Agenda
Laboratory Outreach Communication System (LOCS) Call
Monday, August 15, 2022, at 3:00 PM EDT

- **Welcome**
  - Sean Courtney, Division of Laboratory Systems, CDC
- **SARS-CoV-2 Variants Update**
  - Natalie Thornburg, Division of Viral Diseases, CDC
- **Monkeypox Outbreak Update**
  - Christina Hutson, Monkeypox Response, CDC
- **Laboratory Developed Tests (LDTs) & CLIA Establishment Regulations**
  - Keith Scott, Centers for Medicare & Medicaid Services (CMS)
- **FDA Update**
  - Tim Stenzel, US Food and Drug Administration (FDA)

SEAN COURTNEY: All right. Good afternoon, everybody. Thank you for joining us today. My name is Sean Courtney. And I'm a health scientist and CDC's Division of Laboratory Systems. On the screen is the agenda for today's call. But before we get started, I just wanted to cover a few announcements and some housekeeping items.

So as you've heard on previous calls, DLS is the CDC division that works to advance laboratory quality and safety, data and biorepository science, and workforce competency. We work closely with clinical and public health laboratories across the country to support laboratory emergency preparedness and response activities. And we've been hosting these calls since March of 2020.

So DLS works to support this work across four goal areas-- quality workforce and training, preparedness and response, and informatics and data science. So in addition to the talks that we have today, CDC, and we've received many inquiries around validation material for developing your own diagnostic tests to support the monkeypox outbreak response. And so we wanted to be able to provide you with some resources to help with these efforts.

And so under the guidance of your laboratory's CLIA lab director, labs can develop their own laboratory developed tests to test for monkeypox or non-variola orthopoxes. CDC has provided procedures and sequences specific to these generic tests to help labs develop their own in-house tests. And you should be able to view these in the chat. And they're shown here on the page on the left.

Additionally, there are some sources for genetic material that can be used for creating contrived specimens for validation material, or as positive controls. And they're available from sources such as NIST and BEI, as well as some other commercially manufactured sources.

And so additionally, CMS and CDC seek public comments for the proposed rule change regarding updates to CLIA fees and requirements for histocompatibility, personnel, and alternative sanctions for the CLIA certificate of waiver laboratories. The public comment period for the proposed rule is open until August 25. And you can read the proposed rule and submit comments at www.federalregister.gov. And so please share this with any colleagues or partners that may be interested. And encourage them to submit comments.

And so as always, we'll be sharing slides from today's call along with audio and transcripts. And we'll post them online by next week. You can find them on CDC's Laboratory Outreach Communication Systems page at the link shown here.

And so we want to hear from you. Our Training and Workforce Development Branch would like to hear any questions that you have regarding education or any training gaps. And so please, if you have any input, we'd like to ask you to reach out to labtrainingneeds@cdc.gov.

And during today's call we'd like to ask that if you have any questions, that you please use the Q&A function within the Zoom system. Please do not use the chat menu. Please use the Q&A function. And when you do ask the question we ask that you also please include your email address so that if we're unable to address your question during today's call that we can follow that up at a later time.

And if you have any-- if you're media, if you have any media questions, please contact CDC media relations at media@cdc.gov. And if you're a patient, to please direct any of those questions to your health care provider. And as always, slide decks may contain presentation material from panelists who are not affiliated with CDC. And presentation material from external panelists may not necessarily reflect CDC's official position on the topics covered.

And with that, it's my pleasure to introduce our first speaker. We have Natalie Thornburg from CDC's Division of Viral Diseases. And I'm going to go ahead and turn it over to you, Natalie. And I'll stop my screen share so that you can share from yours.

NATALIE THORNBURG: Thank you. Let me get situated here. Here we go. All right, can you see my screen and hear me OK?

SEAN COURTNEY: Yeah, everything looks good. Thanks.

NATALIE THORNBURG: Great, thanks. So I've got just a couple of slides today. Sean asked me to show the genomic proportions this week, and then he also asked me to do a couple of slides talking about what we know about infection in the population right now in comparison to the past, and why that might be able to affect the performance of at home rapid antigen tests. So I'll show that after the genomic proportions.

So the posting of our national Nowcast estimates has changed. We are still doing the postings weekly. But they have changed to Friday updates. And this started last Friday. So this is data that was posted on Friday. And therefore there won't be an update tomorrow. The next date will be this coming Friday. And as you can see from this, all lineages, all circulating lineages continue to be Omicron. Like we saw with Delta, we are starting to see diversification in lineages and sub lineages. So over the past two months, we've seen an increasing proportion of BA.4 and BA.5 viruses. And BA.4 had actually peaked in prevalence a few weeks ago and had been declining in overall prevalence. BA.5 has continued to increase in prevalence, although it's really leveling off because it's reaching about 90% of circulating viruses.

One sub lineage of BA.4 has been broken out on the Nowcast, on the Nowcast a few weeks ago. Because it is continuing to increase in prevalence. And that is BA.4.6 While BA.4 is overall decreasing in prevalence, the sub lineage, BA.4.6 is increasing modestly. But it is now at about 5% nationally. BA.4 sub lineages contains two extra mutations in the spike protein. It contains a mutation at residue 658 and one more mutation at 346.

Notably the changes at that 346 position are in other variants. It has been in BA.1.1 and could affect therapeutic-- monoclonal antibody therapeutic activity. And it's the main reason why it was broken out on the Nowcast estimates, because of that 346 mutation.

What it looks like regionally is a lot more homogeneous than it has in the past. Really in all regions BA.5 is dominant and is sitting somewhere between 80% and 95% of circulating viruses. And there's not a whole lot of differences between the different regions.

All right, so I'm going to switch gears a little bit. That's the variant proportion updates today. And then Sean asked me to talk about different phases of the pandemic and how that could be affecting at home rapid antigen tests.

And so you guys will remember there was some talk in December, especially about changing sensitivity of at home rapid antigen tests as we saw the wave move from Delta to Omicron. And I think there are probably several indications as to why this might be.

One, there has been some indication that some variants-- and this is not our data. This is data that was published in Nature, I think-- sorry, Science using a hamster model, challenging hamsters with Delta viruses versus Omicron viruses. And there are some inherent differences in circulating viruses in how well they replicate.

Their spike genes are a little bit different. They might bind to ace a little bit differently. And they might get matured inside infected cells a little bit differently and release different amounts. And using hamster models, it looks like Delta increases the lower respiratory tract more efficiently in hamsters early in infection than Omicron viruses. And that's shown in panel D.

And that later, Omicron is cleared faster than Delta. And that's shown in panel D here in the middle, where you can see early in infection, nasal turbinate is kind of equivalent between Omicron and Delta infections. And then two days later, you already have some clearing of that Omicron virus.

But that wouldn't necessarily explain why some people are having symptoms and testing negative and then a couple of days later testing positive. Whereas that wasn't necessarily the case a year ago, a year and a half ago. And I think-- so this is data that we have from a household transmission study looking at-- this was done last summer. So it has some vaccinated people.

Most of the infections were Alpha, Epsilon, and Gamma-- so not Omicron. But what you can see is sort of a different kinetics of rapid antigen test positivity, PCR positivity, and recovery of virus. In the symptoms, day 0 is symptom onset on that x-axis.

And so what you can see is this includes both vaccinated and unvaccinated people. I think there were 225 cases, that 550 total people enrolled in this study, is that recovery of live virus peaked at about one to two days of post symptom onset. And rapid antigen test positivity is delayed by a couple of days. And then PCR positivity comes up much earlier. You can really detect it a couple of days before symptoms. And then it sticks around. Which, we all know about PCR tests.

But whenever you sort of break this out in vaccinated and unvaccinated people, you see a difference in the kinetics. So unvaccinated persons here are in navy blue. And persons who had at least one dose-- so some of them only had one dose of vaccine since we started this in May of 2021-- is they have a much different kinetics of percent positivity.

And this is not recovery of culturable virus. This is at home rapid antigen test. And so you can see even when we're not talking about Omicron at all, vaccinated people may not test positive until two, three, maybe even four days after symptom onset. And this is pretty different than what we see in unvaccinated people.

And then they clear their positivity faster than unvaccinated individuals. And I think what we're seeing here is likely the immune system doing its job, what we call an anamnestic response. So you should have some antibody around, but maybe it wasn't high enough to block infection completely. But then your memory B cells respond really quickly. Your memory T cells respond really quickly to stop that, to stop that virus replication and clear the infection faster.

And maybe you had a little bit of residual-- maybe you had some antibody there that blocks and delays some of that really active replication. But it wasn't quite enough to stop infection completely. And so it's not totally surprising that we're seeing sort of decrease in sensitivity or delayed positivity, as the population has more and more exposure to vaccines and/or infections.

And I think we probably really saw this much more dramatically during the Omicron surge, is because there was just much lower VE because of the number of changes that we saw in the Omicron spike. And

therefore, there were only a couple of changes when we looked at Delta, Alpha in comparison to what we see in Omicron. And so vaccinated persons are just more susceptible. And so you have more of the population who might have this sort of delayed kinetics of test positivity virus replication, and then an enhanced clearing after you get infected.

So that's all I really have to talk about that. Sean, I'll let you decide if I'm taking questions now or later.

SEAN COURTNEY: Thank you so much for that, Natalie. I really appreciate that. There was a question that came in right at the end regarding your last slide. And it was around if you could explain the discrepancy at day 18, how they kind of start to flip over. I wasn't sure if you could cover that.

NATALIE THORNBURG: Oh, I would have to look at the exact-- I would have to look at the data. My guess is this was really-- this was a pretty small number of specimens. And maybe we had one person pop up as positive here. Because you see, this is only like 7, 9 specimens here. I don't know the specifics about this particular case. But it is possible that we had someone there go rapid antigen, test positive at day 19 or 20 again.

SEAN COURTNEY: All right, thank you. Another question that came up. Why is the PCR test able to detect when the antigen is not? Is it merely a matter of sensitivity?

NATALIE THORNBURG: Yeah. I think it's just a matter of sensitivity. PCR is always going to be more sensitive than rapid antigen test.

SEAN COURTNEY: OK, great. I'm just going to take one more quick look through these. However, if not, if you could just hang around on the call today and just kind of peruse the Q&A function. If you have any relevant questions, go ahead and take care of those for us. And I would appreciate that. But thank you again for providing us this update today.

And with that, I'm going to move on to our next presenter. We have Christy Hutson with CDC's Monkeypox Laboratory and Testing Task Force. And Christy, I am going to share the slides in one second.

CHRISTY HUTSON: Thank you, Sean.

SEAN COURTNEY: All right. And you should be good to go. Thank you.

CHRISTY HUTSON: All righty. Thank you. Good afternoon, everyone. So I'm Christy Hutson, as Sean said. I'm the lead of the Laboratory and Testing Task Force for the monkeypox response. So just be giving an overview of monkeypox, what we know from the past, and what we're learning from this current outbreak. Next slide, please.

So this is a current update from across the globe. As of August 12, there are 35,492 cases. This is in 83 countries that historically have not reported monkeypox. And this figure is on our CDC monkeypox web page. The link is at the bottom.

You can see in the table that the United States is unfortunately leading with cases, at 11,176, followed by Spain, Germany, and then the UK. Next slide, please. And in the United States, again, as of August 12, we have 11,177 cases in the United States.

New York has the highest number at 2,295, followed by California, Florida, and then Georgia. And again, these are also up on our web page. Next slide. So just an overview of what CDC is doing-- and this is probably not all encompassing. I know it's not. But we are providing advice to our state and local health departments.

We're supporting our diagnostic testing and our Laboratory Response Networks (LRN) and the five commercial labs that we've onboarded-- the CDC, FDA cleared tests. We're providing front line health care providers and public health officials with information on symptoms and how to manage illness, keeping the public, our clinicians, laboratorians, informed with updated information on our CDC website, social media, and media briefings.

We work closely with community partners and raising awareness with multiple partners throughout the community. And we're seeking our public health partner's feedback. And also throughout the globe working with other countries on this outbreak. Next slide.

So I just wanted to touch on what clinically or classically we saw for the clinical illness for monkeypox within endemic areas and during the 2003 us outbreak. So generally the incubation period was 5 to 13 days, with a range of 4 to 17 days, and typically was preceded by a prodrome where you saw a fever, perhaps malaise, headache, weakness, lymphadenopathy, sometimes generalized or localized.

And then the rash typically appeared shortly after the prodrome. Usually the lesions would develop simultaneously and evolve together on any one part of the body. And there are four stages-- macular, papular, vesticular, to pustular before they scab and resolved. These are well circumscribed, deep seated with umbilication, and oftentimes described as being painful. And when they were disseminated, they tended to be centrifugal, meaning there were more on the arms, legs, hands, and feet, and could also involve the palms and soles. And classically, the illness duration was around two to four weeks. Next slide. So these are just some pictures of what we typically saw with those lesions on different parts of the body. Next slide.

During the 2022 outbreak, the lesions have a slightly different location for the most part. So we do see that scattered or localized to a body site rather than diffuse. And often it's starting in the mucosal area, such as the genital, parietal, or oral mucosa. It may not develop simultaneously on all body parts.

Proctitis is a common symptom seen in monkeypox patients, as is oral pharyngitis. And that prodrome period I mentioned for the classical monkeypox cases, we really haven't been seeing before the rash. But instead it's either absent or it follows shortly after rash onset. Next slide.

So this was from a number of patients early on in the outbreak, a total of 528. And you can see that when we look at the number of lesions, around 39% have less than five lesions. So sometimes with these patients they're not having very many lesions at all. And then around 11% have up to 20. I will mention, it's not shown here but in recent data of the information we have for the patient so far in the US outbreak, 99% do have some form of lesions that present. So that is the number one symptom still during this outbreak.

And then the site of mucosal lesions can vary from being just an anogenital area. But some patients do have lesions on the nasal or eye area. Next slide.

For testing, many of you are probably familiar with our testing. So at the start of the outbreak, we had a CDC, FDA cleared test in our public health laboratory within the Laboratory Response Network (LRN), which is across the country. And that test was there because it had been developed under the smallpox research agenda.

So at the start we were able to test around 6,000 to 8,000. The LRN labs have now increased to be able to test 10,000 tests a week. And then they send any orthopox positive specimens to CDC for monkeypox specific PCR and sequencing. In our commercial labs that we brought on board they are able to test around 70,000 tests per week. And so that's in four of our commercial labs that have brought our CDC, FDA cleared test on board, and then one lab that's running a monkeypox specific laboratory tests. So currently throughout the country we now have testing capacity at 80,000 tests per week. Next slide.

The specimen type for right now is lesion material. So we know from previous surveillance studies and from the studies we're seeing come out of some of the European countries and other countries, that lesion tends to be the most accurate and the best diagnostic specimen type for determining if someone has monkeypox.

For the CDC cleared test, a swab of a lesion on any body part is acceptable. So it can be in the oral cavity, anywhere, as long as you can actually see that lesion. And it's really important to remember that they do not need to be debriefed or lanced. We just asked for vigorous swabbing. There is enough virus there that as long as you do vigorous swabbing, you are going to get a PCR positive test with our CDC PCR test.

I did want to mention, though, that we are evaluating other specimen types or research protocol. We're especially interested in, perhaps, if there's a lesion before-- or excuse me, a specimen before lesion onset that we can use to detect monkeypox. So that study is just getting started.

And then there are some differences between the labs and what type of lesion specimen, whether it's a dry swab or a swab and BTM. And that really just depends on the laboratory's CLIA approval. So if you are a submitting clinician, it's important to reach out to the lab to confirm what they can take.

We've tried to stress that clinicians should initiate diagnostic testing for any suspect monkeypox patient. And this is based on clinical presentation and/or epi criteria. However, if there are no epi risk factors or known exposures to monkeypox, all other differentials should really also be considered in parallel to any monkeypox testing that is done. Next slide.

For vaccines, which many of you are probably familiar with now, again, these were developed under the smallpox research agenda. So we have JYNNEOS, which is also known as Imvamune or Imvanex, and then ACAM2000. And we're working to get additional doses of JYNNEOS.

There is ample supply of ACAM2000. However, this is a live vaccine. It has contraindications for individuals with weakened immune system or skin conditions, such as eczema. So it is contraindicated in some individuals.

We are still working to see the data that comes out of the current use of these vaccines to understand its effectiveness. Because they haven't been tested in a real-world setting. And then people are considered fully vaccinated after two weeks after the second dose of JYNNEOS and four weeks after the first dose of a ACAM2000. Next slide.

For treatments for monkeypox, Tecovirimat is approved for smallpox treatment. It is an oral capsule and an IV formulation, which was approved in July of 2018 and May 2022. And it's available from the SNS as an oral capsule formulation or an intravenous vial. It is indicated for the treatment of human smallpox disease in adults and pediatric patients. And CDC holds an expanded access investigational new drug, which allows it to use for non-variable orthopox infections, such as monkeypox. So that is how we're able to use it for treatment of monkeypox, although it's FDA approved for smallpox. Next slide.

And one of the things we've worked really hard on is to make this rebias on EAIND more user friendly for clinicians. So we've reduced the number of case report forms, changed all patient assessments to virtual, or in person, giving flexibility there. And then reduced the required assessment and follow up visit to three time points that can be done via telemedicine. So just trying to ease the burden of administering Tecovirimat to patients. Next slide.

And then I just wanted to touch on some of our research efforts. This is not an all-encompassing list, but some of the things we're focusing on. I mentioned that we're looking at other specimens besides lesions, especially prior to rash onset. So especially blood, throat swabs, and rectal swabs.

We're doing some serologic retrospective studies to see if there's any evidence that monkeypox was circulating prior to the first confirmed case, looking at bank serum samples. We're also looking at the

prevalence of undetected monkeypox within high-risk populations, so in the current population doing serologic prospective studies and also PCR testing bank specimens.

We have a household transmission study to help us understand the transmission dynamics during this outbreak. That study has not yet begun, but we're hoping to get it started soon. We're also interested in and concerned about if there could be transmission to animals, both domestic and if there's escape to wildlife. So that's something we're closely monitoring. And we've actually been sampling some of our domestic pets and monkeypox case homes.

Wastewater detection is another area we're interested in. And we have ongoing efforts. And then finally, we continue to sequence. We do whole genomic sequencing to look for any changes, especially focused on the target for Tecovirimat, making sure there are no changes there that could impact sensitivity to that job. Next slide.

And just quick conclusion, we all know this is the largest monkeypox outbreak outside of Africa. There are multiple medical countermeasures developed through the US smallpox research agenda, which I mentioned throughout the slides. That includes the CDC, FDA cleared diagnostic assay, and then two antiviral therapeutics, and then finally the two vaccines that are approved for smallpox.

And with that, I'm happy to take questions, Sean, if there is time, or wait until the end.

SEAN COURTNEY: Yeah, no. Thank you so much, Christy. I really appreciate today's update. There are a few questions in the chat. I'll go through some of them. And then I'll probably leave some of them open for you to just take an answer as the rest of the call continues. But we'll go through some of them now. And the first one was kind of on a topic that you discussed here towards the end. And that's around kind of human and pet transmission. And it was, should labs prepare for receiving samples from animals? And if so, what type of changes would be needed for those protocols?

CHRISTY HUTSON: Thanks for that question. So this is something that we're actively thinking about. CDC is able to test those specimens. So we have received from some suspect pets. But we do want to work with our vet lab partners and other partners that conduct animal testing.

As far as changes, there shouldn't be too many changes obviously this would be one under non-CLIA which makes it a little bit easier. We routinely run our PCR assays at CDC for animal lab studies. So you just have to change the internal controls that you use. Because like RNase P, obviously, that's a human control. So we have to use a different control.

So there are some small changes like that that would need to be done. And then biosafety would obviously need to be addressed. So we prefer vaccinated staff when possible. Otherwise, we suggest additional mitigation. So that would need to be a risk assessment performed by your laboratory. And we have some of that information up on our CDC monkeypox page for laboratory workers that are thinking about doing such testing.

SEAN COURTNEY: All right, thank you. Appreciate that. Next question is, are the increasing case numbers indicative of viral spread, or of increased test availability?

CHRISTY HUTSON: It's a great question. And I don't think I'm going to try to guess. It might very well be a combination of that. We, from the start of the outbreak, felt like the capacity was there. But we definitely wanted to improve convenience of testing, which we've tried to do by onboarding those commercial labs to make it much more convenient for people to get tested. So I'm not really sure. That's a really good question and it might be in part to both of those things.

SEAN COURTNEY: Thank you. Next question is other than increased mortality, is there a clinical difference between the two clades?

CHRISTY HUTSON: Sure. So WHO recently announced that Congo Basin clade is going to be renamed clade 1, and West African clade will be clade 2. It will have two sub clades within that clade. But for clade 1, which is formally Congo Basin, it's typically tended to present more like what you saw with a smallpox patients, so lesions extensively on the body.

When you looked at pictures, quite often you could not differentiate between that clade of monkeypox compared to smallpox. So again, Congo basin or clade 1 just causes much higher morbidity as well as mortality. And back, then we did tend to see, before this outbreak, there was higher human to human transmission associated with that clade than what we saw with the West African or clade 2. There's several differences in disease presentation and dynamics between the clades.

SEAN COURTNEY: OK, thank you. Next question is, is there data or ongoing studies comparing sensitivity of saliva and swab samples? And so this one's really about are other specimens being tested to see if there may be cases that do not have lesions or swabable patients?

CHRISTY HUTSON: So the study we're looking at is focused on with our DC public health lab partners. And it's looking at people that are coming in for their first vaccine dose that are at high risk. So they're in the PEP++ group. So they're not going to have lesions. But they could have some prodromal symptoms. They could have had an exposure.

So for that we're looking at throat swabs and rectal swabs and blood. I do know that there are other public health law partners that are starting to look at saliva compared to lesion, so just seeing if that's another alternate site or an alternate specimen when lesions are present, which will also give us some really good data to understand if saliva might be a good specimen type.

I do know that there was one study in the United States. And then I've seen some studies internationally where if there's lesions present, that some of those other specimens are not 100% accurate compared to your lesion. But still worthwhile to see if there's other specimens. And that's what we're doing, along with several other groups throughout the country.

SEAN COURTNEY: All right, thanks, Christy. All right, so last question just to save some time for our other speakers. But what's the temperature requirement for transportation of swabs in UTM?

CHRISTY HUTSON: So we at CDC are not testing swabs in UTM. This is something we don't yet have approved under our CLIA. We started working on it. And then the outbreak hit. And so we have not finished the stability testing.

So it's going to depend on the lab you're sending it to. So I would suggest you reach directly out to them to find out the temperature and if they accept swabs in UTM.

SEAN COURTNEY: Awesome. Thanks so much, Christy. Really appreciate your update today. If you could hang out on the line and just answer some more questions within the Q&A function itself, that would be great. But again, really appreciate you jumping on this call and providing an update for us.

And with that, I would like to move to our next speaker. We have Keith Scott from CMS who's going to be talking about laboratory developed tests in CLIA establishment regulations. Keith?

KEITH SCOTT: Thank you. Today I'll be talking about the CLIA establishment requirements for laboratory developed tests. Next slide, please.

First, let's define laboratory developed tests. It's a type of in-vitro diagnostic test that's designed, manufactured, and used within a single laboratory. I believe that definition came from the FDA. Next slide.

And this is the regulation which it falls under, the Establishment Studies, this 493.1253. And it falls under this one because it's not subject to FDA clearance, at least at this time, or approval, including methods developed in-house. And that's an LDT. Next slide.

Before you ever start, you need to have a procedure signed off by the lab director on how you're going to do your establishment studies. And it does need to include acceptance limits. So once it's done, you'll have something to go by to see if it worked or not. So the first element is accuracy. The lab's responsible for establishing that the method produces correct results. Next slide.

Precision-- the lab's responsible for establishing the precision of each test system by assessing day-to-day, run-to-run, and within run variation, as well as operator variance. Next slide.

Analytical sensitivity-- the lab's responsible for determining the lowest concentration or amount of the analyte or substance that can be measured or distinguished from a blank. Minimum detection limits are how much of the analyte must be present to be measured. Next slide.

Analytical specificity-- lab has to determine the extent to which the method measures the analyte for which its reporting results. That includes interfering substances from product information, literature, or its own testing. Next slide.

Reportable range of test results for the test system-- the lab has to establish the upper and lower limits of the test system. Next slide. Reference intervals are normal ranges. The labs have to establish a reference range that is appropriate for the lab's patient population. Next slide.

And lastly, I think they threw this one in as technology progresses, the CLIA regulations don't always keep up. So this one is, if there's any other performance characteristics required for test performance, they must be part of your establishment study.

And lastly, if you have any specific questions-- that's fine, you can go to the question slide. I would prefer that you send them in to the Lab Excellence mailbox. That's LabExcellence@cms.hhs.gov. They have a slew of subject matter experts that can give you a rapid and hopefully complete response to your specific questions. And that's it. Thank you.

SEAN COURTNEY: All right. Thank you so much, Keith, really appreciate that update today. I'm going to ask you a question here that we received in the chat. And it is, how do laboratories establish analytical sensitivity for a qualitative assay?

KEITH SCOTT: That's a good one to send into the Lab Excellence mailbox. Each individual test system kind of stands on its own. So I can't give a general answer to that. OK, great. Thank you.

SEAN COURTNEY: And I see that was just added to the chat, as well. So that was again, labexcellence@CMS.hhs.gov, I believe.

KEITH SCOTT: Yes sir. That's the best place if you have any specific questions.

SEAN COURTNEY: Perfect. Thank you. So if no other questions pop up, I'd just like to ask you to hang out and just kind of peruse that Q&A function. If any relevant ones do pop up, you can just answer it directly in the chat now. I'm going to take one last look through here.

All right, I don't see any right now. So thank you, Keith. Really appreciate you today. And we'll move to our next speaker. And that is Tim Stenzel with FDA. Tim, go ahead.

TIM STENZEL: Thank you, Sean. So two topics that I'll briefly cover today. And, if there's time, open it up for questions. So one was to cover a topic that Natalie touched on a little bit earlier on COVID having to do with antigen test sensitivity, especially for Omicron. And then go into monkeypox.

So monkeypox has had a declared emergency by the Secretary under the Public Health Service Act, Section 3.19. And there are questions in the chat. But I think there's lots of questions out there in the lab community about what might happen with tests and EUAs for tests. So I'll cover both of those topics.

The first topic has to do with antigen test sensitivity for COVID. I'll just say that historically when the FDA was reviewing tests during the Delta period, when Delta was prevalent, the antigen tests were continuing to perform in clinical studies for submission to the FDA and other available data that was available to the FDA for review, as they had been from the very beginning of the pandemic.

But as we transitioned from Delta to Omicron, the FDA and others began to observe a change in the sensitivity of the antigen test. And the FDA, in collaboration with the University of Massachusetts and the NIH, which supported the research, just completed a more than 7,000 patients study looking at serial testing.

Primarily, we looked at asymptomatic patients. We were trying to understand the performance of antigen tests in serial testing mode in asymptomatic patients. So everyone who was formally enrolled was asymptomatic at the time of enrollment. But later on, some of them became symptomatic. So as they were doing their serial testing, we were able to observe performance of the antigen test both in symptomatic as well as asymptomatic patients.

The study design was that every other day patients would test with both the candidate antigen tests that they had-- these were all-- there were three antigen tests used in the studies. All of them were EUA-authorized tests and were being currently being used in the United States for testing. They were known entities.

And then their performance was compared against-- this was all a home study, by the way. So the home users would get the antigen test. They would also get home collection samples or kits for central lab molecular testing. We use three different EUA-authorized molecular tests in the study. I am going to share, in the chat function, a preprint of this study.

There have been a number of different preprints of this study. This is the most recent one. It's not going to go through the same analysis that I'm going to describe today, though, and for which another publication is being written. But I just say that the chat function.

So again, we're enrolling patients who are asymptomatic. We were following them with testing, both molecular and antigen tests at home every other day. We then looked at when someone became molecular positive, and what the antigen test performance was.

So I'm going to kind of jump to the conclusions here because I'm not ready to present all of the data. The-- [AUDIO OUT]

SEAN COURTNEY: Tim, I think we lost you for a second there. I think you're muted. I'm not sure if it was the phone or computer. I can hear you, you're good.

TIM STENZEL: It was my VPN line, I'm sure. I'm back on now. Hopefully you didn't miss much. So what was observed-- and this was both a compilation of both Omicron and Delta patients-- that was if you were symptomatic, it was really helpful for a symptomatic person to test twice. And did it not go through? I did put the link in, at 3:46 in the chat window, in the chat box.

So even though they were symptomatic, it was really helpful to test twice. And sometimes that first test was negative, but the second test would be positive a lot more times. And the performance moved above 80% sensitivity when you tested symptomatic patients twice. So that is also reflective of some tests that have been authorized by the FDA this year, where, even for asymptomatic-- for symptomatic patients, that the authorization was for two tests rather than one.

The other observation was that in those patients that remained asymptomatic, that it was important to test not once, twice, but three times, to be able to detect above 80% of the patients who were experiencing a COVID infection. So the FDA did come out with communication last week explaining this.

The preprint that I shared here is already out there and more details will be forthcoming. But that's an important point, I think, to make about the use of antigen tests, especially potential for false negatives. That repeat testing, serial testing, is very helpful.

Next, I'll move on to monkeypox. So the FDA has been involved in monkeypox from the very beginning and assisting CDC and other federal agencies, HHS and the White House, in the response effort, and has been in communication with a number of labs and manufacturers as well as societies, such as-- I'll just leave it at that, a number of professional societies, both academic and others.

And we have endeavored to increase availability of testing as quickly as possible working with the CDC. We expanded and we helped expand and provided enforcement discretion when it would speed up the expansion of capability within the LRNs as well as in the reference labs that was mentioned earlier in the talk by Christy. And we'll continue to do that. We'll continue to work with all stakeholders to provide access to more and more testing.

And as I've said on this call previously, the FDA has been providing enforcement discretion for monkeypox so that an LDT developer can go ahead and develop a test and doesn't even need to notify the FDA and can offer that test to support the emergency or the outbreak response here.

There are two different declarations that the Secretary of HHS can make. And that is a 319-section declaration under the Public Health Service Act. And the second one is the 546-- 564 rather-- 564 section of the Food, Drug, and Cosmetic Act. The second section in the Food, Drug, and Cosmetic Act allows the EUA authority. The primary reason for EUA authority is to rapidly authorize a test that can help respond that gives assurance that accurate tests are being used in an emergency situation.

The EUA authorities can be very specific within the FDA. For example, EUA authorities have always been declared for vaccines for monkeypox, but not yet for tests. And so the tests can be declared under the EUA authorities but have not yet.

But I did want to give some idea of the process that we might follow if such a declaration is made. First of all and first and foremost, the reason is to expand test capability or test access with tests that can be relied on, they're accurate. But also for those who manufacture test kits, if there isn't an emergency declaration, the level of work that's needed to get a authorization from the FDA is much more significant than under the EUA authority.

The EUA authorities allow us to lower the bar and allow much fewer samples to be used to validate the test and to waive some of the other requirements that are required for full authorization. And that's and that's one of the main benefits of the EUA authority. So right now without EUA authorities, because there is already an FDA test on the market, the CDC test, which was granted a De Novo application-- and all subsequent tests come in as a 510(k). But still, a 510(k) is a whole lot more work than an EUA test can.

So the FDA has already drafted a template of recommendations for test developers. It is going through the clearance process. The FDA has already drafted guidance that may be used if such a declaration is made. So this is all in preparation for the declared need of EUA authorities for tests.

The templates with recommendations are going to be very similar to what the FDA was recommending early in the COVID emergency. And that is that we recommend that 30 positives and 30 negatives be used to validate your test. Because some labs and developers have a hard time accessing monkeypox samples, as they had a difficult time accessing COVID samples for many weeks, if not months at the beginning of the pandemic, the FDA would allow the use of contrived samples.

So plasmid constructs, other control materials, extracted DNA from monkeypox, things like that, can be diluted into a negative patient matrix down to about 2 to 3x LOD in order to validate on 30 positive and 30 negative samples. We would ask that those 30 samples be collected from negative swab patients, negative for monkeypox. They could be positive for something else. But that they would then dilute the constructs into negative samples.

The same samples that are negative when they're source can be used for the negative samples. And then the construct diluted into those negative angles to use for the positives. So you don't need to collect more than 30 samples that are negative for monkeypox.

And then in order to do it down to 2 to 3x LOD you need to do a LOT determination. And then for inclusion and exclusion, that is, does your primer and probe set, does it detect the circulating strains of monkeypox in the United States, you can do an in-silico examination and make sure that it is able to detect the strains that are circulating.

And then also for exclusion, for anything else that might cause a false positive that might be on the scan, herpes or whatever, you can do in silico analysis, as well. And only if your homology is 80% or greater would we ask for actual wet testing for any of those potentially confounding targets in a sample.
So in a nutshell, that's what we're seeking to do if needed for this emergency. And I'm open to questions if there's any.

SEAN COURTNEY: All right. Thank you so much, Tim. Really appreciate that update today. I think you've actually answered a lot of the questions that were in the chat. I will just ask one, since we're limited on time, though. And it's really around just use of RUO test kits for diagnostic testing.

TIM STENZEL: So the FDA does have an RUO policy. I would say that the FDA is open to labs developing a test and using it. And they can look to our guidance on our RUO kit.

SEAN COURTNEY: All right. Thank you, sorry about that. Thank you again, though, Tim, today for your update from FDA. And with that, I'll go ahead and end today's call. I just want to thank all of our speakers today. And that as a reminder--

TIM STENZEL: Sean.

SEAN COURTNEY: Yes?

TIM STENZEL: I think there's an important question. There's an important question. It was, does a testing shortage need to exist for EUA pathway to be open, or are there other factors considered? And since there is a clear test but it is not available to all laboratories, that would be one factor.

The other thing that I wanted to actually say is that the FDA, if EUA authorities are invoked for testing, will seek to make sure that there's no limit on the availability of tests. That is, if you're an LDT test developer you're already doing it. We want you to continue to do it while we have a dialogue with you following the guidance. That's it. Sorry, Sean. I just want to make sure that was clear.

SEAN COURTNEY: Oh, no. I appreciate that. Thank you. Thank you for adding that. All right, thanks, Tim. And again, thanks to all of our speakers today. As a reminder, I just want to let everybody know that our next call is scheduled for Monday, September 19 from 3:00 PM to 4:00 PM.

And as I mentioned at the beginning of the call, the slides, audio, and transcript should be posted to the web page by next week. And with that, I just want to really thank everybody, thank all of our callers, and thank everybody for listening in. We're really appreciative of all your work you do. And we will talk to you again on Monday, September 19. Thanks, everyone. Have a great day.