Clinical Laboratory COVID-19 Response Call

December 28, 2020

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JASMINE CHAITRAM: Hey, everyone. This is Jasmine Chaitram with CDC. And before we get started, I'm just going to ask all of our panelists to mute themselves so that we don't have any background noise as we start the call. As I mentioned, I'm Jasmine Chaitram. I'm with the Division of Laboratory Systems at CDC. I'm the Associate Director for Laboratory Preparedness. And DLS, the Division of Laboratory Systems, has been hosting these calls since March to provide information to public health and clinical laboratories across the nation in regards to the COVID-19 response.

Today we've got a full agenda, and we're going to do something a little different at the end, which is have a panel of subject-matter experts on different topics which will answer any of your questions. So you can submit those in the chat, and I'll go through those instructions in a minute, because I do have a few announcements and housekeeping tips.

But before we get started, I wanted to remind you all that the Division of Laboratory Systems has been working with the clinical and public health laboratory community since before COVID. This isn't something new for us. We've been doing it for many years. And we've been doing it in the areas of training and workforce development, safety and quality, informatics, biorepository and data science. We've also been doing it in public health preparedness and response. And so this is our opportunity to put all of those things that we've developed specifically for the COVID

response to use. And communication is one of those and coordination with the clinical lab and public health community as well as liais~~on~~ing with the CDC Emergency Operations Center during this time.

So the first thing I wanted to go through as far as announcements is that we have three new testing infographics on our point-of-care web page. I had announced previously that CDC has a new web page with information for point-of-care tests. And I know a lot of you may not be using point-of-care tests, but we do ask you to share this information with your partners or other colleagues that you know that are using point-of-care test. This is really good information, especially these infographics, lessons learned on how to perform the tests. They're very specific things that have come up that CDC has recognized or has heard from other facilities that have been doing testing about issues they've come across, and so we want to highlight that these are available now and can be easily downloaded from that page.

The next thing I wanted to mention is the links that we always have available on these slides so that you can quickly find whatever information you need. And those links are on the Preparedness Portal that DLS hosts and has recently created specifically in response to COVID-19. We've had preparedness information on our website before, but this is now a one-stop-shop location for information, including all of the slides, the transcripts, and the audio from each of these calls.

We also have all of our Laboratory Outreach Communication S~~s~~ystem messages that we've sent out. We've sent out over 100 messages to date ~~of~~ related to COVID-19. So if you've missed any of those, you can go to this website to find them, or if you just want to go back and see anything that you are unclear about. The next call will be on Monday, January 11. We host these calls every other week. And so that will be our next date for this call.

We also asked for information about training and workforce development needs. Please email those to LabTrainingNeeds@cdc.gov. And then finally, the how to ask a question-- please use the Q&A button in the Zoom webinar system. It's towards the bottom, I think, of your page. It could be, I guess, on the side or on the top depending on how you set up your screen.

The most important thing is we don't want you to submit those questions in the Chat box. The Q&A allows us to record the questions and keep them in case we're not able to answer them. We do have a number of questions that come through doing these calls, and sometimes not able to answer all those questions. And if you do want us to get back to you with a response, please include an email address, and we will get back to you after the call.

And then my standard couple of things that I also say is that if you're with the media, please address your questions to media@cdc.gov. And if you're a patient, please address your questions to your health care provider. And with that, I think we are now going to head into our first agenda item, which is not exactly COVID-19, but it is an important announcement about a clinical laboratory surge testing survey that will be distributed and has been developed in collaboration with Gryphon Scientific and CDC. And this is an effort that has been in

development for some time before COVID as we were working on some of our preparedness activities that I mentioned previously.

And with that, I'm going to turn that over to Corey Meyer with Gryphon Scientific. Corey.

COREY MEYER: Thanks, Jasmine. Next slide, please. Thank you. Perfect.

Yeah, so thanks. As Jasmine said, my name is Corey Meyer, and I am with Gryphon Scientific, which is a scientific consulting company in Washington, DC. So we are working with DLS to conduct a national survey of clinical labs which is going to launch in January, 2021 at a high level. The purpose of the survey is to understand whether and how clinical labs would choose to participate in surge testing during a public health emergency such as the COVID pandemic.

And before I dive into more details of the survey, I just want to briefly acknowledge my collaborators on the effort who bring strong expertise in clinical laboratory science and public-private partnerships to work. So they're listed on the slide. We're working with Apps Associates, Healthcare Ready, Association of Public Health Laboratories, Association of American Medical Colleges, and the National Marrow Donor Program, which oversees the Radiation Injury Treatment Network.

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So as I mentioned, the survey focuses at a high level. It Includes questions about the lab's testing capabilities, capacities, and willingness to perform surge testing with broad focus on chemical, radiological, and biological incidents, including a deliberate release of a biological threat agent or a natural outbreak. Our capability questions cover the types of testing a lab performs and informatics capabilities. Capacity questions focus on challenges labs would face in rapidly increasing testing capacity to meet surge demand. And our willingness questions focus on factors that influence the lab's ability to perform surge testing as well as desired mechanisms for communicating with the public health sector during an emergency.

Our survey also does include a section of questions that are specific to COVID-19 which cover business, logistical and technical challenges that labs have faced in performing COVID-19 testing.

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So after the survey, to give you a sense of what we're going to be doing with the survey data, Gryphon will be convening a series of stakeholder engagement meetings with representatives from the public health and the clinical lab sectors to discuss what we find in the survey and how to operationalize the findings. And ultimately, we'll be putting together the survey analysis findings and also the outcomes of these discussions to develop evidence-based findings for how to strengthen partnerships between the public health and clinical lab sectors to improve surge

testing during COVID-19 pandemic and future public health emergencies. It's really helping provide an evidence base for how these partnerships can be strengthened to improve testing.

And we will be analyzing data on an ongoing basis to try to gain insights that can improve the COVID response. We'll also be sharing the survey findings with the community through publications. Next slide, please.

So here I just wanted to share some survey details. So I mentioned that we'll launch in January, so in just a few weeks-- actually, about a week. So we're selecting a random sample of clinical labs nationwide to participate in the survey. And that's among a set of labs that meet the two criteria that are identified on this slide.

So the first is that a lab is certified to perform moderate or high-complexity testing in a specialty that is relevant to chem, bio, or rad incidents. And that includes microbiology, diagnostic immunology, toxicology, and hematology. And the second is that the lab is independent or hospital-associated. So among the set labs that are selected to participate in the survey, we'll receive an invitation letter in the mail, and that will have instructions for how to complete the survey online.

So we'll be mailing our first batch of invitation letters on January 4, and we'll be mailing subsequent batches about monthly over the next six to seven months. That letter. Invitation letter will have CDC branding. We've shown a mock-up of the letter on the slide. So please, please watch your lab's mail for those invitation letters. And we recognize that you're extremely busy and have received many survey requests. But please, if your lab receives the letter, encourage your labs to participate.

The success of the survey depends on your responses, and we think it will gather really useful information about how CDC and public health partners can best support your efforts to perform surge testing. So please look out.

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So that's all I wanted to share today. But if you have any questions about the project or the survey, please feel free to reach out to me using the email address on the slide. Jasmine is leading the effort on DLS's side, and so she can answer questions as well. So thank you, Jasmine, for the opportunity to share the information today.

JASMINE CHAITRAM: OK. Thank you so much, Corey, for the information about the survey. Do appreciate you coming on and sharing that. And as Corey said, if you any follow-up questions, you can reach out to myself or use the clinicallabsurvey@gryphonscientific.com email.

We are going to move to our next topic today, which is going to be a presentation from the Council of State and Territorial Epidemiologists. Brooke Beaulieu-- I'm terrible with names, so I

apologize if I messed up that name, Brooke-- will be giving us a summary of a survey that was recently conducted by CSTE on electronic laboratory reporting for COVID-19. Brooke?

BROOKE BEAULIEU: Thank you, Jasmine, and good afternoon, everybody. Happy holidays. As Jasmine noted, my name is Brooke Beaulieu, and I work within the Surveillance and Informatics Program at the Council of State and Territorial Epidemiologists, also known as CSTE. Thank you for allowing me some time to talk briefly with you today and share the results from our recent assessment on where state public health currently stands on receiving electronic lab results for COVID-19. Next slide, please.

For those who may be unfamiliar, CSTE serves as the professional home for applied epidemiologists across the nation. Our member community is comprised of those working at state, local, territorial, and tribal health departments, often working on disease surveillance and outbreak response. Our members meet regularly to discuss ongoing and evolving topics of interest to the public health community, and we have been activated to respond to the COVID-19 pandemic for about the past year. Within our programmatic framework, we partner with our extensive member base-- federal agencies, including CDC, and partner organizations such as APHL, to build capacity, fund fellowship programs, an state projects, develop guidance documents for surveillance practice, and adopt standardized national surveillance case definitions, either for reportable conditions or for conditions on the Nationally Notifiable Condition List.

I want to take a moment to highlight how appreciative and grateful CSTE is for our partners in the lab community. Lab data are the driving force for public health surveillance and action, including for identifying or ascertaining possible cases, classifying cases, enumerating and conducting case investigation and follow-up as necessary. Without your work to provide these data, public health response would be stunted.

While lab data are critical for surveillance of many diseases, this importance is particularly highlighted for COVID-19. A positive lab result on a lab report is often the first indication to public health of a possible case. And especially with the larger volume of current lab testing, sometimes it's the only way that public health finds out about a case. As such, reporting of complete lab information to the appropriate public health authority is paramount. Next slide, please.

As you may be aware, earlier this year, the Department of Health and Human Services released guidance to correspond to the lab reporting mandate in the CARES Act. As a reminder, the CARES Act requires every testing facility that performs COVID testing, whether it be molecular, serology, antigen, to report all results, positive and negative, to the state health department in which the individual whose sample is being tested resides. The June guidance stipulated 18 required data elements to report to state public health as well as a list of optional data elements, including the ask-on-order entry questions.

Public health agencies charged with receiving these data from testing facilities were made aware of these requirements at the same time that the guidance was released and have since been working tirelessly on the technical informaticians necessary to receive these required data electronically from the spectrum of reporters. CSTE has sought to systematically capture the progress and challenges of implementing these requirements at the public health agency end.

In October, we launched an online assessment to our members within our ELR, Electronic Lab Reporting, community to understand the current capabilities of jurisdictions related to the following categories. And in the interest of time, I've indicated which results I'll cover today with an asterisk, which include mandated reporting of demographic information, the ability to receive, process, and consume the required data elements, ask-on-order entry questions, and top challenges and barriers to receiving or consuming this information within the relevant information systems. Altogether, we received 44 responses from jurisdictions, giving us a response rate of about 78%.

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Again, I want to emphasize how important these data are for public health case investigation and follow-up, particularly demographic data. There are some demographic data elements that were listed as required within the HHS guidance, and we were interested as to whether jurisdiction had also added specific language to their own state regulations to mandate reporting these data. Our assessment revealed that 82% of jurisdictions have added specific language to mandate reporting of demographic data within their state law, rule, or regulation. And additionally, various states have mandated demographic data elements beyond what is included in the HHS requirements.

Just to give a snapshot of the many different types of stipulated data elements, there are the top five that were mandated-- full patient name, patient date of birth, patient phone number, full patient address, and ordering provider phone number. However, we do still notice significant gaps in the reporting of some demographic data, most notably for race and ethnicity. Noting the importance of these fields, CSTE welcomes the continued engagement of the lab community to better understand how we can address those gaps in reporting and identify opportunities for improving that completeness.

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In terms of ability to receive these data from reporting facilities, all of our respondents, 100%, indicated that they could receive all 18 of the required data elements if a facility was able to send them. The ability to receive these data holds true even if the information management system or surveillance system are not yet able to process or consume the data elements, meaning that those data elements can still be received even if they are not able to be parsed and placed into the correct component of the surveillance system for programmatic use.

72% of jurisdictions are able to receive, process, or consume those optional ask-on-order entry questions, with 21% anticipating the ability to do so by the end of 2020. As a reminder, this assessment was launched earlier in October. For jurisdictions that are able to receive data and consume data from the ask-on-order entry questions, responses are primarily used to prioritize case investigation when the lab reporting volume is high. And based on the current lab volume, it's nearly impossible for public health agencies to investigate every single case. So these responses are really helpful to triage those limited resources.

These data are also used on other ways. You can see displayed on the screen for those that are calling in on their data analysis, filling in certain data gaps, special fields, or empty fields, contact tracing in case investigations, and then also providing and developing reports for state leadership, compiling daily reports of dashboards for public use, and fulfilling data requests from community partners. While there are still challenges to overcome, we should note that this is tremendous progress that has been made to send and receive these data since the guidance was released in June, and the success is truly a result of an impressive amount of work.

Next slide, please.

Health departments are currently receiving these data through a variety of mechanisms. The ideal for receiving lab data electronically is via an HL7 message. However, in reality, states are using a combination of methods in order to receive these data from various reporting sources. Most jurisdictions are able to receive results if they are sent by a state-produced CSV file. It's about 89%. There's also a national standardized CSV file. National ELR flat file is what it's been termed. That was developed by APHL that many states have also implemented. And many agencies are also still receiving fax spreadsheets.

Now you can see some of the other workarounds, different file formats. Of course, there is still, unfortunately, a lot of manual entry, secure file transfer protocols or secure email messages. A lot of online web applications or reporting portals have been developed across jurisdictions. Certain facilities have developed their own flat file to be able to send results as well as different platforms such as REDCap.

Next slide, please.

Finally, I would like to touch upon some of the challenges that health departments are currently facing to be able to receive, process, and consume these lab data for epidemiologic use, AKA opportunities for improvement and further discussion. Respondents were asked to note their top three challenges, and this table shows how frequently each challenge was rated in the top three. The most commonly selected barrier was just the sheer volume of onboarding new testing facilities for reporting, which oftentimes needed slightly tailored solutions to accommodate each new facility. That challenge was followed by quality control of files within the reporting stream, including identifying missed or delayed files.

And then the third most common barrier in that top three was troubleshooting technical barriers at the sender end. And this was particularly true for facilities that may not have any prior experience with reporting to public health. And we acknowledge that all of these-- that the top three barriers, but also the ones downstream on the list-- are all intertwined.

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To wrap up, again, I would like to emphasize the importance of lab data in your work in reporting those lab results to public health. Jurisdictions have developed multiple technical solutions to be able to receive those data that you're mandated to report, and there's been a lot of progress made in a relatively short amount of time. Public health departments continue to work through ongoing and emerging challenges, especially related to the volume of facilities reporting as well as the increasing volume of lab data coming in. From policy considerations to the necessary technical solutions, we look forward to our continued partnership with the lab community to identify process improvements to achieve our common goals.

And that is all I have, Jasmine. I'm not sure if there's any time for questions, but happy to take some, whether by chat or over email as well.

JASMINE CHAITRAM: Thank you so much, Brooke. That was a great presentation. We do have a couple of questions for you. Hang on one second.

BROOKE BEAULIEU: Sure.

JASMINE CHAITRAM: OK. The first question is, "my state health department has said not to send negative results. What should we do?"

BROOKE BEAULIEU: This is a great question, and the observance might be in response to what is most necessary or priority for the health department at this current time versus when the pandemic first began. So as this response has evolved and definitely continues to change, different surveillance strategies might be needed, and those reporting requirements may change. And we recognize that the most actionable test results are the positives. So that might be the intent if labs have heard that instruction from state health departments.

We're getting to a point with cases numbering in the millions and test results numbering far beyond that. So as a surveillance community, we really have to discuss if this current surveillance strategy of reporting all results is really feasible and meaningful. And I think we'll see a lot of conversations about just that in the new year.

JASMINE CHAITRAM: Thank you. The next question said, "how do I find contacts to help with sending data to state health departments?"

BROOKE BEAULIEU: Great. CSTE has actually developed an ELR Points of Contact page. It is posted publicly on our website, and I can send Jasmine the link for that for dissemination. It

compiles contact for each jurisdiction that facilities can reach out to you with questions about onboarding or reporting.

JASMINE CHAITRAM: Thanks, Brooke. And I'll just note that we have sent out a communication about this before. So if any of you on the phone need to find this, you can definitely send an email to LOCS@cdc.gov or you can search on our Preparedness Portal for the LOCS message with this information. Honestly, I don't remember when we sent it out, but I feel like it was in the fall sometime.

OK. I've got another question for you. "Why don't all states have the same reporting requirements? Why can't this be standardized or harmonized?"

BROOKE BEAULIEU: Another great question. And the answer is that that is just the reality of the United States being a federated system where states are able to have their own reporting regulations. We definitely acknowledge that this is a challenge for labs. And while we do our best within the CSTE community to promote standardized requirements, states might implement modified requirements based on their respective needs or even capabilities.

So we definitely acknowledge that this is a challenge. We are open to engaging in additional discussions with you to address those recognized challenge and definitely encourage you to reach out if there are specific areas of concern. I can work to coordinate those additional discussions to look at those issues further.

JASMINE CHAITRAM: OK. One more. "Why not seek demographic data directly from the people who have it, the ordering providers, rather than from the lab, which often has no access to this information?"

BROOKE BEAULIEU: Yeah. I've also heard this question come up a couple of times of, where should electronic case reporting be leveraged versus electronic lab reporting and putting additional burden on labs? And from what we're seeing in some of the testing in this currently is that not all the folks that are getting tested are currently seeing providers, so that information may not come through in that way. So right now, the lab report is really the most reliable way that we have to receive that information.

JASMINE CHAITRAM: OK. I do have one more question that I think we should address. Do we follow federal reporting guidelines or state guidelines? And I think this is an important question. So can you answer that one, Brooke?

BROOKE BEAULIEU: I can give it a stab. So as I mentioned previously in the response to why don't all states have the same reporting requirements, states have been working to meet the umbrella guidance that was provided federally through HHS and that June reporting guidance that I mentioned in the presentation. However, as noted, there are various needs and capabilities that differ across the state. So I don't really know if I can tell labs to follow one or the other, just the open lines of communication with your state health department, providing

the information that they are needing from you, and recognizing, again, that surveillance strategies might change as this pandemic progresses.

The states are working to meet the federal requirements, but they are also working with you to get the data that you can provide in order for meaningful response. So the open lines of communication with your health department are critical. I'm not sure that really answered the question. Just the best response that I can give to that.

JASMINE CHAITRAM: Well, thank you so much for joining us today. Appreciate you taking the time. I know that lots of people are supposed to be on leave, so I appreciate you being here.

We are going to move to our next topic on the agenda, which is going to be updates from the Infectious Disease Pathology Laboratory at CDC. And our speakers today-- we've got two-- Jana Ritter and Hannah Bullock from the CDC Division of High-Consequence Pathogens and Pathology. And I think Jana will start first.

JANA RITTER: Yes. Thank you. Good afternoon, everybody, and thank you for inviting Hannah and me to provide some updates from the Infectious Diseases Pathology branch. We have a few different topics to cover. I'll go over some of the-- sorry. Next slide. I'll go over some of the histopathologic findings we have seen in pediatric deaths, talk a little about antibodies available for immunohistochemical detection of SARS-CoV-2 and then mention some updates to CDC's guidance for collecting post-mortem tissues for viral testing. And I'll turn it over to Hannah to talk about the use of the electron microscopy for coronavirus detection, including some challenges with virus identification.

Next slide.

In IDPB, we have evaluated autopsy tissues from nearly 300 deaths with suspected or confirmed SARS-CoV-2 infection from nearly 40 jurisdictions. Fewer than 20 autopsy cases submitted to IDPB with evidence of SARS-CoV-2 have been children under the age of 18, and approximately half of those were less than one year of age, and most were found deceased at home or expired in the ED. The most commonly reported clinical signs are those of upper respiratory tract infection. And for the infants, many were found unresponsive.

Most of the pediatric cases we have received have antemortem or post-mortem NP swabs positive for SARS-CoV-2. Pathologic findings have typically been different from what we have seen in adult fatalities due to COVID-19. It's important to note that these relatively few cases are not representative of all pediatric COVID-19 deaths, particularly those who may die in the hospital or those that do not go to autopsy due to certainty of antemortem diagnosis. We typically receive cases where there are questions regarding relatedness of SARS-CoV-2 to the cause of death or observed pathology and more frequently receive cases from medical examiners or out-of-hospital deaths.

So with those caveats, some of the things that we have more consistently found in pediatric cases include tracheal bronchitis, pulmonary edema and hemorrhage, aspiration, and only occasionally mild inflammation in the lung parenchyma. We've also seen myocarditis in a few cases. Importantly, we have not seen diffuse cellular damage, which is the prominent finding in adult COVID-19 cases. Next slide.

So these images show tracheal bronchitis with predominantly lymphocytic inflammation involving the submucosal stroma you can see on the left, and the glands-- you can see on the right inflammation in the glands.

Next slide.

And here we have some pediatric lung tissues with alveolar filling by hemorrhage in the left image. In the middle image, there's alveolar edema fluid with macrophages. And on the right, we have two examples with aspiration-- on the top, filling of a bronchiole by squames and aspirated debris. And down on the bottom, large clusters of aspirated bacteria, and along with hemorrhage. I want to note that the hemorrhage in most cases is largely attributable to resuscitative efforts in these children.

Next slide.

Myocarditis is the most common histopathologic finding in cases of multisystem inflammatory syndrome, or MISC. This is characterized by interstitial inflammation. So you can see in the top images, the purple dots are inflammatory cells within the pink heart tissue. In the middle right, a C4D stain highlights complement deposition in the acutely injured myofibers. And then in the bottom, CD68 and CD45 stains highlight macrophages and lymphocytes infiltrating the damaged myocardium.

Next slide.

Here's a case from here in IDPB with similar lymphocytic interstitial inflammation. In the top left, you can see those inflammatory cells. In the bottom left, you can also see some interstitial edema-- that's that white space in between the myofibers-- and on the right, some myofibril degeneration associated with those changes.

Next slide.

We have also had one case with a prominent eosinophilic component to the myocardial infiltrate. So on the left, we have, again, that interstitial inflammation, the blue cells in the white space. And then on the right, the cells that you see with bright eosinophilics or pink cytoplasm, those are eosinophils. This was a previously healthy child with no reported signs of acute COVID-19.

Next slide.

So I'm going to switch gears now and give you a quick update on immunohistochemical testing for SARS-CoV-2. You don't need to read the details of this table, but it summarizes some of the various commercially available antibodies that we've tested for use in our lab. Many of them are raised against SARS, but also detect SARS-CoV-2.

Next slide. These images show staining of SARS-CoV-2 and autopsy tissues with some of those different antibodies. On the top, we have staining with two of the antibodies raised against SARS, and on the bottom, staining with two antibodies raised against SARS-CoV-2. The antibody on the bottom left was developed by CDC's Immunodiagnostic Development team, while the other three are commercially available antibodies. Next slide.

One of the SARS-C0V-2 nucleocapsid antibodies that we have more recently evaluated shows notably increased staining compared to some of the SARS antibodies we had been using. Here's the same section of SARS-CoV-2-infected lung with IHC using the SARS antibody on the left and the new SARS-CoV-2 antibody on the right. So with this new antibody, we have an even more sensitive method for detecting SARS-CoV-2 in autopsy tissues.

Next slide.

In this slide, I would like to highlight forthcoming updates to the web page collection and submission of post-mortem specimens from deceased persons with known or suspected COVID-19. This web page, for which the content is a collaborative effort of Clinical Team Mortality Unit, Worker Safety and Health Team, and Infectious Diseases Pathology Branch has been available since late February 2020 and has been a critical resource for medical examiners, coroners, pathologists, and health departments, with over 745,000 page visits.

This site describes how to safely collect and test the optimal specimens, including postmortem swabs and fixed autopsy tissues, for the post-mortem diagnosis of COVID-19. As more has been learned about COVID-19 and as testing technologies and PPE and biosafety recommendations have evolved, this site has been updated. The last update occurred in June. For the upcoming revision, considerations for new testing technologies, including antigen testing and multiplexed COVID-19 and influenza diagnostic assays are presenting.

Criteria for submission of fixed autopsy specimens to CDC's Infectious Disease Pathology Branch for SARS-CoV-2 testing has been revised to include more newly recognized pathologic findings seen in the lungs, such as capillaritis and fibrin thrombi as well as recommending that in addition to submitting fixed respiratory tissues, but tissues from other organs, such as kidney and heart, be submitted to assist with an alternate diagnosis if tests for SARS-CoV-2 are negative and also to facilitate the evaluation of possible extra pulmonary complications of COVID-19.

Finally, recommended biosafety and infection control practices have been updated to emphasize the need for strengthening hazard assessment and biosafety requirements to add language to underline the importance of proper selection of eye protection and respirator,

extended use and limited reuse measures to PPE guidance during PPE shortages, other facility designs to help mitigate the possibility of virus transmission, and to provide a refined choice of EPA cleaning solutions. Many of the updates harmonize content on this page with that across other CDC COVID-19 sites.

Next slide.

If you're interested in submitting autopsy tissues to CDC's IDPB for evaluation, please visit the Post-Mortem Guidance website section, Submission of Specimens for COVID-19 Testing, linked on the slide. This outlines that you should contact us at pathology@cdc.gov and the type of information requested in order for us to best assess your request and provide you with assistance.

And now I'll turn it over to Hannah to discuss electron microscopy for SARS-CoV-2. Thank you.

HANNAH BULLOCK: Thanks. Next slide, please.

All right. So switching gears again, I'm going to talk about how we use EM to identify and detect coronaviruses and tissue samples and the recent problems of misidentification of coronaviruses in publications. On this slide, we have a quick overview of coronavirus ultrastructure. The first thing to note is that the appearance of the virus varies depending on the technique used. The leftmost image on the slide shows a negative stain of preparation. So that uses a heavy metal salt solution to coat the outside of the virus, making the well-known spikes of the coronavirus clearly visible.

By contrast, in thin section samples, extracellular particles, as shown in the center image, may have visible spikes, but they appear more as a fuzz or a fringe around the outside of the viral particle rather than as the clearly defined spikes you see in the negative stain image. And intracellular particles, shown on the far-right image, rarely have visible spikes.

Intracellular particles are held within membrane-bound vacuoles in the cytoplasm, and viral particles are produced when the helical viral nuclocapsids bud through the membranes of the endoplasmic reticulum golgi complex to form spherical particles inside of vesicles. The arrowhead in this case is pointing at one of the vesicle membranes, and there's an arrow pointing at a viral particle. Within the inside of the viral particle, you can see the cross-sections through the helical nucleocapsid which appear as electron-dense black dots on the inside of the virus.

Next slide.

Recently, there have been several publications that have incorrectly identified normal subcellular structures as coronavirus particles and COVID-19 tissue samples. A selection of those publications is shown on this slide along with images of some of the structures misidentified as coronavirus particles. As you can see, this encompasses a number of journals

and includes misidentifications in the lung, kidney, heart, brain, liver, intestines, skin, and placenta. And it's understandable. These misidentifications are quite easy to make if those looking for the virus do not have a strong background in viral diagnostic EM.

Next slide.

Here we have a few of the structures that have been most commonly misidentified as coronaviruses. That would be coated vesicles, vesiculating, rough endoplasmic reticulum, and multi-vesicular bodies. In the first panel, the arrow is pointing at a clathrin-coated vesicle. These are involved in normal cellular transport. The confusion with coronaviruses comes from the fringe of clathrin surrounding the outside of the vesicle that could be misinterpreted as viral spikes. However, you'll notice that the clathrin-coated vesicles are found free in the cytoplasm, and those spikes are in direct contact with the host cell cytoplasm.

Next slide.

By contrast, intercellular coronaviruses, indicated by the arrowhead in the lower image, are found within membrane-bound vacuoles, as I mentioned earlier. And any spikes, if visible, would be in contact with the vascular contents and not with the cytoplasm. Additionally, the clathrin-coated vesicles, indicated by the arrows in both images, lack the electron-dense black dots apparent on the inside of the viral particles that indicate those cross-sections through the viral nucleocapsid.

The middle panel shows circular cross-sections through the rough endoplasmic reticulum which have been confused with coronaviruses due to the spike-like appearance of the ribosomes on the outside of the membranes. But again, these are free in the cytoplasm and also lack the black dots, indicating cross-sections through the nucleocapsid, and they also vary more in size than a coronavirus particle would.

Next slide.

Of note with the clathrin-coated vesicles and the rough ER, since the spikes are one of the most distinguishing and well-known features of a coronavirus, that is typically what somebody is looking for when they search through their tissue samples for the virus using electron microscopy. But it's important to note that those spikes are, again, going to be most visible when you use the negative stain technique, as shown in the lower image on the left side, or on extracellular viral particles, as shown on the lower image on the right side.

Finally, the last panel shows a multi-vesicular body. These are involved in normal protein degradation. They have the appearance of a membrane-bound collection of spherical particles, and these can be confused with a vacuolar accumulation of coronavirus particles.

Next slide.

These are shown in the lower panel. The primary differentiating feature here is the lack of black dots, signifying cross sections through the viral nucleocapsid which you can see clearly in the lower panel in the viral particles. But those are, of course, missing from the multi-vesicular bodies.

And with that, Jana and I will be happy to take any questions if there is time.

JASMINE CHAITRAM: OK. Thank you so much. That was a great presentation. I'm not showing any questions for you or Jana at this time. Hang on one second. Let me just kind of look through them real quickly.

OK. We have one question coming through. We'll wait for that in just a second. OK. "Has there been evidence of skeletal and brain tissue?" That's how the question came through. I'm not sure what exactly they're asking.

JANA RITTER: Oh, I think they're asking probably if we've seen evidence of infection in skeletal muscle-- I don't know-- skeletal muscle or bone and brain tissue.

JASMINE CHAITRAM: Right. Viral particles in skeletal or brain tissue.

JANA RITTER: Yeah. And I'm not sure if they're asking about pathology or EM or both. We haven't seen anything in skeletal muscle. I'm trying to think by IHC. But I don't think we have tested much, if any. And then I think there is some evidence coming out that there may be some infection in the brain, particularly in the vascular system. But we have not seen a lot of that in our laboratory. I don't know if you have any comments on the EM. But there are some others that are starting to report some evidence of virus in especially the vasculature in the brain and other tissues.

HANNAH BULLOCK: For EM, I know the samples we've looked at, we have not noticed any viral particles within the skeletal muscle or the brain tissue. And I don't recall seeing anything in the literature that's been published that is actual coronavirus in either of those.

JASMINE CHAITRAM: OK. And then someone also asked about evidence of infection in the heart.

JANA RITTER: I think it's the same situation. Some people are starting to report particularly vascular involvement with multiple tissues. I don't think there's been any evidence of infection of the heart muscle itself.

JASMINE CHAITRAM: OK. Well, thank you so much again for joining us today. We're going to move to our last portion of today's call, which is going to be a Q&A panel. And we've got different representatives from each of the agencies, FDA and CMS and CDC as well. I know that we have several questions in the Q&A on reporting, and we'll get to those in just a minute.

But first, I wanted to turn this first to FDA, Tim Stenzel. I'm sure if you've been on these calls, you've heard Tim talk about and respond to lots of different questions over a lot of these calls in the past. I think he's got a few questions that he received on the last call that he can answer now, and then I have a few for Tim that have come in today. Tim.

TIM STENZEL: Sure. Thank you, Jasmine.

The first series of questions I'm going to handle have to do with some self-collection. And not clear to us if it is self-collection observed or unobserved and in health care facilities or somewhere else. So I will cover all those bases in my response.

So if a CLIA high-complexity lab is running an EUA-authorized assay, they can incorporate, observed, or unobserved self-collection of samples within their health care facility without any way submission forth. However, if they wish to do home collection, that does require an EUA prior to launching the service.

Using any of the previously EUA-authorized home collection kits for a new EUA submission would likely reduce the amount of validation required and so may make this much easier if you want to add home collection to your testing offerings. If you have any questions or want any clarification, you can email us at the FDA. The email address is cdrh-eua-templates@fda.hhs.gov.

So if you are interested in knowing what the validations would be for such testing, whether those that require an EUA submission or not, you can look to the FDA website to the authorized collection kits and the authorized self-collection tests to see what we typically request. We also have a home collection template that should be very useful on the FDA website. And again, you can email us at the templates email address for any clarification.

And finally, there is a question that's specifically for a lab-developed test. What is required in that situation? And again, any collection within a health care facility, observed or unobserved, does not require an EUA submission. At-home collection or unobserved self-collection in a non-health-care setting, and whether or not the core test is a LDT (laboratory-developed test) still requires an EUA.

The notification pathway does not apply for home collection or unobserved self-collection in a non-health-care setting. Their authorization should occur prior to implementation. So just make clear that for all of this, we are talking about high-complexity labs for incorporating this kind of observed unobserved Self-collection. I think that answers the first question, Jasmine.

JASMINE CHAITRAM: Thanks, Tim. There's a couple that have come through. The first one is, "do you have any time frame for approval of the Roche SARS-CoV-2 antigen test?"

TIM STENZEL: OK. So I can certainly look into the status. That would be considered company confidential information for the FDA, so I couldn't report. But you certainly can reach out to

Roche and ask their status. And I'm neither confirming nor not confirming any sort of observation on the basis of Roche. You'll just have to look into that.

JASMINE CHAITRAM: OK. Thanks, Tim. I see a question for CMS, so I'm going to turn to Amy Zale with CMS next.

AMY ZALE: Hi, Jasmine. I'm here.

JASMINE CHAITRAM: Thanks, Amy. So the question-- I'm not even sure that you can answer this question, but it says, "does Medicare fee-for-service reimburse for pooled COVID-19 diagnostic tests?

AMY ZALE: Yeah, that's out of the scope of CLIA. That's our Reimbursement and Medicare folks, so that's not a question that I can answer. But if you want to send that to us, we can pass that on to our folks over in the Clinical Laboratory Fee Schedule Group.

JASMINE CHAITRAM: OK. Thank you. So there's a few questions about reporting, and so I'm just going to quickly check if Jason Hall is on the line and able to respond to a couple of questions. Jason, are you on the line?

JASON HALL: Can you hear me now?

JASMINE CHAITRAM: Yes. Thank you.

JASON HALL: OK. There we go.

JASMINE CHAITRAM: Awesome. So there's been a lot of questions coming through about over-the-counter and at-home tests and how these should be reported. Can you provide some general information on that?

JASON HALL: Yes. So first, generally, these aren't covered under most federal or most state reporting regs. So that's just to get that out of the way up front. But that said, there are efforts underway with the federal organizations-- FDA, CDC-- to assist with getting these data reported because they're needed during the pandemic.

What we've been doing is working with these manufacturers on the data elements and making sure that they have the ability to enable their customers to capture the data and assisting them with connections to get reporting going. But the bottom line is, if the data elements that contain identifiers can't be collected reliably, it's not going to be very useful for states. It may be useful for federal purposes and also let states look at those data so they can see some coverage. But if there's not a reliable way of getting the identifiers captured-- for example, in prescription, if it's not over-the-counter, if it's prescription at-home testing, that will work. But it's going to end up being more work for states, and there's going to be a lot of wasted time, I

believe, if the reporting-- if anyone tries to report incomplete data or de-identified data to the states, it just won't work.

There's a group of people at the federal level that are, like I said, working to try to put in some infrastructure that's going to assist with the current manufacturers and the ones that follow them to hopefully help. But if the identifiers can't be captured, at least the state reporting is going to be not very useful.

JASMINE CHAITRAM: OK. Thanks, Jason. The next question is, any recommendations on how a lab can accommodate all the different reporting formats that the states have? For example, some want AOE questions answered as an HL7 table, and others want SNOMED.

JASON HALL: Yeah. So what we've got out is a specific implementation guide for HL7 and a specific format of a flat file. States should be willing to accept one of those, if not both. If you work with an individual state, they often will ask for additional things or something that's slightly modified. But they all should take the standard that is out for HL7 and for CSV. And if they don't, you can reach out to my part of the response-- eocevents405@cdc.gov. And we can help you work with the states to get what you're trying to produce accepted.

We hear this all the time. And I know that Brooke has spoken to it to some respect on the requirements. But it happens on the reporting end as well where there can be some slight deviations state by state. But we can try to help smooth those out if you run into some real hurdles.

JASMINE CHAITRAM: Great, Jason. The next one is, "we do a lot of point-of-care testing and have our own reporting method. We have only been reporting to the local health departments, not to the state. I assume that it's OK."

JASON HALL: They sort of vary by state. But generally, if it's electronic reporting, you ought to be going to the state. Almost every local in the country uses systems that the states put out for surveillance purposes.

I know that COVID has spawned some new ways of either managing data or actual systems that are being used in states and maybe some locals, especially large locals in big states like Texas and California. But as a rule, you should try to be reporting these to the state health department who get them ingested into the system that all of the counties use.

That doesn't mean there won't be some-- like I said, Houston and Harris County and things like that, and Philadelphia, some of the locals that are big. And they have their own systems, and they run their own data flows. But they still partner with states, and they receive data from the states for a lot of different feeds. So if it's electronic, I would lean toward going toward the state. If you're reporting on fax, paper, going to the local is something that happens a lot in a lot of states.

JASMINE CHAITRAM: Thank you, Jason. I want to thank all of our Q&A panelists that were on today. We're out of time. Hopefully we can do this again in the future where we have a session at the end for just Q&A, and that would help to address some of the questions we received. Before we close out-- I think we've only got a minute left. I just wanted to, again, thank everybody for being on the call, thank all of our speakers for presenting and providing the information. And also, if you are not receiving emails, please sign up for those communications from the Division of Laboratory System. You can go to LOCS@cdc.gov. Our next call is on Monday, January 11, so hopefully you can join us then. And then finally, on behalf of the Division of Laboratory Systems at CDC, we want to wish you all the best for a happy and safe new year.