Development Considerations of Antimicrobial Drugs for the Treatment of Gonorrhea

Friday, April 23, 2021

9:00 a.m.

Remote Proceeding

Washington, D.C. 20001

Reported by: Carl Hellandsjo

JOB No.: 4500552

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C O N T E N T S

P R O C E E D I N G S

MR. FARLEY: We are joined by industry, thought leaders and fellow regulators from the European Union and Japan, we've come together today for discussions focused on facilitating and accelerating development of therapies.

Since FDA published guidance for industry entitled Uncomplicated Gonorrhea, Developing Drugs for Treatment in August of 2015, the need for new treatments remains. Drug resistance continues as a challenge and care standards have evolved to keep pace, leading to the update to CDC's treatment guidelines for gonococcal infection published in December 2020.

We need to consider our approaches to drug development to be sure that we are keeping pace. We have a workshop program for today that will facilitate a rich discussion of data and ideas to consider as we think about the best way forward in clinical trial design and conduct.

At this time -- Laura Bachmann from CDC to the microphone.

MS. BACHMANN: Thank you, John. Hi, my

name's Laura Bachmann. I am the chief medical officer and the acting deputy division director for the Division of STD Prevention at CDC. And on behalf of the acting director for CDC's Division of STD Prevention, Dr. Raul Ramagera [ph] and the rest of my division colleagues, I'm privileged to welcome you to this jointly sponsored workshop today.

While gonorrhea's an ancient infection, it's been curable for many decades. However, we remain challenged to control this infection domestically and internationally. The 2019 CDC STD surveillance data released last week reported gonorrhea case increases for the sixth consecutive year in the U.S. Despite STD clinic closures, reduced staff capacity and molecular diagnostic test kit shortages resulting in certain undertesting for infections -- all as a result of the COVID-19 pandemic -- there are ominous indicators that gonorrhea case numbers will be even higher in the 2020 data.

Yet there is hope. For the first time, the nation has an STI national strategic plan to provide a roadmap for multiple stakeholders to

develop, enhance and expand STI prevention and care programs at the local, state, tribal, and national levels over the next five years.

In addition, the National Academy of Sciences, Engineering & Medicine issued a report in March that further draws national attention to the STI epidemic -- outlines specific recommendations to the federal government and key partners for preventing and controlling STIs in the United States.

Both distinguished documents outline an incredibly important role that science will play in pushing these strategies forward, and clearly call out the need for development and uptake of innovative STI diagnostic technologies, therapeutic agents, preventive products and strategies.

Today, you will hear from leaders in the field of gonorrhea. From basic sciences to epidemiologists, pharmacologists, clinicians, drug developers and specialists in clinical trials. The speakers and panelists all spend a lot of time thinking about this bug. It is clear that the science generated from this group has already contributed to

recent changes in gonorrhea treatment guidance as will be described later today.

I'm confident that sharing science and the lessons learned from conducting the science will lead us forward so that we can bend the gonorrhea epidemic curve down in the future. I look forward to a productive session today.

Over to you, Carolyn.

MS. DEAL: Thank you, Laura. Good morning, everybody. My name is Carolyn Deal. I'm the branch chief of the Enteric and Sexually Transmitted Infections Branch at the National Institute of Allergy and Infectious Diseases at the NIH.

On behalf of the National Institute of Allergy and Infectious Diseases, I want to thank you for attending this workshop sponsored by our three agencies. It has been a pleasure to work with my colleagues at FDA and CDC to organize today's meeting.

As we are all aware, Neisseria gonorrhea presents a significant challenge to the public health community because of the capability to develop antimicrobial resistance quite rapidly. This

potentially limits our ability to have adequate therapeutics in our treatment arsenal.

The development of new therapeutics is one of NIAID's goals and we hope that this workshop will advance the discussions on how to most effectively evaluate potential new candidates.

We very much look forward to your input, your insight and your feedback on how to overcome the challenges in developing these new therapeutics.

Thank you again for attending today and we appreciate the effort of all the speakers and participants, and look forward to a productive meeting.

Now I'll hand it back to the moderators. Thank you again.

MS. YASINSKAYA: Good morning. My name is Yuliya Yasinskaya. I'm clinical team leader in the Division of Anti-infectives in -- FDA in the Office of Infectious Diseases, and it is my pleasure to share section one today of development considerations of antimicrobial drugs for the treatment of gonorrhea

together with Dr. Kyle Bernstein from the CDC.

We will be introducing today's speakers. The first speaker for session one is Dr. Jeanne Marrazzo. She is professor of medicine and director of the Division of Infectious Diseases at the University of Alabama, Birmingham.

Dr. Marrazzo is internationally recognized for her research and educational efforts in the field of sexually transmitted infections.

Please welcome Jeanne Marrazzo.

MS. MARRAZZO: Great. Can everybody hear me? I just want to make sure. I've been having some sound issues. I also don't seem to have my webcam, but I'm going to go ahead and get started anyway in the interest of time. I know we don't have much time this morning.

Anyway, it's fantastic to be here. I'm sorry we're not all in person and I am going to be very brief in these remarks because a lot of the discussion we're going to have is going to be going into a lot more detail about some of these issues. But I thought I would just start by noting that this

is the most recent update, which of course we're going to be talking about a lot, to CDC's treatment guidelines for gonococcal infection. And what we are facing is, of course as everyone in this room knows, the priority for a single dose of intramuscular ceftriaxone. And that's, of course, superimposed on the background of elevated antimicrobial resistance in gonorrhea which we have seen, of course, over the last several decades. And I think most striking in this slide, of course, is the resistance to azithromycin. So just to make sure you're all on the same page.

I'm going to start out with just putting some gaps and challenges in front of you and then go into a little bit of detail.

First of all, remember that the clinicals trials we're going to be talking about today that are looking at new treatments for gonorrhea generally emphasize genital outcomes. In fact, those are more or less the primary outcome of the trials that we're talking about. But I think it's going to be very interesting to consider the conundrum of pharyngeal infection.

Pharyngeal infection, as we'll talk about, of course is a major reservoir not only for disease transmission, but also for mechanisms to promote antimicrobial resistance. And of course, it's complicated because the treatment trials that we're going to talk about require a test of cure at the pharynx, but the test of cure mechanism that we're asked to use is culture, which is quite different than what we use to get people into these trials. So lots of discussion I think around these points.

I already showed you that there is really no universal option for oral therapy given the elevation of azithromycin resistance, and we do need pharyngeal therapy at this time.

Moreover, we continue to emphasize single-dose therapy for our populations, which I think may be doing them a disservice. And I think we want to talk about that today as well.

I'm going to show you some slides that are from the Infectious Disease Society of America and the IDSA, of which I am a board member, has focused quite strongly on antimicrobial resistance.

Unfortunately, even with a lot of pressure, IDSA has had limited success in working with other organizations in moving this forward. And in fact, of course, the FDA has not approved any new antibiotics, period, since 2019. And I'm going to talk about the PASTEUR Act which I think is a good first step, but which is also I think a bit of a challenge.

Now this is a very busy slide, but I just want to use it to sort of show you what the priority organisms are. And it lists various categories that are discussing these organisms on the WHO to the Indian authorities, to the CDC, both in 2019 and 2013. And you can see that Neisseria gonorrhea, which I've marked with a yellow -- a yellow arrow here, has been listed as an urgent threat since 2013. Despite that, we are still -- by the CDC. Despite that, we are still facing the challenge that we are in right now.

So let me go back here. So what is new and what is relevant I think for this discussion, many of you know that the Pew Foundation has been very involved in the issues of antibiotic supply and

antimicrobial resistance. And their website, I think, is a fantastic resource if you do want to go and sort of see what's going on. And I don't want to go into this in detail, but you can see that despite those escape pathogens that I mentioned in the slide before, despite the intense need for new antibiotics for very serious infections, we still have a real pipeline problem. And the Pew Foundation has really emphasized that we should focus on systemically available antibiotics in phase two or beyond given the challenges getting state antibiotics through the initial phases. And you can see here that only 15 antibiotics at this point are in phase one, which is a very, very challenging situation.

So the PASTEUR Act, just to give you a sense of what this is about -- and I think this represents a little bit of a ray of light and this is something that IDSA has been super involved in. It's called the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance. I admit that's a bit of a reach to fit the PASTEUR acronym. The end goal is to support development of new antibiotics and to limit

the increasing spread of resistant infections by emphasizing that it -- stewardship. You do not need to read through this. You'll have these slides, but you can basically see there are a number I think of tangible elements to this act that could really incentivize industry and authority to move these efforts forward. And again, these are the type of things that IDSA has been really championing and hopefully will be able to move forward.

It's important to know that in this highly politicized environment, the PASTEUR Act does have bipartisan leadership as noted here. And it's supported by a lot of organizations that will be familiar to those of you who have been in this field for a while. And it is supported also by some very, very strong -- recommendations.

Now I'm going to shift gears very quickly. Again, recognizing that I had only 15 minutes and probably will take even less than that. Just to talk a little bit about things on the horizon that we are not going to have time to get into today that really will impact how we think about the field

of gonorrhea and STI management going forward. And of course I think almost everybody in the room is probably aware that there is a very critical effort right now, led by NIH largely, as well as pharmaceutical partners to pursue the observation that the genetics of gonorrhea and Neisseria meningitidis, its close cousin, are really very similar. And the critical thing to know about these pathogens is that they share two key antigens. And I think that there's a fantastic story behind this of reverse facts analogy, really how this was described -- mostly by Rena Rampulo [ph] and his colleagues at Merck. But the bottom line is that the outer membrane vesicle and the NHBA antigens are present in both pathogens. They're surface exposed. They are highly conserved for the most part and really represent excellent targets for the development of cross-protections to these two pathogens.

And of course, this has been known for some time, but the efforts to move this forward in a practical sense got a major boost with this analysis -- which hopefully everybody is familiar with from

Helen -- Harris and her colleagues in New Zealand. When they published the study, looking at the effect of a mass meningococcal B immunization campaign using not bexsero, but a specific vaccine developed to control an outbreak in New Zealand of meningococcal -- invasive meningococcal disease and it's called the M-E-N-Z-B vaccine. It was given in 2004 to 2006. And what these investigators did, very creatively, was to go forward and look at a population of people who had or who had not been given this vaccine as part of this outbreak control attempt. They then looked, because they've got fantastic records, at the incidents or detection or report really of both gonorrhea and chlamydia in this group of people relative to controls. And they compared that two to chlamydia detection as well.

And the bottom line is, again, not having a lot of time to go into this is that the meningococcal group B vaccine showed a 31 percent effectiveness against subsequent gonorrhea in young people, age 15 to 30 years old. So very exciting.

It did not show an effect against

chlamydia, so that was good because you had a bit of a way to control for the behavioral aspects of these populations.

And then there are some interesting older data that are coming out as well that show -- that suggest that with perhaps less effectiveness and less precision, that there may even be an effect against gonorrhea associated hospitalization, which is really quite remarkable considering that gonorrhea associated hospitalization is a relatively rare outcome infection.

So that just leads me to let people know I'm going to go forward there that we are now engaged in an incredibly exciting study, and this is one of several studies that are going on. And New Zealand, of course -- is leading another study in men who have sex with men primarily. But this is an NIH supported study being done a spart of the STI clinical trials group that is actually going to test the hypothesis that bexsero, the currently approved meningococcal group B vaccine, does protect against gonococcal infection. And essentially, we're

randomizing 2,200 adults at risk for gonorrhea to either placebo or standard bexsero injection. And you can see the design here, the study's being done at four sites in the United States and two sites in Thailand. And I'm happy to say that as of yesterday, we had enrolled 30 people and are really looking forward to these results probably early 2024, given the -- given the COVID delays that we had, although it's possibly we may -- we may be able to detect -- sooner.

So we'll be following people for up to 15 months and we'll also be, importantly, screening them routinely for STIs. So we should get quite a lot of really interesting data. We'll be looking at antimicrobial resistance of the strains that do emerge, and ultimately hoping to look at some of the genomics associated with strains that specifically breakthrough for people who've gotten -- it'll be critical to look at this.

And I just want to remind you that remember that meningococcal vaccination is actually considered an immunization -- maybe an STI

immunization. I don't know that I would go that far. We don't really know that this is a sexually transmitted infection in men who have sex with men, but we are already recommending the group ACWY vaccine in HIV infected people, given that HIV infected people have a higher risk of invasive meningococcal disease.

So it would be pretty fantastic if we could substitute or augment that recommendation with a vaccine that is also active against gonorrhea, and that's what we will be hoping to do.

Just on my last couple of slides -- asked me to comment on a couple of other issues. Challenges in gonococcal diagnosis, you really can't talk about doing treatment trials without wrestling how you're going to detect not just people who are eligible and the outcomes that you want, but also reinfection and you want to, of course, be able to look at antimicrobial resistance.

The challenge here, of course, is everybody knows -- although not everybody knows this. I've been surprised, particularly talking to many people in industry and also some clinicians, that

many, if not most, gonococcal infections are asymptomatic or may have atypical symptoms. So routine screening is really important. The issue is that it's not being done as it should be, and this is especially true in HIV -- settings and it's especially true at anatomic sites not diagnosed by urine.

So we are really continuing to struggle with screening at the pharynx, screening at the rectum -- in particular in people who are attending HIV clinics and also in other primary care sites where care for people who might be at risk for these populations is being provided. So that is a major issue.

Self-collection I think has made some inroads into that, but you still have to have a clinical setting that emphasizes and makes available the tools to enable self-collection.

Of course we have limited availability of culture and there are practical barriers to getting culture. So if you have a patient who fails -- who fails treatment and you are concerned about antimicrobial resistance, you've got to arrange to

have that be done and that can be a barrier for some people. We also know that the sensitivity of culture is not as high as a nucleic acid amplification test. So you may not even get the organism if you do culture.

And the last thing I'll say is that point of care testing has been very slow to be developed. We've had some very encouraging developments in the last year. You can see there that the FDA very recently, last month, granted -- waiver for chlamydia and gonorrhea tests. This is about a 30-minute test -- really exciting -- but how quickly this is going to be taken up and how widely it's going to be available I think remains to be seen.

I'm going to stop there. I'm hearing Carolyn's audio and I'll thank you very much.

MS. DEAL: Thank you so much, Dr. Marrazzo. We are moving to the next speaker. Dr. Bernstein, are you on the phone?

MR. BERNSTEIN: Yes, I'm sorry. I had some technical difficulties, but I think I'm back in action now.

Good morning, all. My name is Kyle Bernstein. I am the branch chief of the Epidemiology and Statistics Branch in the Division of STD Prevention at CDC and it is my pleasure to introduce Dr. Teodora Wi who is currently a medical officer in the Sexually Transmitted Infections Department of global HIV, hepatitis and STI programs at the World Health Organization.

In WHO Headquarters, she is leading the development of STI guidelines, addressing antimicrobial resistance in STIs and facilitating the development of new STI treatment and diagnostics.

Thank you so much and welcome, Dr. Wi.

MS. WI: Thank you so much, Kyle, and good day, everyone. Thank you for the opportunity for me to talk about the policy, consideration and implication for drug development in relation to antimicrobial resistance in gonorrhea.

The AMR originating group in WHO selected 20 priority bacterias for research and development into new and effective drugs. And gonorrhea has been included as a high priority for

drug development based on the high community prevalence, reported resistance for all drugs recommended for -- treatment. And in addition I think because it's also considered by the US CDC to be an urgent -- of service -- and high priority -- from the Public Health Agency of Canada.

Also, 2016 -- we are also trying to revise our current estimate, but as of 2016, there's an estimate of 376 million new cases of curable STIs of which varies. And 87 million new cases of gonorrhea with the greatest burden in Africa and the western pacific region.

The estimated gonorrhea prevalence is 0.9 percent in women and 0.7 percent in men.

Gonorrhea is a priority pathogen for antimicrobial resistance surveillance. The WHO global antimicrobial surveillance program has been monitoring patterns of resistance to inform treatment recommendations. About 70 countries are currently reporting to the AMR -- data; however, there is also still a lot to be done in some -- gonorrhea AM surveillance program.

As you can see in the current map, just to just give you a little orientation where you look at this, and the blue indicates zero -- resistance or antibiotic. You have yellow which represents less than five percent resistance. Orange, that's 30 percent resistance. And pink, it's less than 70 percent resistance. And if it's red, it's more than 70 percent resistance.

And as you will note in here, 31 percent of countries have already reported the increased susceptibility or resistance to ceftriaxone. With about 41.7 percent of countries reporting "decreased" susceptibility to resistance.

Further down the line, you will also note that there's increasing number of countries reporting resistance to azithromycin with 83.6 percent of countries reporting resistance. And increasing proportion of resistance isolates -- that are being reported.

One hundred percent of countries have reported resistance to ciprofloxacin with majority of countries reporting high proportion of isolate

resistance with majority to ciprofloxacin -- high resistance -- I think it is not then practical to -- implement a guided treatment based on antibiotic susceptibility testing for ciprofloxacin, especially in these high burden countries.

One of the biggest challenge in the gonorrhea AMR surveillance system is the low number of countries reporting gonorrhea AMR data, especially in Africa where burden is high. Only 10.6 percent of countries are reporting gonorrhea resistance, for example in Africa.

One of the goals of the global health sector's strategy on STI is to reduce the prevalence of gonorrhea. This has been a priority STI just as a risk of resistance in a treatable gonorrhea.

In order to address AMR in gonorrhea, priority strategies include strengthening the gonorrhea AMR surveillance system preventing and adequately managing STIs. Again, developing new gonorrhea treatments and delaying emergence of resistance through adequate antibiotic -- including the development of -- point of care tests for

gonorrhea identification and antimicrobial resistance infection.

And lastly, I think as the most important thing is to also properly date gonorrhea vaccine development. A research and development roadmap was developed to address gonorrhea treatment with the following priority study -- priority interventions, but as you can just see, it's not just developing the new chemical entity for a new gonorrhea treatment, but probably also investigating and evaluating potential of existing antibiotics in their combination and also looking at exploring -- packaging and development of -- those combinations. And more importantly also is to support the development of simplified treatment guidelines and foster conservation of current and future drugs as part of the antibiotics -- programs that we have.

As part of the new gonorrhea treatment initiative, TPP -- target product profiles -- for gonorrhea has been developed to guide research and development. And in industry, we know that TPPs are used for planning to guide development --

characteristic. In regulatory context, TPPs are considered a source to frame development in relation to the submission of product -- in the context of public health, TPPs are usually -- to -- for funders and also for developers.

But as you can see in this later TPPs, the latest TPP that we developed, we've really indicate that there's a minimal TPPs -- the treatment for uncomplicated urogenital gonorrhea, but for the preferred TPP, we would rather also prefer that it is also providing treatment coverage for extragenital gonorrhea.

Accessing -- access affordability, as you will note in this TPP, has been really looking into the commitment of access as well as the -- strategy that promotes an availability of fair price. And when we say a fair price, it should be something that is affordable for health systems and patients, but at the same time they provide market incentives for industry to invest in innovation and the production of quality and essential health products.

I’m not going through all this TPP, but

just to give you some pointers on this that it should also be that the drugs should -- invitro activity against Neisseria gonorrhea resistance to extended spectrum cephalosporin and macrolides and that there's no cross-reaction to any other known antibiotic drug. And of course with clinical efficacy, if you should have a non-inferiority to clinical trial versus the current standard of care, and we depend on the US FDA for guidance regarding this -- efficacy.

Those regimen is something that have also been included in the TPPs. And this time, although we know that single dose is preferred, we would of course want to consider one to three doses in up to three days of drug regimen.

One of the things that would happen is that after a treatment is developed, it is critical that recommendations are made as a treatment for gonorrhea -- at the global level and especially also at the national level. WHO develops evidence-based guidelines based on the great process and we try to ensure that this is assimilated for a wider or -- especially for low- and middle-income countries. To

start with, it usually starts with a bigger question. Reformulate this bigger question which includes population -- intervention, this new drug, a comparator which probably would be the standard of care and of course identifying the outcomes like microbiology -- cure, clinical cure, site effects and all of that.

And based on the bigger question, we then gather the evidence, do systematic reviews on available clinical trials and then we access the quality of evidence for each of the outcomes that has been identified as critical.

In making the decision and making the recommendation, in addition to just looking at the quality of evidence for all these different clinical trial, other important considerations are also important to look into and I'm going to be discussing that as we move forward.

And we know for example that very important is making sure that we have good quality, randomized controlled trial so that we then develop high quality recommendations for this and a strong

recommendation for -- for the treatment of gonorrhea.

To start with, I think a clinical trial design is very important for us because I think it would be very helpful for us to develop our gonorrhea guideline and we also wanted to make sure that we have a strong recommendation based on high quality of evidence. And considering that I know all of you are really aiming to have this randomized controlled trial with all this very important factors that need to be considered.

Another area is really looking at the population because I think we need to include and be more inclusive with men, with women -- key population including MSM and female -- and also for HIV positive individuals.

In addition to this, it will be also looking at the intervention and the drug and dosage. I think the biggest area of challenge we have is really how do we make this "dosaging" in terms of the different anatomic sites. And again, it should be compared to the current standard of care.

In the area of recommendations and in

developing this recommendation, very critical is really having data on the outcome. And we do have very good available data on -- for example, clinical cure and side effects. However, there has always been an issue when we see other outcomes that are usually recommended by our guideline development group members, including for example issues related to compliance, complication, transmission to partners and the quality of life.

Overall, I think on all this trial, it would really be very important to look into antimicrobial resistance -- not only within this trial, but also looking at this in the higher community level.

In addition to the clinical trials in the development of guidelines, more data is also needed. Not only based on what the clinical efficacy or the quality of the -- of the -- of the -- of the drug, but looking into other areas or information that relates, for example, to -- and preferences, making sure that it is cost effective. Therefore, we also need data related to resources. Whether this would be

acceptable and feasible to -- to the -- population and also looking into the balance and benefits and harm of doing and -- treatment.

So overall, I think it's not just the clinical trial, but also looking into the use of the drug as part of the recommendation.

One area of work that has also been done is really modeling the issue of the five-person threshold for resistance to change treatment guidelines. Currently, WHO and I think also US CDC, that was an agreement long time ago that we change treatment recommendation based on a five percent threshold. So we did a modeling related to this and we would see that there's no evidence that changing the threshold from treatment change from five percent to ten percent for -- would affect the trajectory of resistance spread. And that if you will also look in here, in MSM -- also resort to current rapid rise in resistance, even faster than already transitioning to a new treatment recommendation. But it is much slower and much more diffused in terms of heterosexual transmission.

Another area I think is that in clinical drug development, it is so important to really develop new drugs because currently, we are the -- treatment. But again, it's also important to look into the access of the new antibiotic. How is it going to be positioned? Are we going to use it only -- drug and how does this affect our essential medicine at least moving forward? And making sure that -- we make sure that we conserve this new drug that we have in terms of having a different -- antibiotic use. So going with a new drug, I think it would be very important to also look into -- developing and introducing this low point of care test that is rapid and affordable.

So thank you very much and I think that's the end of my slide. Thank you.

MS. DEAL: Thank you very much, Dr. Wi, for your wonderful presentation. We're next going to Dr. Laura Bachmann, who's the chief medical officer and acting deputy division director in the CDC division of STD Prevention.

Dr. Bachmann has her license in STD and

HIV care with experience in practicing academic and public health settings.

Welcome, Dr. Bachmann.

MS. BACHMANN: Thank you. Today, I'm going to cover the following topics and I'm going to -- from the framework of some of the changes that were made to the STD treatment guidelines around gonorrhea, I'm going to talk about some surveillance data, but also talk about some of the other considerations that went into those changes -- including antimicrobial stewardship and some of the topics listed here.

I may skip through some of the -- for the sake of time, some of the summary slides. You'll have this slide deck after the meeting.

So starting with the surveillance data, as I mentioned earlier, our report was released last week. We have now had the sixth consecutive year of increases with over 600,000 cases of gonorrhea reported in the United States. Increases in all regions of the U.S. And when we look at the distribution of GC across the United States, you'll note there's a lot of heterogeneity, so increases were

seen across regions, but there's heterogeneity across regions -- and even within states, by county. So while 94 percent of counties had at least one case of gonorrhea reported. Of 3,142 counties, 73 counties accounted for around half the cases. And so this heterogeneity of distribution does have implication for the efficient conduct of studies of therapeutic interventions.

Rates went up in men and women. And since 2015, rates have increased about 56 percent in men, around 40 percent -- 44 percent in women during the same timeframe. And as before, the rates are highest in adolescents and young adults. And we don't have time to go through all of our wonderful epi-slides, but you know, they're diagnosed in STD clinics only, like, 6 to 10 percent of the time, depending on whether you're talking about females or -- or males.

So I'm going to switch gears a bit and cover some of the gonorrhea resistance project that we have. And, unfortunately, don't have time to focus on all of them, but I'm going to focus on just our sentinel surveillance studies in yellow here. As you

can see -- in green and then surge in purple.

And we'll go through this timeline here and you can see in 1986, just as our core national surveillance system of antimicrobial resistant GC that was established in 1986. In 25 to 30 clinical sites, males were sampled only, urethral isolates only.

Over time with increasing concerns of antimicrobial resistance, surge was rolled out. Surge is not a surveillance study or -- or project rather, it's more of a rapid detection and response to antimicrobial GC and also expanded to females and included both genital and extragenital isolates.

And during that time, we also expanded capacity for gonorrhea lab testing through the national laboratory infrastructure for antibiotic resistant organisms -- or the ARLNs -- and this is where all the samples are sent for susceptibility testing through agar dilution. In 2017, surveillance was expanded further through Aegis where Neisseria meningitidis species were detected, female specimens were detected and extragenital isolates also were collected.

Now understandably as the capacity has increased, the capacity to perform antimicrobial susceptibility testing has increased. So prior to 2016, we performed about 5,700 tests a year, and then post-2017, averaged 8,500 to up to 12,000 tests a year.

Similarly for whole genome sequencing prior to 2016, performed about 10 to 200 tests a year, and post-2017, up to 5,500 tests a year. Now there was a dip in 2020 with the pandemic.

Why am I telling you all this? Of course whole genome sequencing is important in terms of being able to track resistance and also have a resource to develop diagnostic testing, but also is a resource for others as well. And over 9,200 sequences have now been submitted to the public archive as of 2020.

I'm going to switch gears a bit and talk about some of the -- data and -- because this directly informed some of the changes. And this is a graph of the percent of isolates with elevated minimum inhibitory concentrations to azithromycin cefixime and

ceftriaxone. And as you can see here, cefixime encephtroaxin in green and yellow respectively, the MIC's elevation to remain relatively low, thankfully. Where azithromycin in pink, that's continued to increase over time. And in 2019, 5.1 percent of isolates had elevated MICs.

If we look at the regional distribution of the prevalence of elevated MICs -- and this is once again to azithromycin specifically -- you can see that there are some regional differences with the prevalence of isolates being higher in the west and the northeast compared to the south. And -- which is an interesting finding.

And then if we look at our -- surveillance data -- and note that these are 2018 data, not 2019 data -- and look at the percent of isolates with elevated MICs to azithromycin. And this is by anatomic site and by gender and gender sex partners, there's a couple take-home points here. So men who have sex with men, in red, had in general higher prevalence of isolates with elevated MICs. But women and men who have sex with women also had a

relatively high prevalence of elevated MICs to azithromycin, and in general, higher pharyngeal prevalence. Though note that the numbers are very small, and so it really -- too small to draw definitive conclusions here, but the point is that we do have some extragenital site surveillance ongoing at this time.

I'm going to move on now to a topic that actually -- this concept really -- a lot of the thinking around not just the gonorrhea treatment changes, but some of the other changes that will come forth in the 2021 document. So -- and that is antimicrobial stewardship and antibiotic resistance. And this is the cover of the 2019 CDC threat report. And as was mentioned earlier, gonorrhea has been in this threat report now several times. And the concept of antimicrobial stewardship or, you know, not exposing individuals to antibiotics unless the benefit clearly outweighs the risks is a really important concept that's gathered more attention since the last treatment guidelines meeting.

Also, the attention to the fact that

antibiotics have collateral impact on cooccurring pathogens is an important concept that we kept in mind.

In addition to that concept, we also were keeping in mind, you know, the rule of extragenital sites. And I want to focus on the second point here and that is that we understand that we don't understand well the interaction between organisms and the environment and these extragenital sites. So, you know, gonorrhea is more difficult to eradicate in the pharynx. We do think the pharynx may be a special place for the development of drug resistance. And the asymptomatic nature of these infections at these sites may select for resistance due to under detection and undertreatment potentially. Understanding the drug penetration at these orifices is limited. And then separately, or maybe related to the drug penetration issue perhaps, we've had concerns about rectal chlamydia and treatment response. So some of these concepts or principles also were considerations in the deliberations.

So going back to the microbiome

concept, this is one that -- one study, but a large study that looked at populations of children where they randomized -- azithromycin distribution versus placebo, and they received azithromycin twice yearly and then compared their gut resistance and found that the children who were exposed to azithromycin had higher prevalence of resistance elements to macrolide and non-macrolide antibiotics, including betalaktams

We also worry about other pathogens that may travel with gonorrhea and other STIs. So mycoplasma genitalium -- in this study of US STD clinics -- there were six STD clinics that were in this study, and then with urethritis who presented in these clinics, about 29 percent of them had MGENT. And of those men who had MGENT -- to see of the 80 percent had resistance, so -- as defined -- or macrolide resistance as defined by the prevalence of 23S rRNA resistance mutation. So obviously quite high and quite concerning.

And then furthermore, we have documentation of increasing macrolide resistance in enteric pathogens. And we don't have time to go

through these different studies, but it's been reported nationally and internationally at this point.

So aside from resistance, the rectal chlamydia issue has been one we've worried about for a while now, and we did also have recently results from a randomized controlled trial of doxycycline versus azithromycin for rectal chlamydial infection and -- that was reported at the 2020 STD prevention conference. And this study is -- was stopped early due to the marked difference in efficacy. As you can see in blue, for doxycycline, versus orange for azithromycin. Doxy was clearly more efficacious than azithro for rectal chlamydial infection. And so this kind of settled that issue as well that we've been concerned about for a while and had other studies that were not randomized controlled trials pointing to concerns.

And while that study was in MSM, rectal chlamydia's also not uncommon in women with chlamydia. And, you know, is actually quite common. A history of anal sex is not predictive of infection in women. And there is some concern that this is an area that still

needs to be further studied, that here could be some autoinoculation from the rectum into the GU tract again. So more, you know, raising concern for inadequately treated rectal infection.

So I'm not going to read through the summaries, but those were some of the deliberations and considerations also that we thought about needs to change therapies.

So also playing into this is pharmacokinetic and pharmacodynamic considerations and my colleagues who come after me will be much more sophisticated in their explanations of this. So I'll give you more of a layman's term breakdown, but ceftriaxone and azithromycin are -- are very different and ceftriaxone has very variable pharmacokinetic. The half-life of ceftriaxone and azithromycin are different, with azithromycin being in tissues for weeks later after dosing. And so there was some concern there about the disconnect there and the longtail for azithromycin maybe making it more susceptible to the development of resistance.

In addition, there's been a very

helpful mouth model that has been developed and used to estimate PKPD parameters for gonorrhea cure at the genital tract for susceptible and resistant gonorrhea. And the lowest of ceftriaxone dose to cure 100 percent of the susceptible gonorrhea at 48 hours post-treatment is estimated to be 5 milligrams per kilogram in the mouth model. And so when we took that dose and extrapolated it back to the human weight, that was an optimal dose for a 50-kilogram human being.

Unfortunately, the reality is the average American is now 80 kilograms, and so when we looked at that, that was -- suboptimal dosing for the average American and -- and implied that we perhaps needed to increase the dose of the ceftriaxone.

So in summary, we have new pharmacokinetic data, some more consideration about the differences in the pharmacokinetics between these two drugs that also weighed in these considerations about treatment changes.

So what did we decide to do? I think probably a lot of you know this, but 2015, this is what we were working with. Ceftriaxone, 250

milligrams plus a gram of azithro. To remind you that azithro was even if chlamydia was ruled out. It was really there to protect the ceftriaxone. And so this was what we recommended up until December 18th when the MMWR was released and the recommendation then changed to ceftriaxone, 500 milligrams IM in a single dose for individuals who weighed less than 150 kilograms. For persons who weighed greater or equal to 150 kilograms, the recommendation was for a gram of ceftriaxone. And this is for uncomplicated gonorrhea of the cervix, urethra or rectum. And it really should say pharynx as well. Same dosing for that.

If chlamydial infection's not been excluded, it's recommended to treat doxycycline for seven days and then test to cure is now recommended for all pharyngeal infections regardless of regimen used.

So in summary, gonorrhea treatment continues to involve. We've had emerging resistance and then also things change over time. Science changes. Antimicrobial stewardship continues to carry more and more weight over time. The azithromycin

resistance continues to increase with impact across multiple organisms. And then we've had new data on efficacy for chlamydia, particularly rectal chlamydia, that factored in along with the science of pharmacology and pharmacokinetics.

Monitoring the emergence of ceftriaxone resistance is even more critical, especially now as we're going to monotherapy. And new preventive and therapeutic agents are needed, and that is what this workshop is all about.

So with that, I would like to thank the following individuals and I will wrap it up. Thank you for your attention.

MR. BERNSTEIN: Thank you, Dr. Bachmann. Our next section will include two presenters that I will introduce before they begin. First, we will hear Dr. Magnus Unemo who is an associate professor at Orebro University in Sweden and directs a global WHO collaborating center for STIs, as well as the Swedish reference laboratory for STIs.

His research spans Neisseria gonorrhea and other bacterial STIs resulting in more than 400

peer reviewed PubMed index publications and numerous chapters in international scientific books.

Dr. Unemo will be followed by Dr. George Drusano, who is a tenured professor and the director of the Institute for Therapeutic Innovation at the University of Florida, College of Medicine. His interest is in optimizing therapeutic outcomes for patients with serious infections and finding algorithms to suppress resistance emergence in pathogens. I will now turn it over to doctors Unemo and Drusano.

MR. UNEMO: Thank you very much for that introduction, Kyle. Can you all hear me?

MR. BERNSTEIN: Yes, I hear you.

MR. UNEMO: Thank you. I'm very grateful and happy for the invitation to this important meeting. I'm also very honored to start this -- I will give together with Dr. Drusano.

Many of you already know, Neisseria gonorrhea has shown an extraordinary capacity to develop or acquire basically all known types of antimicrobial resistance -- which has resulted in --

of treatment. Only antimicrobial as you know now have left the -- gonorrhea treatment -- ceftriaxone in higher doses frequently or without -- sidelines.

Clearly -- some problems with -- clearly, new drugs for treatment are essential. As many of you also know and also have read about in -- now evidence of the first international spread of ceftriaxone strain or clone. Obviously it's the -- biologically fit to spread -- cases have been identified in -- countries, Canada and -- 2018 was the first -- combined with high level resistance -- identify. However, there were only occasion -- and Australia.

As also shown -- there is an -- number of countries -- resistance of ceftriaxone -- global -- gonococcal -- lacking in our geographic -- can be help served -- including large parts of Africa, Central Asia -- Central America and Caribbean. However, the important thing is obviously this -- resistance translates into clinical failures to cure -- cases. Fortunately, the surveillance of suspected and verified treatment -- vast majority of countries --

sporadic and -- surveillance re-expanded and strengthened.

We looked into the -- verify treatment -- ceftriaxone, verified according to -- WHO or even -- criteria that these are rather few -- ceftriaxone, but they still have failures -- those have tried -- azithromycin -- therapy as well as the ceftriaxone 1 gram of therapy. We can also -- one were in the pharynx and the ceftriaxone plus azithromycin -- subsequently treated several of these failed cases, which may of course also --

Obviously, the WHO global cost will collaborate with most -- of significant -- but it also -- the limitations that have been discussed previously include things like -- number of countries -- as well as about -- some countries -- lack of standardized global -- lack of harmonized -- as well as I mentioned --

But what is also -- lacking -- my opinion -- very limited understanding of the dynamic --

UNIDENTIFIED SPEAKER: Sorry, Dr.

Magnus. You're actually cutting out. Can you get to a better area so we can hear you better?

MR. UNEMO: Is it better now?

UNIDENTIFIED SPEAKER: Yes. Thank you.

MR. UNEMO: Thank you. What we also have mainly not discussed this sufficiently is the dynamic and direction between the bargain antimicrobials as well as about the ideal dosing for effective dose -- Neisserian gonorrhea kill as well as suppression or resistance emergence and amplification, which are basically two different goals of the therapy.

We had not had any detailed understanding of the antimicrobial -- dynamics basically -- the microbiology and pharmacology. And this is -- focus much more. So for new antimicrobials as well as some currently used, we really need to avoid the same fate by improved PKPD knowledge and -- all relevant PKPD and prediction studies before the new antimicrobials are introduced for treatment.

The requirement of more appropriate PKPD -- to optimize treatment using current novel

drugs have also been earlier addressed. It was very nicely emphasized in -- workshop in 2018 hosted by STI -- by NIAID and -- MID -- some key questions -- essential in this -- were formulated.

What do we really know? In 2019, Fabian Kong [ph] in Melbourne, Australia, attempted to compile all relevant data and published a review about pharmacokinetic considerations regarding the treatment -- STIs. The main focus on azithromycin, but all relevant STI antimicrobial -- then became clear that even for our best gonorrhea antimicrobial, ceftriaxone, having -- limited knowledge of why it works so well. Of course -- it is -- by good urine levels and by availability; however, it also has a low volume -- high protein -- rather poorly -- and what also became clear that protein binding -- active antimicrobial -- if there's really a lot between antimicrobials that these carry -- some antimicrobials also dependent on the -- for example -- finally, the fact we don't know at all how these protein bindings vary --

Furthermore, it also appeared

relatively clear that the antimicrobial -- and really not be strongly associated with -- as you see concentration of ceftriaxone -- extremely low -- ceftriaxone evidently is very effective in curing all pharyngeal -- and similar situation for --

So for the most asymptomatic pharyngeal gonorrhea, which are more difficult to cure and potentially -- for emergence of resistance -- antimicrobial, we really lack a lot of -- the lack of strong correlation between -- and treatment -- can only be hypothesized to be -- also the high saliva flow rate, swallowing of saliva that -- is that -- of that bacteria is replaced about every -- hours.

But we also have suboptimum knowledge regarding all the possible sides of pharyngeal gonorrhea that is based on the findings -- combined with the fact that we do not know how antimicrobial distribution can be -- different pharyngeal -- create further difficult --

Finally, the fact that pharyngeal gonorrhea's usually asymptomatic. And accordingly limited inflammation and the tight junctions

presumably -- of many antimicrobial --

First very nice study for gonorrhea in my opinion was the one by Horro Jester [ph]. Nearly 40 years ago, he examined the PK determiners of cure of gonococcal -- penicillin -- when male prisoners had been volunteering to be experimentally infected with the gonorrhea strain -- different penicillin -- the males cured -- sorry. The males cured from gonorrhea had the theorem concentration of total penicillin which -- remaining for more than seven to ten hours, about three, four times -- penicillin MIC of the infected -- however, this study had some limitations. As all studies, it -- only limited number of -- the culture for diagnosis, instead of a more sensitive modern molecular diagnostics, and also the -- only the total penicillin -- not the free one.

Worryingly, in my opinion, that the -- that have also been expanded to the efficacy of several other antimicrobials -- classes.

Another very nice study I think is in the early -- ceftriaxone -- MIC of more than or equal to 20 hours is required for cure with ceftriaxone.

This study also suggested ceftriaxone MIC of the .25 up to 2 milligram per liter. Basically, the resistant strain resolved in low -- all of only zero to -- hours for the currently identified ceftriaxone -- which clearly indicate that even ceftriaxone 1 gram would cure all the gonorrhea -- also this study of -- limitation -- only use treatment -- dose -- ceftriaxone was only theorem of plasma concentration -- ceftriaxone and pharyngeal infections were not --

So based on all what I have described so far, which knowledge is really lacking regarding -- gonorrhea treatment -- answer this, obviously we approach in outstanding research, we approach to Dr. -- then became very clear that we had a knowledge of -- of the gonococcal -- resistance suppression, which can also -- those two -- knowledge about the possible -- to optimize alkyl and -- as well at the same time --

And finally, infection -- by a lot of -- also have learned how extremely complex -- therapy is to -- understand, even more difficult to optimize --

Finally -- competent STIs like

chlamydia, in addition -- Dr. Drusano, we have a lot of work to do -- topic. Because we need to start obviously somewhere -- at the previously mentioned workshop to optimize -- sexually transmitted infection -- formulate to some key aims -- focus on. That is for gonorrhea. Ideally, in all different side and all currently -- to determine -- optimize those based on those. Evaluate the -- and suppressional resistance. Obviously -- side effects -- examine and understand -- not before we have this -- single antimicrobial -- start to understand and optimize dual therapies.

-- subsequently organized the very -- national PK workshop in Geneva -- create -- focus on PKPD considerations -- therapies for uncomplicated gonorrhea. Both challenges -- is a workshop -- future area for PK -- research on antimicrobial for treatment of gonorrhea -- further discussed in detail -- and strongly emphasized that we need better models for these examinations -- models, which Dr. Anne Jerse will talk about, so we will avoid in our talk. But also, the dynamic type of invitro hollowfiber infection models and properly address -- PD

considerations in -- this type of hollowfiber infection models -- gonococcal infections and PKPD treatment efficacy in single -- doses and identify deal doses and also address resistance emergence and suppression at different doses. Basically -- address most of the questions that formulated this -- and no hollowfiber infection -- although unfortunately -- existed for gonorrhea, a lot due to the difficulties -- develop this model for Neisseria gonorrhea -- which is very -- sensitive to many factors -- difficult to properly grow and synchronize manner -- however, in 2020, Brian VanScoy -- in collaboration with PFK published a very nice study regarding the relationship between -- exposure and prevention of -- therapy resistance amplification -- Neisseria gonorrhea hollowfiber infection model. It very nicely showed how -- doses of 0.5 gram or more -- doses -- gram administered -- hours and -- gram after eight hours. Both effectively killed Neisseria gonorrhea as well as prevented -- amplification.

We have also in our laboratory developed, standardized and quality assured

hollowfiber infection model based on the geographically -- genomically diverse -- strains -- behaviors and current treatment -- reconsider the importance to use -- in order to further relate our outcomes to outcomes in the --

Dan Jacobson [ph] is doing most of this work which fall in close collaboration with Dr. George Drusano and his team, as well as of course -- many great people -- who currently also found our -- perform the collaboration -- companies.

We'll hopefully also soon publish our first azithromycin data where we can show based on ceftriaxone -- urine concentration that 125 milligrams up to 1 gram of ceftriaxone effectively eradicate highly susceptible strains -- they can show that 1 gram eradicates all susceptible and resistant -- however, 500 milligram does not eradicate high level resistant strains -- MICs of 1 or more -- but as we know, the most -- for azithromycin treatment -- where we have extremely limited PK data as I explained.

Accordingly, based on the very limited literature, we had to basically do our best to guess -

- as mentioned, the ceftriaxone concentration in saliva is very low, so it can really not be associated with treatment outcome in the pharynx. And due to this research, that you -- data from an old paper -- they -- concentration -- compared to serum.

So with this tonsil concentration was best guessed that we could use and we combine this concentration -- ceftriaxone protein binding -- shedding another very nice study by Jeffrey Bloomer [ph] and George Drusano.

Based on these estimated ceftriaxone pharyngeal concentrations, based on the tonsils, we can show that ceftriaxone, 1 gram, eradicate all except high level resistant strains -- 500 milligram do not eradicate strains with -- resistance -- that is MIC of .5 -- liter or more. And this is of course worrying and even more worrying that we have performed -- simulation of interpatient variance in the PK parameters -- simulated 5,000 patients based on the data from the -- by Bloomer, et al. Based on this simulation, many patient -- three -- sufficient time of -- ceftriaxone over MIC, which is efficacy driver.

Here we have only estimated -- hours. Consequently, essentially more failures to -- with ceftriaxone 500 milligram and 1 gram can be estimated -- particularly on the pharynx, but not exclusive --

We have also very recently finished pharmacodynamic evaluation of dosing -- and resistance of suppression for -- dynamic hollowfiber infection model. This project is obviously in collaboration -- team at -- and is now in review.

Very briefly, the dose range hollowfiber infection model experiments for -- WHOS -- strains that simulated zoliflodacin or those of .5 to 8 grams and follow for seven days. Zoliflodacin doses of 2 gram or more were required to both kill Neisseria gonorrhea and suppress -- emergence of zoliflodacin resistant -- sorry -- oral doses of zoliflodacin 1 gram or lower also failed in the dose -- hollowfiber experiment where the total doses were equally divide -- doses and gave them -- 12 hour or 8 hours. At this stage, I will leave over to Dr. Drusano.

MR. DRUSANO: Can you hear me?

MR. UNEMO: Yes.

MR. DRUSANO: Hello? Okay, good. Thank you. Well, thanks to everybody for having someone onboard that doesn't know anything about gonorrhea, neither personally nor professionally.

So if you would go back one, Magnus, please? Or whoever's doing the slides, go back one? Thank you.

So this is the outcome -- one more forward now. One more forward, please.

This is the outcome of the two hollowfiber studies that we analyzed in a population sense. I would urge you to look carefully because there will be a quiz afterwards.

And now the only things I would like to point out is if you look at the -- growth for the sensitive strains, it's about 1.1 on the mean, 1.09 in the median, but if you look at the resistance, it's .56 and .6. The point being that the resistant isolates are less "viofit."

When you look at the rates of chill, it's 4.5 and 4.7 for the mean and the median. And when you go for the resistant, it goes down by a third

to 1.5 and 1.5. And then the C50s are higher, and so what this is telling you is it's a heck of a lot harder to kill the resistant isolates.

Next, please. Next, please. There we go.

This is just for the PKPD geeks amongst you. This is just the idea that we have actually fit the model to the data. And on the top row is the so-called pre-Bayesian or population fits, and on the bottom row is the Bayesian or individual fits. And this actually is pretty good because it's all the data modeled simultaneously in this particular circumstance.

There are three panels, that's because there are three system outputs. The drug concentration is in, A, pre-Bayesian. The total bacterial burden is B, and then the resistant bacterial burden is in C. And the same three in D, E, and F, but in the -- for the so called individual or Bayesian fits. So at least for this one, the fit of the model to the data was quite acceptable.

Next, please.

Okay. So in point, the parameter vector -- oh, I'm sorry. Yeah. You went one too far.

This is for WHO X and we see pretty much the same sort of circumstance. And we had a little bit more difficulty with the resistant clones in this one in the pre-Bayesian or population fits, but in the Bayesian posteriors you can see the slopes are very near one, small Y intercept and very high R squares. So again, quite acceptable.

Next, please.

So employing the parameter vector identified in the slide a couple of slides ago, we calculated that a dose slightly greater than a gram but less than two grams will suppress resistance emergence. And actually, the number that we came up with was about 1.1 grams and above will suppress amplification of less susceptible populations for zoliflodacin. Now, this really isn't an enough, and there's two things that make it not enough. And that is we have to look at Neisseria gonorrheal strains that potentially are predisposed to resistance emergence. Hypermutators. Ones that already have a B

subunit type of mutation for zoliflodacin. That's mission critical, so more information is required.

We must then use a population, PK parameter vector and covariance matrix to perform a Monte Carlo simulation and you look for a dose that would attain the resistance suppression exposure for a larger portion of the target population.

Generally, we look for at least 90 to 95 percent target attainment in this particular circumstance. And it helps immensely to have that human PK information in the population of interest. That is patients who got zoli who also had Neisseria gonorrhea.

Next, please. Almost done from me.

So we -- okay. Go back one, please. Go back one, please. Go forward, sorry. One more. There we go. Stop there.

Okay. So what we did here is we took the WHO X reference strain and we look at the rates of kill for 1 gram, 2 grams, 3 grams and 4 grams and we look at them in different ways. We look at the whole dose once, half the dose twice and a third of the dose

every eight hours. And what you see is quite straightforward. The single dose once actually gives the highest rate of kill that intersects zero earliest. You see that for the 1-gram dose. You see it for the 2-gram dose. What you also see as the dose goes up, things start to pull together. By the time you get to 3 grams, there's very little difference between what one sees with the once, twice and three times dosing. And then when you get to 4 grams, once and twice layover one another. And this is not a surprise because zoliflodacin is very concentration dependent in rates of kill.

Next, please.

So daily administration always produced the most rapid rate of kill. The advantage dissipates as the dose escalates. Rate of kill approaches a maximal rate, as it always does. The real advantage though is that if you give it once a day, this -- one need not worry about adherence with subsequent doses.

Now, the impact of exposure -- rate and resistance suppression is the real reason to take the hollowfiber data and perform this mathematical

modeling exercise. Let me also say this only applies to zoliflodacin. I guarantee you that as you get more resistant ceftriaxone -- higher MICs and you're trying to prevent resistance, I can absolutely guarantee you that multiple administrations are going to give you a much better system outcome for suppressing resistance. So you have to understand what you're trying to do and with what drug you're trying to do it.

Next, please. I think that's it for me, but I guess we'll see.

Yes. And now we're very quickly going back to Professor Unemo. Thank you for your attention and I'll mute.

MR. UNEMO: Yes. You can hear me?

MR. BERNSTEIN: Yes, we can, Magnus.

MS. DEAL: Yes, we can.

MR. UNEMO: Thank you. Finally, we also -- I just wanted to stress that the additional need to perform for new antimicrobials investigations -- predictor assistance emergence, sickness of those resistant strains that spread as well as -- potentially causing a resistance or only predisposing

for resistance emergence. And this we need to do before the antimicrobials are used in clinical practice. And due to this -- we have also performed zoliflodacin study examining gonococcal strains preexisting and/or invitro selected -- zoliflodacin resistant mutants.

And conclusions -- next slide, please.

Conclusions basically what I had said, we need much more surveillance. I want to stress that we really need to have appropriate PK data for all infection sites, particularly pharynx because those data we use in all these models. These examinations also need to include interpatient variance that is modeled for these PK data in population modeling. We really need to determine and optimize the PKPD -- and doses for both kill and the resistant suppression while obviously avoiding serious adverse effect.

We need to improve the understanding of a single and multiple doses as we now try to do. The potential benefit depends on the PKPD drivers -- specific antimicrobials. And when we have a single antimicrobial knowledge in regard of PKPD

considerations, then we can go forward trying to optimize also dual therapies.

And finally, we think PK status as well as -- infections as pharyngeal -- should ideally be included in all treatment trials. Thank you for your attention.

MS. DEAL: Thank you very much, Dr. Unemo and Dr. Drusano, for this presentation. We're moving on with our agenda and the next speaker before the break today is Dr. Anne Jerse. And Dr. Anne Jerse is a professor in the Department of Microbiology and Immunology in Uniformed Services University in Bethesda, Maryland. Dr. Jerse has pioneered the -- animal models of Neisseria gonorrhea genital tract infections, and -- gonorrhea and chlamydia coinfection, which her laboratory uses to study -- genesis and the spread of antibiotic resistance through compensatory mutations.

Dr. Jerse, take it away.

MS. JERSE: Thank you. Good morning. Can everyone hear me all right?

MS. DEAL: Yeah, we can hear you well.

MS. JERSE: Okay. Great. Okay. So it's true that we've been working on animal modeling of gonorrhea for a long time. And more recently, we've been trying to adapt the models we've developed for product testing. Much of this work has been done in collaboration with NIAID to try to accelerate product development and we are really enjoying doing this.

I have a couple disclaimers. We work with a lot of companies under subawards with their NIH grants or CRADAs. We also have an interagency agreement with NIAID to help test products. And then of course my opinions do not necessarily reflect the opinions of our university, the US government or the Department of Defense.

All right. So as you know, most STDs are very host-restricted and the gonococcus is as well. It's a human-specific pathogen with no outside animal or environmental reservoir. And as such, it is very well adapted to human mucosa. It has evolved a lot of host-restricted factors and interactions that ensure its survival on human mucosa. That's its main

place that it lives. It's the only place it is. And so that's cause -- that causes a lot of obstacles then when trying to develop animal models.

And so for lower urogenital tract infection models, the only animals that have been successfully infected long-term are chimpanzees, both males and females, that's not used anymore for gonorrhea research. And then female mice that are given estradiol to stabilize their estrous cycle or their reproductive cycle in the most hospitable phase for the gonococcus.

And so I'm going to just talk a little bit about what experimental murine infection looks like in terms of how well it mimics a human infection. It's a vaginal inoculation and the bacteria are localized in the vaginal lumen. In vaginal tissues, cervical tissue, and we do see them in the lamina propria. So it does invade into the tissue.

They do replicate in vivo. We get about 100 to 100,000 CFUs per single vaginal swab during infection. Infection can last as long as a couple weeks, depending on the estrogen used. And the

recovery with gonococcus is cyclical, so if you look at the red line, that's the number of CFUs we recover over the course of two weeks. And you see it goes up and down. This has been reported in cervical isolates for women and we've shown that it's hormonally driven. And it also appears to be hormonal driven in women as well based on work in the early 1980s.

In Visby mice, we have a -- influx which is the blue line. And that's also cyclical, also hormonally regulated. And then important for vaccine development, there is a very poor adaptive response and it's not protective. Mice can be reinfected with the same strain, just as occurs with humans.

So we have tested a lot of products and we have a protocol. This has been pretty -- established by Christie Connolly [ph] in my lab. And what we do is we inoculate the mice vaginally with Neisseria gonorrhea and we let them be infected for two days. We take pretreatment cultures and then we administer the antibiotics. We can do up to four test groups in an experiment and then the positive control

depends on whether you want to test a ceftriaxone sensitive or resistant strain. Then we can use ceftriaxone or gentamicin in as a positive control, and then we compare that to the product vehicle.

Vaginal cultures then are taken daily for eight days, and so you get a number of CFUs recovered over that period for individual mice, and then the average for the group. So clearance rate is also followed this way. And we have several strains then that we have used in the mouse model. These are Visby mice and they differ in their antibiotic susceptibility.

All right. So again, we do a lot of testing and there are four published reports using mice then to predict the efficacy of antibiotics, which are shown on the slide. One of them is a model that's used by -- that Dr. Hiltke will be talking about. That's the bottom one that -- mice. But I think this has now become part of the preclinical testing of antibiotics -- gonorrhea.

And so Dr. Bachmann talked about the PK studies that NIAID helped us do. This was very

largely led by Ann Ekon [ph] who was really helpful in helping us understand this and how to do this. We started with ceftriaxone. And so on the top left, what you see is a dose response for ceftriaxone looking at plasma levels. The MIC of the sensitive strain that we usually -- FA1090 is indicated. And the MIC of the ceftriaxone in resistant strain H041 then is much higher.

And so this is an antibiotic that's driven by time over the MIC. And you can see it's much more challenging then obviously for the H041 strain.

So when we infected mice with FA1090 and gave the same doses of ceftriaxone, if you look at the middle panel, you have the clearance over time, and then below that is the bioburden. And the green color indicates the lowest dose then that cleared infection within 48 hours. So if you look on the right, you can see that as well. So the 5 -- per kilogram at 100 percent clearance -- lower doses did not. And then below that, the time required then was -- or that dose was above the MIC was 23.6 hours.

This model was also useful for predicting or helping us design treatment regimens then for H041. So here we have the MIC again on the upper left. And so by doing modeling -- using modeling software then we could see that if you give two or maybe three doses of ceftriaxone at 120 mgs per kilogram, you might be able to get the concentrations high enough then to clear this strain.

If you look at the middle panel then, the only one that got 90 percent and then 100 percent at 48 and 72 hours respectfully -- respectively was the three-dose regimen of 120 mgs per kilogram. So if you look, that's shown also on the upper right. So 90 percent of mice were clear then with that treatment regimen. And that also corresponded to 23 hours.

So there seems to be a lot of interest in the community in developing improved fluoroquinolones. And so -- inhibitors. And so we tested ciprofloxacin as well. This is not published yet. And so here we have the plasma levels of ciprofloxacin in the upper right. We did in parallel then treatment of infected mice with these

concentrations below that. And the top dose, 60 mgs per kilogram then cleared infection of a sensitive strain, which is shown also on the top left within 48 hours. And that corresponded to an area under the curve of 264, which is a little more like what you would give someone with a complicated infection. But at least we have that number and that may be helpful for people who are designing treatment regimens for antibiotics that are driven by area under the curve.

So when you're continuing to do these types of studies and one of the things that is very useful for us is by doing the in vivo efficacy studies, we're able to identify some inhibitory doses and that is helpful when trying to test adjuvant therapies that don't directly kill the gonococcus, but you want to give it with another antibiotic. So these are really valuable data. We're also starting to look at two different antibiotics at once. We have -- going in the lab now and we hope to have protocols for testing that in the future.

Okay. So, as has been mentioned by every single speaker, gonococcus infects many

different sites. And so one site of infection that we're interested in then is the upper reproductive tract in females. Women suffer the most morbidity and mortality and we were inspired by a comment in the 2015 treatment guidelines by Kim Workowski and Gail Bolen [ph] that there aren't many assessments of treatments for clearance of these upper tract infections. There's one example I've shown here, Walker 1991, they looked at 108 different women given broad spectrum antibiotics plus doxycycline. They had either gonorrhea or chlamydia or both with and without anti-ropes. And of those that failed, all of them had gonorrhea. And that suggests that maybe we're not effectively treating gonococcal PID as well as we should. And this study predates the emergence of resistant strains of cephalosporin. And so this I think needs to be revisited.

And so obviously one of the things that might be happening is the bioavailability might not be as good in the upper tract and that literature that helps us think about this that I know of is women that undergo prophylactic antibiotic treatment before

hysterectomy, they've done studies to show that while plasma levels may be the same, there's differences in levels in the upper tract, in the endometrium particularly. And they may be not high enough then to kill STD pathogens.

So there are no upper -- there weren't any upper tract models for Neisseria gonorrhea until we -- I'll show you the one that we've just published. And so we're hoping that we'll be able to use that then to look at this better.

Two other considerations for women is pregnancy, and so there are many physiological changes during pregnancy that can affect how well antibiotics profuse into the uterus. So there may be a pregnant mouse model would be useful. And then I can't find anything in antibiotic bioavailability with respect to the menstrual cycle. I think that's another understudied area.

So here's our upper tract model. This should be in JID maybe by -- by fall. And so what we figured out after years of trying is that the gonococcus doesn't grow in the endometrium because it

doesn't have a usable iron source. And so we're giving my human -- and there are also trans -- mice out there. And you can see on the left, the vaginal swabs -- mice that got human transferrin have a higher colonization load, but it's not critical for infection because the untreated mice also are colonized, which we already knew. But then if you look on the right, you can see that we now get endometrial cultures for as long as seven days, even ten days in our newer studies. And they also can be recovered from the oviducts. And so our plan is to do pharmacokinetics with this model and in vivo efficacy studies to see if we can get this established -- we're looking at this body site of infection.

Hand in hand with this are chlamydia gonococcal coinfections. Dr. Bachmann talked about this. They are very common. They really, really need to be considered when developing drugs. And they are in fact listed as a goal in the target product profile that Emily Allorel [ph] published in 2017. So dually active agents I think are coming -- coming into the pipeline.

And we have a couple models of coinfection. We use chlamydia muridarum because that better mimics the disease that occurs in humans and nice. This is one that we published years ago where we pre-infect the mice with chlamydia and then give them Neisseria gonorrhea. And the reason I think it's really important to look at coinfection with testing drugs is in this model, we get a higher number of gonococci recovered from mice that have chlamydia. So look at the blue line versus the red line. And that has been reported in a study on adolescent girls who were infected with chlamydia, gonorrhea or both. And so we think as a target that you're looking for, it may be higher than in a coinfected host.

So it's really important to look at upper tract infection with these pathogens and we can now, with the human transferrin protocol, infect the endometrium and oviducts with those pathogens. Recovery of Neisseria gonorrhea is on the left and chlamydia's on the right. The open symbols in both cases are just the single pathogen and the closed are the coinfected pathogens. And so hopefully this will

be useful.

As a first step towards doing this, we have given -- established coinfection and given them just ceftriaxone and doxycycline. A and B is recovery from the lower tract. It's pretty good. Day three and day five -- inoculation. And then the upper tract, we were able to clear both infections and we need to continue this, but this is one way that we're going.

So unfortunately, there isn't an extragenital tract infection model yet. So pharyngeal model -- the pharynx I think has many more host-restricted -- human transferrin alone doesn't help. We've given human factor H, that doesn't help. We think colonization receptors are important and we are working on this. There's some hints from the meningeal coccyx carriage literature of what receptors might help. And so I don't know, but maybe we can get that -- that going, or another lab can.

Rectal infections have been unsuccessful. We've tried -- just not gone anywhere. And then there's disseminated gonococcal infection,

which is on the rise. And there are some models just looking at bloodstream -- recovery from the bloodstream, but nothing goes from the epithelial site -- site into the bloodstream yet, but I think as we understand those restrictions in different body sites, that maybe one day we can get something like this going.

So in summary then, my time's up, so it is indeed a work in progress. We I think have made progress in upper tract infections. We now have a coinfection model that will be available and we're working on extragenital tract infection models. And these are all the people I need to thank. This was NIAID together with Walter Reed [ph] and our group at -- is Dr. Connolly who's critical for these studies. And then Michelle Colleguia [ph] and Clara Constantinople [ph] have worked on model development, the upper tract and the coinfection model. Thank you.

MS. YASINSKAYA: Thank you so much, Dr. Jerse. And Dr. Jerse's presentation today completes half of our morning session. We're ready to take a break. We're going to be on the break until 10:55.

Please come back at 10:55 so we can continue on with our agenda. Thank you very much.

MR. BERNSTEIN: Thank you all for returning after the break. Our next speaker is Dr. Tom Hiltke and he is the chief of the STI section in the Enteric and Sexually Transmitted Infections Branch at NIAID. He's also the program officer for the STI therapeutics and vaccine grant portfolio within the branch.

I'll pass it over to Dr. Hiltke.

MR. HILTKE: Thank you, Kyle. Thank you everyone for attending this session. I'm going to talk to you today about preclinical efforts to support gonorrhea drug development. I'm not sure if my camera is working because I can't move a little -- a little box here to -- to maybe preview it, but if it isn't, it's your loss.

So I work in NIAID, but I am part of the Division of Microbiology and Infectious Diseases -- it's, well, called DMID -- and I was asked today to present to you our efforts in the offering preclinical services -- DMID preclinical services to developers of

-- of antigonorrhoeic therapeutics.

So in order to do that, I thought I'd first just outline and show you the graphic representation of all the support that DMID has to reduce the risk for product development of therapeutic agents. On the backdrop of this slide is the product development pipeline. And you see on the top in these blue boxes from left to right, the initial hit to lead optimization going through preclinical phase one and phase two and so on.

Looking at the boxes below that, just point out that we have -- DMID offers a large portfolio of grants for the research on product development -- therapeutic product development. Many different grant types, and these span from the initial basic research in -- identification all the way through phase two, clinical trial support.

Next under that is a green box. This is the product development contracts. These are contracts that are to product developers. They come through a funding opportunity known as the broad agency agreement. Broad agency agreements are offered

or issued by DMID usually on a yearly basis and often times they are concerned with antimicrobial resistance. And often times they're also concerned with therapeutics development, so something I could talk to someone -- anybody who wants to go over any of these funding options after the meeting, if they want.

The next two green boxes are the what we call collectively all the services that DMID offers. The preclinical services, which I'm going to talk to you in more detail in this talk and then we offer phase one services and phase two -- phase one services through our new IDCRC program, which if you know anything about DMID, this replaces our initial or original BTEU clinical trial services. I can, again, talk about that with anybody. I'm not going to touch upon those services -- clinical services at the moment in this talk.

Just a note that the preclinical services and the phase one IDCRC services are services where we access contracts and we perform the work on behalf of a product developer. In contrast to the product development contracts and the grants where we

provide direct funding to the product developer and they use -- and they use those funds to develop their product.

Lastly, I have CARB-X written there. CARB-X with an arrow. That signifies that we at DMID don't put money into CARB-X. The agreement we have with CARB-X is that we preferentially prioritize services for product developers who have one CARB-X projects.

And so if you look on the very right then, our whole goal is to de-risk product development such that we can help companies or developers bring products to late-stage development partners such as BARDA, DOD and industry.

We'll drill down a little bit more on the preclinical services. I took this from another set of slides on the preclinical services, so it still has the -- another depiction of the product development. In this case, it's an arrow and it shows how we cover all facets of the product development arrow with our services. But this -- this slide has a nicer list of the characteristics of the service.

So DMID as I kind of showed in the last slide supports extra -- research to control and prevent disease causes by virtually human infectious agents. If HIV, we have another division for HIV as you know. The -- preclinical service program provides broad based services wherein preclinical product development, we provide project and product specific data, provide difficult to source -- research reagents. Try to facilitate basic research through all phases of the preclinical development pathway.

The two I have on are probably the most important that I have of the characteristics here bolded, are the last two. And we really feel that these services are intended to be gap filling. As the first statement here says, "We are really responsible for almost all human infectious agents." So we really don't have the funds to fully fund the development of a -- the preclinical development of a product. And what the whole intent is is that we will work closely with you to define the gaps, what are the things that are holding you back that we could fill to move your product along.

And then the last one is something that we just get -- you always get questions about is there is no need for preexisting or -- or past NIAID or NIH funding to access preclinical services. And also preclinical services are -- are available to non-US entities.

To drill down a little bit farther, this is a graphic pictorial representation of the preclinical services. I didn't mention this before, but we also -- we both use both therapeutics and vaccines are covered in our preclinical services. And so the right-hand side -- right-hand corner of this slide we can ignore for this particular talk.

And so if we focus in under the bar of therapeutics, we have broken up the preclinical services into large chunks and these are -- these are then chunks that are actually representative of individual umbrella contracts -- and I'll get into that structure in a minute in the next slide. But these umbrella contracts fall under these categories -- invitro assessment of antimicrobial activity and interventional agents, pharmaceutical products and

chemistry manufacturing and controls documentation per IND. So these are the major foci of the umbrella contracts.

And you'll note that we even go to large ticket items such as G&P in this -- in these -- in these contracts.

If you look all the way over to the right then, we feel that this is the full suite of capabilities to address -- key caps in your product development.

Underpinning all of the therapeutic and vaccine contracts or services is what we call the research resources, which is mainly composed of the preclinical models of infectious diseases. And these are mostly animal models, as you can see by the pictures. And then the all-important BEI resources, which is another research resource which most of you are probably familiar with -- which is the very large repository for -- for -- for DMID.

So drilling down even a little bit farther, this is what the pharmaceutical product -- I just chose this one. The pharmaceutical --

biopharmaceutical product services umbrella contract looks like. We call them umbrella contract because this contract was -- after a series of contractors were admitted to a pool. And so these contractors provide all of the services that you see in the green box.

We use a task order system, so for example, someone like me who is interested in helping one of you out for providing a services for your development of your product, we would put a task order for process development. For example, it's that center -- it's that center green box there. Our pool of contractors can bid on -- on that particular task order. Once we award the task order, then we introduce you and you work intimately with the -- with the contractor in order -- who will provide the service for you.

What you get in return, of course, is the final and official -- final report and the complete dataset.

So you see pharmaceutical product services via product development and planning --

development and process development, G&P manufacturing, regulatory CMC documentation and support.

I have a similar slide on the interventional agent services. This is something that would be a little farther to the left if you look at the product development pipeline. And these are services where we can help you with lead identification, development, chemistry, medicinal chemistry, manufacturing, invitro and in vivo preclinical safety talks, PK, preclinical development and planning. We do offer PDP development or -- to those who are really just starting out in the -- in the -- in the product development space.

So I'm going to have two slides on individual task orders that are specific for Neisseria gonorrhea. As you can imagine, the last couple slides there were just for general therapeutic development.

The first one is Neisseria gonorrhea MIC testing task order. This is in the invitro assessment of antimicrobial activity umbrella contract. The service or the task order itself

consists of 100 clinical isolates from the CDC DISK [ph] program which was described in a previous talk.

And we have -- these are strains that are -- are recent strains. They have Y-geographical diversity, but only within the US since this is -- these are from the DISK program. And they have diverse antibiotic sensitivities. Although I do point out that -- because I get this question a lot -- we currently don't offer a true ceftriaxone resistant isolate in this panel because it hasn't come up in the US yet. We hope to get one if one does, but we do have what would be considered the decrease susceptibility isolates at .125 for ceftriaxone.

This -- we employ the CLSI outer dilution method along with your dilutions of your product, you get six control antibiotics listed here. And the timeline for this task order is you get your full report two months from the receipt of the compounds by the contractor.

Sorry. The other one is the -- gonorrhea infection model task order. This comes under our preclinical models of infectious disease

umbrella contract. As Anne even mentioned, we are currently using the overoptimized -- estradiol treated -- model. This model is similar to that of what Anne described, except that the mice a couple of weeks before use are -- the ovaries are removed. This allows for when estradiol is given to the mice, that essentially 100 percent of the mice will be locked into the appropriate stage of the cycle that is permissive for gonorrhea infection.

We use only -- so far right now -- we're new to this model. We're only using the FA1090 challenge strain. Typical experiment you can get is up to 10 groups of 5 mice per group. There's a baseline group that is sacrificed at two hours and those are used to determine dose. And then ceftriaxone positive control, usually a vehicle negative control group and then the rest -- the seven other groups you can choose as you will. You'll work closely with the contractor to setup the treatments in those groups. This only has one timepoint which would be -- counts after 26 hours post-challenge.

So for these services, if you're

looking for services specifically for a gonorrhea therapeutic or something related to gonorrhea, or any -- any STI besides HIV -- I recommend that you either contact me -- and I'm sorry. These things are yellow, but I'm sure you'll get a copy of these slides and you'll have my email. Or you would contact -- Kim Murphy [ph] who is our branch's product development specialist.

For any other information on the preclinical services, these are the catchall emails for those umbrella contracts that I showed you in the previous slides. And then there's a preclinical services website that you can access for -- for more information.

So finally, I would just end with one -- one item. I was also asked if I can comment on new tools for antimicrobial resistant gonorrhea and therapeutic development. And I -- and I -- and I think we got a thorough -- in the last several talks, we got a thorough education on what I think is the new and important innovations and research going on now for the development of new tools as far as PK,

hollowfiber, looking at doses, using the animal model to abridge PK from animals to humans. So I think that's probably the most important tools that are coming out for drug developers to use.

So the only one thing I could think of that wasn't covered in all those and I just want to bring your attention to Jeff Klausner's recent study on resistant guided treatment for gonorrhea. This is where he showed the proof of concept that you could use PCR assays or genetic assays to determine -- insensitivity and provide that information in real time to -- to guide treatment of gonorrhea patients. And so I suggest you take a look at that.

And then what most -- in that same vein is this rapid diagnostic for gonorrhea. Federal -- 19 million federal prize. That was issued to Visby Medical [ph] and Visby Medical was nice enough to show -- give us a picture of their prototype device. And if you can see that there, it's based on their PCR platform, point of care diagnostic where within 30 minutes, you could get the results on a swab for a positive for gonorrhea and sensitive to ciprofloxacin

to guide treatment of -- of gonorrhea.

So I just wanted to point that out, that I think this is -- on the horizon, this is something that is going to happen. We're putting some funds and support into these types of diagnostic point of care platforms.

Going also beyond genetic determination susceptibility. The technology's growing where we'll probably have -- we'll probably have phenotypic determination of sensitivities in a point of care device.

And that's all I have. Thank you for listening to my talk.

MS. YASINSKAYA: Thank you, Dr. Hiltke. We are moving onto the next presentation by Dr. Erin Duffy. Erin Duffy is the chief research and development at CARB-X. CARB-X is a global nonprofit partnership dedicated to -- research to tackle the global rising threats of -- welcome, Dr. Duffy. Take it away.

MS. DUFFY: Thank you very much. As was just said, CARB-X is a global not-for-profit

organization funded by the US, the UK and the German governments, as well as the Welcome Trust and the Bill and Melinda Gates Foundation.

Our vision is life-saving innovation to keep the world prepared for dangerous bacterial infections. Our mission then is to accelerate a diverse portfolio that will prevent, diagnose and treat -- or treat bacterial infections. And our goal is to progress those products towards clinical development and -- and regulatory approval.

In addition to funding, we support these programs with a large network of external experts, subject matter experts and cross project initiatives.

As said here on the slide, we do focus on the AMR threats identified by both the WHO and the CDC.

To date, we have funded 85 projects since inception, which was 2016. Presently, we have 56 active projects across the three pillars of treatment, prevention and diagnosis. We've deployed or obligated a little over 300 million dollars towards

those programs. These programs come from all over the world and have represented 11 countries. We've had eight project graduates for therapeutics and prevention. That means the successful completion of a first inhuman program, and for rapid diagnostics it means successful completion of verification and validation.

Two of our projects have gone onto receive contracts with BARDA -- advanced development contracts -- and of course that's our goal, not to end, you know, at first inhuman, but rather to bring these products all the way to patients.

Our portfolio is large and -- and certainly scientifically diverse. Today it represents 34 therapeutic products. So these are largely either new classes or new classes with a novel mechanism of inhibition. It also comprises a number of non-traditional approaches.

We have 13 products in prevention. This covers not only vaccines, but antibodies, live biotherapeutics, phage -- both engineered phage and also phage uses delivery vehicle and small molecule

programs.

Finally, just yesterday I believe we announced the ninth program -- active program in rapid diagnostics.

Okay. So among of course the programs or the bacteria that we do focus on is in fact Neisseria gonorrhea. In our treatment portfolio today, we have three active programs focused on gonorrhea. I'll just take them from left to right. We have a program that is focused, of course, on membrane biogenesis by inhibition of the -- ACP -- fatty acid biosynthesis enzyme. This is a program from Debbie O'Farm [ph]. The program is at the preclinical stage and the molecule is noted as W1453.

In the middle, we have a program with microbiotics. This is focused on trans-translation which is main ribosome rescue pathway and bacteria. I think there was a recent paper disclosed -- or recent molecule disclosed as exemplary of this program and nature in communications. This is a new class and a novel mechanism of inhibition, of course of a very highly validated target for antibiotics. This is an

early-stage program and we are very excited to be advancing it with them.

Finally on the right is a program by Venatorx. This is a program looking to block cell wall synthesis by binding to the bacterial penicillin binding proteins in Neisseria gonorrhea. The molecule is a cyclosporin A and this is also an early-stage program. I should mention as well that all three of these programs do have the option for an oral form.

We also very recently have announced our first program focused on gonorrhea in the prevention space. Of course, this is the native outer membrane vesicle program of the Jenner Institute and Oxford University. Of course we heard earlier today about bexsero and -- and, you know, somewhat importantly, this approach of course is -- risk because of that work. And so we're very much looking forward to advancing this with them. It is in the lead optimization stage.

And then finally, building on Tom's comments at the end of his talk, we do also support two programs today that are focused on diagnostics for

gonorrhea. We recently announced a partnership here with novel micro devices. This is a rapid point of care molecular diagnostic program. Multiplex nucleic acid amplification technology, plus detection of resistant markers, "decipro" and third generation cephalosporins from vaginal swabs and urine. A neat thing about this is it's battery powered, which you know should serve to, you know, broaden its use not only from high income countries, but also low- and middle-income countries. It's rapid turnaround and of course it employs microfluidic technology.

On the right is a program from Talis using slip chip technology. The neat thing about this is it's a disposable cartridge containing all the reagents necessary for isolation and purification through amplification and detection. So here, we're looking at bacterial ID and phenotypic AST with a rapid turnaround.

I want to mention that CARB-X is a lot more than funding. I said this on the first slide. And so we like to call these acceleration activities or acceleration themes. And in here I listed many of

them, so there's -- there's work that we do on the pre-award side to help applicants prepare for a successful transition into CARB-X. Once the programs are in CARB-X, of course, we surround them with a strong company support team. That does include subject matter experts. We have about 150 that span the range of breast -- and depths of expertise necessary for discovery in early development of these products.

We also support them through an internal RND team that we've built in -- in just the last few years.

I've highlighted here something called cross project opportunities and I'll describe that on the upcoming slides, particularly how it relates to our gonorrhea efforts. And of course we do have and are constantly looking to build or accelerate to our network that, you know, is geographically diverse and helps our programs both in terms of business and also scientific pursuits.

So in terms of these cross-project opportunities -- and I should say these are led by my

colleague, Richard Alm [ph], who's a leader in our RND team internally at CARB-X. The goal is to identify and fund areas where CARB-X can accelerate the portfolio. So this is not to -- you know, when -- when product developers experience problems, there are often common themes there. And rather than build individual units of work to ask questions about, you know, existing pools of resistance or anagenic conservation or, you know, challenges with toxicology. Rather than to do this in every one of these programs and learn and relearn the same themes, let's take a step back as CARB-X and identify some common themes, build the research plan around that and either sole source it or work among our network. Work with our colleagues at NIAID to try to bring a work product forward that we can share not only with our product developers, but also with the greater ecosystem.

So there are a variety of projects that are underway. Today, we have one looking at preexisting resistance. This is for our treatment portfolio that does include looking at contemporary isolates of gonorrhea. We're doing this in

conjunction with IHMA and -- and, you know, our product developers are taking advantage of that. Also looking in the prevention space of anagenic variability.

We also have programs focused on key safety risks. So we do have a number of peptide programs in the portfolio. And there, of course, a concern is nephrotoxicity. Not isolated to peptides, but -- but certainly known there. And we are working with the University of Queensland in order to determine whether there is a suite of invitro and/or in vivo preclinical models that would be helpful in terms of putting into -- flow downs for different programs to most expeditiously determine an advantage in nephrotoxicity.

We have been heavily engaged with our colleagues at NIAID in terms of discussing improved animal models of infection. This includes both Neisseria gonorrhea as well as urinary tract infections.

So let me just get to some thoughts here on animal models and infection. It was really

nice to follow this morning's talks because, you know, in a way, Anne Jerse answered a lot of questions here.

So, you know, for us as we know, you know, what we have been focused on as a community is this so-called time therapeutic or therapeutic time, you know, which has emphasized the number of hours drug concentrations are over the MIC90 or some mathematical multiplication of that. However, of course, as we know for drugs that aren't driven by time, there hasn't been an understanding of -- of what the particular drivers should be. So it was great to see Dr. Connolly and Dr. Jerse's publication of ceftriaxone -- and the results there. It was great to hear that there's been some activity looking at the -- at least the ciprofloxacin. And what we want to encourage and get involved with is really then building this picture out for the multiple classes and examples therein that have been either used clinically or studied more recently clinically so that we can get a very good understanding of both the tie of efficacy and PK among several strains so that we can best drive these programs forward.

Hollowfiber's terrific and there was -- it was great to hear Dr. Unemo and Drusano's presentation today, but certainly early in discovery, a more cheap and cheerful animal model that we can understand the key endpoints and how to drive programs forward is very much in our interest.

And so with that, I thank you very much and I'm looking forward to the rest of the day's talks.

MR. BERNSTEIN: Thank you. Our next session is two speakers. And -- sorry. We have two clinical doctors -- sorry -- who are coming to speak next. First, we have Dr. Hilary Reno who is an associate professor at Washington University in St. Louis, in the Division of Infectious Diseases with a focus on sexually transmitted infections and HIV. And Dr. Reno will be followed by Dr. Candice McNeil who is an associate professor at Wake Forest University, School of Medicine, in the Department of Medicine section on infectious disease.

Dr. McNeil is also the site principal investigator for the Wake Forest STI Clinical Trials

Unit and the CDC-funded North Carolina Strengthening the US Response to Resistant Gonorrhea or SURRG site.

Thank you and the floor is yours, Dr. Reno.

MS. RENO: Thank you. I'm going to confirm that you can hear me.

MS. DEAL: Yes.

MR. BERNSTEIN: Yes, we can.

MS. RENO: Great. So thank you very much for having myself and Dr. McNeil discuss the environment in STI clinics as pertaining to the clinical trial recruitment of patients.

Our motivation is that research and recruitment should center the people that we serve. To inform that goal, I'm going to review the evolving nature of STI clinics as well as the impact of expanded care models on patient recruitment and these new clinical environments that we find ourselves in.

Dr. McNeil and I will present two case studies by exploring the successes and challenges we have observed at each of the traditional STI clinics that we direct. Dr. McNeil will then examine the role

and continue the engagement and summarize our point.

So STI clinics or sexual health clinical settings are evolving environments, even outside of the COVID pandemic. Traditional STI clinics see a high volume of patients, usually from underserved communities -- changes, funding availability and other factors mean that STI clinics know how to be adaptable. And of course that's been very useful in this past year.

STI clinics are increasingly using innovative care models to increase services for our patients, and those are listed here. We're going to hit on each of them a little bit.

So sexual health clinics have been using express visits to reduce wait times and increase number of patients seen for many years. I'm going to go through express visits in a little more detail in a moment, so put a pin in that one.

STI clinics also can offer PREP and PEP services. And these patients may be a group that return regularly to the sexual health clinic for care. Of the 31 clinics that were recently engaged in a

training and technical assistance program by the National Network of Prevention Training Centers, all but 1 of 31 clinics offered at least a PREP assessment and referral. And 22 or 77 percent offered PREP by prescription for patients seen in the clinic.

Patients that follow-up with the same clinics will have frequent STI testing, and perhaps this could offer another population of patients for trial recruitment.

With the pandemic, we also saw that telehealth was a hot topic and is being used by sexual health clinics. I don't think we know how telehealth would impact patients potentially for recruitment, but it will be interesting to follow that.

So each of these services influences how long a patient is at clinic, how familiar they are with our clinical studies, etcetera. And therefore, their availability and willingness to participate in trials.

So let's take a closer look at express visits. So express visits are a triage-based STI testing without full clinical exam. So this is not --

they don't look universally the same from clinic to clinic, but this is the pretty important principle. That there's not this physical clinical examination occurring during these visits.

So at first glance, I really thought express visits might be a hindrance to recruitment for trials. My clinic currently, 15 percent of our visits are express visits and there's some clinics that could certainly have a higher percentage of visits using this pathway. But after thinking about it for a while, I actually think patients that use them might present an opportunity and not a missed opportunity for patient recruitment.

With express visits increasingly used in clinics, do remember that there's lack of a -- in these visits because the physical exam wouldn't have been performed. But on the other hand, they have not received preemptive treatment until their test comes back. So this is an opportunity to give patients info on current trials running in the clinics, but they also may be having limited staff contact. So a lot of this would have to be automated and looking at

pamphlets and things that they could read.

But again, these patients usually would not have received treatment that day and would be called back for treatment, which could present a population for recruitment in treatment trials.

So the -- I kind of already hinted of the impact that the pandemic has had on our services, but I think we need to take a little bit of a closer look at this. We have evidence in the St. Louis region that actually the pandemic has resulted in a few traditional STI health department clinics closing for most of the past year. So where -- how they open and reopen, we're really not sure yet. Other clinics though have remained open, modified their services and are adapting and exploring some of these other models of care. You can see from the same initiative with the NMPTC looking at 31 clinics that a number of them already offered express visits, but it did go up by one clinic during February/November 2020. But you saw a really big increase in telemedicine services, noted in purple there.

In addition, clinics were starting to

explore off-site testing and self-collection more. And so that could potentially impact recruitment as well. You can see where more clinics were offering HIV off-site testing and STI off-site testing. Excuse me.

Another impact of the pandemic was unfortunately seen in decreased patient volumes. Dr. McNeil will show you her data, too, but this is from my -- the St. Louis County sexual health clinic. Before COVID, we were seeing over 500 patients a month. And then we had a definite decrease in the height of the first peak, but we have yet to really recover and are still running at about 35 percent decreased patient volume. I'm sure the reasons for this are really complex and we are trying to target ways of increasing that, but that might be something that sites are going to have to adjust for.

Some added challenges because of the pandemic is having enough space to see patients, and therefore, that might affect patient volumes, too. We do need some spacing out in lobbies and in waiting areas, in addition, you know, we're trying to space

out the number of clinicians potentially in a room. Though certainly vaccination helps with that. Also the PPE supply was really tight in the beginning. This has gotten better, but on the flip, we're not so sure how much time PPE is really going to be necessary for our staff.

We also have experienced drug and treatment kit shortages that have hopefully largely resolved. And then we can't forget the staff that work in these clinics and how they've worked very, very hard while balancing everything else going on in their lives -- kids at home, kids supervised/not supervised, family members being sick from COVID, and them -- they themselves acquiring COVID. So staff exhausting is definitely a factor that we need to consider in STI clinical environments.

So for my case study, I'm going to cover some basics in the St. Louis County sexual health clinic, which I've directed for almost 14 years now. St. Louis metropolitan statistical area -- it's a rate of about 280 cases of gonorrhea. It also experienced a 50 percent increase in this rate from

2014 to 2019. So our clinic is staffed for a high volume of patients -- a quick turnover. There's not much wiggle room in how we do things, whether that be space or patient flow.

This is an example of our patient flow. You can see that there's multiple steps along the way -- arrival, registration. We're very well versed in how much time people spend in each of these. And I will tell you that the arrows in yellow would be the steps that would be removed if a patient was being seen for express visits. They would go from registration to instructions by an MA and straight to blood draw, and skip those other -- other stages, which also obviously means they don't have a -- so that kind of gives you an idea of what our flow looks like.

We have two clinicians at a time, seven to eight staff all in our little -- all in our little space. And they're very used to this, but also anything that upsets the flow can make times be longer and can upset their patterns of taking care of the patients.

So in the previous years when we have recruited for trials both in diagnostics and treatment modalities, but also social science studies, we've seen a lot of success. The enthusiastic interest -- interest from the patients has been obvious and the willingness to discuss the trials has certainly never been a barrier.

There is -- we do have lots of space for project equipment, which is nice -- making it easier on researchers. But we have found that studies with one visit are the most successful because of some of the challenges. So -- especially if patients need to follow-up in our off-site research center, transportation is a real challenge here for our patients and often patients are lost along that way.

There's also a culture in our clinic that the staff are -- don't want how -- don't want our effective flow to be disrupted. And so any project that's brought in could present a challenge in staff adaptability because of that.

We also are very sensitive to the fact that the populations that we see and the people that

we serve are populations in which there has been quite a bit of trauma. Not just recently in their communities, but also medicine-linked and medical care-linked trauma. And so these -- all these things have to be considered with recruitment issues.

So with that, I'm going to hand off to Dr. McNeil.

MS. MCNEIL: Thank you, Dr. Reno. All right. So I'm going to be doing a review of our trials unit in Winston-Salem. Our STI trial pub is in Greensborough, North Carolina, in Guilford County. This is located in the Piedmont Triangle area in close proximity to several large medical centers including three emergency departments and a women's hospital are part of our rapid detection response network.

So we also have our academic medical centers, which are also nearby as well of which there are several in our area. And we're talking about a high-clinic volume setting. In 2019, there were over 10,000 visits, and near 1,000 teen clinic visits with approximately 60 percent of those visits were women seeking care.

The gonorrhea morbidity is also high and our rates in Guilford County are about 427 per 100,000, which represented a 30 percent increase from 2015.

Notably, disparities in wealth and access to care drive morbidity. And our trials unit is embedded in this structure and there are a number of studies that we have ongoing and our team works really collaboratively with the Guilford County staff.

Multiple timepoints staff have the opportunity to present research to the clients. And with express interest, our trial coordinator has moved into the visits to begin consent and enrollment procedures.

Now we have some baseline challenges that exist, and these include helping providers understand the role of trials in clinical settings. A length of a visit can be extended significantly depending on the type of study. And then there's an access to appointment issue that is clinical and one that can involve the research activity, and the stigma that is associated with research in some marginalized

populations.

So then the pandemic hit and there were huge disruptions in clinic flow. And with that, trials activities, they had to stop. While we worked along really closely with our public health partners in support of the mission that was going on then. And then we had a slow start and then a go, but this research front was a lot different than what we had seen in 2019.

And in fact, like Dr. Reno mentioned, we were seeing decreased patient visits. And then there was also the issue that we were dealing with where we were seeing less -- less detection taking place. So less gonorrhea tests were being performed.

Baseline challenges, you know, with COVID, they were quite pronounced. And there were transportation issues before that got even worse during COVID. Then we had limited appointment availability. We had shortages. Lots of shortages. And there was fair as well.

So some successes that were worthwhile highlighting during this time, our research team was

very well integrated into the public health structure, and then we also had a strong commitment from the county leadership. So we were able to still continue to do the work that we were charged to do.

And then we had our strong relationships with our academic partners that were there. We had a team that was reflective of the community that we served, and we continued to work for the team to meet the -- that we had in mind.

And one way that we did this -- and, you know, I like to highlight this is we -- we had a side champion. We had several. And we all need a champion sometimes. So this champion was somebody who was interested, committed and motivated to work within the organizational structure. We have used provider champions in our STI clinic with an advanced practitioner. We also have used an STI champion in with our rapid detection response program through our emergency department and found this to be key to really succeeding as a site. And so I would encourage you to consider adopting such opportunities in your organization.

And investment -- so investment in your workforce, invest in your research site are really important. And consider this to be a long-term commitment to support not only current, but future research activities. And with us, that included mentorship opportunities. Through having a educational unit embedded in Guilford County, we were able to have those supportive networks of counseling on really complicated cases and such things with our health department colleagues. We had access to resources that were useful for research including language technology and other advancements.

So when you're trying to set things up at your organization, who do you invite to the table? Well, you can consider community members, representatives from local organizations, and then also working with groups that are already boots on the ground, in the field working with marginalized populations. Working with clinic providers. Working with scientists elsewhere and at other institutions. And while you are stepping up to engagement, once you have your network -- your dream team in place,

consider ways you can grow and support that and maintain that relationship.

Trust is super important. Keeping open lines of communication and identify, prioritize and develop your research goals together.

Strategies that might help you in your journey to success. So having a commitment to understanding and truly addressing the social determinants of health and how they relate to STIs is very important. Making sure that you collaborate with diverse partners. Have a shared decision-making model. Keep open lines of communication and leverage your -- trust, which you've spent so much time putting together. And work to receive -- to achieve the goals that you have planned and have that shared history of success.

So we talked a bit about team components. We've talked about community connections. We've talked about how they can support research. Another important consideration is looking for your sites where you can have the volume and the morbidity you need for enrollment.

And historically, our STI clinics have been the sites that we have looked at for these types of studies; however, with shifts in public funding, some of our non-STI clinic sites are really doing some heavy lifting out there in the community. And they're sites that we should consider, that outside-the-box approach when it comes to clinical trials.

Speaking of those places outside the box, we're talking about -- qualified health centers, our community groups, student health particularly if you're trying to work with those groups where there's high morbidity for STIs in general, like our less than 25, and family planning organizations. Private practice groups, particularly high-volume groups, and urgent care facilities and emergency departments. That one, of course, we are very familiar with at our site.

So the take home points. STI clinics are an evolving environment and innovative clinic models with enhanced services made -- recruitment for research as Dr. Reno mentioned. There are multiple variables that account for a site's success.

Diversity is key. Diversity matters in terms of the people who are conducting research and then also your audience. And we all need a champion sometimes, so look for those in your group that you can promote and use to not only build your -- your team morale but also help you achieve your goals.

Consider workforce and worksite development a long-term investment and one that will be incredibly useful for you in the future. Also look at an outside-the-box approach to site selection while trying to look at diverse audiences and groups that could benefit from research.

And keep in mind that you want to maintain that authentic community engagement and work towards your shared success stories.

That's all I have. Thank you for your time and attention.

MS. YASINSKAYA: Thank you very much. We are getting close to the end of our morning session. Our last speaker for session one is Sarah Wang. She's a graduating fourth-year student -- graduate degree in public health policy at UC Irvine.

And -- advised by Dr. -- to optimize antibiotics stewardship strategies and integrate antibiotic stewardship into the lowest income K-12 school districts in California.

Welcome, Sarah. Please take it away.

MS. WANG: Thank you. Hi, can you hear me?

MS. YASINSKAYA: Yes, we can hear you well. Go ahead.

MS. WANG: Oh, awesome. Thank you. can you see me as well? Sorry. I don't know if my video's on.

MS. MCNEIL: No, we can't see you, but you can go forward with your presentation.

MS. WANG: All right, thank you. Hi, everyone. I'm Sarah and I'm going to be presenting about the need for early education among adolescents and young adults regarding antibiotic resistant gonorrhea.

Oh, sorry. I don't know how to shift the slides.

So currently, females ages 15 to 19 and

20 to 24 have the highest rates of gonorrhea. And in addition, males ages 20 to 24 and 25 to 29 experience the highest rates of gonorrhea. Therefore, there needs to be more attention towards prevention to adolescents and adults regarding safe sex and antibiotic use.

So currently, gonorrhea develops very fast to resistance to antibiotics as ceftriaxone is the last recommended treatment out of over 10. And it is the last resort, so there needs to be more focus on infection prevention and --

Next slide.

So over the summertime, Dr. Ogenstiten [ph] and I conducted a summer undergraduate research program survey to assess the knowledge, attitudes and practices regarding antibiotic resistance, antibiotic use and -- with antibiotics to 200 UCI students. And we analyzed the results with a combination of statistical methods, including "KY square" and -- progression models. So we found -- challenge.

Next slide.

In addition, we found that males have

worse attitudes towards antibiotics than females. As a result, it's important to tailor this potential freshmen seminar or antibiotic stewardship intervention to high schoolers to address this attitude difference.

Next slide.

So currently, Dr. Ogenstiten and I have created an interactive storyline to basically reveal the correct health communication and dialogue specifically for antibiotic prescription for medical students and undergraduates. As a result, it can be used to explain the specific requirements for drug prescription for -- to train future physicians and to teach patients how to respond to certain bacterial and viral situations.

Next slide.

So currently, Dr. Ogenstiten and I are leading a course with four students to integrate antibiotic education into the K-12 curriculum of the four lowest income school districts. And we have a focus on gonorrhea prevention and --

Sorry. Can you go back to the last

slide?

And antibiotic stewardship in specific regard to addressing a need for community capacity building. Because as we all know, antibiotic resistance is very expensive, costing 6,000 to $30,000 per patient.

So this is very important because there is an important issue of non-prescription that's especially common among those outside -- that immigrate here from outside of the US with California having 27 percent immigrants, which is two times the number of any other state.

As a result, it's very important to address the need for antibiotic knowledge among this demographic, especially with compounded factors, like lack of healthcare insurance, inadequate healthcare access and undocumented status.

So there is a high need to address antibiotic stewardship education at the K-12 level, especially in low-income education districts because COVID-19 has revealed the deadly impacts of structural racism and systemic health inequalities on racial and

ethnic minorities, which makes capacity building for the next pandemic incredibly important.

And according to a report by O'Neil [ph] in 2016, the most public health awareness campaigns need to target the youth because they will be the brunt of antibiotic resistance.

As a result, there has to be education in non-traditional settings, like schools and daycares, rather than just hospitals because of this important issue of non-prescription and the need for capacity filling.

And next slide.

Thank you and do you have any questions or would like to discuss anything, please feel free to type in the chat and I'd love to get to know what you think and if you're interested in our studies, please reach out to Dr. Ogenstiten or I at the contact information provided.

Thank you for listening and I hope you have a great rest of your day. Feel free to type your questions in chat or discuss whatever you want.

MS. YASINSKAYA: Thank you very much,

Sarah, for your presentation. You know, we were going to be monitoring, of course, the chat box if there are any questions -- specifically, but at this time, we wrapped up our presentations for the morning session -- session one -- and we are ready to break up for lunch.

Our lunch will be only 30 minutes, so now that it is 11:54, we will be coming back at 12:55. Sorry, 12:25 for -- to begin session two of our workshop today.

So please enjoy your lunch and we will see you in 30 minutes. Thank you very much.

All right. We are about to go live. You can please start the session. Thank you.

MR. KIM: Good afternoon, everyone. Welcome back to this afternoon's session. My name is Peter Kim. I am a medical team leader in the division of Anti-infectives Office of Infectious Diseases at US FDA. I will be co-moderating this session with Dr. Deal.

Dr. Deal, would you like to reintroduce yourself to the group?

MS. DEAL: Sure. My name's Carolyn Deal. I'm the branch chief of the -- and Sexually Transmitted Sections Branch at the National Institute of Allergy and Infectious Diseases at NIH. My pleasure to moderate with Peter at FDA.

MR. KIM: Thank you, Dr. Deal. At this point, we'll begin with our presentations. It's my great pleasure to introduce Dr. Hiwot Hiruy. She is a senior medical officer in the Division of Anti-infectives Office of Infectious Diseases at FDA.

Dr. Hiruy, please feel free to begin your presentation.

MS. HIRUY: Good afternoon, everyone. My name is Hiwot Hiruy and I will be presenting the FDA's perspective on development of antibacterial drugs for uncomplicated gonorrhea.

Let's see. Do you have my slide deck? Thanks.

So as mentioned by previous speakers, there are two main factors that -- unmet need for treatment of gonorrhea. As you have heard in session one, the bacteria has a unique ability to develop

resistance over time to antibacterial classes used for treatment, thereby making previous therapy -- therapy option defunct. This has also resulted in dwindling therapeutic options and recent attempts for normal treatment have not been successful. So these two factors have resulted in this current unmet need we have for treatment of gonorrhea.

Our hope is in today's workshop we'll provide a forum for discussion around how to approach the key challenges around drug development for treatment of gonorrhea. I'll start the presentation by highlighting the statutory requirements a drug needs to meet to obtain marketing approval. This will apply to novel therapy as well as previously approved drugs that are now seeking a new indication.

I'll then review the 2015 FDA guidance for development of drugs for uncomplicated gonorrhea. I'll briefly mention the two recent programs and the challenges they encountered. And you'll hear more about this -- these issues in subsequent presentations as well.

Finally, the presentation will conclude

with highlighting some of, again, the key discussion points that need to be addressed to help drug development program successfully bring about this new therapeutic options.

Okay. Let's see. Okay.

As I mentioned in my previous slide, a data packet supporting a new drug application has to -- a statutory standard to provide substantial evidence supporting the efficacy as outlined in the Federal Food and Drug Cosmetic Act.

Substantial evidence is defined as evidence consisting of adequate and well-controlled investigations to distinguish the effect of the drug from other influences.

In most cases, two adequate and well-controlled investigations will be required; however, section 115(a) of the modernization act further clarifies this requirement and states that data from one adequate and well-controlled trial may be considered substantial evidence if there are additional supportive data.

So the characteristics of adequate and

well-controlled trials are outlined in the title 21 of the Code of Federal Regulations, section 314.126. And reports of such adequate and well-controlled trials provide the primary basis for determining whether there's substantial evidence to support claims of effectiveness of this new drug -- new drugs.

One key aspect of this adequate and well-controlled trials is the control used in these trials. The -- mentioned section of the CFR outlines five types of controls and which control is suitable for a specific trial will depend on the nature of the disease the drug intends to treat.

The first type of control is active treatment concurrent control where the test drug will be compared to a known effective therapy. And this type of control is widely used in infectious disease arena including indications for treatment of gonorrhea.

Another type of control is the placebo concurrent control where a test drug will be compared to an inactive drug that resembles the test drug. No treatment concurrent control uses just the test drug -

- compares the test drug to no therapy.

The dose compares and concurrent control is where the two or more doses of the test drug are compared. And the last control is historical control where the test drug is compared to historical experiences and use of this control is actually reserved for special circumstances that has a disease of high mortality or the course of illness is predictable, or the drug itself is self-evident as -- the case of general aesthetics.

There are also two types of trial designs. Superiority trial design is designed with the assumption that the test drug is better than the control. And the control can be placebo, no treatment, for comparison or active control.

Again, the choice of the control would depend on the feasibility and the -- of that specific indication.

The other trial design is non-inferiority trial where the assumption is the test drug is no worse than an active comparator by a certain prespecified data-driven amount that we call -

- inferiority margin.

In order to calculate this margin, treatment effect of the active comparator compared to placebo needs to be estimated in the population being studied and for the outcome of interest.

As -- so now we are shifting a little bit gears -- a little bit to focus on specific considerations for drug development for gonorrhea.

As for any drug development program, the nonclinical stage provides the foundation for the clinical -- for the development of the gonococcal therapy development programs as well. And this includes proof of concept of activity -- Neisseria gonorrhea, including invitro, hollowfiber and animal models, nonclinical PKPD models and phase one PK assessments. They all -- these all inform appropriate dose and dosing regimens for evaluation in subsequent phase two and phase three trials.

As you've heard in session one, there are several challenges to this nonclinical stage of drug development for gonorrhea. In these challenges may affect the latter stages of development as well.

The current thinking regarding appropriate clinical trial design is -- for design considerations are outlined in the 2015 FDA guidance for developing treatment for uncomplicated gonorrhea.

In that, the guidance recommends a prospect -- randomized, preferably double blinded trial design. However, there may be instances where the test drug and the comparator may have different route of administration. In such cases, double-blinding may not be feasible.

Even then, we recommend that the sponsor be blinded. Given the high effective -- the current standard of care being highly effective for uncomplicated gonorrhea, then that inferiority trial is the one that's recommended with inline margin of 10 percent. And the inline margin justification is -- to the 2015 guidance for your reference.

Okay. So going to study participant considerations. Study entry criteria could be broad and include any patient with evidence of uncomplicated gonorrhea without restriction to site of infection or focus to a specific site, such as urogenital. The

trial should exclude patients that require different -- or duration of treatment, such as patients with disseminated disease, pelvic inflammatory disease or endophthalmitis.

The trial also should exclude subjects that have already received respective therapy for the current gonococcal infection.

Given the burden of disease in adolescence, consideration should be given to include adolescence into phase three trials. However, there are specific challenges to including this patient population such as obtaining informed consent.

Given the current standard of care having high efficacy for treatment of uncomplicated gonorrhea, pregnant women should only be included in trials where the standard of care is not a viable therapeutic option, such as pregnant women infected with isolates resistant to the standard of care.

Next slide.

The recommended -- okay. The recommended primary endpoint is a microbiological cure defined as negative gonococcal culture at the site of

initial infection, approximately three to seven days following treatment. Although nucleic acid amplification test may be used for selection of patient for enrollment, they should not replace culture for initial diagnosis or test of -- establishment of test of cure.

In line with the primary endpoint, the primary analysis population is the microbiological intention to treat population which is comprised of all randomized patients with Neisseria gonorrhea isolated at baseline culture.

Confidential secondary endpoints for consideration include the nucleic acid amplification test results and symptom resolution in a -- patients that have baseline symptoms.

Although the exact number required of safety -- of a drug would depend on our previous knowledge of the drug class and/or any signal -- safety signal identified during drug development programs. In general, a preapproval safety database of approximately 500 patients at the proper build and duration is recommended.

In cases where the new drug or a drug has been studied for another indication, where the -- and duration of the treatment are comparable to that of the gonococcal indication, safety information obtained from the other indication -- safety database of the gonococcal indication.

I'll briefly mention --

If you can get my slide deck back? Thank you. Slide 14.

I'll briefly mention the two recent experiences that with novel treatment gonorrhea of delafloxacin and solithromycin. We are fortunate enough today to have some of the investigators that were apart -- that took part in one of the trials. And they'll give us more detailed presentation subsequently.

But briefly, both delafloxacin and solithromycin development program had a phase three -- inferiority trial with -- margin of 10 percent. Those were open label, single-dose of each test drug compared to an active comparator.

In the case of delafloxacin, the active

comparator was a single-dose ceftriaxone. And in the case of solithromycin, ceftriaxone -- ceftriaxone was the active comparator.

Both trials primarily focused on uncomplicated urogenital gonorrhea patient population. And the primary endpoint for both as per the guidance was the proportion of patients that cleared the gonococcal infection at the site of -- urogenital gonococcal infection a test of cure on -- in both trials, majority of trial participants were male. Both trials failed to meet -- specified -- margin, however, there are several challenges that -- or lessons that we can learn from these two trials including adequacy of the chosen dosing regimen as well as impact of missing data, specifically the test of cure visit.

And again, as I mentioned, these will be further discussed in subsequent presentation.

In conclusion, the agency would like discussion regarding approaches to challenges such as dose and dosing regimen selection, role of -- clinical models and refining optimal dosing, use of single

versus multi-dose regimens, and challenges around trial population including how to improve recruitment of women and adolescents. And also enrollment of urogenital versus extragenital infections within a trial. And then the challenges around trial conduct to include issues with multinational studies and the challenges of having differing treatment guidelines that would impact the standard of care to be chosen for trials.

And also, how to harness technology to ensure compliance and adherence to follow-up visits. Challenges in trial design including optimal timing, diagnostics and role of culture for assessment of test of cure would also need to be facilitated. How to handle missing data in the primary analysis, and finally consideration for safety database for a new class of drug that may be potentially used widely in outpatient patient settings are some of the topics for discussion that we'll have. And hopefully you will have more time in the panel discussion to go over these key challenges.

This concludes my presentation and

thank you for your time.

MR. KIM: Dr. Hiruy, thank you very much for your presentation. Now, I'd like to introduce Dr. Sumathi Nambiar who is currently the director of the Division of Anti-infectives at FDA and will be presenting on behalf of Dr. Junko Sato, who is the director of the Office of International Programs at the Pharmaceuticals and Medical Devices Agency.

Dr. Nambiar, please feel free to begin.

MS. NAMBIAR: Hi. Thanks, Peter. I hope you can hear me okay.

MR. KIM: Yes.

MS. NAMBIAR: Yeah. Great. Thank you. So as Peter said, I'm from the Division of Anti-infectives at the US FDA. I will make this presentation on behalf of Dr. Sato from PMDA who couldn’t join us given the time difference.

Dr. Sato did want me to let everybody know that PMDA recognizes the unmet need for products for treatment of gonorrhea and we look forward to working with sponsors, developers of such products.

So she notes that there are several

antimicrobial agents in Japan that carry a labeled indication for gonorrhea, but the benefit respondence for these products was generally in clinical trials for conditions like STDs, UTI or pelvic inflammatory disease rather than specific trials for gonorrhea.

Also notes that there is increasingly resistance to -- Dr. Sato reference to a guideline that was published in 2017.

Next slide, please.

She referenced a guideline that was published in 2017 regarding clinical evaluation of antibacterial drugs. And this guideline also provides recommendation for developing drugs to treat gonorrhea.

Next slide, please.

So in the current guidelines, they separate our gonococcal urethritis in men and gonococcal urethritis in women. So for entry into gonococcal urethritis trial, men who are symptomatic with the symptoms consistent with those with gonococcal urethritis. A culture for Neisseria gonorrhea should be obtained at baseline.

Next slide. Next slide, please.

The test to cure assessment is five to nine days after the end of treatment. The primary endpoint is microbiologic based on eradication of Neisseria gonorrhea. Clinical endpoints are also assessed, looking for eradicate, improvement or cure, which is the symptoms attributable to urethritis and no longer observed.

Next slide, please.

In gonococcal urethritis in women who are 16 years and older who have clinical findings such as -- cervicitis and --

Sorry. The previous slide? Yeah. Thank you.

And with Neisseria gonorrhea confirmed on culture, there's an end of treatment assessment and a test of cure assessment which is one to three weeks after the end of treatment, and this is the primary endpoint.

Next slide, please.

Clinical success is defined as -- symptoms attributable to cervicitis, as a result are

improved and no longer require treatment with antibacterial drugs.

Next slide, please.

Microbiologic outcomes are also assessed where eradication Neisseria gonorrhea on culture is -- is looked for.

Next slide, please. Yeah.

In the next two slides, Dr. Sato has provided a susceptibility data from nationwide surveillance. The first slide is patients with male urethritis and the second one is female cervicitis. I think the message in both the slides is the high MICs seen for the quinolones -- flucloxacillin -- and two flucloxacillin, and also spectinomycin.

Next slide, please. Yeah. Next slide.

I think this is, again, just to show a comparison of the susceptibility pattern from 2009-2010 to 2012 and '13. I think the message remains the same which is the high level of -- high MICs of Neisseria gonorrhea. Okay. And for the -- against Neisseria gonorrhea.

Next slide, please.

So this is a summary of the treatment guidelines for gonococcal infections. So the diagnostics recommended include a -- culture and PCR, and for treatment, it's generally ceftriaxone and spectinomycin -- two treatment options.

Next slide, please. Yeah. I think that concludes the presentation. Thank you very much.

MR. KIM: Thank you, Dr. Nambiar. I'd like to now introduce Dr. Radu Botgros. He is an infectious diseases specialist working as scientific officer for the Office of Biological Health Threats and vaccine strategy at the European Medicines Agency.

Dr. Botgros, please feel free to begin your presentation.

MR. BOTGROS: Thank you very much, Dr. Kim. I hope you can hear me well.

MR. KIM: Yes.

MR. BOTGROS: I would like to start by thanking the organizer for inviting me to attend this workshop and for giving me the opportunity to speak and provide you with some -- perspectives on development of antibacterials for treatment of

gonorrhea, including some API data from the EU.

I would like to ask colleagues from the background to help me progress my slides as I speak, if possible. So can we please go to the next slide? Thank you.

I will start by reminding you the fact that sexually transmitted infections have been on the rise world wide and in the European Union in the past two decades. So that in 2018, we registered in the EU high incidents of sexually transmitted infections. And actually, for Neisseria gonorrhea, we have an incident of 26.4 in 100,000. Incidents that have increased by 240 percent between 2008 and 2018.

So these were some -- can also be seen on the world map on the right-hand side of this slide, which shows that the highest numbers of new annual cases is on the African continent, while the European region -- still have the lowest incidents as also mentioned in the WHO presentation earlier today.

Next slide, please.

On this slide, we start with this telling logo -- gonorrhea, hard to spell, easy to get.

You see a brief summary of what we all know, so I'm not going to spend time on it, but what I think is important is that because GC is a specifically human infection, as you heard -- as we all heard, there have been many difficulties in developing suitable animal models for the disease. And there are still gaps, like for instance, with the pharyngeal disease as we -- as we just heard earlier today.

Next slide, please.

In the European Union in 2018, 76 percent of gonorrhea cases were reported in men. And this reflects the high prevalence of men who have sex with men and the high proportion of diagnosed symptomatic urogenital infections in men. And you can see here on the left-hand side of the slide, the number of confirmed GC cases by gender, transmission category and the year between 2009 and 2019. And on the right-hand side, we see that the distribution of cases varies by country. With some EU countries having the high notification rate of over 10 cases per 100,000, which are depicted in dark red on this map.

Next slide, please.

Now we all know that since the discovery of antibiotics, recommended treatments for gonorrhea have required continuous adaptation to remain efficient. And actually starting from -- which were the first effective antibiotics introduced for the treatment of gonorrhea in the '30s, continuing with penicillin, with spectinomycin, the -- azithromycin, all these antibiotics have been affected by development of resistance.

And despite azithromycin is now generally included in the -- therapy in combination with ceftriaxone, worryingly high-level azithromycin resistance in Neisseria gonorrhea have been isolated in some countries.

Resistance obviously also affects, as we saw, the use of -- respective of whether it's ceftriaxone -- or another -- to the point that cephalosporins have become ineffective in many countries, specifically in the Asia-Pacific region.

And that of course has led to the introduction of the dual therapy over the past decade, but also this dual combo is affected by resistance in

the recent years.

And all of these developments are linked to the acquisition of mutations and the target size of a variety of antimicrobials by gonococci as we can see on the right-hand side of the slide. But of course, I'm not going to go into all these mechanisms that also have been presented before.

Next slide, please.

On this slide, you see on the map the percentage of isolates with decrease susceptibility or resistance to extend -- according to the WHO -- data. For more country than Europe, we are looking at less than five percent resistance of the test that I -- and you can also see the percentages of resistance of Neisseria gonorrhea by antimicrobial -- year in the European Union with a recent increase in azithromycin resistant strains.

Next slide, please.

There is now general agreement that a new medicine's aimed to treat gonorrhea in particular resistance GC -- need to be developed. And as you know, WHO included third generations of -- resistance

of Neisseria gonorrhea in their priority list of -- drug resistant pathogens to support research and development of effective therapies.

The antimicrobial susceptibility of gonococci in the EU is monitored by the Sentinel Euro Gas Program, which was initiated back in 2004 and is funded, coordinated and expanded by the European CDC. And I would like to mention that Euro Gas Data have already informed changes to the first line therapy recommended in the European guidelines on diagnosis and treatment of gonorrhea.

Next slide, please.

At the EMA, we have also been closely following the topic during the past decade. And when we took the decision back in 2019 to update the EU guidance on development of antibacterials, we decided to actually also address the point of -- specific advice for drug developers regarding the regulator requirements for approving medicines for both uncomplicated urinary tract infection and gonorrhea.

The finalization of the guideline has been unfortunately put on hold when the COVID pandemic

hit, but the draft is published on the EMA website and we are aiming to finalize the guidance as soon as possible.

And on the right-hand side of this slide, you already know that in 2020, the European guideline for the diagnosis and treatment of gonorrhea in adults has also been updated. We have some of the authors with us here today. What we -- what I can say is that it would be good that developers consult this updated version, which definitely has relevance for a number of points.

Next slide, please.

In our updated EMA guidance, we clarify that trial -- to demonstrate non-inferiority of the test regiment to an appropriate reference regimen would be acceptable. And we clarify that if a single -- trial is proposed in support of the claim indications relevant already existing guidance on the topic, and you see them listed here on the slide, would also apply. But the guidance specifies that infection site specific indications for use may be supported by single -- studies with standard levels of

-- under certain circumstances. And you see on the right-hand side of the slide two important situations where this could be possible. And I'm talking about single trials in either C-UTI or uncomplicated UTI, together with a single trial in uncomplicated gonorrhea.

The other important situation is when the antibacterial agent addresses an unmet need, and in these cases the total evidence is sufficient to support a pathogen-specific indication in patients with limited treatment options. Additional infection site specific indications may be granted based on a single -- indication.

Next slide, please.

In terms of selecting patients in the clinical trials, we expect to see evidence of gonococcal cervicitis or urethritis at enrollment. And this is based on finding characteristic -- in the urethra or cervical parts or swabs at baseline.

If patients with evidence of rectal or pharyngeal gonorrhea are enrolled, alone or in conjunction with urethra or cervical infections, we

recommend that there is stratification by infection site -- regarding the test of cure, we recommend that this is conducted within one week of treatment to maximize the proportion with documented eradication. We also agree that late follow-up visit should be planned to capture relapses, reinfections or new infections. And we -- we mandate -- the guidance actually mandates that patients eligible for the microbiological -- population should have a positive culture result for Neisseria gonorrhea.

It is possible to enroll adolescents in the adult trials, and this is something that is also worth mentioning here.

Next slide, please.

In terms of the recommended endpoints -- primary endpoint, this should be microbiological, namely the culture confirmed microbiological eradication of Neisseria gonorrhea in the microbiological -- population after the test of cure. We recommend to conduct comparative trials and the guidance states that a preferred comparator should be one of the best available treatments based on clinical

trials, medical opinion, infection type, specific treatment guidelines and the anticipated prevalence of resistance to the comparative agents at the trial sites.

Now you will note in this -- this is something I put on this slide, that the recent EU treatment guidelines, 2020, is recommending ceftriaxone, 1 gram, plus azithromycin, 2 grams, in combination. That also works on azithromycin resistant strains, or ceftriaxone monotherapy, 1 gram, but not in ceftriaxone resistant infections or in oropharyngeal disease.

What's worth mentioning is that our guide -- our EMA guideline is not prescriptive in that respect, so I suppose we can discuss any proposal in the framework of our EU scientific advice with -- with developers.

Next slide, please.

In terms of the primary analysis, for example, if the standard ceftriaxone/azithromycin combination is used as a comparator, this should be confined to MITT subjects with Neisseria gonorrhea

that is susceptible to both agents. Sensitivity analysis should be conducted in MITT subjects with culture-proven GC, susceptible to only one of the two comparative agents and in MITT subjects with culture-proven GC regardless of susceptibility to either agent.

We think that an open label design could be acceptable, but we encourage sponsors to discuss their proposals with the EMA at all times.

Next slide, please.

In terms of enrollment of patients with extragenital gonorrhea, it is worth mentioning that it would be possible to collect the assessment of efficacy against pharyngeal or rectal gonorrhea as a secondary objective in a study that involves urogenital gonorrhea. We would need to see separate estimates provided for each infected side and we mandate that the -- resulting -- intervals should exceed 90 percent at least for the subset with urethritis and cervicitis, or with -- with genital gonorrhea.

In terms of resistance, this should be

obtained at baseline and post-baseline in isolates obtained from treatment failures.

Next slide, please.

As you know and as you have heard from our FDA colleagues, there are a number -- unfortunately, not as large as we would want it to be -- a number of -- trials ongoing from a number of new candidate drugs which are depicted on the slides. I'm not going to go through them, but what is worth mentioning is that some of them will be delivering soon some results and we hope, of course, to see also some positive results among them in contrast with the negative ones that we saw for solifenacin and delafloxacin in the recent two years.

Next slide, please.

During the interest of time, I will close here. These are -- is my summary, you know, so I won't go through all of them. What's important is indeed that, you know, we agree that developing new antibiotics for -- for gonorrhea that would be active -- some of them -- resistance Neisseria gonorrhea strains are currently considered an unmathematical

need and that we strongly encourage sponsor whenever they design the clinical development to review both 2020 update of the European clinical recommendations for diagnosis and treatment, as well as our new draft guidance on antibacterials.

And of course, for discussing any of the -- you may have, we -- we invite you to apply for the EU scientific advice. And with that, I would like to thank you for your kind attention and I will give the floor back to the chair. Thank you very much.

MR. KIM: Carolyn, I think you're still on mute.

MS. DEAL: Can you hear it now?

MR. KIM: Yes.

MS. DEAL: Okay. Yeah. It was -- it said I was off. Sorry. So I'd like to thank our three regulatory speakers for the regulatory perspective. And now we're going to hear some perspective from the therapeutic developers. From their past experiences and what's some of the challenges and lessons they've learned.

Our first speaker is Dr. Sue Cammarata.

Sue is at Tunnell Government Services serving as a senior clinical subject matter expert consultant to BARDA. Dr. Cammarata is a primary care physician by training, but most of her pharma career has been in support of anti-infectives and rare diseases.

Sue, over to you.

UNIDENTIFIED SPEAKER: Sue, can you unmute, please?

MS. CAMMARATA: Can you hear me now?

UNIDENTIFIED SPEAKER: Yes, ma'am. Thank you.

MS. CAMMARATA: Hi, all. Can you hear me?

MR. KIM: Yes, we can hear you, Dr. Cammarata.

MS. CAMMARATA: Okay, thank you. Thanks for the opportunity to speak today. There have been a couple trials done in the last few years in gonorrhea by pharmaceutical companies. They were actually done about five years ago. I've presented on this a couple of times because of development work in pharmaceutical companies is -- has been limited.

There's a variety of reasons for that and much of the work has been done in -- by public health as well as academic colleagues.

So in the session here, we'll be talking a little bit about lessons learned and then for those folks that are currently developing products, we'll be talk -- they'll be talking a little bit about their current experiences and planning.

Think back to about eight years ago. The trials I'm going to be talking about were performed around 2014/2015. As a result, the planning for those trials would have occurred years before that. So when you go through the checklist of what we can do with antibiotic development, it's clear that there's a list of things that we do when we are drug developers in antibiotics. Our goal is to kill the bug. So you want to have no impact on the human, but you want the drug to get in at a high enough level, long enough to be able to kill that bacteria.

And there's steps that antibiotic developers can do to look at the level of antibiotic that they need and how long they need it to kill the

bug.

So I know a lot of you have excessive backgrounds in the audience, but some of this might be new to some of the audience members. And there are differences in what we've done in antibiotics, for example, an infection in lung or skin infections versus what we can do with gonorrhea.

So again, this is looking back at what developers had had as a test to do a few years ago.

So of course we can always measure drug levels that kill the bacteria in a Petri dish. We can do MICs. And yes, we can do that for gonorrhea, too. Preclinically, however, there is lots of in vivo data that we can generate looking at efficacy for pneumonia in animal models. Looking at bacteremia, looking at skin infection models. However, there has not been a clear, accepted model -- animal model for gonorrhea for example.

In addition, we've not been able to -- there was a discussion this morning about PK and PD. How much drug you need to kill the bug. We can do that and compare it in animal models or in vivo --

invitro and in vivo models for other infections, but we've not been able to do that with gonorrhea previously.

We can test in phase one. We can do that for skin infections and pneumonia, and we can look at blood levels systemically. And we can also do that in humans, looking at drug levels for a treatment of gonorrhea. At least in -- in the blood -- systemic exposure. But when we look at antibiotics for treatment in pneumonia or skin, we can look at those systemic levels, urine levels, lung levels, but right now, we don't really quite understand what fluid levels do we need, what tissue levels do we need and where do we need those to be able to treat gonorrhea well.

You can do phase two studies to sort of help with dose selection, but those are very limited because the numbers are very small and there may be still risks with those studies. And I'm going to describe these phase three studies. Even with these phase three studies, you can still have failures for a variety of reasons.

So as mentioned by a couple of the speakers, there were two antibiotics studied around 2014/2015 in the treatment of urogenital gonorrhea. These compounds are both very potent against gonorrhea with low MICs in the petri dish. And they have intracellular accumulation. But when you look at these antibiotics -- solithromycin is a novel macrolide, so it's in a class that's been known to be active. In addition, it has this good activity, it has intracellular activity, and good oral penetration or absorption.

Delafloxacin is antibiotic -- quinolone. It's broad spectrum in activity as well. It accumulates intracellularly and it's also rapidly absorbed.

And although these -- both of these are from classes that have been known to be used in the treatment of gonorrhea previously -- the macrolides and the quinolones -- both of these compounds have activity against resistant -- organisms that were resistant to other drugs in the class. So that makes it interesting that these compounds were taken

forward.

Both products had almost identical non-inferiority studies that were designed in uncomplicated gonorrhea. And this was the same time at around 2015 when the guidance, for example, was developed with the FDA. So these were very close to the guidance at the time.

In both studies at baseline, the patients with uncomplicated urogenital gonorrhea were randomized and they received either the standard of care or the new treatment as a single dose. And the solithromycin trial, the patients randomize one to one to either get soli or to get the active control. And in this study, they sued ceftriaxone and azithromycin. And this was an open label study.

And I would note that at the time of this trial, azithromycin had already had a successful pneumonia trial, and also they had a small successful gonorrhea study.

In the delafloxacin study, the patients randomized two to one to get either soli or ceftriaxone. And in this study, the patients who had

chlamydia at baseline received azithromycin treatment at the test of cure visit, which was around day seven. And at this point in time when the study started, delafloxacin had already had a successful pneumonia and skin studies and has since been approved in pneumonia and -- a treatment of -- pneumonia skin infections.

In both of these studies, the outcome was micro response at that test of cure. So were they able to eradicate the pathogen? The test of cure visit was at day seven, plus or minus three. So it was assessment made at either day four up through day ten, after that single dose of treatment. And the focus of these studies were those patients who had gonorrhea GC at baseline. Cure was eradication of the bacteria. Failure was persistent infection or the use of rescue antibiotics or, as all these trials are, if you have missing data, the patient is assigned to failure.

This slide just shows both of these studies have since been published. And both compounds failed in their overall input. The goal was to show

that each of these compounds in their studies were comparable or not inferior to the standard of care and in the micro-ITT populations. Anybody who had genital GC at baseline. And the punchline is they both failed to meet the primary endpoint. For soli, the cure rate was 80.5 versus 84.5 percent. For DELLA [ph], the cure rate was 85.1 percent versus 91 percent.

I would point out that in those ITT populations, there was a difference. Again, I've mentioned -- and other folks have mentioned -- the assessment's done in the ITT population. So if patients are missing, they're called failures. When you remove those patients who did not come back for follow-up, the cure rate for ceftriaxone was actually 97 to 100 percent.

So despite the discussion of resistant organisms, these studies that were done -- the DELLA study was in the US only. The soli study had sites in the US and in Australia. They had a very ceftriaxone cure rates.

There were differences as I show here in both studies in the -- in the -- in some subgroups.

And both groups, you know, patients were cured. They actually did well with these single doses; however, there were some groups where there were more failures seen. And in both studies, that was more likely to see a slight increase in failure rate in the men seeking sex with men -- population.

So as I note here, both of these studies have been published. And in both of these publications, the authors have suggested that one dose was not enough for everyone. It actually worked in many patients, but it did not treat everybody. And you may need to have more than one dose. You need to think about these factors.

I would point out that with failed studies and pharma, many of the companies currently working in antibiotic development just don't have the time or money to go back and repeat these studies. So neither of these products have been further studied in the treatment of gonorrhea.

It would seem to be that this is straightforward, that you should only have single-dose therapy, but this area is very challenging.

So sort of my last slide, to summarize these as been moted over and over again. The lessons learned in what has been worked on in the last few years and where further work needs to be done. To be successful, drug developers need to understand the antibiotic level and what -- how much exposure do you need to treat that infection.

We need new methods, whether it's invitro or in vivo methods that are accepted by regulators and researchers to be able to understand that. We also need to make sure that we treat -- are able to treat patients, but you need to strictly focus on the tougher to treat population and some of these various subgroups.

You also need a large enough sample size to gather patients with lots of different bacteria -- different resistant patterns, and that's always an issue with phase two studies in antibiotics.

You need to understand the dosing strategy as shown here in these studies. A single dose was not enough. Could there be alternate formulations besides oral dosing. And single doses

that might be acceptable to prescribers and patients.

Also, are there considerations of whether there should be different regimens used in populations that are at-risk for a more resistant bacteria.

I know this is not the point of this workshop, but I am going to point out and you will see that clearly this is a public health issue; however, almost all the development currently occurring is based on public funding. A single dose of antibiotic doesn't pay the pharma bills, and in general, investors and companies have abandoned antibiotic development because of the high cost and low revenue. So funding is limited. And so this is something that, outside of this workshop of course, has to be considered how to support this very high unmet need for the public.

And I think that's my last slide. My fellow presenters will talk about their view on these development issues. Thank you.

MS. DEAL: Thank you very much, Dr. Cammarata, for the overview of the two previous

trials.

And now I'd like to introduce Dr. Ricardo Chaves. Dr. Chaves is the executive medical director at Debiopharm International in Switzerland. He brings 13 years of -- clinical experience as well as microbiology in the hospital, followed by 20 years in pharma.

I invite you, Dr. Chaves, to start your presentation.

MR. CHAVES: Can you hear me well?

UNIDENTIFIED SPEAKER: Yes, we can hear you.

MR. CHAVES: All right. So I am Ricardo Chaves, responsible for the clinical development program in infectious diseases at Debiopharm.

On behalf of our company, I'd like to thank you for the opportunity to contribute to your workshop.

Today, I will present our thoughts about Development of novel drugs for Neisseria gonorrhoeae – and especially Translational challenges.

So in the first part of my talk, I will briefly share with you some of the drug development activities in our portfolio. I will then touch upon our considerations concerning novel drugs against Neisseria gonorrhoeae, including some perspectives on the respective Target Product Profile. And finally, as our compound is heading towards IND, I selected some highlights from our preclinical activities as well as translational challenges to complete this presentation.

At Debiopharm, we are committed to develop novel antibacterials and specifically to successfully develop the first FabI inhibitors and hopefully provide a game changing drug class to treat bacterial infections. The Mechanism of Action of FabI inhibitors is novel – they disrupt the bacterial fatty acid biosynthesis and consequently prevent bacterial growth. As expected from new antibacterials, FabI inhibitors have low potential for spontaneous resistance development and no cross-resistance with other antibiotics. Besides their potency, unique properties are a very narrow spectrum of antibacterial

activity with potential for pathogen-specific therapies. Well, for those working with antibiotic stewardship, this could be a real dream! The resulting low offset selection pressure allows the use of FabI inhibitors without any relevant effect on the normal gut flora.

MR. KIM: Dr. Chaves? Dr. Chaves? This is Peter Kim. We're having a difficult time hearing you. Is there any way you could either be closer to your microphone or speak more loudly? Sorry to interrupt.

MR. CHAVES: Is it better now?

MR. KIM: Yes.

MR. CHAVES: Okay. I hope. Should I start it right again or should I continue?

MR. KIM: Please feel free to continue.

MR. CHAVES: Okay. So besides their potency, unique properties are a very narrow spectrum of antibacterial activity with potential for pathogen-specific therapies. The resulting low offset selection pressure allows the use of FabI inhibitors without any relevant effect on the normal gut flora. We believe,

these advantages can bring a significant improvement in the treatment of infectious diseases. By the way, for Neisseria gonorrhea, the effect on the pharynx flora will be of interest. Our front runner in clinical studies is AFABICIN/ in the treatment of staphylococcal infections. This drug has achieved promising results in phase two trial in skin infections vs vancomycin and linezolid – and note: AFABICIN is inactive against all non- staphylococcal gram-positive and gram-negative pathogens. Our front runner in our preclinical pipeline is DEBIO1453, a FabI inhibitor against Neisseria gonorrhea, including MDR strains. We have also a FabI inhibitor against Acinetobacter baumannii – and both programs are kindly supported by CARB-X. Can you continue to hear me well?

MR. KIM: Yes, sir.

MS. DEAL: We can.

MR. CHAVES: So one of our key considerations concerning the development of new drugs against Neisseria gonorrhea is the high risk of failures - even after an eventually successful

registration – this means, risks are added to those explained by Sue Cammarata, the previous speaker. The fate of any new antibacterial drug introduced into routine clinical practice to treat this infection is rapid emergence of resistance or rising MICs. Epidemiological and other infection-specific factors in gonorrhea possibly play a major role in this fate, and these factors are not expected to dramatically improve over the next years or decades. Extra-genital sites of infection and especially pharyngeal infections are not well characterized. These infections are often asymptomatic, are difficult to cure and probably play a relevant role in resistance development. In contrast, practicing physicians - and patients - usually prefer single dose treatment, but all factors mentioned before actually indicate that multiple dose regimes are probably well justified at least in a considerable proportion of patients.

Two final considerations: Changes in the treatment guidelines for gonorrhea are frequent and different across countries. This brings relevant regulatory challenges for developers. Assuming

successful pivotal program and regulatory approval, standard of care may have already changed - and is at launch different from your comparator; this is not the situation developers would like to face when bringing a new therapy for patients. Finally, an additional point to mention is the uncertainty about the best choice (intracellular vs extra-cellular bacterial killing) as a criterion to select drug candidates.

Based on the situation analysis described in the previous slide, I listed here points to discuss on the target product profile. Let’s start with the indication by site of infection, urogenital; fortunately, these are the most frequent infections and the ones with higher treatment success rates; they are therefore well placed in the acceptable case. Pharyngeal infections belong in the ideal case. Target population of adults belong in the acceptable case, while inclusion of adolescents can be in the ideal TPP - difference being driven by time to perform studies and costs. I think, there are good reasons to keep the doors open for intramuscular formulations both in the

acceptable and the ideal TPP, as well as for multidose treatment regimens.

Highlights of the preclinical activities up to IND. The Toxicology Work Package is well defined – this is very helpful. There is one key point to mention: In cases where the API synthesis activities are complex and costly, it is tempting to target short GLP toxicity studies only covering the intended treatment duration in humans, for example, 1-3 days, to reduce project costs and expedite the start of studies in humans. There are regulatory paths that support this approach. While this flexibility is highly appreciated, other regulatory bodies such as EMA do request 2-week GLP studies; therefore, Developers may prefer to conduct 2-week studies - or longer - to support global development and avoid additional in vivo studies down the road.

Neisseria Gonorrhoeaea is a fastidious bacterium and has very specific requirements to grow – it is typically cultured using agar. The microbiology work package is the soul of any antibacterial

development and may reveal the potential of the drug candidate in the clinic. However, the respective guidance documents include a number of assays that are to be performed in liquid cultures. In case of Neiseria gonorhoeae, results of conventional assays in liquid medium (MBC, killing curves, etc) are particularly affected by test conditions – standardized and validated tests are missing. Therefore, it is challenging for us to compare the performance of different compounds or drug candidates. We believe that data from liquid cultures should be considered exploratory for N. gonorrhoeae.

Neisseria gonorrhoeae has also particularities when we look at the In vivo work package. Animal modelling of gonorrhoeae infections is challenging due to the strict adaptation of this bacterium to humans. Accordingly, most development programs have relied on surrogate models, for example using the neutropenic mouse thigh model with Staph aureus. Regulatory guidance documents mention, however, that - ideally - the animal model of infection should be similar to the infection of

interest in humans. In addition, the bacteria used in the model should have similar characteristics - as virulence factors for example - as the one causing the disease of interest. Fortunately, there is growing published evidence that the mouse vaginal model for Neisseria gonorroheae is a good option not only for research but also as a translational PK/PD tool. Debiopharm has generated data suggesting robust Pk/PD using this model: Reproducible, quantitative dose-response as well as the identification of appropriate PK-PD indices. We believe that these data should be considered appropriate for regulatory purposes.

Future challenges are expected in our development program once IND is achieved. In contrast to the mentioned advances for vaginal infections, reliable models for extra genital sites have never published. Alternative approaches may be used to try to predict antibacterial activity in extra-genital sites, such as Physicochemical characteristics of drug candidates to assess cell permeability, tissue distribution and penetration, intracellular killing and impact of treatment duration. These approaches

however remain very exploratory, and new developments in this area are paramount to bridge the challenging PKPD gap for Neisseria Gonorrhea. Thank you very much for your attention.

MS. DEAL: Thank you very much, and particularly for highlighting some of the questions from the industry point of view. Thank you very much, Dr. Chaves.

And now I'd like to introduce Dr. Caroline Perry. Caroline is the asset lead and clinical development director for gepotidacin which is a novel antibacterial agent in development by GSK in partnership with BARDA, with the indication for gonococcal infection and uncomplicated urinary tract infections.

Dr. Perry has over 20 years of experience in drug development at GSK and I welcome you to the floor, Dr. Perry. Thank you very much.

MS. PERRY: Thank you very much, Dr. Deal. And thank you to the organizers for inviting me on behalf of GSK and BARDA to discuss some of the challenges and the lessons that we are learning while

we have a phase three study ongoing right now.

So gepotidacin is the molecule. It's a novel antibacterial agent. It's in development, in phase three. For both GC and uncomplicated -- tract infections. I've listed its study and its -- and NCT code there on clin-trial.gov if anybody's interested to sort of see some of the details.

The study actually started in October 2019. Our original completion date was due to be this month with an estimated about 600 participants enrolled. Unfortunately, because of the -- the COVID pandemic, revised estimated completion date is now pushed way out into 2023. So -- and that has been based upon current enrollment rate that we're observing and the -- the lockdown issues also within different countries, and in different sites in relationship to sort of COVID.

So that is going to be one of the challenges that I will talk about as I get into this sort of presentation.

Also, the study is lower H is 12 years. We don't have enough for age limit at all, but we are

restricted to individuals with a body weight of -- of 45 kilos or greater.

The study is actually following the FDA guidance for industry as has been described earlier this afternoon. And the study, we have sites open in six countries, so it's a global study -- in the US, Australia, the UK, Germany, Spain and Mexico. The last country opened its sites just earlier this month. So that is just an indication of how the COVID pandemic has driven some of these operational challenges. It's been 18 months to be able to open our last -- the last of the six countries.

So one of the -- the first of the challenges we faced in setting up the study was to identify the selection of the comparator. With a -- to sort of run a global study in multiple sort of countries, that presented a huge issue. And I've got listed here, back in 2019, the standard of care in the six countries that we were interested in conducting this study in. And then you can see that none of them are identical. They're all different. But those -- doses that we chose was actually 500 milligrams of

ceftriaxone plus 1 gram of oral azithromycin. And really at the time it was only -- majority of the countries were using the combined dual therapy, but now both US and the UK have actually modified their recommended standard of care and are just now using just ceftriaxone.

So what is really urgently sort of needed is a global agreement either on standard of care or the -- the standard comparator that we can actually utilize for clinical trial purposes.

So the challenge that we faced by slighting the comparator, we needed to then negotiate with each of the agencies and -- committees in the six countries. But the comparison that we were choosing was acceptable within the framework of the clinical trial.

The second challenge that we sort of faced was really culture versus NAAT testing as a part -- used a primary endpoint. We've heard the FDA guidance in 2015, the primary endpoint is a culture confirmed eradication of the infection and that defines the micro-ITT population. That's how our

study's actually setup and that testing is used to richen the enrollment of valuable participants. And we can use that data to define the secondary endpoint.

However, what is challenging is the principal investigator both capability and also capacity to be able to participate in a clinical trial becomes a challenge, particularly when there's very little standard training for PIs to -- to learn how to obtain cultures. There's very little bedside plating availability or the availability of a local lab to be able to maintain the viability of those cultures.

So while it's easy to spread the infection, the viability of the organism is -- is -- it's very hard to maintain and needs to be plated immediately or within a number of hours.

So, you know, with a limited global network of experts, because in that majority of you on this call are experts in GC. You know how to culture. You know how to be able to really identify the right patients. They aren't sufficient of you to be able to sort of support the number of clinical trials that require patients that are presenting with GC

infections. And so there's plenty of competition from other sponsors. So whether we're, you know, we're a sponsor looking to develop a treatment or a vaccine or even a diagnostic, we're all hunting for your time and your capability. And quite often, that is not always available to all of us.

So again, there's a limited network of experts, and so that does present some operational issues in where you're going to place your study and how quickly you can actually enroll your study.

Also for all sponsors to be able to sort of have the ability to have access to some local or other regional WHO or the testing laboratories, you have reliable culture and isolate transportation conditions established would help to reduce the variability. And as of for the window shipment that we're observing, to help improve pathogen recovery and isolate transport.

You know, we have to be able to sort of setup local labs for those sites that don't have them, and then have to be able to ship those isolates to essential labs for -- for susceptibility testing.

Having an opportunity to link into those established laboratories that are part of surveillance networks would be really useful for all sponsors.

Also consideration -- primary endpoint and perhaps thinking about using cultures for the secondary endpoint. You know, more countries and more PIs and more clinics, they utilize NAAT routinely. Culture and susceptibility testing is still required. You need that to be able to determine your break point, but perhaps that could be done from a subset of sites or subset of the subjects within the study rather than all of the subject.

Another challenge that we sort of face is, you know, body site sampling and enriching the patient population. So our study is setup to sample all three body sites. The prime site is urogenital, but we also sample the pharynx and also the rectum. And we do this for both culture and also NAAT. This is a huge burden for both the participant and also the site staff to be able to conduct. We also do tests for chlamydia and also mycoplasma genitalia.

So that sort of, as I say, increases the burden for the subject. The burden -- in terms of their number -- has to be collected and the actual time on site for those subjects.

Also very challenging as you've heard today, enriching for -- for women, for females -- adolescent participants. At least 50 percent of women are asymptomatic. It's also more difficult to obtain good cultures for women. And also, not all women present at STI clinics. A high percentage will present at the OBGYN clinic. So it's, again, women are very difficult to obtain within a clinical trial environment.

And then also it's very difficult to obtain adolescents. We've heard quite clearly that the highest -- of diseases in the adolescents in that very sort of young adult population. In the adolescents, it is a challenge to obtain consent. And each country, each site or each ethics has a different set of requirements. Some don't even like to and will not agree on having adolescents participate in adult studies. Most of the minimum age that is allowed is

16. As you saw in one of my earlier slides, our minimum age is 12 and that was at the request of the regulators. It is very challenging to find adolescents to be able to participate in these studies.

The other challenge that we -- we faced is that gepotidacin is being dosed in the multi -- you know, it's a multidose regiment. It's requiring two doses and we need to ensure that that second dose is -- is being taken. So we had, you know, the battery of the PKPD studies that you've heard -- both Magnus Unemo and George Drusano discussed earlier this morning that enabled us to determine the right dose that we feel is needed for this indication. But it's a two-dose regimen. We need to make sure that those subjects are taking that second dose.

So with the ascent of the pandemic, a number of other challenges have arisen. Some of which I think we also heard from Dr. Reno and Dr. McNeil in a sense that sexual health has been totally deprioritized. Rightly so. All of you are infectious disease specialists. You've been redeployed to

support your institutions and your hospitals to treat the patients with COVID. But also, the regulators and the ethics have also deprioritized review of trial applications as well because those with COVID take precedent.

Also, we've seen that health authorities, particularly from the UK and Australia -- there's sort of three steps of the application. The regulator, the ethics and then the health authority. We have to reapply because they put the studies on hold.

So that all, again, is a challenge. It takes time to be able to get the sites back up and running again. As you sort of see, we're having these waves of the pandemic and each time, it -- you know, we're coming out of a particular lockdown. We get the sites back up and running again and then we're locked down again. So it's been a real sort of challenge each time we see another lockdown to keep the studies running.

The other challenge that we've also observed -- again, discussed earlier -- is the

restrictions with the lockdown and the impact on clinic visits. It's a huge burden for the patient. It's a huge burden for the clinic staff as well. And participants are really reluctant to spend time in clinic. You know, the study is setup. We need to collect cultures, so those participants need to be able to come back into the clinic to have a culture, particularly the test to cure culture as well. That is a huge challenge to be able to minimize the time on site for those patients, but also to encourage them that it is -- it is safe to be able to come back on site because they're very, very concerned about COVID.

So we've been exploring things like using Eco sense such that we can consent the patient prior to coming on site, and also going through the -- the general medical history. Both consenting a patient for a trial, going through the standard -- sort of listing the medical history can take a fair amount of time. And if we can reduce that time on site by doing it remotely before the patient comes in, that's -- we hope will really sort of help encourage participants in this study.

Also, we're, you know, looking to explore telemedicine as well. As I said, this would collect a lot of that sort of medical history, and also turn the follow-up visit into a remote visit by the use of telemedicine.

So these are some of the -- the operational sort of challenges we didn't realize we were going to face, but have experienced because of the pandemic. But I think some of these perhaps could be here to stay, particularly a lot of -- using a lot of the technology now. The remote consent, telemedicine, I think will help not just for the studies in gonorrhea, but all clinical trials.

So in looking at how we can sort of reduce the delays that we're experiencing, it's also -- to think about the non-inferiority margin. And as, you know -- discussed sort of earlier, the -- margin, it's only in the FDA guidance of 2015, is 10 percent. Now that margin is based on trials in which the effective therapy was compared to perhaps a less effective or ineffective therapy. And three trials were used in that -- that particular sort of

metanalysis to determine that non-inferiority margin. And those studies were from 1986 and also 2001. So that's pretty old studies.

Now there are a lot more recent trials that could be used to recalculate that non-inferiority margin and could actually be, you know, using a more appropriate standard of care, ceftriaxone alone. And giving the obstacles that I just sort of discussed in developing, you know, new medicine for gonorrhea, currently having a larger acceptable difference or a larger non-inferiority margin could be considered based on a new updated metanalysis.

So these are some of the thought processes that we as an organization are sort of having to try and make the study much more sustainable and we can complete it in a shorter period of time than what is currently predicted.

I'd just like to sort of wrap up by sort of saying, you know, we need pragmatic trial considerations. All of us, as Sue has mentioned, as utilizing public/private, you know, partnerships and can those public funds be used more effectively? Can

we think about apart from trial design or a master protocol, absolutely, that idea could certainly drive efficiency.

So I can give you an example there, probably taking a bit of a liberty, but perhaps sponsored by NIAID, a single comparator and then multiple sponsors could then join that trial. So something to think about.

Also a global network of GC professionals that would support that platform trial with -- together with a number of sites that specialize perhaps in recruiting women, and sites that have the ethical and the preapproval to recruit adolescents. This would help all sponsors.

Some of the other things that would be really, really useful, harmonize regulatory trial approval and ethics review. It's different in every country and presents a number of challenges. And the thought about -- thinking about using NAAT testing for a primary population definition would be very, very useful. And then access to the surveillance labs that -- by who or the -- would be -- really help I think

all sponsors. So thank you. I'll end there and pass back over to the chair.

MS. DEAL: Thank you very much. And I think we've all experienced delays in so many trials because of COVID, so -- but thanks for pointing out what some of the practical challenges are, Caroline.

And so now I'd like to introduce our next speaker, which is Dr. Seamus O'Brien. Dr. O'Brien is with the Global Antibiotic Research and Development Partnership -- GARDP. He is the R&D director since July 2018 and is responsible for strategic development and delivery of the antibiotic R&D portfolio.

Currently, he is also the interim lead for the STI program area and the soloflormycin project. I invite you to come to the floor, please.

MR. O'BRIEN: Thanks, Carolyn. And first of all let me just check whether you can hear me.

MR. KIM: Yes, we can hear you.

MR. O'BRIEN: Excellent. Okay, great. First -- first task completed.

Okay. So first of all, I'd like to thank the organizers for the opportunity to speak here today. I'm going to share some thoughts. Some of them will not be new and I'll try not to repeat what others have said, but I'm going to share some thoughts about addressing the sort of global public health need when we consider future development programs for antibiotic treatments for gonorrhea. And my thoughts are based on challenges and opportunities we see with our current and also future programs.

Just to start, a little bit about GARDP for those of you who don't know. GARDP is a not-for-profit international foundation focusing on developing and delivering of public health orientation portfolio of antibiotic treatments. For those priority -- particularly impacted by antibiotic resistance for which there are limited treatment options.

If I can just get -- let's see if I can get the next slide, Grace. Okay. So sexually transmitted infections are a key disease area for GARDP and are particular gonorrhea and related infections.

This slide outlines our framework approach we take to develop portfolio development projects for gonorrhea. The goal is to develop public health treatments and to do that to go beyond primary regulatory approval. We wish to focus on those antibiotics that have the best potential to address that need and delay the emergence resistance.

We understand that the initial development plan is defined by the regulatory pathway for uncomplicated gonorrhea, and that would be our first step on the public health pathway.

We understand -- treatment is in place until rapid bacterial identification of susceptibility testing is widely available. And that even if you're developing a monotherapy by the uncomplicated gonorrhea root, combination therapy is expected to be required to provide adequate coverage.

And with current regulatory pathways, if you get past the primary indication, significant development will be required to confirm regimens to cover the key populations and the pathogens involved.

So the first project within this

portfolio approach is a co-development with entasis therapeutics. We are partnering to develop a novel -- inhibitor developed specifically to treat gonorrhea.

Just in quick comment on -- on the history of this antibiotic, really demonstrates the challenges faced and partnerships needed in bringing new treatments forward. It started developing in AstraZeneca, went with -- when it was still up in the independent -- tech and AstraZeneca since developed -- developed antibiotics. And NIAID has been a key partner in the phase two. In the phase two demonstrated -- efficacy for uncomplicated urogenital to the rectal gonorrhea. And NIAID also a key player in the clinical pharmacology --

And now -- in phase three and other supporting clinical pharmacology studies, we're also developing a public health access strategy for the priority of lower, middle income countries that we are responsible for.

So here we have an overview of the phase three study. And before I -- before I start on this slide, I'd just like to say I echo strongly all

the comments that Caroline made from GSK on all the challenges generally with a phase three study, and particularly the impact of COVID on the conduct of a gonorrhea study during the pandemic.

So the design and -- here is very similar to the studies described by both Caroline and Sue previously.

The study's ongoing. With all countries -- study in the US, Netherlands, South Africa and Thailand. Lineal sites now are activated, we're just pending a couple in Thailand which will be activated shortly.

Now we need to randomize over 900 patients to achieve just over 600 culture-positive patients with uncomplicated gonorrhea. We are comparing an oral monotherapy and the combination of -- ceftriaxone and oral azithromycin -- oral azithromycin. And that is a combination that rarely fails with very high cure rates.

The primary endpoint is microbiological cure in the micro-ITT population. This population includes all those with a positive culture baseline --

will include all those who have missed test of cure and those -- the follow-up as failures.

So if we look at the phase three, what does success look like? And I'm talking here very much in the context of oral monotherapy as a - as the agent that we're developing and thinking about future development programs.

The regulatory approval is the first step on the pathway to address both US and global public health need. Now what we all want is to avoid failing a drug at this first step.

So my slide got off my screen. I can continue talking, but I'm -- can you -- can you see the slides? I'll just wait to see if it's coming up. Okay. And, Crystal, can you hear me still?

MR. KIM: Yes, we can hear you.

MR. O'BRIEN: Can you see -- can anybody else see the slides or is it just me?

MR. KIM: Yes, we can see the slides.

MR. O'BRIEN: Okay. Well, I'll just try and do it off a paper copy then and -- for the interest of time.

Okay. We're back on. Great.

Okay. So where was I? So what we want to do is to avoid failing a drug at the first step. So my comments here are based on considerations for our current study, obviously, but also for future development options. And the now case thinking about the public health value of an old drug.

The regulatory success for a new treatment is currently based on the demonstration of non-inferiority, based on a different -- 10 percent at the lower bound of the confidence interval in the primary endpoint using a micro-ITT population.

So is this a significant barrier to reach the first base for success? Well, it is if we consider the comparator that rarely fails at a high -- greater than 99 percent microbiological cure rate.

Firstly, we need a large -- just to demonstrate that the active is not worth the 10 percent. But also to demonstrate that the -- is greater than the accepted CDC threshold of 95 percent of the lower bound of the 95 percent --

And also for some recent analysis of

the -- that Sue talked about in phase two studies, we need to consider a baseline for the -- of at least minus four percent between oral monotherapy versus this comparator as the starting point.

Also, if we consider the analysis population, considering the patient population for these studies, the risk of increased failure due to loss of follow-up or patient exceeds the window of the test to cure visit is considerable and is not necessarily controlled -- controlled by randomization, but the percentile for greater impact therefore on a new, active treatment.

So this risk has been particularly impacted by COVID, potentially increasing the number of patients who could be missing the test of cure and being lost to follow-up.

If I summarize this -- this slide with a 10 percent non-inferiority margin with a minus 4 percent fail -- if there are 10 to 15 percent missed test to cures, could lead to failed study. And this is particularly concerning for drugs which we may believe have a public health value.

Okay. So thinking of the current study and future development studies and programs. You know, what is the definition of success when we are thinking about addressing the public health needs?

Well, if we think about the -- phase three, that would really address personal health. What I mean there is I describe that as a treatment efficacy -- safety at the level of the patient in front of the physician in the clinic. As been mentioned, we also need to think about how effective and suitable the intervention is or treatment is for key impact populations -- women, the MSM population, adolescents and -- and partners.

Can we demonstrate that -- treatment of HIV patients and other at-risk populations.

Can we demonstrate reduced transmission of disease, which is the real value for efficacy at the pharyngeal side.

And related to that, can we demonstrate treatment of difficult -- to treat with resistant infections? We know lower cure rate and -- we know there are lower cure rates in patients with isolates

at higher MIC and the lower cure rates in the MSM population.

I should have said linked to transmission is linked to also suppression of spread -- resistance.

So I think the point to make here is really that we need diverse options that have -- may have different impact. Different modalities and value depending on what we're trying to address.

I think we can all accept -- overall, we can all accept -- overall, we can all accept our current reliance of a single class of antibiotics and one member of that class is not sustainable.

In our case and for other programs, a -- related to another model of action can provide strong public health options for patients and partners, but we have to -- we have to understand they may fail based on the current guidance of the first step.

So, you know, what are we doing as developers now to address public health needs. Caroline mentioned some of this. We're probably not

doing as much as we would like because of the risk the phase three study conduct and outcomes. For example, we of look at the area that we are focusing on -- is to include more -- there needs to be significant sample size increase to include more asymptomatic women. We need to factor in significant prescreening, which does come with high failure rates, and very high numbers up to 50 to 70 percent are randomized female participants based on exposure who will potentially be ineligible for the MITT population.

You've heard previously on the ethical and regulatory challenges to include adolescents. Also, if we wish to include some of those priority populations I mentioned in countries with significant burden of disease, we need to commit to build capability as sites may not be as experienced as more research -- sites.

So therefore, when we address -- talk about -- when I talk about addressing public health needs, there is a balance to increase the public health value of the phase three versus increasing the risk of -- of failure.

So overall, before I go onto the last couple slides, we can exist -- sorry. We can exhaust all the operational actions to increase the valuable participants to focus on the true microbiological success and failures within the micro-ITT population, but it may not be enough with the current design to -- failure at the first regulatory approval step.

So I'm going to finish with just some thoughts and considerations and questions that we can look at to improve the likelihood of success from a public health perspective.

My first slide is focusing on the phase three. So for example, what could be considered a successful outcome from a public health perspective for these studies? For example, could we look at defining a percent success rate, for example, a different threshold which could be compared historically maybe to the historical placebos? So a different threshold approach to define a success rate for public health value.

As mentioned by the previous speakers, if a large and non-inferiority -- now justified from a

public health need perspective, we do have examples from other infection syndromes and priority pathogens -- like gonorrhea is a priority pathogen -- including other single pathogen targets which maybe we can consider. And these -- these pathogens here are -- antibiotics are being developed by streamline development programs to address the infections caused by those pathogens.

Should the prime analysis include only patients that are truly valuable and we could consider the efficacy analysis of the modified micro-ITT population as a key secondary point for example.

As has been mentioned in the recent 2019 CID publication, could we consider other endpoints such as the desirability of outcome ranking in combination with inferiority outcome to provide a more broader value assessment for a new treatment. And is one well-controlled -- adequately well-controlled study, which is based on an aggregate of individual outcomes, really a way forward for all candidates which may differ -- attributes and modality to address public health value. For example, as

others have said, some interventions may have a better value for -- for women and -- women, partners. Other interventions may be more suited for MSM population or population with infections due to raised MIC, for extragenital -- one regimen is not university-appropriate maybe and therefore, one study may not be appropriate. One study type I should say may not be appropriate.

Maybe considering the -- as we have seen, do we now need to think about what could be implemented to ensure we have options in place in advance of what would be the -- utility --

And lastly, just to think about the broader development program -- I'm not going to talk about the preclinical aspects. I'm thinking here more about the clinical development and how it links to evidence generation required to support -- mention about the economic challenges. I think we have to understand that most new drugs currently are not going to be used initially for the broad indication even if they achieve it. So maybe we should spend more time earlier in development addressing evidence of how the

drug may actually be used.

Therefore, you know, if the urogenital gonorrhea program with a single phase -- crawl the way forward. Can future development programs supported by regulatory frameworks address those key public health and access questions for new treatments? For example, can we support studies and specific investigation? Maybe with a greater waiting to address questions with specific populations, resisted infection -- treatment, transmission impact, modes of administration.

These also maybe particularly suitable not just for other -- but also maybe for repurposed antibiotics.

We talked about -- that study and -- and linking to - approach -- new networks to support such study in the investigation in addition to maybe more pragmatic core phase three studies.

And the last point in my slide may be linked onto the next speaker. Without true point of care test, should syndrome and infection pathways still be considered as an option and an alternative to the current pathway for developing gonorrhea drugs?

So I hope I've stuck to time. Thank you everybody for your time and attention. Thank you very much.

MS. DEAL: Thank you very much for raising those interesting questions. We'd ask all -- all the speakers to do so.

And so now we'll turn to the last speaker in this block of developers. And I'd like to present Dr. Steve Gelone who is president and chief operating officer and director at Nabriva Therapeutics. Steve has over 25 years of experience in research and development of anti-infectives and rare disease products at all stages of drug development in both academic and corporate settings.

I turn the floor over to you. Thank you very much.

MR. GELONE: Thank you, Carolyn, and thank you to the organizers for inviting us to participate and allowing me to present on behalf of Nabriva.

So I will sort of pick up on where Seamus left off to discuss a little bit about this --

approach to uncomplicated urethritis and cervicitis.

If I could have the next slide, please.

So there is obviously throughout the course of the day a number of considerations and challenges have been brought up as it relates to things to consider. This I certainly by no means an all-encompassing list, but what I suggest is that the lenses that we've been viewing these challenges and some of the other challenges through is the lens of the desire to have a single-dose therapy to treat uncomplicated urethritis and cervicitis caused by gonorrhea.

And clearly, that has many, many important advantages from a public health perspective and a patient convenience perspective.

I think it's also fair to say -- and has been shared throughout the earlier part of the day -- that not all things are created equally and maybe not all drugs are able to -- to sort of meet that bar for gonorrhea or even beyond. And whether or not it has to do with extragenital site of infection, the development of resistance over time, specific patient

populations, or as I'll talk about a little bit more in detail here, the common coinfecting pathogens that are often present in patients who have gonorrhea, including chlamydia mycoplasma, syphilis and others which most often require multiple-dose therapy. It certainly results in us sort of needing to squeeze the balloon a little bit.

Obviously this sort of fundamental thinking has led to many approvals from uncomplicated gonorrhea. These are just a couple of excerpts of commonly used drugs like ceftriaxone and azithromycin here, and I recognize that ceftriaxone's label is certainly a little bit older. But a couple of things sort of jump out beyond the pathogen-specific approach here. One, the idea that including something around resistant strains, depending upon what phenotypes are most meaningful to the compound has certainly been part and parcel to prior approvals.

Certainly with azithromycin, the ability to have approval for both gonorrhea and chlamydia is -- is covered here. What I don't show on this slide is that the dosing regimens are not the

same -- as many I think know on this call -- for these two indications. And -- and it's also I think important to mention that the two indications were done through sort of unique-specific studies for chlamydia alone and for gonorrhea alone.

And then lastly as it relates to co-pathogens, to date, no agent has been approved for the treatment of -- genitalium. So you know, again, as we think about the challenges that are faced here as it relates to the number of compounds and development and fast forward certainly contemplating whether or not a pathogen-specific approach jumped into our minds.

The next slide.

So, you know, mindful of the existing challenges and -- and albeit as many have shared earlier in the day, we've gotten far more informed as it relates to the preclinical things that can help us figure out the best dosage and de-risk programs moving forward. And also being mindful of the fact that there are a small number of compounds and development for gonorrhea.

One can certainly envision what a

potential target product profile could look like and the package insert of a product that would go through a syndromic treatment approach, certainly not a pathway that's uncommon for development of antibacterials. There are numerous examples and obviously the treatment guidelines, even for gonorrhea as they exist today in the newest version and -- and for prior versions. Certainly contemplate the necessity of -- of assessing potential coinfecting pathogens that would require more than the standard of care treatment with a cell wall active agent for a single dose.

And so we can certainly imagine drug -- and antibacterial that's indicated for uncomplicated urethritis and cervicitis. And depending upon the pathogens that were identified in this type of a trial, it may include both gonorrhea, chlamydia, mycoplasma, ureaplasma, whatever was -- was seen in that study.

The target population can be debated, whether it's adults or adults and adolescents, and how much of a presence for gonorrhea specifically having

concurrent extragenital infection would be required in order to have evidence to include that within -- within a potential label -- need for discussion.

But you can certainly also -- like with azithromycin -- envision that you have a dosing regimen that may be different and unique that's pathogen-specific. So a certain dose for some number of times per day or some number of hours per day, and gonorrhea may be one dose and one duration, and chlamydia and mycoplasma may require a very different dose and duration.

Next slide, please.

So as we've contemplated, our potential development of Lefamulin, which is -- antibiotic that was discovered and brought through phase three development by Nabriva Therapeutics. We certainly reflected back on what -- what pathways may be most viable for -- for this compound as it relates to STIs.

For those not familiar with the drug, it's the first -- pleuromutilin. Its initial approval has been granted in the US, Europe and Canada for the treatment of -- acquired bacterial pneumonia.

Pleuromutilins are protein synthesis inhibitors. They bind to a highly conserved region on the ribosomal "pectital" transferring center that is unique and different than other ribosomally active drugs. And this importantly conveys a lack of cross-resistance to antibiotic classes.

As it relates to the -- you know, the treatment of acute infections like STIs, the oral product obviously is -- is attractive. The PK profile results in very rapid absorption. Typically, rapid concentrations are achieved within 60 minutes. And the distribution of the drug throughout the body tends to be a much more high distribution than the tissue sites relative to -- to plasma concentrations.

Next slide, please.

So as we think about it from a microbiologic perspective -- are some of the data we've generated around Lefamulin's activity against the most common pathogens associated with urethritis and cervicitis, as well as some other STIs. And as you can see here against gonorrhea, M genitalium and chlamydia. There's relatively potent invitro

activity. That activity is maintained regardless of the resistant phenotype. So whether there's ceftriaxone macrolide -- tetracycline resistance, the MICs don't really change and that will be expected given the unique mechanism of action.

I'd also add that at least from invitro studies, Lefamulin has been shown to be bactericidal both against gonorrhea and M genitalium, which may present some benefit as -- as we think forward about the program.

In addition, there's activity against some other important pathogens that may be associated with PID as well as haemophilus ducreyi. And being a pleuromutilin -- pleuromutilins are classically active against spirochetes and we're currently evaluating the activity of Lefamulin against treponema pallidum to see if it might be something that could affect incubating syphilis in patients who have STIs.

If you could go to the next slide, please.

As was discussed earlier, you know, ensuring that the drug gets to the site of infection

that you'd like, we've obviously done a lot of work related to pneumonia given the phase there studies that have been conducted and the approval for the -- the commune acquired bacterial pneumonia indication.

As we've begun to explore, the potential of the compound for the treatment of STIs, we've done some animal work already and I just share that the male data -- we've done it in females as well. And if they're single-dose of IV "radio label" Lefamulin, what we've been able to see is high concentrations in the genital urinary tissues using micro autoradiography to -- to show where the drug concentrates. And in particular in women, we see high concentrations in the -- in the endometrium, which -- earlier in the day may be important for upper tract infection with gonorrhea.

You can go to the next slide, please.

And so as we've contemplated the potential path forward for this compound, you know, we're internally debating whether or not a gonorrhea pathway versus a syndromic pathway is something that we should pursue. There have been a number of

questions that certainly have been debated internally at length, and with external folks. Not the least of which is, you know, how best to stratify patients in an all -- type trial such as this. What would be the -- the appropriate comparator, especially recognizing that there are no approved treatments at the moment for M genitalium, and how best and what level of evidence would need to be available to support an indication in this type of an outcome or trial as well as what level of evidence for resistant pathogens would be sufficient.

You can go to the next slide, please.

So I think, you know, at the end of the day, I think we're squeezing the balloon a little, right? And sort of balancing out what are the important things. Is it to try and come up with a one-dose or one-day regimen that may be sufficient for treating uncomplicated gonorrhea or is there -- if there's an appetite for -- for regimen that is longer than that, would there be benefit as it relates to things like resistance development, potential ability to cover common coinfecting pathogens potentially

interrupting the transmission cycle of subacute infections that are currently present as well.

And so these are things that we continue to debate and look forward to the conversation as the meeting continues. Thank you very much.

MR. KIM: Thank you, Dr. Gelone, for giving your presentation on development considerations related to potential pseudoatomic treatment approach. This concludes our block on developer perspectives, recent challenges and lessons learned. We'll now begin our next block related to investigator perspectives on development considerations for antimicrobial drugs for the treatment of gonorrhea.

And with that, I'd like to introduce Dr. Edward Hook. Dr. Hook is Emeritus professor of medicine and epidemiology at the University of Alabama at Birmingham.

As an internist with subspecialty expertise in infectious diseases, much of Dr. Hook's academic career has been focused on the management and prevention of sexually transmitted diseases.

With that, I give you the floor, Dr. Hook.

MR. HOOK: Peter, thank you very much. I'll turn on my webcam and start my presentation. Let me start by saying how much I have enjoyed today's meeting and how important I think it is for the future of treatment trials for uncomplicated gonococcal infection.

Let me also apologize in advance for any redundancies that I present. I think many of us have shared perspectives on the problems and barriers encountered in terms of conducting clinical trials for the treatment of gonorrhea, and that's the basis for it.

Let me also mention that I was asked to present this along with Dr. Stephanie Taylor [ph] from LSU. Dr. Taylor was unsure that she would be unable to participate today and has asked me to make the presentation on her behalf.

On the other hand, Dr. Taylor and I have both worked together on assembling this presentation and this represents both of our thoughts

and feelings.

I'm in the habit of presenting disclosures, so I will let the audience know that obviously I've had research support from national institutes and allergy and infection disease, and I am presently a consultant both for GARDP who we heard from earlier today, as well as Visby Diagnostics who make a point of care test for diagnosing gonorrhea that was mentioned earlier today.

Dr. Taylor has received research support from GlaxoSmithKline, GARDP and -- all of whom have been represented in today's presentations as well.

Between Dr. Taylor and I, I also think that we probably participated in every -- in every clinical trial that's been done for gonorrhea treatment in the United States in the last 30 or 40 years.

This is the outline of my presentation. There are a number of topics and a number of complexities and I'll try to just work my way through them in the time I have allocated.

Starting though, let me acknowledge that I am not only an investigator, but a clinician. And I think those two perspectives bring a somewhat different and perhaps complimentary perspective to the topic.

As a clinician, I can tell you that I have great confidence in the current therapies. On the other hand, I wish I had more treatment options as-- as has already been mentioned. Right now, we only have a single treatment options, a single class of medications. And in fact, really only a single medication is the backbone of those treatments -- that's ceftriaxone. And ceftriaxone does have some limitations. For instance, it's an injectable antibiotic. As an injectable antibiotic, many clinicians' offices, if they don't see an awful lot of this disease, may not stock it in their office.

Also, a patient can't go to a pharmacy to receive an injection of ceftriaxone, so that's an issue.

Finally, also as an injectable antibiotic, Dr. O'Brien mentioned earlier we find

ourselves constrained with one of the important initiatives for controlling gonorrhea from a public health perspective. That is delivery of therapy for partners exposed through individuals with gonorrhea who may not be willing or able to come for treatment. This is the so called expedited partner treatment initiative, which is then backed by the CDC in which is legal in most states of the United States.

The other issue regarding clinician perspective that I'd like to bring up has to do with the issue of the fact that we do have only a single class of medications available for treating this. And that class of medication has relative barriers. About 10 percent of the patients we see on a regular basis believe that they are allergic to penicillin and therefore other beta-lactamase antibiotics. And while that may or may not be true, what that does do is introduces a certain amount of concern to clinicians and many, many clinicians will avoid using the recommended drug because they do not have an alternative available for penicillin allergy.

So those are my perspectives as a

clinician. As an investigator, there are a few other observations that I'd like to make in an introductory fashion.

One is that clinical -- while clinical design or clinical trial design has really changed little in the last 40 years, the epidemiology of the disease has. Indeed, Dr. Bachmann mentioned earlier today we see more and more infections in men who have sex with other partners. Nonetheless, we persist in expecting greater than 95 percent efficacy. We also expect that efficacy to occur at all potential sites of infection. I'll be talking more about that later.

Lastly, in that four-year period where we've been pretty much locked in in the same sort of clinical design -- study design, we've had a number of things that have come up to challenge our thinking about these.

A number of times today, starting with Dr. Wi, Dr. Bachmann, Dr. Deal -- and many others have all mentioned the threat of antimicrobial resistance. Right now, however, as was mentioned, that is primarily threat as opposed to a reality. And as

mentioned as well, in any site, ceftriaxone -- very, very effective for treating gonorrhea.

I've already mentioned the problem of reliance upon a single medication class as a potential problem and a reason that I'm very invested in new therapies. And then as I'll be talking about later, we've learned that uncomplicated gonorrhea is not just urogenital gonorrhea. Certainly approvals and clinical trials in the past have focused on your urogenital infection, but as we've gotten better diagnostics for -- for gonorrhea, we've realized that rectal and oropharyngeal infections are far more common than they used to be. And particularly, oropharyngeal infections may be more difficult to treat than other uncomplicated gonorrhea at other sites.

So now let me work on and start with my discussion about clinical trial sites -- law tells us that investigators should go where the disease is most common because that's where clinical trials could be conducted most efficiently. That means, and indeed as a result most clinical trials in North American being

performed in sexually transmitted disease clinics. Now increasingly called sexual health clinics.

These are dedicated. These clinics and these research programs are generally located in public health clinics, only a fraction of which have the capacity and ability to do research on a regular basis. Doctors Reno and McNeil both mentioned that. Nonetheless, there are a handful of sexual health clinics which do conduct the -- the majority of -- of STD and specifically gonorrhea research in North America.

There's several other sites that have the potential, and I'll comet on them briefly. But preview those statements by saying that none of those sites have proven to be highly effective. And I think in order to develop in those research sites, there would be no more -- there would be more work to be done.

The first site that comes to mind are family planning clinics. This has the potential to address one pressing need, which is to enroll more women in studies. Enrollment of women, as I'll speak

about a little later, is relatively inefficient from a clinical trial perspective for a number of reasons as problematic.

Family planning clinics have the opportunity. They routinely screen their patients for gonorrhea. They detect a moderate amount of gonorrhea and, if dedicated and developed, these research centers could contribute in important ways to research going forward.

A third set of sites are adolescent medicine clinics. And we've heard today on numerous occasions about the importance that many adolescents and young adults get gonorrhea frequently. They have a high burden of disease.

Unfortunately, adolescent clinics by and large again have not proven to be very good trial sites for clinical trials. Sometimes adolescents attend the clinics with their parents and that's the barrier to trial participation. Adolescent investigators may have challenges in doing that research.

The first fight, which is just emerging

and Dr. Marrazzo mentioned earlier, is HIV clinics. More and more screening for sexually transmitted infections is being carried out in HIV clinics and is identifying large numbers of infected persons.

The HIV clinics that do research and, of course, like all the other sites I've mentioned, not all do. Typically, and most prominently are engaged in addressing the multiple research needs related to providing better, more efficient care for persons with and at risk for HIV. So again, those have proven not to be major clinical trial sites to date, although that has the potential to change.

What about the participants themselves? Well, again, with different participant groups, there are different sites of infection and infections become more and more common.

For instance, in men -- in men who have sex with female sexual partners, the predominant site of infection are urogenital infections. Rectal infections become vanishingly rare in this group of people, and oropharyngeal infections are somewhat uncommon.

In contrast to that are men who have sex with other men. And in those individuals, multiple site infections are very common. And in fact, of the sites that are typically diagnosed, urogenital infections are perhaps the least common in a number of studies. Rectal infections are most common. Oral pharyngeal and urogenital infections follow in the relative prevalence of oropharyngeal and urogenital infections vary from population to population. As I already said, multiple site infects are also very prominent in this group of people.

In terms of trial participants, women -- again, urogenital tract infections predominate, but rectal and oropharyngeal infections are relatively common in this group as well. More on this a little bit later.

In adolescents, the sites of infection involved with diagnosis are highly variable.

Before I go any further, we've heard a number of comments today about oropharyngeal and rectal infections. And please, I would urge all the participants in this study to step away from the term

"extragenital infections." It's an imprecise term and there are important differences between these two sites of infection.

For rectal infection -- pardon me -- infections can occur in two different ways. They can occur through direct inoculation through receptive rectal intercourse, or in women -- as was mentioned earlier -- local contamination with cervical vaginal secretions may lead to rectal colonization with the organisms as well. This has been proven not only for gonorrhea, but for chlamydia.

So rectal infection, there are questions as to what the complications associated with these infections are. And let's remember that it's the complications of uncomplicated gonorrhea that really drive the morbidity and do so much to make this a major public health challenge.

Going onto the topic of oropharyngeal infection, let me first say that acquisition of oropharyngeal infections occur only through direct inoculation. However, performance of fellatio may be a more efficient mechanism of inoculation than

cunnilingus or analingus for acquisition of infection.

Let me also mention that for oropharyngeal infections unlike both rectal and urogenital infections, sampling may be challenging. There is not a standardized method for sampling the oropharynx. So some investigators may challenge only a single -- the single swab at the posterior pharynx while others may do a more complete sampling, sampling both the tonsils and the posterior pharynx.

Standardization of sampling would be important if we were to consider those sites of infection.

Also, as a generalization -- and it's a generalization which occurs even for ceftriaxone. The oropharynx represents a site where treatment failures are more common. The majority of treatment failures with ceftriaxone have been described at the oropharynx. We know that previously antibiotics -- the fluroquinolone, spectinomycin, etcetera all had higher treatment failure rates at the oropharynx, but at other potential sites of infection.

Just as for the rectum and finally

complicating our thinking regarding oropharyngeal infections is the fact that there are a number of important questions yet to be addressed regarding complications related to these infections, as well as their transmissibility to others. Not to mention the epidemiologic question which is unproven, but widely discussed today that the oropharynx is the predominant site where antimicrobial resistance evolves and -- and moves forward.

So these sites beyond the urogenital infection really are things that need to be considered going forward. What about trial participants? I thought it might be useful to talk about how as a clinical investigator we enroll participants in our study.

Certainly, gonorrhea is present and prevalent throughout the population. However, the prevalence varies in different population subgroups as do the enrollment strategies. And though as investigators, we employ different strategies for enrolling different sorts of patients.

Men, we typically -- at least men who

are having sex with men -- or excuse me, with women, and men in general are generally enrolled as symptomatic men. Most commonly with urethritis in which gonorrhea can be differentiated from non-gonococcal urethritis by a simple almost immediately available test, such as a -- or other rapid --

Within the male participant site though, as I mentioned and eluded to earlier, the epidemiology has changed. And in the 1980s, and even the early '90s, in our clinical trials, the enrollment occurred disproportionately amongst men who had sex with female sexual partners. But today, as described by Dr. Bachmann, rates of infection have gone up particularly rapidly amongst men who have sex with men who have a higher treatment failure rate than men who have sex with women.

What about enrollment strategies for women? Well, this is a notoriously inefficient mechanism -- group of people to enroll.

First of all, symptoms are absolutely unreliable in -- in woman candidates for enrollment in gonorrhea treatment trials. Stains, such as the gram

stains, are unreliable and inefficient with sensitivities of 50 to 60 percent, even in -- in the best of hands.

And then once we've identified a potential candidate, the question comes up as to whether or not she's contracepting as well. I'll bring that up in just a moment as well.

That -- the other group of women -- so as an enrollment strategy, we predominantly try to enroll either women identified as sexual contacts to men who are identified as treated, or following positive screening tests in women who did not receive treatment at the time they were screened.

Adolescents I've already mentioned. Enrollment strategies vary. Most of the adolescents enrolled in clinical trials at the present time, that enrollment does occur in sexually transmitted infection clinics.

Going on on the topic of enrollment strategies and challenges, let me go on to say that for men who have sex with female sexual partners, there really are few enrollment challenges. We can

find them in sexual health clinics. We can identify them readily. And for that reason, as mentioned in earlier presentations, they often represent the bulk of patients enrolled in clinical trial.

Amongst men who have sex with men, certainly urogenital gonococcal infections occur and can be readily identified. But as I've already mentioned, rectal and oropharyngeal infections represent the bulk of infections in this group.

In women, I've already mentioned are the challenges of identifying infected persons. And once we identify a potential study participant, we have still more challenges. That has to do with using adequate and appropriate birth control.

Again, 20, 25 years ago individuals were willing to enroll women who pledged to use condoms regularly throughout their evaluation period in clinical trials. But more and more, sponsors of clinical trials have preferred a more reliable and more proven contraceptive method which really relate to either tubal ligation, the oral contraceptive pill or other reversable contraceptive methods including

the IUD.

Pregnancy also needs to be ruled out in women. And all of those things just make enrolling women, even ones we've identified potential candidates, a bit more challenging.

Also mentioned earlier was the problem of enrolling adolescents. There is state to state variation as well as institution to institution variation in the ability of adolescents to consent to participating in research. Sometimes there's a difference between their ability to consent to research and their ability to consent to care for sexual health. Dr. Perry mentioned that earlier in her presentation and I certainly can tell you that that does represent a challenge for investigators.

Another topic of importance for an investigator and again, potential challenges represent the issues of diagnosis and outcome measurement.

The gram stain is often usual for enrolling -- helpful for enrolling men, but not particularly useful for enrolling other patient groups or non-urogenital sites of infection.

As already mentioned multiple times today, culture is the gold standard for clinical trials and gonorrhea treatment trials. The reason for this is then you have organisms which you know are viable and can be used for susceptibility testing. Something that can't be done uniformly with non-culture methods.

We also, however, in the past 15 years have learned more and more that culture for gonorrhea is not a particularly sensitive method. That even for diagnosis of urogenital infections, culture may miss as many as 10 percent of infections and oropharyngeal and rectal infections culture may miss even more.

That leads us to comments about the nucleic acid amplification tests, which have really simplified, revolutionized the diagnosis of gonorrhea and other sexual health pathogens. These are the standard of care. They are widely used. They are easier to collect. They are more sensitive than culture and they don’t have the barriers to culture processing, such as specimen transport and viability issues that we deal with on a regular basis with

culture.

That means that culture is less and less availability and more and more investigators want to use nucleic acid amplification tests. Unfortunately, however, these tests with the exception of determination of fluoroquinolone resistance do not -- are not even in -- on a routine basis available to determine susceptibility to drugs. And there's a problem in that dead organisms may still be present and -- and shed residual nucleic acid at sites of infection, compromising our ability to determine whether treatment has been effective or not.

The last category that I want to mention, however, represents something that's on the horizon that really promises to change our management of persons with and at risk for gonorrhea, but also may challenge clinical trials. And that has to do with the revolutionary development of new point of care tests, which will provide accurate diagnosis of gonococcal infections in less than 30 minutes. This has the potential to really increase and enhance enrollment efficiency, particularly for detection of

females and extragenital infections.

However, a downside is that most of these tests couple diagnosis of gonorrhea and chlamydial infection, and some of them have talked about having multiplex capacities for diagnosis of other infections such as mycoplasma genitalium or trichomoniasis. That then leads to the issue and the topic of what do we do in patients with coinfections and who we're trying to enroll for clinical trials? I've listed on this slide four different coinfections of concern that have been mentioned. Chlamydia trachomatis is -- is relatively common. For a long time, co-therapy for possible chlamydial infection has been recommended with its basis being that in the past, detection of chlamydial infection was a time consuming and not uniformly available process.

That's -- that's changed, however -- those early days, however, individuals would be enrolled with gonorrhea or at risk for gonorrhea. And if they had chlamydia, they would -- their treatment would be deferred until they returned for their treatment test of cure testing in four to seven days

following enrollment.

Trichomoniasis is another very common coinfection particularly in women. The good news with trichomoniasis is the currently recommended therapy has been proven not to be effective for gonorrhea, so that's less of a concern.

Historically, the issue of incubating syphilis and treponema pallidum has also been a concern. Steve Gelone mentioned that. That is a relatively less common coinfection and less of a problem for clinical investigators.

And then finally, there's the emerging issue of mycoplasma genitalium which at the present time is not recommended for routine testing. And as was mentioned earlier, there is no routine therapy recommended for treatment of this.

Despite that, and in a sense of preparedness, clinical trialists and investigators are -- are typically looking for this organism and wondering whether their new drugs will be effective or not. This also represents a potential challenging issue for the clinical trialists going forward in the

future. And as we have more and more point of care tests detecting all these infections, that may complicate things even more.

My final slide has to do with sort of a summary of my -- my random thoughts or our random thoughts on -- on clinical trials. You know, there -- there certainly are published and I've been an author on issues related to a wish list for the ideal therapy. Something that's single-dose, orally administered, has low toxicity, is safe in pregnancy, etcetera. But right now, I can't help but wonder whether a pursuit of perfection has become the enemy of the good and whether our current criteria for treatment are a bit too stringent.

Should we be considering multiple-dose therapy, we certainly used it in the past until we had the advantage of more recently available therapies. What about oral versus injectable regimen? Is the juice worth the squeeze? What does it do in terms of expedited partner treatment? And so forth. The topic of rectal and oropharyngeal infections is huge. And right now, inclusion of that in clinical trials, at

least in my opinion, while an important to collect the data, is probably not ready for primetime since we don't know enough about the complications of these infections, about their transmissibility about their role as public health problems, which after all, should be driving our decisions about what we want in an ideal drug.

What about outcome measurements? I think the time has come where we need to figure out the limitations of using nucleic acid amplification tests for evaluating treatment and be able to use that more broadly in clinical trials for gonorrhea.

And then finally, and again, circling back to my role as a clinician -- as a previous clinic director and parroting what doctors Reno and McNeil have said -- we need to think about the fact that where these trials are done often are in our SafetyNet clinics, public health clinics and the studies do have impact on clinic flow. That's the reason that more of the clinics do not participate in those.

I think the question about how to encounter that is also an issue for further

discussion.

So I think that completes my slides and my further comments. I've managed to stay on -- on time and I thank you for the opportunity to present and share my thoughts. Again, thanks very much.

MS. DEAL: Well, on behalf of Peter and myself and all three of the agencies, I want to thank all the presenters in this session for the regulatory information, for the experience from our product developers, and for the thoughtful questions that they have posed, as well as the clinical and public health perspective that has been discussed by quite a few of the presenters. I think this sets the stage for our panel discussion and I'll turn it over to Peter.

MR. KIM: Thank you, Carolyn. Once again, thank you to all the presenters for all of your time preparing your slides and for the presentations as well -- and your thoughts. We'll now take a 10-minute break and we'll return I believe at 3:00 p.m. Thank you.

MS. DEAL: We are about to begin the final session of the meeting, which is the moderated

panel session. I'm going to turn it over to Dr. Hook and Dr. Workowski. Thank you.

MR. HOOK: Thank you very much. This is Ned Hook. Dr. Workowski and I will be moderating the discussion. I'd like to take just a few seconds to talk about the ground rules for our discussion. We have over 40 different presenters who've been invited to comment on these discussions, and clearly there's not enough time for everybody to do that.

So we're going to have to be a little strict. We have a little over 15 minutes available to answer each of the five questions that you will see -- the total of five questions that you'll see on your screen shortly. That means that we're going to ask people to be succinct. We're going to ask people not to necessarily join the -- the talk to agree with something that's already been said, unless the silence coming over the internet is deafening.

I'd also like to tell you that we've heard issues regarding the problems and challenges of clinical trials throughout this very interesting and productive day. Now it's time to shift. We want to

hear from you folks out there about solutions. We want to know what we need to do and we want to know about evaluation of new antibiotics and bringing them to clinical trials. This is not about necessarily repurposing drugs unless it's for a totally new indication.

Also, we're going to ask everybody who has a comment to use the raise your hand function to identify yourself as having a question. Then depending on the question, Dr. Workowksi or I will be choosing to -- the people to speak and will be calling upon you.

We may not call on people in the order they raised their hands, because we're interested in a mixture of perspectives. So if we have -- if we hear from several clinicians or public health people, we may want to hear from industry and take people out of order in order to get the most varied presentations we can.

Also, during your question-and-answer period, please unmute yourself -- talk and then be sure to mute yourself again once you finished your

question. At the end of each question, we're going to ask everybody to lower their hands so that we can start anew with people who are asking questions.

Finally, there will be five questions listed on your screen and then -- and then we will -- we pledge to go to all of them. When you received the agenda, these were listed as one through five, but we have chosen to reorder those questions because we wanted to particularly get the questions three, four and five, and felt like the discussions of questions one and two could take even longer and be more involved. But it was important to get through all the questions.

So that's my -- my two cents' worth. I will stop at the moment and turn the microphone over to Dr. Workowski who will introduce herself and then start the questions. Kim? Thank you.

MS. WORKOWSKI: Thanks so much, Ned, and first I want to say that I am very honored to be present with each of you. Each of you gave a tremendous presentation and there's so much to talk about.

There's a couple of things that I wanted to start with that I had written down some notes during the presentations. And one was thinking about number one is the issue that was just brought up several times during the day that I want to comment on first, which is the stringent endpoint that we have.

As you know, those endpoints of greater than 95 percent efficacy and a greater than 95 percent lower confidence interval was -- was thought about back in the mid-'90s. And it had to do with the plethora of the medications that we had available.

So I wanted to think about that in the context of now we're in a different situation where we don't have medications that are going to be easy to meet that endpoint.

And so one is to think about that perspective to begin with for people to comment on, thinking about that's the endpoint that's going to potentially be used. And can, as you know, make or break some of these drugs.

So looking for comments -- for people to comment on that endpoint. It is now the time to

change. There was a paper that was written a number of years ago that we had proposed going down to the 90 percent lower confidence bound. So thinking about what people's thoughts are to get the discussion started about that. Please raise your hand.

So I'd be interested -- since I don't see any hands raised yet - in terms of the thoughts regarding this from our FDA colleagues to start the discussion.

Daniel?

MR. RUBIN: Hi, this is Dan Rubin, a statistician at FDA. Can you hear me?

MS. WORKOWSKI: Yes.

MR. RUBIN: Okay, great. So if -- you framed it in terms of the confidence level, and I guess a similar way to think about it would be in terms of the margin. Whether it should be 10 percent or possibly wider as some other speakers had mentioned.

And the appendix to our guidance, we had justified a fairly large treatment effect for antibacterials relative to a hypothetical placebo.

And in terms of accepting more statistical uncertainty about efficacy then, I don't think the question is whether we would lack -- the new antibacterial was better than placebo. The question would really be weather or giving up too much efficacy relative to the existing treatment regimens.

So I know some speakers had mentioned that in other areas with unmet need, we'd had relaxed statistical standards, but I think it's more of a clinical question then about how much efficacy are we willing to give up in the setting of ceftriaxone or ceftriaxone or azithromycin really providing, you know, very effective therapies. If that's having, you know, close to 100 percent test rates in some trials, we're willing to consider it an investigational drug that is now dropping to -- to 90 percent or lower in terms of eradication rates.

MS. WORKOWSKI: Thank you so much, Daniel. Matt, I see your hand is raised. Can you unmute for us, please?

MR. GOLDEN: Yeah. I think one way maybe to think about this is that there's a difference

between FDA approval and CDC recommendation. It may be that there'll be some drugs that would be FDA approved to lower efficacy that we could use as second line agents in the event we were in very bad shape with ceftriaxone. If something really change -- but it may be worth thinking about it that way.

MS. WORKOWSKI: And it is if you remember, Matt. Thank you for that. Back when this was thought about back in 1995, again, there was a lot of choices. There was a lot of drugs. There was a lot of wiggle room that we could do and that was -- even the discussion with the treatment guidelines, and you bring up a good point, because the question is how many quinolones do you need to put into the box versus all the quinolones? And so would be interested in some of our folks from industry -- how they would see this. So I would think first about our two phase three trials that are being done. And I would first ask the comment from Dr. Perry, if you can comment on what you think about this discussion.

MS. PERRY: Hopefully I'm off mute. Thanks -- thanks, Kim. I do think that if we could

certainly have, you know, that widened non-inferiority, a lower overall sort of confidence, that would really, really help certainly developers to be able to sort of bring more -- perhaps consider them in second line because like yourself, CDC and others equivalent in other countries, you set the guidelines. It's not as though -- there's a choice -- you know, there's a choice. There's a recommended set of guidelines that all prescribers follow for GC, and that is very well controlled.

So it's not as though, you know, you're bringing -- it would be used without good reason. So I do think that it would be very valuable to have that option available.

MS. WORKOWSKI: Seamus? You can unmute. Seamus, can you unmute? If not, we'll go to Jonathan while you're trying to unmute.

MR. ZENILMAN: Can you hear me, Kim?

MS. WORKOWSKI: Yes, Jon.

MR. ZENILMAN: Can you hear me?

MS. WORKOWSKI: Yes, we can hear you.

MR. ZENILMAN: So anyway, there were

two things -- a couple of things. One is first of all, in the chat -- in the transcription, quinolone was transcribed as quaalude which was kind -- which was kind of funny. But I have a couple comments. One is the 10 percent -- let's think about the 10 percent differential, which was arrived at 90, 95. That was all urogenital disease and it was in the culture era. And I think we have -- as to the -- as to the issues which were raised before, you know, by Ned, I think we're now -- we're now dealing with a lot of, you know, rectal infections and pharyngeal infections in the treatment -- in the treatment trials. And I think those may call for a widened differential compared to what we've seen before.

The other thing that I'd like to really emphasize, too, is something that was mentioned before. And that is how our loss to follow-ups because of the intensive treatment analysis, how loss to follow-ups treated. And those, you know -- certainly we have a -- you know, they're -- these are challenging issues in our population. But if loss to follow-ups need to be -- you know, how are they

evaluated and are they automatically designated as treatment failures as they have been in some previous studies? With these low differentials, I think that really makes -- that really -- I think we really need to have a discussion about how those are managed. And I'll mute.

MS. WORKOWSKI: I'm going to go to George Drusano next. And, George, if you can unmute? And then we're going to pivot to something else.

George, can you unmute?

MR. O'BRIEN: I can come back to your previous question, Kim, if you can hear me?

MS. WORKOWSKI: Oh, yes. You're there. Okay, great.

MR. O'BRIEN: Yeah. I'm sorry, I'm sorry. I've just -- I've switched from the phone to the computer audio and I was having problems. I think some of the responses to the questions have covered the area. I think it does go back to -- and I don't want to repeat what I said on the slides, but if -- you know, it's -- it's really what we're trying to achieve from the study. And I think looking at

urogenital gonorrhea and trying to have a study which covers all the populations and the other sites, oropharyngeal and rectal, it's -- we have the -- we have the risk of using this non-inferiority -- of not being able to select a therapy which would have value in maybe something other than -- urogenital. So I think -- I think that's an overall point I -- I -- I would make.

I do think that how we're treating -- you know, actually Sue mentioned this in her study, but if you look at the sort of valuable population and more -- analysis for the studies that failed, the actual cure rate for -- for -- also the test stages is much higher and they would have qualified from the CDC threshold, and they may have qualified for the -- margin.

And I think on the point around how to deal with -- I think we still -- we still need to make sure we have the analysis to sort of control bias, but I think we maybe could consider that being a secondary endpoint and moving more for a valuable population as the primary endpoint.

I hope that would help with the concerns in terms of moving away from an endpoint which we know is there to control bias. It's sort of classical microbiological variant of an ITT analysis. I'll leave it there because I know you've got to move on.

MS. WORKOWSKI: Okay. Thank you so much. I think a couple of the things that have come up, if you -- if the rest of you can put some questions in the chat if it relates to this? I think we want to move to a different area. And this one relates to specifically what's written in question number three. The impact of revised guidelines.

When we're trying to think about clinical trial design and think about different countries that have different treatment recommendations, and how best to handle this. Thoughts about how best to do this from the regulatory standpoint of what the -- what you are doing in your country guidelines, and how best to handle this when now, as was previously mentioned, we have monotherapy both for the US and for the UK.

So I will be looking for hands about this -- thoughts about this going forward. I know that Caroline Perry talked about the difficulties and the challenges that it put for industry to be able to do that, and all the administrative hurdles that had to be done.

And so I'm really curious in terms of what people's thoughts are on how we can kind of come together. Is there any way we can come together with a protocol that would be comfortable from multiple different angles? And I'd be interested in particular with the thoughts -- I know that there was a lot -- there was, you know, a great presentation from our partners in the European Union. And thinking about how they thought about this in terms of their regulation and how they could potentially modify what they are doing based on what the -- what industry wanted to do or how they wanted to do these trials.

So, interested in comments.

MR. BOTGROS: I don't know if you can hear me. It's Radu Botgros here from EMA. Well, I think, I mean, we are -- we are well aware of -- of

what has been discussed and about all these challenges. I think I tried to explain in my -- in my intervention that, you know, in our guidance, actually the preferred comparator is not -- you know, is not defined as being one or the other. It's actually something that we would be willing to discuss with sponsors and, you know, with a -- with a good justification I suppose. You know, we could accept different options. That said of course, you know, looking at the GSK presentation and about the really variable, you know, doses that -- that have been -- have been presented there from the different countries, I suppose that we would potentially have to -- you know, to -- to limit ourselves to maybe, I don't know, two doses or something like that, and test those. And, you know, if -- if we can see evidence for those, what would be acceptable and would be, you know, the -- the data would be supportive. Then that could be one of the way to do it. But of course, you know, having too many -- too many regimens would be -- would make the interpretation quite difficult. Thank you.

MS. WORKOWSKI: George Drusano, I see your hand raised. Did you have a comment?

MR. DRUSANO: Yes, ma'am. I do.

MS. WORKOWSKI: Please unmute and share with us. George, we can't hear you. I think we lost George. I don't see a phone connection.

Anybody else have any comments about how to do this from a regulatory standpoint?

MR. DRUSANO: I'm back.

MS. WORKOWSKI: Oh, you're -- okay. Great, George. Yes.

MR. DRUSANO: Okay. I think this essential problem is the fact that all of what's going on is from studies -- studies that were ancient, to all intents and purposes. And as Ned said, it may be time to look at an outcome with NAAT. You know, what's -- what's the downside of NAAT? Well, you've got false positives because if you pick up just a little bit of something that can be amplified, okay. But that -- that will work itself out between whatever is there.

I think that it's maybe time to accept

the NAAT, do a trial and see what, with NAAT, the response rates are so that we don't have to bat our heads against a wall, expecting you to have greater than 95 percent at a lower confidence bound at 90.

I -- I think that, you know, doing those sorts of things will -- will make things a lot easier for developers. I'll -- I'll go back on mute.

MS. WORKOWSKI: Thanks so much, George. I think that's an interesting point and I'd be interested in hearing people's perspectives, in particular Jeff Klausner on the master protocol. And your thoughts about that and the use of a NAAT as a -- as a gold standard. Perhaps using several NAATs together and one as an adjudicator.

Jeff, can you unmute?

MR. KLAUSNER: Sure. So we use the master protocol with several different NAATs to, you know, validate the pharyngeal and rectal molecular assays for several manufacturers and for the, you know, ultimate FDA approval of those assays. So, you know, as opposed to just using one device compared against some gold standard, we are going to use and

evaluate multiple devices in the same protocol.

So that's kind of a study design innovation that potentially allows for, you know, multiple, you know, molecular products or, you know, antimicrobials to be studied at the -- at the same time.

I mean, the issue of whether the NAAT is an adequate, you know, clinical outcome, I think that's a little bit separate. I think it certainly could be. I mean, if you have a -- a comparison -- similar to what we do with syphilis studies, you know, sometimes we look at six months' outcome and we just say there's no difference. And that may be, you know, sufficient to say, okay, well the clearance is the same in terms of nucleic acid clearance in the same group, and people agree that may be sufficient to show, you know, non-inferiority.

MS. WORKOWSKI: Thanks, Jeff. I think one of the other things that has come up that FDA would like some advice on from our panelists is the concern about using the urogenital endpoint as the primary endpoint. And the rectal and pharyngeal

endpoint as secondary endpoints. And whether or not there should be kind of non-comparative trials that should focus on the rectal and pharyngeal site, versus inclusion in a urogenital trial.

So thinking about trial design and how should we have -- continued to have urogenital endpoints as the primary endpoint and then the secondary endpoint being rectal and pharyngeal, or doing non-comparative trials just looking at the rectal and pharyngeal sites.

Thoughts on that, please. Seamus, is your hand raised again? Yes?

MR. O'BRIEN: Yes. I think this is a really interesting question. So I -- I think particularly for pharyngeal gonorrhea, I do think we need to think of a way maybe outside of the phase three to address that. Because the way I -- the way I think about this is that the bacteria is -- is -- particularly in symptomatic cases, is like a -- is like a biomarker for the disease, but not so much in pharyngeal gonorrhea because we don't -- we don't know yet the -- what are the complications of pharyngeal

gonorrhea diagnosis.

And I think therefore, it doesn't really align with the approach we take for urogenital gonorrhea, particularly systemic urogenital gonorrhea.

So I -- you know, we heard some great talks today from George Drusano and Magnus Unemo around the PKPD models. I think we need to have -- I know there's some good work going on in European collaboration that GSK are involved in as well.

We need -- we need the sort of assays and the science to move forward, but I think there's a case for looking at the sort of totality of the evidence approach for some of the populations and some of the issues. Particularly, pharyngeal gonorrhea, to use more of the PKPD argument and less of the clinical trial data requirement for -- for some label wording for pharyngeal gonorrhea.

And I think -- I also -- moving on from there is to think about what actually are we trying to achieve when we treat the pharyngeal gonorrhea? Is it clinical? Is it disease or is it transmission? If it's transmission, you know, I don't -- I haven't got

-- how to assess that, but that's maybe something you need to think about also.

So I do think there is sort of a sub study approach more so than even a subgroup -- a way -- a way forward. So I'll leave it there.

MS. WORKOWSKI: Thank you so much. I think next is Matt. Did you have a question? If you could unmute, please.

MR. GOLDEN: I have a comment. I think that with the issue of the pharyngeal infections in particular, it may be that that's not the trial endpoint, but the trials need to be designed. Give us some reasonable estimate of what is going to be efficacy. And I -- I don't think that PKPD data is going to be enough. We need clinical outcomes. And ultimately, that will influence how we use the drugs, even if it doesn't -- even if it's determinative in FDA approval.

MS. WORKOWSKI: Thanks, Matt. Jeff, do you have a comment?

MR. KLAUSNER: Sure. So I don't think we need a one size fits all approach. I mean, I

think, you know, sometimes we have indication to treat urogenital gonorrhea and we'd like to have a reliable urogenital gonorrhea treatment. And sometimes we need to treat pharyngeal or -- or rectal gonorrhea. So -- and I would not, you know, want to create a barrier to drug development that says, you know, your single drug has to be equally efficacious at all -- at all anatomic sites.

I agree with Matt that we do need to know and, you know, what the efficacy is at those anatomic sites, but you know, clinicians ideally should have a big toolbox where, depending on what we're treating, we can go to the most, you know, liable antimicrobial.

MS. WORKOWSKI: Thank you. George, can you unmute?

MR. DRUSANO: Yes, ma'am. So one of the things I just want to throw in for evaluation in these kinds of decisions, particularly about pharyngeal GC, is this site is a resistance generator. And it's a resistance generator in two different ways. And one is mostly with Bata lactam drugs. Something

where we're talking about, for instance, ceftriaxone. Because of the commensals and you wind up getting mosaic chromosomes. And so the rate at which that is going to increase is something that probably should be looked at over a number of the next couple years to see if that's going to be continuing to be a bad problem.

Because of penetration issues, it may also be a resistance generator site just because not enough drug is getting there in some instances. I'll stop there.

MS. WORKOWSKI: Thanks so much for everybody's comments. I think in the interest of time, we're going to transition to the next question, which I think Ned is going to lead. Ned?

MR. HOOK: Thank you, Kim. And I'll ask everybody who has their hand up to lower it now and we'll reset and start again with question number four, which is the second one on our list.

Regarding -- considerations regarding optimizing dose and regimen selection, specifically how do people out there feel about the potential for

multiple -- multiple dose, whether that's two or five days of therapy for treating uncomplicated gonorrhea.

Also, how important are -- are animal models for defining optimal dosing and dosing strategies? Do they translate completely? Is that ready for primetime? Where does that fit into our development process?

And then finally, what about the phase one trials? Does that -- how -- how much should we rely on that? Dr. Drusano mentioned the issues of the pharynx, but -- but do we even know where we kill gonorrhea within the throat, George? I don't know the answer to that. So maybe I've stirred the pot a little bit. I'm going to look for raised hands and would welcome comments.

I'm not used to this group being this quiet. There's one. Sue Cammarata, I see your hand. Please tell us what you're thinking.

MS. CAMMARATA: Well, I -- it's getting back to what I presented on those trials a couple times. And I think that since I -- those trials were in -- you know, five years ago that failed. And it's

clear that understanding PKPD is a key factor and there's been a lot of work around animal models as well as hollowfiber models. But we still don't quite understand exactly what you just said, Ned. What tissue -- what fluid do you need to have exposure in and how high? So it's great to be evaluating those, but unlike things like urine and skin infection where we have an understanding and way to measure tissue or fluid or a level, I -- I have not seen any data that has been -- I know there's been studies that have been proposed or I've seen that they started, but I've never seen data that looked at -- is there a way to even understand drug levels that are required for GC besides dosing people and looking at clinical outcome?

You know, I know, Jonathan, you were involved in something a while back, but I've never seen any publications. So I don't know if people have been successful in doing those studies. And that would be my question for folks that have been involved in this. Have you been able to look at tissue levels that -- or fluid levels that could help developers figure out the right dose?

MR. HOOK: Great point. Thank you so much, Sue. I -- I called out George and in a nanosecond, his hand went up. So, George how are you feeling about this?

MR. DRUSANO: Well, as a card-carrying member of the PKPD -- mafia, at the end of that particular day, I'm going to flabbergast everybody by completely agreeing with Dr. Klausner.

PKPD is great. It gives you a roadmap, but the important part is you need to make predictions from the PKPD and then you need clinical outcomes, and you need to be able to show that your outcomes are -- are correctly predicted. You know, one of the things that has to go on -- there are two things here. We've been talking about hollowfiber units. We've been talking about animal models.

Animal models are, you know -- they're a completely different ball of wax and they're for real because, you know, it's a living thing. On the other hand, you have to be careful because animal models can mislead you because mice in particular have way different kinetics that -- that you see in just

about anything else, and way faster clearance and shorter half-lives.

And actually, that can cause something that's -- that's called driver switching. So when you get to a certain short half-life, it goes from being -- MIC to time above MIC. So you have to humanize dosing when you want to use mice in that circumstance and I -- I -- I'm absolutely certain that -- that our colleagues from -- know all about that. So hollowfiber systems, you know, are not alive and so they're different. And they don't have an immune system. And so the last little bit is when you get your target out of either one of those approaches, you now have to get PK involved in real people and that you do Monte Carlo simulation. And that is what's going to help you choose the right dose to optimize dose and schedule. And when you have to give multiple doses and when you don't. I'll -- I'll go back on mute.

MR. HOOK: Great. Thank you very much, George. I thought Lindley Barbee had a comment and I know she's thought about the issue of pharyngeal

infections, and then I'll warn that I'd love to hear from Jonathan Zenilman. Sue Cammarata mentioned that Jonathan has led a number of PK studies and phase one studies, which his thoughts would be of interest to us.

But, Lindley, if you're on mute, please unmute yourself and share your thoughts.

MS. BARBEE: Can you hear me?

MR. HOOK: Yes, we can hear you fine. Thank you.

MS. BARBEE: Okay. I think my one comment was just to Sue, who asked if there was any data on the pharyngeal compartments. And I just wanted to say that yes, Jonathan and I worked on a study trying to get it pharyngeal fluid, and it really wasn't predictive. Because as Ned eluded to in his introduction to this question, we really still don't know where the gonococcus is living and which is the best predictive compartment.

And I think that's a real limitation to be able -- at this point, to model what doses we're going to need at the pharynx.

And just on that point, I think in the last question Jeff said something about treating urogenital separate from pharyngeal. And I think one of the biggest issues, you know, in the clinic setting is where we don't actually know who was infected at the pharynx at the time of urogenital treatment.

And so we need to have drugs that are effective at the throat at the same time they're effective at the urogenital site.

So that's just something to keep in mind why we need to prioritize making suer that we have efficacious drugs for the throat. Thanks, Ned.

MR. HOOK: Great, thank you. Thanks so much -- those are important observations.

Jonathan Zenilman, I told you I was going to call on you. Do you want to come on and -- and follow-up?

MR. ZENILMAN: Sure. So I actually put -- I put in the chat that Lindley led a study before -- that we did actually. We also -- and I think -- I want to reinforce the points that she made.

We also did some very similar work with

azithromycin. These were -- which actually yielded actually some -- some interesting results as well. I think the important points of these are -- these studies are really intensive to do. They're phase ones. They require a lot of support from PK labs with assay validation and so forth. However -- and I think we're at a very primitive place, but we're much further along than we were years ago.

I think this is something that we definitely need to work on with new drugs, identify doses in the -- you know, in the tissue matrixes. If we can -- you know, if we can develop these assays, I think these are very informative.

MR. HOOK: Thank you, Jonathan. Let me see if I can also solicit some -- some input from our presenters on two other topics.

George Drusano said what about combination therapy? And I'm interested in perspectives of the presenters both and how you evaluate combination therapies for -- for therapy and also whether it's fair to compare a single new drug to a combination of drugs as the comparator.

So there's a question that would be great to hear something about. I'm looking for hands. I don't -- I don't see it. Also, how do people feel? Do you trust your patients to take one -- more than one dose of medicine? Multiple dose therapies, would that be okay? That seems to be the basis for instance of EPP. So we trust people to deliver it. Should we trust our patients to take the second or -- or multiple doses of antibiotics?

MS. WORKOWSKI: So I'll just make a comment. So we trust people to take multiple dose therapy for chlamydia. So what's different about chlamydia than gonorrhea?

MR. HOOK: Fair enough. I see Sue. Sue, is your hand still up or is this --

MS. CAMMARATA: Oh, I should put it down, but I can make a comment. I mean, I -- I know that in this -- the DELLA study, they had incredibly reliable people because they were chosen to be reliable. They had like 95 percent of the patients come -- come back and everybody took meds. I mean, they didn't have missing data. But that was very much

the investigators choosing patients. And so, I mean, it seems like you may be able to choose those patients that you think are higher risk to come back, and not coming back or not taking their meds. It -- I'd be curious about what you all think about that. That you -- if you had different regimens, would that be something that you could actually consider in your patients?

MR. HOOK: Thank you, Sue. I see Matt Golden says we should trust them. And Lindley Barbee seems to feel the same way. So I think the -- the sense in Seattle is they can trust Seattleites to take -- take their medications.

Other comments and thoughts? Dr. Jang says just until PKPD issues a result, the dose ranging studies should be considered for dose optimization. Is that a necessary first step for studies?

Dr. Drusano I think either left his hand up or still has it up, but I don't see other hands. So, George, take a shot.

MR. DRUSANO: I'm going to go back to the combination therapy business. I just want

everybody to be aware that you have to be very careful with combination chemotherapy. And for instance, fluoroquinolones basically are antagonized horribly in rate of kill by protein synthesis inhibitors. This was shown by JT Smith [ph] in the '80s and in the late '90s by Laura Pittick [ph] very, very mechanistically.

You know, here's one place where something that had come up before is maybe you treat the -- the GC first, get it out of the way, and then you give the second drug.

It is -- you know, it's very difficult. So, you know, combination chemotherapy is not easy. You know, we worked it out now for tuberculosis, but it is -- it is very, very difficult and very -- you know, there can be times when it can turn around and bite you. So I'll stop there.

MR. HOOK: So it sounds good on paper, but it's not as easy as it sounds is my summary of Dr. Drusano's comments.

Other comments and thoughts? I'm looking for raised hands.

MS. WORKOWSKI: So we have to -- Ned,

that if we require pharyngeal eradication for every new compound, too high a bar is set. It may not be necessary.

MR. HOOK: Thank you, Kim. I feel -- I see that Khalil Ghanem's hand is up and we haven't heard from Khalil yet. We're sort of getting towards the end of this topic, so this is almost a going, going, gone situation. But Khalil, I don't know if this will be the last one or not. Go for it.

MR. GHANEM: Thanks, Ned. Can you hear me?

MR. HOOK: Yes, we can hear you well.

MR. GHANEM: My comment really is about the comparator arm when we're talking about several days' doses of medications. I think the -- the problem is that while I agree with Lindley and Matt that patients may take their medications and these are reasonable, it becomes much more challenging when the comparator arm is let's say ceftriaxone, 500 milligrams times one dose. Then you have to take into account the point estimates and perhaps adjust -- adjust your approach with the point estimate of

efficacy.

So in those cases where you're actually dealing with a -- with a regimen that is over several days, instead of saying a 95 percent, for example, efficacy, you would drop it down to say a 90 or an 85 percent efficacy. Take into account the differences between the two arms.

MR. HOOK: So what we want is we want a level playing field. That certainly sounds reasonable to me.

I see two more hands up and then we'll go -- let me start with Dr. Marrazzo who after passage of the day is -- is ready to share more thoughts with us. Jeanne?

MS. MARRAZZO: Ned, can you hear me now?

MR. HOOK: Yes, we can hear you well.

MS. MARRAZZO: Great. Thanks. I just wanted to make a quick comment about the sort of -- and this is getting into structural issues of what happens when we stereotype patients and -- and all kinds of structural challenges. I think that I have

been continually surprised at trying to predict who and who will not be adherent to various interventions. And I think it's very dangerous territory for us to go down that path of saying this person will or will not comply.

So I just wanted to put that out there because I -- I think it really puts us in a position where we're judging our patients in ways that we don't want to put ourselves in.

MR. HOOK: That's a -- that's a great and worthy comment. We need to be careful of judging and making assumptions. That gets people into trouble all too often.

Jeff Klausner says requiring a novel drug to eradicate pharyngeal GC may be too high of a bar. Jeff, do you want to elaborate on that? If so, it'll be the last word. If not, I'm going to ask Kim to go onto the next question.

MR. KLAUSNER: Yeah, no. It was just a kind of a counterpoint. So I mean I think there are populations with low -- low frequency of pharyngeal GC, such as, you know, heterosexual men and there are

ways to exclude pharyngeal GC, such as with a nucleic acid amplification test. So, you know, I think something that we need to think about, there are clinical strategies that can be deployed that we can use drugs with different efficacies in different sites, you know, smartly.

Similarly, with a drug with, you know, a low 90 percent efficacy, maybe we would do a test to cure. So CDC has recommended for years alternative treatments. Please obtain a test of cure.

So I think, you know, we should be openminded that there are different ways that drugs can be used with different efficacy, different anatomic sites with different strategic thinking.

MR. HOOK: Great. So one size does not fit all. I think that's a great point and a great point to sort of move onto our next question.

Dr. Workowski, do you want to sort of take over the rodeo here?

MS. WORKOWSI: Sure. This next question relates to safety considerations for new products. And I think unfortunately my editorial

about this is that we're not seeing products that are really being marketed for GC. They're being marketed for something else. And they're coming to us with potentially a GC activity.

So the question regarding the safety database and collection of additional post-marketing safety data. What comes to mind was what I first mentioned that, you know, everybody's not jumping at the top to -- to get a new GC drug. They just want it for other things because of thinking about the cost of drug development and things. So would be interested in industry perspective on this, but also the issue of the safety database in terms of some of the newer products related to QT prolongation and the collection of additional post-marketing data as patients may be on other medications at the same time.

So I would be interested to see first about what our industry colleagues have to say about the safety database and post-marketing data.

So I'd be interested in thoughts from the current trials that are undergoing phase three, including zoli and "gepto" in terms of your thoughts

about that and how you're thinking about monitoring post-trial and safety issues regarding to QTC in particular is what I thought about.

Yes, Seamus? Please unmute.

MR. O'BRIEN: Yeah. I think essentially we -- fairly comprehensive clinical pharmacology package of studies include an authority to -- which -- which was negative in terms of -- I think what's probably more important is the use of the drive-in certain population and you mentioned, Kim, in terms of use of the drug in HIV patients. So I think in our study currently, we have an exclusion for -- inhibitors and that's something we are working on in terms of DDI study to look at the interaction with drugs metabolized by that root.

So in terms of the outcome of that study, then that'll be used to determine sort of wording in the label and the use of the drug. And I think -- I think -- as other people have said, I think the reason -- the reason -- and there's an opportunity actually I think to look at use of the different -- different drugs for different populations. And then

maybe within those populations, committing to having post-marketing assessments.

So if you -- if you're able to go forward maybe with a more limited -- if your drug was more suited for a certain type of population, you could -- you could connect to -- to demonstrating both efficacy and safety if you have a limited database.

I think -- I think the database, as it stands at the moment, I don't have any particular concerns about that and I don't have really any comments on whether it's relevant or not. I think it's more -- it's more about the suitability of the drug to be used in combination with other therapies from particular patient groups.

And also -- and also in the context of gonorrhea and -- and related infection, it's -- it's being able to demonstrate that if your drug needs a little bit of a push to get greater efficacy of -- chlamydia, that's -- the drug that you were using, combination, there are no -- there are no additive issues around QT prolongation or -- or other safety liabilities such as liver toxicity, etcetera.

So I think it's -- I think a thorough evaluation has to be taken in parallel with -- with the overall clinical -- parallel with the overall clinical efficacy studies.

MS. WORKOWSKI: Thank you. And I think one additional question before I go to Caroline is that that has come up is these -- these medications used in women, women that are at risk of pregnancy and in pregnant women. And this brings to mind a consultation that's happening next week regarding the use of, you know, products and thinking about women in clinical trials. And enrolling folks in clinical trials and most of the trials are excluding pregnant women and the concerns about pregnancy.

So we'd be interested in thoughts about that as well. Caroline, I'm going to call on you now.

MS. PERRY: Okay. Thank you. So similar to the comments that Seamus just sort of made -- conducted authority TC study. We've also conducted a number of DDI studies. So, you know, we're both characterizing, if you like, the cardiac effects of gepotidacin. And like you said, it's more the

interaction with other -- other medications that some of these populations may be taking.

Now the -- says we allow HIV patients in, but 50 percent of the total population are on some form. Either they're HIV positive or they're taking PREP. However, we do have ECG to enter the studies. So they have to have an ECG, you know, 450 or below. So it's a very controlled -- you know, it's very controlled. Sort of once, you know, the drug's on the -- on the market, how do we -- your question was how do we gain more data? These -- these particular individuals, they, you know -- they don't want to spend more time in the clinic when they come in for their sort of checkups. ECGs take a fair amount of time to obtain. Also most of the STI clinics don’t have -- equipment. And so we're certainly sort of looking to sort of see the advancement in the wearables. They're getting much better and, you know, I think there's probably a -- wearable that's now available. Don't think it's fully on the market, but it's -- but it's -- it's there from a research perspective. We need to have better advancements in

some of this technology to help obtain information and build a better post-marketing, post-approval perspective of the safety of these new medications.

MS. WORKOWSKI: So I wanted to bring up the issue about women again that was brought up throughout the day in terms of, you know, one of the barriers of women and adolescents to enrollment.

So any of the investigators that have had a significant luck enrolling women and adolescents of our clinical investigators would like to comment on that?

MR. HOOK: Kim, while you're waiting for that, if I could just go back to Caroline's comments a little bit.

I'd also like to stir the pot a little bit and can our presenters imagine putting a drug in the STD treatment guidelines where you had to have an EKG before you treated a patient for gonorrhea?

MS. WORKOWSKI: No. That's a simple answer for me. Jeanne, did you have a comment you want --

MS. MARRAZZO: Yeah, Kim. I just

wanted -- sure, I just wanted to build on your question about enrolling pregnant women.

It's not just pregnant women. It's women at risk of conceiving, right? Because all of these trials require often, they say, dual methods of contraception. So a barrier method plus hormonal contraception. And that essentially excludes a huge -- - of the representative and relevant population.

So the consultation next week's going to be really important because we're going to talk about that. Even if we could get women in who were not contracepting to these trials and carefully monitored them for pregnancy, it would be a huge win and I think we really need to think about that.

MS. WORKOWSKI: Thanks, Jeanne.

MS. PERRY: So can I --

MS. WORKOWSKI: Caroline?

MS. PERRY: Yeah. Just a -- I mean, from a different type of perspective, we have conducted long clinical studies and participants -- women can come into the study as long as they have a negative pregnancy test. They don't need to be on

contraception.

MS. DEAL: Well, that's great.

MS. WORKOWSKI: -- I -- I see -- are you writing a comment or do you have a comment? Jeanne, do you have another comment about --

MS. MARRAZZO: No, I'm sorry. I'll lower my hand. Sorry.

MS. WORKOWSKI: Oh, okay. Any other regulatory issues concerning this question that anybody wants to bring up, or we'll move on?

Okay. Ned, do you want to go to question one?

MR. HOOK? Sure, I'll be glad to. Thank you very much, Kim.

So question one, which we're taking fourth, has to do with the practicalities of clinical trial enrollment. How to get to relevant patient populations. Do people have thoughts about better or new strategies to facilitate enrollment of women and adolescents?

What are we going to do about coinfections? I mentioned that in my comments and we

-- we very soon are going to have the technology to screen our patients at the time of enrollment for a variety of coinfections. And is that going -- what's that going to do to clinical trials? As I mentioned earlier, in the distant past, we would test for chlamydia and if a person had a positive test, they would get their chlamydial treatment five or six days later.

And my recollection is there were -- we never -- perhaps it was just luck, but we never had complications -- incident PID in -- in those patients who were brought back and -- and treated.

So what about patient enrollment screening, how to move them forward in our studies? I'd love to hear some comments.

Dr. Deal, you've got your hand up I see. So, Carolyn, why don't you start?

MS. DEAL: Well, I was going to root back, if it's okay, Ned, to what Caroline Perry just said. Which was they require negative pregnancy tests, but not contraception. And I'd really be interested from our industry colleagues or our

regulatory colleagues what is the distinction about -- that they make when they design a study of the characteristics of the products they're testing as to whether contraception is required or not?

Because I think that's a very practical consideration that gets to what Jeanne's point was about a blanket requirement versus can it be more tailored based on the product being evaluated.

MR. HOOK: Great question. Caroline, would you like to comment on your thought process there at GSK?

MS. PERRY: I have to apologize, both Ned and Carolyn, I am not the expert in -- in nonclinical, but we have conducted, you know, a series of rodent studies that look at both contraception, look at both maternal neonatal impacts. Those studies allow us with a highly sensitive pregnancy test at the beginning of the study, to allow patients that are not on contraception predominantly because the duration of treatment is so short.

And even if they enter into the study and there is a fertilized embryo, it takes three days

before that implants and that you would then see -- a positive response from a -- a pregnancy test. And it's those three days before implantation where there's no impact.

MR. HOOK: That's very interesting. Thank you for sharing that. And again, I guess part of your answer is that all drugs are not created equal. That you had a great safety profile on your drug as opposed to fluoroquinolones early on for instance. There were concerns about their safety in pregnancy.

So either we welcome more comments on that or going back to the challenges of clinical trial enrollment in regards to patient populations or coinfections or other issues.

Also, let me just throw in, what about international trials? Dr. O'Brien mentioned the challenges of conducting trials at multiple nations with different standards and different processes. I know that doctors Klausner and Marrazzo have a fair amount of experience working internationally and in multiple countries -- excuse me. And obviously

perhaps Dr. O'Brien or -- or someone else wants to talk a little bit about multinational trials.

Seamus, your hand's up. Go for it.

MR. O'BRIEN: I just -- since you mentioned -- I obviously can't speak for all the -- all the sites -- study, but I think -- what I would say is it's sort of microbiological challenges are common. It's the same bug wherever you -- wherever you work. So I think that -- that's -- that's not -- that’s not an -- sorry. That's a common issue, but it's more accentuated because there's -- there's a less -- any specialist knowledge in Neisseria gonorrhea.

And I think the other big challenge is that the sites that we've been working on, many of them come from an HIV background. That has a real positive in terms of community engagement and their engagement populations. But it's just moving towards that -- that sort of particular aspect of antibacterial study and -- particular gonorrhea study. The difference is what's unique to them in that sense.

And I think that's where the capability

bit comes around. And some of the comments -- you know, some of the things that Caroline mentioned earlier on her presentation, somewhat exacerbated as well in -- in -- in those sites.

I think I would just move a little bit more over to access to sort of the -- the currently enrollment question you asked as well. I think there was obviously some cultural sort of challenge. There is definitely need to get community engagement -- women in -- in many countries. We've seen that particularly in -- in South Africa. With a real can-do attitude to try and -- and integrate -- integrate the study into practice and to get community engagement.

One of the issues we have seen is to your point of -- infections is that, you know, we have -- we have some sites that are really motivating doing -- doing prescreening to include asymptomatic women, but the problem is is that -- high end prevalence of chlamydia on its own, or chlamydia in combination -- coinfected with -- with -- with Neisseria gonorrhea and you -- you can't include those patients into the

study if you -- if you know they've got a chlamydia infection prescreening. That's one of the problems.

So I don't know -- it does -- that's a shame because you -- they could be -- they could be suitable patients for therapy, but they can't go on the study because you know -- you know it involves some enrollment.

Thailand is very experienced site again in HIV. It's just that getting up to speed and understanding the particular nuances of an antibacterial study and a particular gonorrhea study. But in terms of quality practice, good links with ministry of health, good links with the local community. They're all extremely positive.

And, you know -- been several -- particularly in South Africa, the challenges for -- for the site -- trying to setup a study, reactivate it and run in COVID has been a massive challenge because they've all been impacted at staff levels, but also becoming involved in the community action around -- around managing the pandemic in terms of testing, rollout of vaccines now as well. So just -- sort of

more of a different challenge, COVID, but also possibly -- again in some of the countries that we've been working in.

MR. HOOK: Thank you. That's very helpful. Dr. Klausner has his hand up. And, Jeff, as you make your comments, I don't know if it's part of the plan or not, but I'd love to hear both your comments or the comments of others about issues regarding building infrastructure. Now you're talking maybe Dr. Wi from WHO will want to make comments on those same topics. The issues of differences in infrastructure capacity from location to location.

Jeff, take it away.

MR. KLAUSNER: Sure. That's what I was going to highlight. I mean, we've been doing clinical trials now in South Africa, Botswana, you know, Peru and now Vietnam. And, you know, there's been investment in infrastructure and, you know, training on staff and investment in equipment and, you know, training with, you know, GCP, adherence and ethics, and etcetera. So, I mean, I think it can be done and, you know, certainly, you know -- you know, COVID was

more than a hiccup. You know, it was a retching experience in terms of disrupting, you know, clinical programs.

But, you know, the -- there's the post-COVID in the future and, you know, we need to continue to invest in those sites. I mean, we learned from HIV, you know, that if you setup, you know, well resourced trials, you work with, you know, community partners, you can be very successful. And, you know, people need to remember the first successful PREP trial came out of Peru really. You know, and that was a long time ago and a big investment. And other clinical trials have been done in low- and middle-income countries.

But it takes resources and it also takes, you know, people, you know, believing in their low- or middle-income country, you know, clinical investigators that it can be done. But I've been, you know, successful and still encouraged about, you know -- you know, certain sites and the ability to get things done, you know, outside in -- in low- and middle-income country settings.

MR. HOOK: Thank you, Jeff. Perhaps you want to -- I'm going to push you a little bit and ask if you'd like to comment a little bit on the difference between building infrastructure and sustaining it? And then after you're finished, Dr. Marrazzo has her hand up and I'd welcome her comments as well.

MR. KLAUSNER: Sure. So, I mean, you know -- you know, building it is a larger investment. Sustaining it is, you know, a little bit smaller, but does take, you know, continuous investment. So, you know -- have sustained sites with, you know, smaller NIH projects, also smaller kind of independent projects with, you know, pharma or diagnostic test -- manufacturer just to kind of, you know, keep things going. So it's important that, you know, when sites are identified, there is an effort to maintain those, you know, study sites with a variety of different, you know, types of trials. From behavioral trials to, you know, surveys, to clinical studies as well. And, you know, I'm a fan of we should pick, you know, a dozen or so key international sites and investigators and

invest them in those sites, you know, for the long haul which is, you know, 10 to 20 years.

I mean, we've been in Peru since 1999. It's been a fantastic investment in terms of productivity.

MR. HOOK: Okay. So diversity is important. Dr. Marrazzo?

MS. MARRAZZO: Sure, Ned. Just two quick things. First of all, I think you or someone raised the question of, you know, country specific regimens and how do you handle that.

I think you -- you can't study new regimens without taking into account what the standard of care is locally. And I know that sounds obvious, but if the standard of care locally is not something that you think should be the standard of care, then you've got to find a way to deal with that. And whether that means having a comparative arm or working with regulators and effaces in country and stakeholders to sort of say look, way forward actually is a better way than what your standard of care is. I think that's the way you handle it.

The other huge lesson I would remind people of our PREP trials in African women. Remember, they did not take the study products that we -- or the large majority of them did not take the study products that we were studying for HIV prevention, right? They didn't take their -- they didn't take Truvada. They didn't use their vaginal -- gel. Yet 99 percent of them stayed in the study. Why? They wanted contraception and they wanted STI screening. STIs are hugely important to these women and, you know, I think we've -- we've put huge resources into HIV prevention for these women and we've put a fraction of that into STI prevention, yet that's what drove many of these women to continue in the -- in the HIV prevention studies because as Jeff notes, the studies provided a care infrastructure for their sexual health needs. So can't -- can't let that pass I think in thinking about how we structure these trials and also really make them relevant to people's desires and needs.

MR. HOOK: Great points and important ones that hadn't been raised. Thank you so much. I'm looking for other hands up. If I don't see them, I

think we're going to shift to our last question and -- and we're doing great time-wise, by the way. So after we do this last question, we would sort of -- if we have time left, we might take a few minutes to ask all of our presenters what did we miss.

Kim, do you want to go on and take our last question here, please?

MS. WORKOWSKI: Sure. So this is really a solutions question. After we've had this discussion with multiple issues that have come up, the issue is what can we do to help facilitate clinical trial conduct and overcome some of the challenges that were presented?

One of the things that Jeanne just touched on was differences in standard of care. And do we need to conduct multi-country clinical trials where there's differences in standard of care? And the regulatory hurdles that have to be undergone versus smaller trials. So that's kind of one consideration.

What are -- what are some solutions that people have in terms of trying to think of

designing these? As -- as -- when Dr. Wi was presenting her data, looking at the tables of antimicrobial resistance and looking about how much azithromycin resistance there is and how much there has been an increase in the last five years. And the incredible geographic variation that there is. How do we best give advice on how to -- thinking about what our comparator arms are when there's differences between countries.

So these are big issues, right? This is a lot of money that goes into designing these clinical trials. And so thoughts about continuing to do what we're doing in terms of these big, multinational countries with -- with all the multinational trials, with all the regulatory and in-country hurdles versus more targeted trials in -- in comparison. We were talking about before having the discussion about extragenital, have a secondary endpoint or whether that just has to be a separate trial.

So let's first think about what I first mentioned was the kind of standard of care comparator

and thinking about the difference in antimicrobial resistant in terms of geography, and what people's thoughts are kind of going forward. If you were advising some solutions to what we've all discussed today, what would you -- what would you advise?

So and another way to frame it is that if you had to do this over in terms of your trials. So in particular, the two phase threes that are going on now, what would you do different? And not talking about COVID because COVID just changed everybody. But thinking about the discussion we had today. Thinking about kind of going forward to get regulatory approval for your particular medication. What -- what would you have done different thinking about how we might change things for the future?

So thinking about -- I would like to hear in terms of particular -- if Sue's still on, because her comments about the trials that -- that really had some data that maybe if we would have tried a little harder or used an extra dose, we just kind of looked at those trials and moved on.

So you -- you mentioned the issues that

we -- that we had. Should we go back? Should we look again? Should we look at those drugs again or are they just dead in the water?

MS. CAMMARATA: This is Sue. I'll go ahead and comment since you just brought my name up. I think the challenges -- and there's a lot of challenges, and a lot of it is just the money involved in doing these trials. They're complicated. And people have brought up the issues around body sites and patient populations.

And so from a treating physician point of view, you want a treatment where you can say, you know, high volume clinics where you don't want to think about -- I'm assuming, you guys should comment, that you don't really want to think about this is where is the site of infection? I can treat all of these versus the drug developers that say hey, we can get something for your genital GC in maybe the lower risk population, and then we can get something for pharyngeal or for rectal. But it -- but it may not be one treatment fits everybody. And that's been brought up by some other folks.

But I don't know that that can work in various -- in the -- in the treating -- for the treating physicians. It's something that's a challenge for the developers since we really don't understand what tissue or fluid, we have to treat what levels we need. And knowing that maybe two doses of a drug, like those two products, I think for most people they would have been cured with two doses. But it's -- it's something now that we just -- it's hard to go back and look at that now.

But is having different treatments for different populations of patients or different sites and infections, something that's really viable or is it really -- you do need something that's one size fits all? Because that will change how we would do trials and potentially get approvals.

MS. WORKOWSKI: Any other thoughts about that?

MR. O'BRIEN: Yeah. It's Seamus and maybe I'll just -- I think for me the question is more at the level of development overall, not just -- not just the phase three. I think -- I think, you know,

you say looking back at the study, I -- I think it's -- it is a challenge and I think we should consider whether we should be including all the population into one phase three. It's -- it's -- I think it's too much of a challenge. It's too much diversity and -- which creates an issue in terms of getting -- result which you can use and apply across those populations.

You know, I think there's -- I think -- I know this might be going against the -- our key partner's WHO in this as well, but I think -- I think there is a case for looking at really conserving your safety and efficacy in a population which is more of a straightforward urogenital population. And looking to do some studies in parallel for the more difficult treat populations. And you can't -- you can't -- you can't get resistance data from a phase three. You know, those of us who've got experience in looking at -- you know, working in the -- area and also -- very difficult to do that in -- phase three.

So, you know, resistance is not so much of an issue now as Ned said earlier, but it's something that is coming. And for resistance -- we

need to look at more -- more defined, more smaller studies which will be non-comparative to really maybe, you know, to -- to deal with --

And I just want to talk about the comparator. You know, as I said in my -- I think for me, the main issue with the comparator is the fact that we're looking at all drugs versus an I am an all comparator. From our study, the whole issue was really changing comparators. We initially went from ceftriaxone, ceftriaxone to azithromycin and then the CDC guide change and there's no way you're going to change it mid-study, but also because of the fact that it's ceftriaxone and azithromycin is more recognized globally still at the moment. Well, that -- that may change.

So if it does change, I'm really interested to see how that's really addressed at different countries. I know that would be guided some way by the WHO guidance, but I think it's still -- you still have an issue when it comes to a study. If you're -- if you're going to do a study -- a gonorrhea study, and even if you say that, you know, chlamydia

will be dealt with at the test of cure, you can -- therapy there, I -- I do think some investigators are still going to say, well, we'd like to see some coverage of chlamydia in this gonorrhea study from the get-go.

So I think we might still have some push to have some sort of combination. If ceftriaxone is not thought to be sufficient to -- chlamydia, I just think that's something we need to consider. And that goes to the point around what is the study about? Is it about gonorrhea or is it more about the syndrome of infection?

MS. WORKOWSKI: So are you saying that you would not in particular want to have pharyngeal GC as a secondary endpoint? You'd rather do a comparative -- you'd rather do a non-comparative study in let's say a population of MSM that has a higher prevalence of pharyngeal GC? Is that what your idea is?

MR. O'BRIEN: Possibly. I -- I think -- I do think -- I'm not going to come down -- directly on that, but I think that's a way we could look at it,

but I'd take -- comments on that. But yeah, I think within -- within the current phase three studies, I think it's a key secondary endpoint, but it probably doesn't get -- quite get the attention it does in that -- in that -- in that sense.

I think if we -- if we need drugs particularly for that, they may not be the drugs that we need for the more broader and more straightforward urogenital gonorrhea population.

As others have said, maybe we need more injectables for pharyngeal or -- not monotherapy -- sorry. More frequent dosing for -- for that population.

It's getting late on a Friday here. I'm getting a bit tired, so --

MS. WORKOWSKI: Yeah. It's late for everybody. Matt, do you have a comment?

Thank you so much. That was great.

MR. GOLDEN: Now I think some of this might have to do with the sequencing of the studies and -- and how you make your investment. In the delafloxacin study, if we had been more judicious in

retrospect and just tried to treat a few people in an environment where there was widespread quinolone resistance, you never would have done the phase three study the way we did.

So there was --

MS. CAMMARATA: I was going to agree with you, Matt. I think that -- yeah. I agree with you. I think it's -- that was, to me, one of the points to people that are doing trials in this area is that they have to include those tougher to treat, otherwise you will -- you know, if you have to have one treatment that fits all, you need to know that it fits all. And if you do a study that only has, you know, 30 patients and they are 100 percent successful in phase two, it doesn't necessarily mean it's going to work in phase three.

It would have been good to have done some type of study in a very challenging population to know that it's going to go.

MS. WORKOWSKI: Thanks so much, Sue. George, do you have a comment?

MR. DRUSANO: I do, just very quickly.

Some of the -- the commentary, I just think sells treating physicians short. I -- I don't think that one size necessarily needs to fit all. When it comes to antimicrobial chemotherapy, physicians dealing with serious infections choose different drugs for different types of reasons all the time, and it's often times backed up from the micro lab or from some kind of, you know, testing. And as we pointed out multiple times today, we're going to be entering into a time when we're going to be getting multiple, multiple pieces of information back for both identification of pathogen as well as identification of some resistance mechanisms.

I think that going forward, the data will be there and I -- I think physician -- treating physicians are perfectly adequate to make judgments about what to employ. I'll stop there.

MS. WORKOWSKI: Thanks, George. Carolyn?

MS. DEAL: Yeah. I think, Kim, you asked I think particular to Sue about what might have been done differently for delafloxacin and -- and

azithromycin. And I think if you look at the timeframe of those trials, that's when very much all developers were encouraged to only have single-dose therapy.

And I do think -- and Sue please, you know, weigh-in on this, I think you made the suggestion that if the community has now moved to, say, two dose is quite reasonable, you may have had a different outcome in those trials.

And so the fact that for many newer drugs, the -- what we're seeing and looking at what is the toxicities that go along with what you would need for a one-dose therapy versus -- that it would push the toxicities too high that if you could have a two-dose therapy, you may still achieve your time of 24 hours, you know, above the MICs with that two-dose regimen, but not have the toxicity concerns.

And so, Sue, it'd be great if you could just maybe comment on the two-dose and the difference in the timeframes of when those studies were conducted.

MS. CAMMARATA: So for both those

studies -- yeah. Those were both done, you know, five years ago. And I think -- even if you read the FDA guidance, I think it still says the preferred treatment is a single dose. I don't think that's changed. Maybe somebody at the FDA can confirm, but the last time I looked, it still says one-dose therapy is preferred.

And I think for the gepotidacin study currently is two doses. I think that for the ID community, there's always the concern about a single-dose, the emergence of resistance. So if the treating community is more comfortable with, you know, having patients take more than one dose or a daily dose overtime, that may be -- that's the signal they need to get. Drug developers need to know that that's something that you're willing to consider because I think it does contribute to a higher likelihood that these products will be successful and that we hopefully would have a less emergence of resistance than giving people that single dose and, you know, pushing the dose for some of these has a lot of -- especially with the orals, a lot of GI toxicity.

There's a limit of how you can push them for single dose. A two-dose therapy or two days of therapy, might be more palatable and doable, but we have to feel comfortable that's going to be acceptable to the treating community.

I guess my other drug folks can comment as well.

MS. WORKOWSKI: I see Anne has her hand raised. Anne?

MS. JERSE: Hi. Thank you. Just following that thought. I think one thing I was really encouraged about today is hearing the recent progress with the preclinical PKPD, including the hollowfiber and the animal models. And I just wonder, you know, if we could utilize that progress and that new experience to analyze some of these prior drugs and actually collect some of the preclinical data retrospectively to look into things like more than one dose and otherwise help pressure test some of those new preclinical approaches to PKPD with some products that have successful and, you know, perhaps less successful for completely identified reasons. Drugs

that -- that have been in the clinic at any rate.

MS. WORKOWSKI: Yeah. That's an interesting thought. I think that what came out before is, you know, that we don't have many drugs. So there's been a rush to try to get something out and something we can look at, but as part of the development, is that something that we should really spend some time looking at? Thinking about the time that it takes to do that versus kind of no drugs in the pipeline, which is a little challenging.

So the other interesting thing I was wondering about as George brought up the issue about combination therapy, the question is anybody looking at combination therapy in this model? Jeanne?

MS. MARRAZZO: I definitely wasn't going to comment on that. I had another comment about George's comment. So I can do that or I can wait until someone answers your question.

MS. WORKOWSKI: No, go ahead.

MS. MARRAZZO: Yeah. I want --

MS. WORKOWSKI: I don't see George's hand raised yet.

MS. MARRAZZO: It is related to this concept of combination therapy and I just want to, not pushback, but just comment on George's -- I think -- I think correct comment that, yes, infectious disease physicians are very good at mixing and matching and reacting to antimicrobial susceptibilities and crafting regimens. Who treats gonorrhea? It is not the ID specialist. Number one, we don't have enough ID specialists in this country, let alone the world. And number two, when you look at who provides sexual healthcare, you are not talking generally about specialists, let alone MDs -- or MDs, let alone specialists. So I think we have to think carefully about the treating community as a very diverse group of people. They may provide prenatal care. They may provide sexual health. They may provide contraception in a huge way. It's a huge audience, right? Family planning. So I think it's an important concept that maybe people who particularly are not in the world of cure delivery, just -- just don't realize. And I would say that it's a pretty widespread misconception that it's mostly MDs who are treating our patients.

MS. WORKOWSKI: Thank you. Those were great comments. Carolyn?

MS. DEAL: I just want to make sure that we also have a bit of a caution about language. Because I think when people use combination therapy -- and I know there's been confusion in the past -- what is the actual meaning of that? Is it like it is in TV where you have more than one drug to treat one pathogen or are you talking about treating coinfections where you're using two drugs, one for one pathogen and one for the other? And I think potentially as a community, we have to make sure that we don't confuse which one we're talking about because I think sometimes those two intents are used interchangeably, the same term, and yet they have very different meanings. And that was one of the things I think our colleagues at CDC tried to clarify in the new treatment guidelines.

MS. WORKOWSKI: Thanks, Carolyn. George, you want to comment?

MR. DRUSANO: Please. A couple things. Recognize that, you know, the vast majority of this is

empirical. And I completely agree with Dr. Deal in the sense that yes, there are two different reasons and we call them the same thing. But by the same token, the vast majority of people aren't going to have two pathogens simultaneously and the two drugs can interact and actually can change the outcome for the one single pathogen. So -- so that's number one.

The second thing is -- and this is very quick and I'll shut up -- is giving the second dose. It does not prevent emergence of resistance. Actually, the shorter you go with pressure on the organism, the less likelihood there is of emergence to resistance.

For fluroquinolones, it's the one thing that is, if you will, the exception that proves the rule. And that's because fluoroquinolones wind up inducing error prone replication. And error prone polymerases basically really push the organism into -- throwing out a lot of -- a lot of mutations. Most of them are lethal, but you also have a higher probability of hitting one of the, you know, hot spots to give it a resistance mutation.

So, you know, you have to be very careful. You know, the longer your therapy goes, the worse it is for probabilities of emergence of resistance. I'll stop there.

MS. WORKOWSKI: Thanks, George. I don't see any more hands raised. So a number of other issues. I think we've -- we've hit on everything. Jeff has a comment that private developers are unlikely to invest unless they can expect to be included in the guidelines, not solely FDA approval.

So I think that I don't have any other -- George, did you have your hand raised again?

MR. DRUSANO: No, ma'am. I'm sorry.

MS. WORKOWSKI: That's okay. Ned, do you have any other comments? Any closing comments?

MR. HOOK: I think the hour's getting late. I think the discussion has been quite rich as the entire day, but I think it may be time. If anybody has a final comment or two, we would invite people to briefly succinct -- and succinctly mention them in case we've missed something. And I'll ramble for a moment or two while I look for raised hands.

But if there aren't any, I think we'll -- we may get ready to close this discussion and -- and ask for final closing comments from the sponsors of this -- of this great meeting.

I think that's what we're going to do. Thank you all for your participation, for your questions, for enriching the conversation that we've had. I'll stop now.

MS. NAMBIAR: Thank you, Dr. Hook. This is Sumathi Nambiar. I hope you can hear me okay. So I try and provide a high-level summary of the workshop and at the onset, my apologies to each speaker, I really will not be able to do justice to your presentations. As -- has noted in her -- in the chat box, all the meeting materials, the slides, transcripts will be available on our website in the upcoming weeks.

So what I'll try and do is just provide some key highlights from each of the presentations and I'll go through it rather quickly. I know everyone's tired and want to get the workshop packed up quickly.

So Dr. Marrazzo set the stage for us

this morning when discussing the unmet need for therapies to treat gonorrhea, and also the challenges facing antibacterial drug development. I think some gaps identified included the importance of studying pharyngeal infections, which represents a major -- infection and spread of AMR. The fact that there's no universal option for oral therapy and the requirement for pharyngeal therapy -- culture and slow uptake of point of care testing.

Dr. Wi from the WHO provided her perspective from a global policy standpoint and highlighted the importance of access to new therapies, appropriate use and the need for low-cost point of care testing. Provided example of a minimal and preferred -- from WHO perspective. And very importantly highlighted some of the clinical trial design considerations that are used to support the development of gonorrhea guidelines and clearly outline the importance of randomized control trials as a preferred source of evidence. The importance of having data on all study participants and all study outcomes. The populations to be diverse. And

important also to have information beyond microbiologic -- clinical care. So information such as complications, transmission to partners, quality of life, etcetera.

Dr. Bachmann from the CDC provided information on surveillance tools in the United States for monitoring resistance to Neisseria gonorrhea. Noted that the susceptibility to -- remains low, however there is elevated MICs -- azithromycin, and that continues to increase. She reviewed with us the revised treatment guidelines and the rationale for doing so, including availability of more PKPD data, emergence resistance and the importance of antimicrobial stewardship -- stewardship. Sorry.

Doctors Unemo and Drusano provided an overview of antimicrobial resistance in Neisseria gonorrhea and PKPD considerations. The noted the limitations of the currently available tools and the need for additional work. They presented some of the PKPD work that they've done with new therapies and development as discussion around the hollowfiber infection model and the importance of predicting AMR

emergence with new antimicrobials. I think one of their recommendations was that PK studies be ideally included in all treatment studies and that we need to improve our understanding of single versus multiple dose -- monotherapy versus dual therapy.

Dr. Jerse discussed the work her lab has done with the -- model of lower reproductive tract infection, including its use to evaluate some drugs in development. She also discussed the work on Neisseria gonorrhea of the reproductive tract infection and Neisseria gonorrhea/chlamydia coinfection models. And highlighted the need to develop models for extragenital and -- gonococcal infection.

Dr. Hiltke from DMID provided a summary of the -- services provided by DMID to support development of drugs for gonorrhea that cover preclinical and CMC aspects of product development. And also noted potential funding for diagnostics and point of care tests.

Dr. Duffy from CARB-X spoke about funding at first to support gonorrhea drug development. We heard about the CARB-X supportive

programs, so products -- drugs and bacteria, including the three active programs, the treatment of gonorrhea, for prevention and diagnostics. And Dr. Duffy also noted that one of the key priority areas is development of improved animal models of infection.

We heard from Dr. Reno and McNeil about their viewpoint from providers in STI clinics and their experience with two case studies -- the challenges they face and successes they achieved. And very importantly, they also highlighted the challenges that the COVID pandemic has imposed and provided some suggestions for greater engagement in clinical trials. Some of the suggestions included use of innovative clinic models and enhanced services, investment in the long-term success of the study site to support current and future research. They certainly highlighted the importance of community engagement and engaging a site champion and -- and potential role of telehealth in the future.

In the public comment period, we heard from Sarah Wang about the need for early education about antibiotic resistant gonorrhea among adolescents

and adults, and some ongoing work that she is doing with high school students.

That took us to session two which focused on trial design challenges and considerations. The first -- regulators. We heard from FDA, EMA and PMDA. And all three agencies recognized the unmet need for therapies to treat gonorrhea and expressed their willingness to work with drug developers to facilitate the development of such products.

And to great extent, there is alignment between the regulatory requirements across the three agencies; however, there are some differences. The current PMDA recommendations separate out two clinical conditions -- gonococcal cervicitis in women and gonococcal urethritis in men. And the endpoints of the two conditions are different. I do want to point out that PMDA has noted that they are flexible and recommend that the sponsors of clinical trials seeks scientific advice that they would like to consider appropriate study design based on the product characteristics.

FDA and EMA recommendations with regard

to key aspects, which is trial design, trial population and endpoints, are generally aligned. As are the expectations for data packages including the number of trials in support of indications.

We then heard from -- Dr. Cammarata provided an overview and noted that while there are some similarities between drug development for gonorrhea and antibacterial drug development programs, there are some key differences, particularly with regard to animal model, exposure at sites of infection, challenges -- and challenges with PKPD assessment. Dr. Cammarata discussed the delafloxacin and azithromycin trials and noted that the overall conclusion from both trials suggest there might have been issues with those selections.

And Dr. Cammarata also noted that in addition to the need for new methods with invitro and in vivo dosing strategy, think it's important to have funding in -- products to treat gonorrhea.

We then heard from four different developers. Dr. Chaves discussed afabicin, which is Debiopharm's product. And the challenges from a

developer's perspective -- focusing on the preclinical considerations such as emergence of resistant Neisseria gonorrhea, the importance of understanding PKPD relationships and the unique transitional challenges. The microbiology challenges with regard to generating data in solid media rather than liquid media, and the lack of appropriate models for extragenital sites of infection.

Dr. Perry -- discussed the clinical considerations and their experience with the gepotidacin and solifenacin development programs respectively. They covered a lot of the operational challenges such as differences in standard of care, the difficulties with using culture as primary endpoint, access to local or regional labs that have reliable culture and transfer conditions. The difficulties with sample multiple body sites. The difficulty with -- enriching trials for women or adolescents, and the operational challenges with multidose regimen.

In addition, they highlighted the challenges due to the impact of COVID. Changing

priorities and considerations for telemedicine. Some suggestions for making trial feasible, such as master protocol, adaptive trials, role of clinical trial networks, shared access to testing laboratories, etcetera.

There was also discussion about considering a syndromic approach in the future. Endpoints of proposals about moving away from a culture-based endpoint to potentially an -- based clinic or using clinical endpoint including the use of --

There was discussion around NI margin considerations, whether there's flexibility in using wider NI margin.

Dr. Gelone from Nabriva discussed development considerations for a syndromic approach, uncomplicated urethritis and cervicitis, rather than a pathogen-specific approach, and discussed some attributes of the nupharamine [ph] as it relates to STI packaging.

Dr. Hook provided an investigator's perspective and noted that clinical needs have evolved

over time because of the threat of resistance. The need to rely on a single medication. And had some very useful suggestions for us about the considerations from clinical trial site perspective, the type of infection, the trial participants and -- strategies -- methodologies to diagnosis and assess outcomes.

And some suggestions in terms of future -- to reconsider what is considered an optimal drug. What do we do about rectal oropharyngeal infections -- don't want to pool them into one category of extragenital infections because there are considerable differences between the two.

Should we revisit outcome measurement and also take into consideration -- studies on the clinical -- of patient care.

So I think that's a very high level of a quick summary of -- of all the presentations. And certainly, the materials will be available in the upcoming weeks if you'd like to review them in greater detail.

So with that, I just want to thank

everybody on behalf of the Division of Anti-infectives and the Office of Infectious Disease at the FDA, and our federal partners, the CDC and NIH -- many times to all of you for participating in today's workshop. Special thanks to all the speakers, panelists and moderators for making today's workshop a big success. And also want to thank the participants for joining today's workshop.

Special note of appreciation to Cindy Tashukna [ph] and James Byrne [ph]. This workshop would not have been possible without their hard work in helping managing the logistics.

We certainly plan to consider all the points raised today as we continue to refine our approaches to developing drugs to treat gonorrhea so that safe and effective therapies are available to meet patient needs.

With that, my sincere thanks and appreciation to each one of you for joining us in workshop today, and hope you have a good evening. Thank you.

(Whereupon, the meeting concluded at

4:47 p.m..)

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