Good afternoon. I'm Commander Ibad Kahn, 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, Epidemiology, Testing, and Management of Extensively Drug-Resistant Shigellosis. 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 products 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, with the exception of Dr. Louise Francois Watkins's discussion of treatment options for shigellosis, some of which are considered off-label use for infectious diarrhea. 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: Discuss the clinical characteristics, populations at risk, and evolving epidemiological transfer extensively drug-resistant shigellosis; describe outbreak investigations of extensively drug-resistant shigellosis in the United States and the United Kingdom; outline strategies and resources to support the clinical management of extensively drug-resistant shigellosis, and educate healthcare professionals about appropriate antibiotic use; and review what CDC is doing to learn more about extensively drug-resistant *Shigella* in the United States and how clinicians and public health officials can help through testing and reporting. 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 often receive many more questions than we can answer during our webinars. If you are a patient, please refer your questions to your healthcare provider. If you're a member of the media, please contact CDC Media Relations at 404-639-3286, or send an email to media@cdc.gov.

Now I would like to welcome our presenters for today's COCA call. We're pleased to have with us Lieutenant Commander Naeemah Logan, who's a Medical Officer; Meseret Birhane, a Surveillance Epidemiologist; and Dr. Louise Francois Watkins, a Medical Officer, all with CDC's National Antimicrobial Resistance Monitoring System for Enteric Bacteria Team within the National Center for Emerging and Zoonotic Infectious Diseases. We would also like to welcome Dr. Laura Hinkle Bachmann, who's the Chief Medical Officer for the Division of STD Prevention at CDC; Miss Rachel Jervis, who's a Program Manager for the Foodborne, Enteric,

Waterborne, and Wastewater Diseases Program at the Colorado Department of Public Health and Environment; Dr. Gauri Godbole, who's a Consultant Medical Microbiologist at the UK Health Security Agency; and Miss Hannah Charles, who's a Senior Epidemiologist at the UK Health Security Agency. Now it is my pleasure to turn it over to Lieutenant Commander Logan. Please proceed.

Thank you, and welcome for joining us today. The title of my presentation is, What Clinicians Need to Know About Extensively Drug-Resistant Shigellosis in the United States. Please note additional information on this topic can also be found in CDC's recently released Health Alert Network Message, HAN number 46.

In terms of an outline, we will be covering these four topics. First, we'll share some background on *Shigella* infections, including transmission and populations at greatest risk. Next, we'll provide an overview of the national surveillance systems used to detect XDR *Shigella* infections. We'll then share CDC data on the evolving and concerning emergence of these strains. And, finally, we'll discuss treatment considerations relevant for conditions in the US.

By way of background, shigellosis is an important cause of domestically acquired and travel-associated acute bacterial diarrhea. An estimated 450,000 persons each year in the US are infected with *Shigella*, resulting in over 6,000 hospitalizations and over 3 million dollars in direct healthcare costs annually. There are four known *Shigella* species, and the vast majority of infections in the US are caused by *Shigella sonnei* and *flexneri*. Transmission is fecal-oral and can occur either directly through person-to-person, including through sexual contact, as well as indirectly through contaminated food, water, or fomites.

Shigella bacteria are easily transmitted, requiring as few as 10 organisms for infection. Because of its low infectious dose, outbreaks are common, typically among people in close contact settings and areas with crowded living conditions.

Historically, young children have been at highest risk for shigellosis. More recently, however, CDC has observed an increase in antimicrobial-resistant *Shigella* infections among vulnerable populations, specifically, men who have sex with men, or MSM; people experiencing homelessness; international travelers; immunocompromised persons; and people living with HIV.

Although shigellosis is mostly self-limiting, antimicrobial treatment can be recommended in certain scenarios to reduce symptoms and decrease bacterial shedding. And my colleagues will discuss this in greater detail. More recently, however, treatment decisions have been complicated by increasing antibiotic resistance and the use of PCR-based culture-independent diagnostic tests, which make it difficult to provide laboratory informed antimicrobial treatment. So this concludes the introductory segment of our presentation, and I'll now transition our talk to Miss Birhane.

Good afternoon. And thank you, Dr. Logan. I'll be presenting on some of -- some of the methods that we use for surveillance and resistance testing at CDC.

I'd like to begin by providing a few definitions. Antimicrobial susceptibility testing, or phenotypic resistance testing, is the process of determining the concentration of an antimicrobial needed to inhibit the growth of an organism like *Shigella* bacteria. Whole genome sequencing is the process that determines the genetic code, or DNA, of an entire organism, again, like *Shigella.* Next, please. Next, please.

Predicted resistance, also called genotypic resistance, is analysis of an organism's genome for the presence of resistance determinants, which can then be used to accurately predict phenotypic resistance. Next, please.

And resistance determinants, or genes and mutations, are known elements in a bacterium's genome that confer resistance to a certain antimicrobial or class of antimicrobials. Next, please.

CDC currently defines XDR *Shigella* as strains resistant to all commonly recommended empiric and alternative antibiotics, including ampicillin, azithromycin, ciprofloxacin, trimethoprim-sulfamethoxazole, and ceftriaxone.

CDC uses data from two surveillance systems to monitor resistance in enteric bacteria like *Shigella.* NARMS is the National Antimicrobial Resistance Monitoring System. The CDC NARMS Laboratory receives a sample of isolates from state public health departments and performs phenotypic resistance by broth microdilution. This process can take one year or more due to the time involved with shipping isolates. PulseNet is a national laboratory network that receives whole genome sequencing data from state public health laboratories. Between 2015 and 2019, PulseNet partnering laboratories gradually increased the number of sequenced isolates.

From 2019 onwards, whole genome sequencing was routinely used as a primary subtyping method. Sequencing data uploaded to PulseNet can be used to predict resistance, usually within two to four weeks of patient's illness. Next, please.

This slide illustrates the process of isolate submission and testing. The process begins when an ill patient visits a healthcare facility, and the clinician orders a sample for culture. Next, please.

If the specimen tested in a clinical laboratory yields a *Shigella* isolate, the clinical laboratory then sends that isolate to the public health laboratory for further analysis. Some *Shigella* isolates undergo whole genome sequencing at the public health lab. The percentage of isolates that are sequenced depends on the state's resources. Some state labs may sequence very few of their *Shigella* isolates, while others sequence nearly 100 percent. All sequenced isolates received by PulseNet are analyzed by NARM scientists for genotypic resistance. In addition, every 20th isolate is shipped to NARMS for phenotypic resistance testing. Next.

Here is what public health laboratories can do to help identify and monitor XDR *Shigella* isolates. Clinical laboratories should submit known or suspected XDR *Shigella* isolates to their local or state public health laboratory. Public health laboratories should perform whole genome sequencing of *Shigella* isolates if possible. I'll now turn this back to Dr. Logan to describe the epidemiology of XDR *Shigella* cases.

Thank you. Now I'd like to share some of the data generated using CDC surveillance data.

This graph shows the total number of *Shigella* isolates sequenced by PulseNet during 2015 to 2022, stratified by species. Orange bars are *sonnei*; blue are *flexneri*; and then yellow are other species, which are negligible. As a reminder, very few isolates were sequenced prior to 2015. Additionally, this figure depicts sequence isolates captured by PulseNet and not all surveillance data in the US.

As you can see, over 13,000 Shigella isolates were tested; and the vast majority, 99 percent, were *sonnei* or *flexneri.*

This slide shows the percentage trends of *Shigella* collected by PulseNet during 2015 to 2022. As noted earlier, most domestic cases of shigellosis are caused by *sonnei* or *flexneri*. You can see that, in 2015, most cases of shigellosis in the US, 91 percent, were caused by *sonnei*. However, this changes. And, since 2021, shigellosis in the US is primarily driven by *flexneri* strains. This challenges the conventional view that *sonnei* predominates in high-income countries while *flexneri* predominates in low- and middle-income countries. The recent increase of *flexneri* in the US demonstrates the incredible opportunistic ability of this pathogen to afflict vulnerable populations, and perhaps also urges us to reconsider previous views. Wherever suitable living conditions and risk behaviors coexist, *flexneri* transmission can occur.

This figure depicts sequenced Shigella species collected by PulseNet. The number of isolates tested is muted and overlaid with the trends for XDR Shigella. Over 13,000 isolates were submitted to PulseNet during 2015 to 2022. Among these, 237 were XDR. You can see the percentage of XDR *Shigella* dramatically increased during this time period from 0 percent in 2015, to 5 percent in 2022.

This is a case map showing the distribution of the 237 XDR *Shigella* cases in the US during 2015 to 2022. And I apologize as some of the labels may have gotten misplaced. But, regardless, what we're trying to convey in this figure is that darker blue equates to higher number of cases and, lighter blue, fewer cases. And we'll share a revised slide of that. From the map, you'd be able to see that the uh states with the highest XDR cases were highest in California, Colorado, Massachusetts, and Texas.

There are a few important things that we'd like to note with this slide. First, the figure represents case counts of XDR *Shigella* infections, as identified in PulseNet by state, not incidents. Also, the extent of lab-based surveillance may differ by state. Some public health laboratories may not have the capacity to routinely perform whole genome sequencing on *Shigella* isolates. Therefore, case counts might not represent the full scope of XDR *Shigella* infections in those states. Finally, duplicate records might exist in PulseNet but not enough to skew information presented in this report.

This chart shows XDR by demographic group for *Shigella*. On the X axis are years from 2015 to 2022. And on the Y axis are the number of XDR *Shigella* isolates. The orange bar corresponds to isolates from adult men. You can see that, overall, for each year, adult men have the greatest

number of XDR *Shigella* cases. And, among adult men, that number increases each year from 0 in 2015, 2016 to 130 in 2022.

Compared to other demographic groups, adult men also have the highest proportion of XDR at 2.3 percent. And this number increases to almost 85 percent when the denominator is restricted to XDR cases. These trends are also consistent with recent increases in drug-resistant shigellosis outbreaks among MSM. I'll now transition the presentation to Dr. Francois Watkins.

Good afternoon, and thank you, Dr. Logan. For the next few minutes, we're going to discuss treatment considerations for *Shigella* infections.

For the sake of time, we're not planning to discuss clinical presentation or diagnosis on this call. But please note that these slides will be available through the COCA site after the call, and you'll see QR codes on these and future slides where you can find additional information. And next, please.

So there are four main components to keep in mind during the management of shigellosis: supportive care, antimicrobial treatment, counseling for infection prevention, and public health reporting. I will walk through each of these for *Shigella* generally and discuss some considerations for XDR *Shigella* specifically.

Supportive care is the mainstay of treatment for shigellosis and centers on fluid and electrolyte replacement. Oral rehydration therapy is often sufficient, but some patients may require IV fluids. Non-pharmacologic measures may help with patient comfort. Anti-motility agents such as loperamide should typically be avoided in shigellosis because they may prolong fever, diarrhea, and bacterial shedding.

Antimicrobial treatment can be helpful in the management of shigellosis. The goals of treatment are to reduce the duration of illness typically by one to two days, and to prevent secondary transmission by limiting shedding of the bacteria in stool. Antimicrobial treatment is typically recommended for patients with severe illness or risk factors for severe illness, such as immunocompromised. But patients with mild illness or who are already recovering may not require antimicrobial treatment. The choice of antimicrobial is complicated by several factors including availability, efficacy, route of administration, and resistance.

Here are some guidelines that may be familiar to clinicians in the United States. This is not an exhaustive list, but other guidelines tend to have similar recommendations. Here you can see that ciprofloxacin or other fluoroquinolones, azithromycin, and ceftriaxone are often recommended as first-line agents, while trimethoprim, sulfamethoxazole, and ampicillin are often recommended only once susceptibility results are known due to high rates of resistance. The obvious challenge here is that emerging XDR *Shigella* strains are resistant to all of these recommended agents.

Therefore, we'll next turn to some agents that have been proposed as potential alternatives to recommended treatments. Again, this is not an exhaustive list. This table shows some of the most common challenges in identifying a suitable alternative. I've started with resistance because,

although our working definition of XDR focuses on agents recommended for treatment, *Shigella* isolates are also commonly resistant to amoxicillin, chloramphenicol, nalidixic acid, and tetracyclines.

Next, some agents that work quite well for other types of diarrheal disease do not penetrate the intestinal mucosa well and, therefore, have limited clinical efficacy for *Shigella* specifically. These include first- and second-generation cephalosporins, amoxicillin, aminoglycosides like gentamicin and kanamycin, and nitrofurans.

And then some agents that have been shown to be effective against shigellosis are not available in the United States. We do not have access to oral formulations of chloramphenicol or pivmecillinam, for example, although you may see these agents recommended in some international guidelines. Likewise, older penicillins such as temocillin, and oral carbapenems like tebipenem are not currently available here.

And then some potential treatment agents have simply not been very well-studied for *Shigella*. I've put fosfomycin and carbapenems such as meropenem in this category. Although we do not currently have enough information to recommend either fosfomycin or meropenem for the treatment of XDR *Shigella*, these agents are worth a closer look.

This table compares fosfomycin and meropenem on some of the metrics that are relevant to the treatment of shigellosis. In terms of phenotypic resistance, CDC does not have data for fosfomycin because it is not included on our surveillance panel. But we have tested *Shigella* isolates for susceptibility to meropenem since 2016 and found no resistance. We have also screened all *Shigella* isolates from US surveillance isolates for genotypic resistance. Fosfomycin resistance genes have only very rarely been observed in *Shigella* isolates, and we have never seen genotypic resistance for meropenem. CLSI clinical breakpoints are available for meropenem but not for fosfomycin, which may make it more difficult for clinical laboratories to provide susceptibility information for fosfomycin.

Because many patients with shigellosis do not require hospitalization, oral treatments are often desirable. Fosfomycin is available as an oral formulation, while meropenem and other carbapenems must be given IV. Neither fosfomycin nor meropenem has been extensively studied for the management of shigellosis, but there is some limited information from clinical trials available for fosfomycin. Much of it is older, was conducted outside of the United States, or involved pathogens other than *Shigella*. Neither of these agents have an on-label indication for use for shigellosis in the United States. Finally, there are a few potentially relevant insights from the international community.

Interestingly, a 2021 study by Ono et al. reports that fosfomycin is currently the most prescribed antimicrobial for the treatment of acute infectious diarrhea in Japan, both overall and among children. In a few moments, we will also have our colleagues from the United Kingdom share their experience with an outbreak of XDR shigellosis, where both fosfomycin and meropenem were recommended as potential treatment agents.

So these difficulties in treating patients with XDR *Shigella* infections help to underscore the importance of doing all that we can to prevent them. Patients with shigellosis should always be counseled on prevention measures. Children should stay home from school or daycare, and adults should stay home from high-risk jobs while sick or until the health department says it's safe to return. During the two weeks after illness, patients should also abstain from sexual activity; wash hands often, particularly after using the bathroom; avoid preparing food for others; and stay out of recreational water.

Shigellosis is a nationally notifiable disease. Healthcare professionals and clinical laboratory should report all cases to their local or state health department and should also consult the health department for guidance on when patients may return to child care, school, or work because exclusion policies vary by jurisdiction. Finally, if you are a clinician or healthcare professional and would like to help CDC gather data to better understand XDR *Shigella*, you can report information about treatment response and clinical outcomes to entericbacteria@cdc.gov.

I'd like to wrap up by reviewing an approach to the treatment of XDR shigellosis. As you've likely already realized, we do not have all the answers today. But there are a few things we can suggest. First, it is worth reiterating that clinicians should always consider whether the patient truly needs antimicrobial treatment.

In this era of rapidly emerging resistance, it's important to remember that antibiotics can have side effects and sometimes do more harm than good. Next, clinicians should order a culture in patients who do require antimicrobial treatment and carefully review the AST results. Although some isolates are resistant to all recommended treatment agents, most remains susceptible to one or more, although it has become increasingly difficult to predict which one. For cases of XDR infection, it may be helpful to consult an ID specialist. They may not have all the answers, either, but a consult can often be helpful in terms of determining the best approach for an individual patient.

Clinicians should be aware that there is limited evidence-based guidance for the best management of XDR *Shigella* infections. For this reason, CDC does not have official recommendations for antimicrobial management at this time. However, it may help to be aware of what we know about resistance of XDR *Shigella* isolates to other antimicrobials, as well as treatment strategies that have been used internationally.

More information on the management of shigellosis is available. These slides including QR codes will be posted on the COCA website following this call.

And now we have come to our first knowledge check question. Among sequenced *Shigella* isolates reported to CDC in 2022, what percentage was extensively drug-resistant or XDR: A, 1 percent; B, 5 percent; C, 10 percent; or, D, 80 percent. I'll give you just a moment to reflect on that response.

Okay. The correct answer is B. In 2022, 5 percent of all *Shigella* isolates uploaded to CDC's PulseNet surveillance system had an XDR resistance pattern. This represents a marked increase

from just a few years ago, as you can see from this line graph. And I will now transition to Dr. Bachmann. Thank you.

Thank you. Today I will briefly cover aspects of the current *Shigella* outbreak relevant to the sexually associated nature of some of important opportunities that we have to improve sexual health. This slide demonstrates 2021 surveillance data increases in reportable -- I think I was muted, and I don't know where I -- I'm going to cover this slide again. Preliminary 2021 surveillance data demonstrate continued increases in reportable STIs, and congenital syphilis cases and the associated morbidity and mortality also continue to increase. Current epidemiology reveals that, while anyone can acquire an STI, the group's currently most impacted by these increases include young people, gay and bisexual men, pregnant people, and racial and ethnic minorities. Next slide.

Sexual health is threatened on multiple fronts. The Mpox epidemic saw the vast majority of cases transmitted through close personal, often sexual contact. Gonorrhea continues to challenge us with reports from the UK and more recently Massachusetts of strains with decreased susceptibility to cephalosporins, the only recommended treatment. Next slide.

A recent study evaluated the prevalence of STIs within 12 months before or after a confirmed *Shigella* case from six US jurisdictions between 2007 and 2016. The Y axis represents the proportion of individuals diagnosed with one or more STIs in a 24-month timeframe, and the X axis demonstrates the STIs of interest. Blue bars are male cases and burgundy bars female cases. As you can see, 20 percent of men with confirmed *Shigella* reported an STI within 12 months of their *Shigella* infection, approximately 8 percent each of gonorrhea, chlamydia, and syphilis. While not demonstrated on this slide, the same study also showed that the percentage of male *Shigella* case patients with at least one STI reported increased from 11 percent in 2007 to 28 percent in 2016 and that almost a quarter of these patients were known to be living with HIV. Next slide.

Similar findings were found when focused on *Shigella flexneri.* Next slide.

There are specific behaviors that are associated with sexually transmitted enteric infections, and they include any activity that results in feces from an individual with *Shigella*, even microscopic amounts, coming into direct or indirect contact with the partners' mouths. Some of these activities include oral anal sex, condomless sex, multiple sex partners, attendance at sex parties, and using social media to find sex partners. Many of these behaviors are also associated with STIs, including HIV. Next slide.

While it's important that we understand risk factors for XDR *Shigella* infection, we should not approach this infection in an isolated fashion, given the significant overlap of *Shigella* infections with other STIs including HIV. Sex is a basic part of life, and integrating sexual health into general healthcare simultaneously destigmatizes the issue and results in the provision of more comprehensive care. Next slide.

There are several practical steps that can be taken to integrate sexual health in the clinical care. The clinical environment should be welcoming. This starts with a culturally competent staff,

including front desk staff. It should extend in the physical environment as well. Sexual history should become a routine part of the social history. And, as providers, it is important for us to be introspective, aware of our own biases, and to not make assumptions that can interfere with the care that we are providing. Also, screening and vaccination should be offered per guidelines. Next slide.

There are various methods that can be used to take a sexual history. The five Ps is one approach. The provider starts by setting the stage for asking the sensitive questions. For instance, one could say, Now I would like to ask you some questions about your sexual history in order to provide the best care to you. Questions about partners may include questions about partner number and gender of sex partners. For sexual practices, a broad question could be asked like, Are you having sex of any kind, followed by more specific questions about the types of sex, whether that's oral, vaginal, anal, or other. These specific questions can give the provider insight as to whether the patient is at increased risk for enteric infections, for example. And it's important to take your cues from the patient in terms of their level of comfort and understanding. But being comfortable with these types of questions as a provider can go far in putting the patient at ease. In the interest of time, I cannot go into detail on the rest of these bullets, but I would refer you to the website on this slide for more information. Next slide.

In terms of screening, let's first talk about men who have sex with men. Gay, bisexual, and other MSM should be screened for gonorrhea and chlamydia at anatomic sites of exposure, syphilis, and HIV at least annually but more often, for instance, every three to six months if at higher risk for STI acquisition. Hepatitis A, B, and C screening should also be performed, as well as a digital and a rectal exam to screen for anal cancer. Next slide.

Women should be screened for gonorrhea and chlamydia if less than 25 years of age or if older and at risk. Syphilis screening and trichomonas screening should be performed in high prevalence areas or settings or if at increased risk. All women aged 13 to 64 should be screened for HIV through opt-out testing, as should any woman seeking evaluation treatment for STIs. There's new proposed guidance for hepatitis B screening that will include at least once-in-a-lifetime screening for persons 18 years of age and older, in addition to expanded recommendations for risk-based screening. And all adult adults over age 18 should be screened for hepatitis C. Next slide.

The 2021 CDC STI guidelines expanded screening recommendations for transgender and gender diverse individuals, which includes consideration for syphilis screening at least annually based on reported behaviors and exposure; HIV, hepatitis B, and hepatitis C screening. Gonorrhea and chlamydia screening should be based on current anatomy and gender of sex partners. Next slide.

Vaccination for other pathogens plays an important role in preventing infections that can be sexually transmitted, including hepatitis A, which is an indicator for men who have sex with men; and other individuals at increased risk of acquiring hepatitis A or at increased risk for severe disease from hepatitis A. Hepatitis B vaccine is indicated for most of the population now. And all adolescents should receive the HPV vaccine at age 11 to 12 with catch-up vaccination through age 26 and also should be offered vaccine based on shared clinical decision-making for certain adults 27 to 45 years of age. Next slide.

While on the topic of prevention, there are some basic actions that individuals can take to prevent sexually acquired enteric infection, including avoiding sexual activity with individuals with diarrhea or have recently recovered from diarrhea. Fecal oral exposure during sex may be reduced by washing the genitals, the anus, and hands before and after sex, as well as for the use of barriers like condoms and dental dams during oral genital and oral anal sex. Latex gloves should be used during fingering and fisting. And, finally, latex internal or external condoms should be used during anal and vaginal sex to prevent other STIs. Next slide.

So let's do another knowledge check. Which of the following steps can be taken to integrate sexual health into clinical care: A, include sexual history as a routine part of care; B, provide clinical staff with opportunities for cultural competency training; C, implement a syndemic approach to testing and vaccination strategies; or, D, all of the above. All right. Maybe -- okay.

Yes. All of the above. All of these are strategies to integrate sexual health into clinical care. Next slide. Next slide.

I'm going to go through these resource slides, and you'll have them at the end of the presentation. Next slide.

And move on to Miss Rachel Jervis. Next slide. Thank you.

Thank you very much. So today I'll be talking to you about Colorado's response to an outbreak of XDR *Shigella*. Next slide.

On August 29, during a routine weekly lab epidemiology whole genome sequencing meeting, our CDPHE lab colleagues notified us of four *Shigella sonnei* cases within 0 to 1 allele differences. All of the cases were men in the Denver Metro area. On September 6, CDC notified us that these cases were part of a multistate cluster with cases in California and Florida. On September 9, an infectious disease doctor treating one of these cases requested a treatment consultation. We connected this physician with CDC. And while CDC cannot give clinical guidance for patients they're not treating, they were able to talk through options with the doctor and share a recent paper about XDR *Shigella* cases in the UK. Next slide.

As of January 18, there were 17 Colorado cases in this multistate XDR *Shigella* cluster with onset dates ranging from late July to late December. Next slide.

Each case receives a thorough public health interview to collect symptom information, collect exposure data, provide disease control guidance, and detect and solve outbreaks. Through these case investigations and medical chart review, we learned that the median age of our cases was 40. All cases resided along the front range of Colorado. Almost half were hospitalized. Eighty-two percent were male, and 59 percent of them reported being a man who has sex with men. Twenty-four percent were experiencing homelessness, 29 percent reported drug use, and 59 percent were immunocompromised. It's worth noting that five of the cases were lost to follow up, which further underscores the importance of whole genome sequencing to our public health investigations. Next slide.

In response to the increasing number of cases and treatment concerns from providers, we issued a notice to our health alert network. The HAN included three ways that clinicians can join public health in responding to XDR *Shigella*. Next.

One, request antimicrobial susceptibility to guide treatment decisions when treatment is indicated. Two, report all *Shigella* cases to public health, and submit either isolates or clinical material in accordance with our state reporting rules. And, three, counsel patients with *Shigella* not to attend childcare and/or work in healthcare, food service, or child care until cleared by public health. And educate patients on how to reduce the risk of sexual transmission of diarrheal illness. Next slide.

Our HAN got some unexpected attention from members of the MSM community on TikTok, including more than 30,000 likes on the day that I happened to screenshot it, which, honestly, that was great for us because -- next slide –

Our government issued public health materials are a bit more buttoned up. And while they exist and they're available on our website, we've also handed them out as printed palm cards at events like Denver Pride and even paid to have them as advertisements on dating apps. Next slide.

As you can see here, the messaging for this public education was really addressed to and focus on men who have sex with men. Next slide.

However, it's really important that we are updating our public education as we learn. And we receive feedback from members of the LGBTQ+ community during Mpox response that really everyone needs to know about all of the ways a pathogen is transmitted, and we shouldn't really be parsing out our health education messages the way we were. So we worked with our communications team to create a new *Shigella* toolbox that has more inclusive and extensive information about *Shigella*. And you'll see that we've shifted our language around behavior-based sexual transmission information versus person-based. So it now reads that, people who engage in oral-anal or oral sex are more likely to get *Shigella* infection. Next.

So you have another self-knowledge check. So during an XDR *Shigella* outbreak, public health case interviews are used for all of these except: A. Collect symptom information; B, collect exposure data; C, determine antimicrobial resistance of *Shigella*; D, provide disease control guidance; and, E, detect and solve outbreaks. Next. So the correct answer is C. While public health case interviews are incredibly valuable, they cannot determine antimicrobial resistance; and laboratory testing is required for that. Next slide.

And, with that, I will pass things along to our next presenters. Thank you.

Hello everyone. And thank you for the invitation to present today on Lessons learned from an outbreak of sexually transmitted, extensively drug-resistant *Shigella sonnei* in the UK between 2021 and 2022. Next slide, please.

So this figure shows trends of *Shigella* species diagnosed in England by gender and travel history. So I want to draw your attention to the dark blue dashed line, which is the number of

diagnoses among adult men without a recent history of foreign travel. As this data is from laboratory surveillance, which does not collect information on sexual orientation, we use adult males without a history of foreign travel as a proxy for gay, bisexual, and other men who have sex with men, herein referred to as GB MSM. Data is presented quarterly from 2015 to 2022. And we'll see an increasing trend of *Shigella* diagnoses among GB MSM between 2016 and 2019 and then a substantial decline in 2020. And then, from quarter 3 of 2021, a sharp rebound in the number of diagnoses among GB MSM so that, by the end of 2022, we were back to pre-pandemic levels. Next slide.

If we now look at *Shigella* diagnosis among GB MSM in England by species, we have *Shigella flexneri* in the dashed line and *Shigella sonnei* in the solid line. And we can see this substantial and rapid increase in *Shigella sonnei* diagnoses from quarter 3 2021, as indicated by the arrow. When we identified this at the time, we did further investigations to understand this increase, such as understanding if a single strain was causing this increase and the antimicrobial resistant profile of cases within this increase. Next slide.

So these further investigations included use of whole genome sequencing, and this revealed that the increase was due to a single 10 SNP cluster called CC152 and also called UK MSM Clade 5. So, in September 2021, not only did we see a rapid and substantial increase of this cluster of *Shigella sonnei* but there was a concerning trend -- change in the antimicrobial resistance profile of isolates from multi to extensively drug-resistant. And this included resistance to ceftriaxone. This can be seen in red in the figure. Next slide, please.

So we set up an incident management team to take forward further investigations and public health actions. So as of the 21st of January 2023, we've had 185 confirmed cases in England. The vast majority so 95 percent were adult men with a median age of 36 years. Among male cases, 92 percent was thought to be GB MSM. Cases reported classical symptoms of diarrhea, abdominal cramps, bloody stools, and fever, which lasted for a median of 12 days. So nearly half of cases attended the emergency department, and nearly a quarter were hospitalized. And just over half required antimicrobial treatment. Seventy-three percent of cases were HIV negative and taking HIV pre-exposure prophylaxis, whilst only five cases reported living with HIV. Thirty-eight percent of cases reported being diagnosed with another bacterial STI in 2021. Next slide, please.

So in the initial phase of the outbreak, we used an enhanced surveillance questionnaire to collect additional epidemiological information so that we only have enhanced data for a subset of the total outbreak, so 44 percent to be exact. So this enhanced information validated our proxy of presumptive GB MSM in the first instance and found that 90 percent of cases self-reported being a gay or bisexual man. Eighty-five percent reported being of any white ethnic background. And we used this enhanced data to understand contexts of sexual transmission and found that most cases acquired the infection during sex with one or more new partners, often met through geospatial apps such as Grindr or Tinder. These were either private sex events or in dark rooms or sex clubs. So when we asked cases their suspected route of acquisition, the majority reported sex between men. But there were small numbers of cases reporting household transmission, occupational exposure. But, also, this route of acquisition was unknown. The majority of cases

suspected they acquired their *Shigella* infection in England, but a few reported other European countries. And I'll now hand over to Gauri.

Thank you, Hannah. So I'll be covering the microbiological and clinical management aspects of this outbreak. In England, we routinely use whole genome sequencing to characterize isolates referred from the hospital laboratories to the *Shigella* reference laboratory. The box on the left shows you the antibiotic resistance determinants that we found in the outbreak strain using whole genome sequencing. So the first resistance determinant of concern was a beta lactamase, CTX-M-27, which confers resistance to penicillins and third generation cephalosporins. And what we found was that it was present on a plasmid and, therefore, was a potential transmissible resistance. The other determinants included resistance to aminoglycosides erythromycin, [inaudible] trimethoprim, sulfonamides, and tetracycline. The strain was susceptible to carbapenems, chloramphenicol, fosfomycin, and temocillin. The figure on the right depicts the annotated phylogenetic tree of the strains of *Shigella* which were isolated from a subset of cases. What it shows is the strains are very closely related and clustered quite tightly into a monophyletic cluster, indicating a common source, which belong to this sequence type 152. We are still continuing to see cases of this outbreak strain, indicating ongoing transmission. Next slide, please.

So an important part of the outbreak management included raising awareness of XDR *Shigella* amongst primary healthcare physicians, hospital physicians. And some of the key messages were that the main thing is to take a sexual history in cases of diarrhea in adult patients. The second key message was to ask for a culture and antibiotic sensitivity in addition to enteric PCR test if you suspect shigellosis. The next message was to use antibiotics if there were severe symptoms, for example, bloody diarrhea, sepsis; hospital admissions in patients who had prolonged diarrhea, which was beyond seven days; or if they had underlying immunodeficiency. We recommended that they start using antibiotics as per their local hospital policies and then rationalize once they got the microbiology results back. Some of the oral treatment options we recommended were chloramphenicol, pivmecillinam, and fosfomycin. Pivmecillinam was given, recommended a dose of 800 milligrams TDS and fosfomycin in 3 grams on day 1, 3, and 5. These were off-label and unlicensed. And what we recommended was that they use these oral antibiotics for uncomplicated cases, for example, cases with prolonged diarrhea. The efficacy of these drugs in serious infections is not known and, therefore, they should not be used if a patient's hospitalized or has severe sepsis. Intravenous agents for sicker patients included ertapenem or meropenem for 3 to 5 days, they were asked to notify the infections and follow the usual public health exclusion measures. The British Society of Sexual Health has come up with a guideline for the management of sexually transmitted enteric infections in 2022, and some of these recommendations are included in that. Next slide, please.

In addition to that, there was advice given to patients if there was advice on sexual hygiene and hand washing and avoidance of any sexual contact for one week after complete resolution of symptoms. So these are some of the campaigns that were launched. And we had a lot of engagement with sexual health clinics. Next slide, please.

So, this is the final question. A 45-year-old fit male presents with watery diarrhea 7-8 times a day for 3 days. He suspects he has food poisoning from chicken wings which he consumed in a

local restaurant 3 days prior. What additional history would you take: a recent sexual history, recent foreign travel, profession, severity of illness, recent contact with healthcare or antibiotic use, all the above. Next.

So the answer is all the above, and the rationale for that is shigellosis is one of the differentials for gastroenteritis in men and including GB MSM, and it should be suspected in all adult men. A majority of the cases in developed countries now are in GB MSN. And a lot of patients did not necessarily or do not associate illness with a recent sexual encounter. Infection can be acquired by extensive sexual networks home and abroad, and risk of transmission may be enhanced by use of dating apps. Certain professions have criteria that must be met before they are returned to work. Most patients recover from shigellosis without antibiotics, but severe cases might require antibiotics and hospital admission. Previous antibiotic use or exposure to healthcare settings may increase selection for resistant pathogens. Next slide, please.

Thank you. Those are my acknowledgments and contact details. Thank you very much. If I can hand over to the moderators, please.

Presenters, thank you so much for providing this timely information to our audience. We will now go into to 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. And please note that we often receive many more questions than we can answer during our webinars.

So our first question for our presenters is, Would working in a high-risk location or setting be a supported reason to prescribe antibiotics to prevent spread?

This is Louise Francois Watkins from CDC, and I can take a stab at answering that question. So I'm interpreting this to mean, if you are seeing a patient who works in a high-risk setting, for example, a healthcare setting or a food handling setting or something like that, is that a reason to give your patient antibiotics. And it's not essential to give antibiotics to a patient just because of their occupation. If the patient is otherwise well and recovering, it's not, you know, clinically indicated. However, many states do have exclusion policies, meaning that they restrict who is able to return to work in high-risk occupations. So this -- these policies do vary according to different health jurisdictions. But, in some cases, it may be advantageous to try to find an appropriate antibiotic and to treat the patient because it can reduce the duration of shedding; and it can sometimes help people to get back to work faster. Thank you.

Thank you very much. Our next question asks, Is fosfomycin for shigellosis given IV in Japan in that case presented? Or is the lower dosing for oral fosfomycin that's used for cystitis adequate for treatment?

This is Dr. Francois Watkins again from CDC. So in that paper by Ono et al., the authors were looking specifically at oral treatments. So this -- none of these patients were treated with IV fosfomycin.

They did not go into the details of the dosing, so we don't have information about exactly what doses were most -- or dosing regimens were most common in Japan. Thank you.

Thank you very much. Our next question asks, Can you differentiate risks and concerns about transmission among people with HIV based on whether they have well-treated HIV in the presence or absence of advanced HIV disease?

This is Laura Bachmann. I'll take a stab at that but may ask some of my enterics colleagues to pitch in on if I misstate. So, in general, I mean, there's a significant proportion of individuals that based on the epidemiology of the current outbreak are coinfected with HIV. And people with more advanced HIV may have more severe presentation, clinical presentation. So, you know, in terms of how that translates into actual transmission risk, I'm not sure that we have strong data to support that.

But, you know, theoretically, I think there's more concern with shedding in someone who has very, very low CD4 count compared to someone who, you know, is over 500. But I would invite my enterics colleagues to correct me if I misstated anything there.

Wonderful. This is Naeemah Logan from CDC. And I would just add onto that. You know, there's a really interesting article by Mohan and colleagues. It's titled, What is the overlap between HIV and shigellosis epidemics in England. And the study investigated the overlap between *Shigella* and HIV epidemics, linking to public health surveillance datasets. And they found -- they were also looking at travel history. So they found that, among cases of *Shigella* without travel history and diagnosed with HIV, 91 percent were reported to be MSM but that also, in most cases, HIV preceded the *Shigella* diagnosis. And most patients with HIV, the most recent viral loads were undetectable. So that's an interesting study that I wanted to share.

And then also, just to round this question out, you know, HIV infection has several effects on *Shigella* transmission, and I believe that's what the question is getting at as well. So even though compromised persons may have extended carriage of *Shigella* species and may have prolonged symptomatic or asymptomatic shedding, HIV infection may also have some nonbiologic effects on behaviors, as well. There have been papers that have commented on the social adaptation of people living with HIV in the age of hard [phonetic] and how that may affect behaviors, which may influence transmission of these drug-resistant pathogens. Thank you.

Thank you very much. Our next question asks, Is there any data supporting use of ertapenem instead of meropenem for extensively drug-resistant shigellosis?

Hi. This is Dr. Francois Watkins from CDC again, and the answer is not to our knowledge. We do examine the sequences for resistance elements that would confer resistance to carbapenems, and we've never seen these in any *Shigella* isolates. So we don't have any isolates that appear like they're going to be resistant to any of the carbapenems at this point within our collection of isolates in the United States. So it makes it difficult to look at differences between different drug classes. Phenotypically at CDC, we do only test meropenem. But we don't have a reason to think that susceptibility to meropenem and ertapenem would be -- would be different for *Shigella*. Thank you.

Thank you. And we have time now for just one last question. And the question asks, Can you share any data on extensively drug-resistant *Shigella* infections specifically in pediatric patients?

This is Louise Francois Watkins again. So what we know about XDR *Shigella* infections in the United States, which are still relatively uncommon overall, is that most of these are occurring in adult men, as you saw from the data that Dr. Logan presented earlier in this talk. However, about 5 percent of these XDR *Shigella* infections have occurred in children, which we defined as people under age 18. So we do have reports of infections in the pediatric population also. It will probably take us more time to be able to really understand if there are any age-specific considerations for the management of these types of infections, given how rare it's been up to this point. Thank you.

And this is Naeemah Logan from CDC and just to chime in. So, you know, the CDC surveillance data showing that kids younger than five years old, tend not to have drug-resistant infection. So susceptible infections are most common in that age group. But drug-resistant *Shigella* infections are more common among adults within this very vulnerable group. And so we mentioned several of those. Those are MSM. Those are people experiencing homelessness. Those are people living with HIV and international travelers.

Thank you very much. And, again, thank you to our presenters for answering these questions and for sharing your time and expertise with us today.

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