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At the conclusion of this session, participants will be able to accomplish the following; discuss background on influenza tests and antivirals for treatment of influenza; review influenza testing guidance for patients with acute respiratory illness for the 2022 to 2023 season, including during community co circulation of influenza viruses and SARS-CoV-2; and describe antiviral treatment recommendations for patients with suspected or confirmed influenza for the 2022-2023 season, including during community co circulation of influenza viruses and SARS-CoV-2.

After the presentation, there will be a Q&A session. You may submit questions at any time during today's presentation. To ask a question using Zoom, click the Q&A button at the bottom of your screen, then type your question in the Q&A box. Please note that we often receive many more questions that we can answer during our live webinars.

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I would now like to welcome our presenter for today's COCA Call. We're pleased to have with us Dr. Tim Uyeki, who is the chief medical officer in the Influenza Division in the National Center for Immunization and Respiratory Diseases at CDC. Dr. Uyeki, please proceed.

Thanks very much, Commander Khan. So, I'm going to speak about the 2022-2023 seasonal influenza testing and treatment during the COVID-19 pandemic. Next slide, please.

I'll try to speak a little bit about this past season and the influenza activity during this current season. I'll give some background on influenza season burden, talk about influenza vaccination for this current season, and then I'll talk about influenza testing and conclude with discussion about antiviral treatment of influenza. Next slide, please.

So, let's start with the past season and the current season. Next slide.

This slide depicts the number of specimens, respiratory specimens that tested positive for influenza reported to the WHO's Global Influenza, Surveillance, and Response System. What you can see is that in early to mid 2020, specimens testing positive for influenza globally dropped off precipitously and remain very, very low throughout 2020 and into about mid 2021. And in mid to late 2021, what you could see to the right is there was an increase in influenza virus activity. There was a bimodal global peak in activity. Most of these were due to influenza A H3N2 viruses. And you can see in the upper right corner there that more recently this fall there's been an increase. Next slide, please.

So, for the 2021-2022 season, we had a relatively mild season compared to pre COVID-19 pandemic seasons. We also experienced a bimodal peak in activity. We had primarily an influenza A H3N2 virus dominated season. We had a long season that extended out to mid June. But overall, it was a rather mild season. And you can this is illustrated by the right figure. What you see is overall weekly rate of hospital admissions reported to laboratory confirmed surveillance. And you can see that at the very bottom, the dark blue line, the 2020-2021 season, there was hardly any activity in the U. S., and, therefore, not many hospitalizations.

And then above that in the red line, the 2021-2022 season, also a rather mild season in terms of the weekly rate of hospital admissions. And contrast that to pre COVID-19 influenza epidemics where you see much higher weekly rates of hospital admissions. Next slide, please. So, this was not the case worldwide earlier this year. So, in the southern hemisphere, which is our summer and their winter, we saw typically an early season.

And this is data from Australia in the top graph, which shows a very robust rise and peak in the number of lab confirmed influenza cases that were reported to nationally there. And typically their seasons tend to peak more in the summer of really July and August. But they experience a very robust season that started in April and really peaked during May and June, and then came down rather abruptly. You can see that the number of cases reported was even higher than some of the pre COVID-19 seasonal epidemics in Australia. However, what you see in the bottom graph is that there were not as many hospitalizations, although there was an increase.

But compared to the 2017 or 2019 seasons, there were not as many numbers of hospitalizations in Australia that were reported. And overall, this was an influenza A H3N2 virus predominant season. But overall mortality was lower than what's typically expected during an influenza A H3N2 season. So, early and robust season in Australia. But not quite as much in terms of mortality.

And this is something we were thinking, well, could we experience that in the U. S. ? Next slide, please.

So, in fact, here is influenza virologic surveillance. And this is the most accurate way to know what's going on with influenza activity in the U.S. And you can see as we get to the right, this is data through November 5. This is information reported to CDC from state health departments. You can see that the percent positivity has really increased sharply. And there's no question that the influenza season in the U.S. is underway, and is expected only to increase in the coming weeks to months. Now, you can see that percent positivity by week is about 13%. During the peak of national influenza, influenza activity, we typically see about 25 to 30% positivity in weekly respiratory specimens testing for influenza. Next slide, please.

Let's go to influenza disease burden. Next slide.

So, the disease severity and clinical manifestations of influenza virus infection, they vary by age, host factors, immune, immunity, influenza virus type and subtype. And there are people clearly that experience asymptomatic influenza virus infection, but most people experience uncomplicated illness. And that's typically upper respiratory tract illness with or without fever. And fever may not be present at any age in a person with influenza and upper respiratory tract symptoms. But particularly elderly persons and immunosuppressed persons may not always mount a fever with influenza.

The classic description of influenza is really the abrupt onset of fever, cough, chills, muscle aches, fatigue, headache, and sore throat, and runny nose. This is not the gradual onset, but rather the abrupt onset. But not everybody clearly experiences classical influenza.

Just a couple other things. Gastrointestinal tract symptoms, such as diarrhea are more common in young children, less common in adults and older children. And just to highlight in young infants, they can present with fever alone and irritability. And they may not have any respiratory tract symptoms. And they may get worked up for potential sepsis without a source.

But if you take a history and you find out there are other people with acute respiratory illness in the family, it's always a good idea to take a respiratory tract specimen and test for influenza during influenza season. And there are unfortunately people that do experience complications of influenza. Next slide, please.

So, influenza complications can basically be grouped into those that result in moderate illness, such as otitis media in young children, or sinus infections, or worsening of underlying chronic disease. However, there are complications that can result in severe to critical illness, most commonly exacerbation of underlying chronic disease, and respiratory complications that include viral pneumonia, croup, status asthmaticus, bronchiolitis, tracheitis, respiratory failure, leading to ARDS.

And there are, is an increasing recognition of cardiac complications of influenza, particularly myocardial infarction and ischemic heart disease. Less commonly myocarditis and pericarditis can be precipitated by influenza. And neurologic complications are not so common, but they have clearly been described worldwide, including encephalopathy and encephalitis in all ages, but more commonly in young children. Influenza can precipitate a stroke. And less common

complications include Guillain-Barre syndrome, acute disseminated encephalomyelitis, and Reye syndrome, particularly in children who are exposed to salicylates.

Now, bacterial coinfection complicating influenza can occur in any age, resulting in invasive bacterial infection. So, community acquired pneumonia, particularly, is more common with influenza than COVID-19. And that most common bacteria implicated, but they're not the only ones, include staph aureus, both methicillin sensitive and methicillin resistant, pneumococcus and group A strep. But there are others, depending upon the host colonization of the upper respiratory tract and other host factors. Musculoskeletal complications, resulting in inflammation, and worse resulting in rhabdomyolysis, and myoglobin area, leading to renal failure, can occur. Sepsis and multiorgan failure clearly occurs. And don't forget nosocomial infections, which also include healthcare associated infections, such as bacterial, fungal, ventilator associated pneumonia. Next slide.

So, groups at particular increased risk for influenza complications and severe illness include children less than two years old. We tend to say less than five years old, but it's really those the younger you are. So, particularly less than two years old. And adults 65 years and older.

Persons with certain chronic medical conditions, including pulmonary, cardiovascular, but excluding isolated hypertension, renal hepatic neurologic complications, including those persons who have had a stroke, neurodevelopmental, hematologic, metabolic, or endocrine disorders, including diabetes mellitus. Persons who are immunocompromised, persons with extreme obesity, children and adolescents who are receiving aspirin or salicylate containing medications, residents of nursing homes and other long term care facilities, pregnant persons and people up to two weeks postpartum, and 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, seasonal influenza epidemics vary in severity, in severity. And we don't really know how many people have influenza virus infection or are symptomatic influenza every year. And, therefore, we rely on surveillance data and modeling, utilizing surveillance data. And over a number of influenza seasons, CDC estimates a range of illnesses ranging from about 9 million to 41 million symptomatic disease, 140,000 to 710,000 hospitalizations, and 12,000 to 52,000 deaths per year. Now, preliminary estimates for this past season are that there were about 9 million illnesses, 4 million medical visits, 100,000 hospitalizations, and 5,000 deaths.

And if you look at the triangle on the left, you can see that really falls onto the lower side. So, just verifying that we estimate that last season was really a mild season. And you can see from the upper figure that really seasons are quite variable in severity. Most severe recent season was the 2017-2018 season, which was when we had an influenza A H3N2 virus predominant year. Next season. Or next slide, please.

So, this slide illustrates data on estimated disease burden due to influenza from last season. And the point of this slide is to look towards the right under hospitalizations and deaths. And you can see that the percentage of hospitalizations and deaths is dominated by people 65 years and older. In particularly deaths. And we also know that mortality rates and hospitalization rates are dominated by people 65 years and older. Next slide.

This is data from, prior to the pandemic, or just as SARS-CoV-2 was emerging, it illustrates a typical influenza season, in that we see, these are lab confirmed influenza hospitalization rates by age group. The highest cumulative hospitalization rates are in people 65 years and older. The next highest rates are typically in young children.

And then people 50 to 64 years of age, because of the increasing prevalence of high risk comorbidities. But then you can see that in non elderly adults and school children, the hospitalization rates are rather low. Next slide.

However, we do experience racial and ethnic disparities in adult influenza hospitalizations in the U. S. These are data recently published in the MMWR. And what you see in this figure on the left is age adjusted influenza associated hospitalization rates among adults by race and ethnicity. And the point of this is to show that hospitalization rates are highest in black non Hispanic persons. And next it's in American Indian and Alaska Native non Hispanics. And then in Hispanic persons. And this data is shown by season, 12 seasons on the right graph. So, the point is that unfortunately disparities in adult influenza hospitalizations have existed for many seasons in the U. S., and we need to do a much better job at reducing these disparities. Next slide.

So, we have very preliminary in season burden estimates for the current season. And just to say that it's quite likely that these estimates will change. These are very preliminary. But at a minimum so far, CDC estimates there have been about 2. 8 million influenza related symptomatic illnesses, 1.4 million medical visits related to influenza, 23,000 hospitalizations related to influenza, and about 1,300 deaths related to influenza so far in the U. S. So, although it's very early, there clearly has been an impact on disease burden due to influenza in the U. S. to date. And it's only going to increase in the weeks to months to come. Next slide.

So, let's move on to influenza vaccination. Next slide.

So, this slide shows influenza vaccines that are available for the current season. They fall into basically six categories; inactivated standard dose egg based vaccines, inactivated cell cultures, standard dose base vaccines, high dose inactivated egg based vaccine, adjuvanted standard dose egg based vaccine, recombinant HA vaccine, and live attenuated egg based vaccine. All of these vaccines are quadrivalent, containing four antigens. And they are approved for different age groups. And I'll just highlight something that I'll mention again in a minute, that for high dose vaccine, that contains four times the normal hemagglutinin content of standard dose vaccines. That is approved for, that is licensed for persons 65 years and older.

The adjuvanted vaccine is also licensed for persons 65 and older. And the recombinant vaccine, which has three times the hemagglutinin concentration of standard dose vaccines, is licensed for persons 18 years or older. Live attenuated vaccine is recommended for persons who are not pregnant and otherwise healthy. So, it's not for people with chronic medical conditions, age 2 through 49 years. Next slide.

So, hopefully everyone knows that annual influenza vaccination is recommended for all persons aged six months and older who do not have contraindications to vaccine. All of these vaccines, as I mentioned, this season are quadrivalent, and they contain one influenza A H3N2, one

influenza A H1N1 pm09, one influenza B/Victoria lineage, and one influenza B/Yamagata lineage virus antigens.

And I want to call your attention to a recent recommendation, a new recommendation from the Advisory Committee on Immunization Practices for persons aged 65 years and older. ACIP recommended that influenza vaccination of persons aged 65 years and older should be done with higher dose and adjuvanted vaccines. This means the high dose or four times the antigen concentration, adjuvanted or recombinant, three times the antigen concentration of influenza vaccine for persons 65 and older. And the reason for this is because of the lower vaccine effectiveness in persons 65 years and older, and the lower immunogenicity that results in lower vaccine effectiveness, and so all of these strategies are to improve the immunogenicity and vaccine effectiveness in older adults. If these vaccines are not available, then standard dose vaccine is recommended. You should not lose the opportunity to provide influenza vaccination. Next slide.

So, influenza vaccine effectiveness does vary by virus antigen and the match to the circulating virus strains. There is a wide range of vaccine effectiveness against medically attended influenza illness. So, uncomplicated illness, mild illness, that results in a medical visit. And that is range from low to moderate of about 10 to 60% since 2009. But note that of the H3N2 viruses that have been analyzed in the United States since May 2022, most of these viruses are genetically and antigenically closely related to the updated influenza A H3N2 vaccine component. That is good news.

And the majority of the influenza viruses identified this year characterized in the U. S. are influenza A H3N2 viruses. We are also seeing influenza A H1N1 pdm09 viruses. And not many influenza B viruses circulating to date.

But the fact that these H3N2 viruses that have been analyzed look like they're a good match to the H3N2 vaccine component. These do suggest that influenza vaccination this season should offer protection against the predominant influenza A H3N2 viruses to date. I just want to say that not only can influenza vaccination provide benefit against uncomplicated influenza illness. There are data to show that influenza vaccination can prevent severe influenza. And I'll just provide some examples of studies here.

In one study, there was influenza vaccination effectiveness of 51% against hospitalization for H1N1 pm09 in adults, although notably vaccine effective was zero, essentially zero for H3N2 related pneumonia in adults in hospitalization. But in children, there are some nice studies showing the high, moderately high vaccine effectiveness of 65% against intensive care unit admission, and similarly 65% effectiveness against preventing, sorry, 65% effectiveness against influenza related death in children. So, I think that we need to do a bit better messaging that not only can influenza vaccination reduce the risk of influenza illness, but it can reduce the risk of severe influenza. Next slide, please.

Unfortunately, we have racial and ethnic disparities in adult influenza vaccination coverage in the U.S. And what this slide highlights over a number of years is that for white non Hispanic and Asian non Hispanic individuals, influenza vaccination covers in adults was higher than for black

non Hispanic, Hispanic, or American Indian, Alaska Natives. And so what this basically highlights is that even though vaccine coverage overall is not good for any group, we need to do much better among all racial and ethnic groups. We clearly need to address these disparities in vaccination. And we need to really increase efforts to vaccinate these different racial and ethnic minorities to mitigate these disparities.

And I'll just say that this is showing adult data, but there are data during the COVID-19 pandemic to show that pediatric influenza vaccine coverage among all racial and ethnic groups has dropped over the last few years. Next slide.

So, so far this season, influenza vaccination coverage in adults and pregnant people is significantly lower to this time compared last season. And while influenza vaccination among children is similar to last season, at least this time last season, coverage among children is down six percentage points from two years ago. There have been about 150 million doses of influenza vaccine distributed throughout the U.S. to date. And that will increase. But the number of doses in, distributed in doctor's offices are down steeply. Although the number of doses of influenza vaccine given in pharmacies and retail locations is similar to last season.

We clearly need to do a better job at reaching a lot of people who remain unvaccinated. And the time to get influenza vaccination is right now. And so I think that is something for providers to really do outreach to their patients. Next slide, please.

Let's move to the influenza testing. Next slide.

So, why test for influenza? Well, I don't think I need to really convince people that the signs and symptoms of influenza are really non specific, and they overlap with those caused by other co-circulating respiratory viruses, especially SARS-CoV-2 and RSV. But other respiratory virus as well.

So, accurate and prompt influenza diagnosis is really important for clinical decision making, particularly in both ambulatory and in patient settings to help guide antiviral treatment. That is if influenza testing is going to change clinical management in the outpatient setting, versus prescribing empiric antiviral treatment based on a clinical diagnosis of influenza. Which is okay in the outpatient setting during periods of high influenza activity in the community. But influenza testing can also facilitate implementation of infection prevention and control measures in healthcare settings to reduce the spread of nosocomial transmission and reduce the spread of influenza institutional outbreaks. Could also help guide other clinical decisions, such as reducing inappropriate antibiotic use, reducing the use of other diagnostic tests, reducing the time in clinical care, such as in the emergency department. Next slide, please.

So, there are a variety of influenza diagnostic tests available to clinicians to detect influenza viruses in respiratory specimens. They differ by the time to produce results, the information provided, the accuracy, and approved respiratory specimens, and what settings you can use these tests in. And these fall to three categories; point of care tests that are CLIA-waived that can be administered at the bedside; moderately complex, which requires a clinical laboratory; or highly

complex, which really refers to large, to tests being performed in large clinical laboratories and public health labs. Next slide.

So, let's first talk about antigen detection. These influenza tests detect influenza A and B viral antigens and respiratory specimens. They're generally cleared by FDA for upper respiratory tract specimens. They are rapid immunoassays. One is a there is at least one that's really a rapid immunofluorescent assay. But they essentially produce a result in about 10 minutes. And in the past, they have not used an analyzer device.

Most rapid antigen detection tests available now do have an analyzer device, which helps standardize the reading and improve sensitivity. Direct fluorescent antibody staining also is antigen detection. It takes longer, and it requires a fluorescent microscope and really a trained technician. And sensitivities are also not as good as other influenza tests. So, overall, antigen detection tests have low to moderately high sensitivities, they do have high specificity to detect influenza viral antigens compared to molecular assays. Next slide.

So, the other category, main category of influenza tests are those that detect nucleic acids. We refer to these as molecular assays. And basically they detect influenza A and B virus nucleic acids in respiratory specimens. Most are FDA approved for upper respiratory tract specimens, but some are cleared for lower respiratory tract specimens. They fall into two categories; the rapid molecular assays that produce a result in 15 to 30 minutes, and other molecular assays that take about an hour or longer to produce results. These are both single plex, only detect influenza A and B viruses in multiplex, which detect other respiratory pathogens as well as influenza viruses. And I think people are pretty familiar with many SARS-CoV-2 assays that were made available through FDA emergency use authorizations. There are molecular assays that were made available that also detect influenza A and B viruses, along with SARS-CoV-2. Overall, molecular assays have high sensitivity and high specificity to detect influenza viruses in respiratory tract specimens. Next slide.

This just illustrates the point that rapid antigen detection tests have lower sensitivity than molecular assays. This, the top part is a metaanalysis that looked at rapid influenza antigen tests and rapid molecular assays. And you can see that even in the middle there, that rapid antigen tests with an analyzer device had sensitivities of about 75%, whereas molecular assays had sensitivity greater than 90%. And then a metaanalysis of rapid influenza molecular assays showed that sensitivity was about 88%, and specificity remained very high.

So, this just highlights the point that molecular assays, including rapid molecular assays, had much higher sensitivity than rapid antigen tests that are available today for influenza. Next slide. So, this just breaks down sort of the advantages and disadvantages of the different kinds of influenza diagnostic tests, the rapid antigen tests at the top with low to moderate sensitivity and high specificity, the rapid molecular assays that detect viral RNA with moderately high to high sensitivity and high specificity. And then in red there, molecular assays that have high sensitivity and high specificity. Next slide, please.

So, it's important to understand that influenza virus shedding typically peaks within 24 hours of illness onset. In symptomatic individuals, virus can typically be detected the day prior to illness

onset. And then they peak within a day of illness onset, symptom onset. And they drop thereafter. And the highest infectious period, you can see in the figure on the right, is typically within three days after symptom onset.

Just to note that young infants can be infectious for longer periods. And critically ill patients might have longer influenza A viral replication in the lower respiratory tract. And severely immunocompromised persons can be infectious for weeks to months. Next slide, please.

This is just to show on the left that influenza viral RNA detection is longer in persons who have more severe or critical illness than those who have uncomplicated illness who are not in the hospital.

So, the longer viral RNA detection is those, in those who are in the intensive care unit, also those who are hospitalized, and less so in those who are in the community and not hospitalized. On the right, viral RNA shedding is similar in children and adults. Next slide. So, what are the optimal specimens? The highest yield for detecting influenza viruses in respiratory specimens are nasopharyngeal swab samples, ideally collected within three to four days of illness onset. But if you use molecular assays, you can detect viruses longer than three to four days. Whereas antigen detection tests really are most reliable within the first three to four days after illness onset. There are other acceptable upper respiratory tract specimens. But one should consult the package insert for what FDA recommended or cleared respiratory specimens for the particular diagnostic tests that you're using. So, there is a difference. Some assays are cleared for nasopharyngeal specimens and nasal specimens, but not others.

Understand that viral replication in RNA detection may be prolonged in persons who are immunocompromised, including those who are on moderate to high dose corticosteroids. And it is possible in critically ill persons, so persons who are in the intensive care unit, ventilated, that influenza viruses might be detectible in lower respiratory tract specimens when they're no longer detected in the upper respiratory tract. And we know this from data, particularly from the 2009 H1N1 pandemic when sampling of the upper respiratory tract in critically ill patients did not yield a diagnosis of influenza, whereas bronchoalveolar lavage fluid detected influenza viral RNA in about 10 to 19% of patients when it was missed in the upper respiratory tract. So, if the patient is in the ICU, particularly with respiratory failure, consider sending a lower respiratory tract specimen, it's easy to send an endotracheal aspirate. We would not necessarily recommend a bronchoalveolar lavage be performed, except if the patient is being investigated for a range of pathogens, and then influenza virus could be tested as well. Next slide.

So, it's important for clinicians to understand how influenza prevalence affects influenza testing interpretation. It does clearly also affect when you want to use tests. And it also impacts decisions on clinical diagnosis and when you might be okay with a clinical diagnosis in prescribing empiric antiviral treatment.

So, it's important that clinicians should be aware of local influenza activity in their community. And they can rely upon local public health influenza surveillance data, or that from their state health department, or their local hospital. And then they can refer to CDC data, which we produce both national as well as regional information on a weekly basis. Next slide.

So, this just highlights sort of the issue of prevalence and predictive values. And so during periods of low influenza activity, so let's just say typical summer in the U.S., influenza activity is typically low. So, the negative predictive value is highest. True negatives are more likely. And the positive predicted value is lowest. That means false positives are more likely. But as we get into peak community influenza activity in the middle, the positive predictive value is the highest, so true positive results are more likely. And the negative predictive value is the lowest. And false negatives are more likely. And so that's where some of these rapid antigen tests in particular, you may see a negative result that's actually a false negative.

So, it's important to incorporate the issue of prevalence into interpreting the result of an influenza test, particularly negative results. Next slide.

So, which outpatient should be tested for influenza during influenza season? Typically, you only want to test them if the results are going to influence their clinical management. So, high risk persons with influenza like illness, pneumonia, nonspecific acute respiratory illness, patients with acute onset of respiratory symptoms, and exacerbation of chronic underlying medical conditions, or known influenza complications. And you could consider testing people who are not at high risk for complications of influenza who present with acute respiratory illness. Because this still might, whether you get a positive result or a negative result, this might change clinical management decisions about prescribing antiviral treatment, reducing unnecessary antibiotic use, reducing the time in the emergency department, and reducing more diagnostic test ordering. And just to note, I think everyone should be aware that a history of influenza vaccination does not exclude a diagnosis of influenza in the patient. Next slide.

So, in hospitalized patients, all patients require admission who have acute respiratory illness during influenza season should be tested for influenza. This includes patients with pneumonia, with or without a fever, patients have acute worsening of chronic cardiopulmonary disease, immunocompromised patients, and high risk patients with acute onset of respiratory symptoms, with or without fever.

And don't forget nosocomial influenza as a possible etiology. So, all patients with hospitalization, during hospitalization who develop acute onset of respiratory symptoms, with or without fever, or have respiratory distress, with or without a clear diagnosis. Next slide.

So, what specimen should be collected? In outpatients, collect upper respiratory tract specimens as soon as possible. After onset, preferably within four days of symptom onset, nasopharyngeal swab specimens are ideal. If they are not available, collect a combined nasal and throat specimen. But do consult the package insert for what specimens are optimal. Mid turbinate nasal swabs in general are, should be collected over throat swabs. And flock swabs should be used over non flock swabs. In hospitalized patients, you should collect upper respiratory tract specimens from those patients without severe or lower respiratory tract disease.

But if in those patients who are critically ill, particularly receiving invasive mechanical ventilation, if a diagnosis of influenza has not been established by testing upper respiratory tract specimens that collect endotracheal aspirates for influenza testing. Next slide.

So, what tests are recommended? In outpatients, rapid influenza molecular assays are recommended over rapid influenza antigen tests. These are recommendations by the Infectious Diseases Society of America, IDSA. Similarly, IDSA recommends that RTPCR or other molecular assays are recommended for hospitalized patients and rapid antigen detection tests, including immunofluorescence assays are not recommended and should not be used unless molecular assays are not available at the hospital.

In immunocompromised patients, you may want to test for a wide range of respiratory pathogens, including influenza viruses. Do not order viral culture for initial or primary diagnosis of influenza. It takes at least three days to get a result, and will not inform clinical management. In certain situations, it might actually be helpful to know. And one example I can think of is in immunocompromised patients who have very prolonged viral replication.

But, in general, its viral culture is not going to inform clinical management. Do not order serology for influenza, although commercial laboratories do offer influenza serology. The results of a single serum specimen is uninterpretable. And you really need appropriate collection of paired acute, and convalescent sera two to three weeks apart. And they are tested at either public health laboratories or clinical research labs.

And, in general, serology for influenza is only useful for epidemiologic studies or vaccine studies. And so really you want to focus on molecular assays overall and not ordering a serology for influenza. Next slide, please. So, in periods where there is co-circulation of influenza virus, such as in SARS-CoV-2, and that has happened during the last almost nearly three years, and is happening right now, and may increase, there is a possibility of co-infection with influenza A or B viruses and SARS-CoV-2. It has been documented in case reports and case series, although we don't completely understand the frequency and the severity of risk factors. But it does appear to be uncommon. It clearly occurs, but is uncommon. And on the right is just a figure from colleagues at the Mayo Clinic. They did extensive testing in their patients who had SARS-CoV-2 positive specimens. And they found a very small percentage of patients with influenza virus co-infection.

So, overall, they reported, this is through April, early April of this year, 0. 061% had evidence of co-infection with SARS-CoV-2 and influenza viruses. So, it's uncommon, but it does occur. And one of the reasons why this, it might be important to test, well, there are overlapping signs and symptoms of COVID-19. There are some differences.

The incubation period is generally shorter for influenza in general than for COVID-19. The duration of viral shedding is generally shorter for influenza than for patients with COVID-19. Disorders of smell and taste are more common with COVID-19 than influenza. Diarrhea is really something we see with influenza in young children. Whereas with COVID-19, diarrhea can occur at any age.

And the onset of complications and progression to severe disease tends to occur earlier with influenza than with COVID-19. And although the high risk groups for influenza and COVID-19 are similar, just note that young children, particularly very young children, are at increased risk for influenza complications. So, all of this kind of highlights why testing for both influenza and

SARS-CoV-2 can help guide appropriate antiviral treatment in persons at high risk for complications, and also identify co-infections. So, you can target your antiviral treatment to influenza, or target it towards SARS-CoV-2 in high risk persons, and then you may identify co-infections. Next slide, please.

So, there are multiplex assays that do detect SARS-CoV-2 and influenza viruses. And there are antigen detection assays that have received FDA Emergency Use Authorizations. They can be performed in a variety of clinical settings. Results can be realized in 15 minutes, but also appreciate that with antigen detection, for both SARS-CoV-2 and influenza viruses, the sensitivity is lower than for molecular assays. And there are a number of multiplex nucleic acid detection assays that have been either cleared, sorry, that have been received FDA Emergency Use Authorization, or there are a few that have received FDA De Novo 510(k) clearance or premarket approval.

And these vary in turnaround time to results from 20 minutes to much longer, many hours. And they vary in the kinds of settings that they're actually authorized to be used in. Next slide. So, I just want to highlight a point here that co-infection with SARS-CoV-2 and influenza virus can result in severe disease. These are two studies from the United Kingdom.

The first study is from really when SARS-CoV-2 emerged in the UK. So, data through April of 2020. And in that study, influenza virus infection was associated with a lower risk of SARS-CoV-2 infection. But that co-infection was associated with a higher risk of intensive care unit admission or death compared to just having SARS-CoV-2 infection alone. In another UK study that extended through December of 2021 reported that SARS-CoV-2 and influenza virus co-infection was significantly associated with about four times the odds of invasive mechanical ventilation versus SARS-CoV-2 infection alone.

And interestingly, when they looked at SARS-CoV-2 and RSV co-infection, or SARS-CoV-2 and adenovirus co-infection, they did not find any significant differences compared to SARS-CoV-2 infection alone. And then co-infection with SARS-CoV-2 and influenza virus was significantly associated with about 2. 35 times the odds of in hospital mortality versus SARS-CoV-2 infection alone. So, these studies suggest that co-infection with SARS-CoV-2 and influenza virus can result in very severe outcomes. And we need to really prevent both virus infections through vaccination, and early antiviral treatment, particularly in those at high risk for complications. Next slide, please.

So, self knowledge check. The following is true regarding recommended influenza tests, rapid influenza molecular assays are recommended over rapid antigen tests for outpatients. B, molecular assays and serology are recommended for hospitalized patients. C, viral culture is recommended for hospitalized patients. Or D, all of the above. Next slide.

The correct answer is A, rapid influenza molecular assays have high sensitivity and high specificity and are therefore recommended over rapid influenza antigen tests for detection of influenza viruses and upper respiratory infect specimens in outpatients. For hospitalized patients with suspected influenza, molecular assays are recommended. But antigen detection tests, such

as rapid antigen tests and immunofluorescence, as well as viral culture and serology, are not recommended. Next slide, please.

So, let's move to antiviral treatment. There are four FDA approved antivirals that are recommended for treatment of influenza this season. All of these have demonstrated efficacy in double blind placebo controlled trials, and are FDA approved for early treatment, so within the first two days after illness onset, in outpatients with uncomplicated influenza. They have all been shown to reduce the duration of influenza illness compared to placebo.

The first category are the neuraminidase inhibitors. And these include Oseltamivir, Zanamivir, and Peramivir. These drugs are chemically related. All of them neuraminidase inhibitors block the release of infected virus particles from respiratory tract cells that are infected. They do not interfere with viral replication, but they reduce the spread of influenza viruses in the respiratory tract.

The other category is a polymerase inhibitor, more specifically a cap dependent and a nuclease inhibitor, called Baloxavir marboxil, or we would just refer to it as Baloxavir. This antiviral does interfere with viral replication. It does reduce viral replication and viral shedding. So, just to highlight that Oseltamivir is available in an oral preparation, in pediatric outer for suspension in children, and capsules in older children and adults. CDC recommends Oseltamivir in all ages for treatment, as well as IDS8 recommends Oseltamivir for all ages for treatment of influenza.

Zanamivir is available as an inhaled powder. It's given twice daily for five days, for persons seven years and older. Peramivir is an intravenous medication. It's a single infusion for persons six months and older. Baloxavir is a single dose tablet.

It is now FDA approved for otherwise healthy persons aged five years and older, or high risk persons aged 12 and older who have uncomplicated influenza. Just to say that for clinicians, a number of years ago, particularly during the 2009 H1N1 pandemic, we did have investigational intravenous Zanamivir that was available for emergency use. It is no longer available in the United States, including for emergency use. Next slide.

So, CDC 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 as soon as possible for any patient with confirmed or suspected influenza who is hospitalized. And that includes without waiting for testing results. Outpatients with complicated or progressive illness of any duration, and outpatients who are at high risk for influenza complications. For those persons who are otherwise healthy, not in a high risk group, who have confirmed or suspected influenza, antiviral treatment can be considered, because there are studies that have shown clinical benefit in treatment of otherwise non high risk persons. However, the treatment should only be done for those patients who are non high risk persons if treatment can be started within 48 hours of illness onset. And this could include empiric treatment, either through an in person visit, or via telemedicine. Next slide, please.

So, I just want to say a couple things about antiviral resistance. So, currently there is no evidence of any concern about antiviral resistance in circulating influenza viruses worldwide, including

viruses that we've detected in the U.S. to the recommended antivirals that I've mentioned. So, Oseltamivir, Zanamivir, Peramivir, or Baloxavir. And, therefore, we don't have really any hesitation about recommending these drugs. So, for outpatients with complications, progressive disease, who have suspected or confirmed influenza, treatment with oral Oseltamivir is recommended as soon as possible. For patients with suspected or confirmed uncomplicated influenza, oral Oseltamivir, inhaled Zanamivir, intravenous Peramivir, or oral Baloxavir may be used for early treatment, depending upon approved age groups and contraindications.

Just to say that in one randomized control trial, in patients with influenza B virus infection, Baloxavir had greater efficacy than Oseltamivir in high risk adolescents and adults. And also just to say that in persons, in patients who a clinician is considering starting empiric antiviral treatment for influenza, they should also think about other etiologies of influenza, like illness at this time of the year, or throughout the winter respiratory virus season. And that includes other respiratory viruses, such as SARS-CoV-2 and RSV.

And so that highlights the role of influenza testing and testing for other respiratory viruses, including SARS-CoV-2 and RSV, depending upon the clinical situation, and depending upon respiratory virus circulation in the particular community that the patient is from. Next slide, please.

So, let me just summarize sort of the data on Oseltamivir efficacy and uncomplicated influenza and outpatients. So, randomized controlled trials have generally shown that Oseltamivir treatment has significant clinical benefit when started 36 to 48 hours after illness onset versus placebo. Pooled metaanalysis of five randomized controlled trials in children reported that when treatment is started within 48 hours of illness onset, the duration of illness was reduced by 18 hours. And when you excluded children with asthma, the duration, the reduction in illness duration was 30 hours. It was also a reduction of the risk of otitis media by 34%.

For adults, when treatment was started within 36 hours of illness onset, there was a reduction of the duration of illness by 25 hours. But a 44% reduction in the risk of lower respiratory tract complications that occurred starting 48 hours after Oseltamivir treatment was started that required antibiotics. So, some benefits, other than just treating influenza with Oseltamivir early. Next slide, please.

I'll summarize the efficacy of Baloxavir in uncomplicated influenza.

So, randomized control trials have shown that Baloxavir treatment has similar clinical benefit to Oseltamivir, it's significant clinical benefit versus placebo when started 48 hours after illness onset. So, in this top study in children, single dose Baloxavir had similar immediate time to alleviation of influenza signs and symptoms versus five days of twice daily of Oseltamivir treatment. And then in adults, two different randomized controlled trials starting treatment within 48 hours of illness onset, single dose Baloxavir significantly reduced illness duration by about 26. 5 hours versus placebo in non high risk persons, the immediate time to alleviation of symptoms was similar for Baloxavir and Oseltamivir. And single dose Baloxavir significantly reduced illness duration by a median of 29 hours versus placebo in persons with at least one high risk condition. These were adolescents and adults. The median time to improvement of

symptoms was similar for Baloxavir and Oseltamivir. But then as I mentioned before, that for those with influenza B, Baloxavir significantly reduced the median time to improvement of influenza B symptoms by 27 hours versus Oseltamivir, showing that Baloxavir is better than Oseltamivir for treatment of influenza B and outpatients. Next slide.

There are some special populations to note.

CDC recommends for treatment of influenza in pregnant people and those up to two weeks postpartum oral Oseltamivir is preferred and recommended. Baloxavir is not recommended for treatment of pregnant people or breastfeeding mothers. And the reason is there are no efficacy or safety data available for Baloxavir in pregnant or lactating people. In a preclinical toxicity study, there was a bit of a concern in pregnant rabbits. And so overall we don't recommend Baloxavir.

And the other reason why Oseltamivir is preferred for treatment of pregnant people and those who are two weeks postpartum or lactating persons is because there is substantial evidence of Oseltamivir safety during pregnancy for both pregnancy and birth outcomes. There is no signal of increased harm at all. So, this reassuring data so that clinicians should not hesitate to treat influenza in a pregnant woman with Oseltamivir as soon as possible. For immunocompromised persons, I mentioned that prolonged influenza viral replication is a possibility, with emergence of antiviral resistant viruses during or after treatment, and so it's important to monitor antiviral resistance, particularly if that person has any evidence of prolonged viral replication. And it's very important in the healthcare setting to maintain infection prevention and control precautions that are recommended in persons who are immunocompromised, because they may present a nosocomial transmission risk. And this also includes persons who may have asymptomatic prolonged influenza virus replication.

So, we do recommend that neuraminidase inhibitor treatment is recommended. We do not recommend Baloxavir. And the reason is in immunocompetent persons, there is a higher frequency of emergence of resistance to Baloxavir during and after treatment than with Oseltamivir. And so that risk is actually higher the younger you are, particularly in young children, the frequency of Baloxavir resistance has been reported to range even up to greater than 20% in those who are treated.

And so there is concern even though we have no data in immunocompromised persons, because we know the risk of prolonged replication is a possibility. So, avoid at least monotherapy with Baloxavir, and use Oseltamivir therapy. And what we really need is trials of combination antiviral treatment using antivirals with different mechanisms of action. And there are some trials in progress. Next slide, please.

So, for hospitalized patients, Oseltamivir is the antiviral treatment that is recommended for treatment of influenza as soon as possible for those who have confirmed or suspected influenza. And for those who have suspected influenza, do not wait for testing results. This recommendation is based on a lot of observational data. Note that there is no fully enrolled, sufficiently powered, double blinded placebo controlled trial Oseltamivir treatment of influenza in hospitalized patients, so we look towards many, many different observational studies. And I'll just summarize those studies to say that starting Oseltamivir at the time of hospital admission is

associated with reduced hospital length of stay in adults, and early initiation of antiviral treatment with Oseltamivir is associated with shorter duration of hospitalization in children and adults, including children who are admitted to an intensive care unit, and may reduce mortality risk in adults.

We do not recommend the use of inhaled Zanamivir, oral Baloxavir, as monotherapy in hospitalized patients, because of the lack of data in hospitalized patients. There is a study that was published somewhat recently that was a study essentially of neuraminidase inhibitor plus Baloxavir versus neuraminidase inhibitor and standard of care. So, essentially it was looking at Oseltamivir plus Baloxavir versus Oseltamivir. And it did not show clinical benefit. Although it did show virologic benefit of adding Baloxavir to Oseltamivir.

So, currently, we're not recommending combination antiviral treatment. We do recommend Oseltamivir treatment of patients who are hospitalized with influenza. There are really insufficient data for Peramivir treatment of hospitalized influenza patients. I'll just mention that patients who are critically ill, you can administer Oseltamivir through an oral or nasogastric tube. So, enteric administration.

But there are patients who you do not want to do that to. And those are patients who cannot tolerate or absorb an oral or enterically administered antiviral. Those who have gastric stasis, malabsorption, gastrointestinal bleeding. And so in those patients who are critically ill, intravenous Peramivir is an option. But overall, we really don't understand the optimal duration of antiviral treatment for critically ill influenza patients. Next slide.

So, I'll just conclude by saying there are a number of resources for clinicians to consult. That includes our influenza homepage. It includes our weekly report on influenza activity, which is not just virologic data, but also data on hospitalizations, pediatric influenza associated deaths, and overall burden of influenza. There's data on influenza vaccination coverage.

And we do have information and recommendations for clinicians about influenza vaccination, including this current season's ACIP vaccine recommendations, as well as influenza testing recommendations, and influenza antiviral recommendations. With that, thanks so much for your attention. And I'd be happy to answer a few questions if time permits. Thank you.

Thank you, Dr. Uyeki. We appreciate you providing this timely information to our audience. We will now go into a brief Q&A session. So, our first question is regarding vaccine effectiveness and vaccine administration.

And the question asks, do you think older and/or immunocompromised individuals should receive a second influenza vaccine later in the season to provide sustained protection?

This is a great question. And so typically for immunocompetent patients, persons, we do not recommend, ACIP does not recommend sort of a booster influenza vaccine dose. For immunocompromised patients, there is no current ACIP recommendation. And I think that is an area where we do need further research. I would say that in immunocompromised patients 65 and

older, clearly giving either high dose vaccine, recombinant vaccine, or adjuvanted vaccine is the way to go.

And in persons who are immunocompromised who are younger than 65 years of age, one option to consider, although there's not a lot of data in this group, would be a recombinant vaccine in an adult less than 65 years, because that vaccine is three times the antigen content of standard inactivated vaccine, and it is available for those 18 and older. Again, this is an area that I think we need a lot more research. It is true that there are studies that have suggested that influenza vaccine effectiveness decreases by month over time during the influenza season. And so I think this is an area where research is needed. Thanks.

Thank you, Dr. Uyeki. Our next question asks, you mentioned that there's a significantly lower influenza vaccine coverage as compared to last season. What do you attribute that to?

I think the easy answer is I don't know, but I can speculate. And this is just my personal opinion, that there seems to be a lot of vaccine fatigue, particular, unfortunately, COVID-19 vaccine booster fatigue. And that may be spilling over into influenza vaccine fatigue. Whatever the reason, influenza vaccine coverage is lower among many different groups. And as I mentioned, we have a lot of disparities in influenza vaccine coverage unfortunately.

And so I think all efforts need to be made now. There's just no question that influenza activity is increasing nationally. It's most prominent in the south, southeastern United States, and south central U. S., but it is very likely to increase throughout the country in the coming weeks to months.

And so if there's low influenza activity in your community, there's still plenty of time to get vaccinated, even if there's a lot of influenza activity in the south, southeastern U. S., there's still plenty of time to get vaccine. And we do recommend influenza vaccination, even if there's influenza vaccine, sorry, influenza activity in the community, and this would be true even as we get into 2023. As long as there's people who are unvaccinated and there is influenza viruses circulating in the community, people can benefit from influenza vaccination.

So, I think as clinicians, as public health colleagues, we need to really get the word out, and we need to really ramp up influenza vaccination among unvaccinated persons in the U.S.

Thank you, Dr. Uyeki. That was an excellent guidance that I think we can all heed. We have time for just one last question. And the question is asks, do you think healthcare providers should avoid live attenuated vaccine if they're caring for immunocompromised patients?

This is a great question. The concern is that people who have been vaccinated with live attenuated intranasal vaccine may have ongoing replication. I mean, that is what the virus is designed to do. And these people can be perhaps deferred or move to a different patient population rather than immunocompromised, at least until they've stopped virus shedding. And so it's something to consider.

Other considerations are simply to get inactivated influenza vaccine.

Thank you for that. And with that, I want to thank everyone for joining us today, with a special thanks to our presenter, Dr. Tim Uyeki, for sharing his expertise and time with us.

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