Good afternoon. I'm Captain Ibad Khan and I'm representing the Clinician Outreach and Communication Activity, COCA, with the Office of Emergency Risk Communication at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA Call: 2025 - 2026 Clinical Recommendations for Seasonal Influenza Prevention and Control.

All participants joining us today are in listen-only mode.

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Content will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of Doctor Lisa Grohskopf's discussion of the CDC/ACIP influenza vaccination recommendations that include discussion of the unlabeled use of influenza vaccines in the recommendations for persons with a history of egg allergy and for solid organ transplant recipients ages 18 through 64 years. With regard to persons with a history of egg allergy, history of severe allergic reaction, for example anaphylaxis, to the vaccine or any of its components, which include egg for certain vaccines, is a labeled contraindication to receipt of most trivalent inactivated influenza vaccines and trivalent live attenuated influenza vaccine. However, ACIP recommends that all persons ages 6 months or older with egg allergy receive influenza vaccine. Any influenza vaccine, egg based or non-egg based, that is otherwise appropriate for the recipient's age and health status can be used. With regard to solid organ transplant recipients, ages 18 through 64 years, the trivalent high-dose inactivated influenza vaccine and the trivalent adjuvanted inactivated influenza vaccine are approved for persons ages 65 years or older. However, ACIP recommends that solid organ transplant recipients ages 18 to 64 years who are receiving immunosuppressive medication regimens may receive either the trivalent

high-dose inactivated influenza vaccine or the trivalent adjuvanted inactivated influenza vaccine as acceptable options, without a preference over other age-appropriate trivalent inactivated influenza vaccine or trivalent recombinant influenza vaccine.

In addition, content will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of Doctor Tim Uyeki's discussion that CDC recommends oseltamivir treatment for persons of all ages, FDA approval is for persons ages 14 days and older, and that CDC recommends oseltamivir treatment for hospitalized patients (FDA approval is for outpatients).

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At the conclusion of today's session, participants will be able to accomplish the following: Highlight key recommendations in the CDC Advisory Committee on Immunization Practices' document Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States 2025-2026 Influenza Season. Describe influenza testing recommendations in outpatients and in hospitalized patients with suspected influenza. And review antiviral medications for influenza and CDC's recommendations for antiviral treatment for patients with suspected or lab-confirmed influenza.

After the presentation, there will be a Q and A session. You may submit questions at anytime during today's presentation via the MS Teams platform. Please note that the ability to ask questions during the live webinar is limited to the first thousand attendees who joined the webinar. If you are unable to ask a question during the webinar, you may submit your question after the live session by emailing coca@cdc.gov. Kindly note that we receive many more questions than we can answer during our webinars.

If you are a patient, please refer your questions to your healthcare provider and if you are a member of the media, please contact CDC Media relations at 404-639-3286 or send an email to media@cdc.gov.

I would now like to welcome our presenters for today's COCA Call. We are very pleased to have with us Doctor Tim Uyeki, who's the Chief Medical Officer in the Influenza Division at the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention, and Doctor Lisa Grohskopf, who's a medical officer in the Influenza Division at the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention.

It is my pleasure now to turn it over to Doctor Uyeki. Doctor Uyeki, please proceed.

Thank you, Captain Khan. Today's presentation is an update on influenza, United States, 2025-2026 influenza season. Next slide.

So the findings and conclusions in this presentation are those of the speakers and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Next slide.

In this presentation, we will describe 2024-2025 seasonal influenza epidemiology and disease burden. We'll discuss 2024-2025 influenza vaccine effectiveness and influenza vaccine recommendations for the current 2025-2026 season, and we'll discuss influenza testing and antiviral treatment recommendations. Next slide.

We'll just start off with key points of this presentation. Last season, the 2024-2025 influenza season was a high severity influenza epidemic in the U. S. There was high morbidity and mortality and a wide range of respiratory as well as non-respiratory complications. Influenza vaccine effectiveness last season was moderate against both uncomplicated illness and severe disease in the U.S. Now we know that from our surveillance influenza activity is increasing in the U. S. right now, and therefore the time to get vaccinated for this season is right now for those persons aged 6 months and older who have not received influenza vaccine this season.

Molecular influenza tests are recommended and that includes rapid molecular tests for outpatients as well as rapid and other molecular tests for hospitalized patients, as well as the use of multiplex assays when indicated.

Influenza antiviral treatment is recommended as soon as possible for outpatients at increased risk for influenza complications. Ideally, antiviral treatment should be initiated within two days of illness onset with either oseltamivir or baloxavir. However, for progressive or severe disease regardless of the time since illness onset including greater than two days after illness onset, oseltamivir treatment is recommended. For hospitalized patients, oseltamivir treatment is recommended as soon as possible. Next slide, please.

So we'll just start off with some background information about influenza as well as influenza activity and disease burden. Next slide.

So background and seasonal influenza. This is a contagious respiratory illness caused by infection of the respiratory tract, particularly the upper respiratory tract with influenza A or B viruses and this is associated with seasonal influenza epidemics during fall, winter, and spring in temperate climates of the northern and southern hemisphere, including in the U.S. and worldwide. Transmission is via large and small infectious respiratory particles that are expelled from an infected person to a susceptible individual in close proximity. The incubation period from the time of exposure and infection to onset of symptoms is

approximately 1 to 3 days. So this is a short incubation period. The spectrum of infection ranges from asymptomatic infection, and most people experience mild, uncomplicated illness.

But there are some people that do progress to severe complications, including resulting in death. Signs and symptoms typically of uncomplicated influenza include an abrupt onset of signs and symptoms. This is not typically gradual onset of symptoms over a number of days, but typically abrupt onset and this may be fever or feeling feverish or chills, but not all patients with uncomplicated influenza actually manifest fever or feverishness. Non-productive cough is common. Sore throat, runny or stuffy nose, headache, muscle or body aches, and fatigue. Most people do experience uncomplicated influenza. Next slide.

However, there are people that do experience complications of influenza, and these include moderate or severe to critical complications. Examples of moderate complications include otitis media in young children or sinus infections, as well as exacerbation of underlying chronic disease that is not severe. However, there are many people that have underlying chronic disease that may not be well controlled or influenza may precipitate a very bad exacerbation of that underlying condition and that may require hospitalization.

There are many different respiratory complications of influenza, and most commonly that is pneumonia. Cardiac complications can occur, but they are more common in people particularly adults with underlying coronary artery disease, but in young children and in some adults there are rare complications that can occur in otherwise healthy persons. Neurologic complications there is a wide spectrum of neurologic complications that can be transient to very fulminate and bacterial co-infection, community-acquired is not uncommon to result in severe disease, and the most common bacterial that are associated with a bacterial co-infection with influenza requiring hospitalization, are Staphylococcus aureus, both methicillin sensitive and methicillin resistant, Streptococcus pneumoniae, and Group A streptococcus. There are musculoskeletal complications, inflammation of muscle tissue that can be mild, but in severe cases can result in muscle breakdown and rhabdomyolysis. Multi-organ failure occurs in patients with critical illness, particularly respiratory and renal failure as well as septic shock.

And don't forget healthcare-associated infections, in people, particularly who are intubated because both bacterial or fungal ventilator-associated pneumonia can occur. Next slide, please.

So influenza-associated encephalopathy [inaudible] common and most well described in children, this is a known complication of influenza. We do not have established U. S.

surveillance for this complication. Basically, it's influenza virus infection of the respiratory tract, can precipitate neurologic complications that manifest in impaired consciousness or altered mental status with brain dysfunction. This may be very transient over a number of hours and self-limited, but it also can be fulminant with progression to coma and death within 24 hours.

The most severe syndrome within influenza-associated encephalopathy is called acute necrotizing encephalopathy, or ANE, and what you see in the image is the two arrows point the bilateral thalamic inflammation, which is the hallmark of acute necrotizing encephalopathy.

Last season we started to hear about some of these cases in January and February, and we requested that clinicians and health departments report possible cases of an influenza-associated encephalopathy to CDC. We had 109 influenza-associated encephalopathy cases, 37 that had acute necrotizing encephalopathy. These were typically young children with a median age of five years, of note 55% were otherwise healthy without underlying medical conditions.

And of particular importance was that the vast majority of these cases were not vaccinated. Only 16% of vaccine eligible had received influenza vaccine last season prior to their illness. The median time from symptom onset of influenza to neurologic symptom onset was two days, so rather fulminant after influenza signs and symptoms that occurred. There was very high severity, 74% were admitted to a pediatric intensive care unit, 54% required invasive mechanical ventilation, and 19% died. And of those with acute necrotizing encephalopathy, ANE, 41% died. Next slide.

So we know from many kinds of studies, there are certain groups that are at increased risk for influenza complications and severe illness, and these include young children age less than two years, and adult 65 years and older, persons with chronic medical conditions, including pulmonary or cardiovascular, excluding isolated hypertension, and persons with underlying renal hepatic neurologic conditions, including those who have had a stroke, and neurodevelopmental, hematologic, metabolic or endocrine disorders, and those with certain disabilities. Persons who are immunocompromised persons with extreme obesity, children and adolescents who are receiving aspirin or salicylate containing medications chronically who might be at risk for Reye syndrome after influenza virus infection. Residents of nursing homes and other long-term care facilities. Pregnant women and those up to two weeks postpartum. People from certain racial and ethnic minority groups, including non-Hispanic, Black, Hispanic or Latino, and American Indian or Alaska Native persons. Next slide.

So last season was a predominantly influenza A season. There was a low amount of influenza B circulation, mostly occurring a little bit later in the season, and we had an almost even proportion of influenza A(H1N1)pdm09 viruses circulating as compared to influenza A(H3N2) viruses circulating, and the season overall peaked in late January, early February on a national basis, with some differences regionally as expected. Next slide.

So over a number of seasons and here are 10 season data from a number of seasons. And there is a wide range of severity from season to season. We know that some influenza epidemics are milder than others.

Last season was more severe, but typically there's an estimated range of 9. 3 million to 41 million illnesses due to influenza, resulting in approximately 120,000 to 710,000 hospitalizations and a range estimated from 6,300 to 52,000 deaths per season. So the bottom line is that there is a variability in the severity of influenza epidemics in the U. S. Next slide.

Now this is data from ten seasons, and what you see in the red dotted line is last season, and this is cumulative lab-confirmed hospitalization rates. So this is population-based surveillance, and you can see that last season had very high hospitalization rates. This is all ages compared to prior seasons. Next slide.

What this shows is a breakdown by age group. Same kind of data to highlight the fact that typically in an influenza season, the highest hospitalization rates, cumulative rates are in those 65 years and older followed by those 50 to 64 and then followed by young children. And of note, you can see that adults 18 to 49 years and school-age children typically have much lower rates of hospitalization due to lab-confirmed influenza than other age groups. Next slide, please.

When you look at children, same kind of data, cumulative influenza-associated hospitalization rates are highest the younger the age, and so you can see the highest are those less than one and then school-age kids and particularly adolescents have much lower hospitalization rates. Next slide.

What this slide illustrates looking at different age groups is that in older adults aged 65 years and older, you can see in the purple the deaths and the green the hospitalizations that older adults dominate hospitalizations and deaths due to influenza in the United States. Next slide.

Since the 2004, 2003 influenza season, pediatric influenza-associated deaths has been nationally reportable, so we've been tracking this for many years. What you see are four seasons, including last season, and unfortunately, these are the majority of these are preventable, and this is really, really tragic. Last season, the latest data of incorporated

data that will be presented in the weekly Flu View tomorrow, we had one more death reported, so 288 deaths reported for last season. This is the highest number of deaths for a seasonal influenza epidemic since we've been keeping track and clearly highlights the fact that we need to do a much better job of preventing influenza and preventing influenza-associated death in children in the United States. Next slide.

So last season preliminary estimates of last season's disease burden are that there are a range of 47- to 82 million influenza illnesses, resulting in 21 to 37 million estimated medical visits in an estimated 610,000 to 1. 3 million hospitalizations and a wide estimate of 27,000 to 130,000 influenza-associated deaths in the U. S. There will be in the a little bit in the near future there'll be some final estimates of influenza disease burden for last season. Next slide.

That's all to say that last season, by all indicators, was a high severity season and one of the highest that we have experienced in the U. S. Next slide.

In August of this year, CDC Influenza Division laboratory scientists identified a new influenza A(H3N2) virus, subclade K, which is antigenically drifted, compared with the influenza A(H3N2) vaccine virus for the 2025-2026 influenza vaccine. Now this has drawn a lot of attention with early season activity reported in a number of countries associated with this influenza A(H3N2) virus, subclade K. And we have not been experiencing such early influenza activity in the U. S. as some other countries, but influenza activity is now increasing throughout the U.S. and influenza A(H3N2) virus to date are the most frequently reported influenza viruses, although this is very early, and we cannot predict whether these viruses will predominate throughout the season, but among those H3N2 viruses that we have characterized so far at CDC this season, 87% belong to the subclade K.

And none of the three influenza A(H3N2) viruses collected this season in the United States were well-recognized by post-infections ferret antisera against Northern Hemisphere 2025-2026 influenza vaccine strains. Next slide.

[Inaudible] Flu View will be updated tomorrow as usual on a weekly basis every Friday, just to show that public health laboratories have reported that the vast majority of influenza viruses identified in the U.S. this season have been influenza A viruses. And of those, more than 75% have been this influenza A(H3N2) virus. And of those H3N2 viruses, the vast majority have been the subclade K. So there is still some influenza A(H1N1)PDMO9 viruses that have been identified, almost a quarter, but it's hard to say what will happen throughout the season, and that's why we need surveillance to really track this with a low proportion of influenza B viruses identified to date. Next slide.

So with that, I'm going to turn it over to Doctor Grohskopf.

Hey, thanks very much, Doctor Uyeki. I'm going to be taking you through a brief overview first of what is new in the 2025-2026 influenza vaccine recommendations. Next slide, please.

Now, in the interest of time, we're going to focus on mostly what's new, but I'm going to mention some of the old stuff too, just to remind folks. To summarize some of the top line items that are the same as last season as previously routine annual influenza vaccination is recommended for all persons aged 6 months and up without a contraindication to vaccination. So anybody in that age group 6 months and older who does not have a contraindication to receive flu vaccine is recommended to be vaccinated. And this is to protect against influenza and its complications.

Also as previously multiple formulations and brands of the trivalent influenza vaccine are available in the U.S. for the 2025-26 influenza season, including inactivated influenza vaccines or IIV3s, which are available in multiple brands. The recombinant influenza vaccine, or RIV3, also known as FluBlok. It's the brand name of that one. And the live attenuated influenza vaccine, or LAIV3, which is FluMist.

Also, similar this season, just a couple of things to mention. There are, like we said, a number of vaccines available, total of nine unique brands this season as it were last season. All are trivalent. Each has its own approved age range for approved use by FDA. In general, people should get a vaccine that is appropriate for their age. That is, it's been approved for their age.

The one exception is as Doctor Khan mentioned at the top, solid organ transplant recipients who are between the ages of 18 and 64 years and are on immunosuppressive medications can receive as acceptable options either the high dose inactivate or the adjuvanted inactivated vaccines. That is not a preferential recommendation. That's basically considered an acceptable option. They can also receive any other vaccine approved for their age.

Second point, we don't have any preferential recommendations for a particular vaccine for any one person. For most people, there's going to be more than one acceptable option, but the one exception is the preferential recommendation for adults 65 and older for whom the high dose vaccine, the recombinant vaccine, or the adjuvanted vaccine are preferentially recommended. If none of those are available, any other age appropriate vaccine is acceptable.

And lastly, also as mentioned at the top for egg allergy, we still get a lot of questions about egg allergy. Egg allergies are no longer a consideration for the selection of influenza

vaccines, any person with egg allergy of any severity can get any vaccine for influenza that's otherwise appropriate for their age and health status. So I'll go to the next slide now.

So now we're going to focus on what's new and the recommendations for this year. The 2025-26 influenza vaccination recommendations were published in MMWR on August 28 of this year. It's a shorter format this year that focuses primarily on updates for the season, but you will see some highlights of some things that were from the previous season, including the three things I just mentioned.

The new information just to summarize it quickly for 2025-26 is that we have the updated U.S. influenza vaccine composition. As you know, composition of flu vaccines is reviewed every year because influenza viruses are constantly changing. You can find more information about the exact composition and the influenza statement in the MMWR, but just to mention briefly, there's an update in the H3N2 virus for this season.

Second, we have the availability of FluMist, the intranasal live attenuated influenza vaccine, or LAIV3 as we abbreviate it, for self- or caregiver administration. We're going to go over that in another slide very shortly. Next, a new approved age range for FluBlok, which used to be recommended for 18 and up but now is recommend-- Sorry, approved for 18 and up, but now is approved for 9 years and up. We'll talk about that in another slide shortly.

And lastly, there's a new recommendation that only vaccines that do not contain thimerosal as a preservative are recommended for all recipients. So seasonal influenza vaccines, historically the multidose viral formulations, have contained thimerosal as preservative to prevent bacterial or other microbial growth. There's a recommendation for the season that only seasonal influenza vaccines that do not contain thimerosal as a preservative are recommended for all recipients. Next slide.

So this slide and the one that follows just have a little bit of updates on the two vaccines that had changes in their FDA licensing. The first, we're going to talk about is FluMist, LAIV3, which is now approved for self- or caregiver administration. Essentially, consumers can now order Flumist for delivery for eligible recipients. Eligibility screening is performed by an online pharmacy based on the ACIP criteria that currently exist for who is recommended to get FluMist or who is not recommended to get FluMist because LAIV is not recommended for some populations. LAIV is approved for self-administration for persons aged 18 through 49 years, or if the recipient is younger administration by an adult caregiver aged 18 or older if it's being given to a recipient aged 2 through 17 years. The ACIP recommendations regarding the appropriate populations, contraindications, or precautions to the use of LAIV are the same for self- or caregiver administration as they are for healthcare provider

administration. So of note, one thing to remember, LAIV is approved and recommended only for ages 2 through 49 years. So it has a bit of a narrower age band than some of other vaccines do, and it's not recommended in pregnancy, immunocompromised, and in certain other medical conditions which are detailed in the 2025-26 influenza recommendations. Next slide.

We next have a new approved minimum age for FluBlok, or RIV3. This is the recombinant influenza vaccine. It was previously approved by FDA for those 18 years and older. The new approved age indication is 9 years and older. This approval was based on a study which compared immune response and safety of Flublok among nine through 17 year olds with that among 18 through 49 year olds. Next slide.

So for a next topic, we're going to go over briefly, influenza vaccine effectiveness estimates, focusing primarily on work from our four CDC influenza vaccine effectiveness networks. Next slide.

CDC assesses influenza vaccine effectiveness annually through four networks, which provide estimates in the reduction in medically-attended influenza illness associated with influenza vaccination.

And these networks include the New Vaccine Surveillance Network, or NVSN, which examines influenza-associated medical encounters in inpatient and outpatient settings among children. The Virtual SARS-CoV, Influenza, and Other Respiratory Viruses Network, or VISION, which examines influenza-associated medical encounters in inpatient and outpatient settings among children and adults. The U. S. Flu Vaccine Effectiveness, or US Flu VE Network, which examines influenza-associated medical encounters in outpatient settings among children and adults, and the Investigating Respiratory Viruses in the Acutely Ill or IVY Network, which examines influenza-associated medical encounters in inpatient settings among adults.

So you see there's a bit of variance in among these four networks in the age groups they cover, and whether they cover inpatient, outpatient, or both. But taken together, these networks cover inpatient and outpatient influenza illness in both children and adults. Next slide.

Now, some of these networks you may have noticed by their names, they cover not just flu viruses but other respiratory viruses, but the results I'm going to present to you are focusing on flu only, and these are preliminary estimates for the season that just ended 2024-25.

So first up, we have preliminary influenza vaccine effectiveness estimates from the four networks for the pediatric population that is children aged 6 months through 17 years. Estimated vaccine effectiveness ranged from 32% to 60% for outpatient illness and 63 to

78% for inpatient influenza illness. All of these estimates are statistically significant. That means the 95 confidence interval does not cross 0. And also this is for all viruses, all subtypes.

As would be expected, there's some variability in the VE estimates among the networks, which might reflect regional variations in circulating viruses. The VE estimate is slightly lower here for U. S. Flu VE network compared with the other networks. This network had a higher proportion of subtype specimens that were H3N2 viruses at 67% compared for example with the NVSN for which the proportion that were H3N2 was 48%. Vaccine effectiveness overall is generally lower for H3N2 viruses than it is for H1N1 viruses. Next slide.

These are the preliminary 24-25 influenza vaccine effectiveness estimates from the same four networks for adults aged 18 years and older. Estimated vaccine effectiveness ranged from 36 to 54% for outpatient influenza illness and 41 to 55% for inpatient influenza illnesses. These estimates are also statistically significant.

Again, we see a slightly lower VE estimate from U. S. Flu VE Network, which again might reflect regional variations in circulating viruses, particularly the proportion that were H3N2 in circulation. Taken together, these interim estimates of 24-25 VE indicate that influenza vaccination was effective in preventing medically-attended influenza-associated illness in children, adolescents, and adults in the United States. Next slide.

So we've talked a little bit about the past 24-25 season. Having discussed that, we're going to pivot a little bit and briefly consider the season in front of us 2025-26. At this time, we don't really know what VE is going to be like for the season. Activity is really getting underway in the U. S., and it takes a little while before accumulating enough activity and specimens to be able to calculate VE.

As Doctor Uyeki mentioned, we had the new drifted H3N2 subclade called subclade K, which has been identified and which is antigenically different compared with the 25-26 influenza A(H3N2) virus. That is the virus that's represented in the current season vaccine. It's too early to know what impact exactly this new subclade will have on the influenza vaccine effectiveness for this season; however, early estimates of 25-26 influenza VE against influenza A(H3N2) virus associated hospitalizations in England, where the flu activity is described as having begun earlier than usual for the season, and which is also seeing a predominance of subclade K, VE estimates preliminary so far have remained within the expected range of 70 to 75% for children and 30 to 40% for adults, suggesting at this point that influenza vaccination remains an effective tool in preventing influenza-related hospitalizations for the season so far. Influenza vaccine effectiveness networks

continue to collect real world data to produce early estimates of influenza VE in the United States. Next slide.

And with that, I'm going to turn things over back over to Doctor Uyeki. Thank you for listening.

Thanks, Doctor Grohskopf. Now I'll cover influenza testing. Next slide, please.

So why use influenza tests? And the main reason is because a clinical diagnosis of influenza may be inaccurate, because influenza can present with non-specific signs and symptoms that overlap with other respiratory virus infections. And this is true both for uncomplicated illnesses as well as for severe illness.

Now we know from various epidemiologic studies that clinical predictors of influenza typically are abrupt onset of fever with cough, cough, fever, runny nose or muscle aches and then fever, particularly higher temperatures and cough. But use of influenza tests can really help guide clinical management decisions, and this includes whether to start antiviral treatment.

There are studies to suggest that identifying influenza may actually reduce prescriptions for unnecessary antibiotics, may reduce the use of other diagnostic tests, and actually will help inform infection prevention and control measures. Next slide.

So the point of this slide is that influenza viral shedding typically peaks within 24 hours of illness onset. You can detect influenza viruses in the upper respiratory tract of infected individuals one day before illness onset, and these virus levels peak within 24 hours after symptom onset. We know that the highest infectious period for most people who are immunocompetent is within three days after illness onset, and what you see from the figure on the right is that influenza viral RNA detection in the upper respiratory tract really drops off after two to three days after symptom onset.

So there are some exceptions and that is the very young children can be infectious for longer periods, and critically ill patients might have longer influenza viral replication in the lower respiratory tract. Next slide.

So what are the best respiratory specimens for detecting seasonal influenza viruses? So the best respiratory specimens are high up in the respiratory tract and that would be nasopharyngeal swabs, ideally collected within three to four days of illness onset. And these viruses can be generally detectable for about three to four days by antigen detection tests, but longer about five to six days by molecular assays in people with uncomplicated disease but for longer periods in infants and immunocompromised persons. Depending upon the test, other acceptable specimens may be nasal swabs, particularly mid turbinate

nasal swabs, nasopharyngeal aspirates, nasal aspirates, or combined nasal and throat swabs.

In general for detection of seasonal influenza A or B viruses, throat swabs will have the lowest yield, so you really want to go higher, highest up in the upper respiratory tract. And just to say that in immunosuppressed persons there can be longer viral replication and longer duration of virus detection. Now we know that in persons who have severe disease, particularly critical disease with, say influenza, viral pneumonia, there can be prolonged viral replication. And in fact, some patients may be able clear influence of viruses in the upper respiratory tract, but still have ongoing replication in the lower respiratory tract and we have some data from the 2009 H1N1 pandemic when the diagnosis of influenza in some critically ill patients, these are adult patients, was made by actually using bronchial lavage fluid specimens for testing when upper respiratory tract specimens tested negative for influenza. Next slide.

So there's a wide range of influenza diagnostic tests available to detect influenza viruses and respiratory specimens. These differ by the time to produce results, what information is actually available, what are approved respiratory specimens, and what is the approved clinical settings and they also vary by accuracy.

So in general there are the antigen detection tests and some of these are multiplex assays and some are also available for over the counter use at home. The others are nucleic acid detection, referred to as molecular assays. They're both single plex as well as multiplex assays that detect other respiratory viruses, particularly SARS-CoV-2. And there's one molecular test that can be used over the counter at home. Some of these tests are CLIA-waived for point-of-care that can be done at the bedside or in any clinic. And others, the majority are moderately complex, which require testing in a clinical laboratory. And then there are highly complex tests that require testing to be done in large clinical laboratories or public health laboratories. Next slide, please.

So a summary of these kinds of tests are the rapid antigen detection tests that can produce a result in 10 minutes. You get only an influenza A or type A or type B result. No influenza A subtype information. The advantage is a quick result. The disadvantage is low to moderate sensitivity compared to molecular assays.

There are some multiplex antigen assays as I mentioned that are antigen detection tests that can detect SARS-CoV-2 as well as other respiratory viruses. Now the molecular assays, as I mentioned, have much higher accuracy. They have much-- They have moderate to high sensitivity and both antigen tests and molecular tests have high specificity, suggesting that false positive results are low with either kind of test; however, with the rapid

diagnostic tests, false negative results are more likely, particularly during peak community influenza activity. There are some molecular assays that don't produce results so timely. The rapid assays do produce results in 15 to 30 minutes, but others may take an hour or several hours to do.

The most important issue is to properly interpret the test results, especially when interpreting negative results and thinking about-- [Inaudible] and actually might have influenza in interpreting the results properly, particularly those of antigen detection test. Next slide.

So recommended influenza tests for outpatients are rapid influenza molecular assays. These are recommended over rapid influenza antigen tests and again it's because of the higher sensitivities of the rapid molecular assays.

For hospitalized patients molecular assays are recommended, including RT-PCR and rapid antigen detection tests, immunofluorescence assays, which are also antigen detection tests, these are not recommended, and should not be used unless molecular assays are not available at a hospital.

For immunocompromised patients, one should also consider other respiratory viruses, and so multiplex assays that target a wide panel of respiratory pathogens, including influenza A and B viruses, are recommended. Some key points for clinicians, do not order viral culture for initial or primary diagnosis of influenza, because the results will not be timely to inform clinical management of the patient and do not order serology for influenza because this requires a collection of paired acute and convalescent serum specimens collected two to three weeks apart, and that serological testing needs to be done at specialized laboratories. Next slide.

So self-knowledge check. Which influenza tests for respiratory specimens are recommended to inform clinical management of hospitalized patients with suspected influenza? Select all that apply.

A. Rapid influenza molecular assays. B. Rapid shell vial culture. C. RT-PCR influenza assays. D. Multiplex rapid antigen assays. E. Multiplex immunofluorescence viral respiratory panel assays. Or F. Multiplex molecular assays. Next slide.

So the answer is A. Rapid influenza molecular assays. C. RT-PCR influenza assays, and F. Multiplex molecular assays. And the rationale is that molecular influenza assays are recommended due to high sensitivities to detect influenza viruses in respiratory specimens. However, antigen tests including multiplex immunofluorescence and multiplex antigen tests and viral culture are not recommended for hospitalized patients with suspected influenza. Next slide.

Let me move on to summarize influenza antiviral treatment. Next slide.

So recommended antivirals for treatment of influenza this season. There are four FDA-approved antivirals that are recommended, and there is no evidence of resistance among circulating seasonal influenza A or B viruses to these recommended antivirals. And all of these have demonstrated efficacy in randomized control trials versus placebo, and they are FDA-approved for early treatment within two days of illness onset in outpatients with uncomplicated influenza, and these include two classes, the neuraminidase inhibitors and the cap-dependent endonuclease inhibitor. So the neuraminidase inhibitors block the release of influenza viruses from infected cells. They do not kill viruses, but they result in the reduction of the spread of influenza viruses in the respiratory tract.

The most commonly used and recommended antiviral that's a neuraminidase inhibitor is oseltamivir. Zanamivir and Peramvivir are also available, although less widely available, and there's one cap-dependent and a nuclease inhibitor called baloxavir marboxil. We refer to it as baloxavir, and this antiviral, in contrast to the neuraminidase inhibitors, baloxavir inhibits influenza viral replication and is associated with a reduction of influenza viruses in the upper respiratory tract rapidly within 24 hours of treatment.

So you can see the table there lists the antiviral drugs with different routes of administration and different recommended ages for treatment. I'll just say that oseltamivir and zanamivir are given twice daily for five days. Peramivir is a single intravenous infusion, and baloxavir is a single oral dose. Next slide.

So our antiviral treatment recommendations are focused on prompt treatment of persons with severe disease and those at increased risk of influenza complications. Antiviral treatment is recommended and has the greatest clinical benefit when started as soon as possible for patients with confirmed or suspected influenza who are hospitalized and this includes without waiting for testing results if influenza is suspected. And this would be either oral or enteric oseltamivir treatment, enteric for those who are intubated, who are not able to take an oral medication.

Outpatients with complicated or progressive illness of any duration oral oseltamivir is recommended, and outpatients at high risk for influenza complications oral oseltamivir or oral baloxavir are recommended if the patient has presented within 48 hours of symptom onset.

Now for otherwise previously healthy, non-high-risk outpatients with confirmed or suspected influenza if they present early antiviral treatment can be considered with either oral oseltamivir or oral baloxavir, but we do really focus on those that are more severely ill or at high risk for progression to severe complications of influenza. Next slide.

So there are some special populations just to say that for pregnant women oseltamivir is recommended for treatment of influenza, as well as in those women up to two weeks postpartum. Baloxavir is not recommended for treatment of pregnant women or breastfeeding mothers. And the reason is that there's a lack of efficacy or safety data for baloxavir in pregnant or lactating women. In contrast, there are substantial global evidence of oseltamivir safety for pregnancy and birth outcomes there's no concern.

For immunocompromised persons because severely immunocompromised persons in particular can have prolonged influenza viral replication with emergence of antiviral drug resistance during and after treatment, monitoring for antiviral resistance is advised with serial collection of respiratory specimens and influenza testing, and infection prevention and control precautions are recommended to reduce nosocomial transmission risk in healthcare settings. Neuraminidase inhibitor treatment is recommended, for example with oseltamivir, and baloxavir monotherapy is not recommended because of the increased risk of resistance emergence compared to oseltamivir. Now combination antiviral treatment with antivirals of different mechanisms of action, for example, you could use oseltamivir and baloxavir, this can be considered. There are some clinical trials in progress. Next slide.

So let me just quickly summarize some of the evidence that we have. So for oseltamivir, randomized controlled trials have shown that oseltamivir treatment has significant clinical benefit when started within 36 to 48 hours after illness onset versus placebo for uncomplicated influenza. There's a pulled meta-analysis of five randomized control trials in children. When treatment was initiated with oseltamivir within 48 hours of illness onset, symptom illness duration was reduced by 18 hours, overall. When you exclude children that had asthma, there was a reduction in illness duration by 30 hours, with oseltamivir treatment in children without asthma compared to placebo and overall there was a reduced risk of otitis media by 34%.

It's important to also realize there was a increased risk of vomiting in children with influenza treated with oseltamivir versus placebo. A pooled meta-analysis or randomized controlled trials in adults when treatment was started with oseltamivir within 36 hours of illness onset, there was a reduction of illness duration by a little more than a day. And there was a 44% reduction in the risk of lower respiratory tract complications occurring more than 48 hours after treatment requiring antibiotics. There was also an increased risk of nausea in adults treated with oseltamivir versus placebo. Next slide, please.

So there are many different observational studies of oseltamivir effectiveness in hospitalized influenza patients. The vast majority of these show [inaudible] treatment that there is effectiveness with oseltamivir treatment and hospitalized influenza patients in the trend is that the earlier you initiate antiviral treatment with oseltamivir right at the time of

hospitalization or shortly thereafter compared to later initiation of treatment or no treatment in hospitalized patients with influenza. There is much greater clinical benefit when you start treatment as soon as possible, including a reduction in mortality, during the hospitalization or within 30 days of hospitalization. Also, reduction in the odds of ventilatory support, when treatment is started with early within two days of symptom onset, which may or may not be possible in a hospitalized patient, and so in general as soon as you start oseltamivir treatment after or at the time of hospital admission, there is much greater clinical benefit compared to starting treatment later or not at all. Next slide.

Similarly for hospitalized pediatric patients, there are observational studies reporting oseltamivir effectiveness and the greatest clinical benefit similar to in adults who are hospitalized is that when treatment is started as soon as possible, ideally within two days after symptom onset, but also when you're treated right at the time of admission or shortly thereafter you can reduce the duration of hospitalization, you can reduce the duration of ICU length of stay, you can reduce the risk of readmission, ICU transfer, and reduce the risk of the composite outcome of death or ECMO use. Next slide.

So for baloxavir, there are randomized controlled trials that have demonstrated the efficacy of baloxavir for treatment of uncomplicated influenza, and in these studies in children as well as adolescents and adults. These studies have shown that baloxavir treatment has similar clinical benefit to oseltamivir versus placebo and in children and adults when baloxavir treatment was started within 48 hours after symptom onset, and so a single dose of baloxavir had a similar clinical benefit to reducing influenza signs and symptoms versus 5 days twice daily of oseltamivir treatment. In general, this has also been shown for persons with high risk, with at least one high risk condition. So single dose of baloxavir was equivalent to the clinical benefit of five days, twice daily of oseltamivir.

Now two things need to be pointed out. One is that in these trials, baloxavir significantly reduced influenza viral RNA levels in the upper respiratory tract at 24 hours and reduced infectious virus detection versus oseltamivir. And in a subgroup of patients with influenza B, baloxavir significantly reduced the time to improvement of influenza B symptoms compared to oseltamivir. So if the patient is known or suspected to have influenza B, baloxavir is superior to oseltamivir treatment. Next slide.

Just to close towards the end to show a concerning trend which is in recent years, there's actually been a there's been low utilization of antiviral treatment in children and adults, particularly at higher risk of severe complications.

So here's some data from the New Vaccine Surveillance Network in the U. S. (NVSN) during the 2023-2024 season. And these are outpatients at higher risk for influenza complications

who sought medical care. And you can see that in children aged less than five years and those with a high risk condition, or those both aged less than five years and with a high risk condition, there was a pretty low proportion of those children who are actually treated with antivirals. So 28 to 39%. Next slide.

This slide shows in all ages over a number of years, particularly prior to the COVID-19 pandemic, you can see that there's been a drop off since the COVID-19 pandemic-- in hospitalized-- in antiviral treatment of hospitalized patients in the U.S., kind of in all ages. Next slide.

When we look at children who are hospitalized or high-risk outpatients, a similar thing, but the drop off has been even greater in children, specifically you can see that compared to prior to the COVID-19 pandemic, there's been a big decline in antiviral treatment of children who are hospitalized. That's the figure in the left there. And then on the right two examples. Children hospitalized in a different hospital network VSN only a little more than 50% had received antiviral treatment and at the bottom right you can see that children who presented to an emergency department with lab-confirmed influenza only 32% were prescribed antiviral treatment. Next slide.

So self-knowledge check. Which antiviral is recommended for outpatient treatment of influenza in an older adult resident of a long-term care facility who presents with 3 days of poor appetite, decreased activity, and mild cough, and tests positive for influenza? Select the best answer: Zanamivir, Rimantadine, Baloxavir, Peramivir, or Oseltamivir. Next slide.

The answer is E. The rationale is that oseltamivir treatment is recommended for patients at high risk for influenza complications, even if presenting in this patient. So even if presenting more than two days after symptom onset, this patient presented with three days of symptoms. So rimantadine is not recommended. Both amantadine and rimantadine are not recommended for treatment of influenza in the U. S. and the reason is that they're only active against influenza A viruses and there also there is also very high prevalence of resistance to rimantadine and amantadine. So zanamivir, baloxavir, and peramivir are recommended for treatment of influenza within two days of symptom onset, and this person is high risk. They're an adult, long-term care resident, long-term care facility resident who's been symptomatic for more than two days. And so this is where oseltamivir treatment would be recommended. Next slide.

So just to repeat the key points, as I mentioned at the beginning, last season was a high severity seasonal influenza epidemic with high morbidity and mortality in a wide range of respiratory, non-respiratory complications. Influenza vaccine effectiveness was moderate against uncomplicated illness as well as severe illness in the U. S. Influenza activity is

increasing in the U. S. The time to get vaccinated for this season is now for persons age 6 months and older who have not received influenza vaccine so far this season. Molecular influenza tests are recommended both for outpatients as well as for hospitalized patients and antiviral treatment is recommended as soon as possible for outpatients at increased risk for complications. So for those presenting within two days of illness onset, either oseltamivir or baloxavir for those with progressive or severe disease, regardless of the time since illness onset that would be oseltamivir, and for hospitalized patients with suspected or confirmed influenza oseltamivir treatment is recommended as soon as possible. Next slide.

So these are some resources from CDC on influenza prevention and control. Next slide.

And thank you for your kind attention. And I'll turn it back to Captain Khan. Thank you.

Thank you, presenters. Thank you so much for providing this timely information to our audience. We will now go into our Q and A session. We have time for one question.

The question asks: Can you clarify when baloxavir would be recommended over oseltamivir for treatment of influenza in outpatients and what are the advantages and disadvantage of baloxavir versus oseltamivir?

Yeah, that's a great question. So there are some age approval differences in the recommendations. So baloxavir treatment is recommended for persons aged 5 years and older, whereas oseltamivir is recommended for persons with influenza of all ages. So for a child less than five years of age oseltamivir treatment would be recommended. Baloxavir would be recommended over oseltamivir [inaudible] which we have really not been observing in the U.S., but it might be possible, for example. It could emerge. And also for a patient with known or suspected influenza B, baloxavir has much greater efficacy against influenza B compared to oseltamivir.

The advantages of baloxavir are there are overall fewer adverse events. It's generally well tolerated. And I mentioned that oseltamivir has a higher risk of nausea in adults versus placebo and a higher risk of vomiting in children versus placebo. So single dose of baloxavir is not associated with many side effects and fewer side effects compared to oseltamivir.

The other thing is for patients, I think, every patient would prefer a single oral dose of baloxavir versus 5 days twice daily of oseltamivir treatment. I'll just say the other advantage of baloxavir is that there is a reduction of influenza virus levels in the upper respiratory tract rapidly within 24 hours, but I also should use this opportunity to just mention a few disadvantages.

And one disadvantage of baloxavir is that it is associated with emergence of baloxavir resistance up to about 10% in randomized control trials. in adolescents and adults. So, and in fact, we know from other trials and other studies, there's a higher frequency of emergence of baloxavir resistance in younger children. And this emergence of baloxavir resistance is associated with longer duration of symptoms and fortunately transmission of a baloxavir-resistant virus from person to person has been very, very limited. It's been reported but it appears to be very uncommon and there's no circulation of baloxavir-resistant viruses or oseltamivir-resistant viruses in the general population.

And just to say oseltamivir would be recommended over baloxavir for pregnant women, for hospitalized patients, for patients with progressive illness, and for immunocompromised patients. And I'll just stop there by also saying that I think we need more data for treatment of influenza in hospitalized influenza patients, so severe influenza and for that we need more data for combination antiviral treatment for example oseltamivir plus baloxavir. And I'll stop there. Thank you.

Thank you very much and a reminder to our audience that if you were unable to ask a question during the webinar today, you may submit your question after the live session by emailing coca@cdc.gov.

I want to thank the presenters for their time and sharing their expertise with us today.

CDC has fully transitioned from the Training and Continuing Education Online, TCEO, system that provides access to CDC educational activities for continuing education to CDC TRAIN. If you do not already have a TRAIN account, please create one at www.train.org/CDCtrain.

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Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between January 13, 2026, and January 13, 2028, and use course code WD4520R-121125.

A fully closed caption video and transcript of today's COCA Call will be available on demand next week at www.cdc.gov/coca.

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Again, thank you for joining us for today's COCA Call and have a great day.