Call Date

07/15/2024

Call Agenda

Welcome
Sean Courtney, CDC Division of Laboratory Systems

Situational Update and Response to the Highly Pathogenic Avian Influenza A(H5N1) Outbreak in U.S. Dairy Cattle
Todd Davis, CDC Influenza Division

CDC Efforts to Expand Testing Capacity and Enhance Surveillance
Sean Courtney, CDC Division of Laboratory Systems

BD Update
Chris Beddard, BD Life Sciences

CDC Blood Culture Quality Tools
Jake D. Bunn, CDC Division of Laboratory Systems

Blood Culture Utilization
Valeria Fabre, Johns Hopkins University

Call Transcript

Slide 2 (00:00:00)

Sean Courtney: All right, good afternoon, everybody. Thank you for joining today's call. My name is Sean Courtney, and I'm in CDC's Division of Laboratory Systems. On the screen is the agenda for today's call, but before we get started, I want to cover some housekeeping items and just some general announcements.

Slide 3 (00:00:21)

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

Slide 4 (00:00:36)

DLS supports this work across four goal areas: quality, workforce and training, preparedness and response, and informatics.

Slide 5 (00:00:45)

As always, we want to hear from you. Our Training and Workforce Development Branch is interested in hearing more about the education and training gaps that you're currently experiencing. We invite you to send your feedback via email to labtrainingneeds@cdc.gov as shown here on the slide.

Slide 6 (00:01:04)

We'll be sharing slides from today's call, along with the audio and transcript, and we'll try to get them posted online by the end of next week and we're actually going to try to expedite that process. So hopefully, I'll get that to you even sooner than usual. You can find them on our CDC's Laboratory Outreach Communications System (LOCS) page shown at the link here at the bottom of the slide.

Slide 7 (00:01:25)

If you have a question, please use the Question-and-Answer function within the Zoom webinar system. We asked that you please do not use the chat function. We'd like to be able to address your questions during the call, so please use the Q&A button. Also, when you have a question, we'd like to ask for you to please include an email address so that we can so that if we're unable to get to your question during the call, we can follow it up afterwards.

For any media questions we ask that you please contact CDC Media Relations at media@cdc.gov. And if you're a patient, please direct any questions you have to your healthcare provider.

Slide 8 (00:02:11)

So, I'd like to remind everybody that these slide decks may contain presentation material from panelists who are not affiliated with CDC. Presentation content from external panelists may not necessarily reflect CDC's official position, so please keep that in mind when you go back and look at some of the slides that we have posted on our LOCS web page.

And we are trying to get our first speaker who's having issues joining right now. So give us one second while we have - I think actually we just got them. Todd, are you available? Todd Davis from Influenza Division?

Todd Davis: Hi.

Sean Courtney: Oh, perfect. Great, sorry you had issues joining today's call, but glad to have you. Welcome, Todd Davis. He's going to talk about this influenza outbreak that's currently happening. So Todd, I'll turn it over to you.

Slide 9 (00:03:03)

Todd Davis: Great. Thanks, Sean, and thanks for your patience. So for everyone on the call, I know we spoke last month. Just going to provide a brief update on where we are with the response to the highly pathogenic avian influenza H5 outbreaks in U.S. dairy cattle. So next slide.

Slide 10 (00:03:29)

So as of July 11th, there's been 140 farms that have been confirmed with HPAI in dairy herds in 12 states. And so these numbers continue to increase each week. Little bit dated, there's been a couple of additional farms identified since last Thursday. But again, the number of states remains steady at 12. And so we're hoping that that remains to be the case.

As all of you know, I think that there have been other animal species associated with impacted dairy herds and so USDA is also keeping tabs on animals besides dairy cattle that are impacted. That includes wild birds, and now more than a dozen cats associated with different states, as well as raccoons and possums. And those data are updated daily on those links below on the USDA website. Next slide.

Slide 11 (00:04:25)

On the human health side, CDC and other partners, primarily state and local public health departments, are continuing to monitor exposed persons. And so this is done by active outreach to states after positive herds are identified. Working to be sure that when there are positive herds identified that if there are any symptomatic individuals that are exposed to those animals, that they have availability of testing.

CDC has also enhanced our summer influenza surveillance. We talked about this during the previous LOCS Call, which included ramping up our National Influenza Reference Centers over the summer months, as well as our Influenza Sequencing Centers, which do sequence analysis of viruses now throughout the year rather than slowing down during the summer. There's also been a number of epidemiological studies that have been planned and some that have been initiated in the state of Michigan to look more closely at the risk of exposure and outcome of infections.

The other thing we, you know, are confident in that is we're detecting these viruses. Since March of 2024, we've tested more than 32,000 specimens across the U.S. public health network, and all of these, samples, we think, would be detectable using CDC's H5 assay, given they make it to public health laboratories that are able to provide that testing.

But looking more specifically at the numbers that have been monitored, there's been nearly 10,000 individuals that have been monitored after poultry virus outbreaks and exposure. This has been happening since February of 2022. And then in relation to specific cattle exposures, there's been more than 1,300 individuals that have been monitored and at least 61 persons that have been tested, with only 4 individuals that have tested positive after exposure to infected dairy cattle. Next slide.

Slide 12 (00:06:33)

So our total of individuals remains at 4 of those that have been directly exposed to infected dairy cattle. First case was detected in Texas followed by the 2 that were reported from Michigan. And then more recently on July 3rd, Colorado announced a fourth human infection. These are all in adults that we're working on dairy farms in contact with cows.

The first, second, and fourth cases reported only conjunctivitis, and the third reported minor respiratory symptoms. All were offered oseltamivir, the illness was mild, and all recovered without hospitalization without any signs of additional human-to-human transmission. Next slide.

Slide 13 (00:07:18)

So, in addition to the dairy cattle human-associated infections, just yesterday the Colorado Department of Public Health and Environment reported a total of 5 human cases of avian influenza and workers that were responding to an avian flu outbreak on a commercial egg layer operation. So this is data in a press release that was just submitted yesterday afternoon. The CDC received 4 of these 5 samples over the weekend and did confirm that 4 of these 5 are positive for influenza A(H5).

The fifth specimen we expect to receive in the coming days to do confirmatory testing. But keep in mind these are individuals that were responding to a commercial egg layer operation in Colorado not associated with dairy cattle. So we'll continue to monitor this evolving situation and hope to provide additional updates as they're available. Next slide.

Slide 14 (00:08:25)

So I won't go through this in too much detail. Just to say that there's now a number of publications and online reports that CDC has posted working with our state public health departments in both Texas and Michigan to look at the genetic information from the case in Texas, as well as the cases in Michigan. And I just wanted to show this and give you a few references if you're interested in learning more about the detailed genomic analysis. But the bottom line really is that these viruses remain really avian H5N1 viruses, despite the circulation and spread among dairy cattle, and the viruses that have been sequenced from humans do not show any mutations that we think would enhance the infectivity or transmissibility from person to person. They remain really fully avian at the receptor binding sites that are the primary drivers of infectivity and transmissibility.

The virus has also not been detected with any known markers of resistance to antiviral drugs. And in our in vitro analysis, we've been able to demonstrate that antiviral drugs are effective against these viruses as well. There have been a couple of molecular markers that have been associated with Mammalian adaptation. For example, the case from Texas had a change in the PB2 gene at E627K.

This is a mutation that's been associated with increased replication within a mammal and potentially sometimes leading to more severe disease, but not in the case from Texas. Next slide.

Slide 15 (00:10:09)

The case from Michigan also did not have additional amino acid changes in the hemagglutinin, so again, this is really an avian-like virus. The case from Michigan did not have the 627K change but did have a different change in PB2 at M631L, and this is a mutation that's been found in more than 99% of the dairy cattle sequences and has also been previously associated with enhanced replication in mammalian hosts. So it's interesting to see the difference between the Texas and Michigan cases likely representing the emergence of those viruses in dairy cattle when the cases were identified.

We were able to isolate virus from both the case in Texas and Michigan and have been able to do additional phenotypic analysis showing that our existing vaccine candidates cross-react with these viruses very well, and again, that they are susceptible to antiviral drugs. Next slide.

Slide 16 (00:11:12)

And then finally, the second human case from Michigan had relatively low viral load and the specimen that was positive, high CT values. We were only able to generate partial HA but a full-length neuraminidase, also confirming that there were no changes in the receptor binding site that would impact infectivity or transmissibility, and also no changes associated with reduced antiviral susceptibility.

The case from Colorado had an even higher CT value, indicating an extremely low viral load in the sample despite the positive PCR result. We were not able to generate sequence data from this case, and virus isolation was not successful. Next slide.

Slide 17 (00:12:00)

So we hope to have some additional data again from the poultry outbreak in Colorado and the associated human cases, so some more to come there. That's really very fresh information as of this weekend. A few other things before I pass it on to Sean. So diagnostic testing continues to be challenging, of course. We're working with FDA still and have just received notification that FDA will

extend the enforcement discretion to use conjunctival swabs with the CDC's H5 assay, so that has been extended to November 1st.

We have also been working with our partners in some of our medical officers here at CDC to develop specific recommendations and protocols for conjunctival sample collection methods. And so there's now a link on this slide that will take you to an illustration describing how to collect a conjunctival sample, which has been helpful for some state public health departments responding to these outbreaks. Also, CDC has a protocol with more detailed information that we can share with partners. APHL has also distributed this to all APHL members as well.

And then, finally, there have been quite a few requests to include Universal Transport Media as a matrix for specimens to be tested using CDC's H5 assay. Currently, the assay can only be run on samples on Virus Transport Media, but we did receive confirmation from FDA that they will allow us to do a change to our instructions for use. And we're now just working through CDC's quality control process to make that change to our instructions for use for CDC's H5 assay and hope to have that completed, looks like within days now, and we'll share that information once it's available. But that should also help with the enhanced summer surveillance and ongoing testing around the U.S. And with that, I'll stop. I think there's one more slide just to say thanks for the invitation to speak again, and happy to take any questions.

Slide 18 (00:14:12)

Sean Courtney: All right. Thank you for that update, Todd, I appreciate that. Just a couple of quick questions. The first one is: Will a flu antigen test pick up the influenza A(H5N1)?

Todd Davis: Yeah, so we have done some preliminary work at CDC and have been able to confirm the antigen-based rapid tests will detect the virus. It will detect these and determine them to be influenza A positives, right - but they will detect these viruses as flu A.

Sean Courtney: Great, thank you. Next question is: Are there data that verify that all or a subset of the FDA-cleared influenza A tests, antigen and NAAT, can detect the H5 strains and report those specimens as influenza A positive without a designation of H5?

Todd Davis: Yeah, so that is something that FDA monitors closely. Let me see if I can find the link to some of the work that they've done where they do some analysis of all of those assays. And a lot of it's done in silico, but there's some other work that's been done as well to be sure that they are detecting H5 as influenza A positives, at least.

Sean Courtney: Great, thank you. And then the last one, before we switch over, is: Is it still accurate that these strains of high-path avian influenza to date have not demonstrated the ability for efficient person-to-person transmission?

Todd Davis: Yeah, that's absolutely right. So again, these viruses do look like they really have the hallmarks of an avian virus. We don't see any mutations in those key genes like the hemagglutinin that would make them more transmissible or even more infectious from person to person, so good news there. We're still looking at really what we believe is an avian virus that, for reasons we don't completely understand, replicates well in the mammary glands of cattle.

Sean Courtney: Great, thank you. All right, Todd, I appreciate that. We'll move on to our next presentation. I've seen a lot of comments kind of in the Q&A, and just to reiterate the agenda for this call, the first two presentations are over the H5 outbreak that's currently happening, and in the second half, the call is going to be covering the blood culture media bottle shortage.

Slide 19 (00:16:36)

So, I'll go ahead and switch over to the next presentation which I will be providing here, which is CDC's efforts to expand influenza testing capacity and enhance surveillance.

Slide 20 (00:16:50)

So, basically, CDC has been working in multiple areas to improve readiness for H5, specifically testing capacity, by engaging with laboratories interested in assisting with H5 test development and validation studies.

Notably, we've offered royalty-free access to the CDC H5 diagnostic assay design since the spring of 2023. And we continue to work closely with partners at APHL and ACLA to improve readiness and disseminate information to public health and commercial laboratories. Simultaneous with the testing happening at state public health laboratories, CDC continues to meet with commercial laboratories to discuss this H5 assay licensing agreements and interests in commercial H5 test development.

CDC's Tech Transfer Office and Influenza Division are actively establishing licensing agreements with several companies for the CDC H5 assay design, of which eight of those licenses are currently in place, along with several more, that are pending or are in progress.

Slide 21 (00:17:55)

As I just mentioned, CDC has licensed its test design with several test manufacturing companies for the development of an H5 test and has been meeting with some manufacturers to discuss assay designs for molecular, multiplex, and rapid testing options.

Slide 22 (00:18:13)

These tests can be designed and validated as an LDT if additional H5 diagnostic test availability is needed based on the transmission of cases and case number or submitted to FDA in the event of a 564-declared emergency.

Slide 23 (00:18:30)

To do this, specific studies are needed to validate a new test and to meet regulatory requirements, and to do this, test developers would require viral control material to perform these studies. Both the wild-type and candidate vaccine viruses require special USDA permits to receive this material, along with higher biosafety levels, to handle the virus. Because of this, we are working to develop a non-virulent positive control material for test developers to use in their studies that would not require these specialized USDA permits or enhanced biocontainment facilities to handle them.

Slide 24 (00:19:09)

Since the influenza A(H5) subtyping tests were only available at CDC and in state public health labs, there have been concerns about lack of access to testing. Therefore, on June 10, 2024, CDC initiated an open call to industry for innovative solutions to meet diagnostic development and validation needs in response to this H5 response. This was a competitive process for test developers to potentially obtain

funding from CDC to develop, validate, and manufacture a test if awarded, and to apply for FDA regulatory approval for distribution of that test for H5 if it was obtained.

This call was closed on June 26 and concept papers are currently under review. The goal is to make one or more of these awards available by the end of August.

Slide 25 (00:19:57)

And like what Todd just mentioned, CDC has been looking at monitoring for cases of H5 and we've really stepped up the surveillance efforts around that. Typically, surveillance for influenza slows down during the summer months due to a very low number of cases. However, this year we've asked laboratories continue specimen submission over the summer to public health labs and to increase the number of specimens that are submitted.

On May 31st, in collaboration with APHL, we published guidance on criteria for specimen submission to public health laboratories for surveillance of H5. And this is an extra precautionary step to identify any additional cases that have not been identified through monitoring of dairy farm workers and others that meet specific epidemiological criteria.

We'd like to request commercial laboratories to continue sending the following specimens to public health labs as soon as possible for further testing and characterization, including influenza A positive specimens that are subtype negative on tests designed to provide an influenza subtyping reflex and confirmed upon retest, as well as influenza A positive specimens that are subtype influenza A(H1) and not influenza A(H1)pdm09 on tests designed to provide an influenza subtyping result and that are confirmed upon retest.

Slide 26 (00:21:19)

And with that, sorry, I kind of quickly got through that, but I want to thank you guys for listening to that. And if we have any questions. I think Todd is still available to help out and, we'll just take a look really quick and see what we have.

All right, Todd, so the first question I'm seeing is: In terms of birds being affected, does that apply to wild birds only or also domesticated birds?

Todd Davis: Yeah, thanks for the question. So, certainly, some wild birds have been impacted. We know that the virus can actually spread among wild birds, and in many cases, it's not lethal to wild birds. So in the migratory seasons, they're still spreading the virus quite widely. On the other hand, poultry, especially gallinaceous poultry, terrestrial poultry, are highly impacted by the virus. It can be extremely lethal and can wipe out a chicken farm within a matter of days. And so those wild bird exposures to poultry can be quite devastating and it's something that USDA monitors as closely as possible.

Sean Courtney: All right, thank you. The next question that came in is that: Twist Bioscience has a full-length synthetic H5 material; is CDC going to distribute these to labs?

Todd Davis: Yeah, thanks for the question. So we have done some assessment of Twist products. We're working with them currently to look at new products as well that we believe will work even better than the existing products that would be distributed by Twist. And so more to come there. The product, depending on the specific assay design that's being used, you know, do work well. We just want to be

sure that it's optimized with CDC's H5 assay as a control specifically for this version of H5 that's been causing dairy cattle outbreaks.

Sean Courtney: Great, thank you. Appreciate that, Todd. The last question was: Is there any transmission of this avian virus to any other animals like pigs, or do we even know what the length of the bovine transmission chain is?

Todd Davis: Thanks. Pigs are certainly a big concern. To date, there has not been any H5 detected in swine herds in the United States, so we don't believe that pigs are at high risk of exposure to dairy cattle viruses. And there is some preliminary data suggesting that if they are infected the virus doesn't replicate at very high levels and that it doesn't produce morbidity mortality in pigs. That's done in experimental systems. Nonetheless, USDA, through their anonymous surveillance systems, do test thousands of pigs every year and continues to do that through the summer months as well, and have not seen any H5 infections in swine herds in the U.S.

Sean Courtney: All right, thank you, Todd, I appreciate that. I appreciate you for joining today's call again. And if we have if any other questions pop up during the rest of the call, if you're able to hang on and answer them within the chat, I would really appreciate that.

Todd Davis: Me too, thanks.

Sean Courtney: Thank you. All right, so let's move on to the next part of our presentation today. Please welcome Chris Beddard from BD Life Sciences. She's going to provide us an update on the blood culture media bottle shortage. Chris?

Slide 28 (00:25:25)

Chris Beddard: Thank you, thanks for having me, my name is Chris Beddard. I'm the Vice President, Global Platform Leader, for Microbiology at BD Diagnostic Solutions.

I'm assuming that many of the people on the line here have received the update in terms of our reduction in available plastic blood culture vials from our supplier. We initially expected this to be temporary in nature but after working with the vendor and doing some additional investigation analysis, we determined that the issues were more complex than we originally thought for the vials to meet global demand.

We have been working very closely with the supplier and we have actions in place to improve production and output. We anticipate that to support us through the next two months as we move forward through the summer. We've been additionally managing our global supply throughout this challenge via a manual allocation process, improving our distribution transit times, and optimizing our production schedules to meet supplier shipments.

We've also discussed, or we've also deployed, a strategy to work with our supplier previously of glass media vials. We're going to be temporarily sourcing the glass bottles for our BD BACTEC anaerobic culture vials, and as soon as we have the clarity on dates, we will provide another supply update by the September timeframe. So this is an active, evolving situation, and again, we'll be coming back out to our customers by September 24.

We are looking at this time because we expect to have the confirmed consistency in our output by our vendor, but we also have timelines and volumes for glass bottles in the United States and potentially

other markets as we think about the challenges on a global basis. I would like to also mention that we've been working very closely with the FDA throughout this challenge, exploring all options to improve our supply, including providing our supplier with communication to their material vendors to reinforce the need, the prioritization, and the availability of required components to help us with the BACTEC bottle production.

So based upon a lot of the moving discussions and comments and questions that our customers have, we've stood up a website. It's https://bdbactec-update.com so that you can visit this website for all future updates and resources that are required for this challenging time. Again, we'll also be supported by the CDC and IDSA for a lot of you might have about clinical practice and will be enabling those to this website as well, and I'm happy to put the website in the chat.

So that's my update, and we will be providing updates as soon as we have them through our sales organization and also through the website that I just mentioned that we have. That's it for me, Sean, if you want to move on to our next speaker.

Sean Courtney: Yes, thank you, Chris. I appreciate that update. And just let everybody know, we're going to go through these next three presentations and then we're going to open up a larger question-and-answer at the end. So with that, I'll move on to our next speaker. Please welcome Jake Bunn from CDC's Division of Laboratory Systems. He's going to present on CDC's blood culture quality tools. Jake?

Slide 29 (00:29:06)

Jake Bunn: Hey, everybody. Thank you, Sean. My name is Jake Bunn. As a federal employee, I'm going to share the content you're about to see as data of my own and doesn't necessarily reflect the views of CDC.

So, the CDC recognizes the importance of timely and accurate blood culture results. We are also committed to ensuring best practices are followed, so the potential patient safety events that may occur due to inappropriately collected blood cultures are mitigated and eliminated. Next slide, please.

Slide 30 (00:29:35)

Due to this commitment, the CDC serves as a measure steward for the CMS Consensus-Based Entity National Patient Safety Measure for Blood Culture Contamination, or BCC. In support of this measure and generally to improve patient outcomes, the CDC developed quality tools for use by clinical laboratories and stewardship teams. Next slide.

Slide 31 (00:30:00)

The first quality tool developed by our colleagues in the Division of Healthcare Quality and Promotion is intended to help infection control and antibiotic stewardship programs work with their laboratories to improve the quality of blood cultures. This tool includes a list of interventions that could be implemented using a multidisciplinary approach. Next slide.

Slide 32 (00:30:20)

The second quality tool developed by the Division of Laboratory Systems provides an overview of the BCC measure for clinical laboratory and points them towards antibiotic stewardship teams. Next slide.

Slide 33 (00:30:33)

In this tool, available to the public as a web page and downloadable PDF, we've provided an overview and purpose of the measure, the why behind the measure, applicable CLIA regulations, critical steps to including your stated operating procedures, calculations for BCC and single set rates, information on how to classify microorganisms using the National Healthcare Safety Network's common commensals list, and some suggested nudges to inform clinicians of low blood volume and blood culture contamination. Of note, we are working to adapt this quality tool into a Spanish version as well, which would be available in the coming weeks. Next slide, please.

Slide 34 (00:31:16)

A more in-depth presentation was done on our OneLab Network in December of 2023 if you would like to learn more. In this presentation, we mentioned training materials for blood culture collection, which we have been we have been focusing on this year, and these are expected to be available to the public in the next few months. Next slide, please.

Slide 35 (00:31:36)

Hopefully, you'll have seen the notices from the FDA, but we wanted to highlight them again here. On July 10th, the FDA released a letter to healthcare providers about the disruptions and the availability of BD BACTEC blood culture media bottles. They also updated the medical device shortages list to include blood culture and media bottles. Like the FDA, the CDC will continue to keep healthcare providers and the public informed if new or additional information comes available. Next slide, please.

Slide 36 (00:32:10)

Now I realize I just threw a bunch of links at you all, so I want to be sure to reinforce some take-home messages. These qualities assurance considerations are always in play, but during times like these, it's a good opportunity to recalibrate your processes and procedures. Therefore, if you take anything away from this part of this part of the call, it's important to emphasize those who collect blood cultures should be performing routine skin disinfection prior to collection to minimize the risk of contamination of the blood culture and the need to recollect additional blood cultures.

Also, you should ensure the proper volume is collected to avoid a need to recollect additional blood cultures. Next slide, please.

Slide 37 (00:32:53)

As a former clinical microbiology manager, I can comprehend the stress these types of supply challenges place on clinical laboratories and hospitals. We want to know what you need and how best we can support you and your patients and caregivers. Please send this info to our inbox at DLSinquiries@cdc.gov. Thank you, Sean, back to you.

Slide 38 (00:33:19)

Sean Courtney: All right, thank you for that update, Jake. Really appreciate that. We're going to move into our last presentation on this topic before we open up questions. So please welcome Valeria Fabre from Johns Hopkins University. She's going to present on blood culture stewardship opportunities. Valeria?

Slide 39 (00:33:38)

Valeria Fabre: Thank you very much. Good afternoon, everyone, and thank you for inviting us to speak about our blood culture stewardship. And this is an area that Dr. Milstone and myself have been working on at Hopkins for quite some time. Next slide, please.

Slide 40 (00:33:59)

And we are hoping to share our experience in working on this topic. We don't have any relevant financial disclosures and we have received funding from CDC and AHRQ for blood culture stewardship projects. However, the content of the presentation represents our own views. Next slide, please.

Slide 41 (00:34:24)

So, about 90% of blood cultures obtained from hospitalized patients are negative and this audience very well knows that that could be related to suboptimal collection practices, but it also tells us that likely many patients are being tested with blood cultures that are not likely to have bacteremia.

We try to quantify inappropriate cases of blood cultures at our own hospital at Hopkins and using an evidence-based algorithm that I'm going to show on the next slide, we found that about 30% of blood cultures in our medical ICU and about 50% of our blood cultures in our medicine floors were not appropriate based on the indication and this was done through chart review.

Since then, this algorithm that we have developed has been adopted by other institutions, and as you can see here on the slide, a tertiary center in New York City evaluated their blood culture use in their ICU and found that up to 60% of blood cultures were not appropriate and there are some other examples there that you can see.

So clearly, there's a range in terms of inappropriateness based on local practices, but we are all seeing that we have room for improvement. And again, lots of opportunities to improve how we collect both cultures with some data indicating that up to 80% of blood cultures do not have the appropriate volume, and as you all know, this will negatively impact the sensitivity of blood cultures. Next slide, please.

Slide 42 (00:36:30)

So, this is the evidence-based blood culture algorithm that our group developed and this was published in Clinical Infectious Diseases a couple of years ago. The target population is non-neutropenic adult patients.

And it's a busy graph, but I'll walk you through it. So, there are two pathways within this diagram. The pathway on the right side of this slide, it's what we call the follow-up blood cultures. So, these are blood cultures obtained after the documentation of bacteremia, usually for the purpose of confirming either diagnosis or to document clearance of bacteremia. And the pathway on the left is what we call initial blood cultures. So, this would be blood cultures that are ordered when the patient presents to the hospital or maybe the patient has been hospitalized and there's a new clinical event.

So, if you focus on the left, on the initial blood cultures, we summarized when blood cultures would be indicated, or when blood cultures would not be indicated based on, not only the yield of blood cultures, so the likely—they would be positive, but also based on the impact that the blood culture result may have on patient management.

And so, as you can see, the first box asks if the patient has severe sepsis or septic shock. Those patients need a blood culture, or if they have—there's a suspicion for an intravascular infection. And then any other situation that is not bad, we basically group them in high probability, intermediate probability, or low probability of bacteremia.

So those situations that have a low probability of bacteremia - those are the situations where blood cultures are not recommended and some classic examples would be lower urinary tract infection, post-op fever within 48 hours from surgery, or isolated fever with or without leukocytosis. We know that less than 5% of patients may have a positive culture and many of those positive cultures are actually contaminants.

And so, you can see there are also the other two buckets, intermediate and high probability bacteremia. And those are the situations where both cultures are recommended, but the category in the middle, intermediate, there's some room for discussion there, especially in the circumstances in which we are now, that, you know, some hospitals are very severely affected by their shortage, and they might need to implement more restrictive strategies in terms of indications.

And I'm obviously, I will be taking questions if there are any at the end. I highly recommend reviewing this paper if you haven't seen it. There's a lot of discussion of how we ended up making this classification, and that will be helpful to understand the clinical context.

And then I might say one other word regarding the right pathway, the follow-up blood cultures. So, obviously, blood cultures are recommended for documenting clearance *S. aureus* bacteremia for multiple reasons, including determining duration of therapy, but also understanding the prognosis of that patient. We decided to put *S. lugdenensis* in the same category given the nearness of this pathogen and obviously, any organism causing an intravascular infection.

But outside of those scenarios, there are many patients in whom repeating blood cultures to document clearance of bacteremia is not really impactful. Such as, for example, *S. pneumo* bacteremia, the setting of pneumonia, or, for example, *E. coli* bacteremia in a patient clinically improving without any, you know, suspicion for persistent bacteremia from a urinary source, right? So, there are many examples. Another one would be, for example, repeating blood cultures for a single contaminant in a patient who is not at risk for endovascular infection in, such as, for example, implanted hardware or cardiac hardware in an immunocompetent patient. And so these are some of the really low-hanging fruit that you can quickly address at your institutions. Let's move on to the next slide, please.

Slide 43 (00:42:16)

So, we've implemented this algorithm in our medical ICU and the medicine wards. And as you can see on the slide, graphs A and C. So, the two graphs on the left represent the use charts of monthly blood culture utilization before and after implementing the algorithm, and you can see that for the medical ICU there was an 18% reduction in overall blood culture use.

In the medicine wards, the drop was more pronounced at 30%, and you can see the graphs on the right, B and D, represent our surgical unit counterparts, which were the control units.

So, basically the intervention was implementation of the blood culture algorithm. We did have some sessions so we could you know explain the content and, you know, be able to answer some question about how to use the algorithm. And we also provided regular feedback regarding blood culture

utilization, but more importantly, regarding inappropriate cases so that the clinicians could reflect upon and change their practice.

So, in the intervention, not only we saw a reduction in overall blood culture use, but also we saw a reduction in single sets. The intervention was mostly about indications, but as we were working on this initiative, we realized that single sets were a problem, and we also educated clinicians on not getting single sets.

So just keep in mind that, you know, we increased the number of two sets, but overall, we brought down the utilization. We saw an increase in blood culture positivity in the ICU. This was not statistically significant in the wards. And we did not see a negative impact on our compliance with the CMS step one measure and other metrics, such as readmission or mortality.

Also, I would like to point out that other institutions have adopted our blood culture algorithm in ICUs, both medicine and surgical ICUs, and have also seen a reduction that goes between 20% to 70% in blood culture use.

Again, I'm not surprised to see a range of, you know, just because the practices vary from one hospital to the other, but again, everyone has room for improvement. And also, no known safety concerns when they implemented the intervention there. Next slide, please.

Slide 44 (00:45:17)

Very quickly, this is to show that there are some data, you should look at your own data in terms of, you know, which areas in your hospital have the highest volume of blood culture use. We also, at Hopkins, had a greater use among the medicine units, and that seems to be the general finding for other hospitals, but you should definitely become a with who's using more blood cultures in your hospital. And then next slide, I think I'll turn it over to Dr. Milstone to cover the work on pediatric blood culture stewardship. Aaron, please?

Slide 45 (00:46:04)

Aaron Milstone: Hey, thanks, Valeria. I've been monitoring the chat and the QA, so just to reassure some people of questions. I mean, what we've all learned from doing this for many years now is that there's a lot of overuse.

I understand labs are worried about not having resources, but I think we can make a big dent before that comes by just improving unnecessary use, just to kind of reiterate what Dr. Fabre was just mentioning. We've done this in over 20 children's hospitals now in the U.S. and the U.K. for about 10 years, and this slide just points to you to some consensus guidelines for kids, but the simple thing is, as someone mentioned in the chat or the Q&A is, if you think your patient has sepsis, you should get the blood culture.

But there are many, many patients in the hospital who get blood cultures where the clinicians don't think they have sepsis. And we've shown before that clinician intuition is pretty good. So, if clinicians have low suspicion, then they should, in this instance especially, consider not getting a blood culture.

So, I point you to these consensuses for kids, but a lot of the things we found in kids apply to adults, like don't get surveillance blood cultures, don't get blood cultures in patients with central lines if the lines

come disconnected or crack. They're basic practices where cultures are often obtained, they're probably unnecessary. Next slide.

Slide 46 (00:47:20)

And then this is just for people that are concerned about the safety of blood culture reduction. I just wanted to point to this paper that we had that was from 14 centers. We call this the BrighT STAR collaborative, where we showed about a one-third reduction in blood culture use across these 14 hospitals. And these occurrences were safe. We looked at many other balancing metrics, like sepsis, severe sepsis and shock, mortality, length of stay, and readmissions, as well as looking at every positive blood culture in all those units during the post-intervention period to exclude any delay in the detection of bacteremia. We found this to be very safe and then also reduced broad-spectrum antibiotic use and central-line-associated bloodstream infections.

So just to, kind of, bandwagon that there's a lot of work that can be done to reduce use and that will help this resource shortage.

Slide 47 (00:48:30)

Valeria Fabre: Next slide, please. I think there are only 10 minutes left, so perhaps I don't know if you want us to address the questions. I think the audience will get these slides, so people can review the slides on their own.

Sean Courtney: All right. Yeah, sorry.

Valeria Fabre: I think with the summary, people can read that.

Sean Courtney: Yep, perfect. Thank you, I appreciate you guys for joining our call and providing this update and some of these recommendations right now. There are a lot, a good bit of questions in the chat, so thank you. Obviously, we're not going to be able to get to all of them, but at least give us a little bit of time to cover some of them.

One of the ones that came up actually was just around if we're aware of any other potential shortages, and I'll just kind of open it up to the panel if we're aware of any other products that may be of concern.

Ryan Lubert: Hey, all, this is Ryan Lubert from FDA and I can share, you know, we're continuing to monitor the situation, but if you all are aware of any shortages, we do ask you send those to the Device Shortages inbox in the FDA letter to healthcare professionals as you all are sometimes more in tune to the scope of the problem, but I saw Chris come off mute so maybe she could speak for BD.

Chris Beddard: Yeah, I was just actually suggesting that FDA answer the question. We're not, again, on the front lines as it relates to other vendors and it's not appropriate for us to answer that question. So, thank you for jumping in there.

Sean Courtney: Great, thank you. Next question I'll ask is: What is the approximate percentage of blood culture bottles that will be unavailable? So, for example, is there a 10% shortage of normal demand, a 50% shortage of normal demand? Any idea on that?

Chris Beddard: Again, it's an evolving situation. We don't have percentages that we're supplying to the market right now. I would suggest that whoever asked that question maybe directly work with their sales rep, and we can have a one-on-one discussion on that. There are no broad communications as it relates

to percentages. As I was saying, every week, we're managing this appropriately for what we are able to provide to our customers in the U.S., so there's not an overall percentage that we're stating overall.

Sean Courtney: Great, thank you. And I think you kind of touched on this actually during your update, Chris, but they were wondering if there's any more information you could share around a timeline and just clarity around that regarding the shortage.

Chris Beddard: Yeah, the actions that I spoke about earlier, once we have the consistency from our vendor, which with all of the work we're doing, we believe, will be shortly in the August timeframe.

But that's really what our goal is, if not sooner. As soon as we believe that the consistency is there. And we have a projection and an outlook, we'll communicate back to our customers. The other piece with bringing the lytic anaerobic media back in glass. We are accelerating that availability for our customers to do validation as required. As soon as I have the dates that I feel I can 100% confirm to our customers, I will bring those out as well.

We'll be updating the website. I'm seeing that some people have problems. We haven't had any problems, but we're going back to the vendor to make sure that there's no issue. We'll communicate it on the update on that website. So again, everything we're doing is to provide the right clarity of information. The worst thing we can do is give information out, and it's not a hundred percent accurate as you can possibly imagine for us to be able to provide this information to our customer base.

Sean Courtney: Great, thank you. Another related question: Is there any indication that this shortage will expand to other products, or is it unique to this?

Chris Beddard: I can't answer for any other company. All I can say is that this vendor is unique for BD BACTEC plastic vials. So, there are no other BD products that are impacted from this vendor. So, it's unique to BD BACTEC vials.

Sean Courtney: Thank you. The next question we see is individuals being currently out of ANA, and they're working with their rep, but in the meantime, are there any recommendations we can provide regarding best practices in these situations, such as using aero- or pediatric bottles?

Jake Bunn: So, we highly rely on guidance from IDSA and the Clinical and Laboratory Standards Institute. I saw this question in the chat, so I just popped up that CLSI standard. It does say that the anaerobic [aerobic] bottle is the more critical one. [**Correction**: The aerobic bottle is the more critical one, according to CLSI M47 ED2:2022 Principles and Procedures for Blood Cultures, 2nd Edition].

So, if you're out of ANA, I would just focus on making sure that you have that 10 ml of blood volume, at least in that aerobic bottle. And there probably should be a comment put on that report as well stating which bottles were used. That would be good to inform the clinicians. Thank you.

Sean Courtney: Thanks, Jake. Appreciate that. Another question - you know we're running out of time, so I appreciate individuals including their email addresses for the questions that we're not able to reach today. Should laboratories consider validating glass bottles in the event that there's a shortage on those?

Jake Bunn: Yeah, if you're receiving glass bottles in your laboratory, you would have to perform verification studies. We had talked with BD about this before, and Chris, please correct me, but I think you all were going to try to provide a resource about that. I was in the lab when we switched from glass

to plastic, so I don't know if it's going to be that rigorous of a verification, but there will have to be something that the laboratories will have to show that those verification studies were done.

Chris Beddard: Right, so we'll be providing the resources through our scientific affairs and medical affairs teams for the glass vial validation, but certainly, the laboratory would make the final decision on how they would manage that. Our goal is to have that information well ahead of the vials being shipped for validation, so we'll continue to update our website with that information and timing as we get the level of confidence we believe we need. But again, for glass vials, our goal is to have those vials to our customers in early to mid-September. That's what we're working towards right now.

Sean Courtney: All right, great, thank you. And then last question, because I see we're pretty close to time. Are there any studies being performed currently around extending expiration dates for the bottles that laboratories already have?

Chris Beddard: Right, so we're working with FDA on certain SKUs to extend the timing. I don't mean to keep asking people to contact their sales rep, but the sales rep would then just would actually forward the questions to my team and myself so that we can answer those questions individually for every customer.

But we have talked to FDA about the ability to do that, so more to come. But it's really based on an individual laboratory and the SKU or media type they have on hand.

Sean Courtney: All right, great. Thank you, I appreciate you joining today's call, Chris, and everybody else who was able to join. Obviously, this is an important topic and we're glad we were able to at least touch on it today.

So, I just do want to remind everybody that if you do have questions or if we're unable to get to them, if you can go in there and again add your email to your question so that we can hopefully try to address it.

Also, you can send questions to DLSinquiries@cdc.gov that we posted earlier, and I do want to remind everybody that these slides, the transcript, and the audio from today's call will be posted, hopefully within the next 2 weeks, hopefully, sooner than that. That's hopefully being conservative with that estimation. But yeah, obviously, this is a concern, and we're hopefully trying to get ahead of it and give you guys the best advice for ensuring coverage in your laboratories.

Slide 51 (00:57:43)

Again, I just want to thank all of our callers. I'll remind everybody that our next scheduled call is Monday, August 19th, at 3 p.m. We'll be working on the agenda for that call. This is an ongoing situation, and we could be talking about it again, but we'll also be sending out updates around that.

Slide 52 (00:58:02)

You can always follow CDC's social media on Facebook, Twitter, Instagram, and LinkedIn.

Slide 53 (00:58:09)

With that, I just want to thank everybody for their time. I appreciate you all and have a great day. Thank you.