

Good afternoon. I'm Commander Ibad Khan and I'm representing the Clinician Outreach and Communication Activity COCA with the Emergency Risk Communication Branch at the Centers for Disease Control and Prevention. I would like to welcome you to today's COCA Call, What Clinicians Need to Know about Available Therapeutic Options for COVID-19. All participants joining us today are in listen only mode.

Free continuing education is offered for this webinar. Instructions on how to earn continuing education will be provided at the end of the call. In compliance with continuing education requirements, all planners and presenters must disclose all financial relationships in any amount with ineligible companies over the previous 24 months, as well as any use of unlabeled product or products under investigational use. CDC, our planners and presenters 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 our on patients, except for Dr. Eric Daar, who would like to disclose that he provides research support and is a consultant related to HIV for Gilead Mark and GSK. All of the relevant financial relationships listed for these individuals have been mitigated. Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use, with the exception of Dr. Farley's discussion of unapproved drug products currently authorized under EUA for treatment of COVID-19. CDC did not accept financial or in-kind support from ineligible companies for this continuing education activity.

At the conclusion of today's sessions, the participants will be able to accomplish the following: describe key points about COVID-19 rebound after use of Paxlovid. Describe Paxlovid use, prescribing and availability, and discuss where to find more information about COVID-19 therapeutics and their availability.

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

We have introduced self-knowledge checks throughout the presentation. We hope you enjoy these opportunities to assess your understanding of today's session. Please do not type your answers into the Q&A, box as this may disrupt the Q&A portion at the end of the session.

I would now like to welcome our presenters for today's COCA Call. We're pleased to have with us Dr. Pragna Patel, who's the Chief Medical Officer of CDC's COVID-19 response.

Dr. Eric Daar, chief of the Division of HIV medicine at Harbor UCLA Medical Center, COVID-19 researcher and member of the clinical guidelines panel at the National Institutes of Health.

Dr. John Farley, the Director of the Office of Infectious Diseases at the Office of New Drugs at the Center for Drug Research at the US Food and Drug Administration. And our final presenter today will be Dr. Meg Sullivan, Chief Medical Officer of the COVID-19 response at the Office

of the Assistant Secretary for Preparedness and Response at the US Department of Health and Human Services.

It is my pleasure now to turn it over to Dr. Patel. Dr. Patel, please proceed.

Thank you. It's my pleasure to be here representing CDC, and I will give you a brief update on the COVID-19 pandemic. Next slide.

So these data are from CDC's COVID data tracker which you can find online. Basically, we're showing here the daily trends in COVID-19 cases in the United States. The blue bars are the actual number of daily cases, and the red line represents the seven-day moving average. And as you can see, as of June 12th, 2022, there were approximately 30,000 cases of COVID-19 in the US. This is considerably lower than the peak we noted in January of this year, where the peak was about 800,000 cases. And the seven-day moving average of daily cases in recent weeks as of June 12th was about 100,000 cases. Next slide.

So we're in a time where we're not sure if we have peaked or plateauing or if cases are increasing. And it's always important to take note of what variants are circulating. So this graph shows variants of concern that are available on the web through the NOWCAST model. And these are detected variants that we're seeing in the US since the end of February 2022. And since that time, most of the variants have been almost exclusively Omicron or Omicron sublineages. And as you can see, noted by the pink bar, BA. 2 rose in proportion of detected cases through March and April, but it's now supplanted by the sub lineage BA. 2. 12. 1, which is depicted by the orange line. And that lineage currently represents approximately 60 to 68% of cases. Due to the growth and proportion of detected sequences, BA. 4 and BA. 5 now represent a significant -- not significant number of cases, but an increasing number of cases. And they're depicted by the Green Line. BA. 4 is the light green line, BA. 5 is the darker green line. And it's estimated that there's approximately 6 to 11% of detected sequences due to BA. 4 and 10% to 17% due to BA. 5. And there's some suggestion in the literature that these two lineages may have more immunescape than BA. 2 and could be more infectious. So CDC is currently watching that carefully. Next slide.

And here we see daily trends of COVID-19 deaths in the US. Again, the blue bars are the number of daily deaths and the red line is the seven-day moving average. On June 12th, there were 30 deaths reported to us. The seven-day moving average being 276. This is much lower than the recent peak in early February of this year, where the seven-day moving average was almost 3,000 reported deaths. Next slide.

And here we see weekly deaths per 100,000 population reported by age group. And I just want to point out this dark purple solid line which represents persons aged 75 and older. They have experienced the highest COVID death rate throughout the pandemic. And there was a large surge in deaths among this age group during the recent peak of cases during January and February. And we also additionally see that the age groups for persons 65 to 74 in the dashed pink dotted line were also increased during the most recent wave. Next slide.

And here we have new hospital admissions for COVID-19 by age group. And again, you can see that the oldest age group represented here, persons 70 and older, experienced a large surge in COVID-19 hospitalizations during January and February. And the age group of persons 60 to 69 in dark pink, also experienced an increase in hospitalization during that wave. Next slide.

So here we have some data that was generated by CDC through an analysis using COVID Net surveillance data on hospitalizations, and provisional death counts provided by the National Center for Health Statistics. We examined the relative risk for COVID-19 infection, hospitalization and death among different age groups. These data represent hospitalizations and deaths reported from March 2020 through June 2nd of this year. And because these data cover outcomes throughout the pandemic, it's important to note that they reflect outcomes during a time period when vaccination and evidence-based therapeutics were not available widely. And they are not stratified by time period or vaccination status. So the age group 18 to 29 is used as the reference group. And as you can see, if we look at hospitalizations, the risk of hospitalization tends to increase incrementally, particularly among the 65 and older age group. And if you look at the rate of COVID-19 deaths, particularly among the older age groups, there's an exponential increase with increasing age. Persons aged 50 to 64 have experienced a rate 25 times then persons aged 18 to 29. And this increases to 65 times in the 65- to 74-year-old group, and more than 100 times higher in the age 75- to 84-year-old group. And above 85, it's 330 times higher. Next slide. Next slide.

So a recent MMWR examined risk factors for severe COVID outcomes among persons having received a primary vaccination series, and demonstrated similar findings. This study was conducted in the US and had a sample population of approximately 2,200 persons. Severe COVID-19 outcomes were defined as diagnosis of acute respiratory failure, need for noninvasive ventilation, ICU admission or death. And as you can see by the bars represented on this graph, persons aged 65 and older were at the highest risk of severe COVID outcomes, with an adjusted odds ratio of 3.2 compared to persons aged 18 and 39 years old. Persons with many of the comorbid conditions examined demonstrated higher risk for severe COVID-19. But age greater than 65 was the predominant risk factor. One limitation of this study was that persons aged 40 to 64 were aggregated, which can limit the interpretation when it comes to the more narrow age groups, particularly persons aged 50 to 65. And another characteristic of this study is that it was extended through the wave of COVID-19 related to the Delta variant. However, the study only examined data through October 2021 and therefore were not capturing infections related to the Omicron variants. This study also demonstrates that there is a substantial impact that age has on the risk of severe COVID-19 outcomes, even among persons receiving a primary vaccine series. And at the bottom of the slide, I've included two links to recent systematic reviews that tend to suggest that rather than looking at categorical age, we should consider that with increasing age, the risk for severe COVID-19 outcomes do increase. Next slide.

And so here's a screenshot of the page that CDC uses to outline underlying medical conditions which are associated with higher risk of severe COVID-19. This evidence, the evidence used to update this list is currently being reviewed. And I imagine that we will be making an update to this page in the near future. But we just wanted you to be aware that there was a public facing page that was available for healthcare providers specifically to provide information on factors associated with higher risk of severe COVID-19 disease. Next slide.

And so now I'll just move to the self-knowledge check. So which of the following individuals with SARS-CoV-2 infection are at high risk for progression to severe disease? A, 45-year-old obese person with diabetes and chronic obstructive pulmonary disease. B, a 68-year-old woman with mild arthritis who remains relatively active. C, an 82-year-old man with hypertension. D, A and C only. Or E, all of the above. Next slide.

So the correct answer is E. And the reason for this is because increasing age is the most predominant risk factor for progression to severe disease, with persons greater than or as equal to 65 years old being at highest risk compared to younger individuals. Therefore, patients B and C are at risk given their age alone. Multiple comorbidities increased risk as well. So patient A, although younger is that risk given their history of chronic conditions, particularly lung disease and diabetes. We think it's important to use the CDC risk factors as a guide for deciding who may be eligible for treatment. But we do feel it's important for clinicians to use their own clinical judgment in deciding who they might put onto treatment, considering their concomitant medication use as well as their comorbid conditions.

And so with that, I would like to pass the baton over to Dr. Daar who will review the NIH COVID-19 treatment guidelines with you to go through the details of what is recommended.

Over to you, Dr. Daar.

Dr. Daar, can you check your mute settings, please?

Thank you. Thanks, Pragna. Thanks. Sorry about that. And I appreciate the opportunity in being invited here to present some of the clinical data that informed the current NIH guidelines on the management of patients. Next slide, please.

So I'm going to be talking about therapeutics for both treatment and prevention of patients importantly at high risk for severe COVID-19. So this previous discussion is really critically important because the therapeutics that are being used for both treatment and prevention are largely targeting people who are at risk for bad outcomes, like hospitalizations and death. Next slide.

My disclosures were already shared. The next slide, please.

So this is a summary of what the current NIH guidelines are recommending for patients who do not require hospitalization or supplemental oxygen. So these are primarily these non-hospitalized patients with mild to moderate COVID-19. And the recommendations are general about offering symptomatic management. And importantly then talk about specific therapeutics. And I encourage you to review this document, save it as a favorite and use it frequently to see where we are with therapeutics. Because this like SARS-CoV-2, these guidelines have been in a state of constant evolution. These are the most recent recommendations and they're broken down into preferred therapies with ritonavir-boosted Nirmatrelvir, or Paxlovid, and remdesivir. And then alternative therapies, Bebtelovimab and Molnupiravir The next slide.

It's important just to give you an idea as to how things have evolved to at least comment on the fact that there are several therapeutics that had been on this list not that long ago and are no longer there. And these are three monoclonal antibody products that were demonstrated in large placebo-controlled trials of high-risk, non-hospitalized patients to significantly reduce the risk of hospitalization and death. And it was because of the emerging variants and the recognition of decreased in vitro susceptibility of these products to these variants that distribution has been halted. This started with the Bamlanivimab and Etesevimab products, initially losing susceptibility during the evolution of beta and gamma. Suddenly it looked like it might have some utility with Delta, and then again, to be lost based on susceptibility for Omicron. The REGEN-COV, Casirivimab and Imdevimab was another combination that actually looked like it was maintaining its susceptibility, until eventually with Omicron in vitro susceptibility was markedly reduced, and it was no longer distributed. And then most recently Sotrovimab, which again looked like it was maintaining its activity until the subvariant of Omicron BA. 2 emerged. So all three of these products had been on the guidelines list and are no longer there based on emerging variants. Next slide.

So where are we? Well, we have the Nirmatrelvir for high-risk, non-hospitalized adults. This is boosted with ritonavir. And this was the pivotal trial, the EPICHR study that randomized high-risk individuals to therapy versus placebo. And there was a marked reduction in the events of hospitalization or death through day 28. Eight events in the active arm, versus 66 in the placebo arm, which translated to almost a 90% reduction in risk of hospitalizations and death. An important thing to note with this study, and frankly, all of the studies that we're going to talk about for our current products, is these studies tended to exclude people that were vaccinated and were not done during the current Omicron variant -- the prevalent Omicron variant. So it's older variants and unvaccinated individuals. And that's at least important to keep in mind as we discuss these products and the guidelines with our patients. Next slide.

So one of the things you're probably familiar with is that this drug is combined with ritonavir as a pharmacologic booster. This is a potent inhibitor of the cytochrome P450 system. And we know that therefore it will be associated with drug-drug interactions. And it's a little bit intimidating, because it's important that we look for these interactions and be careful when prescribing this drug that's otherwise quite easy to administer since it is given as an oral agent in an active protease inhibitor product. I will say that having been treating people with HIV for more than two decades, we've been using ritonavir effectively as part of our combinations of therapies for all of this time. And it really can be done without a lot of difficulties, but it's important to know about it and to have resources. At the bottom I have the Liverpool reference. This is an online resource that you can plug in agents, and it will tell you about the interactions and what you might do about it. There are a variety of other resources, but the COVID-19 treatment guidelines, the NIH have also updated some tables. The next slide.

And in order to try to make this as easy for people as possible, there are several different tables with different headings. And this first one is medications without clinically relevant interactions. So this is a partial list. But just to give you a sense as to what it looks like, it will allow you to say, I have a patient who's on another drug, I want to quickly find out if I need to worry about it. You can start with this table; it's broken down based on the class of the drug or the type of the agent it is. And if you find it listed here, and these are some of the most commonly used drugs

that our patients are taking, you can move forward without worrying about any interactions. Now if it's not listed here, you would look at some of the other tables. And the next slide shows the breakdown.

So there are products that you adjust concomitant medication dose and monitor for adverse events. There are those that you might temporarily withhold the concomitant medication if clinically appropriate, usually for at least two to three days after completing the ritonavir-based regimen. And then there are other products where you simply should not give with this drug, so you need an alternative COVID-19 therapy. And for each of these different tables, there is a list much like in the first one I showed you, broken down by the type of drug it is or what disease it's treating, so that you can quickly go through it and hopefully be able to identify if there are any issues and what to do about it. Next slide.

So that is one of the two preferred options. The second one is Remdesivir Remdesivir, as you know, is FDA approved for inpatients and more recently now for outpatients based on this data. These are for people with mild to moderate disease at high risk for progression to severe disease, such as hospitalization and death. This is a nucleotide adenosine analog that terminates RNA transcription. It's given us an intravenous infusion. And in the outpatient setting, in this PINETREE study, it's given over three consecutive days. So this is one of the challenges with this product, is it's an outpatient drug that needs to be given not as a single infusion, but a single infusion on day one, two, and three. But what was shown here that it was quite effective at reducing the risk -- about 87% of hospitalizations or death. And you can see the number of endpoints were relatively small. It was approximately four in the active arm, 21 in the placebo arm. And again, this was the previous variants, and in an unvaccinated patient population. But highly effective and generally quite well tolerated. So those are our preferred options. One of them you have to deal with drug-drug interactions, but can be given orally, the other one, you need to manage the issues surrounding giving the infusion. The next slide.

Now, we're going to talk a little bit about what are listed as alternative options. And as you would expect, that's because they have disadvantages, but still potential activity if you can't use one of the preferred options. So Molnupiravir, this is an oral agent. It's taken up by the viral RNA-dependent polymerase. And it has broad antiviral activity against RNA viruses. And the pivotal trial, the so called MOVEOUT study, randomized people to this oral agent versus placebo, and demonstrated a reduction in hospitalizations and death. During an interim analysis, when the first half of the people were enrolled, that reduction was about 50%. When the study was completed, with all the enrolled participants, it was about a 30% reduction. So this is considerably lower than the 80% to 90% we've seen with some of the other products, some that are no longer being used because of variant issues, as well as our preferred options. And this is one of the major reasons why this is listed as an alternative, because at least it appears based on this study to be effective, but less effective than the preferred options. The next slide, please.

And then finally, the second of the alternative options is Bebtelovimab, excuse me. This is a monoclonal antibody that's been demonstrated to have maintained susceptibility in vitro to all the circulating variants. And that's all great news. The problem is, and the reason it's listed as an alternative and to be used when other treatment options aren't available, is because it lacks the clinical efficacy data. So it's basically been made available because of the limitations of the

previous monoclonal antibody products and the desire to have agents available for people who need them based upon the in vitro susceptibility and some antiviral activity that you can see in the figure here on the left. The two that received this monoclonal antibody you can see at day five have lower viral loads than those who received placebo. And that's how this is currently available as a one-time infusion. So the next slide summarizes some of the key things to know about the four available products. Next slide, please.

So we have listed at the first two rows our preferred options. You need to make some adjustments for GFR, for Nirmatrelvir and Ritonavir. It's given over five days, twice a day for five days. And it's given to people who have onset of symptoms within the last five days. And the big issue is DDI, is drug-drug interactions. Remdesivir has to be given as the infusion and can be given within seven days of onset of symptoms. And then we have all our alternative options. We have our monoclonal antibody, that's a single infusion given over at least 30 seconds and within seven days of onset of symptoms. And Molnupiravir, given over five days as pills twice a day, again for people less than five days. Our oral agents need to be given within five days of the onset of symptoms, our injectable agents within seven days of onset of symptoms. The one other thing I might add for a Molnupiravir is that there are some concerns based on animal models for potential teratogenicity. The EUA does not recommend it in pregnancy. The NIH guidelines are supportive of the EUA recommendations but say that in the setting of a high-risk woman who's pregnant who has no other options, that perhaps it could be considered as long as she's effectively counseled about the risk, and particularly if it's after 10 weeks of pregnancy. Next slide, please.

I'm going to now transition to prevention. Again, we've had two other products that had previously been available for post exposure prophylaxis. This is the Bamlanivimab, was given as monotherapy in this study in a skilled nursing assisted living facility and showed marked reduction in the risk of symptomatic COVID. And we have the Regeneron products, Casirivimab and Imdevimab which was given in household exposures and showed marked reduction in symptomatic disease. The bam was ultimately, emergency use authorization was made available for pap in combination with Adalimumab because of concerns about susceptibility for bam with circulating variants. But ultimately with time, those variants once again got in the way of our ability to use these products, most recently losing CASIMDEV because of the reduced susceptibility to Omicron. So they're no longer being distributed for post-exposure prophylaxis. So we have one product, the next slide.

And that's an intramuscular combination of monoclonal antibodies, Tixagevimab and cilgavimab, that can be given for pre-exposure prophylaxis. And that's based on this PROVENT study, which took individuals that were unlikely to respond effectively to vaccines, or unable to take vaccines because of potential adverse events. And they were randomly assigned to be treated with this product or to get placebo. And although the event rate was quite small in this study, there was an about 80% reduction in the risk of developing symptomatic COVID in those who receive pre-exposure prophylaxis. And that led to the next slide describing the initial emergency use authorization. Next slide, please.

And this was issued in December of 2021. And the recommendation was key, not to be used as a substitute for COVID-19 vaccines. That is still the preferred means for prevention. But this can

be used as pre-exposure prophylaxis in people greater than equal to 12 years and greater than 40 kilograms, who do not have SARS-CoV-2 infection and who have not been recently exposed to an infected individual. That would be pep, not prep. And are moderately to severely immunocompromised and may have an inadequate immune response to COVID vaccine or are not able to be fully vaccinated due to the history of severe adverse reactions to COVID vaccine or any of its components. And the dose, at that time, was the dose used in the clinical trial, 150 milligrams as consecutive intramuscular injections of each of the two monoclonal antibodies. And based on the half-life, it was stated that if the person continues to meet these criteria, that it could be repeated at six months. The next slide.

But once again, variants get in the way. And Pragna already showed you this updated Nowcast data set. And what happened was when BA. 1 was the predominant variant, there were concerns about reduced susceptibility to this combination of monoclonal antibodies. And therefore, either it couldn't be used or potentially the dose could be increased. And that's the decision that was ultimately made, especially knowing that it appeared to have preserved susceptibility to BA. 2, which as you can see was rapidly rising at that time. But now we have to note that things are changing. We still have BA. 2 -- BA. 2. 12.1. But we also now have that BA. 4 and 5 that are rapidly emerging. And while susceptibility looks good for BA. 2, BA. 4 and 5 the data is still kind of mixed. So we're ultimately waiting to see how those continue to evolve, and more information about the susceptibility to determine the optimal way to use this. But based on the data available with BA. 1, the next slide summarizes an update to the EUA.

This is just looking at the susceptibility. You can see if you look at the second to last column, the fold reduction for BA. 1 was pretty dramatic. But then a return to susceptibility with BA. 2. And that led to the next slide.

During the BA. 1 being the predominant circulating variant, on April of 2022, four months after the original EUA was issued, the UAE was updated. The population that it was supposed to be administered to was the same but the dose was doubled to 300 and 300 in consecutive IM injections to try to overcome the resistance. And it was recommended those previously dosed with the original recommended 150, 150 In the last three months come back and get another 150, 150 dose. And if it's been more than three months, to come back and get the 300 and 300 dose. And at that point, there was no authorization for repeat dosing pending more information. Next slide.

So our self-knowledge check, which of the following individuals would be appropriate for administration of TIXCIL for pre-exposure prophylaxis of SARS-CoV-2 infection? A COVID-19 vaccinated person with history of solid organ transplant. An asymptomatic person recently exposed to someone with COVID-19. A person who was not fully vaccinated for COVID-19 because of documented adverse events to available vaccinations, A and B. A and C, or all of the above. Next slide.

The correct answer is E. Remember, this is not to be given to people that are recent exposure or people who are infected. It's for people who are unlikely to have responded to vaccination, such as the solid organ transplant patient, or those who are unable to receive vaccination because of adverse events. Next slide.

Thank you for your attention. And now I'm happy to hand this over to John Farley.

Thanks, Dr. Daar. And we can move to the next slide, please.

Great, so I'm just going to begin my discussion by focusing on treatment of non-hospitalized patients with mild to moderate COVID-19 at high risk of disease progression. Next slide, please.

So there are a number of therapeutics authorized or approved for this group. And they are authorized or approved for the treatment of mild to moderate COVID-19, adults and certain pediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. And primary care healthcare providers can play a key role utilizing these therapeutics to help reduce the risk of hospitalization or death in these patients. Next slide, please.

Just a couple of remarks on factors that are common to all of the authorization statements or indications. The first is direct SARS-CoV-2 viral testing. As everyone knows, there are two types of diagnostic tests -- molecular tests such as PCR tests, or rapid antigen diagnostic tests. And patients in the authorized population who report a positive home test result from a rapid antigen diagnostic test to their provider are eligible for the therapeutic. A positive PCR also meets this requirement, but confirmation of a positive home rapid antigen diagnostic test with additional testing such as a PCR is not required. Next slide, please.

Dr. Patel made some remarks about risk factors for disease progression. And just to underscore that our intention is to encourage healthcare providers to make an appropriate benefit risk decision for their individual patients. CDC has a very nice webpage resource specifically for healthcare providers, and we at the FDA will be updating our fact sheets to point to these web pages. Patients in the authorized population with a risk factor for progression to severe COVID-19 are eligible even if they are fully vaccinated and up to date on their COVID-19 vaccines. Patients do not have to have more than one risk factor to be considered high risk. Next slide, please.

The first therapeutic just to highlight is Paxlovid, which contains nirmatrelvir which is a SARS-CoV-2 main protease inhibitor, and ritonavir, a strong SIP 3A inhibitor included as a pharmacokinetic enhancer to increase nirmatrelvir plasma levels. It's available through an emergency use authorization. The age range for this is adults and pediatric patients, and those pediatric patients should be 12 years of age and weigh at least 40 kilograms. The standard dosing is two 150-milligram tablets of nirmatrelvir, and one 100-milligram tablet of ritonavir, orally twice a day for five days. Next slide, please.

Paxlovid needs to be started as soon as possible after COVID-19 diagnosis, and within five days of symptom onset. There are a number of special considerations. The first is renal impairment. For patients with moderate renal impairment, a GFR between 30 and 60, the dosage of Paxlovid is 150 milligrams of nirmatrelvir and 100 milligrams of ritonavir for five days. And we now have special packaging which is available. It is not recommended for patients with severe renal impairment or a GFR less than 30 milliliters per minute. In addition, hepatic impairment is a

consideration as the drug is not recommended for patients with Child-Pugh Class C. And there are special considerations for potential drug interactions. Next slide, please.

As Dr. Daar mentioned, there's a potential to affect other drugs because ritonavir is a strong SIP 3A inhibitor, as well as for other drugs to affect Paxlovid as the components are SIP 3A substrates. There are now very usable resources for primary healthcare providers. The FDA has resources on its web pages, and then the COVID-19 treatment guidelines is a very valuable resource, as well as the University of Liverpool. I would encourage all physicians to become more comfortable with this drug. Those of us who go back to the initiation of HIV Hart in the late 1990s learned how to prescribe ritonavir, and we know that you can too. Next slide, please.

The second therapeutic to mention is Veklury, or remdesivir. That's a nucleotide analogue RNA polymerase inhibitor. That is an approved drug. It is commercially available. The age range for this product is adults and pediatric patients 28 days and older and weighing at least three kilograms, so it has the broadest approved pediatric use. The dosing in non-hospitalized patients is a single loading dose on day one, followed by once-daily maintenance doses on days two and three by intravenous infusion. Next slide, please.

Timing is as soon as possible after diagnosis and within seven days of symptom onset. There are a number of special considerations. For renal impairment, the drug is not recommended in patients with a GFR less than 30 milliliters per minute. Hypersensitivity reactions are a risk. And it's recommended to monitor patients during infusion and for at least one hour after infusion is complete. Blast from the past, there are special considerations with chloroquine and hydroxychloroquine for your rheumatology patients who are taking this drug, potential antagonistic effect of Chloroquine metabolite on the antiviral activity of Veklury. Next slide.

Bebtelovimab is a human IgG1 monoclonal antibody that targets the SARS-CoV-2 spike protein. It is available through emergency use authorization, limited to patients for whom alternative COVID-19 treatment options are not accessible or clinically appropriate. The age range is adults and pediatric patients, pediatric patients being 12 years of age and older and weighing at least 40 kilograms. The dose is 175 milligrams, which can be administered as a single intravenous injection over at least 30 seconds. Next slide, please.

Its timing as soon as possible after diagnosis and within seven days of symptom onset. Special considerations include hypersensitivity reactions for this class of products. It's recommended to monitor patients during the infusion and for at least one hour after infusion is complete. In terms of variant, based on variants based on authentic virus and/or pseudo typed virus like particle neutralization data, there's no reduction in susceptibility to BA. 1. 1, BA. 2 and BA. 2.12. 1. And we will have data soon available for you for B. 4 and 5. I should mention that for all of the small molecules that we've talked about, we also do have data on preserving activity with the various variants, and there have been no issues noted with the currently circulating variants. Next slide, please.

Second product alphabetically in the alternative list is look Lagevrio. It's molnupiravir, a nucleoside analog that inhibits SARS-CoV-2 replication by viral mutagenesis. Its regulatory status is emergency use authorization but limited to patients for whom alternative COVID-19

treatment options are not accessible or clinically appropriate. In terms of age, it is not authorized for use in patients less than 18 years of age, and its dosage is 800 milligrams or four of the 200 milligram capsules orally every 12 hours for five days, with or without food. Next slide, please.

Timing is as soon as possible after diagnosis within five days of symptom onset. There are a number of special considerations. There is embryo fetal toxicity which was demonstrated in animals. It's not recommended for use during pregnancy. Special consideration for bone and cartilage toxicity also noted in animals. It is not authorized for use in patients less than 18 years of age, because it may affect bone and cartilage growth. There are special considerations for contraception. People of childbearing potential should use contraception for the duration of treatment and four days after the last dose. Individuals who are having sex with people of childbearing potential should use contraception during treatment and for three months after the last dose. The risk beyond three months is unknown as non-clinical studies have not yet been completed. Next slide, please.

I'll spend a few minutes on COVID-19 rebound. As all of you know on this call, recent case reports document that some patients with normal immune response who've completed a five-day course of Paxlovid for laboratory-confirmed infection and have recovered can experience recurrent illness two to eight days later, including patients who've been vaccinated or boosted. Both the recurrence of illness and positive test results have improved or resolved without additional antiviral treatment based on reports to date. Next slide, please.

So in the Paxlovid clinical trial which supported the EUA -- that's the EPICHR study that Dr. Daar talked about -- a small number of participants had one or more positive SARS-CoV-2 RT PCR test results after testing negative, or an increase in the amount of SARS-CoV-2 detected by PCR after completing their treatment course. And these were obtained by nasal pharyngeal swabs samples. This finding was observed in persons randomized to Paxlovid and in persons randomized to placebo. There was no increased occurrence of hospitalization or death. And there was no evidence that the rebound in detectable viral RNA was the result of SARS-CoV-2 resistance to Paxlovid. Next slide, please.

So at this time, there's no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound. These reports do not change the conclusions from the Paxlovid clinical trial, which demonstrated a marked reduction in hospitalization and death. Electronic health record-based data analysis may more fully characterize incidence and risk of disease progression associated with COVID-19 rebound. However, prospective data are likely needed to fully understand pathophysiology and association with drug treatment. Next slide, please.

I'll just close with a mention of Evushield. Dr. Daar has mentioned that it is authorized for pre-exposure prophylaxis rather than treatment. Next slide, please.

And it's authorized for the pre-exposure prophylaxis of COVID-19 in adults and certain pediatric individuals not currently infected with SARS-CoV-2 and have not had a recent known exposure to an individual infected. They should have moderate to severe immunocompromise due to a medical condition or receipt of immunosuppressive medications or treatments, may not mount an adequate immune response to vaccination, or for whom vaccination with any available vaccine,

according to the approved or authorized schedule, is not recommended due to a history of severe or adverse reaction to a COVID-19 vaccine or vaccine components. Next slide, please.

So let's do the self-knowledge check. This should be easy for the pediatricians. A one-year-old male weighing 9.6 kilograms is post bone marrow transplant for severe combined immune deficiency. He developed rhinorrhea and a cough one day ago and tests positive on a home rapid antigen diagnostic antigen test rather for SARS-CoV-2. His physical exam is unremarkable and oxygen saturation by oximetry is measured at 98%. Which of the following authorized or approved therapeutics would be appropriate? A, Paxlovid. B, Veklury. C, Bebtelovimab. D, Lagevrio. Next slide, please.

The correct answer is Veklury, B. The reason for this is because Veklury remdesivir is approved for adults and pediatric patients 28 days and older and weighing at least three kilograms. Paxlovid and bebtelovimab are authorized for adults and pediatric patients 12 years of age and weighing at least 40 kilograms. And Lagevrio is not authorized for use in patients less than 18 years of age.

Thanks very much. And I'd like to introduce Dr. Meg Sullivan, who will give the last presentation.

Thank you, Dr. Farley. And good afternoon, everyone. Next slide, please.

I am Meg Sullivan. I am the -- next slide -- Chief Medical Officer for the Office of the Assistant Secretary for Preparedness and Response at the US Department of Health and Human Services. Next slide.

And I'm just going to give a brief update on ASPR's roll with therapeutics including specifically distribution utilization overview and our efforts kind of agency wide to increase access and utilization, the test to treat program, utilization challenges, work we're doing around ensuring equity and allocations and utilization and then provide some resources. Next slide.

So just briefly, kind of looking at the current therapeutics landscape, we have been actively distributing products at no cost since November 2020. We know that treatment availability has fluctuated based on circulating variants. And as we just heard from Dr. Farley and Dr. Daar, we currently only have one available monoclonal antibody, bebtelovimab, that's available for treatment. We have Evushield pre-exposure prophylaxis and oral antivirals for treatment -- Paxlovid and Lagevrio. These are the four products that we are currently distributing. Of note, remdesivir, which is currently approved, is not being purchased by the US government and not being distributed in this way. We are fortunate right now to have an increased amount of supply for most of these products. And what we do is set thresholds each week for our central partners. We work incredibly closely with our states and territories and federal entities to help them distribute to sites within their jurisdictions. And then recently opened a federal retail pharmacy partner channel where our private retail pharmacy partners are able to order products directly and have it go to theirs as well. Next slide.

This is just a snapshot of the distribution and utilization that has occurred to date. You can see that we've shipped over 11.4 million courses of these products, have over 44,000 active providers that are receiving products. And again, you can see the data on usage. 5.2 million total reported usage and 46% of the distributed supply used. Next slide.

This slide just shows another snapshot of a summary of utilization between December 17th, 2021, and June 5th, 2022. This data is posted publicly on our website, which is listed on our slide and updated weekly. And I think one of the main takeaways from this slide is that we are fortunate right now, particularly with oral antivirals, to have adequate supply and have worked really hard to get it distributed in the field so that it should be widely available in the field. Bebtelovimab, we still do have supply. We know that we have due to funding considerations have really been monitoring that closely. And as we heard, you really want to make sure that providers are using it judiciously in accordance with the EUA and clinical guidelines. But you can see the data there. And then if we go to the next slide, I'll talk a little bit more about where we are.

So just to repeat, you can see Paxlovid and Lagevrio, which we currently have ample supply, that first graph just shows the trends in utilization. And really as the COVID-19 cases have gone up, we can see that utilization has increased as well, which is reassuring and shows that it is being used. However, we know that we still have work to do. We still know that there are barriers to access, particularly in communities with high social vulnerability and are engaged in significant outreach and operational efforts to increase use, especially with a focus on prioritized populations. We're seeing bebtelovimab has also increased with rising cases. Again, though, it's important to know it serves, as I mentioned before, as an alternative for patients for whom other authorized or approved treatments are not recommended. And then the bottom graph I also want to draw your attention to which shows the Evushield administration over time. And I think one of the things that you can notice from this graph is it really has leveled out, especially over the past several weeks. And we know that the utilization continues to be lower than expected. There are many people still that could benefit immensely from Evushield that have not received it yet. And again, we are engaged in significant outreach and operational efforts to increase use. Next slide.

I just want to spend a couple of minutes talking about federal efforts that are done to increase access and awareness of therapeutics. So first, I just talked about supply, and we've worked hard to acquire supply of the four products we currently distribute. We do want the message to get out there that many of our products are not currently supply constrained. Early on, there were specific guidelines around prioritization of only those at highest risk. We now have enough supply in the field again to be able to effectively counsel and consider prescribing to any patient who meets the criteria that we just heard about. We've also worked to make sure that the oral antivirals are widely available. They're currently available at more than 35,000 -- actually 40,000 locations nationwide. And we continue to look to increase those numbers. We are supporting medical providers with increased guidance, such as this one with CME opportunities, stakeholder engagement, enhanced provider guidance and tools, including the Paxlovid checklist that we heard about, and I'll share some at the end of this slide. And then really working hard to communicate to the American people that safe, effective treatments are widely available, and

really relying on stakeholders from every single level to help us with this and take every opportunity to talk to people about these safe and effective treatments. Next slide.

And as we look at these efforts and really trying to get the message out there widely, that if you test positive and you are at high risk of getting very sick from COVID-19, contact your healthcare provider and do so right away, because treatments must be started within a short timeframe in order to be affected. This is a message we've been working hard to get out there. But recognizing we need to have a second sentence that said, if you don't have a healthcare provider or you can't access your healthcare provider within five days, here's an additional access point for you. And this is really where the test to treat initiative came from. Again, to increase access to COVID-19 therapeutics, particularly for individuals who don't have ready access to healthcare providers. And building upon the existing distribution of oral antivirals we are already making available at thousands of locations nationwide. So we really want to still say an individual's healthcare provider remains the first option for care, but test to treat sites really help to provide that one additional access point. Next slide.

And really with a focus on removing barriers to access. And so our goal with these test to treat sites is to provide comprehensive, end-to-end test to treat services to support the seamless patient experience. So to have COVID-19 testing on site or evaluation of an at home test linkage right there to a clinical evaluation by a licensed healthcare provider of their positive results to provide the prescription when appropriate -- this can be on site or via telemedicine -- and then a co-located or affiliated pharmacy to be ready dispense the medication. So again, a one-stop shop to be able to access these medications as one additional point of access in our broad efforts around therapeutic access and awareness. Next slide.

This is just a snapshot of our test to treat locator which we launched on March 30th, which tries to provide an up-to-date map and search function of all of the test to treat locations nationwide. But also, importantly, we include all places where individuals can fill a prescription again, so if they're going through their healthcare provider, know a pharmacy nearby their home where their product is available. And we're also working hard to increase the visibility of telehealth options on the locator. Next slide.

Just one quick slide about our federal test to treat sites, as again an additional access point in addition to all the efforts that I talked about. We are recognizing that there still are barriers to individuals accessing services, including cost barriers. And so we are partnering with state, tribal and territorial governments to establish federally supported test to treat sites, which offer resources in the form of testing support in the form of provider reimbursement, or provider support and pharmaceutical or therapeutic support in terms of additional supply to offer sites within states, tribal or territorial locations to provide no cost services. Again, these comprehensive, end-to-end services that we have talked about. Next slide.

And I just wanted to mention a couple of things that we really are monitoring is all of these efforts that we've talked about. We know that despite them, inequities still persist in the use of these therapeutics. And we know we still have challenges around inconsistent awareness, as well as unequal community access and inequities and technology use. And we know that the fall and winter months are only a few months away, and we need to double down on all of our efforts to

further increase access and remove barriers, and so continue to work to do ongoing and new innovative approaches to address these challenges. Next slide.

And really again, equity has been at the forefront of our response and our working closely with our states, with our territories, with our HRSA and other federal partners to really work to make sure that these products are getting where they need to go and that the barriers are as low as possible. Next slide. Next slide, please.

And I just want to end by just a highlighting a few resources. First, this slide just lists some upcoming stakeholder calls that we hope to share widely for anybody who would benefit from learning more about the products, about the distribution, who wants to ask any questions. These are great avenues for you. And you can see all the details on how to find out how to join. Next slide.

And this is just again, some other helpful information and resources with links that include resources that have been mentioned here, whether it's the Paxlovid eligibility screening checklist or the therapeutics locator, or a number of different resources that would be helpful. Next slide.

And just again, some additional resources, some of which have already been highlighted. More clinical resources, particularly around checking drug-drug interactions or referencing some of the clinical guidelines that we've talked about today. Next slide.

Just a couple of really quick slides, this is just one of the resources that's highlighted. It is a clinical implementation guide that really walks through the key information on COVID-19 outpatient therapeutics, it is updated regularly to reflect current guidelines. It really is a great tool that is available on our website. Next slide. And this is just another example of a resource which really walks through that decision path that we've heard about in previous presentations today.

This is the resource for adults. And if you go to the next slide, this is the resource for pediatric patients.

Again, it's available on our website. Next slide. And I'm just going to end with a quick knowledge check.

So based on current supply, COVID-19 therapeutics should be considered for any COVID-19 patient -- positive patient, sorry -- who meets which of the following criteria? First, A no additional criteria needed. B, has mild to moderate symptoms and are within five to seven days of symptom onset. C, has one or more risk factors for severe COVID. D, due to current supply constraints, COVID-19 therapeutics should be considered only for individuals who are severely immunocompromised. Or E, B and C only. And next slide.

The answer is E. And the reason for this is that oral antivirals -- and as we talked about, medications are not currently supply constrained, so we want them to be considered for anybody who meets the criteria. But we know that again, you have to meet the specific criteria, which is mild or moderate symptoms and have one or more risk factors for progression to more severe disease. Next slide.

And again, just some additional resources. And with that, I will turn it back over to the moderator.

Thank you very much, presenters, for sharing this timely information with our audience. We will now go into the Q&A session. As we are at the top of the hour, we only will be able to ask a couple of questions.

So the first question we have is for our presenters, is there any indication for combination treatments such as Remdesivir and an oral agent such as Molnupiravir in case of patients who can't take Paxlovid?

So this is Dr. Farley. Maybe I'll start with that, Dr. Daar, if that's okay. So I think it's a great question, but it's a great question for which there is equipoise.

And we don't have any data at this time. Dr. Daar, any comments?

No, completely agree, I think at this point, we really don't have the data, and at least the EUAs for the non-approved products wouldn't support it, I'm sure.

Great, thank you for illuminating that. And the last question we have that we will have time for for the session is -- this is something we've seen in the in the Q&A box a few times -- is, are you aware when the endpoint data for Bebtelovimab are anticipated?

So with we are working with the company -- this is Dr. Farley again -- on pediatric data. We do not have a trial ongoing with an endpoint. Part of that challenge in today's world is that at least in the United States it is difficult to randomize high-risk patients to placebo in such a trial because we have treatment alternatives. So that's been part of the challenge.

Thanks. Thank you very much. And with that, I want to thank everyone for joining us today with a special thanks to our presenters for sharing such great information in such a comprehensive manner.

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