Good afternoon. I'm Kondra Williams, and I'm representing the Clinician Outreach and Communication Activity, COCA, with the Emergency Risk Communication Branch at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA Call, Algorithms for Diagnosing the Endemic Mycoses, Blastomycosis, Coccidioidomycosis, and Histoplasmosis. All participants joining us today are in listen-only mode.

Free continuing education is offered for this webinar, and instructions on how to earn continuing education will be provided at the end of the call. In compliance with continuing education requirements, all planners and presenters must disclose all financial relationships in any amount with ineligible companies over the previous 24 months, as well as any use of unlabeled product or products under investigational use. CDC, our planners and presenters, wish to disclose they have no financial relationships with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients. Content will not include any discussion of the unlabeled use of a product or a product under investigational use. CDC did not accept financial or in-kind support from ineligible companies for this continuing education activity.

At the conclusion of today's session, participants will be able to accomplish the following. Describe the epidemiology of blastomycosis, coccidioidomycosis, and histoplasmosis in the United States and the impact of delayed and underdiagnosed cases. Discuss diagnostic challenges associated with blastomycosis, coccidioidomycosis, and histoplasmosis. Identify populations clinicians should consider testing for blastomycosis, coccidioidomycosis, and histoplasmosis. Describe diagnostic tests clinicians should consider initially and after a negative test for blastomycosis, coccidioidomycosis, and histoplasmosis. And discuss the implementation of the clinical diagnostic algorithms for blastomycosis, coccidioidomycosis, and histoplasmosis.

After the presentations, there will be a Q&A session. You may submit questions at any time during today's presentation. To ask a question using Zoom, click the Q&A button at the bottom of your screen, then type your question in the Q&A box. Please note that we receive many more questions than we can answer during the webinars. If you are a patient, please refer your question to your healthcare provider. If you are a member of the media, please contact CDC Media Relations at 404-639-3286 or send an email to media@cdc.gov.

I would now like to welcome our presenters for today's COCA Call. We are pleased to have with us from the Centers for Disease Control and Prevention's National Center for Emerging and Zoonotic Infectious Diseases, Dr. Mitsuru Toda, who is an epidemiologist and outbreaks and epidemics unit lead for the Mycotic Diseases Branch. Ms. Samantha Williams, who is an epidemiologist for the Mycotic Diseases Branch, and Lieutenant Dallas Smith, who is also an epidemiologist for the Mycotic Diseases Branch at CDC. I'll now turn it over to Dr. Toda. Dr. Toda, please proceed.

Thank you very much. Next slide, please. Here's our agenda for today. Next, please.

Today I'd like to start with a story about a 38-year-old man living in Indiana, healthy with no apparent immunosuppressive conditions. He was a construction worker on large-scale projects, including buildings for retail, healthcare, and hospitality. Next, please.

He had not traveled recently. Next, please.

He started to feel sick and develops a fever and a cough. Next, please.

His cough was treated with intranasal steroids and antibiotics. Next, please.

And the treatment appeared effective and the cough resolved, but the fever persisted. Next, please.

About eight weeks after symptom onset, he presented at the hospital. He'd been experiencing ongoing fevers and significant joint pain. Next, please.

He underwent a full-body CT, which revealed significant lymphadenopathy and several small lung nodules. These were attributed to a genetic disorder, an enlargement of the liver and spleen. Next, please.

Based on his symptoms and a clinical workup, he was diagnosed with adult-onset Stills disease, a rare type of inflammatory arthritis typically associated with fevers, rash, and joint pain. Next, please.

He was prescribed steroids and anti-inflammatory medication, and symptoms temporarily improved. Next, please.

But four months later, he presented at the hospital with sepsis. His wife reported that his condition had worsened significantly, starting two weeks prior, with substantial weight loss, persistent high fevers, low blood pressure, and elevated heart rate. Next, please.

His workup showed a low blood cell count and signs of acute kidney injury. Next, please.

Cultures were obtained, and he was started on antibiotics. Next, please.

Over the first four days of his hospital stay, his symptoms did not improve, despite two additional rounds of antibiotics. Next, please.

Unfortunately, on hospital day six, the patient died after cardiac arrest. Next, please.

Two days later, on what would have been hospital day eight, blood cultures returned positive for histoplasma capsulatum. Next, please.

Histoplasma is a fungus that causes an infection called histoplasmosis. Next, please.

So this is clearly an unfortunate and complex case. However, there are some clues that may have indicated fungal disease. The patient's infection didn't improve or respond to multiple rounds of antibiotics, which suggests that reexamination may have been useful in this case. He also resided in Indiana, which is endemic for blastomycosis and histoplasmosis. His job was a construction

worker, which is considered to be a high-risk occupation for several environmental fungal diseases. Next, please.

But this wasn't necessarily a classic case of histoplasmosis. For starters, there were no noted exposure to bird or bat guano, which is known to be associated with histoplasmosis. While these exposures are frequently noted in outbreak settings, actually only 25% of people with sporadic histoplasmosis report these exposures. Next, please.

Also, the patient did not have HIV. There's actually been a substantial decline in HIV-associated histoplasmosis cases in the U.S., thanks to effective antiretroviral therapy. Recent literature suggests that autoimmune diseases, cancer, and diabetes are now more common risk factors than HIV. Next, please.

So if fungal diseases had been considered sooner, an alternate diagnostic testing approach may have improved the patient's outcome. The results of cultures that were obtained during the patient's last hospitalization took over a week. And on the other hand, urine antigen or serology testing typically provide results in a couple of days, if not sooner, and could have led to earlier diagnosis and treatment. Next, please.

Histoplasma is one of several pathogens that are causative agents of what's commonly referred to as endemic mycoses. These are pathogens that are endemic in certain areas in the U. S. Next, please.

Based on the current estimates, the combined distribution of endemic mycoses spans most of the country. They account for over 10,000 hospitalizations annually and constitute a substantial financial burden based on direct medical costs. There are also substantial indirect costs because of missed school or work. Next, please.

These fungi live in the environment, most commonly in soil, and exposure typically occurs through the inhalation of microscopic spores that have been aerosolized. Next, please.

Endemic mycosis are dimorphic in nature, meaning their life cycle includes an environmental form as hyphae, which produces spores that are aerosolized and dispersed. And then the host-associated form, where the spores are inhaled into the lungs of a susceptible host, and the warmer temperature inside the host body initiates the transformation to spherules or budding yeast, in which some cases they may travel into the blood and to the other parts of the body. Next, please.

Blastomycosis and histoplasmosis are primarily associated with the eastern half of the country, while coccidioidomycosis is endemic to the southwestern states. These maps are based on skin testing data, public health surveillance, outbreaks, and case reports. Next, please.

Trends for these diseases are monitored through national surveillance. States can designate whether or not a disease is reportable. In the states where a disease is reportable, healthcare providers, laboratorians, and other providers notify the public health departments of a diagnosis. And then the case data is voluntarily submitted to CDC when the patient meets standardized criteria that's set by the Council of State and Territorial Epidemiologists. Next, please.

As you can see, the endemic mycoses are not reportable in all the states in the U. S., and reportable states also don't align with endemicity. Coccidioidomycosis has the highest number of reportable states, but it's only 26 states and the District of Columbia. Histoplasmosis is only reportable in 13 states, and only five states report blastomycosis. Next, please.

So here's our first self-knowledge check. The fungi that causes blastomycosis is thought to be endemic to A, Pacific Northwest, B, Hawaii and Alaska, C, Midwest states, D, A and B only, and E, all of the above. I'll give you three seconds to ponder. Next slide, please.

The correct answer is C. Blastomyces mainly live in the Midwestern, South Central and Southeastern states. However, clinicians can diagnose these infections everywhere in the U. S. due to travel-associated cases. Next, please.

As you can imagine, we actually have a lot of gaps in understanding the epidemiology of endemic mycoses due to limitations with public health surveillance. However, we know that the geographic range of endemic mycoses are likely wider than what's currently estimated. Next, please.

The map on the left shows the distribution of coccidioidomycosis based on skin testing conducted in the '40s and '50s. The CDC map on the right was created to highlight our current understanding of where it is endemic. Next, please.

In 2020, locally acquired cases were reported in Washington state for the first time, an area that was not previously thought to be endemic. Next, please.

Histoplasmosis maps did not include the upper Midwestern states like Michigan, Wisconsin and Minnesota, but enhanced surveillance projects showed high incidence rates in these states. Next, please.

For blastomycosis, literature reviews showed that while most published cases are described within the estimated endemic states, more than half of the published blastomycosis cases occurred in jurisdictions where blastomycosis is not reportable. Next, please.

The New York State Health Department was alerted to several cases of blastomycosis around the Albany area in 2018. After the investigation using discharge code data from hospitals, they found that blastomycosis incidence was relatively high in areas along the Mohawk River. This analysis combined with case reports suggested that blastomycosis may be endemic in the eastern parts of New York. Next, please.

More recently, Vermont public health officials looked into all-pair insurance claims data to look at ICD discharge codes for blastomycosis. They found high incidence rates statewide, particularly in the north-central portion of the state. Next, please.

These investigations showed that blastomycosis may be expanding beyond historic regions. In both New York and Vermont, public health officials are taking considerable steps to make blastomycosis reportable. Next, please.

This is a study looking at incidence of endemic mycoses across the U. S. by county using Medicare fee-for-service beneficiaries. For histoplasmosis in particular, shown in red, you can see high incidence in areas along the west coast, which is not known to be endemic areas for histoplasmosis. While some of these are certainly related to travel, some of these pockets could potentially be areas of emerging endemicity. Next, please.

So not only are geographic distributions likely wider than historically recognized, they're also predicted to expand due to influence from changing climate. Next, please.

This map shows an output of a climate niche model of coccidioidomycosis based on temperature and precipitation. In a high-climate warming scenario, we see that the area of endemicity would extend to the north and the east, more than doubling the current known estimated area of endemicity for coccidioidomycosis. Next, please.

This map looked at soil suitability for coccidioides using data from USDA, like pH level, temperature, precipitation, and water holding capacity. Next, please.

If a two-degree Celsius warming is imposed on the model, we see that the range expands considerably. Next, please.

This is another soil suitability model looking at histoplasma this time, using characteristics like land cover, distance to water, and soil pH with data from U.S. Geological Survey. Next, please.

This map shows the current estimated suitability for histoplasma, with red showing more favorable conditions and green areas less favorable conditions. The higher suitability is generally where we might expect, though certainly extends beyond the traditional Ohio and Mississippi River Valley areas. Next, please.

Evidence from national surveillance suggests that cases are on the rise for coccidioidomycosis, as seen by the increased reports of case counts since 2014, driven primarily by Arizona and California, which account for the vast majority of reported coccidioidomycosis cases nationally. Next, please.

Similarly, we've seen a steady increase of histoplasmosis hospitalization rates nationally. Next, please.

These increases are, of course, concerning, but they're also compounded by the idea that reported case counts likely represent only a portion of the true disease burden. This is because detection of endemic mycoses is subject to several factors, such as underreporting, particularly if the disease is not reportable in the given jurisdiction, underdiagnosis, between missed and delayed diagnosis, and healthcare-seeking behavior, as some people will never see a healthcare provider if they experience mild or no symptoms at all, making them virtually impossible to detect. Next, please.

While all of these factors influence our understanding of the disease, for the remainder of the talk, we'll focus on the underdiagnosis aspect. Next, please.

By underdiagnosis, we're referring to diagnoses that are missed entirely and never diagnosed accurately, as well as diagnoses that are delayed until reexamination after symptoms don't resolve. These can have wide-reaching implications that we'll discuss further. I'll now pass it on to my colleague, Samantha Williams.

Thanks, Mitsu. Next, please. Now we'll go through some of the challenges related to diagnosing these endemic mycoses. Next, please.

And part of what makes them so difficult to diagnose is that they can mimic a variety of other illnesses, including bacterial or viral community-acquired pneumonia, lung cancer, tuberculosis, as well as other fungal infections. Next, please.

For these endemic mycoses, clinical manifestations can vary across a wide spectrum. The majority of the infections are actually asymptomatic, and people may never know that they experience disease. Acute pulmonary infections are typically characterized by mild to moderate symptoms, and these may resolve on their own within a week or two. But disease can also become quite severe and disseminate to other parts of the body. This is of particular concern for people with weakened immune systems, and disseminated disease is associated with high mortality rates. The severity of the disease primarily depends on the fungal inoculum as well as the host's immunity. Next, please.

So even though most infections are asymptomatic, when infections turn severe, they can be very severe. So in a recent analysis of surveillance data, 54% of histoplasmosis patients were hospitalized and 5% died. Those numbers were even higher for blastomycosis patients, with 65% who were hospitalized and 9% who died. These numbers do come with the caveat that surveillance data does tend to skew towards the more severe cases, but still very concerning. Next, please.

For the most part, when people do develop symptoms, they may experience mild or nonspecific symptoms, including fever, cough, fatigue, headache, night sweats, and muscle aches, which are also present in other lung infections. Radiographic results are also generally nonspecific. So to diagnose a patient with these three endemic fungi, laboratory testing is a key factor. Next, please.

And since they can be clinically indistinguishable from community-acquired pneumonia of other etiologies, there is frequent misdiagnosis before testing for a fungal infection is considered. Next, please.

Previous studies of pneumonia etiologies didn't include fungal testing if fungus or mycobacteria had not been previously identified. So this is a study describing 2,000 adults who were hospitalized with community-acquired pneumonia, and 62% had no pathogens detected. We suspect that fungal diseases likely could have been detected in some of these if they had been proactively tested for. Next, please.

However, despite the clinical similarities between these endemic mycoses and community-acquired pneumonia of other etiologies, the current Infectious Diseases Society of America's community-acquired pneumonia guidance does not recommend testing for these diseases, despite

evidence showing that cocci, for example, accounts for up to a third of community-acquired pneumonia in some of the endemic areas. Next, please.

We also know that provider awareness and testing practices can differ substantially based on factors like specialty and region of training or practice. In two separate surveys, one of primary care providers and another of infectious disease physicians, providers were asked how often they test for blastomycosis, coccidioidomycosis, and histoplasmosis in patients with community-acquired pneumonia. We can see that overall, testing is higher among infectious disease physicians compared to primary care providers. These numbers are from a national perspective, but we did see similar differences in endemic areas. Next, please.

And choosing the right laboratory tests can also be difficult. There are multiple methods available, including antibody and antigen detection, molecular methods, culture, and histopathology or cytopathology, and each has its own pros and cons. Next, please.

Tests for antibody and antigen detection have relatively quick turnaround times, and antigen testing in particular can be useful early on in the illness. However, these tests also have relatively high cross-reactivity compared to other methods, and the sensitivity is heavily dependent on the host's immune status as well as the disease course. Next, please.

Molecular methods, such as PCR, also have quick turnaround times, but they're relatively new to the scene and therefore not widely available from a commercial perspective. Additionally, there have only been a few studies conducted regarding the test's performance, so there's still a lot to be learned about their utility as well as potential drawbacks. Next, please.

Culture is considered to be the gold standard as it's highly specific, but some of the drawbacks include long turnaround times, as we saw in the initial case report, as well as invasive procedures, the personnel training required for technical expertise, and specialized facilities, including biosafety level three labs. Next, please.

There are similar benefits and disadvantages to histopathology and cytopathology, although turnaround times are generally somewhat faster than culture. Next, please.

So there's a lot going on in this table, and just to orient, this table shows the sensitivities and specificities of histoplasmosis diagnostic tests. And again, there's a lot of information here, but the key takeaway is really that performance can vary significantly, not only across the different test types, but for a given test, it can vary based on the quality of the specimen, the timing related to disease progression, as well as the host's immune status. Next, please.

So we'll stop here for our next self-knowledge. The question is, blastomycosis, coccidioidomycosis, and histoplasmosis are most often diagnosed by, A, primary care providers, B, infectious disease physicians, C, urgent care providers, D, primary care providers and infectious disease physicians, or E, primary care providers and urgent care providers. And I'll leave a few seconds for thought. Next, please.

So the correct answer here is B. Most blastomycosis, coccidioidomycosis, and histoplasmosis diagnoses are made by pulmonologists and infectious disease physicians. Next, please.

So we mentioned earlier that there can be serious implications of underdiagnosis, so we wanted to go through just a few of those now. Next, please.

The most direct impact is to the patient who experiences unresolved illness and repeat health care visits. Studies have shown that the median time between seeking health care and a diagnosis of one of these endemic mycoses can range from 23 to 38 days. Next, please.

More than half of patients receive another diagnosis before they're tested for an endemic fungal infection. Next, please.

And the majority of patients see a provider at least three times before they're tested for an endemic fungal infection. Next, please.

So not only can this take a financial and emotional toll, but it can also lead to the overuse of unnecessary and ineffective antibacterials. Studies show that over 50% of patients who receive antibiotics before they were diagnosed with histoplasmosis or coccidioidomycosis. And most patients received at least two rounds before they were tested for an endemic fungal infection. Next, please.

And lastly, missing endemic diagnoses also limits accurate surveillance. And this can really hinder our understanding of the epidemiology and exposure risks of the disease, which can have downstream effects on messaging and risk mitigation. Next, please.

As a result, resources are needed to improve both provider awareness and testing practices in order to promote early diagnosis and improve patient outcomes.

Now I'm going to turn it over to Dallas to go through the development of the algorithms and the algorithms themselves.

Thank you much, Sam. Next slide, please.

In order to address some of these problems with testing for the endemic mycoses, as Sam mentioned, we worked in partnership with the mycosis study group to create diagnostic algorithms for blastomycosis, coccidioidomycosis and histoplasmosis. And we did this for three main reasons. The first reason was to increase levels of testing, particularly among primary care and outpatient providers. Next slide, please.

We wanted to aid in the accurate interpretation of diagnostic test results. Next slide, please.

And also, we wanted to offer a standard diagnostic approach for the endemic mycoses. Next slide, please.

While we encourage anyone and all clinicians to use these algorithms, they are primarily targeted to primary care and outpatient providers, given the considerable testing gap for patients presenting with community acquired pneumonia between primary care providers and infectious disease physicians. And so I just wanted to revisit these stats that my colleague Sam presented about the differences in testing for the endemics. Next slide, please.

And so, as I mentioned, we were looking at when are patients first being recognized or first presenting in order to get tested for endemic mycoses? And that we're seeing that less than one third of new diagnoses of, for example, coccidioidomycosis, blastomycosis, histoplasmosis are occurring outside the hospital. And so about 73% of diagnoses are occurring in the hospital. Only 22% are in ambulatory clinics, 3% in emergency departments and only 0. 5% in urgent care settings. Next slide, please.

And so we also did an enhanced surveillance project for histoplasmosis in the United States. And when we looked at the data, we saw that 43% of patients first sought care in a primary care facility. But when we actually looked at the providers who first tested for histoplasmosis, only 11% came from primary care providers. Next slide, please.

And although we do want to make sure we are increasing testing endemic areas, these algorithms are meant to reach providers across the country because we see that, for example, some patients, some patients who travel, for example, and we see a lot of travel associated disease. And so providers in low endemic or non endemic areas still need to be aware of these diseases. And what we've seen is that they're less aware from certain studies. And also, we want to be aware that providers frequently move around to new areas of practice. And so we want to make sure they're trained if they do move to a new area of practice. Next slide, please.

And so, as I mentioned, travel associated infections occur regularly. This map is from a mycosis enhanced surveillance project that showed travel links between cases identified outside of endemic areas. And we especially see this in the snowbird populations or those who move from it to a warmer climate in the winter, but spend more time in temperate areas during the winter months and then return home. Next slide, please.

So in order to develop these algorithms, we went through a few different steps. So the first thing we did was work in consultation with experts. So fungal disease experts, clinicians, ID physicians and primary care physicians to review performance characteristics of available diagnostic tools. We then sensitize these learnings into a draft diagnostic algorithm. And then once we got this draft diagnostic algorithm up and running, we presented to specialty groups and experts both within and external to CDC to solicit feedback. And finally, with this feedback, we revise the algorithms accordingly and finalized them. Next slide, please.

One of the first decision points was to address when a provider should consider testing for an endemic fungal infection. So the first point of consideration is whether the patient lives in or has traveled to a disease endemic area as estimated by these maps. But with the caveat that some of these diseases can occur at lower levels worldwide. But geography alone really isn't enough for testing consideration. Next slide, please.

So if the patient meets the geographic criteria and communicable pneumonia of unknown etiology is not responding to empiric antibiotics or antimicrobials, we recommend that fungal testing be considered. But each endemic mycoses also has other risk factors to be taken into account. And this first set of criteria also means that the patient has had to undergo one round of antibiotics. Next slide, please.

So on the first visit, fungal testing should be considered if the patient meets geographic criteria. And next slide, please.

For blastomycosis, has skin lesions present or linked to a known blastomycosis outbreak. Next slide, please.

For coccidioidomycosis, if the patient has initial presentation of CAP or erythema nodosum which is characterized by red bumps and is commonly seen in initial presentation of coccidioidomycosis, but keeping in mind that erythema nodosum should occur in the setting of recent respiratory symptoms. And if people have lived in or traveled to a highly endemic desert region of Arizona or the San Juan Valley of California, or have a link to a coccidioidomycosis outbreak. Next slide, please.

And finally, for histoplasmosis, if the patient has initial CAP visits and have notable exposure to bird or bat droppings, imaging showing new nodules or lymphadenopathy, or a link to a known histoplasmosis outbreak. Again, these are sort of the entry criteria to consider testing for an endemic fungal infection. Now I'll take you through each of the algorithms to get a sense of what's included and some of the nuances of the diseases. Next slide, please.

And so first, we'll start with the blastomycosis algorithm. Next slide, please.

And so for blastomycosis, an EIA or enzyme immunoassay urine antigen test is suggested first because of its high sensitivity and quick turnaround. Next slide, please.

If it's positive. Next slide, please.

A positive antigen test almost always indicates active infection, although as a caveat, cross reactivity with other fungal diseases, particularly histoplasmosis, is possible. It could be interpreted as probable acute pulmonary blastomycosis if the initial EIA urine test is positive. Next slide, please.

If the test is negative, there are a couple of different pathways that the algorithm shows. Next slide, please.

First, you can consider alternative diagnoses. You can consider alternative pathogens, alternative etiologies of community acquired pneumonia. Next slide, please.

Or if there is still a high degree of suspicion of fungal etiology or blastomycosis. Next slide, please.

You can, one, consider consulting an ID physician or pulmonologist. Next slide, please.

Or you can consider additional testing. This additional testing could include a variety of different diagnostic tests, including obtaining sputum, obtaining a BAL or bronchoalveolar lavage or tissue culture and microscopy, performing a skin biopsy for microscopy and culture if a skin lesion is present. Serologic antibiotic tests can also be considered, but it's worth noting that they typically have low sensitivity for blastomycosis or Blastomyces, but may be useful when antigen is negative or in trying to differentiate between blastomycosis and histoplasmosis. You can also evaluate for potential disease manifestations in other parts of the body. Next slide, please.

If the test is positive from this additional testing, again, the interpretation is probable acute pulmonary blasto. Next slide, please.

If this additional testing is negative, you should probably consider alternative diagnoses. Next slide, please.

So now we'll transition to the coccidioidomycosis algorithm. Next slide, please.

An enzyme immunoassay or EIA antibody test with immunodiffusion and complement fixation are suggested. EIAs often have faster turnaround time, usually a lower cost and generally higher sensitivity than IDNCF, or immunodiffusion and complement fixation, with some variability by test manufacturer and laboratory. Immunodiffusion and complement fixation antibody tests exhibit greater specificity than EIAs, although are typically available only at reference laboratories and high-volume academic clinical centers. Next slide, please.

If the EIA is positive, consider follow up testing with ID or CF to rule out a false positive, since these tests are more specific than EIAs. For patients in highly endemic areas or with highly suggestive clinical findings, clinicians might start treatment for pulmonary coccidioidomycosis based on the positive EIA while awaiting ID and CF results. CF testing also provides a quantitative value that is useful prognostically during longitudinal care. Next slide, please.

Generally, an IgG or an IgM positive result can be interpreted as pulmonary coccidioidomycosis. Next slide, please.

If both IgG and IgM are negative, there are a couple different considerations or pathways that one can take. Next slide, please.

First, just like the blastomycosis algorithm, you can consider alternative diagnosis, alternative etiology, or alternative microbes. Next slide, please.

If a high degree of suspicion remains, progression of illness occurs, or if symptom onset was recent. Next slide, please.

You can first, or one, you can obtain infectious diseases or pulmonary consultation. Next slide, please.

Or you can repeat serology two to six weeks after initial EIA. Antibody testing can be negative early in the illness course. Culture and microscopy can also be considered, although they have a low sensitivity. Serology is preferable to antigen testing for coccidioidomycosis, but antigen testing can be useful in immunocompromised patients who may not be able to mount an antibody response. Next slide, please.

If this repeat testing, either through serology or other message, is positive, this positive test would indicate pulmonary coccidioidomycosis. Next slide, please.

While a negative test would suggest to consider alternative diagnosis. Next slide, please.

Now, we know that this won't apply to all cases, and there are still many challenges. So now we'll go into a self-knowledge check. And so the question is, the clinical diagnostic algorithm for coccidioidomycosis recommends which diagnostic test initially? A, enzyme immunoassay antibody test. B, polymerase chain reaction test or PCR test. C, immunodiffusion. D, both A and C. Or E, B and C. I'll give you a few minutes to think about the answer. A few seconds, sorry. All right. Next slide, please.

And so the correct answer is D. The algorithm that was developed by CDC, along with Mycosis Study Group, recommend ordering an enzyme immunoassay or EIA antibody test with immunodiffusion or complement fixation initially for coccidioidomycosis diagnosis. However, as we mentioned during the algorithm’s presentation, initial testing with EIA or ID and CF may depend on availability and performance characteristics of tests at facility. EIAs have a quicker turnaround time than both ID and CF. If the EIA is positive, clinicians may consider follow-up testing with ID and CF to rule out false positives and confirm the diagnosis. Next slide, please.

And so now I'd like to talk about the final diagnostic algorithm for histoplasmosis. Next slide, please.

For histoplasmosis, an EIA urine antigen test is suggested first. Consider obtaining a concurrent immunodiffusion or complement fixation antibody test to increase sensitivity. False positives from previous infection can occur during antibody testing, but immunodiffusion antibody positivity typically wanes within three years after infection. Next slide, please.

If the test is positive. Next slide, please.

A positive antigen test almost always indicates active infection. Although cross-reactivity with other fungal diseases, particularly blastomycosis, is possible. Note that antibody tests can be negative early in disease. Next slide, please.

If the initial test is negative, we'll also see these similar pathways again that we saw with coccidioidomycosis and blastomycosis. Next slide, please.

First, you can consider alternative diagnosis or other etiologies. Next slide, please.

If there's a high degree of suspicion, next slide, please, you can first, or one, consider consulting an ID physician or infectious disease physician or pulmonologist. Next slide, please.

Or you can repeat antibody testing, since antibody testing may be negative early in illness. Or you can consider alternative diagnostics, including ordering a sputum or bronchoalveolar; lavage or BAL culture or microscopy. Next slide, please.

If the test is positive, again, the interpretation is probable acute pulmonary histoplasmosis. Next slide, please.

If this retest is negative, you can consider alternative diagnoses. Next slide, please.

Now, we know this won't apply to all cases, and there still may be challenges interpreting results. These are complex diseases, and they may not always follow a standard protocol. But these algorithms are designed to provide a standard approach, especially for those who may be less familiar or may not see these endemic mycoses very often. They aim to improve early diagnosis and reduce misdiagnoses, reduce unnecessary antibacterial use, and improve patient outcomes. Next slide, please.

And so, we are pleased to announce that these algorithms are up online on the CDC's website. We also have an article coming out that will be published soon that will go through a little more detail on the algorithms. These three websites that are listed on the screen will take you through the three different algorithms. Also, I want to mention that our partners at the Mycosis Study Group has a continuing medical education activity that you can take that goes through cases that use the algorithms in real-life cases. Next slide, please.

So in terms of next steps and future directions, we hope to assess the uptake and impact of this guidance, particularly on whether early diagnosis improves patient outcomes, and incorporate new diagnostic methods into these algorithms as they become available. This is our first pass, but we don't expect it to be the last. We want these algorithms to be iterative as new information becomes available. We're also hoping to quantify the proportion and geographic distribution of community acquired pneumonia and other lower respiratory infections so that we are able to better inform algorithm development and include other diseases in these algorithms. Next slide, please.

And so, coccidioidomycosis, histoplasmosis, and blastomycosis are fungal diseases known to the endemic in the United States. We think that increased awareness and testing practices can improve health outcomes. Next slide, please.

Early diagnosis and treatment can help prevent severe illness. If a patient has experienced symptoms consistent with the endemic mycoses and does not improve antibiotics, please consider fungal testing. Next slide, please.

And so as we end our presentation today, we want to make sure that everyone celebrates Fungal Disease Awareness Week, which is taking place this week through the Mycotic Diseases Branch. And so, here is a link to our Fungal Disease Awareness webpage, but we encourage you to check

out the wide variety of activities that we have offered throughout the week that raises awareness of these important fungal diseases, both the ones we've talked about today and many others. Next slide, please.

Thank you so much for your time, and I'll turn it back to the moderator at this time.

Presenters, thank you for providing this timely information to our audience. We will now go into our Q&A session. Please remember that to ask a question using Zoom, click the Q&A button at the bottom of your screen, then type your question.

Our first question states, why aren't histoplasmosis and blastomycosis nationally reportable diseases? This would really help with our understanding of the true epidemiology, particularly as this changes with the changing climate.

Thank you so much. I can take that one, and that's a great question. I think, first, it's important to distinguish between reportable and nationally notifiable. But reportability is a state-level decision. So we're unable to mandate that, and even with coccidioidomycosis, which is nationally notifiable, it is actually voluntary that states do submit data to the CDC. But again, reportability is a state-level decision, and we do understand that there is a lift and a burden that goes along with kind of reporting and investigating those cases. So we're always happy to consult with states who are considering making those diseases reportable, because we agree we would love if more states would make some of those diseases reportable, and it would really help with the understanding of the epidemiology. So we're very happy to consult about that. But reportability is a state-level decision, and then national notifiability is designated by the Council for State and Territorial Epidemiologists with state input. But please feel free to reach out if you do have any questions or are considering making a disease reportable in your state.

Thank you.

Thank you. Our next question. The range of endemic mycoses seems to be expanding. Histoplasmosis seems to be distributed nationwide. Why do these algorithms not recommend testing everyone with community-acquired pneumonia for fungal etiology?

I can jump in and take that question. And so, I think we realize these tests already are underutilized for whether it's serum, whether it's antibody testing, antigen testing for all three of the fungal diseases. But we realize there's still limitations to widespread use of them and recommendations for testing everyone. I think two of the biggest ones are the cost of the agents -- the cost of the diagnostic tests, access to all the diagnostic tests, especially for coccidioidomycosis, for example, and also some of their performance characteristics. As we continue to improve, these recommendations may change if they become cheaper. But right now, we believe that using the geographical indication is a good way to implement testing in a coordinated way for these endemic mycoses.

Thank you. Our next question. Is there any ongoing work to measure the impact on the algorithms at a facility or provider level?

Sure, I can take this one. This Mitsuru. We are partnering with the mycosis study group and a couple of academic centers to do quality improvement projects to look at pre and post improvement of testing practices at certain urgent care and emergency care departments at these institutions to see if these algorithms helped. And based on feedback, we are open to potentially updating our algorithms. And also, I think these efforts would inform us in terms of how we disseminate this information and also identify the right audience that we should be disseminating these algorithms.

Thank you. Our next question is, how do you plan on updating these algorithms based on newer diagnostic technology?

I can go ahead and take this one. This is Dallas. And so we are working with partners both at a facility level, a clinician level, state and local health departments. And we're constantly talking with them about how we can improve these algorithms and this testing in general. And so if we do see that there's a new EIA test that comes out or more widely available, we will be updating these algorithms through the same messaging and the same venues that we're kind of getting out these initial algorithms with. So we're going to be potentially doing another COCA call. We'll get them out through social media because we really think that when these are updated, we want to get them out to those who need it the most, who may not always be seeing these diseases most commonly. Thank you so much.

Thank you. Our next question asks, do the presenters have any comments on positive IgG results for coccidioidomycosis and whether an IgG positive only is indicative of present or past infection?

I can take this one. This is Mitsuru. Yeah, these are really difficult to interpret. And we did have a lot of back and forth with various experts. And as Dallas mentioned, we did consider the availability and access to these testing as well. And so the diagnostic testing algorithm is what it is right now as a first pass. But I think we were definitely open to getting feedback and things like that. But in terms of whether a certain test is a definitive test, I don't think there's a consensus on that in this field, unfortunately.

And I'll just add something to that. Thanks, Mitsuru. I think that's an excellent question. And Mitsuru explained it well that, I mean, it's really hard to interpret most of these tests, especially for coccidioidomycosis. And so, one of the things that we really emphasize in these algorithms is always consulting with an ID physician if you're unsure of the results, because it is difficult. If you only get an IgG positive, it is difficult to really 100% say if it's present or a past infection. And the biggest thing is that we don't want people to be missed for an opportunity for early treatments. And so, if we are able to start treatments, if it is an active infection, that, of course, is going to improve outcomes. And so, for those who are using these algorithms, if you're unsure of a certain result, it's always good to consult with a local ID physician or pulmonologist.

Thank you very much. Our next question. What are some barriers to clinical diagnostic testing for endemic mycoses that health care providers may face?

I can go ahead to this question. And I think there are a variety of barriers. I think one, availability of tests. I think actually someone mentioned this in the Q&A, but sometimes there's quite a big turnaround time for some of these tests, even like a histoplasma antigen test. It can take four to five days, I saw that one person posted. And so, I think availability and turnaround times are really important, can be barriers. I also think cost and making sure that insurance coverage covers all of these different diagnostic tests is also a concern. And then I think something that we've been harping on throughout this presentation is, even if you do get these diagnostic tests, how do you interpret them? It can be very difficult. And so we hopefully design these algorithms to make it as smooth as possible to kind of interpret some of these results. That's all I had. Are there any other barriers that I missed?

I think the other thing, this is Mitsuru, the other thing to add is this issue of access to testing. There are only certain laboratories that might be able to perform some of these tests, especially for coccidioidomycosis. And so that could also be a barrier as well. And then the other thing we've been talking about throughout this seminar is the fact that, especially for primary care and urgent care providers, fungal diseases are not really at the top of their differential when they're looking at patients with community acquired pneumonia. And so, trying to improve that knowledge gap is something that we would like to strive for. And we also see that as a big barrier as well.

Thank you. And we have time for one more question. Why are the main audiences of the clinical diagnostic algorithms primary care providers and urgent care providers?

I can go ahead and take this one. This is Dallas. I think the reason that these algorithms are targeted towards primary care and urgent care providers is that these are the type of providers that are normally going to see patients first with community acquired pneumonia with a fungal etiology. And we've seen from data that they are often diagnosed in hospitals first, and we also are seeing that this leads to higher morbidity, higher mortality, and just worse outcomes. And so, if we're able to catch these patients early on during their first or second visit, get them treatment, we really think we can make a huge public health impact and really save lives and prevent some disability or prevent hospitalization. And so, we think primary care and urgent care providers are very busy. Very busy. They see a lot of different diseases. They do the whole spectrum of illness, and they're our first line providers out there. And so, if we're able to equip them with tools to just increase their knowledge and just give them another tool to be able to think fungus, think fungi, think fungal diseases, that was the main reason for targeting that audience. And we hope it's a useful tool for them.

Thank you. Again, thank you so much for answering these questions and for sharing your expertise with us today. All continuing education for COCA Calls is issued online through the CDC Training and Continuing Education online system at tceols.cdc.gov.

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Again, thank you for joining us for today's call.