Clinical Laboratory COVID-19 Response Call March 8, 2021

Agenda

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JASMINE CHAITRAM: Hello, everyone, and thank you for joining the Clinical Laboratory COVID-19 Response Call. Today is Monday, March 8th, and we've been hosting these calls for almost a year now. We hope you find them very useful. I'm Jasmine Chaitram. I'm the Associate Director for Laboratory Preparedness and the Division of Laboratory Systems at CDC. The Division of Laboratory Systems has been providing information and support to clinical and public health laboratories before COVID and during COVID, and we'll continue to do that after COVID.

We do this in specific topic areas such as quality and safety, training and workforce development, informatics, biorepository science, data science, and preparedness and response. And in the preparedness and response area, we've also been working as a liaison to the CDC Emergency Operations Center during the COVID-19 response, and that's how we're able to provide you these updated topics during our calls and also answer any questions that you provide to us.

Showing today is our agenda. And we've got a shortened agenda, but I am sure that there's a lot of good information there. We probably will have more time for questions today. I am going to go through some housekeeping items before we get started.

Just one thing that I want to remind you all that the slide decks may contain presentation material from panelists that are not affiliated with CDC. And the presentation context from external panelists may not necessarily reflect CDC's official position. So when you go back and look at some of the slides that we post on our Preparedness Portal, just keep that in mind.

Also, another announcement that I guess I have for you today is the Specimen Collection Guidance web page was recently updated, so you can find that on the CDC COVID-19 web pages. The important update here, besides just some grammatical fixes and some cleaning up of the web page was that we now have added information about capillary fingerstick specimen collection.

As with other slide decks that we present, we have links to other information that we find that we think will be useful for you and easy to find. And we put these links in the slide so that, when you want to reference them or go back and check something from a previous presentation, they're here for you to easily access.

I've mentioned already the CDC DLS Preparedness Portal, which has links to our COVID-19 response call information. Here you can find the transcripts from previous calls as well as our slides and audio recordings. You can also find here a link to our Laboratory Outreach Communication System messages. That's LOCS. Those are emails that we've been sending out since the beginning of the response. I think over 100 have gone out to date. And there's other information and other links to CDC information that will help with your response to the COVID-19 pandemic.

Our next call will be on Monday, March 22 from 3:00 to 4:00 PM. We host these calls every other week. And we are looking to get some feedback from you on our training and workforce development areas of effort and focus. And you can email those topics or even any questions that you might have to LabTrainingNeeds@cdc.gov.

And then, finally, I just want to review how to ask a question during the webinar today. Please use the Q&A button in the Zoom webinar system. If you type your questions in the Q&A box and submit it, we should see it. Unfortunately, that doesn't mean we will answer it live. We do get a lot of questions during these calls, and we have to manage that as well as the amount of time we have for our speakers.
If you submit a question and you provide your email address, we will do our best, if we don't answer it live, to get you a response after the call. We also sometimes take those questions and use them to develop agenda and topics for future calls, and so you may hear your question answered on the next call. But we do try to send a response to you by email so that you at least have some answer that you were looking for.

So with that, please don't put your question in the chat box. It's hard for us to track them when they're put there, so use the Q&A. And also, if, for some reason, you have a media-related question, please send that to media@cdc.gov. And if you're a patient, please direct your questions to your healthcare provider.

And with that, we are ready to start with our first topic, which is going to be Vivien Dugan from the CDC Laboratory and Testing Task Force. And she's been giving updates, I think, for the last three calls now on the status of the variants, and we are glad to have her here again today. Vivien?

VIVIEN DUGAN: Thank you, Jasmine. OK, so I'm going to give kind of an overview of where we are with the variants. So I can go to the next slide, please. And just to give you a little bit of background on who I am, I'm the team lead for the Strain Surveillance and Emerging Variants team in CDC's COVID-19 response and the Laboratory Task Force.

But my regular day job is the Deputy Director for the Influenza Division at CDC. So for emerging variant cases in the United States, again, this data is publicly available. We are looking at a total of actually-- I'm realizing that this chart is not correct. So I can actually look at the current data that's right.

And Jasmine, I don't know if we had a slide mix up or what happened. But the actual total number of cases is looking at 3,133 total US COVID-19 cases caused by variants. For B117, we have 3,037 reported cases in the US with 49 jurisdictions reporting. For B1351, we have 81 cases in the US with 20 jurisdictions reporting. And for the P1 variant, those are 15 cases in the US from nine jurisdictions reporting.

So for the B117, that's often termed as the UK variant. That's the variant that first showed up in the United Kingdom. The B1351 is the variant that was first detected in travelers from Brazil or in Brazil and-- sorry, South Africa. And then the P1 is the South African-- the Brazilian variant, which is from travelers from Brazil. So we'll go to the next slide, but I am not sure-- OK, that's the side I want to show. There we go. OK, 3,133-- so this, again, the data are available online. They were last updated last night, Sunday night. They're updated three times a week, Sunday nights around 7:00 PM, Tuesday nights around 7:00 PM, and also Thursday nights at 7:00 PM. So you can kind of see the color shading based on how many cases are reported.

And so just to give you an idea of the data that goes into making this particular map, there's a lot of different data sources where cases are determined. And so when we talk about a case determined by variant, it's based on reports that are sent to CDC from state health departments and local public health authorities, the number of cases of COVID-19 within the local jurisdiction that meet their case definition, right?

So it's not going to capture everything. It's not going to capture all of the sequences that are publicly available. This is based on case criteria at the jurisdiction level. So you're going to have sequence data that can come in from the public health labs.

Most of the-- a good handful of the public health labs are sequencing SARS-CoV-2 positive specimens. CDC is sequencing specimens as well through-- we have several contracts with commercial laboratories and then also through our national SARS-CoV-2 strain surveillance network. We get specimens on a regular basis from public health labs across the US so lots of different data sources going into making these case maps that we have.

Next slide, please. So this is our CDC genomics dashboard. Again, it's public. You can easily find it by just googling CDC genomics dashboard. I think it'll come up. So these data are updated on a weekly basis on Sunday evenings.

And this is basically showing the number of sequences of SARS-CoV-2 that have been put into the public domain. And so they're reported by the week ending date. If you're familiar with a lot of our epidemiologic data, that's always tends to be the structure that we report data for. So for example, the week ending in March 6, 2021, you can see in the blue bar there, these are published sequences from our national SARS-CoV-2 strain surveillance and from our contract labs just shy of that 7,000 dotted line mark, which is really the goal of where we want to be.

What we've added to this, from the last time, I think, that we reviewed this is that we did not have the public health lab data. And so we've added that in the gray bar kind of stacked above the blue bar. And you can see that they've made a very significant contribution and have been making big contributions since, well, way before December. But at least this chart kind of gives you an example of where the data are coming from and where they're going.

So they are available in NCBI and GISAID. And as we count them here, they're duplicated because, at least from CDC, we submit to both repositories. And so this data, which often includes variant data, are available to inform public health actions before they are published.

So publishing is kind of like our last step in getting the data out. We try to do that as quickly as we can as long as the quality metrics and the data look like they meet all of our quality values. And so these weekly totals may reflect different submissions. They may change over time as data are increased.
There's often backfilling. That does happen as well. So we can go to the next slide, please. Again, on our genomics dashboard, this is like an overview of all the US sequences available in public repositories. These can be submitted to NCBI, or GenBank, and GISAID, from academics, public health labs, other sources, other studies.

And so you can see, we're reaching close to 160,000 sequences in GISAID from US submitters that are publicly available. And then for NCBI, we're close to-- where are we? We're just above 60,000. So I think this kind of gives you an idea of the overall production level as far as what's being generated and where it's going, which is a huge amount of data.

Next slide, please. OK, so also on our genomic dashboard, this map shows the total sequences submitted to GISAID based on a state-by-state level. And if you actually go to the dashboard, it's a lot more interactive than this static picture here. But this basically shows the number of sequences submitted to GISAID per state with the different ranges.

You can see some of the stronger states that have sequenced more or put more into the databases versus some of the other states that may have-- or just ramping up in increasing their number of specimens as well as specimens that CDC is receiving or CDC is sequencing through our contract labs from across the US. Next slide, please.

And then looking at the same data, but a percentage of cumulative cases sequenced, these are the various percentages. Again, it's more interactive if you go online-- if you go to the National SARS-CoV-2 genomic surveillance dashboard. But this shows percentages of cumulative cases sequenced overall. So I think this is kind of, again, a nice snapshot of the national level, which is, ultimately-- CDC's efforts are more of the bigger picture, national level, although we do have some really strong data from various states that can drill down in a more granular level. And we're really looking at national trends.
I think that's my last slide. So Jasmine, should I go through a couple of questions that we got on the last call?

JASMINE CHAITRAM: Yes, that would be great.

VIVIEN DUGAN: OK, so I'm going to start with one of the first questions that we had, where can a lab obtain the different variants used to validate tests or reagents? And so one of the places where anyone can really go to is it's through NIAID, so NIH-funded Biodefense and Emerging Infections Research Resources Repository. It's a mouthful.

It's basically BEI Resources. And so this is how the US government has engaged with domestic and international partners to obtain specimens and isolates of variants of interest and variants of concern. And so they are deposited there with BEI. They're also with the World Reference Collection for Emerging Viruses and Arboviruses, which is WRCEVA. So those are two resources that are able to share - we can share, CDC can share. NIH can share across the government and with academics or local health labs, public health labs.

So you can go to those repositories. The private sector also uses them as well. And so they have a nice catalog of what's available. OK, going to another question - which are the variants that are most infectious?

This is a really good question that we get a lot. There's a lot of preliminary data to look at some of these variants but not all of them because, I think, we're still looking to see how these variants are changing, are they increasing in proportion, and also characterizing them here at CDC as well as many of our international collaborators that were first determining and finding these variants, they're also working to try and figure out a lot of answers to these questions. But based on some of the preliminary data from the United Kingdom and the US, the transmissibility of the B117 variant-- that's the variant originally was determined in the United Kingdom-- that's estimated to be about 35% to 75% higher than previous viruses, or kind of older SARS-CoV-2 viruses, or also co-circulating SARS-CoV-2 viruses.

And that's based on epidemiologic data right now. The modeling data that we have for B1351 that's available publicly-- and a lot of these are preprints - that's approximately 50% more transmissible. Again, these are very preliminary early estimates based on modeling and more of the epi type of studies.
So that's what we know so far. But there's-- the data for the P1 variant-- and that's the Brazilian variant, again-- is really very early, and there's not a lot of data on that one so far. But of course, as more preprints are published, we keep our eye out for them. And we're certainly doing additional laboratory studies here at CDC to try and accurately assess these differences in transmissibility.

OK, another question that we got last time was about antigen tests. So if the antigen test screen for the spike protein, does that mean that the S drop SARS-CoV-2 virus-- so that's the S gene target failure-- is the one where, if you run certain assays like the TaqPath assay with three different targets, that the S gene target actually is negative but the other two targets are positive, which is often associated with the B117 variant. So with these antigen tests, does that mean that these B117 variants are the S gene target failure results that can't be detected by antigen tests?

And I think FDA-- and Tim probably covered this the last time, but just to kind of close the loop. The impact of the current variance of concern on antigen test is estimated to be pretty low. Given that nearly all, except for one antigen test with FDA. EUA, or emergency use authorization, targets the nuclear capsid protein, not the spike protein. The B117 virus actually has a deletion in its spike gene, which causes that pattern that we see it on the TaqPath assay.

It's only a two-amino acid deletion. And so we don't expect that it would have a large impact on current antigen tests. We have evaluation of a limited number of antigen tests, that show no impact on the ability to detect the B117 variant with antigen test. But again, I think we're working together with FDA to really make sure that is absolutely the case, for at least the B117 variant.

And then I think the last question that I can answer right now is, do we need to do genomic sequencing in patients that test positive for COVID-19? Genomic sequencing is not a requirement. It's not needed for patients who test positive. Sequence data can be useful for a lot of different reasons.

It can be useful at the local level for characterizing clusters of cases and differentiating point source outbreaks from multiple introductions. It can also be used to characterize the spread of viruses, different viruses among individuals, where there's a high likelihood of transmission, including congregate or overcrowded settings.

Some examples include health care settings, especially long-term care facilities; places of employment; schools; places of worship; shelters; housing people experiencing homelessness; and correctional and detention facilities. If at any time, the SARS-CoV-2 genetic variant results are used for the purposes of an individual's diagnosis, or prevention, or treatment, or health assessment, the test really needs to be performed at a CLIA-certified laboratory.

That goes for all the sequencing being done by CDC, and funded by CDC, that sequencing is not performed under CLIA. Therefore, that information about a sequence confirmed variant based on CLIA and CMS, that data should not be transmitted back to the patient. Jasmine, I think that covers the top questions that we had. But I don't know if we need to open it up to more, or you want to keep going?

JASMINE CHAITRAM: I think, since we only have two other topics on today's agenda, I'm going to ask you a couple more questions. And then, if you're able to stay on and answer some of the questions in the Q&A box, that would be helpful because others can see your responses. Some of the questions are asking about CDC's plans to show how the variants are trending overtime, as a proportion of total versus time from sample collection. Are there plans to do that?

VIVIEN DUGAN: Certainly, it's something that we are very eager to see. And in order to do that at the national level, we need a substantial amount of data. And so I think we're getting to a place, where we feel we have enough data to feel confident in some of the trends that we are looking at. Really specimen collection date over time, and how those proportions of different variants are changing. And so we have some preliminary data. And we hope to finalize it soon and have it available on our website as well.

JASMINE CHAITRAM: And we do have another question here. And I'm kind of generalizing these because some of them are similar in nature. And the question is about plans to add other variants, to what CDC has on its web pages and dashboards. Other variants like the B1526 from New York. Or even to highlight more the mutations, the E484K, the Australian variant. There's just a bunch of questions about our plans to expand the information that we're sharing.

VIVIEN DUGAN: I think it's certainly challenging, because as more data gets put into the public domain and more analyses are run, there are lots of trends that are being observed from a genetic standpoint. And so we know that viruses change, especially RNA viruses. We expect them to change. We expect them to have some level of variation in their genetic code, that may or may not change their protein expression, especially for this spike.

The entire point of the NS3 program, and part of the team that I'm co-leading in the task force, is to look at how these changes impact vaccines, therapeutics, diagnostics, and also transmissibility pathogenicity. We're tracking pretty much every variant, whether it's potentially of interest or concern. There are a lot of definitions that have been brought up by different countries. I know Canada has their own definition. WHO is working on some definitions. On how we define and what do we call these variants.

We are working on a list of classifications that we expect to make public pretty soon. But as far as when we put the data out there, we want to be able to say with some level of certainty, based on criteria, whether we think this is something really important, this particular variant. Versus something that may be more interesting, or just kind of garden variety changes, that may be happening as the virus continues to spread.

We do have plans to update our website with that information. It's taken a lot of effort to bring everybody together. And to come to a consensus on how to define these different variants, and how do we discuss them and talk about them. That data and that information is forthcoming. And as soon as we have it up, we'll let you know.

JASMINE CHAITRAM: Vivien, thank you so much for being with us today. If you have the time and are able to answer a few more questions in the Q&A box, I'd appreciate it. There were several more in there that were addressed to you. Thank you. Thanks again for that great update. We're going to move to our next topic on the agenda, which is a molecular pathology update from Julu Bhatnagar from the CDC Division of High-consequence Pathogens and Pathology. Dr. Bhatnagar, are you ready?

JULU BHATNAGAR: Yes. Thank you, Jasmine. Good afternoon, everyone. My name is Julu Bhatnagar. I work in the Infectious Diseases Pathology Branch, as Team Lead for Molecular Pathology. And today, I'm happy to share with you some updates focused on the molecular identification of SARS-CoV-2 from formalin-fixed, paraffin embedded tissues. Next slide, please.

I'll start with some background on tissue-based molecular techniques and assays and then discuss about our initial experience of performing these assays on fixed autopsy tissue specimens from COVID-19 confirmed as well as suspected case-patients. I'll also summarize the initial findings, and, in the end, I would like to share the information about how you can send fixed tissue specimens to our branch. Next slide, please.

JASMINE CHAITRAM: Before we go the next slide, I am getting a few folks telling us that it's hard to hear you and to understand you. Is there a way you can either move closer to your mike?

JULU BHATNAGAR: Sure. Can you hear any better now?

JASMINE CHAITRAM: I think so. I think it's a little better. Let's try it for the next slide and I'll let you know.

JULU BHATNAGAR: The main purpose of developing these tissue-based molecular assays was to expand diagnostic opportunities for SARS-CoV-2 in fatal cases with suspected COVID-19. Particularly, these assays can be very useful for the cases when no prior testing of SARS-CoV-2 was performed and no other specimens, except autopsy tissues, were available. And we have seen this scenario many times, unfortunately, particularly in the initial stage of the outbreak.

In addition, molecular assays can improve specificity and sensitivity of tissue-based analysis, especially since the viral RNA generally persists much longer in tissues, in comparison to the viral antigens.

Also, if the assays are sequencing-based, just like ours, they can provide additional information about the viral strains retrospectively - which can be helpful for the epidemiologic studies.

In addition, tissue-based assays can be important to understand the mechanism of severe disease outcomes and viral pathogenesis, by identifying cellular targets of replication and tropism.

So, there are lot of advantages, but there are lot of limitations also with the fixed tissues. Two major problems are fragmentation of nucleic acids and the presence of PCR inhibitors. I have also listed several others on the right-hand side. But, to overcome some of these limitations, it is important to develop assays that are specifically optimized for the FFPE tissues. Next slide, please.

In the end of January 2020, we developed two sequence-based conventional RT-PCR assays that were specifically optimized for the identification of SARS-CoV-2 in FFPE tissues. The assays target two genes, nucleocapsid and spike, to maximize the detection. And we also designed the primers to improve amplification from the fixed tissues. In addition, we use two days long manual RNA extraction process, to obtain good quality RNA -which is, in my view, is the key.

I have described the workflow here, but the details of the procedures, are available in the article that we have just recently published in the Journal of Infectious Diseases. And I have listed the reference at the bottom of the left side, if you are interested to see. Next slide, please.

We also use in-situ hybridization-based assays to localize SARS-CoV-2 RNA directly in the tissues. The probes again target the same N and S genes. And the technology is based on the RNAscope, which is a signal amplification technology, as I described at the bottom figure.

Here on the right-hand side, in the images A and B, you can see, in red color, SARS-CoV-2 viral RNA, within the SARS-CoV-2 infected cells in FFPE cell culture controls. In the figures C and D, MERS-CoV and NL63 cultures are shown - that were clearly negative by these ISH assays. Next slide, please.

Here I would like to share our initial experience of testing of autopsy tissues, using these molecular assays. Again, I'm summarizing the initial findings that we have just published in the JID article. And here is a summary.

We evaluated FFPE autopsy tissues from total 64 case-patients. Twenty-one of these were COVID-19 confirmed cases, while 43 were suspected COVID-19 cases. Confirmed cases were the cases with prior laboratory evidence of SARS-CoV-2 by respiratory swab RT-PCR and suspected cases were the cases with clinical or epidemiologic suspicion of COVID-19, but prior SARS-CoV-2 testing was either not performed or negative

These cases were submitted to the IDPB, our branch, from various state and local health departments, medical examiners, and pathologists from 23 U.S. States for diagnostic consultation. And we had received them between January 23rd to August 4 of 2020. So, most of these cases were from initial stage of the outbreak. Here are some of the tissues tested. Next slide please.

JASMINE CHAITRAM: Just a quick question, are you using a speakerphone or a computer speaker?

JULU BHATNAGAR: Speakerphone as well as computer.

JASMINE CHAITRAM: Because I think folks are still having a hard time hearing you clearly. And I'll just remind everybody that we will post the slides and the transcript after the call. If you've missed anything, unfortunately, you might have to go back and get it there. We're still getting a bit of muffled sound when you're speaking, so I think that's what people are referring to.

JULU BHATNAGAR: I'm not sure. I have increased volume. I'm speaking on my phone. Also, I tried initially using the computer speaker. Should I move on?

JASMINE CHAITRAM: Go ahead.

JULU BHATNAGAR: Here I have the tissues tested. As you can see, we have tested FFPE respiratory tissues from all case-patients. In addition, FFPE non-respiratory tissues, whenever it's available, were also tested. They were heart, brain, kidney, liver, and many other tissues.

All cases were initially tested by hematoxylin–eosin stains to identify histopathological changes and by these recently developed conventional tissue-based SARS-CoV-2 RT-PCR assays.

SARS-CoV-2 tissue RT-PCR positive cases, after initial testing, were also tested by ISH assays to localize viral RNA in tissues. We also tested all RT-PCR positive tissues by sub-genomic RT-PCR assays, to detect active viral replication. And in addition, NGS analysis was also performed on the tissue RT-PCR-positive cases, if enough RNA sample was available. And it was done in collaboration with Respiratory Viruses Branch of CDC.

In addition, we also tested other viral and bacterial pathogens in FFPE respiratory tissues by RT-PCR or PCR assays. Next slide, please.

Here are the results. SARS-CoV-2 was detected by tissue-based, conventional RT-PCR in respiratory tissues of 32 out of 64 case-patients and all of these were confirmed by sequencing of positive amplicons. Out of these 32, 21 were previously confirmed COVID-19 cases. And, interestingly, tissue RT-PCR also identified SARS CoV-2 in 11 suspected COVID-19 cases. Thus, this provided the evidence of infection retrospectively in about 26% of cases.

As you can see in the table below, sub-genomic RNA showing active viral RNA application, was detected in 53% of 32 positive cases. SARS-CoV-2 RNA was also detected by in-situ hybridization in 63% of 32 positive cases. And full or partial genomes were obtained from 26 cases and D614G variant was identified in 9 of these. Just wanted to emphasize that we mostly have early-stage outbreak cases in this series. Next slide, please.

Here I have shown the ISH and histopathological findings in the respiratory tissues. Predominant histopathological finding in the lung was diffuse alveolar damage. And in the airways, it was tracheitis or tracheobronchitis, which was detected in almost 86% of cases.

As you can see in the figures A and B, on the right-hand side, SARS-CoV-2 RNA, in red, was localized by ISH in hyaline membranes, intra-alveolar pneumocytes and macrophages in the lung. Viral RNA was also localized in the epithelial cells and goblet cells of the airways, as shown in figure C.

And here, figure D, shows viral RNA in the lymph nodes also. Another important finding was the detection of pulmonary thrombi in the lungs of 8 tissue RT-PCR positive cases, so, in about a quarter of the tissue-positive cases. Next slide, please.

Let's look at some additional interesting findings. In one tissue RT-PCR positive case, by ISH, we detected SARS-CoV-2 RNA within the endothelial cells of blood vessels and blood vessel wall of meninges of the cerebellum, as shown in the figure A and in the brain stem. Viral RNA was also detected by ISH in the vascular endothelium of kidney, as shown in figure B, and in heart, pancreas, liver, and lung tissues.

Interestingly, in a second case also, SARS-CoV-2 RNA was noted in the blood vessel wall of the lung, as shown in the figure C. In fact, in one area endothelial staining was also observed closer to the thrombus. These factors support the hypothesis that direct endothelial infection may play a crucial role in modulating vascular dysfunction, thrombosis, and subsequent severe disease outcomes.

But, it is important to note that - although the ISH staining was detected in blood vessel cells and blood vessels wall of non-respiratory tissues, no staining was observed directly in any non-respiratory tissues, such as in the heart muscle or kidney tubule. So, the virus may not be directly impacting the non-respiratory tissues, based on this series of the work. And just want to emphasize that these numbers are small.

And, in addition, SARS-CoV-2 RT-PCR found to be positive for heart, gastrointestinal tissues, kidney, brain, liver, or pancreas tissues in 14 tissue RT-PCR positive case-patients. But their viral load level appears to be much lower, in comparison to the respiratory tissues. Next slide, please.

The last but not the least, we have also detected co-infection of SARS-CoV-2 with other viral or bacterial pathogens in respiratory tissues of 31% of tissue RT-PCR positive cases. And I have listed some of those here, like influenza B virus, parainfluenza virus, Streptococcus species, and Staph aureus. And more importantly, we have also detected other non-SARS-CoV-2 respiratory pathogens in 44% of tissue RT-PCR negative case patients. Next slide, please.

In summary, we can say that tissue analysis is a valuable tool for retrospective diagnosis and genetic characterization of SARS-CoV-2, particularly in fatal cases when no other conventional specimens are available, or no prior testing was performed. It can also help in the detection of co-infections and infections of the other etiologic pathogens.

And as we have seen in this work, tissue analysis can also provide important insights into virus pathogenesis and mechanisms of severe outcomes of COVID-19. And I have mentioned some major findings here, we have shown direct evidence of SARS-CoV-2 RNA replication in lung and airways of COVID-19 patients. And also identified the cellular targets of viral tropism and replication. Again, replicative viral RNA was detected in lungs and trachea within the areas of histopathological changes that suggests direct virus-induced injury and inflammation.

And another important finding was, the cellular localization of SARS-CoV-2 RNA in endothelial cells that provides strong evidence of endothelial infection The next slide, please.

Here we have the information about how you can submit fixed tissue specimens to us. The email address we have is pathology@cdc.gov. And healthcare providers, pathologists, medical examiners, and coroners, please contact your health department. That's all I have. And thank you so much for inviting me and for your attention, in spite of all these issues with my audio and other communications issues.

JASMINE CHAITRAM: Thank you very much. It was a little bit hard to hear, but I think the most of it was able to come across effectively. I did have a few questions for you if you're willing to answer some. The first question is, is there a limit on the age of a fixed specimen that is submitted to CDC?

JULU BHATNAGAR: In terms of fixation, the tissues should be fixed in 72 hours in formalin. But we can also accept the cases, where tissues are fixed in formalin for up to two weeks. But beyond that, sometimes it's hard to amplify RNA from the fixed tissues. In terms of FFPE tissue blocks, there is no limit. If the tissue blocks were prepared in timely manner, they can be tested at any time.

JASMINE CHAITRAM: What is the expected turnaround time on an autopsy case for testing on paraffin blocks once they have been sent to the CDC?

JULU BHATNAGAR: This, again, is somewhat tricky question. Depending on our workload, but in general it takes about six to eight weeks total time. And that's not because of just the quality of analysis, but we perform various assays. Today, I focused on the molecular analysis only. But we perform histopathology co-analysis, immunohistochemistry. Also, electron microscopy, besides molecular analysis. Depending on the complexity of the piece, it takes a bit longer. But we try our best to provide results as soon as possible.

JASMINE CHAITRAM: Were the patients with clots tested for clotting disorders, such as Factor V Leiden?

JULU BHATNAGAR: No. I think in our group, we just performed the histopathology co-analysis to see that whether it's any clots, or any of them correlation on vascular dysfunction.

JASMINE CHAITRAM: All right. Thank you so much. In the interest of time, we are going to move to our last agenda item, which is our-- and thank you so much, Dr. Bhatnagar, for being here today. We appreciate the presentation. We're going to move to our last speaker, Tim Stenzel, from the FDA. He normally gives updates and answers questions, until we are at that point again in the agenda. Tim, are you on?

TIM STENZEL: I am. And thank you, Jasmine. Pleasure to be on again this week. I have three questions to attempt to answer. First one is, do you see any molecular testing systems receiving a waived classification in the near future? There are currently 12 molecular tests that we've authorized for use in the CLIA Certificate of Waiver settings. There are more molecular point-of-care tests in the pipeline, including those that will show up in home. Including those in the RADx program.
And also as previously mentioned multiple times, point-of-care tests, whether they're antigen or molecular, are a high priority review area for us, as are home tests and home collections. And of course, we recently authorized the Cue test for over-the-counter home use. We'll be seeing more. And this is a high priority. And as soon as we have a submission that looks good, we rapidly work through the authorization.

The second question has to do with antigen test and variants. What guidance can be shared about the efficacy, if the current rapid antigen testing options approved under EUA, in detecting the new variants of COVID-19? We have been approached with an opportunity to increase testing volume for return to campus, using the Abbott BinaxNOW testing. Before we commit to such a large investment, we'd like to understand the efficacy of this test with the new variants.

Vivien earlier very accurately portrayed the topic. The FDA has authorized 15 unique antigen submissions. Only one of those targets the spike protein. The rest target primarily, if not in all cases, the N protein. However, there are amino acid changes that occur in the N protein too. And so the FDA, in cooperation with other agencies, and the developers themselves, are working to understand if there are any performance risks.

At this time, and the information we have is limited. But some of it, which is non-public now, suggests that-- I'll just come out and say, we don't know of a mutation yet that would block antigen tests from detecting the target. But our knowledge is very limited. And we are striving to find ways to advance our knowledge about this.

At this time, we don't have any reason to be concerned, regarding the currently authorized antigen test. However, as I said, this is a really difficult thing to do, relative to the molecular tests where we know primers and probes. And we're still working through how we can assure laboratorians and the public, that these tests are still performing well. It is a high priority.

The final question is, on the status of FDA-approved, your EUA antibody tests for COVID-19, with commercially available kits that could be used on serum sample testing or saliva samples testing, to determine that vaccinated individuals had developed an antibody response?

We haven't approved, or cleared, or granted a serology test or any COVID tests yet. There are developers who are pursuing a full submission. And that's obviously important to us. Although, we are placing a priority on authorization of EUAs. Since that is an easier path, and we have so many hundreds of submissions that we are working on.

But we do not have an EUA authorization for saliva either, for an antibody test. And we don't have a traditional blood sample serum plasma blood fingerstick that has come in, that we've authorized for determining if vaccinated individuals had developed an antibody response to the vaccine.

But even though we haven't authorized these, that we know of interested developers. And the FDA is certainly very open to such tests. That said, for any of the authorized tests that may work in this situation, the FDA is not going to object to clinicians ordering these tests and in assessing themselves.

Hopefully, as more research is done on vaccinated individuals. And the different vaccines, especially the messenger RNA vaccines, may present some challenges depending on serology tests. Hopefully, there will be research on this that will be published in the near future, that will help us all better understand this

question. And certainly, one of the reasons, and a key reason, for us to authorize serology tests. I think that ends the questions that I had prepared a response for. Back over to you, Jasmine.

JASMINE CHAITRAM: Thanks so much, Tim. There are a couple more questions for you, and we have some time. This first one, I think you've answered this before on other calls, but we do have different participants sometimes. The question is regarding tests approved under the EUA. What is the process for testing facilities operating this, if the EUA were to expire or go away?

TIM STENZEL: I have addressed that, as other members of FDA leadership. There are a couple of answers, a couple of parts to the answer. One is, it's highly unlikely this emergency will stop from being declared. We still have Zika, Ebola open as emergency declarations, as well as others. Because of the importance, obviously, in this pandemic, we do not foresee the secretary or HHS pulling back the emergency declaration any time soon. If ever. But that's up to the secretary.

If the Secretary at some point should pull that back, then we have drafted, and is going through the clearance process, guidance that will allow manufacturers and other developers to stay on the market for some period of time, until they can convert their assays to full submission. We are aiming to continue to make available every authorized test for a very long time, in some shape or manner.

And then there may be a question of, if you now have a product that was EUA authorized, but now it is a fully authorized product. That's a great question. I haven't necessarily thought about that until just this moment. But we would certainly look to make sure that, as long as it has not reached its expiration date, that it would be my hope that you can continue to use that. But that's really not something that's going to happen any time soon. Thank you.

JASMINE CHAITRAM: Thanks, Tim. And I'm not sure if you were answering this other question, that sounded very similar to the one that I just gave you. But maybe you can just quickly go over it again. How will you handle conversion from an EUA to a full FDA approved assay? I've been told that once there's a single assay that has full FDA approval, that the EUA will cease for others, is that true?

TIM STENZEL: The law allows that to happen. But in our history of six prior emergencies, that has never been done. In fact, if you go to our EUA authorization page, which lists all the prior emergency responses, you will see an assortment of EUAs that are still in effect. Even though the law allows that, we look at test availability. And it's unlikely that a single provider could provide enough tests for our needs any time soon. And if ever. We have leeway in doing that. But there is a formal process that we go through that's required by law.

The EUA that was given to the developer who has achieved full authorization is revoked, that's clear. But that's because they have a fully authorized product. But you may hear that we send out letters. And we haven't figured out how we're going to do this yet, because there's so many, sometimes hundreds of authorizations to solicit input on the question.

It's a great question practically speaking, which I will also be looking into as well. Probably something that if we can get into the guidance, that would be great. Because following the normal process by law would be very onerous for everyone involved. And we're busy enough as it is.

JASMINE CHAITRAM: Last question for you, Tim, for today. Will there be a path for approval of SNP tests, for surveillance of variants of concern or interest? Technology is available for large-scale rapid inexpensive monitoring to complement sequencing.

TIM STENZEL: SNPs-- single nucleotide polymorphisms? Genotype assays, as well as sequencing assays, are a priority at the FDA. We are not actively regulating any true surveillance activity during this pandemic. But if results are going to be reported back to individuals and in your kit developer, then that would require an EUA.

And it would follow the guidance that we have right now. And could be subject to a notification pathway, where you develop tests to validate, you notify us, and then you can launch your test. And then submit your EUA within 15 business days.

JASMINE CHAITRAM: All right. Thank you so much, Tim, for being consistently present on these calls. We do appreciate your time, and you answering many questions for us. With that, I'm going to close out today's call. I did want to make one comment about some of the questions that we're getting. They're not necessarily about laboratory or about testing, and we do want to focus these calls on those topics. We don't have subject matter experts (SMEs) to answer some of the general questions about travel, and vaccines, and policy. Or implementation of health, or the vaccine rollout. And so, we would ask that participants restrict their questions to be about testing specifically. And if it's testing pre- or post-vaccination, that's OK. But some of the questions are more general about just vaccination, and travel policies, and things like that. And we don't have the folks to answer those calls.

I do want to thank everybody for being with us today. And remind you that our next call will be in two weeks on Monday, March 22nd. If you're not receiving emails from CDC that announced these calls, and you got the invite forwarded to you by someone else, please send us a message at LOCS@CDC.gov, and we will get you on our distribution list.

And you're welcome to submit those questions in advance of the call. And that'll give us some time to prepare answers or find SMEs to answer those questions. As I said before, we will do our best to try to answer the questions that were submitted today that we couldn't get to you. And thank you again. And please stay safe.