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Moderator: **Derrell Powers**

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Dr. Gail Bolan: Good afternoon to all of you, either good afternoon or good morning. And I'd like to welcome you to the 2021 STI Treatment Guidelines webinar. And I'm joined by my colleagues, Kim Workowski, Laura Bachmann, and I'm Gail Bolan, the Director of the Division of STDs at CDC. We're going to start with an overview of the state of STIs in the nation. Laura Bachmann, who is the chief medical officer at CDC in the division, as well as the clinical team lead in our Program Development and Quality Improvement Branch will follow my introductory overview comments. And then, we will have Dr. Workowski present in detail what are the proposed changes to the draft guidelines that we have today. We would like to let all of you know, that there are no disclosures at this time.

And so, I'm going to move on to an overview of this webinar. The intended audience is interested parties, specifically clinicians and other staff who provide clinical care for persons with, or at risk for, STIs in public and private healthcare settings. And we are going to, as I said provide an overview of our draft guidelines highlighting key recommendations, important changes and additional resources. We are allowing potential users of the proposed updated guidelines to ask questions and provide feedback during this webinar. So, it's important that you figure out on this webinar platform how you can put comments into the chat box. We're only taking comments during this webinar today, so please put your comments and questions in the chat box and a recording of the webinar and the accompanying transcript will be posted online at www.cdc.gov/std/treatment/default by January 17, 2021. And our responses to these questions

from the webinar will be available February 15th. And if you have other questions, you can also contact us at STDTXguidelines@cdc.gov.

I'm sure many of you are aware of the current state of the STI epidemic in the United States, we had sort of unprecedented increases. And every year in the last six years, we seem to be at an all-time high. So, based on our preliminary data for 2019, our surveillance report will not be coming out until January, a total of 2.49 million combined cases of chlamydia, gonorrhea and syphilis were reported to CDC. This is the sixth year of these steady increases. And, the majority of our primary and secondary syphilis cases continued to be among men who have sex with men (MSM); however, rates among women of reproductive age continue to rise steadily.

This is a graph that some of you've probably seen of our congenital syphilis epidemic. Again, in 2019, by the blue bars, we've had almost the highest number of cases of congenital syphilis ever reported to CDC. Forty-three states now have reported at least one case of congenital syphilis in 2019, but half of our reported cases still remain concentrated in two states, California and Texas. We certainly believe that congenital syphilis is a sentinel event that we can prevent, but we're finding there's a lot of gaps in opportunities in the healthcare system, as well as in public health, and we are working hard to reverse these trends.

We also want to acknowledge, as many of you know, that COVID has had a significant impact on our ability to do STD prevention and control, especially at the local level. We recognize that many STD programs have either had to close their STD clinics or reduce capacity to essential workers and essential patients with symptoms or contacts because of not having enough PPE equipment, not being able to test for COVID and not having enough staff who have been diverted to COVID clinical work. So, we're very concerned that, especially asymptomatic individuals who represent the majority of patients with STIs, are not getting the recommended screening services. Therefore, they don't know they're infected because their infection is asymptomatic and they're continuing to spread their infections because they haven't been

able to be tested and appropriately treated in a timely fashion, which we would be doing under normal circumstances.

Our challenges have also been compounded by the fact that at certain times we've had some drug shortages, specifically azithromycin. Some of this was related to supply chain disruption. Some of this was related to some recommended treatments for COVID by some people in our administration, but those shortages seem to have been resolved. We're now dealing with a more concerning shortage of diagnostic, molecular test kits supplies, and there's been surveys done by ASM that are monitoring the number of Clinical Laboratory Improvement Amendments CLIA certified labs. As of the week of December 2, 45% of 142 labs are reporting shortages of supplies for molecular detection of STIs, and that's mainly the nucleic acid amplification test (NAATs) for chlamydia and gonorrhea. I would also note that those of us who also work on the public health side recognize it's not just test shortages that are problems in other areas. The machines that are used to run these tests are also the same machines that are used to run COVID tests, and those machines have been diverted to COVID testing.

Also, microbiologists in public health labs have been diverted to COVID testing, so we've got kit shortages, machine shortages and some personnel shortages contributing to this concerning trend, although we hear the shortages may be improving as kit shortages and supply shortages may be resolving. I like to say that, you know, it's important to recognize our main strategy for STD prevention in the United States. And if you happen to have been around yesterday, there was the release of the first federal STI National Strategic Plan by the Department of Health and Human Services (HHS). And if you read the plan, it mainly talks about the need for many federal agencies, in the populations they serve, to do a better job of diagnosing and treating STDs in their settings, not expecting those patients to come to an STD clinic or seek care in the primary care network.

We know there's significant health consequences related to women's reproductive health, infant morbidity, and mortality in HIV transmission, in our current estimates that are being updated and will

hopefully be published in time for the NASEM report that's being developed at least using older data. We were, a number of years ago, spending $15 billion on direct medical costs.

Our populations at greatest risk for STIs really haven't changed. Youth in the age group of 15 to 24 represent nearly 50% of STIs but do not represent 50% of the sexually active population. Racial and ethnic minorities have always been hardest hit. In 2018, for African Americans, chlamydia was 5.6 times the rate of whites, gonorrhea 7.7 times and primary and secondary syphilis 4.7 times, and MSM have persistent morbidity with syphilis and account for more than half of the syphilis cases.

And, there's a high HIV coinfection rate among those populations. I think we were very pleased at CDC that the HHS steering committee, that represented many federal departments and HHS departments, recognized the need to prioritize. And they have actually included these populations in their plan as priority populations. Our key principles to prevention are outlined in our treatment guidelines and the sections have really not changed. We want to make sure that providers are doing the appropriate risk assessments and behavioral counseling, including motivational interviewing to reduce STI acquisitions. Obviously, we want to screen asymptomatic persons according to national recommendations. We want to make sure we do absolutely timely diagnosis and treatment of individuals with symptoms associated with STIs. We need to manage sex partners, and we need to remember we actually have some vaccines, HPV and hepatitis A and B, that should be part of the care if you are serving people at risk for STIs in your clinical setting.

And again, we always say that we are not going to be successful preventing STIs sitting in Atlanta. We need our clinicians. We need our clinicians knowledgeable about the role they play. And, it's important for clinicians to be culturally humble and competent and understand how stigmatizing STIs are for some individuals and how some individuals need trauma informed care. But, it's really critical to make sure you have a welcoming environment because that's when patients make judgements about the type of care

they're receiving. That routine sexual history and risk assessments are being done in all populations, don't make judgments about people's sexual activity based on some biases providers may have.

Screen appropriately, not just for STIs. We want to make sure that at least people serving patients at risk for STIs, as we know, there's a lot of co-occurring conditions and we need to do a better job of screening for substance use disorders, alcohol, depression, and intimate partner violence. Obviously, STD specialists may not have time to deal with all those problems, but there at least needs to be more linkage to services to address these other co-occurring conditions. Because we're not going to solve our STI epidemic without addressing needs like homelessness, unstable housing, substance use disorders, et cetera. Make sure you vaccinate, make sure you have some prevention messages that you can offer your patients, including condoms and pre-exposure prophylaxis for HIV and HIV post-exposure prophylaxis, and make sure appropriate diagnosis and treat, and that's what our guidelines are for. So, you have something you can look up and know what the latest evidence is and how you should be managing your patient, and again paying attention to partner services.

If you can't offer pre-exposure prophylaxis (PrEP) yourself, make sure that you're linking patients who could benefit from PrEP, and those are obviously many patients, especially MSM with STIs. There's clear data that now estimates about 10% of new HIV infections are attributable to chlamydia and gonorrhea among MSM and the risk of acquisition for HIV is significant within the next year. So, we used to always talk about the coinfected patients and the needs for their screening. It's also now just as important to look at people who are not living with HIV, but have STIs that really could benefit from PrEP.

We rely on you to report cases. It is important to us because we fund our state and local health departments with a formula that is based on reported cases, as well as the proportion of the population that is at risk for STIs, which we defined as of reproductive age. So, it's not just reporting cases for us to be counting cases, there are people behind these cases and we actually are targeting our resources

based on morbidity and population at risk. So, with that overview, I want to thank you. I am going to turn it over to Dr. Bachmann to talk about the guideline development process. Laura.

Dr. Laura Bachmann: Thank you, Dr. Bolan. As Dr. Bolan mentioned, healthcare providers play a key role in combating the STI and HIV epidemics by increasing the appropriate diagnosis and treatment of STIs. Physicians and other healthcare providers play a critical role in reducing the severe impact of these infections. The dissemination and use of the CDC STI Treatment Guidelines play a role in this effort as it is the most widely referenced and authoritative source on STD treatment and management in the United States. The updated 2021 STI guidelines advise physicians and other healthcare providers on the most effective methods for risk assessment, diagnostics, evaluation, treatment regimens, and prevention and vaccination strategies. The guidelines should be applicable to various patient care settings, including family planning clinics, health department settings, private physician offices, managed care organizations and other primary care facilities and all those guidelines emphasize treatment prevention, strategies and diagnostic recommendations are also discussed.

Keep in mind that the CDC recommendation should be regarded as a source of clinical guidance and not as standards or inflexible rules. Also, keep in mind that the guidelines focus on the treatment and counseling of individual patients and do not address other community services and interventions that are very important in STI and HIV prevention. A blueprint for developing trusted guidelines was outlined by Graham et al in 2011 in an IOM (Institute of Medicine) report. And there were several key characteristics of robust trustworthy guidelines that were discussed. One, they're based on a systematic review of the evidence. They were developed by a knowledgeable, multidisciplinary panel of experts and representatives from key effected groups.

Important patient subgroups and patient preferences are considered as appropriate. And the guidelines are based on an explicit and transparent process that minimizes bias and conflict of interest. The guidelines should provide a clear explanation of the logical relationships between alternative care options

and health outcomes and provide ratings of both the quality of evidence and the strength of the recommendations. And finally, guidelines should be reconsidered and revised as appropriate when important new evidence warrants new recommendations.

I'm going to briefly take you through the CDC DSTDP process as outlined on this slide. These guidelines were developed by CDC staff who worked with subject matter experts from other federal agencies, non-governmental academic and research institutions, and professional medical organizations with expertise in STI clinical management

In 2018, CDC staff identified key questions regarding treatment and clinical management to guide the update of the 2015 STD Treatment Guidelines to answer these questions and synthesize new information available since the publication of the 2015 guidelines. Subject matter experts (SMEs) collaborated with CDC staff to conduct a systematic literature review in June 2019.

The SMEs presented their assessments of the literature review at an in-person meeting of governmental and non-governmental participants, and each key question was discussed. Pertinent publications were reviewed in terms of strengths, weaknesses, and relevance, and participants evaluated the quality of evidence, provided their input, and discussed findings in the context of the modified grading system used by the USPSTF. CDC staff also reviewed the publications of other professional organizations. Discussions culminated in a list of participant opinions on all the key STI topics for consideration by CDC.

CDC staff then independently reviewed the tables of evidence prepared by the SME's individual comments from the participants and professional organizations and existing guidelines from other organizations to determine if revisions to the 2015 guidelines were warranted. CDC staff ranked the evidence per the USPSTF's modified ratings, developed draft recommendations that were then peer reviewed by public health and clinical experts. And that brings us to today's public comment webinar.

There were a few several prominent themes from the STI treatment guidelines meeting that I'm just going to briefly cover with you. The overarching theme was anti-microbial stewardship. Microbial stewardship has garnered increasing attention since the 2015 guidelines were published and the increasing awareness of the negative impact of anti-microbials on the microbiome, as well as the collateral damage, including the development of resistance on commensal organisms and pathogens, emphasized the need to minimize antibiotic exposure, unless the benefit of antibiotic use clearly outweighed the risk.

There was an increased emphasis on pharmacokinetics and pharmacodynamics drug properties by therapeutic agent, by anatomic site of infection, whether that be the oropharynx, rectum, or the genitals and by body weight. This was of particular relevance in the development of the updated gonococcal treatment recommendations, some of which were released yesterday in the MMWR as a special policy note.

And finally, consistent with anti-microbial stewardship principles, resistance guided therapy was discussed for both *Mycoplasma genitalium* and *Neisseria gonorrhoeae.*

Highlights for the meeting included a name change in the document, which I will cover shortly. There were updated treatment regimens that will be discussed for gonorrhea, chlamydia, trichomonas vaginalis and pelvic inflammatory disease (PID).

The prevention section of the document was expanded with more emphasis on HIV pre-exposure prophylaxis, post-exposure prophylaxis and expanded language around expedited partner therapy (EPT) for MSM. Finally, screening recommendations for specific special populations and for specific pathogens were expanded.

So, let's talk about the name. This is the most noticeable change in the document. This document will now be known as the STI Treatment Guidelines. There's been a lot of conversation about the use of the

term STI versus STD through the years and STI, as many of you know, is a term that refers to an organism that has infected a person's body via sexual contact, while STD is a recognizable disease state that develops from an STI. It was felt that the STI term was more inclusive and consistent with our goal to prevent and treat infection before developing disease. And this term also recognizes the asymptomatic nature of the vast majority of these infections.

So, with this it is now my pleasure to introduce the lead author for the 2021 CDC STI Treatment Guidelines, Dr. Kim Workowski. Dr. Workowski is well known to many of you. She's a medical consultant for the CDC, and she's a professor of medicine in the Division of Infectious Diseases at Emory University. Dr. Workowski has spent her career on the front line, taking care of patients, training future generations of healthcare providers, and conducting the cutting-edge research that informs the ever-evolving standard of care. Dr. Workowski started working with CDC on this document in 1998, and this is the sixth document that she has led. Welcome, Dr. Workowski.

Dr. Kim Workowski: Thank you Dr. Bachmann, and good morning and good afternoon to everybody. What I'm going to try to do, in a short period of time, is talk about a huge document and kind of distill down what we think are the most important additions, deletions, and expansions of the document. Since I started back in 1998, the number of pages and the number of references have increased and that has a lot to do with the ever expansion of our literature, the integration between HIV and STIs, and the important information that we need to get to you on an evidence-base. And so, before I even get started, I want to thank everyone involved in the development of this process. This is almost like birthing a baby. It takes a long time, and we're almost there. But labor is very difficult. Every time we go through it, in terms of the final product.

We wish we would have had these to you in 2020, but then came COVID, and we're doing our best and working as fast as we can to get these advances in information to you in the field. So, the next couple of slides, I'm going to talk about what is new and what has changed and would welcome your comments. I

want to tell you first, that these guidelines are a complement to the guidance that was released earlier this year for quality STI clinical services that encompass primary care and specialty care settings, Recommendations for Providing Quality Sexually Transmitted Diseases Clinical Services, 2020. So, this is a companion document to the STI guidelines.

So, let's go ahead and get started. I've decided to talk about the prevention section first and kind of go the way the guidelines go with prevention. I'm not going to talk about every single section, but I thought we would discuss what's most important. Of course, there's specific attention to the behavioral and biologic risk assessment. What's a little different in there is the modification of the five-p's to make it more gender neutral, and the general theme throughout this is to really stress harm reduction as part of this assessment. As Gail previously mentioned, there's particular attention to pre-exposure vaccination for HPV, hepatitis A and hepatitis B, particularly with the new recommendations that came out which we'll talk about for hepatitis A, There's updates on male latex condoms, male circumcision, and emergency contraception.

There's some expansion in terms of the sections on PrEP and post-exposure prophylaxis (PEP), and there are separate sections, both for HIV and STI. And the reason here is not to recommend their use, but to talk about them and realize that they exist. People have performed some studies on doxycycline PrEP and doxycycline PEP. Additional studies are underway or in development, and we felt as important to mention that in the guidelines, there's also a section on U=U or undetectable equals untransmittable, which was very important to put into this document. We've also added a new section on multipurpose prevention technologies. These are methods that combine STI/HIV prevention with pregnancy prevention, and it is important to think about this as a package kind of going forward. I already mentioned the importance of aligning with the recommendations for the QCS guidelines.

There also are recommendations on retesting because our retesting rates remain low and reminding people that after chlamydia, gonorrhea, and trichomonas, a three-month test post-therapy is

recommended due to the high incidence of reinfection. Partner services. This was mentioned a little bit before. I think what's important here to mention is that the language is a little bit more permissive in MSM. There is limited data, but, because of the potential for bacterial STIs in MSM partners, the wording we'll talk about shared clinical decision-making between a client and a provider to individualize and see what works best for them.

In the special population section, you saw highlights of the increase that we're seeing in congenital syphilis, which is just very unprecedented. If you actually look from 2013 to 2018, the rates in the U.S. have increased markedly. As you know, most states require some prenatal syphilis testing, but there's a high variability to those requirements. So, there's a little bit more intention in this section, as well as the syphilis in pregnancy and congenital syphilis section on what are the risk factors that would put pregnant women at risk for syphilis acquisition during pregnancy, and also, thinking about the community one lives in with a high syphilis morbidity. As you remember from the 2015 guidelines, there was a range from 24 to 28 weeks (note: this was misspoken and should have been 28-32 weeks). If somebody was thought to be at high-risk we're now defining that at 28 weeks and then in women that are at high risk, again, repeating that at delivery.

The other new component for pregnant women is the recommendation from CDC regarding universal testing for hepatitis C. And what this means for pregnant women is, in communities that have a prevalence of greater than 1.1% that every pregnant woman with every pregnancy gets rescreened for hepatitis C. In the adolescent section, there is some more permissive language for the use of a rectal chlamydia testing and gonorrhea testing to be considered in females based on reported sexual behaviors and exposure. And this is one through shared clinical decision-making between the patient and the provider. Also, there's a discussion of PrEP in adolescents and persons in correctional facilities. The use of gonorrhea, chlamydia, and trichomonas opt-out testing, which is important because of the high prevalence of these infections in correctional facilities.

In the MSM section, there's an expansion of talking about PrEP and PEP for STI prevention. We thought it was important to put this in this section, as well as in the clinical prevention guidance as many individuals use our guidelines and go to the specific section they're looking for instead of reading the whole guidelines entirely.

There's also some expanded section on the importance of rectal and pharyngeal testing. A new section on counseling education, a new section on HPV, and the importance of doing at least annually digital, anal rectal examination. And we'll have some expansion, talk a little bit later, about the expansion of the anal cancer section, and then, there's another subsection on enteric pathogens that can be sexually transmittable.

The other thing that we've expanded on is, as you know, that there's a recommendation for HIV screening at least annually, and there's now some new language to consider more frequent screening based on individual risk behavior. So, it can be a decision that's undertaken between the person and the provider. The other thing that we're really proud of is that the transgender and gender diverse section has been really expanded based on excellent expertise and input. It really has now some nice screening recommendations that are based on behavior and sexual practices, and really talk to individuals that have undergone genital reassignment surgery with the creation of a neovagina or a vaginalplasty using an intestinal graft, and thinking about the potential complications that can occur from those type of surgeries and what STIs folks could be at risk for.

Moving to the next section on genital anal, we've added perianal ulcers, similar to what we talked about before is the importance of coupling HIV and STI testing. HIV testing should be performed on all persons not known to have HIV infection who present with genital anal or perianal ulcers. This is going to be clearly stated in the guidelines. The other STIs that we don't see much in the U.S. are still in the document, chancroid and granuloma inguinalein particular, --it is uncommon in the United States. And as you know because sexual contact is the primary road of transmission in the United States, if there is a

diagnosis of chancroid in infants and young adults, especially in the genital or perinatal region, we still are suspicious of sexual abuse.

However, we do know that chancroid can be a cause of non-sexually transmitted cutaneous ulcers in children in tropical regions. And we felt it was important to put that in the document. So, that will be included for chancroid. For granuloma inguinale there was a very rich discussion about whether we should still have this in the guidelines because it's an uncommon infection. But the thought was that we're going to still have it in the guidelines because as you know, things may come back up, and they may resurface, and we need to have a reference for individuals to look in case they come across a case of granuloma inguinale. And there are some antimicrobial changes, but again, that's an uncommon infection, but we're going to be leaving it in the document.

Moving to genital herpes, herpes PCR is the preferred diagnostic test, but language regarding the use of culture, especially in cases of acyclovir resistant herpes need to be retained. There's been a significant revision in the serologic testing section, the type specific serologic testing. What hasn't changed is the indication for who you should test. That includes patients that have recurrences that have a negative PCR or culture folks that have signs of general herpes, but no laboratory confirmation and a partner with genital herpes. So, there's really some more granular discussion about the use of herpes testing in particular, the serologic two-step testing because we know that the use of the immunoassays is often falsely positive at low index values. It really goes into specifics in terms of what constitutes a low index value and when you should use confirmation you can see that listed on the slide. I won't go into the particulars, but I think it's really important to point out that a separate test using a different antigen needs to be used.

And so, the recommendations in the guidelines will call for a Biokit or a Western blot as the second test for confirmation. There are also new sections on we're separating out herpes type one and herpes type two, in terms of different counseling messages. I think it's important to remind providers about herpes

hepatitis, because this is associated with fulminant liver failure and high mortality, even though it's an uncommon event. In the instance in pregnant women that presents with fever and unexplained, severe hepatitis, disseminated herpes should be considered and empiric acyclovir should be initiated. So, felt it was very important that folks really knew about herpes hepatitis, because it's one of those emergencies that you can really make a great intervention by starting acyclovir empirically.

And then, in the section on herpes and HIV, felt it was important to include some data that has been published in the last couple of years, showing that suppressive acyclovir after the initiation of antiretroviral therapy can reduce the risk of herpes reactivation in those with a CD4 count less than 200.

Moving next to adult syphilis, there's expansion in terms of the clinical presentation and which patients there's an increased clinical notability of atypical presentations of syphilis, including painful, multiple lesions, especially occurring perennially that can mimic herpes presentation. There's an enhanced clinical description noted of ocular and otic manifestations, and really some more granular language talking about the use of LP in patients that have isolated ocular findings whether or not they have cranial nerve findings and patients that just present with isolated otic manifestations in terms of the need for LP. There's more discussion about the serologic testing with the traditional or the reverse sequence, and either can be used and there's pros and cons listed for both. There's no new data at this point that would warrant a shift in treatment recommendations. As most of you know, there's an ongoing randomized clinical trials (RCT) in early syphilis looking at one versus three injectionsof Benzathine, and that includes both HIV uninfected and HIV positive individuals.

This is really needed in the field to definitively say that one is as effective as three and we're awaiting the results of that trial. For alternative regimens, there is some more data on the use of ceftriaxone with the dose of one gram for 10 days. We also comment on the use of what some have been using, especially during the pandemic and when there were Benzathine shortages, amoxicillin and probenicid, and have a statement that there's insufficient data on this regimen to recommend its use. There's also been some

revision in terms of what we constitute as a serologic failure after treatment. Again, we're looking for a lack of four-fold decline. This may not occur if you're starting titer was less than or equal to one to four.

We're changing those recommendations for serologic response. It used to be six to 12 months for early syphilis. It's now changed to 12 months with the realization that the serologic response can be inadequate and may take a longer time to occur. And for late latent syphilis or syphilis of unknown duration, it's now 24 months. And some of these serologic changes can be really associated with the stage of the syphilis, their initial rapid plasma reagin (RPR) and the patient age.

Under neurosyphilis a little bit stronger recommendation. We had this recommendation in 2015, but it's a little stronger now so that there is no repeat CSF examination recommended at six months in individuals that have an adequate RPR response in both HIV negative individuals and patients with HIV on antiretroviral therapy (ART) in syphilis in pregnancy and congenital syphilis. I mentioned this previously about the maternal risk factors expanded for high risk of syphilis acquisition during pregnancy.

And you see some of those findings there. I'm not going to read them to you, but they will be highlighted based on several reports in the literature. The risk of reinfection should be based on ongoing risk behaviors or partner treatment. We already talked about this serologic screening twice in the third trimester based on community prevalence and maternal risk factors. The other thing that we did in both sections is we really gave a little bit more guidance on individuals that are managed either using a traditional algorithm or a treponemal based screening test. The specific timeframes for repeat serologic testing based on gestational age and then, clarified some of the, when you need to repeat the testing after somebody has syphilis in pregnancy and at least eight weeks after treatment and less signs of primary or secondary syphilis. If you're suspecting re-infection or treatment failure, we're looking for a fourfold increase in titer post-treatment that's sustained at least two weeks.

In the penicillin allergy section, there's no known alternatives for treating neurosyphilis, congenital syphilis, or syphilis in pregnancy. This section has been very nicely revised to talk about the imprecise definition of what we say by allergy and what patients think are allergy and really parse out the differences between an IgE mediated response, drug intolerance or idiosyncratic reactions, the use of validation of penicillin or other beta lactam allergies. There are some updates there on penicillin skin testing, the use of ceftriaxone and other cephalosporins in individuals that say that they're penicillin allergic and the use of an oral challenge. There is also a discussion about modified desensitization protocols based on the clinical syndrome drug route of administration. Because there's so many desensitization protocols out there, we're not referring folks to just one protocol. Most institutions have their own desensitization protocol, but we have some examples for folks if they don't have one. So, I think this has really been nicely revamped.

In the lymphogranuloma venereum (LGV) section, as you know, there's no national surveillance for LGV. We saw two studies, one from New York city and one from San Francisco, and patients that presented with symptomatic proctitis showing the prevalence of LGV. These two cities had the ability to do testing to confirm that it was LGV and found the association with HIV infection, related to age and of certain ethnic groups, that our diagnosis should really be based on our clinical suspicion, epidemiology and the *Chlamydia trachomatis*. Now more strong language that the use of chlamydia serology either complement fixation or micro immunofluorescence has no established diagnostic utility and really remembering that the ability to even do this molecular testing is not available for management as we don't have a point of care test to tell us that the patient has LGV.

And so, if you're suspicious to treat for LGV and the optimal treatment duration, it's not really based on clear evidence is based on more of a historical precedent of the 21 days of doxycycline. There is one trial from Britain looking at a short course therapy and another very small trial looking at weekly azithromycin. However, what continues to be recommended in the guidelines will be the 21 days of doxycycline.

In the urethritis section, there's a discussion about the identification of neisseria meningitidis as the ideologic agent of urethritis. When you can see the organism on gram stain, but a negative NAAT testing for gonorrhea, this would require confirmation by culture, and it would be treated as we would treat an individual with gonorrhea. However, it's important to recognize that this has occurred. In terms of the diagnostic cut-off, there is some discussion about differences may vary depending on if you're in a high prevalence or a low prevalence setting, and there's some literature to support either using a higher or lower cut-off, depending on your setting. The direct diagnostic testing that's recommended for a man presenting with urethritis is testing for gonorrhoea and chlamydia. For chlamydia, doxycycline is going to be the recommended regimen and azithromycin is demoted to an alternative. We'll talk a little bit more about that in a minute.

In patients that have persistence or recurrence, and if it's not based on compliance issue or potential re-exposure, we have to think of other organisms, in particular trichomonas vaginalis, and whether there's a high community prevalence or in populations that it's prevalent. So, it's uncommon in MSM, it's much more common in men who have sex with women (MSW). *Mycoplasma genitalium* to test for persistence or recurrence in somebody that has persistent urethritis, and then there'd be prescriptive recommendations for what to do based on, in particular *Mycoplasma genitalium*, since that is the most common infectious cause of persistent nongonococcal urethritis and the recommendation will be if doxycycline was used at the initial regimen, you see the recommendation for azithromycin as an extended therapy. And if azithromycin was used as the initial regimen, you're going to follow-up with doxycycline and then give sequential therapy with moxifloxacin. And we'll talk a little bit more about that when we get to *Mycoplasma genitalium*.

For cervicitis, trichomonas or gonorrhea is the most common aetiology. *Mycoplasma genitalium* can be considered initial testing, but we're going to really recommend it in instances of persistent cervicitis. There's a clear statement that's been added with ureaplasma or *Mycoplasma hominis* has not been

consistently associated with cervicitis and shouldn't be tested or ordered. In instances of persistent cervicitis, there's other things that we're going to be listing in terms of abnormality of vaginal flora and other irritants and other idiopathic inflammation.

There is a specific statement that will say no data to support use of antimicrobials in persistent cervicitis without an aetiology. And that's negative testing for chlamydia, gonorrhea, mycoplasma, BV, or trichomonas. Moving next to chlamydia. As you know, we now have FDA cleared test do use these tests, the NAATs at the rectal and pharyngeal sites, both for chlamydia and gonorrhea for rectal testing will be recommended in MSM and to consider in women, as I mentioned before, under the adolescent section based on shared clinical decision-making.

For treatment what's going to change in this section is that, you know, that the available evidence has shown us that doxycycline is efficacious for chlamydia infection of the urogenital, rectal and/ or pharyngeal sites. And although azithromycin has high efficacy for urogenital infection in women, there is concern about the effectiveness for women that have concomitant rectal chlamydia trichomonas infection which can occur commonly and cannot be predicted by sexual activity.

So, the other importance here is that we are concerned about the studies that have been done. The studies that are observational studies that have been done showing that there may be decreased effectiveness of rectal chlamydia infection with azithromycin. And, as you know, there was a recent study in a RCT that was presented at the STD prevention conference and a RCT comparing doxycycline versus azithromycin which showed the effectiveness of doxycycline over azithromycin. So, doxycycline will be recommended, azithromycin will be alternative. If there are situations where you're concerned about the compliance with taking the doxycycline, there are some discussion about non-adherence concerns, especially in individuals that have rectal infections.

And if azithromycin is used because of adherence issues they should receive a test after treatment to make sure that they've eradicated their infection. Erythromycin was discontinued because of GI side effects and Ofloxacin because of availability. So, they will not be available as they will not be listed as treatment for gonorrhea. Most of this information on gonorrhea for treatment you have seen published in the MMWR yesterday, and as mentioned before, some of the thoughts associated with the changes had to do with antimicrobial stewardship, PK/PD and what we're seeing in the trends of azithromycin susceptibility through our GISP program.

So, the increasing concern we have for stewardship the potential impact of dual therapy on other organisms with the low continued incidence of ceftriaxone resistance and the increase in azithromycin resistance, we have seen has led to us re-evaluating the past recommendations and the recommendations will be ceftriaxone 500 milligrams, in individuals that weigh less than 150 kilos.

And if chlamydia has not been excluded by a NAAT to treat with doxycycline a hundred milligrams BID for seven days. What's changed in the alternatives? The [inaudible] alternative if there is an issue with ceftriaxone allergy continues to be there, but what's changed is the alternative is the cefixime has gone up from 400 to 800 milligrams. Again, thinking about the PK/PD and the sites we're trying to reach. And if chlamydia is not excluded, to use doxycycline.

There is some information there about a potential use of the gyr-A testing. You know, this test is not FDA cleared yet, but if it does get FDA clearance, that's a particular use of Ciprofloxacin in asymptomatic patients where you have that test available for you where ciprofloxacin might be able to be used.

Test of cure will now be recommended for pharyngeal infection because those infections are much harder to treat historically and for EPT the recommendations will be to increase the dose of cefixime and if chlamydia was not excluded in the index patient to give doxycycline instead of azithromycin. Also, there's some mention of the changing epidemiology that we're seeing with disseminated gonococcal infection

(DGI) with being more common now in men and seeing the continued presentations of the monoarticular septic arthritis and the tenosynovitis dermatitis syndrome, but a little shift in the epidemiology. So, that section was updated.

There are some very transparent recommendations in a suspected cephalosporin treatment failure. We know that most treatment failures are due to reinfection. There hasn't been a documented cephalosporin treatment failure here in the United States, but it's important that people know if they are suspecting treatment failure, where do obtain a culture so that an antimicrobial susceptibility test could be done. If reinfection is most likely we would recommend retreating with the initial regimen. And then if there are concerns for cephalosporin minimum inhibitory concentration (MIC) elevation, you see another recommendation there for therapy with gentamicin and azithromycin. And then, a test of cure in cases of treatment failure to be done after retreatment.

There was a very lively discussion. I would say most of the guidelines meeting, the most lively discussion was about opthalmia neonatorum. And that had to do about whether or not the routine use of neonatal ocular prophylaxis should be discontinued. And the decision was that, as you know, the U.S. public health service task force has recommended routine ophthalmic ointment for every neonate born in the United States. The concern that came up was that we still are not doing an adequate job of prenatal screening and treatment, especially in some populations. So, the recommendation will stay the same for routine neonatal ocular prophylaxis. And as you know, in many states, that's mandated by law. There was recommendations more granular recommendations again, in this section about the importance of prenatal testing and retesting and women at increased risk for acquisition.

For *Mycoplasma genitalium*, if you remember from the 2015 guidelines, there was a special section on emerging infections. We don't think this is emerging anymore. We've given it its own section. And again, the concern here is in men and women with persistent urethritis or cervicitis, and that you can consider its use in pelvic inflammatory disease. The natural history of untreated infection has not been well-defined.

So, there are no recommendations for screening population level for asymptomatic infection. We do have a cleared nucleic acid amplification test that's useful for the urine, urethra, penile meatal, endocervical and vaginal areas. The concerns here are again, thinking about antimicrobial recommendations as our resistance to azithromycin is increasing. And if you remembered what we talked about with persistent urethritis, these are the same recommendations, and they're going to be recommendations based on whether or not you have the ability to do macrolide resistance testing.

Unfortunately, in the United States, we don't have a commercially available FDA cleared test yet to be able to do that. So, we do list what the recommendations are. If you do have somebody with persistent urethritis due to *M. genitalium*, how to treat doxycycline, followed by moxifloxacin in an instance where we don't have testing, if we do get testing where we're able to look for macrolide resistance, there'll be granular recommendations on how to do this dependent on whether you have a resistant or sensitive isolate.

Moving to vaginal infections for bacterial vaginosis (BV), some new data about BV increasing the risk of other STIs that were not previously mentioned in the guidelines, including *Mycoplasma genitalium*, herpes, and HPV listing certain BV associated bacteria that may increase the susceptibility to HIV. There are now several BV NAATs that are available for diagnosis, and that's gone over in the diagnostic consideration sections in terms of the different tests.

There's no change in the recommended regimens, but there are some new changes in the alternative regimens, which are single dose therapies in non-pregnant women. There are caveats to all three of these that you see listed and those will be specifically mentioned in the text of the document. We mentioned biofilm disrupting agents, which are not commercially available, but are under clinical investigation. There's some more data in asymptomatic pregnant women that should not be screened for BV. These are women that are low risk for preterm birth. There was an important study that showed us that there's no reason to screen asymptomatic pregnant women for BV. There also are changes in terms

of the nitroimidazole, and disulfiram type effect that you remember was listed in the guidelines. It is very interesting because metronidazole does not inhibit SLE. I can't even pronounce this. The chemical that interferes with disulfiram ethanol alone or ethanol independent side effects might explain the suspicion for disulfiram type effects. So, the bottom line is, there will be no linking with alcohol-use while taking metronidazole. We couldn't find good data that links those two together, so, that will be taken out under trichomonas. There was a meta-analysis that looked at OB outcomes associated with trichomonas, showing an increase risk of preterm rupture of membranes, pre-term birth endometritis, and HIV acquisition. There are advances in rapid NAAT diagnoses and the recommendations for testing are in women that present with vaginal discharge and women with HIV who present for initial evaluation. And there is still language in there about considered testing in women in different situations, including high prevalence and women at high risk of infection. And there are specific parameters that define what that high risk of infection is.

What's different in terms of the treatment for trichomonas is there's now data that women without HIV infection that metronidazole is 500 milligrams twice daily for seven days is more effective than single dose therapy. We don't have that data on tinidazole, so tinidazole will be an alternative regimen, and metronidazole twice daily for seven days will be the recommended therapy in women.

We don't have any data on using multi-drug duration of therapy in men. So, we will still continue to recommend the two grams orally. For persistent infection that area of the guidelines has been expanded to again, talk about resistance testing and the use of combination therapy and in instances of persistent infection getting consultation from CDC, having you ship a specimen to CDC for resistance testing, and then, getting recommendations in terms of treatment. Also mentioned in terms of clearance by NAAT can take up to three weeks after infection.

Under Vulvovaginal candidiasis, what's new in this section is that there are PCR tests for yeast, but many are not FDA cleared. And if you're going to use these tests, you should be familiar with performance

characteristics of the test, culture, which can identify a very broad range of yeast remains the gold standard for, or the reference standard for diagnosis and susceptibility testing. Candida albicans, azole resistance is becoming more common in vaginal isolates. And remember that non-albicans candida, candida is intrinsically resistant to azoles.

So, it's really important to get culture and susceptibility testing when patients remain symptomatic. We talk a little bit about the economic burden of recurrent vulvovaginal candidiasis and the recommendations there have not changed. What's a new section that was kind of added, was new information on the use of fluconazole in pregnancy. There are epidemiologic studies that indicate just a single 150 milligram dose of fluconazole might be associated with spontaneous abortion and congenital anomalies. Therefore, it should not be used in pregnancy.

Recent studies report that the proportion of PID cases that is attributable to chlamydia or gonorrhea is decreasing and of women that receive a diagnosis of acute PID, less than 50% test positive for either of those organisms. There are, again, some permissive language to the use of using *Mycoplasma genitalium* testing for PID and no new data that refined the acute PID diagnosis. What's different in the treatment section? Based on the results of the ACE trial that was recently published in the new England journal of medicine talking about whether or not we should be using metronidazole with our other antimicrobials, the trial indicated that the use of metronidazole was really associated with less pelvic pain and improvement. And so, this recommendation of ceftriaxone, doxycycline plus metronidazole will now be a recommended regimen.

We're going to demote clindamycin and gentamicin to an alternative regimen. This was an older regimen, and it was basically recommended by studies that were done decades ago, and because of the concerns of the suboptimal anaerobic activity from clindamycin it was demoted to an alternative and there's no clinical data that we have to support therapy for use of *Mycoplasma genitalium* upfront in parental regimens. For epididymitis instead of age, risk assessment should be used to think about how you should

treat and it should be based on whether or not you think chlamydia or gonorrhea is likely depending on sexual practices, chlamydia and gonorrhea, plus enteric pathogens, or enteric pathogens alone. So, based more on behaviors and other clinical signs that may be going on with the patient for epididymitis due to STI, it's often accompanied by asymptomatic urethral infections.

So, the importance of testing diagnostics are important for persistent epididymitis to think about *Mycoplasma genitalium* and then the treatment changes reflect changes in the gonorrhea regimen to say that the dose to cover gonorrhea has increased from 250 to 500. For HPV, the vaccine recommendations align with the American College of Physicians (ACP), including the catch-up vaccination aged 26 for those unvaccinated and the language per ACP regarding shared clinical decision-making for those who are between 27 to 45 years. So, the decision between the provider and the patient, there's no changes in the treatment of genital warts. What we're really excited about is the new cervical cancer screening and surveillance recommendations.

And this is, there's two really nice tables that were going to be created. And this is basically looking at what the recommendations are from the United States public service task force, American College of Obstetricians and Gynecologists (ACOG) and American Cancer Society, all in one table and looking at the different recommendations and also including HIV and other immunocompromised individuals, those that have been exposed in utero to diethylstilbestrol and those who have a previous diagnosis of CIN2 or 3. So, I think that's a really nice explanation of thinking very clearly and succinctly in terms of the recommendations. There's also an enhanced section on anal cancer screening which includes the importance of a digital, anal rectal examination, a section on early detection and some section that talks about screening and treatment for pre-cancer.

For viral hepatitis A we'll have the updated ACIP prevention recommendations. There'll be some tables from that publication talking about the risk factors the available agents and how to administer them, the importance of current outbreaks in the homeless, MSM, and the importance of post vaccination testing

with revaccination. So, this has been a question, especially in providers that take care of immunocompromised individuals, and there will be a recommendation now to do post vaccination testing with revaccination, for those that are seronegative.

For hepatitis B updated vaccine recommendations, including the use of Heplisav B and the importance of doing serologic testing in person starting prep. For hepatitis C screening, the recommendation recently came out from CDC including at least annual testing for women during pregnancy, as I previously mentioned, and the one-time screen for any person over the age of 18 and the use of rescreening for individuals that are on PrEP.

Proctitis the importance of diagnostic testing for rectal STIs, including chlamydia, gonorrhea and herpes, the use of LGV molecular testing, HIV serology, and an RPR. *Mycoplasma genitalium* for persistent proctitis. The thinking about enteric pathogen testing for fever and diarrhea, especially with the increases that we've been seeing in Shigella and Campylobacter and the concerns for antimicrobial resistance. The empiric therapy really relates to changes in the recommendations for treatment of gonorrhea and chlamydia, and then, in the presence of perianal ulcers to think about herpes treatment and to base the decision to make LGV, as I mentioned, to treat it based on the severity of the presentation especially with blood, ulceration and severe pain to treat empirically for LGV, and then, there's some language also on prevention, including genital hygiene and barrier protection.

And the last section I want to mention is on sexual assault. Again, the testing should be individualized based on the prevalence, risk factors, the nature of the assault. There's specific guidance on which tests to do both point of the NAAT test, as well as serology. And what we've put in this section this time is actually talking about male sexual assault. So, there'll be specific treatment recommendations for males that have been assaulted and females that have been assaulted that we also discuss HPV vaccination, post-exposure HPV vaccination, and then HIV post-exposure prophylaxis, according to risk. And that's really based on existing CDC guidance.

In children, we define specific risk factors to consider STI testing, low threshold for three site testing, especially in pre-verbal or non-verbal children. There is going to be specific mention now that we can use NAAT to test for chlamydia and gonorrhea with the caveats that go with the individual NAAT that you're using and with expert consultation, so that some of that language has been nuanced a little bit, and then the importance of herpes culture and being able to differentiate whether it's HSV-1 or HSV-2.

So, I know that was a lot of information that I went over really fast because there's a lot of things that have changed. This whole process would not have been possible without the expertise and dedication of a large group of people. This is a picture that we took in front of our marathon meeting. Unfortunately, there are some people here that are missing, but I am personally thankful and have heartfelt gratitude to people that leave their day jobs and come to us and really bring the brain trust we can really rely on to make sure we're headed in the right direction. And, I am eternally grateful for the expertise, the collegiality and the importance that people place on this document. This is a sacred document to us. We put a lot of our hard work and evidence and just feel great about giving this to the field.

It's a great body of work. And, my specific thanks for all this is, this takes a large number of people to do. I especially want to thank the leadership of Gail. She's retiring at the end of this month and I've worked with her for many decades. I appreciate her wisdom, her guidance and the ease with which we can work together and the banter back and forth that we have when we disagree.

Laura has been instrumental in terms of bringing this whole process to almost closure and specific attention to the folks that actually helped us really get down to the details, including Phil Chan, Christine Johnston, Christina Muzny, Ina Park, Hilary Reno and Jonathan Zenilman. And then, in particular the folks behind the scenes, in particular, shout out to Amber Herald, Quinn Haaga and Allie Coor. So, with that, I will let Laura talk about the resources and we are very excited for you to see our product in a couple of months. Stay tuned. Laura.

Before we move into the Q and A session, and thanks, it looks like people are entering comments and questions, so we appreciate that. I wanted to just to go through a few resource slides just to remind you at the time of the publication of the guidelines we will have evidence tables and screening recommendations available at www.cdc.gov/STD/TG2021. There will be limited copies of the MMWR, the pocket guide and the wall chart available for order in 2021. And, we're working hard to update the STI Treatment Guidelines app for Apple and Android devices and this should also be available in 2021.

I wanted to call your attention to another important resource, and that is the National Network of STD Clinical Prevention Training Centers (NNPTCs). This CDC-funded network is dedicated to increasing the quality of STD care in areas of diagnosis, treatment, and prevention through the provision of training and technical assistance. So, please take a look at this map to see which training center serves your area. Many of you on the phone are directly affiliated with the PTCs. You can find more information on the network website that's cited here at NNPTC.org.

I wanted to call your attention also to the STD Clinical Consultation Network that is hosted by NNPTC. This clinical consultation network provides STD clinical consultation services within one to three business days and links your consultation to your regional PTC expert faculty. So, this is another website to keep in your back pocket. Last but not least, the National STD Curriculum, hosted at the University of Washington, is a rich resource of information about the most recent developments in STI diagnosis, management, and prevention. The curriculum will be updated with the 2021 guidance when that is ready, so this is a place that you can go to learn more and obtain free continuing medical education (CME) and continuing nursing education (CNE) credits. With that, we're going to go ahead and move into the question and answer session.

Dr. Erin Tromble: Okay. So, Laura, I'm going to start off with some questions for you. Most of these are some kind of process questions, as well as some questions about some issues that typically or may occur

at the local level. I wanted to start off with a couple of questions related to shortages. So, the first question is asking about test kits shortages. What about the prioritization of tests for MSM, for example, where positivity of urine test is in asymptomatic screening, it's so low and specifically asking maybe during COVID, is it time to think more about it?

Dr. Laura Bachmann: I think that's an excellent point. I think we know from the literature that, particularly for MSM, that depending on the individual and their behaviors that, in asymptomatic MSM, that extra-genital sites are higher yield than the urethral site. In the dear colleague letter that was issued in September, on prioritization of testing and the setting of test kits, shortages, or diagnostic shortages, because it's not all, as Gail said, about test kits, but the bottom line being when you don't have the resources to test as much as you would like, the oral and the rectal sites be prioritized and individuals who endorse exposure at those sites and then even the rectal site being prioritized before the oral site. So, we did issue that guidance in September. I don't think we really have this reflected right now in the 2021 guidance, but in this setting of shortage agree that decisions to have to be made.

Dr. Erin Tromble: Thank you. And so, a related question is also asking about test shortages and the recommendation for a test of cure for pharyngeal gonorrhea. So, the question is asking how will this work given the shortage and this recommendation?

Dr. Laura Bachmann: I mean, that's another important point. We're all, you know, very challenged right now by, in particular, swab shortages. There is some evidence that we should be getting some relief early in the new year with this. But you know, this is a situation where the local program will have to decide based on what the resources are and whether or not that they can do this. But this is a guidance that we're issuing in order to help keep even closer tabs, if you will, on the oral site to ensure that the gonococcal infection clears, especially given that we are changing our treatment recommendations right now. But yeah, so, the local jurisdictions will have to determine and prioritize accordingly.

Dr. Gail Bolan: Okay, great. So, speaking of local jurisdictions, another actually, Erin, this is Gail. Could I add to that? I think it's common to focus on the patients that you're seeing. But we're also very, very concerned about all the people that probably have pharyngeall gonorrhea that aren't even getting tested and aren't even getting treated. So, COVID has really challenged us in many ways. I think we're just, trying to put our guidelines out as we feel needed for what to do during COVID. But I just want to kind of remind everybody we're going to have a lot of work to do once we get back to our new normal.

Dr. Erin Tromble: Great. Thanks Gail. Sorry. I should say Dr. Bolan.

Dr. Gail Bolan: Oh, no, no. I've always been Gail.

Dr. Erin Tromble: Dr. Bachmann related to the sort of local jurisdictional decision. One person was wondering if you had any suggestions for what they might do when state health departments or medical board members are not advocating on behalf of screening pregnant women routinely in the third trimester of gestation due to the cost. And I assume this is about syphilis.

Dr. Laura Bachmann: Okay. Syphilis. Okay. so really, that's a difficult situation and it's also not entirely straightforward which women benefit the most from third trimester screening and at delivery. And that depends on individual risk, but also prevalence of syphilis in the local area. You know the guidance that we issue is based on the best science and also individual experts. And we take a lot of things into consideration here. So, it is challenging if a local site is perhaps not endorsing screening guidance that may be desirable. And so, I guess, I would say the approach would be to really educate and use data when possible to make the point to convince local decision makers about the need for the testing.

Dr. Erin Tromble: Okay, great. Thank you. So, then the next set of questions that we had were kind of related to just processes for the guidelines themselves. So, the first question and you addressed this

somewhat already but was related to whether there is a preferred terminology in terms of STI versus STD, or will they be considered equivalent?

Dr. Laura Bachmann: So, that's still, it's not really clear to be honest, I don't think CDC is going to come out and say to use one or the other. You will notice that, there is a trend now to go more towards the STI terminology. The STI federal action plan, which was had a webinar yesterday is using the STI term. But at the same time, our division will still be the Division of STD Prevention, at least for the foreseeable future. So, I would say they could be used interchangeably, but we are leaning in general, more towards the STI term as being more comprehensive or reflective of the nature of these infections

Dr. Gail Bolan: And Laura, if I could add you know, that it's a term that, and there actually was one study, I think after we said, people had a feeling that for clients STI was less stigmatizing and we're very worried about stigma in our field. So, clearly, the family planning community moved to STI, WHO moved to STI. So, and obviously, the national HHS plan now is STI. And we felt that it was time to move these guidelines because they are oriented towards clients and their providers you know, to use STI because a lot of people don't understand the biological distinction between an infection and a disease. So, I would say we had a discussion within our division, whether we should move to the STI division. But we also felt with our level of resources, there's a lot of STIs--I think we're over 35 right now.

And we are a disease prevention agency. Our job is to prevent disease. We don't monitor things that are just causing infection that don't have a lot of serious outcomes. So, we chose to keep STD. We still have the American Association of STD. Eh so, I think there's, we just felt with our, you know, with what we do at CDC, we wanted to make sure that our impacts were going to be in the disease area. So, that's the reason why we're still using it from a prevention, public health, programmatic reason, but we felt that it was time for the guidelines to move to STI and for providers to be using that term.

Dr. Erin Tromble: Great. Thanks, Dr. Bolan. so, the next question is just related to how the guidelines were developed themselves and it was related to the selection. So, the question is asking how were the peer reviewers for the guidelines selected?

Dr. Laura Bachmann: Sure. So, for the peer review piece of this process, we selected peer reviewers based on expertise in infectious disease, epidemiology prevention, and care and treatment of STDs and HIV and viral hepatitis individuals who've had you know, experience in direct patient care, but also STD program. And also, from different backgrounds or disciplines such as obstetrics and gynecology, pediatrics, adolescent medicine, and they were given a charge and specific questions to address that they responded to.

Dr. Erin Tromble: Great. Thank you. Somewhat related topic. The question, the next question is asking when will the updated treatment guidelines be to refer to publicly and should clinicians change practice now based on the information provided today or await formal release of these recommendations?

Dr. Laura Bachmann: That's a good question. So, the goal is to have these guidelines published in early 2021. Unfortunately, we can't promise when that is going to be exactly, which I know is frustrating to all involved. But I would say this is a public comment webinar. And so, we do you know, we will take the comments into consideration too, in finalizing this draft. So, I would say at this point treatment should not be changed. You should adhere to the 2015 guidelines with the exception of the Gonorrhea MMWR that was released yesterday, that was specifically for uncomplicated gonococcal infections in adults and adolescents. So other than that, until this goes through the final stages of the process and is published in the MMWR I would not encourage people to start to change treatment regimens.

Dr. Erin Tromble: Okay. Again, in a related topic this question is saying, it seems like we sometimes use outdated recommendations for an extended period. Would CDC consider releasing recommendations on a rolling basis and a process similar to how the gonorrhea recommendations were released yesterday?

Dr. Laura Bachmann: Yeah. So, that is something we are actively evaluating right now. And you know, as you can see from the details that we shared today around the process that is quite involved and takes a lot of effort, not just on CDC side, but also our colleagues. And those of you, many of you on the line today that it does take a great investment of time, but yes, we are interested as an agency in providing up-to-date guidelines for the field and that is something under active consideration right now.

Dr. Erin Tromble: Okay. Thank you so much. This is the last question that I have for you, and then I think we can turn the questions, at least initially, over to Dr. Workowski. So, this is I think a big topic that I suspect Dr. Bolan might want to chime in on. It asks, given the continued nationwide rise in all the major sexually transmitted infections, what are we doing wrong? And, what, if anything, are we sure we're doing correctly?

Dr. Laura Bachmann: Oh my goodness. Gail, do you want to take that?

Dr. Gail Bolan: Sure.

Dr. Laura Bachmann: I'll sneak out the back door.

Dr. Gail Bolan: I've been very successful in controlling STDs at the national level. So, first of all, I think that we know that recommended screening recommendations are completely underutilized in this country. So, we're missing a lot of timely detection and treatment of individuals. I think we're doing a good job of treatment and curing infections when we finally get individuals into the healthcare system and get them diagnosed. So, I think that there's opportunities to really evaluate and we, the problem is we live with limited data in our field, in some areas of things that we do. So, I think there's opportunities, especially with PrEP, for us to really evaluate. Can we kind of screen and treat our way out of these epidemics?

So, that's one thing. I think we can improve on, obviously, our tools in our toolkit for primary prevention besides the HPV vaccine is pretty anemic.

It's an area that we really need to come up with some strategies that will make the primary prevention choice, the healthiest choice. And so, that's an area that is complicated in our society for a variety of reasons. The other reason that we're being challenged now that I've seen over the last six years, is that the social fabric of our society is falling apart. We have so many social determinants of health. You know, we are going to be challenged by our STI epidemic and that's a complicated issue that needs to be addressed. And so, I like to say, I've always felt this way. You know, our budget at the federal level is not going to solve this problem, and that's why this is so exciting about the HHS plan.

We're now asking what can other people do to contribute to STD prevention? We've always been asked, what can you do to contribute to HIV prevention, but we need to be asking HIV, what can you do also that will advance HIV prevention as well as STD prevention in the patients that you serve or ask our substance use disorder programs? So, I think there's that, that we need to do better at providing holistic, comprehensive care wherever the patient is seen. Don't ask people to come to us. We need to be starting to integrate our prevention services wherever we can.

And lastly, I started my career in vaccine diseases, vaccine preventable diseases, and I'm very excited that NIH is now interested in developing more of a robust vaccine research agenda. Because I honestly think in some areas with the challenges that we have, boy, our lives would be easier if we had some more vaccines for STIs, I'll stop there. So, STIs are our collective responsibility. They are a whole society problem and we all need to be, you know, working on it together. And I also feel like they are a reflection of the health of our nation, you know, where you see STDs going up, you also see maternal mortality going up for pregnant women. You see chronic diseases going up, we see COVID going up. So, it's really a reflection of the health of our society and it could almost be considered a social determinant of health marker.

That's my brief answer to the question, Laura, you want to add anything?

Dr. Gail Bolan: The hope, my boss is hoping that the new director is going to have so many new ideas that these trends are going to be reversed. And I said, well, I used up all my ideas, so, I'm happy to have some new ideas on the table.

Dr. Erin Tromble: Well, thank you so much, Dr. Bolan. So, that's the last question that I had, at least for now, to pose to Dr. Bachmann. I think I'm going to turn it over now to Dr. Quilter and Dr. Workowski.

Laura Quilter: Great. Thank you. So, I'm here with Dr. Workowski. We'll start our first question. Dr. Workowski, for asymptomatic contact to chlamydia, is doxycycline preferred over azithromycin?

Dr. Kim Workowski: Yes. What we're recommending is that the azithromycin will be an alternative therapy. I listed some of the concerns that we have with adherence, if there was a concern with adherence. So, we're really switching azithromycin to an alternative therapy based on the concern of the data that we've seen in retrospective observational studies, meta-analysis, and the recent RCT showing that doxycycline is more efficacious than azithromycin. So, whether or not you are an asymptomatic person with chlamydia or a symptomatic person, the recommendations will be the same. Doxycycline preferred over azithromycin with the caveat that if doxycycline compliance is in question, then you can consider azithromycin.

So, there will be some caveats. Again, these are recommendations based on the evidence. If you, on an individual basis, feel that your client is not going to be able to take the doxycycline for whatever reason, there's some shared clinical decision-making there between you and your client, and there is some more explanation. There was another question that when we were reviewing the questions that had to do with recommendations in women, and this is basically the concern, if there is a symptomatic infection in the

rectum in women, there is a potential to autoinoculate the vagina. So, in particular, if you're using azithromycin.

And then, if you autoinoculate infection that wasn't adequately treated is that concern would be extension of chlamydial infection up into the upper track. So, there'll be some specific wording in the chlamydia section that really addresses that comment. And again, this gets to the point that these guidelines are recommendations based on the best available evidence. There may be wiggle room for individuals to discuss with the individual patient, if there are concerns about your client in front of you. So, you're going to have to just be adaptive and flexible depending on what decisions you make together: the provider and the client.

Dr. Laura Quilter: Great, thank you. The next question regarding the management of rectal chlamydia in women, could you please review the recommendation of indications for testing?

Dr. Kim Workowski: So, again, the issue is that this is not really related to particular insertive anal sex. It has to do with the data that women can have asymptomatic rectal infection, just due to, if they're infected in their cervix and the secretions basically can get into the rectum. So, the thought is that again, this is shared decision-making is just permissive language. It's not making a recommendation that all women get rectal testing. As we make the recommendations for MSM, it's permissive testing, it's making the statement that there can be asymptomatic infection in the rectum in women, and that there may be differences in treatment efficacy. If you choose one treatment over another, we know that doxycycline is more efficacious for the rectum. And so, if you choose for whatever reason to give azithromycin the concerns are that you may have treatment failure in the rectum based on existing evidence and that you may consider a test of cure.

So, again, these are permissive recommendations. There are some prescriptive language in there to try to help you with individual counseling for your patient. And getting back to what we said about

adolescents there's permissive language relating to infection in particular rectal infection in women and recommendation, not so much recommendations, but some permission you can do it if you think there's a potential of infection. And it is not a strong recommendation is just permissive language.

Dr. Laura Quilter: Great. And can you comment on whether a test of cure will be recommended for chlamydia when the alternative regimen one gram of azithromycin is used?

Dr. Kim Workowski: Yes, that's what we talked about in the rectum. There is language in there if you're going to be using and you're concerned about the rectal site the only other place that test of cure is recommended in the guidelines is in chlamydia treatment in pregnancy and recommended that you wait four weeks after treatment because of the concern of persistence of DNA or RNA that can be picked up in the rectum. So, the recommendation is four weeks after treatment.

Dr. Laura Quilter: Great. Thank you. And what about testing for ureaplasma in women with vaginal discharge who test negative for gonorrhea, chlamydia, trichomonas, candida, bacterial vaginosis, and aerobic vaginosis?

Dr. Kim Workowski: So, the issue as we mentioned, there's going to be a particular statement that will be put in the guidelines concerning Mycoplasma hominis and ureaplasma. So, the problem is a lot of there are a lot of tests available that have multiplex tests where you get a full panel of 15 to 20 organisms, and nobody knows how to interpret them. In particular, the data for ureaplasma causing persistent cervicitis is just not there. And that's why there is a statement that is going to be inserted in the guidelines. So, you get these multiplex tests, because you're trying to help your patient, that you don't know why they still have discharge. You get 15 results and ureaplasma shows up, then you see the positive test results, and then you try to decide, what am I supposed to do for treatment when there's no defined treatment recommendation.

We don't know anything about the natural history about ureaplasma, except to say that it is associated with sexual activity. So, there's, it's kind of a, what I call the hamster wheel of testing. You get the testing, you don't know what to do, you pick a treatment. And then that leads you down another kind of area, especially when you give them, let's say doxycycline, and then, they get a yeast infection and it goes on and on. So, the issue is, that's why the statement was put in there. There is no data that shows that treating ureaplasma leads to eradication and leads to alleviation of persistent vaginal discharge due to cervicitis.

Dr. Laura Quilter: Great. Thank you. Now some gonorrhea questions, Dr. Workowski, can you please clarify the gonorrhea treatment? Wasn't the dual treatment useful for decreasing resistance?

Dr. Kim Workowski: So, whilst a dual therapy was initially when it was recommended back over a decade ago there was, what was seen by surveillance was there was an increase in, cefixime MIC's and the thought was we wanted to shield the ceftriaxone zone by using another drug. That was the point in terms of using the azithromycin, this was not based on data. This was using two drugs against gonorrhea as a theoretical strategy to kind of protect our cephalosporin, kind of like a shield. And what happened was what we've noticed over the past 10 years, since this was done was that there's a continued low incidence of resistance to cephalosporins in particular to our workhorse ceftriaxone. And in contradistinction, what you see is a steady increase in azithromycin resistance.

If you go look at the most recent CDC surveillance report from 2018, you can see what we're talking about, but you can also look at the MMWR that was published yesterday. There's a figure that really clearly articulates that and shows what we're talking about with the rise in azithromycin resistance. So, as we talked about previously, with the concerns that we have with antimicrobial stewardship, following what the epi shows us through the use of this wonderful national surveillance system that we have looking at trends in antimicrobial resistance, we realized that we're coming to a point that there are dramatic differences when you look at over what's happening with azithromycin.

Also, because of the concerns of its effect on other pathogens. In particular, we talked a little bit about what we're seeing in *Mycoplasma genitalium* and as STIs kind of travel together, we're also concerned about the collateral damage that is being done with the use of azithromycin. So, it's complicated. We tried to articulate that in the MMWR. So, I would refer you to that MMWR that came out yesterday. Because I think it very clearly articulate the rationale between why the decision was made to discontinue azithromycin and use monotherapy and then use doxycycline in instances where chlamydia has not been ruled out.

Dr. Laura Quilter: Great. can you comment on what happened to gemifloxacin as an alternative treatment for gonorrhea?

Dr. Kim Workowski: Great question, and it's due to unavailability in the U.S. So, there was a problem with production and it's just really hard to find. The last I was aware was it wasn't available, but it's due to production issues. And I think there was also a question that came up with where did the gentamicin azithromycin alternative regimen come from, and that is based on a clinical trial that was done. So, that's why that is in the guidelines for an alternative therapy, because we have a clinical trial that shows its utility for use, we don't have that data using gentamicin plus doxycycline. So, that's where that is coming from.

Dr. Laura Quilter: Great, regarding gonorrhea diagnostics, if gyrA testing becomes FDA cleared as a point of care test, why not treat symptomatic or asymptomatic patients with Ciprofloxacin?

Dr. Kim Workowski: So, the issue is that that's what is put in the guidelines that it will be, it could potentially be a tool especially in patients that are asymptomatic. Because again, this is not something that's done at the point of care, right, where patients present. So, if patients have asymptomatic infection and it could be reflexed to a gyrA, then that is a potential to use ciprofloxacin. And so, that language will be in the guidelines concerning that potential.

However, I mentioned that test is not FDA cleared and there could be a potential niche in instances where you do have Ciprofloxacin susceptibility. So, I do think there's a niche for it. However, my concerns are, if you go back and look at the trends in the antimicrobial susceptibility testing and you look at the trends in just over time, what you notice is that even though Ciprofloxacin or the quinolones were discontinued more than a decade ago, despite us not recommending them, there still has been an uptick in for quinolone resistance in gonorrhea, despite 10 years of us not using it.

So, I do remain concerned because they're so widely used for other things. But that particular question is an interesting one. So, what I would refer you to looking at trends in the surveillance report in particular, following the fluoroquinolones resistance, and then putting that into perspective of also the people that you're treating, the population. There are certain populations that may have higher baseline for quinolone resistance. And so, you have to think about all those factors. There may be a niche for it. I agree. And that's why it's mentioned.

Dr. Laura Quilter: Great. For recurring gonorrhea, why are culture and nucleic acid amplification testing both recommended?

Dr. Kim Workowski: The reason for that is that nucleic acid amplification tests are much more sensitive than culture, but culture will also allow you to do anti-microbial susceptibility testing, which we can't do often with nucleic acid amplification tests. So, they both offer benefits. So, one's a more sensitive and specific test and the other one has the ability to do anti-microbial susceptibility testing.

Again, as I mentioned, when we were talking about gonorrhea, it's really important that you as a provider know where you could get cultures if you need it. So, the issue is that it's more as everybody's using NAATs. And how are we going to find an individual, or if somebody presents to you to your clinic that has a treatment failure, how are you going to treat them? Number one what are you going to use? We have

some recommendations in the guidelines, but number two, we need to identify those folks that may potentially have a treatment failure. I mentioned that we haven't had a treatment failure here in the US but you need to know where to get your culture. How are we going to figure out which antibiotic? If there is a problem with cephalosporins, we're going to need to identify it on a culture plate, not by a NAAT. So, that's why we use two tests.

Dr. Laura Quilter: Great. And regarding Pharyngeal gonorrhea, what is the rationale for recommending testing here for all pharyngeal gonococcal infections?

Dr. Kim Workowski: I think the concern is several-fold. Number one is it's well-known that it's very, it's much more difficult to eradicate infection from the pharynx. And this has been known for decades that our treatment failure rate there is much more difficult. Plus, it's a very hard area in terms of to really get good data on antimicrobial penetration. We really thought closely about this, about do we have good data in terms of penetration of antimicrobials into the pharynx. We remember how we used to do this years ago when a new antimicrobial would come out. And we would look at the package insert and try to determine its distribution in terms of different body areas. One of the ways that we used to do that was, to do tonsillar levels, right?

So, somebody would administer an antimicrobial to a patient, and then they would have a tonsillectomy and we'd be able to measure levels of antibiotics to look at penetration. We don't do those things. We don't do those studies much anymore, right? So, we don't have a good way to quantify that 500 milligram dose we're giving to somebody. Does it reach the level in the pharynx that it really needs to thinking about the pharmacokinetics of the beta lactam, which remember thinking about how it penetrates through tissue is not the same way that other antimicrobials penetrate through tissue. So, trying to put the pharmacology together with what we know about the volume of distribution of the dose that we're using the weight of the patient, and knowing that what's happening in the pharynx is where kind of

antimicrobial resistance is happening and brewing those gonorrhea, having microbial interactions with other bacteria in the throat and they're sharing DNA with each other.

And so, it's a very challenging place to study. And because when you look globally at where these treatment failures have occurred outside the US, most of them have occurred in the pharynx. And so, that's why it's combination. That's a long-winded answer, but it really gets to the complexity of what's happening at the pharynx. And because of what's happened at different places in the world where the treatment failures have occurred, we think that the pharynx is a very special site, and that's where we think we're going to see it [treatment failure] happen first.

Dr. Laura Quilter: Great. And I think we have time for one more question regarding mycoplasma, what is the guidelines language going to say regarding testing for asymptomatic *Mycoplasma genitalium* infection?

Dr. Kim Workowski: So, as I stated during the presentation, that because there are some parts of the natural history that we just don't understand with *Mycoplasma genitalium (MG)*, there is going to be no recommendation for asymptomatic testing. The recommendations in the guidelines will call for in instances of urethritis, cervicitis, proctitis for persistent infections that don't respond to first-line therapy to consider *Mycoplasma genitalium*.

As we outlined before, this is complicated, it's a complicated organism. We see a lot of antimicrobial resistance in azithromycin, and it's an organism that's going to take sequential therapy. That's a lot of antibiotics. And we're still learning about this organism about its effects about its potential effects. We don't have some of those long-term effects that we do for chlamydia and gonorrhea on long-term reproductive track outcomes that we see in women. We know most of the information about MG in men. So, we're learning more about women. We don't have a, kind of a public health program that's dedicated to MG because we're still learning about some of it, but we know it can be a potential cause of persistent

symptoms. And so, that's why the decision was made to look for it in cases of recurrent or persistent urethritis, cervicitis, or proctitis.

Dr. Laura Quilter: Great. Thanks Dr. Workowski. And now Dr. Bachmann will give us some closing remarks today. Thank you all for your questions.

Dr. Laura Bachmann: Thank you. We appreciate all of your attention today and the time that you spent, the questions and comments that you've submitted. I wanted to let you all know that we will have a recording of the webinar and accompanying transcripts. I just wanted to remind you of that. That will be posted online by January 17th and also, the questions that were not addressed today will be responded to and posted as well by no later than February 15th. So, we appreciate your participation and look forward to speaking with you in the near future and continuing to make advances in the STI control. Thank you.