Diagnostic Testing and Treatment Guidelines for COVID-19 and Influenza

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 would like to welcome you to today's COCA call. Diagnostic Testing and Treatment Guidelines for COVID-19 and Influenza. All participants joining us today are in listen only mode.

Free continuing education is offered for this webinar and instructions on how to earn continuing education will be provided at the end of the call. In compliance with continuing education requirements all planners presenters and moderators must disclose all financial relationships in any amount with ineligible companies over the previous 24 months, as well as any use of unlabeled products or products under investigation abuse. CDC, our planners, presenters and moderators wish to disclose they have no financial relationships with ineligible companies whose primary business is producing, marketing, selling, reselling or distributing healthcare products used by or on patients. Content will not include any discussion of unlabeled use of a product or a product under investigational use. CDC did not accept financial or in-kind support from ineligible companies for this continuing education.

At the conclusion of today's session participants will be able to accomplish the following. List of available tests and when to test for SARS-CoV-2 and influenza viruses, including indications for repeat testing. Describe recommended antivirals for treating influenza and COVID-19 and clinical benefits. Site factors for deciding who to treat for COVID-19 and influenza. And review indications for empiric treatment of influenza and COVID-19.

After today's presentation there will be a Q&A session. You may submit questions at any time during today's presentations to ask a question using zoom click the Q&A button at the bottom of your screen and type your question in the Q&A box. Please note we often receive many more questions than we can answer during our live webinars. If you are a patient, please refer your questions to your healthcare provider. If you're 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 pleased to have with us Dr. Pragna Patel, the Chief Medical Officer in the Coronavirus and Other Respiratory Viruses Division in the National Center for Immunization and Respiratory Diseases at CDC and Dr. Tim Uyeki, the Chief Medical Officer in the National Center for Immunization and Respiratory Diseases at CDC.

I would now like to turn it over to Dr. Patel., Dr. Patel please proceed.

Thank you. It's a pleasure to be here today and I will talk to you about COVID-19 diagnosis and treatment. I wanted to start with a quick look at hospital admissions due to COVID-19 and influenza. You can see here the orange line represents COVID-19 and the blue line represents

influenza. We have seen a little over 26,000 COVID-19 hospitalizations in the past week, down 14% from the previous week and slightly lower than this time last year.

However, hospitalizations for COVID-19 are higher than hospitalizations for flu. Currently, J and one is the predominant variant with the prevalence of about 80% and it's important to know that existing vaccines, tests and treatments still work well against J and one. So this slide essentially shows the rates of hospitalization for the 19 by age. The left side is a depiction of the rates from March 2020 two December 2023, and it gives you a little bit more granularity. I want to draw your attention to this hatched purple line which represents hospitalizations among patients who are greater than 75 years of age.

They actually experience the hospitalization 2 to 3 times greater than other age groups followed by infants who are less than six months and adults who are 65 to 74 years. We are actually seeing some evolution epidemiology of COVID-19 with hospitalizations more and more being focused in the older age groups. Next slide.

So what are the risk factors for severe disease? I took this from our CDC webpage. Essentially the risk factors for severe COVID include being age 50 years or older. As you can see, the risk increases substantially at age 65 and particularly for the 75 and older age group. Being unvaccinated or not been up-to-date on your COVID-19 vaccinations. I didn't show the data but recently we looked at this and saw 46% of patients who are hospitalized are actually up to date on their COVID-19 vaccinations.

Specific medical conditions including immunocompromised, chronic lung disease, cardiovascular disease, diabetes and obesity can render someone at higher risk. There is some groups that are disproportionately affected by COVID-19 because of many factors including limited access to healthcare. This is important in considering medical conditions that are not well controlled. So uncontrolled HIV infection or uncontrolled diabetes may contribute to risk for severe COVID. Next slide.

So, I just want to shift gears a little and talk about testing. Next slide.

This slide depicts the viral kinetics of SARS-CoV-2 infection relative to symptom onset. The Y-axis is viral load, the X axis is time since symptom onset in days. I want to draw your eye to the blue bar at the top which is essentially the duration within the early days of infection. That PCR also a NAAT test is positive. Under that you see the yellow bar which basically detects the window detection for the antigen rapid test. It’s got a narrower window detection but it's less sensitive then PCR or the gold standard. This is important in the timing of the testing that is conducted when using antigen tests. Next slide.

So, what we recommend is that if a person is symptomatic they should test immediately. Limit their exposure to others and start treatment as early as possible if they test positive and they are at high risk for severe disease and eligible. But if a person is asymptomatic and have a known exposure, for example someone in the household has COVID, they should test at least five days after exposure. The reason we recommend this is there is an incubation period for SARS-CoV-2 and it may take that long for a person to mount enough of virus to test positive on these tests.

Because I mentioned before the rapid antigen test is less sensitive there is possibilities for patients to have false negative test results. The way we can get around false negative tests is to repeat testing. FDA recommends if somebody is symptomatic and test negative they should test at least twice, 48 hours apart. The third test might be needed if the patient is really concerned they have COVID-19 to rule out the diagnosis. If a patient is asymptomatic and they believe they've been exposed and they are testing a rapid antigen test they should test at least three times each 48 hours apart to be considered truly negative.

The other option is to reflex test to NAAT testing if the NAAT is available that is the gold standard. If the NAAT is negative then alternate diagnoses should be considered such as a flu, RSV and strep throat. There's also muti-plex testing available now that can help distinguish between these common pathogens that present in a similar manner. Next Slide.

Let's talk a little bit more about treatment. Next Slide.

For this talk we will focus on outpatient therapy. I'm basically referencing the COVID-19 treatment guidelines. Treatment is an appointed intervention in secondary prevention due to COVID-19. It really is an important tool to minimize severe disease. The recommended first line therapy by the NIH panel is Ritonavir-boosted nirmatrelvir or Remdesivir, and for patients were neither of these preferred therapies are available feasible to use or clinically appropriate the alternate of recommended therapy is Molnupiravir. Next Slide.

I thought it would be important to talk briefly about the mechanism of action of these drugs. This is a slide that essentially depicts the viral replication cycle of SARS-CoV-2. As you can see Nirmatrelvir is a oral--inhibitor it's packaged with a P4 50 inhibitor and a boosting agent which is required to increase Nirmatrelvir concentrations to the therapeutic range. Ritonavir can also affect the metabolism of other medications but has been used safely for decades in HIV medicine. Both Remdesivir and Molnupiravir are pro drugs that inhibit RNA replication and Molnupiravir specifically results in viral mutations and lethal mutagenesis. Next slide.

So, the mechanism of action of these drugs actually contribute to their advantages and disadvantages. This slide summarizes the clinical trials that were conducted for each of these medications. I should mention that the eligible population for these trials were all people who had mild to moderate COVID-19 and they had at least one risk factor for severe disease. The trials were also conducted at the time when patients were unvaccinated and that is an important distinction to make. As you can see, the relative risk reduction or efficacy of Nirmatrelvir and Remdesivir are pretty high 88% and 87% respectively but for Molnupiravir, much lower, 30%.

And then if we talked briefly about the advantages and disadvantages of each of these medications Nirmatrelvir + Ritonavir it’s highly efficacious, it's an oral drug. Ritonavir has been studied and is safe to use in pregnancy, but it does have these drug/drug interactions that make it a little bit hard to use. Remdesivir is highly efficacious, safe in pregnancy, few drug interactions but it's hard to give because you need to give it through an I.V. infusion. And then Molnupiravir, another oral agent, without many drug interactions has a lower efficacy and because of its mechanism of action the concern is mutagenicity, which means, it’s not recommended in pregnancy or to children. Next slide.

I wanted to briefly talk about dosing issues I won't go into this in much detail but for Nirmatrelvir/Ritonavir renal dosing is needed in some cases. It's not a medication that should be used in patients who have severe renal disease or severe liver disease. And of course we've already mentioned the drug/drug interactions. Remdesivir on the other hand requires an I.V. infusion over up to two hours and for three consecutive days. Which makes it a little bit hard to use. Molnupiravir, patients who do take this drug if they are of reproductive age should use birth control. All of these medications should also be started early in the disease course within 5 to 7 days. Next slide.

So the questions have arised being that the clinical trials were conducted in an unvaccinated population. Do these drugs maintain their efficacy among vaccinated individuals? I wanted to just highlight this systematic review that was conducted. They looked at 23 studies involving over 300,000 patients and essentially you can see that there was still a significant reduction in odds of mortality or hospitalization. Combined there was 83% reduction in both mortality or hospitalization. 60% for hospitalization, 75% for mortality. Next slide.

For Molnupiravir, which hasn't been used that widely in the U.S., this is a study that was conducted in the UK. It's randomized controlled trial where they enrolled vaccinated patients. They did not see a reduction in the frequency of COVID-19 associated hospitalizations or death. What they did see is that participants that used Molnupiravir often reported earlier recovery. It does reduce the disease course or symptoms severity, which is basically depicted on the figure on the right, the blue line is the Molnupiravir group and the redline is the usual care group. You can see the proportion that recover quicker is a little bit higher. Next slide.

I also wanted to talk quickly about some considerations for treatment because we are getting some questions about treatment, particularly Nirmatrelvir/Ritonavir. Next slide.

The first question that often comes up his rebound. When I say rebound, I'm talking about a return of symptoms after recovery or a positive test after testing negative. CDC conducted a review and there was a recent publication in December of last year. It showed that really there isn't a consistent association between using antiviral treatment and COVID-19 rebound. Rebound has also been seen with other medications, but the important thing to point out is that patients that did experience rebound had mild symptoms and there were no hospitalizations or deaths due to rebound in the studies that were reviewed. This really highlights the fact that perhaps the risk of rebound should not be outweighed by the benefit of antiviral treatment. This is life-saving medication for patients who are at high risk of severe disease and if they are eligible to receive it, they should. Next slide.

I think the drug/drug interactions can be a little bit overwhelming for clinicians and so I wanted to highlight all of these resources that are readily available on the web. The NIH guideline has a nice drug/drug interaction chapter. I will show you a screenshot of a piece of that later. It really listens the drugs that need to be considered. This Liverpool COVID-19 drug Interaction Database is one of my favorite tools to use because it's so easy. It essentially allows you to enter the drug that the patient is taking and it will tell you what you need to do if you want to use Ritonavir-boosted Nirmatrelvir and the FDA also has a few resources on their webpage. Next slide.

This is the snapshot of the Liverpool drug interaction database, so if you can look at the left side you see the COVID drug you want to use is entered there. Here we have entered Nirmatrelvir/Ritonavir. The middle column you enter the medication that the patient is taking that you might be concerned about, in this case, atorvastatin. On the last column you will see it will show you whether there is some concern with that drug. So, statin has come a lot and not all need to be stopped in order to take Nirmatrelvir. So, this is a nice tool to see which are safe, which need to be stopped and which may need to be dose adjusted. Next side.

Here is that snapshot of the NIH drug/drug interactions chapter. I'm highlighting the ones here if you look on the left side of this slide under the red bar that says describe alternate therapy these are the drugs you really need to be concerned about and should not be prescribing Paxlovid with these medications. There are a number of cardiovascular medicines that need to be considered. There have been concerns with these medications. I want to also point out sometimes there's medications on these lists we don't commonly ask about. If you look at the miscellaneous groups St. Johns Wort is on this list so we think it is important to take a good history and review of the patient's medications before prescribing Paxlovid. Next slide.

And then this was something I wanted to show you because I do think it is really important for a team to provide care to patients who may benefit from COVID-19 antiviral therapy. Pharmacists are great clinic staff that can help understand drug/drug interactions but there are these nice tools the American Pharmacy Association has put together. This is a snapshot of a questionnaire that a pharmacist can go through with a patient to understand if they are eligible for treatment and this feeds into a larger algorithm that did fit on this slide. There have been tools that have been developed to make this easier for a busy clinician to do. Next slide.

Now it's time for a self-knowledge check. So my question is, Based on current evidence, what is the most effective public health intervention to prevent long COVID? The answers are A. convalescent therapy, B. COVID-19 vaccination, C. early antiviral therapy, D. handwashing , E. masking. The answer is COVID-19 vaccination. The rationale for this is that current evidence shows patients who received two doses of the COVID-19 vaccine had 36 to 40% lower odds of developing long COVID. Next slide.

This is the study that actually supports that assertion. It was basically a systematic review, a meta-analysis, of 12 studies involving greater than 600,000 patients. And what they showed was that vaccination before SARS-CoV-2 infection was associated with the lower risk of long COVID, but vaccination after SARS-CoV-2 infection was not associated with symptomatic changes of long COVID. Next slide.

It's a perfect reason for me to reiterate the importance of vaccination. Vaccination is the most effective way to protect patients against COVID-19. CDC recommends one updated COVID-19 dose for everyone six months or older. There is no additional dose for adults 65 or older recommended at this time. Children six months to four years and immunocompromised patients may need an additional dose. I've included a link to the clinical considerations at the bottom of the slide for further information. Next slide.

This is not a slide I'm going to go through right now. But we have been receiving a lot of questions about access to COVID-19 antiviral therapeutics and we have our colleague on the line today to answer any questions you may have about these programs. She will be available during the Q&A to take questions about this. With that, I thank you for your attention and I will pass it to my colleague Dr. Tim Uyeki to talk to us about influenza. Thanks.

Before I discuss influenza testing and antiviral treatment of influenza I'm going to summarize influenza activity this season and cover disease burden. Next slide.

So, this slide shows influenza positive tests reported to the CDC from clinical laboratories throughout the U.S. as is by a weekly basis, as of a week ago. What you can see from this slide is that although the numbers of positive tests peaked at the very end of the year there is still a substantial amount of influenza activity occurring in the U.S. from public health laboratory, testing we know the majority of influenza viruses circulating the season in the U.S. are influenza A viruses and of those the vast majority have been influenza H1N1 PDM 09 viruses with a smaller proportion H3N2 viruses. Overall, influenza B viruses have been circulating to a much lower extent. Next slide please.

This slide shows the cumulative lab confirmed influenza hospitalization rates by age groups for this season. As of January 20th, you can see the highest cumulative hospitalization rate are in people 65 years and older. The next moderate rates are those adults 50 to 64 and children less than five years with much lower hospitalization rates in nonelderly adults and then in school aged children. Next slide.

Now just to cover the spectrum of influenza virus infection the divvies severity and clinical manifestations are going to vary by patient age, host factors, immunity, underlying chronic disease and so forth, other conditions and also by the influenza virus type or influenza A virus subtypes. We know people can have asymptomatic influenza virus infection, but for clinicians what's most important are people who are symptomatic.

So most people, when infected with influenza viruses in the upper respiratory tract and have symptomatic disease, most people have uncomplicated illness. The incubation period is very short, typically 1 to 2 days. Most people may have the abrupt onset of upper respiratory tract signs and symptoms with or without fever. Many people do not have fever and this also includes elderly persons and immunosuppressed persons. Typically, the classic presentation is the abrupt onset of fever, cough, headache, sore throat, runny nose. Not gradual onset over a number of days but all signs and symptoms coming on once. There are gastrointestinal systems such as nausea, vomiting and diarrhea, but these are much more common in young children than in older children or adults. Some groups such as infants can have fever alone and irritability without manifesting respiratory signs. And then there are a lot of people that can have complications of influenza. Next slide.

Influenza complications I classify those into moderate and severe to critical. Examples of moderate complications not requiring hospital admission but might prompt an outpatient visit.

Would be Otitis media in young children or sinus infections and the worsening of underlying chronic disease but not enough to require hospitalization for severe disease.

In terms of what a patient with influenza might be hospitalized for, it might be for worsening of chronic disease that is much more severe, respiratory complications are the most common. Both viral pneumonia as well as secondary bacterial pneumonia, but also other upper and lower airway complications including croup, status asthmaticus, bronchiolitis, tracheitis and acute respiratory distress syndrome. There are cardiac complications in particular, influenza can precipitate myocardial infarction with people with coronary artery disease rarely, but it can occur. Influenza virus can precipitate myocarditis and pericarditis there is a very wide spectrum of neurologic complications that range from febrile seizures to encephalopathy and encephalitis to precipitating strokes, Guillain-Barre syndrome is very uncommon but can occur within influenza. Other complications such as Acute Disseminated Encephalomyelitis or Reye syndrome are much less common but can occur.

In terms of community acquired bacterial co-infection I will just mention there are three bacteria more common than others. Those include Staphylococcus aureus -- and pneumococcal infections as well as group A streptococcus. Other bacterial can cause community acquired influenza complicating community acquired pneumonia complicating influenza depending on what the host has colonized within their upper respiratory tract and possibly their lower respiratory tract.

Musculoskeletal complications that range from myositis. It might just be muscle pain, but then the worst would be rhabdomyolysis which can precipitate renal failure and multiorgan failure in critically ill patients can occur both respiratory and renal failure as well as septic shock. And don't forget in patients who are hospitalized, healthcare associated infections including bacterial or fungal ventilator associated pneumonia. Next slide please.

In terms of estimated disease burden, what you see on the upper right figure is 12 influenza seasons it excludes data from 2020 to 2021 season where we saw very little influence activity in the U. S. and actually worldwide probably because of nonpharmaceutical and conventions implemented to control the COVID-19 pandemic. But a wide range of disease severity from season to season. We see seasonal epidemics that result in estimated deaths of about 5000 to 52,000 per season and hospitalizations of wide range for anywhere from estimated 100,000 to 110,000 in a more severe season. 9. 4 to 41 million illnesses occurring.

You can see from the top figure on the right that among those 12 seasons the most severe we had was during the 2017 -18 influenza epidemic in the U. S. which is the higher range of 710,000 and 52,000 -- 710,000 estimated hospitalizations and 52,000 estimated deaths. For this season, preliminary estimates as of January 20th and we will update these regularly as we have data, estimated 18 to 35 million illnesses have occurred. Anywhere from 8. 4 to 16 million medical visits. 210,000 to 440,000 hospitalizations and 13,000 two 38,000 deaths.

Based on these data we would classify the season to date as a moderate season in terms of the – disease severity, there is much more influenza to go although nationally, we have peaked. Just to say although I showed hospitalization rates are highest in people 65 years and older mortality

rates are also much skewed towards people 65 years and older. It's much higher the older you are above 64 years old. Next slide please.

We know from a lot of observational data there are groups that increase risk for influenza complications and severe illness. These include children less than five years old but really it's children less than two years old who are at the highest risk among children and adults 65 years and older, and the people with chronic medical conditions. A wide range, this does exclude people who only have hypertension.

But it also includes people with neurodevelopmental, hematologic, metabolic disorders in addition to chronic pulmonary, cardiovascular, renal and hepatic disease and neurologic disease. People who are immunocompromise, people with extreme obesity, children and adolescents who are receiving aspirin or salicylate containing medications because of the association of influenza and salicylate with rise syndrome. Children and adolescents receiving aspirin or salicylate containing medications really need to be vaccinated as does everyone six months and older but they need to especially be watched for signs and symptoms of influenza and might need to stop the salicylate medications. Residents of nursing homes and other long-term care facilities are at higher risk. We see influenza outbreaks in nursing homes every season with high attack rates and unfortunately a lot of complications and deaths.

Pregnant people and people up to two weeks postpartum are at higher risk for influenza complications and we also know from epidemiologic data that people from certain racial and ethnic minority groups, including non-Hispanic black, Hispanic or Latino and American Indian or Alaska native persons have higher hospitalization rates. Next slide.

Let's move on to influenza testing, Next slide please.

So just as background before I cover influenza test, just to say that influenza viruses can be detected in the upper respiratory tract one day before illness onset. And that virus levels peaks after 24 hours after illness onset, you can sort of see that the figures on the left as well as lower right. That viral level RNA levels really drops off the upper respiratory tract after about three to four days after illness onset. There are some exceptions, those are typically generalizations for immunocompetent people, but in young infants with influenza virus infection they can be infectious for much longer periods. Critically ill patients in the hospital might have longer influenza virus replication particularly in the lower respiratory tract and immunocompromised persons may shed very prolonged periods. Next slide please.

In terms of the best respiratory specimens to detect influenza viruses in the upper respiratory tract influenza viruses are generally detectable for about 3 to 4 days by Antigen Test's and about 5 to 6 days by nucleic acid molecular tests and people who have uncomplicated disease. But as I mentioned, young infants and immunosuppressed patients can have longer viral shedding. So a longer duration of detection. The optimal specimen for detecting influenza viruses in terms of the upper respiratory tract are nasopharyngeal swabs. They should be collected within 3 to 4 days of illness onset. Other acceptable specimens are nasal swabs, aspirates, nasal aspirates or combined nasal and throat swabs.

Throat swabs alone have a much lower yield for detecting influenza viruses. Saliva specimen are not a specimen you would detect influenza viruses in and are not approved for any assay.

I mention there's slower clearance of influenza viruses both from the upper respiratory tract and particular lower respiratory track and those who have severe disease. Just a reminder to clinicians that influenza viral replication and therefore viral RNA detection may be prolonged with corticosteroid use.

In terms of the lower respiratory tract we know that influenza viruses might be detectable in the lower respiratory tract specimens when they are no longer detectable in the upper respiratory tract because a patient may have cleared them from the upper respiratory tract but they might have ongoing lower respiratory tract replication particularly in intubated patients or those with respiratory failure but who are not intubated. Next slide please.

There are a variety of influenza diagnostic tests that are available in clinical settings to detect influenza viruses in respiratory specimens. These differ by the time to produce results. What information you get from a test result, what specimens are actually proof for the tests, what clinical settings can you use a test and then the accuracy. These basically fall into two categories, antigen detection and nucleic acid detection or molecular assays. In terms of antigen detection, they are FDA-cleared single-plex only detect influenza A and B viruses, there are multiplex assays and some of these are authorized by FDA. There are authorized assays that can detect influenza A and B viruses as well as SARS-CoV-2 and these are antigen assays.

On the molecular side there are FDA authorized multiplex assays that also can detect influenza A and B and SARS-CoV-2. Some can detect RSV. There are other multiplex assays that can detect other respiratory viruses as well as some bacterial respiratory targets. There are a number of single-plex assays that only detect influenza A & B viruses.

There are also some assays that will detect some types of influenza A, such as H1 and H3 viruses.

There is one test FDA authorized for home use now and it's authorized to use self-collected nasal swabs in people aged 14 years or older or in those two years up to age 14 for adult collected interior nasal swabs. The kinds of assays, in terms of settings, point of cure assays that are CLIA-waived so they can be used at the bedside in any healthcare setting. There are those that are moderately complex that require a clinical laboratory then there are those that are highly complex that require large clinical laboratories and public health labs and these are particularly RTPCR assays. Next slide please.

This slide summarizes influenza tests that are available in clinical settings. The antigen detection, molecular assays and just to highlight the purple circles there, the time to results, the antigen detection assays, single-plex about 10 minutes to results, multiplex about 15 minutes to results. There are rapid molecular assays that can produce results within 15 to 30 minutes and there's some multiplex assays that can yield results in 36 to 45 minutes.

These are pretty rapid time results in terms to really inform clinical management without having the patient wait too long. Then there are other molecular assays that take much longer and these are particularly performed hospital, in clinical labs or public health laboratories that may take one hour up to many other hours. In all of these, what's important to know is that Rapid Antigen Tests and even the multiplex antigen detection tests have low to moderate sensitivity. Some have moderately high sensitivity which means that false-negative results are not that uncommon. When you move to the rapid molecular or other molecular assays the sensitivities are high among all of these. Among antigen tests and molecular assays all of these tests have high specificities so that false positive results are uncommon.

It's more a concern of false-negative results, potentially with the antigen detection tests. So proper interpretation of test results in the context of what is going on with influenza in the local community where the patient is from as well as understanding the time from when a patient's symptoms started to when you're testing the patient. All these factors in understanding prevalence of influenza virus activity and characteristics of the test antigen versus nucleic action is important to consider when interpreting negative results.

Self-knowledge check. The following statements regarding influenza testing are true except A. nasopharyngeal swab is preferred respiratory specimen to detect influenza viruses. B. Molecular assays have high sensitivity to detect influenza viruses in respiratory specimens. C. Rapid Antigen Test's and molecular assays can detect influenza viruses in saliva specimens up to seven days after symptom onset. D. Some molecular assays can yield results within 30 minutes. E. False positive results are uncommon with Rapid Antigen Test's and molecular assays because of their high specificities. Next slide.

The answer is C. Rapid antigen tests and molecular assays can detect influenza viruses in saliva specimens up to seven days after symptom onset. This is false. Saliva specimens are not recommended and not proof detection of influenza viruses by any assay. All the other answers are true. Next slide please.

So what influenza tests are recommended? The infectious disease Society of America and their influence a clinical practice guidelines recommend for outpatients the use of rapid influenza molecular assays are recommended over rapid influenza antigen test. That is basically because of the much higher sensitivities of the molecular assays over the antigen tests. For hospitalized patients, RT-PCR or other influenza molecular assays are recommended. Rapid antigen detection tests including immunofluorescence assays are not recommended and should not be used because of their lower sensitivities. The only exception is when molecular assays are not available and all you have are antigen detection assays for immunofluorescence assays.

For immunocompromised patients, they recommend considering multiplex RT-PCR assays that target a panel of respiratory pathogens, including influenza viruses. The reason is because immunocompromised patients can actually have lower respiratory tract diseases and severe disease due to many different respiratory viral pathogens in addition to influenza and in addition to SARS-CoV-2. Some key points I want to make do not order viral culture for initial or primary diagnosis of influenza. The results are not going to be timely to inform patient management. Viral culture is very important for public health purposes and might be important for

investigating an outbreak in a nursing home but it's not going to inform individual patient management because of the time to results will take it a minimum of three days. Do not order serology for influenza. There are large commercial laboratories that do offer influenza serology. You cannot properly interpret the results of serology from a single serum specimen. It requires collection of acute and convalescence, 2 to 3 weeks apart and the testing needs to be done at specialized laboratories, particularly public health laboratories. Serologic studies are important for vaccine studies, epidemiologic studies but they're not going to inform patient management. Next slide please.

Let me move on to antiviral treatment of influenza. Next slide please.

The CDC antiviral guidance is focused on prompt antiviral treatment of persons with severe disease and those at increased risk of influenza complications. We recommend antiviral treatment as soon as possible because it has the greatest clinical benefit for patients with confirmed or suspected influenza who are hospitalized. The reason why we say suspected influenza, we know there can be delays in diagnosing influenza and we know from observational studies that when you start antiviral treatment at the time of hospital admission there is clinical benefit particularly in reducing the duration of hospitalization compared to initiating antiviral treatment later after admission. We do say empiric antiviral treatment should be initiated if you suspect influenza in a hospitalized patient. You should test the patient but don't delay treatment.

We do recommend oseltamivir. It can be oral oseltamivir or for an intubated patient or enterically delivered through an oral or nasal gastric tube. For outpatients with complicated or progressive illness of any duration we do recommend oral oseltamivir and for patients who are at high risk for influenza complications we recommend oseltamivir and baloxavir and I will go over this next. For patients who are previously healthy, who are not at high risk for complications of influenza who present with influenza-like illness you can make a clinical diagnosis of influenza or if you test them, if they present within 48 hours of illness onset it is clinical judgment and up to the clinician and patient if they want to be treated. There are studies that have shown clinical benefit when antiviral treatment is initiated within two days of illness onset in otherwise healthy people. It's not the priority group. Our priority is focus on those with the most severe illness, high risk people, and those with progressive disease. Next slide please.

In terms of antivirals recommended for treatment of influenza this season there are four antivirals that are recommended. There is no evidence of resistance with any of these antiviral drugs amongst influenza A and B viruses in the U.S. or worldwide. All of these drugs I'm going to talk about have demonstrated efficacy in randomized controlled trials versus placebo and they’re FDA approved for early treatment within two days of illness onset and outpatients with uncomplicated influenza.

The first group includes the class we call neuraminidase inhibitors. Neuraminidase inhibitors block the release of influenza viruses from infected cells. They actually don't interfere with viral replication, but they block the spread of influenza viruses and respiratory tract. Neuraminidase inhibitors include oseltamivir which is available in oral formulation, also it’s available not just oral capsules but oral suspension. It should be given twice daily for five days, and dosing depends upon age and weight. Oseltamivir is an inhaled powder you must use a disk inhaler

device and treatment is twice daily for five days. Peramivir is intravenous infusion it’s given as a single dose.

The other class of drugs we recommend are captive and endonuclease inhibitor drugs or you can call them --inhibitors. Unlike the neuraminidase inhibitors that don't interfere with influenza virus replication, baloxavir marboxil, which is the one drug in this class that’s approved; does inhibit influenza viral replication and really does reduce viral load rather rapidly within 24 hours. Just to summarize the four drugs here Oseltamivir, Zanamivir, Peramivir and Baloxavir. To note, you can see not only is the route of administration differ, but recommended age and proof for treatment differ. You should check those. The reason I've highlighted oseltamivir and baloxavir is because these are the most widely prescribed antivirals. The others are very infrequently used in the U.S. Next slide.

Let me talk about the efficacy of oseltamivir in randomized control trials. Meta-analyses, let me go over to. One is of five randomized controlled trails in children. When you start treatment within 48 hours of onset compared to placebo in these five trials oseltamivir reduced illness by 18 hours overall. When you excluded children who had asthma the benefit was 30 hours in reducing the duration of illness. There was a reduction of otitis media by about one third. In adults, treatment is started within 36 hours of illness onset. Nine RCTs. There's a reduction of illness duration by about a day. A 44% reduced risk of lower respiratory tract complications occurring within 48 hours after treatment was started that required antibiotics.

I will mention in the meta-analysis of children, oseltamivir was associated with an increased risk of vomiting in children. The adult analysis reported there was an increased risk of nausea and vomiting with oseltamivir compared to placebo in adults. Next slide.

In terms of Baloxavir efficacy there are a few randomized controlled trials versus placebo when started within 48 hours after illness onset in the randomized controlled trial in children age one to less than 12 years, single dose Baloxavir, just a single dose, had similar medium time to alleviation of symptoms versus five days of oseltamivir. In the trial in adolescents and adults when you started treatment within 48 hours of illness onset Baloxavir single dose significantly reduced illness duration by a little more than a day versus placebo. These are in non-high-risk persons. Importantly, a single dose again was similar to five days treatment twice daily of oseltamivir. Of note, in this trial, Baloxavir significantly reduced influenza viral RNA levels at 24 hours and reduced infectious virus detection versus oseltamivir. 24 hours versus 72 hours for oseltamivir.

In another trial in high-risk people the median time to improve symptoms again was similar for Baloxavir versus five days of oseltamivir, but importantly Baloxavir significantly reduced the median time to improvement in this patients with influenza B by more than one day versus oseltamivir. Baloxavir has higher efficacy against influenza B then oseltamivir. Next slide please.

To say there are special populations I wanted to mention. Pregnant people, oseltamivir is recommended for treatment of influenza in pregnant people and those up to two weeks postpartum.

Baloxavir is not recommended for treatment in this group because we have no efficacy or safety data for Baloxavir in pregnant or lactating people. There was a possible signal toxicity in preclinical studies and toxicology studies in pregnant rabbits. In contrast for oseltamivir where we have a lot of safety data there is no concern of adverse pregnancy or birth outcomes for oseltamivir treatment of pregnant people with influenza. We don't recommend Baloxavir, we do recommend oseltamivir for treatment of pregnant people and those up to two weeks postpartum.

For immunocompromised persons I mentioned prolonged influenza viral replication is a possibility. There can be emergence of antiviral resistant viruses during and after treatment. It is really important to monitor patients for antiviral resistance if there is evidence of prolonged viral shedding and in healthcare setting it is important to maintain infection and prevention and control precautions. There have been outbreaks on bone marrow transplant units for example. We do recommend for immunocompromised persons neuraminidase inhibitor treatment, we do not recommend monotherapy with baloxavir because there is an increased risk of resistance emergence to baloxavir then for oseltamivir. What we really need our combination antiviral treatment studies, in this immunocompromised patient population and there are some phase two clinical trials of influenza plus baloxavir -- sorry, oseltamivir plus baloxavir compared to oseltamivir alone in progress but we don't have such data yet. Next slide please.

Just as a reminder as I mentioned, although the influenza season has peaked nationally there's still a lot of influenza viruses circulating throughout the U.S.A lot of communities are still in influenza. We expect it to continue for many weeks to come this season. For unvaccinated people I want to remind clinicians and public health colleagues that vaccinations are the most effective way to protect against influenza.

We recommend annual vaccination for everyone six months and older. For children six months to eight years who have previously not received vaccination they will need one additional dose. For those 65 years and older who are unvaccinated there is a preferential recommendation for high-dose recombinant or adjuvanted influenza vaccines over standard dose vaccine. There's still plenty of time to get vaccinated. There's plenty of influenza vaccine available. Nest slide.

With that, I would like to highlight some resources that we have on our CDC influenza webpages for clinicians about influenza testing including some clinical algorithms and recommendations, including when SARS-CoV-2 and influenza viruses are co-circulating. We also have information for antiviral treatment of influenza on our CDC webpages as well as the link to the IDSA influenza clinical practice guidelines. Next slide.

Here are some resources for SARS-CoV-2 testing as well as antiviral treatment of COVID-19. With that, it will turn it back to Commander Khan, Thank you.

Thank you very much presenters I appreciate you sharing this valuable information. We will now go into the Q&A session. Joining Dr. Patel and Dr. Uyeki is Dr. Meghan Pennini. Dr. Pennini is the Chief Vaccines and Therapeutics Officer in the HHS Coordination Operation and Response element at the Administration for Preparedness and Response within the Department of Health and Human Services.

Our first question is regarding COVID-19 antiviral access. Can you please explain how these access programs work, who can enroll and how can they enroll patients? And Can you tell us what the process entails? Thank you for that question. I want to stress up front that there are these access programs in place, particularly for Paxlovid which of course is the first line treatment for COVID-19 due to its efficacy and accessibility.

We do have a program in place that is using and continues to use U. S. government procured Paxlovid to get this absolutely free Paxlovid to patients who are eligible for the program. The best way to understand more about that is to go to Paxlovid.com. This is a program that'soperated by Pfizer so that is a Pfizer website. This means that anyone who has any public insurance, meaning anyone who has Medicare coverage whether secondary insurance, they have a part D or do not, anyone who has Medicaid, anyone who is uninsured so long as they enroll in the program and enrollment is very quick and can be done by the patient and caregiver, can be done with a pharmacist, anyone can help enroll and they will get absolutely free Paxlovid once they are prescribed the medication if they are in the high risk category. That is a program for anyone who has Medicare, Medicaid or is uninsured. For anyone commercially insured there's also a program in place that will buy down the cost of that medication as well. If you go just to that site which I can put in the chat you will get directed to the correct program depending on which insurance you have.

If you are hearing of anyone who is getting told they owe a large amount of money for this product please make sure they understand there are programs in place where they can get that product for zero dollars or for very low cost and so they should be directed to those programs. As far as who is eligible, anyone really is eligible. It depends on what level of coverage you get against the cost. I talked about Paxlovid but there are programs in place for -- again, the slide in this deck has links out so you can understand more about those programs.

Thank you. If you are not able to catch the link in the chat please download the slides as well as the on-demand video after this call where you can revisit those resources.

Our next question asks, can you talk a little bit about patients who may be up-to-date with their COVID-19 vaccines? Would you consider them eligible for these treatments?

I will take that. This is Pragna Patel. I think that's a great question and we've received this question a lot. It's important to get vaccinated to prevent severe outcomes from COVID-19 before you get infected. But once you get infected if you're at high risk for developing severe disease--antiviral treatment offers an added benefit. Prescribers should consider antiviral treatment among patients who are at high risk regardless of their vaccination status.

Thank you very much. **Our next question asks what are your recommendations about using combo therapeutics for influenza? Using antivirals that may have different factions?**

This is Tim Uyeki, I will take that. Thanks for that question.We don't have data right now from any randomized controlled trials but the patient population where it is most important would be immunocompromised patients with influenza virus infection because of the risk for prolonged viral replication. There are at least two clinical trials in progress phase two studies, looking ---

with both clinical and urologic endpoints. Hopefully we will know more from that. There was a randomized controlled trial and hospitalized patients with influenza that essentially compared oseltamivir plus Baloxavir versus oseltamivir alone.

It wasn't actually quite set up that way. It was set up as inhibitor treatment plus Baloxavir versus neuraminidase inhibitor treatment alone. It ends up being oseltamivir plus Baloxavir versus oseltamivir alone. The addition of Baloxavir actually did not provide significant benefit in terms of reducing duration of illness. We don't currently recommend combination antiviral treatment for influenza patients who are hospitalized.

That trial did show that by adding Baloxavir to oseltamivir there was a significant reduction in viral shedding compared to oseltamivir alone. Although that did not have clinical benefit for the patient I would argue that there is clinical benefit in the hospital setting because a earlier time or reduction in viral shedding can actually reduce the need for infection prevention control precaution. There is some benefit. Basically, we still don't know the optimal duration of treatment, the optimal combination of antiviral treatment for hospitalized influenza patients so there' still a lot more. What I would say for hospitalized patients with influenza what we really need, and there are trials in progress now, is we need to look at immunomodulator treatment of severe influenza. We have learned a lot about treatment of severe COVID-19 and the use of immunomodulator therapies. We need to now study that in influenza patients and there are at least a couple studies in progress. No data for a while.

Thanks. Thank you. We have time for one last question.

This is a question we have seen in different forms today. The question boils down to you have talked about coadministration off influenza vaccine and COVID vaccine simultaneously. The question is actually regarding in the case of co-infection with COVID-19 and influenza, what are your recommendations for providing simultaneous therapeutics for both COVID-19 and influenza? Are there any adverse effects or interactions or guidance that physicians should be aware of?

This is Tim Uyeki. I will take that. High risk outpatient, a patient at high risk for progression to severe COVID-19 you want to treat those patients ideally as soon as possible within five days if it is for Paxlovid. If you are treating that patient for Paxlovid you should also treat them for influenza. The reason is although co-infection and influenza viruses are not common they tend to be infrequent. When they do occur and they require hospitalization disease severity is much higher and more severe in those with SARS-CoV-2 plus influenza virus co-infection compared to either SARS-CoV-2 infection alone or influenza virus infection alone.

There are no interactions of the antivirals to treat influenza with the antivirals or other therapies you would treat patients either in the outpatient setting for COVID-19 or the inpatient setting for severe COVID-19. Whether in the outpatient setting or inpatient setting, for an outpatient who is high risk for severe disease and there are a lot of overlapping high risk conditions so high risk person for severe COVID-19 is probably going to be high risk for influenza complications I would treat them both for COVID-19 and influenza.

Thank you very much. That concludes today's program.

I want to thank everyone for joining us today with a special thanks to our presenters, Dr. Pragna Patel, Dr. Tim Uyeki and our special guest Megan Pennini. We have some updated continuing education information. Starting January 1st, 2024, CDC moved from the continuing education online system for continuing education to CDC Train.

If you do not already have a TRAIN account, please create one at www.train.org/cdctrain. All new activities that offer CE from CDC will only be listed in CDC TRAIN. CDC TRAIN is the gateway into the train learning network and most apprehensive catalog of shared public health training opportunities.

This transition will allow you to access noncredit and for credit educational activities and track your learning including CE in one place. Many CDC accredited activities are already listed in CDC TRAIN but learners currently use TCEO to complete the CE process. The move to one system will improve efficiency and will make it easier for learners, CDC staff and partners to offer and earn CE in one place. You can continue to use your TCEO for existing activities that have CE that is set to expire in 2024. Since these courses will not move to CDC TRAIN you may also use TCEO for existing activities with CE that doesn't expire until 2025 before the course transition to CDC TRAIN sometime next year.

If you begin one of these courses in TCEO we will let you know when the course will move to CDC TRAIN. You can access and download CE transcripts and certificates in TCEO to the end of 2025. Instructions will be available on both platforms and a learner support team will be available at those resources to answer your questions. All continuing education for this COCA call is at www.train.org.

Those who participate in today's live call and wish to receive continuing education please complete the online evaluation before March 4th, 2024, with the course code **WC4520R-020124**. The access code is **COCA020124**. Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between March 5th 2024 and March 5th 2026. Use course code **WD4520R-020124**. The access code is **COCA020124**.

Today's call will be available to view on demand a few hours after the live call at emergency.cdc.gov/coca emergency. A transcript and closed caption video will be available on the COCA call website next week. We invite you to join us on Thursday, February 29th at 2:00 p.m. Eastern for our next COCA call. The topic will be Xylazine-adulterated Fentanyl Overdose: Clinical and Public Health Implications.

You can visit emergency.cdc.gov/coca for more details about this COCA Call and other upcoming COCA Calls. We invite you to subscribe to receive announcement for future COCA Calls by visiting emergency.cdc.gov/coca/subscribe.asp. You will also receive other products to help keep you informed about emerging and existing health topics. Thank you for joining us for today's COCA Call and have a great day.