal-absorption. However - or I'm sorry. This may not be - let me just clarify. Oseltamivir down - administered through a nasogastric or an oral gastric tube may have some problems with systemic absorption from the gastrointestinal tract if there is gastric stasis or bleeding, …mal-absorption. So some clinicians have utilized parenterally administered intravenous neuraminidase inhibitors.

And during the 2009 H1N1 pandemic there was use of intravenous Peramivir under an emergency use authorization. This expired on June 23, 2010.

It is important to realize that neuraminidase inhibitors for intravenous administration are not approved in the United States.

Slide 30, however it is important to realize that intravenous Zanamivir is available for compassionate use via emergency IND. And this is available through the manufacturer. And the FDA should also be consulted on that.

And this would be indicated in patients particularly in certain circumstances again, documented or suspected malabsorption, patients who may have Oseltamivir resistant virus infection who are severely ill.

However it's really important to understand that clinical trials are needed to better understand optimal treatment approaches especially regarding treatment of severely ill patients, critically ill patients, patients receiving intravenous antiviral drugs or intravenous neuraminidase inhibitors.

Now clinicians who are interested in eligibility and potential enrollment of patients in clinical trials of experimental intravenous antivirals such as intravenous Zanamivir or intravenous Peramivir or for that matter combination antiviral treatment should consult www.clinicaltrials.gov for information about current ongoing clinical trials if a patient might potentially benefit from these.

So I would urge clinicians who are caring for patients particularly if they're severely ill to consult clinical trials.gov if they're considering certain combinations of antiviral treatment or parenterally administered neuraminidase inhibitors such as Zanamivir and Peramivir.

So Slide 31, patients who are hospitalized who are receiving antiviral treatment but not responding to treatment - either no improvement or worsening progression of illness, clinicians should consider the potential for infection with an antiviral resistant influenza virus and to change antiviral treatment.

In addition, antiviral resistance testing may be available through consulting the state health department or CDC.

Now in patients with suspected or confirmed influenza in the inpatient setting, and especially those who are caring for immunocompromised patient in an inpatient setting, it's a very, very important to emphasize that rigid and very, very good infection control measures and adhering to those recommended infection control measures are especially important to reduce the risk of transmission of influenza but particularly of antiviral resistant influenza virus strains including Oseltamivir resistant influenza virus strains.

And because severely immunosuppressed and immunocompromised patients have developed Oseltamivir resistant influenza virus infection while on Oseltamivir is important that infection control measures be followed to prevent transmission if Oseltamivir resistance is to emerge.

Now Oseltamivir resistance, especially within one week of treatment or following the initiation of treatment even later has been reported among severely immunosuppressed and immunocompromised patients with 2009 H1N1 treatment.

Now page - Slide 32. Chemoprophylaxis with antiviral medications is not a substitute for prevention of influenza.

Influenza vaccination when vaccine is available is the primary means for prevention of influenza.

There are certain patients in whom influenza vaccination may be contraindicated or may be thought to not be immunogenic.

For example, very severely immunosuppressed or immunocompromised patients and in some patients chemoprophylaxis with antiviral medications can be considered.

The likelihood of compliance and adverse events should be considered when determining the timing and the duration for administering antiviral chemoprophylaxis.

Indiscriminate use might use - might promote resistance if infection does occur. It also could reduce antiviral availability for treatment of persons at high risk in certain circumstances if there are limited availability.

If failure to complete a course of Oseltamivir for chemoprophylaxis due to gastrointestinal adverse events does occur, this could potentially lead to antiviral resistance if infection is established.

Now Slide 33, decisions regarding whether antiviral chemoprophylaxis should be initiated should take into account the exposed person's risk for influenza

complications, the kind of exposure, duration of contact and recommendations from public health.

Clinical judgment is very, very important. And in general, post exposure chemoprophylaxis should only be used when antivirals can be started within 48 hours of the last exposure. And it's only in certain circumstances when this should be utilized.

Slide 34, early treatment- early antiviral treatment really should be emphasized and it is an alternative to chemoprophylaxis in managing some persons who have had a suspected exposure to influenza virus in a symptomatic person. Such persons should be counseled about the early signs and symptoms of influenza. They should be advised to immediately contact their healthcare provider especially if they're at high risk for complications and to seek early treatment if clinical signs or symptoms develop.

They should be counseled about potential adverse effects of antivirals. And also they should be aware that following antiviral chemoprophylaxis if they are not vaccinated they are susceptible to influenza virus infection after stopping antivirals.

Healthcare providers should use clinical judgment regarding situations where early recognition of illness and treatment might be an appropriate alternative.

Slide 35, post exposure chemoprophylaxis with neuraminidase inhibitors - either Zanamivir or Oseltamivir - should generally be reserved for those who have had recent close contact with a person with influenza.

And such persons who can be considered for chemoprophylaxis are those who are family members or close contacts of a suspected or confirmed case who are at higher risk of influenza complications who have not been vaccinated against the influenza virus strains circulating at the time of exposure, so also this can be considered for residents of institutions during confirmed or suspected influenza outbreaks.

Also for unvaccinated health-care workers. However they should clearly be recommended for influenza vaccination.

We do have a universal influenza vaccination policy for all persons in the US age 6 months and older.

And in unvaccinated healthcare workers who have occupational exposures and do not have adequate personal protective equipment at the time of exposure (not following recommended infection control precautions), they can be considered.

Slide 36, either Oseltamivir or Zanamivir is recommended for chemoprophylaxis of 2009 H1N1, H3N2 or Influenza B virus infection.

Persons who receive an antiviral medication for chemoprophylaxis may still acquire influenza virus infection and might be able to transmit infection even if clinical illness is prevented.

And anti-viral chemoprophylaxis is approximately 70% to 80% effective in preventing illness but again does not necessarily always prevent influenza virus infection when exposure to drug sensitive virus occurs.

Slide 37, patients given post exposure chemoprophylaxis should be informed Again that chemoprophylaxis lowers but does not eliminate the risk of influenza virus infection or illness.

Be informed that susceptibility to influenza returns once the antiviral medication is stopped that these patients should be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness and that might be consistent with influenza.

Now of course such patients should also be recommended for influenza vaccination.

When post exposure chemoprophylaxis is given, it should be typically given up to seven to ten days after the last known exposure to a close contact influenza.

Slide 38, pre-exposure chemoprophylaxis should only be used for patients who are at very high risk of influenza related complications such as persons who are severely immunosuppressed and/or immunocompromised who are contraindicated or might for influenza vaccination and/or who might not develop a good immune response to influenza vaccine and cannot otherwise be protected when there's a high risk for exposure.

Use should be in accordance with the current recommendations from CDC or local public health authorities and when used, pre-exposure chemoprophylaxis should be given for the duration of time when exposure might occurred and also up to one week, seven to ten days following exposure if it does occur.

To be maximally effective the drug must be taken every day for the duration of influenza activity in the community in a patient that might be exposed to that. Prolonged use of antivirals could potentially cause some other effects.

Data are only available for chemoprophylaxis about up to eight weeks - six to eight weeks.

There are studies in progress for up to 12 weeks. So long term chemoprophylaxis events are not quite well understood beyond eight weeks.

Slide 39, in community studies of healthy adults who are – have been given antiviral medications during influenza season, both Oseltamivir and Zanamivir had similar efficacy in preventing febrile lab confirmed influenza illness.

These studies have also demonstrated efficacy for and effectiveness for prevention of influenza among patients in institutional settings.

Data are limited on the efficacy but there are some data describing the effectiveness of antiviral agents preventing influenza among severely immunocompromised patients.

Slide 40, it's important to note that the vast majority, greater than 99% of circulating Influenza A and B viruses, currently are susceptible to Oseltamivir.

In the past we did have seasonal influenza A (H1N1) viruses that had high prevalence of resistance to Oseltamivir.

However seasonal influenza A (H1N1) virus strains have not been detected in the US since 2009. And what we're seeing in terms of H1N1 viruses are the pandemic virus, now a seasonal virus (2009 H1N1 virus strains). These are susceptible to Oseltamivir and Zanamivir.

Again you can see our weekly influenza surveillance report which does have information about antiviral resistance and susceptibility.

And we will change our recommendations if influenza surveillance data indicate a concern about antiviral resistance to Oseltamivir or Zanamivir.

So Slide 41 regarding control of influenza outbreaks in institutions, certainly antiviral drug treatment and chemoprophylaxis are very important for outbreak control of influenza in institutions with patients at higher risk for influenza complications.

Certainly influenza vaccination is recommended for all residents as well as staff of such institutions. Neuraminidase inhibitors have been used to successfully control outbreaks when combined with other infection control measures and influenza vaccination.

Zanamivir should be used with persons who require chemoprophylaxis due to Oseltamivir resistant strains either documented or suspected.

Respiratory specimens from ill persons and suspected outbreaks should be obtained for influenza typing, Influenza A virus sub typing, viral culture to

assess antiviral resistance and provide data on outbreak, the etiology of the influenza outbreak. PCR can also be used.

Chemoprophylaxis if it's indicated, Oseltamivir or Zanamivir, should be started as early as possible and some situations that may be helpful to have preapproved orders from physicians and plans to obtain orders for antiviral medications for treatment or chemoprophylaxis on short notice.

Slide 42, when influenza outbreaks are suspected or documented and antiviral chemoprophylaxis is used, it should be administered to all eligible residents particularly those who are exposed regardless of influenza vaccination status, because especially for long term care facilities because elderly residents may actually have somewhat decreased effectiveness to prevent infection for influenza vaccination.

When chemoprophylaxis is administered, Oseltamivir or Zanamivir should be - the duration should be continued for a minimum of two weeks and actually then should be continued if new cases continue to be identified and continue until approximately ten days after the illness onset in the last identified patient.

Certainly unvaccinated staff should be offered influenza vaccination and antiviral chemoprophylaxis can be offered to those who are unvaccinated and then two weeks following vaccination especially for those healthcare personnel caring for high risk persons.

There should clearly be other measures taken to reduce contact between patients taking antiviral drugs for treatment and other persons including those taking antiviral chemoprophylaxis.

There are measures such as isolation of symptomatic persons or cohorting if possible and the use of recommended personal protective equipment.

Slide 43, these include institution of droplet and contact precautions, re-offering again influenza vaccination, restricting staff movement between wards and buildings, screening and restricting contact between ill staff, ill visitors and patients.

And just to conclude Slide 44, if you can read this it basically the point is to show the recommended dosage of Zanamivir and Oseltamivir for treatment or chemoprophylaxis.

And for pediatric providers, pediatricians, family practitioners emergency physicians, it’s important to note that for children dosing is based upon weight and age. For adults there are standard dosing. And the standard treatment duration is five days.

You can consult this either on our Web sites or sorry, on our Web sites if you can't read this.

And just on Slide 46 just again to repeat that during the 2009 H1N1 pandemic under an emergency use authorization, Oseltamivir was approved for treatment less than one year of age down to birth. And we are continuing to recommend this.

Although it is important to realize that Oseltamivir is approved by FDA for use in persons aged one year and older. So this is an off label recommendation but there was good experience during the 2009 H1N1 pandemic on the use of Oseltamivir down to birth.

So in general we recommend treatment for patients but for chemoprophylaxis generally 3 months and older. And so with that I'd like to conclude. Thank you.

Loretta Jackson Brown: Thank you Dr. Uyeki for providing our COCA audience was such a wealth of information. We will now open up the lines for the question and answer session.

And thank you. If you would like to ask a question, please press star 1. Please un-mute your phone and record your name clearly when prompted. Your name is required to introduce your question.

If you need to withdraw your request press star 2. Again to ask a question press star 1 and record your name. It will be one moment for the first question.

And we have a question from Dr. Robert. Your line is open.

This is Dr. Robert Balls, South Carolina Department of Health. Tim, nice presentation.

Quick question, in persons with early garden-variety suspected influenza we have no test or objective clinical sign to predict which of these persons will progress clinically especially to ARDs and which will do well early on.

So why not simply recommend antiviral therapy with a neuraminidase inhibitor for all such patients whether they're tested or not and recommend to them that they report back if treatment side effects occur which are rare mild and reversible as opposed to limiting the recommendations and advising them to report back when they deteriorate into ARDs.

Tim Uyeki: Balls thanks so much for that question. I think that just to clarify what we're most concerned about is are persons who have medical conditions or who by age considerations (elderly persons or very young children) who are at higher risk for severe complications of influenza.

So clearly there's no doubt about those persons are recommended for empiric early treatment if possible.

Now what you're talking about I think is persons who are not at high risk, so previously healthy persons who have early symptomatic uncomplicated influenza.

And in those persons we are not saying do not treat such persons. What we are saying is that certainly clinical judgment can be utilized and it's up to the clinician, you know, to treat, to make a treatment decision.

So just to clarify, I think there was some confusion during the pandemic. Again we were prioritizing among persons at higher risk for complications

and really emphasizing early treatment of such persons as well as hospitalized patients.

But now we're continuing those recommendations but also clarifying that we never have said do not treat previously healthy non-high-risk persons early with uncomplicated influenza.

We're saying that you, you know, clinical judgment can be utilized. So I think part of it also depends upon availability of antiviral medications.

You're quite right that in the outpatient setting particularly because the influenza tests that are available for the most part for the primary care clinician are rapid influenza diagnostic tests and there are some important limitations, notably the suboptimal sensitivity of rapid influenza diagnostic tests. So a negative test result does not exclude influenza virus infection.

And during influenza season particularly when there's high peak influenza activity in the community there can be many false negatives.

So in fact empiric Oseltamivir or Zanamivir treatment, early treatment of such non-high-risk previously healthy persons, if it can be initiated early, you know, certainly based upon clinical judgment is certainly okay.

And it's also important to realize that our recommendations are just recommendations. They are not the law.

Certainly any decision to initiate or not to initiate antiviral treatment for confirmed or suspected influenza is a - is based upon clinical judgment. So it's

a clinical decision from the provider. So certainly we are not saying don't do that. We permit that.

It is, you're quite right, while it is true that most persons, previously healthy non-high-risk persons with uncomplicated influenza will resolve their illness without antiviral treatment, there are clearly some of those individuals who will progress into influenza complications. And some of those complications include secondary bacterial infection.

So just to clarify fully based upon clinical judgment, you know, we - that is okay. And clearly empiric antiviral treatment will treat some patients with - who do not have influenza.

Patients might have other acute respiratory virus infections. And clearly influenza antiviral medications only have efficacy and effectiveness against influenza virus infection particularly administered early as possible. So I hope that helps answer your question.

Robert Ball: Okay and as expected. Thank you.

Coordinator: And our next question comes from (Wendy). Your line is open.

(Wendy): Thank you. I just have a question about when you have a patient who's appropriately placed on chemoprophylaxis and then they develop classic symptoms and you need to transition from prophylactic dose to a treatment dose how do you recommend doing that and does it matter if it's a community-based patient versus a nursing home patient?

Tim Uyeki: So that's an excellent question. So in a situation where you have a high risk patient and a - particularly a patient who is institutionalized, these are patients who are at very high risk for severe complications and death.

And I think that what you have there is several options. One is certainly to consider the possibility for an antiviral resistant infection.

So in other words if you started a patient on one antiviral medication for chemoprophylaxis and they did develop infection and illness one possibility is that they simply had a failure of chemoprophylaxis.

They do have infection with a sensitive virus so - sorry, yes a sensitive virus. So you would just increase the dose to a treatment dose.

But you must entertain the possibility of a drug-resistant virus infection and therefore you would change to a different antiviral medication.

And since we're recommending in general Oseltamivir and Zanamivir it would really mean most patients, particularly a patient in the long - an elderly long term care facility patient who may not be able to tolerate Zanamivir, orally inhaled Zanamivir would be taking Oseltamivir chemoprophylaxis.

If that's the situation you might consider going to Zanamivir treatment although there are some issues with elderly patients and drug delivery.

So I think you need to consider both the potential that it still could be a drug sensitive virus infection in which you - first thing you would do is increase to a treatment dose.

But you might want to send specimens for antiviral resistant testing. You would want to contact your local and state public health department and then they can contact us at CDC.

But another is to change to a different antiviral medication. The problem is is that we have limited, you know, there aren't many antiviral drugs that are approved that you really have to turn to.

And in such a patient if they are developed - to develop worsening, you know, more severe disease, you know, certainly other supportive care hospitalization must be considered and also the potential for secondary invasive bacterial infection needs to be considered.

So I think you ask a great question. In a patient who is not, you know, you asked in the community setting. I think in general we're talking about a high risk patient here because most non-high-risk patients would not be on chemoprophylaxis.

And so I think that patient has to be watched very carefully. But again you have two options. One is to go to a treatment dose or another is to switch to the other class of - sorry, the other antiviral medication.

But it I think there are potential drug delivery issues. So I think that patient has to be monitored extremely closely.

(Wendy): Okay thank you.

Coordinator: And the next question comes from (Andrea).

(Andrea): Yes hi. Thank you for your presentation. I had a question about what your recommendation would be for when healthcare workers that are ill with influenza like illness in the setting of an outbreak on a psych ward should be permitted to return to duty?

Tim Uyeki: Well I guess the first thing I would say is that in such a situation the local public health department and the state health public department should be involved, should be consulted and they could provide recommendations.

But in general in an outbreak institutional outbreak setting documented or suspected influenza if you have ill healthcare workers, they should not - they should be excluded from the workplace. They should not be working. They should be in fact if they're not vaccinated they should be vaccinated.

And clearly someone, even if they are vaccinated, this is a situation in which one, they should be considered for antiviral treatment especially if they're recommended if they're high risk for complications.

If they are not at high risk for complications I think they can still be treated based upon clinical judgment.

But also this is where some influenza testing might be useful. And by influenza testing I think that one has to be careful about what tests are used and the interpretation of those tests. So it depends upon what influenza tests are available to you.

But certainly in an outbreak situation in an institution where there are high risk patients an ill healthcare workers should not be permitted to care for those patients, should be excluded from the workplace. They should be considered to have influenza until proven otherwise.

But they may have some other respiratory virus infection in which case they should be exposing other patients or healthcare providers as well. So an ill healthcare provider should not be working until they resolve their illness.

(Andrea): Thank you very much.

Loretta Jackson Brown: Operator we have time for one more question.

Coordinator: And (Kathy) your line is open.

(Kathy): Yes in the outpatient setting with people who have been vaccinated in the two groups of people at high risk for complications and those not at high risk should they be treated if they present with an influenza like illness?

Tim Uyeki: Thank you very much for that question. I think it's important to realize that influenza vaccination, while generally the effectiveness is reasonably good there are certain patients in which, particularly elderly in which influenza vaccination is not as effective as in younger healthy persons.

And in any patient population influenza vaccination is not, influenza vaccine effectiveness is not 100%.

And therefore vaccinated persons even if there is a good match between circulating influenza virus strains and vaccine strains, certainly an influenza vaccinated person can actually - can be infected with influenza virus and develop illness.

And so influenza vaccine status should not be used to exclude a diagnosis or entertain a diagnosis of influenza virus infection.

And so someone who is presenting with influenza-like illness even if they have been appropriately vaccinated -- and again there is a universal influenza vaccination recommendation for all persons age 6 months and older in the US -- influenza vaccination is - status should not be used to again exclude influenza virus infection.

So the diagnosis of influenza should still be entertained and strongly considered in a patient with influenza like illness.

And this in a non-high risk patient again it's clinical judgment about whether to administer Oseltamivir or Zanamivir treatment early.

But in a high risk patient we do recommend early empiric antiviral treatment and certainly again for any patient with severe progressive or complicated illness regardless of whether they're high risk or non-high-risk. And in a hospitalized patient again, empiric antiviral treatment should be administered as soon as possible with Oseltamivir and Zanamivir.

And influenza vaccination status should not be a factor in excluding the diagnosis of influenza and deciding not to administer influenza antiviral medication. So thanks so much for that question.

Loretta Jackson Brown: 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 email is forwarded to him for a response. Again that email address is coca@cdc.gov.

The recording of this call and the transcript will be posted to the COCA Web site at emergency.cdc.gov/coca within the next few days.

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Thank you again for being a part of today's COCA conference call. Have a great day.

Coordinator: And that concludes today's call. Please disconnect your lines at this time.

END