

STI Expert Hour Webinar Transcript

Navigating the Bicillin L-A Shortage: A Conversation with Dr. Kathy Yang

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Kelly Johnson, MD, MPH

Welcome to our STI expert hour on navigating the Bicillin shortage. This is a conversation with Dr. Kathy Yang, who is one of my esteemed colleagues in an infectious diseases clinical pharmacist, and is going to be helping us out with some of the questions that have been coming up around this really important topic. My name's Kelly Johnson. I'm the medical director for the California Prevention Training Center, and I'm really happy to be here today. I'm going to be just going over some introductory slides to get us started. So first, a little bit about the California Prevention Training Center or C-A-P-T-C. We're a multidisciplinary training and capacity building assistance center. We are sponsored by the CDC and we're a member of a larger network called the National Network of STD Clinical Prevention Training Centers or N-N-P-T-C. What do we do? We provide virtual and in-person training events, technical assistance, clinical tools like job aids and STI clinical consultation services, focusing on complex issues in STI patient care.

I want to highlight one of our big resources, which is the STD Clinical Consultation Network. This is an online platform. You can go to this website, stdccn.org. You can enter in a difficult patient question that's coming up for you, and a subject matter expert will respond to your question within one to five business days by phone or email, whichever you prefer. Going on right now in only the State of California, we are piloting a congenital syphilis hotline through the same website, stdccn.org. So during the period from January through the end of March, if you're a California clinician and you have an urgent question relating to syphilis in pregnancy or congenital syphilis, you can go to stdccn.org. You can enter your urgent question and you can receive a call back from one of our experts the same day. Now back to information about this webinar.

So here's our financial disclosure. We have nothing to disclose, and here's our CME disclosure stating that today's event is offered at 1.25 units. We get a lot of questions about this, so this slide might be important to you. These are the requirements for how to earn those 1.25 units. So first, you must have registered for this webinar on the N-N-P-T-C site by yesterday. Registration is now closed. You also have to attend the webinar live and in full. We'll record attendance as you sign on, but we're unfortunately unable to provide CME credit if you're watching a recording of this webinar after the fact. Finally, you do have to complete the post-course survey evaluation by February 8th. You'll get a link to the survey evaluation 24 hours after this webinar. That will come in an email from training@nnptc.org to the same email address you used to register for on the NNPTC site for today's webinar. To make sure that you get that notification, just add that email address the training@nnptc.org to your safe and trusted senders list and check your spam and junk folders if you don't see it.

Okay. If you do meet CME requirements, you'll receive notification about that by March the first from a different email address. This one will come from captc@ucsf.edu. Again to that same email address you

used for registration, and the notification will include a claim link to get your certificate from our CME provider, which is the University of Nevada Reno School of Medicine. To make sure you get that CME notification, also add captc@ucsf.edu to your safe and trusted senders list. Next slide, handouts and webinar recordings. We also get questions about this. So our materials from today will be included in the post webinar materials. This will come out to registrants two weeks after today's events. It'll come to that same email address that you use for registration and you don't need to request them separately. Again, make sure you add that captc@ucsf.edu email address to your safe, trusted senders so you make sure you get it.

Alright, a little bit about Zoom. I think you're all quite familiar at this point, but here's how today will work. The Q and A will be turned on during the webinar for attendees, so you can submit questions that way. If you want to use the Q and A, click on that icon from your Zoom tools to open the Q and A Chat, type in your question and click send. You can do so anonymously if you want to. You can submit questions up until the last two minutes of our Q and A section. Questions from you as attendees will either be answered directly in the Chat or we may choose to answer them live now the microphone, the video and the Chat will be turned off during the webinar, so just use that Q and A and if you have any questions after today's event, you can reach out to Elizabeth Olson who's our program manager, or you can see her email on the slide here.

Now I get to introduce our speakers. One of them is me. I'm the medical director for California Prevention Training Center. More importantly, our expert speaker today is Dr. Kathy Yang. Dr. Yang is a health sciences clinical professor in the Department of Clinical Pharmacy and the co Vice Dean of Clinical Innovation and Entrepreneurship at the University of California San Francisco School of Pharmacy. She's also, and this is how I know her, she's also an infectious diseases clinical pharmacist in the UCSF Medical Center. She is super knowledgeable and specializes in pharmacokinetic and pharmacodynamic optimization of treatment, especially for multi-drug resistant infections, particularly gram-negative bacteria like pseudomonas. And she has focused efforts on covid as many of us have during the last several years.

We also, I just want to mention we have Tamara Ooms, who's one of our clinical faculty and program managers at the California Prevention Training Center. She's here to help us out with a Q and A today. So if you see responses from her in your Q and A discussions, don't be surprised, and that's that. So now let's turn over to our content today. So again, we're going to be discussing this really important topic about what do you do with this buy-sell shortage, how do you manage your patients? Here's our disclosures. Again, we don't have any, and here's our learning objectives for today. So we'll be listing at least two factors contributing to these shortages. We'll be describing different frameworks for prioritizing Bicillin supplies when they're limited. We'll be discussing potential alternative treatments, and most importantly, we'll be trying to help you develop some decision-making processes for how to treat syphilis when you can't follow standard guidelines because of these shortages.

To start us off, I am going to ask you all a question. So let's say you have a 23-year-old man who has sex with men who is diagnosed with syphilis. RPR is quite high, one to 256. He had a non-reactive RPR six months ago. So this is an early syphilis case. You have a very limited amount of Bicillin on hand and your supplies are running low. What do you do? Alright, and you can go ahead and launch the poll. All right, so did you treat with Bicillin anyway because hey, that's the first line treatment for syphilis, or do you

give doxycycline for 14 days or do you give doxycycline for 28 days or do you do something else? You maybe heard a rumor that extencilline is now available, should you use that? Alright, let's see what the poll answers are please.

Okay, so we are kind of all over the place, but primarily people are favoring the use of doxycycline at 14 days, which I think is a great answer here. Doxycycline is an appropriate alternative treatment if you don't have a lot of Bicillin on hand, and 14 days is the right duration for early syphilis. Now, of course, doxycycline is only for non-pregnant people, so let's remember that as well. Okay, so we'll now talk a little bit more about what is this problem and what is the background. So I'm sure you all have seen a lot of news stories about this. This has been a really hot topic lately. Syphilis is on the rise. Very timely, the 2022 CDC STI surveillance report actually just came out yesterday and two things I want to highlight about it are around syphilis. So in this report, they looked comparing 2018 to 2022.

If you look at all cases of syphilis, there's been an 80% increase. And then if you focus just on babies, there's been an almost 200% increase in cases since 2018 among babies. So that's pretty alarming, especially with this is a preventable disease. Also a hot topic, there was recently this CDC report called the vital signs report, which is basically like a special MMWR and they chose to focus on this issue of congenital syphilis or syphilis in babies. And they pointed out again these really alarming trends. There were 300 some cases of congenital syphilis back in 2012, and if you fast forward to 2022, there were almost 4,000, and that represents a tenfold increase.

Very sad, very scary and really important because this is a quote that's always stood out to me from the CDC, but important to know that up to 40% of infants born to persons with untreated syphilis may be stillborn or die from the infection. So this is a potentially fatal infection for babies and it is preventable. If you read that vital signs report, they'll talk about some of the ways to potentially prevent CS cases or congenital syphilis cases. And one thing they point out is this second bullet point here in that report where more than half of these cases of congenital syphilis in babies occurred among people who actually were tested for syphilis in pregnancy, but they just didn't receive adequate treatment. And this is where bicillin comes in. It is a critical syphilis treatment, and that's especially true in pregnancy where it's the only treatment.

So just for a sec, I did want to talk about treatment strategies for syphilis. These are the CDC and first line recommendations, treatment for all stages of syphilis. And basically the point is that Bicillin is the treatment of choice for syphilis. Now for primary syphilis, like if you have a chancre, for secondary syphilis where it's disseminated, you might have a rash or for early latent syphilis where this infection occurred within the past year, the treatment's all the same. Recommended treatment first line is Bicillin given once intramuscularly. Over here you see patients who have late latent or unknown duration syphilis, which is basically they're asymptomatic, but you either don't know when their infection occurred or you know it occurred more than a year ago, you still treat with Bicillin, but now it's one dose given weekly for three weeks.

Here's this point again, penicillin or Bicillin is the only treatment for syphilis in pregnancy. What if you have a person with an allergy? You still use Bicillin. You have to desensitize the patient and then use Bicillin. So no other options for syphilis in pregnancy. That's not true for people who are not pregnant. So for example, for primary, secondary, and early latent syphilis, again, Bicillin times one is your

preferred treatment, but there are alternatives here. And one of the main one that comes up a lot is doxycycline. Again, given for two weeks or 14 days, just like 70% of you got in that audience response question. Similarly, if you're not pregnant and you have syphilis of late latent or unknown duration, if you can't get Bicillin because of these shortages, you can use doxycycline and you can give it for 28 days.

So I hope that what we've established is that syphilis is a huge problem, it's affecting babies, it's affecting pregnant people, and we have a treatment for it, which is Bicillin, but what do we do when Bicillin's not available? So this is the problem that we're addressing today. Just to give some historical context, it was in April of 2023 that the FDA first announced these Bicillin shortages and they've pushed this back at least once, but currently the estimated recovery is not until Q2 of 2024. So we are still very much in this thing. I wanted to use this survey from the National Coalition of STD Directors to just kind of point out the impact that these shortages are having on clinical facilities. So this was a survey from NCSA, the National Coalition of STD Directors, and it went out to 151 clinics and 136 health jurisdictions basically asking questions about the Bicillin shortage and about how it's affecting operations. And the responses in yellow here in August are shown in yellow, excuse me, the August responses are shown in yellow, whereas the November responses are shown in blue. And really what I would just want to highlight is that there've been these increases where people have increasingly been reporting that Bicillin was just completely not available or that they couldn't fulfill their orders or that they did eventually fulfill their orders, but they were delayed. So this is a problem, it's ongoing, and in fact it's getting worse.

This is having an impact on pregnant people. This is that same survey and basically 13 of these respondents to this survey were saying that in their jurisdiction, they had received reports of a pregnant person who was unable to access Bicillin initially for treatment in pregnancy. This has really been negatively affecting people, and so we're needing to come up with potential solutions. What do you do? I think the main solution that's been put out there is these prioritization schemes. One example is from the California Department of Public Health. This came out in June and they basically suggested that if your supplies are limited, you should prioritize Bicillin for pregnant people who have syphilis infection or for infants who are exposed to syphilis in utero. So obviously that's a priority group. You should also try to prioritize your Bicillin supplies for people who really can't get doxycycline, like people with anaphylaxis. And you should conserve Bicillin by using other drugs for the treatment of infections, for example, like strep pharyngitis where there are alternative medications.

Here's what the CDC has said about this matter. So these are their reminders and recommendations. They say that you should take inventory, so you should monitor your local supplies and you should contact the distributor, which is essentially just one Pfizer, and there's a link on this slide if you need it, but basically reach out to Pfizer if you're really running out of supplies. They also mentioned that it's important to accurately stage your patients. Meaning if your patient has primary syphilis and they only need one injection of Bicillin, don't give them three because then you're unnecessarily using your supplies.

Of course, like California and many other states, the CDC nationally is also saying to prioritize Bicillin for those pregnant people and for those babies who need it. And then CDC goes, I think a step further than California and says specifically that we should be choosing doxycycline for non-pregnant people to help preserve Bicillin supplies. So this is where a lot of questions have been coming up. So if we can't use

Bicillin, and especially if we're leaning on doxycycline, what does that mean for us and for our patients? So we now have our Q and A session where basically I'm going to ask Dr. Yang some of the questions that have been coming up for us at the California Prevention Training Center. My hope is that some of these questions may have been coming up for you too, and that we can help give you answers or at least practical approaches that you can use in some of these scenarios. So Kathy, we started talking about doxycycline and it's been coming up a lot in the world of STIs lately. For example, it's now the treatment for urethritis. In some patients it's being used to prevent STIs and now it's increasingly being used for syphilis in this era of Bicillin shortages. Given that, what can you tell us about doxycycline? What are the basics? What do we need to know?

Kathy Yang, PharmD, MPH

Yeah, thanks Kelly. So to bore you guys off for a few minutes, we're going to go through some basics except there you go. Okay, a little lag time there on my screen. So just a review of the quick pharmacology. Doxycycline is actually a pretty old drug, right? It's decades old and doxycycline was actually developed because of sort of the toxicities we see with tetracycline. So you can see doxycycline here on the right hand side. It is four rings, that's why it's still within that tetracycline class, and we use it for all kinds of infectious diseases. The oral absorption for doxy is really good. It's greater than 90% from the GI tract, which is why for any hospitalized patients we can use the IV and the PO essentially interchangeably if they can absorb it from their small intestines. So distribution is basically where does the drug go after you take it?

And so this is a drug that goes pretty much to most body spaces within the body, most organs, most compartments except for the CSF. So it does get into sputum, which is why we use it for pneumonia. It does get into synovial tissue, which is why it's sometimes used for osteo. It does get into prostatic fluid, some no fluid, and also into the eye. 40% of the dose does also get into breast milk, and we will talk about that later on because I see there are some questions in the Chat about breastfeeding. And the elimination of this drug has mixed compartments, so it's both eliminated from your kidneys as well as in the fecal route. So what that means interestingly, is when your kidneys are not doing well, if you have some type of renal impairment, it's not a big deal since when your kidneys sort of poop out, your GI tract actually takes over. So there is no dose adjustment needed in renal impairment.

Kinetically, what happens after we take a dose? Here I'm focusing on the hundred milligram oral dose because this is what we would typically give in a patient with syphilis. You can see that it gets a maximum concentration of about two mgs per liter. It's not huge, but it doesn't need to be. The time to see max is the time it takes to get to this maximum concentration, and that takes about two to three hours. And something that we often think about when we're thinking about people who throw up their dose or whatever or thinking about when is the maximum efficacy of this drug. So I once did get a question of does it matter if you're taking the immediate release versus the delayed release? And it really doesn't matter when you look at the time to see max, they're pretty comparable. So regardless of you're taking the immediate release or the delayed release, the time to the maximum concentration is about the same.

The half-life is pretty long. It's about 18 hours, which is why we can dose it twice a day. The longer the half-life usually the longer the dosing interval. And the AUC is this measure that we kineticists use called the area under the curve. And so what that means is if you look on this pharmacokinetic or concentration time curve on the right hand side, the AUC is everything underneath the blue curve. So

the blue curve is what the drug exposure looks like in your body. And the AUC is sort of the area under this curve. It's a measure of the exposure of how much drug that you're getting when you take a dose. And so from a kinetic standpoint, for IV pharmacists, we're always fixated on things like the AUC, the half-life, the time over MIC, because it's this amount of exposure that does the killing.

So for most bugs, interestingly, we do the in vitro studies first. We look to see how much drug we need, and that really informs the dosing. The interesting thing for doxy and syphilis is we kind of went a little bit backwards. We don't actually know what the exposure needs to be for doxycycline. We know that it gets a pretty good AUC, but we don't know what that measure needs to be relative to the minimum inhibitory concentration. So different antibiotics work differently. Some you have to have a really good AUC exposure. Some you just have to be over a little bit. We don't actually know what it is for syphilis. The good thing is the MIC for syphilis is super, super low for doxycycline and also super, super low for penicillin. And that's why we can do sort of these low dose benzathine penicillin and still get enough in.

So that's a great thing about *T. pallidum* them is we know that the MICs is very, very low. So from a counseling perspective, what else do we know? First of all, food doesn't tend to affect doxycycline as much as tetracycline. So with the original tetracycline, you had to be careful about separating your food from your antibiotic dose because the food really did impact the absorption. That's not so much the case with doxycycline, so you don't necessarily have to separate it. You get about a 20% decrease in the exposure, but that's not really that significant. You still do though, have this warning about multivalent cation. This warning is not so great with doxy compared to tetracycline, but it's still good idea to separate. So that includes things like antacids, iron, calcium supplements, et cetera. Food is okay, but your actual Tums and Maalox and Mylanta should be separated.

Kelly Johnson, MD, MPH

Kathy, when you talk about that separation, do you have a standard time that you tell people wait two hours and two hours after to take your Tums if you're taking doxycycline or what do you tell people?

Kathy Yang, PharmD, MPH

Yeah, I mean it doesn't have to be that long. An hour is usually good because the absorption's pretty fast.

Kelly Johnson, MD, MPH

Okay, one hour. Okay, awesome.

Kathy Yang, PharmD, MPH

There.

Kelly Johnson, MD, MPH

So oh, go ahead. Something else.

Kathy Yang, PharmD, MPH

Nope, I was having, I have a little bit of a delay when I advanced the slide, so I'm always like, tap, tap, tap.

Kelly Johnson, MD, MPH

No worries, we've got it now. So I think another question that comes up a lot for us is the doxycycline courses. If you are using doxycycline instead of Bicillin and the doxy courses are kind of long, right? It's 14 days or 28 days depending on what stage of syphilis you're trying to treat. And some people, myself included, struggle with that organization of remembering to take a pill twice a day every day for potentially up to a month. So I was wondering if you have any tips that we can share with our patients for supporting doxy adherence if we're using doxy more?

Kathy Yang, PharmD, MPH

Yeah, that's a great question and this is one of those really good, crowdsourced questions. So if anybody has any good tips or hacks on this, put them in the Q and A so we can see them. I'd love to see what other people. Adherence always works when you put it scheduled to something, right? You need something regular and scheduled to help with that. So putting it next to your toothbrush, taking it with your breakfast, your coffee, setting your timers, your iPhones, your watches. All of that works great for supporting adherence. What becomes difficult is when we have people who have sort of unstable housing or they don't have a regular schedule, and those are just so hard in general. You just have to find something that is regular for them that they can pair sort of a reminder to. But I'd love to see what other people think. So pill boxes I see in the Chat. Take it with breakfast and dinner. Some people say to avoid taking dairy, so is that a concern? It's more of a concern with calcium supplements and so there are lots of ways to do it. The main thing is just to find something to pair it with that they can do consistently. Kelly, do you have any? What are your tips?

Kelly Johnson, MD, MPH

No, I really think you covered all of them that I found effective. Phone alarms. People tend to like pill boxes. People tend to like keeping a little calendar. Some people like that. But basically I think you covered it and we have so many more questions, so you can go ahead and raise that next question up for us. And while you do that, I can just go ahead and phrase them as well. I'm going to kind of combine the next two. I think if you just hit next, it should come up. There we go.

Kathy Yang, PharmD, MPH

I'm sorry.

Kelly Johnson, MD, MPH

No, it's okay.

Kathy Yang, PharmD, MPH

You go. Okay.

Kelly Johnson, MD, MPH

Yeah, just wanted to kind of bring up what are some of the common doxycycline adverse reactions that you hear about and what can we as providers or disease intervention specialists, people working directly with patients, what can we do to minimize those intolerances?

Kathy Yang, PharmD, MPH

And so I have a couple of slides on this, which somehow does not want to advance for me. There you go. I get a little delay there. So the way I think about this is pair your adverse effects to your patient counseling. So some people do get GI upset or esophageal irritation with doxycycline. It's kind of a weird thing with the formulation. Sometimes it floats up and so it can give you a little bit of a heartburn type of reaction. The main thing is don't take any antacids with that. So if you get a little bit of a GI upset. It's okay to take it with food, but don't take it with your Tums. Don't take it with your Maalox and things like that. There's this class effect warning with photosensitivity, and this occurs both with tetracyclines as well as with doxycycline that you can get a sunburn. And so the thing to do about that is always to wear sunscreen. It's any surface on your body that is exposed to UV light. So that could be your hands. That can be your face, the back of your neck. So make sure going out, you wear a hat or you have some sunscreen on.

And what about chest and breastfeeding? So this was a question I also did see in the Chat. So this is an interesting question. So the current labeling includes a warning against use in pregnancy, lactation and children less than eight years old due to the effect on teeth and depression of skeletal growth. So with the original tetracycline, you could get this teeth discoloration where it was permanent, your teeth would fluoresce and you would get a depression of the skeletal bone growth. And this is what led to the warning about not using it in children less than eight and not using it during pregnancy. So this is actually a class effect. So this also is a warning that is in doxycycline, but remember that this is a drug that was made to overcome a lot of the issues that occurred with tetracyclines and doxycycline GI absorption is actually inhibited by the calcium in breast milk.

So that actually does decrease the exposure that you would see in breast milk, and the exposure in general is fairly low. We talked about earlier this thing called the time to C max. So it turns out that the peak levels in breast milk come out about five to seven hours after you take the dose. So for those that are worried, they can always feed or pump before that or feed or pump right before they take their second dose, and the levels are typically very, very low. So as far as I can tell, there are no FDA reports of any type of bone or teeth related adverse events in breast or chest fed babies with doxycycline. Of course, there's no randomized control trial on this. There's no study on this. This is all based on individual case reports and things like that, but there haven't been any of those to date. The only thing that is a little bit more significant system just to monitor for is diarrhea in the breastfed baby, which occurs anytime you have a mother that takes antibiotics.

Kelly Johnson, MD, MPH

Awesome, thank you. That's so helpful to have that context. I know that question about breastfeeding comes up quite a bit, so I think another one we've seen a lot is how do you think about missed doses if you're on some of these longer courses of doxycycline? And we actually have an audience response question so we can advance and go ahead and pull that up. We're going to go through a case.

Kathy Yang, PharmD, MPH

Sorry, I have this little lag time.

Kelly Johnson, MD, MPH

Oh, no problem.

Kathy Yang, PharmD, MPH

There you go.

Kelly Johnson, MD, MPH

For the audience, let's say this, this is actually a question that we got through California Prevention Training Center. So our clinic is treating a non-pregnant 28-year-old cisgender female with doxycycline for 28 days, for syphilis of late latent or unknown duration. She's missed two doses. Now for the audience, do I need to start the treatment course over? You can go ahead and launch that next poll. Do you think yes, you need to go ahead and start the whole treatment over? Do you think it's no, it's fine. Just keep going. Do you have no idea or do you think it depends? I'll give you a second to think about it. Okay, we can go ahead and show the responses. So most people were thinking, no, you don't have to restart, but that's the majority. That's 56%. And then the rest of the audience was very split between saying, yes, you start over, I have no idea, or it depends. So let's ask Kathy. What do we do if somebody missed a dose or missed two doses or how do you think about missed doses?

Kathy Yang, PharmD, MPH

Yeah, that's a great question. So you know what Kelly? Oh, there it goes. Okay, so what if my patient forgets to take their doxycycline? There really is no hard and fast rule on this. And the way I like to think about this from both sort of an infectious disease perspective as well as a pharmacist perspective is, it sort of depends on what it is that they're missing, and if it's a single dose, that's not a big deal. So single doses typically don't affect therapy. They're half-life dependent in terms of when you take your dose. So interestingly, there's no FDA guidance on this, on what you should do if you miss a dose. So the general guidance is take it as soon as you remember it. Don't skip it. Some people will say, let's just hold it and wait until we get to the next dose. You don't necessarily need to, you should just take it.

Don't worry about the food cation interaction at this point. You should just take the dose, take your next dose on time. So the thing to remember is doxycycline is so non-toxic that even if you've compressed your dosing interval for one dosing, it's not a big deal. And we say don't double the dose, but in some infectious disease scenarios, the dose of doxycycline is 200 milligrams. So not to say that you should double it, but that gives you some confidence that even if you have a shorter duration between the dosing interval, that's not going to lead to any toxicity. Add up the missed doses at the end. Just take all their antibiotics so you finish the whole bottle that you're given. So that's the easy thing. So if you've missed a single dose or even a single day. What if you've missed multiple doses or multiple days?

No, that's kind of a harder question. And so that's more of where it gets to be, well, it kind of depends. So this is a PK graph that I'm showing of how many days, how long does it take you to get to steady state? So once you start taking a drug, it takes a little while for it to build up to a certain concentration, and that typically comes out to about three to four half-lives in general for all drugs, not just doxycycline, but all drugs in general. The PK mantra is it takes 3.3 half-lives to get there. The good thing is the MIC for *T. pallidum* is super low and the regeneration time or the doubling time for *T. pallidum* is about 30 hours. They actually kind of match up pretty close. So we don't really know how much doxycycline we need, but this is information that I would often use to help me decide what do I need to do about the patient.

If it's a patient that is missing doses at the start of therapy when your doubling time for *T. pallidum* is a little bit faster and it's more significant that you don't miss doses. In those cases, I will tend to just start

over. If you're towards more the end of therapy, it's likely not as important because you've gotten a big chunk of therapy in already. So I don't tend to think about needing to restart therapy when you've got a good chunk in. It's really more important at the beginning of therapy when you've missed multiple doses or multiple days. So there's no real hard and fast rule. You just have to kind of play it out in terms of how many they've missed and where in their therapy they've done that. At this point, I think then we go back to our other slide as well, in terms of having a conversation of what is going on, why did you miss your therapy? Can I help you figure out a way to make your dosing more consistent? Did you lose it? Did you run out of refills or did you just forget? And at that point, can we pair it with some kind of reminder device?

Kelly Johnson, MD, MPH

Yeah, that totally makes sense. So just I want to summarize. I want to make sure I'm hearing what you're saying properly. So you were saying if you're on a course of doxycycline, let's say you're going to take 14 days, you take one day and then you forget for two or three days. You should just start over because that's early. The doubling time is high. There's still a lot of syphilis around. Just start over, that's what you're saying. And then if it gets towards the end, you're on day 13 and you miss a dose, it's probably fine. Just take it when you remember. At that point you've knocked out a lot of syphilis and things are kind of slowing down anyways. Is that right? Let's say you miss a dose or two right in the middle, somewhere in the middle. You should just tack those on to the end? Is that kind of where we're landing?

Kathy Yang, PharmD, MPH

I would just tack those doses on. So then the question is what if I miss multiple doses in the middle? That's a hard one, right? In general, I would think that a day or two is not a big deal, not worth starting over. When you're getting beyond two days, which is sort of this three to four half lives, then you're sort of in a more stickier position.

Kelly Johnson, MD, MPH

Cool. That makes sense. Thank you. That's helpful. I think just having a framework for what to do because these situations definitely come up. Super helpful. Okay, so I'll do this one because this is one that's been coming up quite a bit for us. What if you run out of Bicillin in the middle of a treatment course? Let's say somebody is getting treatment for syphilis of late, late or unknown duration. They're supposed to get three injections and they get one, and then your clinic has no more Bicillin. What do you do? So this is the scenario, and this is a question for you all in the audience. So now you have a 22-year-old trans woman who has syphilis of late, late or unknown duration. This is the scenario, like I was saying, she got one dose of Bicillin and she got it seven days ago, but now your clinic's totally out of Bicillin. What do you do? You can go ahead and launch the next poll. Please see your options. You can give her doxy for seven days, doxy for 14 days, or just restart everything and give her doxy for 28 days. What do you all think?

Alright, let's go ahead and see the responses please. Great. So 63% of our audience is saying give doxy for 28 days. But a good chunk, about a third, is saying do doxy for 14 days. And I can see the rationale for that. Like you got a dose of Bicillin that covers seven days. If we're trying to get to a 21 day course, maybe doxy for 14 more days works. We don't know. We spent a lot of time, Kathy and myself and others researching this question to find out if anyone knows if there's data on this and you can go ahead and advance to the next slide. But the long and short answer is after extensive research, there is really no data on this. There's no data for a mix and match approach. So for me, I would just recommend

restarting the full course of doxycycline for 28 days because you really don't know how to think about the combination of Bicillin and doxy and is it enough exposure and blah, blah, blah. And Kathy, I'm sure you can say this more eloquently, but this was the dear colleague letter that came out from California Department of Public Health, basically just saying what I said essentially that we really did not find data to support a mix and match approach and to be most safe and most conservative, we wouldn't recommend it and we would just recommend restarting. Do you agree with that, Kathy?

Kathy Yang, PharmD, MPH

I do. I do. And all the data on doxycycline of course is retrospective and observational, so there's never going to be a head to head. But in general, I think the most conservative approach is best in the absence of data.

Kelly Johnson, MD, MPH

Totally, totally agree. Now turning to our sort of next half of the talk, An exciting thing happened as we were preparing this webinar for you all. A new drug came out called Extencilline. It's actually not a new drug at all, but basically this is a European drug actually developed in or at least manufactured in France that the U.S. is now importing for treatment of syphilis exclusively during this Bicillin shortage. So it's a form of penicillin, but it's unfamiliar to us. So we wanted to spend some time talking about extensively.

Kathy Yang, PharmD, MPH

Okay, so the next poll question prior to administering Bicillin, so this is the U.S. version of Bicillin. Do you ask about peanut or soy allergies? And just this is the next poll and the answer of yes or no, give it like 10 seconds or so. Okay, so let's see what people say. So 77% said no and 23% said yes. Great. Alright, let's close that and we'll move on. So what's the right answer? I don't know. It's just the poll. Whenever the poll comes up, my moving forward doesn't like to move forward. Oops. Okay. So interestingly, this Dear Healthcare Letter about Extencilline was actually released in November, but it was not really publicized because there was no way to bring Extencilline into the U.S. at this time. This is an FDA Dear Healthcare Letter saying that the FDA was allowing temporary importation of Extencilline and the diluent for reconstitution.

It's been available to order as of January 22nd from Direct Success. And the links for all of that are actually in the Dear Healthcare Letter. The WAC pricing on this is unfortunately not cheap. So the 1.2 million unit vial is \$250 per vial. And the 2.4 million unit dose, which is our standard, is 500 milligrams or \$500 per vial. So remember this is just the cost of the drug. So unlike benzathine, remember you have to also expend your own cost with regards to syringes and if you use lidocaine and stuff like that. The minimal order for this is five vials at a time and so far there is no 340B pricing. We've asked extensively and I think my understanding is we are working on it. But so for now there is no 340B pricing.

Kelly Johnson, MD, MPH

And just before you move on, can you tell us what WAC pricing stands for?

Kathy Yang, PharmD, MPH

Oh, sorry. So WAC stands for wholesale acquisition costs. So for any pharmacy to buy it or they would have to pay the WAC pricing. With 340B pricing, you get a discounted rate off the WAC. But because there is no 340B pricing on this, so far we are stuck with what it is.

Kelly Johnson, MD, MPH

So it's expensive.

Kathy Yang, PharmD, MPH

It's expensive. Yeah.

Kelly Johnson, MD, MPH

Got it. Thank you.

Kathy Yang, PharmD, MPH

So I have here a major a chart on just the sort of major difference between. Looking at the labels, the one thing I do want to point out is there's been some confusion about the name. So Bicillin L-A is benzathine injectable suspension and Extencilline is benzathine benzyl penicillin. So there has been some questions of whether or not the benzyl component makes this a pro drug and it does not. So Bicillin and Extencilline are essentially the same thing. There is no pro-drug involved. It's just an extension of the chemical name. So this is the totally different both of these drugs from your IV penicillin that you would give in the hospital. And that itself is another big can of worms because IV penicillin has also lots of different names. It's called crystalline penicillin. It's called aqueous penicillin, pen G potassium, pen G sodium. Those are all the kinds you would use for IV use.

These are the two, only two formulations you would use for IM use. So again, you would not be able to do these for IV. So the difference between the two is for when the Bicillin is a pre-filled syringe. The Extencilline comes as a powder vial, which you would then need to use your own supplies to be able to aseptically make like you would do ceftriaxone. It's already packaged with the diluent, which is the sterile water for injection. So it comes as two vials, but you can also replace some of that sterile water for lidocaine if you think because of the pain involved, because it is actually a larger volume. So for the 2.4 million unit dose Bicillin is four mils. So you can do that as one shot. The Extencilline, however it comes out to about seven mils because even though it's five mils, when you get it once with the powder, the volume is a little bit bigger.

So that means it does need to be split probably into two injections, one on each butt cheek essentially. So the nice thing though about Extencilline, and this is I think one of the advantages of this drug over Bicillin, is because you are mixing it yourself, you can actually easier, it's easier to give the pediatric doses when you have to do the dose per kilo dosing. That is actually easier to do with Extencilline because it's not in a pre-filled syringe. So you can actually figure that out easier than with Bicillin where you would actually have to put it back into another bottle and draw it back up. So the storage. Bicillin needs to be refrigerated. Extencilline isn't room temperature. They do have different excipients and this is sort of where a lot of the confusion has been stemming from. So Bicillin actually is made with lecithin as well as Extencilline.

Lecithin is a byproduct of soy. So because of that Extencilline has this warning about hypersensitivity to penicillins and soy, but Bicillin does not. It only has this warning about penicillin. And that's why I wanted to poll everyone to ask if they were asking about soy and peanut allergy because before Extencilline came out, I never even bothered to look at the excipients in Bicillin. So they also have, because of the labeling requirements between EMA, which is the European Medications Agency, the

equivalent of the European FDA and our FDA, they do have different labeling requirements and there are less warnings with Extencilline. But you take the conservative approach and you still take all the warnings you would take with Bicillin and you apply that to Extencilline and you take the warnings with Extencilline and you apply them to Bicillin. That's the way I would think about it. So that you've covered all of your bases.

Kelly Johnson, MD, MPH

Wait, and before we move on, Kathy, just to be explicit, you said excipient to me the other day and I was like, what? What's that? Can you tell us what an excipient is?

Kathy Yang, PharmD, MPH

Yeah, I'm going to cover that in a third talk about it once I can get this thing to advance. Kelly, I think I'm going to turn the control back over to you.

Kelly Johnson, MD, MPH

Okay, yeah, that's fine.

Kathy Yang, PharmD, MPH

Can you advance?

Kelly Johnson, MD, MPH

Yes.

Kathy Yang, PharmD, MPH

Thank you. So the next poll question is "Would you administer Extencilline in a patient with soy allergy, yes or no?" I'll give it like 10 seconds or so. Okay, so let's see what the results are. So 86% said no and 14% said yes. I would love it if anyone was comfortable just putting in the Q and A, why they think they would give it and why they think they would not. But let's go to the next slide. So what about the soy warning? So Lecithin is a phospholipid and it's derived from soybean oil. Until this question came up, I hadn't really thought about this too much, but I spent last week sort of digging into the weeds on Lecithin and soy warnings. Lecithin is used as an excipient in FDA drugs. What that means is it's an inactive ingredient. It's a carrier. So for oral medications it makes the drug more stable.

It means you can make it into a pill form. It sometimes increases, it can be used to increase the delivery of the drug and it's used in basically all types of formulations, oral IV, IM, et cetera. So from the FDA perspective, what's interesting is there are regulations on soy warnings in food, but not for drugs. So the labeling is not the same. So there are these two pieces of legislation that came out in 2004 and 2021, which regulate food allergens. And the first one, this FALCPA, Food Allergen Labeling and Consumer Protection Act of 2004. This had eight different allergies. So it had milk, eggs, fish, crustaceans, tree nuts, peanuts, wheat and soy. And the legislation in 2021 added sesame. So what that means is anytime you buy food, if it has a warning about these allergens on the food that you eat, there's no requirement for this type of warning for excipients because they're considered the inactive ingredients. So interestingly, the European Medicines Agency has totally different rules for labeling. So they do actually include all of this in their medication warnings, but the FDA does not require that for drugs. And so if

you're actually ever interested, you can go to this. The link on the bottom with the EMA shows you all the different excipients that the EMA labels for. It's very extensive. Next slide.

So what is the risk of hypersensitivity? So to qualify this first, I am not an expert. I am not an allergist. I just went and did some digging. So it turns out soy allergies is 0.4% of the population. It's most common in kids. They usually outgrow it. True anaphylaxis is very rare. So when we're talking about a soy allergy, it's usually it's a little bit of itching or some GI upset. There is no safe level that has been established in people with soy allergy for either drugs or for medication. So that's the main thing. But the reaction is due to the soy proteins and the Lecithin that is used as the carrier is due to the phospholipid. There have been reports of excipient associated hypersensitivity reactions to soy in the literature. And when they look at that, that is usually probably due to some type of contaminant from the soy protein into the drug. Not exactly the Lecithin itself. I looked extensively and there are case reports with Omeprazole oral, Propofol IV, and inhalers. They don't have soy in inhalers anymore, but there was only one case of benzathine penicillin associated rash in Europe that I could find. And it was in a kid who received benzathine penicillin monthly and ended up having a reaction when there was a change in formulation, but it was just a little bit of a rash and it was nothing serious. Next slide.

So what about peanut allergy? So I was asked this question also, so I did a little bit digging about this as well. So peanut allergies, allergens and soy allergens actually share quite a bit of similar sequence homology. So there's a lot of overlap in their proteins and cross sensitization to soy is common. What that means is if you take a peanut allergy test, up to 50% of the people will also have a positive skin test for soy. But that didn't translate to actually true clinical cross reactivity. So clinical cross reactivity is actually super, super low. It's less than 5%, it's in some cases series it was even less than 1%. So there's no guideline on allergies with regards to peanuts and soy in drugs. So when you look at the allergy recommendations for food, this is the one thing that I can find, and this was a joint practice update from three different allergy groups in the United States. It was the American Academy of Allergy Asthma Immunology, the American College, and the Joint Council. So the three of them came together and sort of looked at all the data and they have the statement that actually says, because patients with peanut allergies generally tolerate other legumes including soy, a recommendation to empirically avoid all legumes is generally unnecessary. So this is what they said. So this is what I could find in a literature with regards to risk benefit. Next slide.

The other thing I did was to dig a little bit into seeing how many FDA-approved products in the U.S. actually contain Lecithin. This was actually kind of fun. So for anybody who was looking for package inserts for drugs, go to DAILY MED. So DAILY MED is a National Library of Medicine website that allows you to find all the package inserts for every drug that is FDA approved, including prescription as well as over the counter. So when I did this, can you advance, I found 3,124 products and these included things like cosmetics. So there are a lot of bare minerals, face creams and lotions. They included topical medications. I found IV and POs. I found OTC meds. I also found prescription meds and there was 3,124 products. I mean it was a lot. So the chances are even soy allergic people probably were being exposed to them without even knowing. Next slide.

So that of course doesn't help us as a clinician too much because we're worried about the legal aspect of it and it only takes one bad experience to make you afraid. So these are sort of my considerations for managing the soy warning. And I would just do this basically as common sense type of

recommendations, just asking them, do you have a soy allergy? And what kind of reaction do you have? I mean, if it's a little bit of a skin rash or a GI upset, clearly that's different from being having a true anaphylaxis, which is very, very, very rare. Have you ever taken any medications that contain soy that you know of? So patients who will really have soy allergies will know. They are actually the ones that will look to look at the excipients if they have a true anaphylaxis. So I've had patients, the patients that I have that ask about our excipients are the ones that know that they have problems. So like the lactose or whatever. So ask them this question, have you ever taken any meds? And you can also ask them for medications that they have taken and then you check that on DAILY MED and I'll show you how to do that next slide.

So if you go to DAILY MED, you can, on the top right hand there is this thing that says advanced search and you can actually put the drug name in and you can put multiple search criteria in. And so for here you can see I put in acetaminophen as the inactive ingredient and I pressed add, and then I can also put in Lecithin in the inactive ingredient. And I hit search. And what I found here was, if you can see it, there were 117 results. That's what I have circled at the top. And I just showed you sort of a smattering of the drugs that came up with. So there was a lot of over the counter Tylenol products and these included tablets, suppositories, liquids. And it was also in a lot of these multiple symptom cold relief drugs like Theraflu, NyQuil. And it was not just the name branded stuff, but like the CVS branded kind or the Walgreens branded kind.

It came up in all of them. So it's actually very prominent in a lot of products. So you can look at it this way. The other thing you can do is you can just put the drug name in at the top at the search bar. If you know exactly the drug that they're taking, you can put the NDC code in if you have a bottle. And when you pull up the NDC, it will tell you exactly if it has Lecithin than in it. So I hope that was helpful. That's all I have. And Kelly, what do you think?

Kelly Johnson, MD, MPH

Yeah, I think super helpful. I told you this already, but I now feel that you're sort of the world's foremost expert on what is Extencilline. I've learned a lot here. It seems to me that both Bicillin and Extencilline actually have this Lecithin product in it, which is where the concern arises about soy. And the fact it's labeled differently in different countries has to do with the fact that Europe is labeling food allergy in a medication, whereas in the U.S. we don't really do that. Is that sort of a summary of what the takeaways kind of are? But that's not to say if somebody is truly allergic to soy that you should give them Extencilline, but rather to say that you should ask about it and just know in the background that there is a difference in how medications are labeled between our countries. Would you say that's fair?

Kathy Yang, PharmD, MPH

Yeah, and I always worry. I worry twofold. One is that we're not being conservative enough, so we absolutely should ask. But at the same time, if you have a person who really should be getting Extencilline, I worry that we will not treat them optimally if we're too concerned about something where the risk is really low. And of course, that's sort of the balancing act. So doing more digging into each patient before you give the drug probably will make you feel better, make us all feel better that you've done our due diligence and we're sort of doing the best we can with the information that we have.

Kelly Johnson, MD, MPH

Totally makes sense. Okay, I'm going to move us along, just acknowledge some folks who contributed slides and information to this talk. I am going to just point out that the National Coalition for STD Directors does have a forecaster tool available online where you can go enter in your current Bicillin supplies as well as kind of your burn rate, how much you're using them up to be able to forecast how much supplies you may have over time as this shortage is ongoing. And that's just a resource for you all. And then I want to take time for questions. I know we have Tamara Ooms here to help us pick out some of the questions and we'll do our best to get through them all. I know it's been a pretty active Q and A, but we have some time to do this now, so I will stop.

Tamara Ooms, RN, MS, FNP

Great. Yeah, we've had a lot of questions, so I'm going to apologize upfront. Kathy, if I ask you or Kelly to reiterate something you've already said, I was trying to listen and look at the Q and A, so maybe just sticking to Extencilline for just a minute. When you talk about the split doses for Extencilline, Kathy, given this higher quantity of what we're trying to inject, is there a recommendation a person asked, does this mean we're actually giving four injections given that it's double and many people do give two. I mean the quantity and many people give two injections for Bicillin.

Kathy Yang, PharmD, MPH

Yeah. So you don't have to separate it into four, but you can separate what is comfortable. So typically three is about as much as you can handle. So in that case, you could split it into three. It doesn't have to be four as long as you separate them for a part enough on your injection sites.

Tamara Ooms, RN, MS, FNP

Right.

Kelly Johnson, MD, MPH

It does seem like in general, just to add onto that, it's a larger volume. It's probably going to be more painful if you're using Extencilline compared with Bicillin. Accurate?

Kathy Yang, PharmD, MPH

If you split it, then yeah, so it will probably be a little bit more painful. With Bicillin we don't mix it with lidocaine though so because it's in a prefill. You just give it. Right. This gives you the opportunity to do a little bit of lidocaine in it if you needed to. Right. So we don't do lidocaine. We do it with ceftriaxone, but not with Bicillin.

Tamara Ooms, RN, MS, FNP

Did you talk about Extencilline in pregnancy, Kathy, just to kind of make sure everyone gets it?

Kathy Yang, PharmD, MPH

Oh, that's a good question. I did not, but you should feel comfortable using Extencilline in exactly the same way you would Bicillin. They are identical medications. So there's no reason why you would pick one over the other. And part of the reason that the FDA brought the drug in is because of this issue. Right. Because there are populations where we cannot do doxy.

Tamara Ooms, RN, MS, FNP

Before we jump to a number of questions on doxy, that was definitely the most popular drug covered in the Q and A. Can you talk about ceftriaxone? It was mentioned that she saw ceftriaxone was listed as an alternative treatment at the beginning of the presentation. When would you use it?

Kathy Yang, PharmD, MPH

Kelly, do you want to take that one?

Kelly Johnson, MD, MPH

I can speak to that one. Yeah. So technically ceftriaxone is an acceptable alternative treatment for early syphilis. It does involve daily IM or IV injections of ceftriaxone for many days. So it's there, but I have had a very hard time imagining the patient or scenario where that makes sense to do. But it is an acceptable alternative treatment for early syphilis.

Kathy Yang, PharmD, MPH

The way I think about it's when we look at the sort of data, most of the data is with Bicillin or penicillin, and then the next one in line is sort of doxy. And once you get beyond doxy, everything sort of drops off a little bit.

Tamara Ooms, RN, MS, FNP

Thanks.

Kelly Johnson, MD, MPH

Probably our least evidence-based and exactly most logistically challenging alternative treatment. Fair enough.

Tamara Ooms, RN, MS, FNP

So moving to doxy, Kathy, can you tell us about the difference between doxy hyclate and doxy monohydrate?

Kathy Yang, PharmD, MPH

Yeah, it's fine. I mean as long as it's doxycycline, it doesn't really matter. We've had this question before about are the preparations different IR versus DR. And I don't think I've ever seen a case where we would select one or the other. It's just basically what is available in Cubist.

Tamara Ooms, RN, MS, FNP

And covered by insurance for someone.

Kathy Yang, PharmD, MPH

And covered by insurance. Exactly.

Tamara Ooms, RN, MS, FNP

Okay. What about the recommendation to have clients remain upright for an hour after doxy to avoid esophageal irritation? Do you think this is reasonable or warranted? Someone else asked about heartburn with doxy.

Kathy Yang, PharmD, MPH

Yeah, I mean, if they've had, so remember, these are side effects that occur, but not everyone gets them, right. So if it works for them, that's fine. I don't think it's a hard and fast rule that you have to tell everybody to do this, but if they tolerate it fine. It's not a big deal. There are some people who will get that a little bit of esophageal irritation when it floats up.

Kelly Johnson, MD, MPH

Can I ask one? I have one. I was just wondering actually this, it occurred to me one of our learning objectives was actually to understand why the Bicillin shortage is happening. And I'm not sure that in my introduction I covered that very well. So I wanted to raise that question here too. Why is this happening? What do you know? Any thoughts?

Kathy Yang, PharmD, MPH

The companies are always so hush about this, and it usually comes down to some key ingredient or delivery thing that they can't source. So in some cases it's been a raw ingredient. In other cases it's been like we don't have enough vials, so it's hard to know, which I don't know actually, which is the reason for this one. I think it usually is a raw ingredient issue, not so much a delivery system issue.

Kelly Johnson, MD, MPH

I've heard a couple of theories. I've heard one of the problems is just that Pfizer is the only company that produces Bicillin. So if Pfizer has an issue for whatever reason, that's a problem because it's a mono source. And then the other theory that I heard, which is interesting, is that there were actually some amoxicillin shortages recently that necessitated folks using Bicillin in scenarios where they may have otherwise used amoxicillin instead. And so maybe that contributed just a theory that I heard, but I wanted to mention it here too. I don't know if you've heard that.

Kathy Yang, PharmD, MPH

I don't know. That's a good question. We did have a run on amoxicillin a while ago, last year during the flu season. And I was actually concerned a few months back, I don't know if anybody remembers in the headline, there was a Pfizer plant in North Carolina that got destroyed by a hurricane, and we were terrified that that was going to affect drug supply. And that one turns out that the drugs there were mainly sort of the ones that were used in critical care, not so much the ones that were like vaccines and things like that, but they were also very hush about it. So we don't actually really know.

Kelly Johnson, MD, MPH

Thanks. I just wanted to ask that one. I'll turn it back to you now, Tamara.

Tamara Ooms, RN, MS, FNP

Yeah. And the theme of shortages, somebody asked about could there be a shortage of doxycycline? And I remember a colleague actually reminded me there was a brief shortage of doxycycline at some point not too long ago, if I remember correctly. So this person said their clinic had tried to order it recently, it was not available. But they haven't seen anything about a shortage listed anywhere?

Kathy Yang, PharmD, MPH

I haven't either. And doxycycline is different because there are multiple generic manufacturers that make doxycycline as opposed to Bicillin, it only has one. So that's probably easier to source. Right.

Kelly Johnson, MD, MPH

That is interesting question though. And I've heard that same question. It seems like hopefully not, but perhaps plausible if we are using doxycycline a lot. And it sounds like at least in that one clinic, it's been the experience. It's good to know.

Tamara Ooms, RN, MS, FNP

And in that, Kathy, someone mentioned that they were at a facility that treats patients with minocycline instead of doxycycline. What are your thoughts on that?

Kathy Yang, PharmD, MPH

I would stick to doxycycline. So I don't think we can make the leap. So from an infectious disease standpoint, it's difficult to make the leap of sort of activity of one antibiotic against an organism and extrapolate that to another drug, even if it's in the same class. So we do see susceptibility differences even within the tetracycline class. So for instance, minocycline is used extensively for staph aureus, for eliminating staph aureus carriage. We don't tend to use doxycycline for that. And the difference is because the kinetics are different, it gets into different body spaces. So I haven't seen the data on minocycline and syphilis, so I wouldn't be comfortable with it. What do you think, Kelly?

Kelly Johnson, MD, MPH

No, I mean I certainly don't have your sort of background PK PD expertise, but I will just say that would be outside of the guidelines. And so I personally as a clinician just would prefer to probably stick to doxycycline or you could use tetracycline, but the dosing is more difficult. It's four times a day and risk of more side effects and whatever the adherence problems might be. So I would personally stick with doxycycline if I couldn't get Bicillin.

Tamara Ooms, RN, MS, FNP

And maybe one last question, Kelly. I know we need to close soon, but maybe one of you could just briefly explain what a Jarisch Herxheimer reaction is, and then someone was asking, is that possible with doxycycline?

Kathy Yang, PharmD, MPH

Kelly, do you want to go for it?

Kelly Johnson, MD, MPH

Well, I don't know if it's possible with doxycycline, so you go for it.

Kathy Yang, PharmD, MPH

It's the question of whether it's, I mean, I don't think I've ever, I've never heard of it. It's really a thing about penicillin and remember the risk factors for Jarisch Herxheimer, the ones that we worry about are in pregnancy and we wouldn't use doxy in pregnancy anyway.

Kelly Johnson, MD, MPH

But I guess the idea, Tamara.

If a person has a lot of treponemes floating around as part of their syphilis infection and then they get penicillin, there'll be so much killing that'll make them very systemically ill sort of as if they have a really bad flu. And Kathy is correct that in pregnancy, I have found that people are really concerned about the potential for adverse reactions, especially late in pregnancy. That inducing potentially labor and stuff, I think is the concern. Right. Alright, well I think we are right at time, so we should probably close. I know there's still much, much, much that we didn't cover in the Q and A. I'm sorry we didn't get to everything. Maybe we'll have to have Kathy back for another Bicillin or whatever else we decide session upcoming. But thank you all for coming. Thank you. Thank you to Dr. Yang for being here, to Tamara for facilitating our Q and A and to everybody. This was a great session and we'll close there. Thank you all.