FOOD AND DRUG ADMINISTRATION

_____

Development Considerations Of Antimicrobial Drugs For The Treatment Of Uncomplicated UTI

Virtual Public Workshop

_____

DATE: June 3, 2022

TIME: 9:00 a.m.

LOCATION: Client Managed Remote - DC
WebEx
Washington, DC 20001

REPORTED BY: Irene Gray, Notary Public

JOB No.: 5073507

A P P E A R A N C E S

Iain J. Abbott, MBBS, PhD
Tomefa E. Asempa, PharmD
Timothy Bensman, PharmD, PhD
Radu Botgros, MD
Erica Brittain, PhD
Zhixia (Grace) Yan Danielsen, PhD
Dimitri Drekonja, MD, MS
Scott Evans, PhD, MS
Kerian Grande Roche, PhD
Kalpana Gupta, MD, MPH
Tom Hadley
Hiwot Hiruy, MD, PhD
Thomas Hooton, MD
Dmitri Iarikov, MD, PhD
Salim Janmohamed, BSc, MBBS
Nadia Kadry, PhD
Peter Kim, MD, MS
Xianbin Li, PhD
Cristina Miglis, PharmD, MS, BCPS
Harry L.T. Mobley, PhD
Mukil Natarajan, MD

Valerie Price
Sailaja Puttagunta, MD
Jason A. Roberts PhD, B Pharm (Hons), B App Sc, FSHP, FISAC
Keith A. Rodvold, Pharm.D., FCCP, FIDSA
Dan Rubin, PhD
Nicole Scangarella-Oman, MS
Jalal Sheikh, PhD
Ann Stapleton, MD, FACP, FIDSA
Barbara Trautner, MD, PhD
Janice Tufte

P R O C E E D I N G S

DR. KIM: Good morning, everyone. I am Peter Kim. I'm the director of the division of anti-infectives in the office of infectious diseases at the Center for Drug Evaluation and Research FDA. And I wanted to welcome you to this virtual public workshop. We are joined by industry, thought leaders, and fellow regulators from the European Medicines Agency for discussions focused on drug development considerations or antimicrobial drugs for the treatment of uncomplicated urinary tract infections, also known as uUTI.

In particular, we will hear about the current state of clinical care for uUTI, non-clinical considerations, and pathophysiology, microbiology, and clinical pharmacology, tools and approaches, and clinical trial design considerations. We are also looking forward to a robust discussion later today related to primary endpoint considerations for uUTI studies, acceptable active comparator agents for non-inferiority study, and the pros and cons regarding the development and

use of urine specific break points for antibacterial drugs for uUTI.

We would like to thank our speakers and panelists for their efforts preparing for the workshop today. A full list of the workshop panelists is provided on Page 4 of the agenda. And everyone's affiliations can be found using the link to the workshop webpage. Just a bit of housekeeping as we get started, we ask that folks speak clearly and stick to their allotted time so that we can stay on time today and ensure that we have adequate time for discussion.

At this point I'm going to turn the program over to the cochairs of Session 1, Dr. Timothy Bensman from the FDA and Dr. Barbara Trautner from Baylor College of Medicine. So, thank you very much. And Drs. Benjamin and Trautner, please take it away and begin Session 1. Thank you.

DR. BENSMAN: Great. Well, thank you doctor Kim and good morning, everyone. My name's Tim Bensman, I'm a clinical pharmacology reviewer in the division of infectious disease pharmacology in the

Page 6

Office of Clinical Pharmacology at the FDA. And I have the pleasure of co-moderating with Dr. Trautner, our first session on the background of clinical and preclinical approaches or considerations, drug development of uncomplicated urinary tract infection.

This slide depicts our Session 1 speakers. It should be an informed discussion. That will help set the stage for panel discussions at the end of today as well as our future conversations. Mindful of the time, I will now turn it over to my co-moderator, Dr. Trautner who will introduce herself and kick us off as the first speaker.

DR. TRAUTNER: Terrific. Thank you so much. First, a little bit of housekeeping, we're not going to be able to address questions after each presentation, but we will have a discussion session with our panel this afternoon. Please feel free to type your questions into the Q and A box in Zoom. We'll try to address these in the Q and A box or during a related panel question discussion as time permits. And now I will introduce myself.

Perhaps I could have my first slide?

Page 7

All right. So, I'm Dr. Barbara Trautner. I'm an infectious diseases clinician investigator at Baylor College of Medicine in Houston, Texas. And I work as -- also at the Houston VA Medical Center. For the past two decades I've been studying two aspects of urinary tract infection 1.) is novel strategies to prevent and treat UTI and the other is implementation of antibiotic stewardship guidelines for UTI.

I am also currently cochairing the Infectious Diseases Society of America committee to update the UTI clinical practice guidelines. Today I am very honored to have the opportunity to speak with you about clinical care for uncomplicated UTI in the United States. Next slide please. For disclosures I had funding from Genentech to study COVID pneumonia, which is not related at all to what we're covering today. But the main disclosures I've focused this presentation on UTI in the United States ignored some very interesting and important global data.

And also, I will be presenting both data and opinion about urinary tract infection. And I'll try to make it clear between the two of these.

Page 8

Next slide please. What are we going to cover today? I'm going to talk about the definition of uncomplicated UTI. I'm going to talk about what organisms cause UTI and their resistance patterns. I'm going to talk about the current Infectious Disease Society of America treatment guidelines and the reality of what people are using and doing nowadays.

I'm going to talk about three treatment trials that were published since the IDSA guidelines came out in 2010. And then I'll address briefly knowledge gaps about uncomplicated UTI, the most important of which is how important is asymptomatic bacteriuria after treatment. Next slide please. So, for defining uncomplicated UTI, well there are areas of consensus and there are areas of disagreement. Next slide please.

There's a lot of agreement, and everyone seems to agree, on signs and symptoms of cystitis, and by everyone, I mean clinicians, publications, practice guidelines, regulatory advice. Pretty much everyone agrees that dysuria, urgency, frequency, and suprapubic pain are symptoms associated

Page 9

with cystitis or bladder infection. Next slide please.

There's also a lot of consensus on what the signs and symptoms are for upper tract, or systemic disease, these are fever, chills, rigors, flank or costovertebral angle pain, nausea and vomiting in someone with urinary tract symptoms, someone with unstable vital signs, or if you're concerned about prostatitis, pelvic or perineal pain in men would be an important clue. Next slide please. And that's where we get out of the area of consensus, where we look at the definition of uncomplicated UTI.

What's happened is it's evolved over time. I have -- I'm going to discuss four definitions. And we'll start with what I call the classic definition as described in the 2010 Infection Diseases Society of America UTI Treatment Guidelines. Uncomplicated UTI was defined as cystitis or bladder infection in a premenopausal woman without neurologic abnormalities or comorbidities or pregnancy.

The FDA updated this definition somewhat in the guidance to industry in 2019 defining

Page 10

uncomplicated UTI as occurring in a adult woman with pyuria and at least two sides of cystitis without any of the symptoms or clinical manifestations of a complicated UTI. Up to Date, however, in 2021 published a definition of uncomplicated UTI that's much more aligned with clinical practice. And lest you think that it's been different, people doing this, actually the two authors of the Up-to-Date definition are Kalpna Gupta and Mac Hooton.

And of course, Kalpna Gupta was the lead author for the IDSA guidelines, F1810 and Mac Hooton was a co-author. So, their published a change in the Up-to-Date definition, '21, reflects a change in clinicians thinking over time. But acute uncomplicated cystitis is acute UTI confined of the bladder in women or men, so including men in the definition. And then people who lack signs and symptoms of upper tract disease.

And having a anatomic abnormality or diabetes or immune compromised does not necessarily exclude someone from having uncomplicated UTI. For the IDSA guidelines update definition, let's look at

Page 11

the next slide. So, in the guidelines that we're working on now, or the update, we're going to follow very closely the Up-to-Date definition on uncomplicated UTI. And the reason is our guideline's panelists believe that the approach to treatment should guide the definition of uncomplicated UTI.

And when you're treating a patient, what you really care about is, do I have to hospitalize this person? And do they need IV antibiotics? So, our definition will be guided by the extent of the infection in the bladder or beyond and the severity of illness. Uncomplicated UTI is going to be defined as local bladder signs and symptoms in the absence of upper urinary tract signs and symptoms such as fever, flank pain, systemic illness.

We're not going to require pyurial or bacteriuria. Because in clinical practice, it is not mandatory in all cases to get a urine specimen before treating uncomplicated UTI. We will not include catheterized patients under uncomplicated UTI. And again, this is what I think we're going to do, I can't guarantee that this is word for word, what we're going

Page 12

to publish. But this is how our discussions have gone so far.

Next slide please. So, to make it very clear, I put the four definitions of UTI in one table so that we can go through these over time. IDSA in 2010; premenopausal women was the focus. FDA 2019 is adult women, and it's focused on cystitis. Up to Date 2021 is all adults, patients with cystitis, no infection beyond the bladder. And the IDSA guidelines update, we're looking at a similar definition.

Please note that all four definitions really do not consider pregnant women, renal transplant recipients, or catheterized patients to have uncomplicated UTI. All right, next slide please. So, now we're going to talk about what's causing uncomplicated UTI in the United States. Next please. Next slide please. Okay. So, when you want to figure out, for a presentation such as this, how many uncomplicated UTIs occur in the United States per year, I have some news for you.

You're going to have to use older data. There've been two national surveys that really all the

Page 13

papers and references refer back to. One was in 2001 and one was in 2007. Now this is a ambulatory healthcare survey, data published by the CDC. So, that estimate in 2007 was that there were 8.6 million visits for a UTI per year in the United States. Next slide please. So, if you want to figure out how many of those visits for women and men, I got bad news for you, you got to go back farther in time.

And we're going to be using data from the year 2000. And the best sources of this information is the Greibling publications on neurologic diseases in America project, with one publication on women and one publication on men with UTI. And from these publications we can learn that obviously women have a higher lifetime risk of UTI then men. And in women, UTI's common throughout adult lifespan. Whereas in men, it's uncommon before age 50, but not unheard of.

There are men before age 50 that have what I would consider an uncomplicated UTI not related in any structural defects. As women and men age, the instance of UTI comes closer in both groups being very

Page 14

similar by age 90. In year 2000 6.3 million office visits for UTI were made by women and close to 2 million outpatient or office visits were made for UTI were made by men. But the most stark difference is in how many randomized control trials there are of treating UTI.

In women there are many, I would say high quality trials that we look at for guidelines there are 50 to 100. In men, randomized control trials of treatment, I am aware of four trials. So, as a VA care provider, where most of my patients are men, that's a really important knowledge gap for me and other healthcare providers who have male patients. Next slide please. So, now we're going to talk about antibiotic resistance in the urine pathogens that are causing outpatient UTI.

Next slide please. So, there are a lot of different publications. But I will tell you upfront, there's some limitations on the data. It's a little hard to sort out what happened inpatient and what happened outpatient in terms of antibiotic resistance. And a lot of the studies focus

Page 15

specifically on E. coli. But when my patient comes to see me and says they think they have a UTI, they don't have a sticker on their forehead that says, "I have E. coli," or "I have Klebsiella."

So, I think it's helpful to find a study that looks at a lot or organisms, not just E. coli. Also, fosfomycin testing is rarely reported. So, I cannot tell you much about that. However, I put a lot of references on this slide if you would like to look this topic up later. But next slide. I'm presenting just one reference to you all. And this is from the study using Becton Dickinson labs across the United States.

And I chose it because it's relatively recent, those two years 2018 to 2020 made it clear the difference between inpatient and outpatient and looked at a variety of gram-negative organisms. So, what you see is an example of one of the figures from this. And it shows you trimethoprim-sulfamethoxazole are Bactrim non-susceptibility. In other words, this is map of Bactrim resistance across United States.

And as the color changes from blue to

Page 16

lighter to tan, that's increasing resistance. What we know from this publication is that across the United States in general among the gram negatives found in the urine, all of them have more than 20 percent resistance to the -- I'm sorry. All of the drugs that we choose empirically for UTI, there's a higher than 20 percent resistance rate, so Bactrim 22 percent, fluoroquinolones 22 percent, and nitrofurantoin 22 percent.

So, you're thinking to yourself, "Wow, the IDSA guidelines of 2010s that don't empirically use Bactrim if there's a higher than 20 percent resistance rate. So, there's no drug I can use empirically." But that's not the case. What this data are telling us is that we have to focus on patient level resistance factors when we are choosing an empiric agent to treat a patient. Count -- a countrywide antibiogram is going to be too general.

And we'd probably have to drill down on, does this patient have a likelihood of having an organism resistant to this drug that I'm thinking of choosing? Next slide please. So, what are the

Page 17

current recommended treatments for uncomplicated UTI? And what are people doing in reality? Next slide. So, this is from IDSA cystitis guidelines in 2010. And the three first-line agents, nitrofurantoin, trimethoprim-sulfamethoxazole and Fosfomycin.

Fluoroquinolones and beta-lactams were not recommended, those are considered second-line agents and to be avoided if there is a available first-line choice. Now the phrase that everyone remembers is the part about, "Don't use Bactrim is the resistance prevalence is known to exceed 20 percent." So, that's an antibiogram type recommendation.

What people forget, including me, I forgot I was preparing this, if you don't use trimethoprim-sulfamethoxazole, if it was used for UTI in this patient in the previous three months, see that second half of the phrase is directing you to the patient specific risk factors. And we're going to be trying to compile and assemble that evidence on patient specific risk factors in the IDSA UTI guidelines update, because I think that is key to empiric treatment of UTI currently.

Page 18

Next slide please. So, how long do you treat acute cystitis in women? The mnemonic ideas in teaching is 531, nitrofurantoin is five days, trimethoprim-sulfamethoxazole is three days, and Fosfomycin is one day. Now, although this is not stated explicitly in the guidelines, test of cure urine culture for uncomplicated UTI is not recommended. In fact, a urine culture in some cases is not needed at the time of treating the patient, so test of cure urine culture's especially not needed.

And the state clinicians are guided by whether or not the patient's symptoms have resolved. Next slide please. So, there are guidelines and then there's reality, that's why we have implementation research. But -- so -- if you look at data prior to 2015, treating women with uncomplicated UTI, almost half of the drug choice was fluoroquinolones, which of course is not recommended. Looking more recently, data up to 2019 made use of fluoroquinolones was still about a third.

And of course, if you look at how long people are treating, in 2017 75 percent of antibiotic

Page 19

courses were longer than recommended for that particular antibiotic agent. Next slide please. I really like this study because it shows the change from 2015 to 2019, in that fluroquinolone use is decreasing for uncomplicated UTI. But what you can barely see, unless you look right at the top of the slide, is Fosfomycin use, which is less than one percent of all outpatient UTIs treated with Fosfomycin, which is very interesting since it's one of the three guidelines recommended agents.

Next slide. So, now I'm going to talk about three randomized control trials of treating uncomplicated UTI that were published as the 2010 IDSA UTI guidelines. Next slide. So, the first was the male UTI trial led by Dimitri Drekonja was involved in this trial. And what we were trying to find out is, how long should you treat men with UTI because references of literature states 7 to 14 days, but that's a really big difference.

So, patients that could enroll in this were afebrile outpatient men with one or more UTI symptoms. And they had to have been diagnosed with

Page 20

UTI by their provider and prescribed either trimethoprim-sulfamethoxazole or ciprofloxacin. We randomized them to receive seven vs 14 days of those two agents and if they were in the seven-day crew; if they got a matching placebo for the following seven days. Patients who were blinded to what they were receiving, seven or vs 14 days.

And we looked at resolution of clinical symptoms at 14 days. Next slide please. And what we found is that seven days worked as well as 14 days in terms of symptom resolution at 14 days and recurrence of UTI symptoms at 28 days. What I was really intrigued by though is that, out of the men who had a urine culture done before treatment almost 1 in 4, 23 percent had no growth. And we were very lenient on growth, if there were 100 organisms, we'd call that growth which of course is lower than the clinical laboratory thresholds.

So, that means that either one in five or one in four men actually didn't have a UTI, here the provider thought they did. Or, they had a UTI caused by a non-cultivatable organism, which is also

Page 21

possible. Next slide. Study No. 2 I'm going to talk about is Angela Huttner's and team's study of Fosfomycin vs nitrofurantoin for UTI in women. They enrolled adult afebrile non pregnant women with urinary symptoms and a positive dipstick test.

Women received either five days of nitrofurantoin, a one dose of Fosfomycin. This was open label. The patients knew they were either getting one day or five days. And the primary outcome was clinical response at 28 days when they also used a pretty generous standard for a positive urine culture. Next slide. So, out of the women that were randomized, again, much like the men, close to 25 percent or more than 20 percent had a negative culture.

So, these were women with urinary symptoms, positive dipstick negative cultures. So, did they not have a UTI, or did they have an uncultivatable organism? In terms of clinical outcome, the five days of nitrofurantoin was superior to Fosfomycin in terms of clinical resolution at 28 days, as well as microbiologic resolution. Next slide.

Page 22

Now this study has some data that were not published, that Angela shared with me that can give us some bearing on what does bacteriuria at the end of cure mean?

So, to include a woman in the data I'm going to present here, she had to be microbiologically evaluable which meant positive culture at enrollment and also provided a urine culture on day 14 and also had to be clinically evaluable which means they stayed in the study and provided clinical data at 28 days. So, what we're going to look at is there were 224 women who did not have clinical failure day 14 and met all these evaluation criteria.

Of these 224 women, 23 or 10 percent had bacteriuria on day 14. So, they've received their antibiotic treatment but by day 14 they had bacteriuria. So, who went on to clinical failure at day 28? Seventeen percent of those with bacteriuria on day 14 vs nine percent of those who did not have bacteriuria on day 14. Now, the p value is non-significant, these a very small numbers. But it raises the question that is there a signal there?

Page 23

Probably so, I mean it's reasonable to think that bacteriuria may predict subsequent UTI, but it does not necessarily mean that that treatment of the bacteriuria at day 14 is possible to prevent UTI. Okay, next slide. And then the third trial I'll mention briefly was Mac Hooton, Parita Roberts, or Ann Stapleton looked at Cefpodoxime vs Ciprofloxacin, randomized women to three days of either therapy, and their primary outcome was clinical cure at 30 days finding that Cipro was superior to Cefpodoxime for clinical cure and microbiologic cure.

So again, these are two second-line agents, but the fluoroquinolones just superior to the beta-lactams for this outcome. Next slide. So, I presented the evidence, let's talk about gaps in knowledge. It's very hard to know right now what is the best empiric choice of antibiotics for uncomplicated UTI in women were working on updating the data and determining the individual risk factors that matter for the revised UTI guidelines.

There's very little data that guide your choice in men and very little data to guide your

Page 24

choice in pregnant women. We don't really know how long to treat men with UTI. Yes, we did one great randomized trial, but gosh we need more on that topic. And also, do people with diabetes need to be treated for longer? In the United States, at least 1.4 million adults identify as transgender. I have a transgender woman in my clinic. How do I treat her UTI?

I really don't know how long or what to choose. We can use biomarkers that help us determine when someone actually has a UTI rather than a symptomatic bladder colonization. Which also raises the question of the value of the point of cure testing. A lot of companies are developing devices that can tell you at the point of care, if there are bacteria present, what the bacteria are present, and what they're resistant to.

All that will be helpful, but it still won't tell us if the patient has urinary symptoms which is a clinical decision. And that brings me to the question of the clinical significance of bacteriuria after treatment. Next slide please. This

Page 25

is from another study by the Hooton, Roberts, and Stapleton team. They looked at women with a current UTI who were enrolled at the time of presenting for treatment of the UTI. And then three months provided daily assessments of the white blood cells in their urine -- the urine culture, and they kept a symptom diary.

In this study, UTI was defined as the women felt bad enough to come to clinic saying, "I think I have a UTI," and have a culture that had at least 100 organisms. Very interesting data to come out of this study is that asymptomatic bacteriuria defined as at least 10 to the fifth organisms was present on 2.5 percent of the patient days overall, typically it was transient though, only lasted one to two days, and then most cases resolved.

Admittedly it was more common in the days prior to UTI, but there was also a lot of days with these asymptomatic bacteriuria that didn't lead to UTI. Pyuria turned out to be not-predictive at all. Eighty percent of the women pyuria on at least one non-UTI day. And most interesting of all, there

Page 26

were 11 subclinical UTI events. Which meant on that day the women, who all have urinary symptoms, had pyuria, had bacteriuria, but did not come into the clinic.

Sorry about that. And in many cases, the majority of those cases was resolved. Next slide please. I'm really sorry about the phone. Okay. So, I was fortunate enough to do an editorial on this article. And then you can see I used really advanced graphical design skills for the smiley faces. But what's important is I think ASB and (inaudible) are continuum rather than clinically distinct conditions.

And there are a number of women who may start with no bacteria, develop asymptomatic bacteriuria, subclinical UTI symptoms, and then resolve. Or some they bounce back and forth between ASB and subclinical UTI for a long time. Whereas others, as soon as they get ASB, proceed directly to symptomatic UTI. And we don't really know right now what determines the direction in which they go and whether or not they have advanced a UTI.

Next slide please. That's all I have

Page 27

to present with you all today. Thank you so much for your attention. And I'm looking forward to the panel discussion this afternoon.

DR. KIM: Okay. Well, thank you Dr. Trautner. Our next speaker is Dr. Harry Mobley. Dr. Mobley is the Federick Novy distinguished university professor in the department of microbiology and immunology at the University of Michigan Medical School. After 23 years at Maryland, Dr. Mobley was named Chair of the department of microbiology and immunology at the University of Michigan Medical School in 2004 serving in this role until 2019.

Dr. Mobley's research focuses on neuropathogenic E. coli proteus mirabilis, but also has studied helicobacter pylori in gram negative bacteria species causing bacteriuria. With that, I'll turn it over to Dr. Mobley.

DR. MOBLEY: Thank you Tim. And thanks, welcome to everybody out in the virtual ozone. My job is to give a crash course on various studies and properties of bacterial strains, principally E. coli causing uncomplicated UTI. Next slide please.

Page 28

Horizontal DNA transfer has generated a variety of E. coli pathotypes. If we look at our commensal strain -- ancestral commensal strain has been bombarded with virulent strains by transformation, conjugation, and transduction to give us different pathotypes that include bacteria that can cause dysentery, diarrhea, hemolytic uremic syndrome, meningitis, and UTI.

Next slide. Next slide please. So, principally we have two categories of E. coli one that can cause diarrhea. There's six types of E. coli that can cause diarrhea, you could have it your way. And then there are E. coli that live outside the gastrointestinal tract including, what we talk about today, neuropathogenic E. coli but also strains that are associated with neonatal meningitis in cows, mastitis associated E. coli and lung infections in birds.

Next slide please. These neuropathogenic E. coli or UPEC are tremendously genetically diverse. Commensal strains have average size of 4.64 mega base, (inaudible) base that is. And UPEC is 5.16 million base pairs on average, yielding

Page 29

about 500 extra genes. The core genes found in all E. coli are about 2,600, or about half of the genes. And certain strains can have up to hundreds of unique genes that are not found in any other E. coli strain.

To get a feel for the scope of how many genes can be in the E. coli species, two studies were done. Four thousand seventy-one E. coli ST131 isolates, which is spread around the globe, have a total of 26,000 genes in all of those strains. And then ExPEC strains that cause bacteremia in a 10-year study in London, 1,500 non strains yielded almost 70,000 genes. So, this is what we're up against when we're battling E. coli

Next slide please. Just for a moment talk about asymptomatic bacteria. And E. coli is the most common cause of that. These strains evolved from virulent UPEC but have mutations in key virulent factor genes including type 1 fimbriae and P fimbriae. And half of the strains -- only half of the strains have type 1 fimbriae. And less than 10 percent of the strains have P fimbriae. These strains also have slower growth rates in invitro urine cultures in the

Page 30

laboratory.

In one particular strain however outcompetes UPEC invitro urine culture, and the mouse model, and I think also in humans where it's been used therapeutically in Sweden. These strains do not activate the innate immune response, and therefore we don't have the inflammation. And we don't have the symptoms. Other species can cause asymptomatic bacteria including (inaudible). And it's thought that antibiotic treatment is not recommended except in pregnant women.

Next slide. Next slide please. Also, in catheter associated bacteria briefly, long term catheterization, those patients catheterized for more than 30 days is 100 percent chance of infection. And usually, those infections are probably microbial with 10 to the fifth colony forming units with three or four different species simultaneously. Your most common here are probably just (inaudible) proteus mirabilis, a wimpy version of E. coli.

And pseudomonas aeruginosa and Morganella morganii, three of these are urea positive

Page 31

as noted and could be involved in stone formation. Next slide please. Our model of bacterial pathogenesis developed over the years for UPEC. In that colonic organisms and step, one make their way to the periurethral area and contaminate that region, ascend the urethra to the bladder, and then number three, Scott Hoper's Lab has shown that type one (inaudible) that line the transitional epithelial cells and indeed can enter these cells and then later reflex from those cells causing a cycle.

However, the large preponderance of organisms are found planktonically in the urine floating around, perhaps moving up the ureters. Next slide please. So, what's the animal model of the ascending urinary tract infection? This is important, we can't always work on humans. Next slide please. The mouse model of ascending UTI mimics the human UTI quite well. It uses female CBA/J mouse species, or other species. It was developed by Hagberg and colleagues in 1984.

It's been used in greater than 1,000 published studies and 108 in our lab. UPEC strains

Page 32

infect and persist in this model, commensally E. coli does not colonize for more than 24 hours. The bacteria can ascend to the kidneys, that can cause bacteremia. And the histopathology is similar between the mouse model -- between the mouse and the human. Cytokines are elicited which trigger neutrophil infiltration which peaks at six hours.

And finally, UPEC gene expression in mice is highly correlated with that in humans. I'll show those to you a bit later. Next slide please. Visually we can look at one representative mouse in this imaging study. These are live mice that have been inoculated with E. coli reviewing them from the ventral side both from two to six hours and on the dorsal side also during that time period. We've used a light emitting CFT73 bacterium which has lux fusions of flagella genes.

And we could see the ventral side in the top left, an active infection into the bladder once they've been inoculated. And then we can tell as we move to the right, they're spreading somewhere, but it's difficult to see unless we turn the lights over

Page 33

so we could see the back. So, here we see graphicly, like for example, three hours we can see that they ascended the ureter to the kidney. In four hours, they've gone up to both sides.

There's a strong movement in five hours to the right kidney, and then six hours both -- they've moved up to both kidneys. Next slide please. So, we can use this a number of ways but here's one example: We can follow infections over time in the mice. In the top panel what we've done is we've collected -- we've inoculated 10 to the 8th bacteria in the bladder and followed this over a seven-day period. And in red we see the colony forming units per mil of urine.

And we can see that they peak at really early on. They're really growing fast. And then the blue line is a doubling time. And so, the lower the point, the faster the bacteria are growing. So, at six hours they're actually at peak doubling time. They slow down a little bit as they move up. And then consequently the CFU per mil go down. But then something signals it to speed up the gross rate and

Page 34

then the CFU move up again.

In the lower panel we can see that in the black line, the cytokines they'll six -- or peaks at six hours. And that's of concordant with infiltration of neutrophils. Next slide please. So, what are the traditional virulence factors that are expressed by E. coli? Next slide please. In this graphic we'll show you that. Starting at the top left, UPEC can produce any number up to 12 different adherence factors called fimbriae or pili.

They produce LPS like all gram negatives, okay antigens. Seventy five percent of strains are represented by only six (inaudible) types, so these are quite colonel. They also can produce a polysaccharide capsule. They're motile by flagella, which I showed earlier. And they have complex iron acquisition systems which I'll expand on in a little bit. And they produce exotoxins such as somnolescent. Not all strains produce all of these, in fact some are a very limited number of virulence factors produced (inaudible).

Next slide please. Virulence factor

Page 35

genes are often encoded in what we call pathogenistides, maybe 30 to 100 kilobases, DNA that's been acquired by horizontal gene transfer. What I'm showing you is a circuited chromosome of E. coli CFT73 isolated during a ceftazidime vs (inaudible) study of pyelonephritis from the blood and urine of a hospitalized patient with acute pyelonephritis in 1982. And it's a highly cited organism, it'll be a sole professor by now.

The large blocks are the sights of insertion of (inaudible) that carry virulence factors around the chromosome. Indeed, they represent 17 percent of the genome pair. And so, they've acquired various factors from a variety of sources. And each strain is going to have a little bit different pattern. Next slide please. If we look at the prevalence of virialized genes found on (inaudible), it's 315n strains were surveyed.

And we looked at the prevalence in fecal cystitis and pyelonephritis strains. And the prevalence is indicated by the diameter of the circle. So, we can see that the fecal strains have very low

Page 36

percentage of strains with these fimbriated adhesins, toxins, and iron receptors. Whereas cystitis and pyelonephritis strains have significantly greater percentage of strains that carry these virulence factors not surprisingly.

Next slide please. The bacteria fight for iron with the host. The iron sequesters -- I mean the host sequesters iron. So, the bacteria depicted here has developed all of these different systems to capture iron. On the top row there are a (inaudible) receptors that bind (inaudible) that's bound to iron. On the right side we have receptors that bind heme and extract iron from the heme. On the bottom we have transporters that could bring in other compounds such as for citrate.

And so, you can see they've devoted quite a bit of energy to taking iron into the cell. Next slide please. Also type 1 fimbriae expression we think is critical for infection. It's controlled in an interesting fashion by an invertible element. Its phase varies, what that means is it's a gray box the promoter can face these (inaudible) genes and turn

Page 37

those on and make the fimbriae. Or recombinase can flip this in the opposite direction just like a light switch and turn it off.

We've developed a PCR assay to determine whether that switch is in the on or off position. And below are data that I won't go through in detail. But you can determine whether the switch is on during a human UTI where urine is collected immediately during -- in the doctor's office and stabilized. Next slide please. If you look at all of these different, I think 12 strains, we look at the level of type 1 fimbriae expression, for the most part they're elevated.

We don't know when these patients came into the clinic and that's something that we're interested in knowing. Below you can see whether the switch is in off position where it's not expressed or some that were measured in the on position where they're highly expressed. Next slide please. So, are these virulence genes all that are required for infection? So, of course not. Next slide. Here we look to the things that we learn like the TCA cycle.

Page 38

The TCA cycle is that we learn the TCA cycle and then we forget the TCA cycle. But other pathways were glycolysis, gluconeogenesis, pentose phosphate pathway, and Entner-Doudoroff pathway have produced metabolic enzymes that are required for infection. So, which pathways are important for infection? We made mutants in each pathway that inactivated that single pathway and tested all of those mutants in the mouse model. Next slide please.

What we found were that mutants with defects in TCH cycle or gluconeogenesis, that is making glucose, have impaired fitness during UTI. But shockingly, to me anyway, that glycolysis pentose phosphate and Entner-Doudoroff pathways are dispensable in vivo. This is because the bacteria don't use -- the E. coli principally does not use E. coli amino acids are the primary carbon sources. And thus, peptide transporters are induced in urine and required for infection.

To the top right peptides are brought in to make amino acids, broken down into amino acids that can then go to upsell (inaudible), go back up to

Page 39

gluconeogenesis or fuel the TCA cycle. This is quite interesting. Next slide please. So, that prompts the question is, what E. coli are doing during a UTI in women with uncomplicated UTI. We know what they're doing in the test tube I think, but not in women. Next slide please.

So, we conducted this study, 86 women were attending the university health service with symptoms of cystitis. They were provided in the form of consent, and it was obtained. And most importantly we gave them a $10 Starbucks card. Urine collected and stabilized immediately in RNAprotect, which we used 17 liters which were by a small minivan. The samples were cultured. And half of the women, exactly half had bacteriuria, and 88 percent or those were E. coli

So, these strains were isolated in sequence. Next slide please. So, we wanted to know -- we wanted to characterize the core genome expression. If we looked at the number of genomes, they have 14 strains in which -- and how many genes were in all of those strains? On the right-side core

Page 40

genome had 2,653 genes were present in all 14 strains and these are the ones that we focused on in our study. We isolated the RNA that had been stabilized immediately after collection from the (inaudible) and conducted RNA seq. studies.

And let's go to the next slide. And here we have these (inaudible) type diagrams. And I'll -- they're different from other ones you've seen because I'm going to explain them. On the right -- on the left, I'm sorry, there is a volcano plot. And what we see is genes on the right side, or ones that are upregulated during UTI in women. That's compared to culture in filter sterilized human urine that is invitro.

And so, those genes that I've depicted here are associated with the translation replication machinery like ribosomes and amino acid transporters bringing in peptides and amino acids. Things that are downregulated, or things the bacteria doesn't need in the UTI, and that's sugar catabolism genes and sugar transporters because it doesn't use glucose and other sugars principally.

Page 41

We have similar data on the right side which show two panels, urine cultured invitro -- I mean a bacteria culture in urine invitro, and then these patient urine samples, there are 14 strains, so 14 boxes. But then we're looking at what's upregulated. Red is the most highly upregulated. And this represents ribosomal proteins and other translation of machinery DNA synthesis and so on, amino acid transporters. Flagella are downregulated in green.

Next slide please. So, the bacteria have to figure out what resources to allocate. And they allocate them away from metabolic enzyme production. So, on the left panel I'm showing in the blue bars, these are gene expression of E. coli cultured in human urine in the laboratory. And then the red bars are from the patient. What we see is the core genes represent about 50 percent of the total rigs because they're 50 percent of the genes. That makes sense.

But if we look more closely in the second panel, we can see an incredibly difference. If

Page 42

we look at ribosomal subunit gene expression, that is the protein factory. That's important for growth rate. In urine, it's only 7 percent of the genes your associated with ribosome production, but a startling 27 percent in the human UTI. There's no free lunch in these bacteria so they have to downregulate in the patients, other things like catabolic gene expression, breaking down macro molecules for anabolic gene expression, building up macro molecules.

Next slide please. But the gene expression is conserved between patients whether it's cultured in the laboratory or in the patient. So, if we compare the gene expression pattern of each strain to every other strain and all those combinations. We see that whether or not they're cultured in urine or the patient, they have a high correlation coefficient, this creates about 9.2 a Pearson correlation coefficient.

However, if we compare the gene expression of individual strains in the patient and then in the laboratory, we see that they're not the same. And so, we have a different genetic program

Page 43

even though we have highly heterogeneous strains and highly heterogeneous hosts. We have the nearly identical gene expressions of a core genes in the patients. Next slide please. Fortunately, core gene expression of neuropathogenic E. coli in women is recapitulated in the mouse model.

In a beautiful study by Arwen Frick-Cheng and colleagues in our lab, she compared the expression of all genes from one strain where RNA was isolated from the mouse vs isolated from the patient. And we see an excellent correlation of .88. And this is particularly good news to us and so we don't have to retract 180 of the patients. Next slide please. So, this brings us to the point. The ribosome suggested the bacteria are growing, but how fast are UPEC growing during urinary tract infection?

And so, I'll tell you about estimating growth rate in vivo. Next slide please. The number of (inaudible) chromosome replication forks are going to vary with growth rate. So, on the left circle we see the bacterial chromosome, the origin of replication is in red at the top, the terminus is in

Page 44

black at the bottom. The bacteria are growing slowly. They will initiate bad directional of growth and proceed all the way down to bottom without restarting replication.

However, if they're fast growing, they'll begin the replication process. And then they'll start that process again and perhaps even again before it reaches a single replication. Next slide please. So, this can be shown this way. If we sequence the entire genome of bacteria grown in a different -- selected at different times at during at growth curve. On the upper left we see a typical growth curve. Before hours we have exponential growths, rapid growths.

And we can see that at three and four hours the origin of replication, the number of copies of the origin replication are much higher than the terminus. However, when we go into stationary phase, say six or seven hours, we can see that the number of copies are the origin of the same as the terminus because they're slowly growing. Next slide please. So, we can convert this to a standard curve of the

Page 45

peak to trough, that is the origin of replication to the terminus ratio and then growth rates that we've measured.

And to log transform this we can see an excellent standard curve to judge, to measure PTR and then calculate growth rate. Next slide please. So, here are eight genomic sequences from the bacteria that were covered directly from a human UTI. And we can see they haven't exaggerated peak to trough ratio, almost all of them. And if we average these, we actually had to extrapolate the growth rate because it was so rapid with a mean doubling time of 22.4 minutes.

What does that mean? So, that's about 4 or 5 minutes slower than the fastest that E. coli can grow under the optimal laboratory conditions. So, this is a startling finding. It would mean that it would take about 80 minutes to go from 10 to the 4th bacteria in the (inaudible) to 10 to the 5th. So, you can see why these symptoms become so acute so quickly. Next slide please. We'll summarize what I've told you today, that UPEC can infect the bladder, kidney, and

Page 46

also leave the bloodstream.

These bacteria are heterogeneous and have about 500 more genes than commensal E. coli. The virulence gene expression does vary between patients, but the core genome is the same. The mouse model recapitulates gene expression in the women with uncomplicated UTI. And this is a powerful tool for the laboratory. As I said, "Core genome expressions conserve, but ribosomal genes are over expressed suggesting rapid growth. Amino acid transporters are upregulated because these bacteria are doubling up amino acids and peptides available to them in urine, but do so preferentially over carbohydrates.

And they grow extraordinarily rapid in the urinary tract. So, I like to thank all the members of my laboratory and their national institutes of health for their support and for your attention. Thank you very much.

DR. TRAUTNER: Thank you Dr. Mobley. I always really enjoy hearing your work and what's underlining the pathogenesis of UTI. Group, we're going to have a great chance now to take a break. We

Page 47

have a 10-minute break. We will reconvene at 10 a.m. Eastern time. See you then.

(Break)

DR. TRAUTMAN: I assume it's time to introduce our next speakers. Moving along. So, I am very happy to be introducing Dr. Tomefa Asempa to you. Dr. Asempa serves as the associate director of the center for Anti Infective Research Development at Hartford Hospital with a primary focus of understanding the in vitro potency, pharmacokinetics, and pharmacodynamics of investigational and approved anti-bacterial agents and their translation of the positive patient outcomes. Dr. Asempa.

DR. ASEMPA: All right. Good morning, everyone and thank you for this opportunity to present some data. I'm glad we're able to follow Dr. Mobley because we're going to touch on a few things that he mentioned. So, the goal of this talk is to catch us up to speak on the anti-bacterial PK/PD in the uncomplicated UTI animal model. Next Slide please.

Dr. Nicolau and my disclosures are listed here. Next slide please. The goal at the end

Page 48

of the presentation is to touch on the common animal models used for anti-bacterial PK/PD and efficacy for the uUTI model. I'll touch on the strengths and limitations of these models. And then I'll wrap up with some pre-clinical, clinical correlates. Next slide please.

So, just a refresher on anti-bacterial PK/PD. PK/PD has been tremendous in the development of anti-infectives. You look at the FDA packages of the recent approved drugs and you can see PK/PD, especially in animal models, has been influential in the development process. So, PK/PD is key in allowing us to understand the relationship between dose exposure and response. And we can do this in vivo or in vitro.

The two things we are looking out for at the PK/PD index, which allows us to understand if an agent is time dependent or concentration dependent, and then the target, which is the magnitude of exposure required to attain a certain PD endpoint. And these PD endpoints can be stasis, it can be one long reduction. There's a good amount of data out

Page 49

there showing that these endpoints are good microbiological surrogates for clinical efficacy.

The whole goal of PK/PD really is to help us develop an optimized doses and at the end of the day, de-risk clinical studies, so hugely important studies that need to be done in the pipeline. Next slide, please.

So, a little bit of history. The first UTI model was developed in the '70s in the dog, in the canine model. And then after that, we moved on to rabbits and then rats. The first UTI model in the mouse model was developed in '67 by Kenan Freeman. After that, the mouse model by far and large become the dominant workhorse for the UTI model until date. Next slide please.

So, this is a great review people can go to. It touches on the models used to understand virulence and pathogenesis and PK/PD. So, going counterclockwise, you have your c elegans, you have your teleost, you have your avian models. These are really to understand virulence, not applicable for PK/PD. But then the porcine and the rodent model,

Page 50

which I'll touch on in the next few slides, are models that you can use for PK/PD. Next slide please.

So, the porcine model is highly desirable. And that's because it shares similar physiology and anatomy and immune system to humans. So much so it is used for immunological studies. It is also used to study pyelonephritis and renal damage in trying to understand vesicoureteral reflux, which is a huge problem in infants. Vesicoureteral reflux is when you have urine backing up from the bladder and ascending the urethra into the kidney. And this can cause damage. If you do have bacteria in the blood, it can also translocate and cause a kidney infection. I'll talk about that in a little bit. Next slide, please.

So, porcine model does exist. And the investigators were able to show you can have achieved persistent epithelial colonization on the bladder and bacteriuria. Next slide, please.

Unfortunately, the porcine model is tremendously expensive. You need a dedicated facility and large animal expertise to do these studies. So,

Page 51

it's not common in the PK/PD world to be using the porcine model. Next slide, please.

The murine model, by far and large is what most people use. Again, it's relatively inexpensive. It's easy to handle. And there are some similarities. This is an excellent study from Dr. Mobley's lab looking at the transcriptomes of free uropathogens and comparing them between the human infection in the UTI model. And they showed that less than six percent of the three strains had significantly different expression levels. So, meaning, more than 90 percent of them were conserved in terms of expression levels. They showed gene expression levels of metabolic and virulence factors were highly similar between the mouse model and human infection model.

So, the conclusion being that the mouse model recapitulates the human infection model. And he touched on several studies. So, there are studies showing it is useful to mimic the human infection. Next slide, please.

There are certainly some differences in

Page 52

terms of anatomy. The bladder of the mouse is only three to four cells thick, versus five to seven cells thick in humans. The question here is how does this play in terms of colonization or the ability for bacteria to cause intracellular communities between these two infection models. So, that's a question that still needs to be answered.

And in the mouse model, the mouse hardly stow urine. I mean, you pick up a mouse and they will void immediately. The question is does this also affect the shape and the stretching of bladders and how does this affect colonization. So, these are still some unanswered questions. Next slide, please.

So, there's not a lot of data of robust in vivo data for PK/PD. So, I thought it would be best served if I touched on the challenging variables that we have contend with and how as a collective we can move the needle in trying to really optimize this model. Next slide, please.

So, the first being the mode of infection. So, predominately, most people infect through the urethra. So, there's a transurethral.

Page 53

There's also the intraurethral and periurethral. This diagram does a beautiful of showing an episode. The first one is the transurethral that most people do. Most people do this. And a practical reason for this is if you were to do any other method, you're going to have leakage of the (inaudible) and then you're not going to know how much was delivered. That's why lots of people end up doing this. Next slide, please.

Then the question is how does this relate to human infections because, you know, human infections, you have bacteria from the vagina or the GI tract actually get into the periurethral and then transcending up versus in the mouse model, you're actually delivering it straight into the bladder. So, there's a question about what does this do the pathogenesis of your pathogens.

And then vesicoureteral reflux, so this is a huge variable we need to contend with. If you are delivering the bacteria to the bladder, you have vesicoureteral reflux going up into the kidneys. So, you pull many of these papers that are talking cystitis model and you see that they do in fact

Page 54

harvest the kidneys and show CFU and bacteria burden. It's something we need to wrap our heads around. In our lab, we do the complicated urinary tract infection model with the understanding that if you're able to treat a complicated urinary tract infection model, you should have some efficacy with the uncomplicated urinary tract model.

So, it's just something we need to content with. When you're talking about your research or publishing it, you need to highlight it either as a limitation or discuss it. Because the models are different. But unfortunately, for most of the uncomplicated urinary tract infection models in the mice, you do end up causing a kidney infection. Next slide, please.

PK sampling. This is very important in understanding the exposure of the drug, either in plasm and for this infection model in the urine. We need to be able to understand that to actually create a PK/PD model. Unfortunately, like I mentioned, mice hardly store urine, so it's quite a challenge. You're going to need a large number of mice to collect a good

Page 55

number of urine at each time point. And if you do collect the urine, it's highly variable. And this is related to the hydration status, which is also made worse by the ongoing infection in the mice. Next slide, please.

This is just to illustrate this. This is a PK/PD study for mice in the UTI model. It's a dose ranging. So, in the first graph in the top, they delivered 0.75, 7.5, and 30 milligrams of Fosfomycin. So, this is in plasma. You can see the beautiful concentration time profile there.

Below is the drug concentration and urine. The concentration time profile on the bottom is the 0.75. And then you can see the 30 and the 7.5 actually overlap, which is a problem in trying to understand the exposure in urine. Also, look at the Y axis. So, for plasma at the top, it's linear. You look at the bottom and it's a log scale. So, those standard deviations are tremendously wide. Again, this is a problem in trying to actually understand how much of a drug is in there. So much so that the authors of this paper only used plasma. They were

Page 56

unable to use urine. And they noted it, which is a challenge of using urine in the animal model. Next slide, please.

Another variable is the efficacy endpoint. So, the goal is to be able to assess bacterial burden after administration of the drug. You can look at it in urine, bladder, the kidney, or you take slides and look at it under the microscope. And the goal for the UTI model and the consensus is that achieving bacteria stasis is good enough because it's not a CD infection. We reserve one log and two log reduction for CDI infections.

So, I think it's important to note that this endpoint is limited to tissue in the animal model. Whilst, in human, clinically, you're looking at microbiological reduction in urine. So, there's a huge gap in our knowledge in trying to correlate this endpoint and tissue versus this endpoint in humans because they're different matrices. Next slide, please.

Another variable to discuss is the inoculum. So, I think it's fair to say that the goal

Page 57

is to use a uropathogen in the UTI model. And that's because of the presence of pili and fembrey to allow for colonization. Unfortunately, to conduct robust PK/PD in the animal model, you need to include pathogens that have a wide distribution of MIC and diverse resistance profiles. Unfortunately, the Ven diagram of the uropathogens and the Ven diagram of these challenging bugs don't always intersect. So, it's very hard, sometimes, to get a good number of representatives to actually use in the model.

And finally, there's variability in the inoculum that's actually delivered ranging between 10 to the 6th and 10 to the 9th. Next slide, please.

And then the last variable I like to talk about is the actual mouse strain. This is a great study where they infected 10 strains of mice, including BALB/C and C-57 with the same inoculum, same volume. You can see the left is the bacteria burden in bladder. The A is variability of the initial count. And over 14 days, you also have variability at 14 days in how much bacteria was recovered. You can see in two strains, you actually have an increase.

Page 58

Even though this was the intravesical, you can also they recovered bacteria in the kidney. You can see tremendous variability initially and also at the end. So, it's also important to pay attention to the mouse strain that is used. Next slide, please.

I'll just touch on some preclinical and clinical correlates we have in the literature. The first being gepotidacin. They used the rat pyelonephritis model and acknowledged that the authors did say they used this model because it is a worse case and believe if you can treat that, you can treat a cystitis model. So, they hooked up these rates to continuous IV pumps and delivered two doses. Next slide, please.

And they saw significant reduction with these two doses relative to levo. So, this was in kidneys and bladders and there was no urine. Next slide, please.

So, the Phase 3 for gepotidacin is currently ongoing. There's limited data from a Phase 2, so this was in AIDS patients, showing 88 percent (inaudible) at the test of cure and at follow-up

Page 59

achieved microbiological success. So, I think the script is yet to be written for this. But this isn't a classic PK/PD study. It's just an efficacy study. But will still give us data because the dose in rats was humanized. Next slide, please.

The next is omadacycline. They used a mouse cystitis model, delivered transurethraly in immunocompetent mice and did a dose ranging. So, it was two milligram per kilogram to 128 milligram per kilogram. So, this was no formal PK/PD. It was just a dose ranging. And they also saw significant bacterial reduction in kidneys and bladders. There was no urine. Next slide, please.

And there is clinical data. There's a Phase 1B and a Phase 2. The Phase 1B, in 18 patients they saw favorable microbiological response. The Phase 2, though, with 87, omadacycline performed poorly compared to nitrofurantoin such that the sponsors have gone back to the drawing board to try and optimize the dose for omadacycline. But again, in vivo, there was no formal PK/PD study in the UTI model. Next slide, please.

Page 60

Okay, this is work from our lab using the mouse pyelonephritis model. We administered humanized cefepime/taniborbactam dose to neutropenic mice and measured bacteria burden in kidneys. Next slide, please.

And we saw significant reduction across the pathogens we used. Now the phase 3 for cefepime/taniborbactam was not published. But there are topline results. And cefepime/taniborbactam met the primary endpoint of noninferiority and demonstrated superiority to meropenem, which is recapitulated in our mouse model.

I just want to mention that we didn't use -- we didn't always use uropathogins. And that's because we really wanted to assess the efficacy of this drug. So, you can see in the last bar graph, you actually have growth of one pathogen. This was a highly resistant bug that we used. It wasn't a uropathogen. But just to show that if you deliver clinical doses to a bug that is resistant, you can see failure, which we're able to show in the animal model. Next slide, please.

Page 61

All right, so the take home points are there are several UTI models, uncomplicated UT models and the mouse model being the most common. Each of them has its strengths and weaknesses and costs associated with it. I think the take home for all of us is the uncomplicated UTI model ultimately leads to a kidney infection model, most of the time. You can optimize the volume and change that, but most of the time it does lead to a kidney infection model.

So, the question is does complicated UTI, is that appropriate in trying to translate to efficacy in the uncomplicated UTI. Which the consensus is that it does, which is what we do. Urinary endpoints and breakpoints are challenging to ascertain in rodent studies. And that's, again, because of the variables I mentioned.

There's not a lot of robust in vivo PK/PD data. That's why in our lab we develop PK/PD models in the dye infection model. And then with the sponsor, develop the humanized dose and then do a confirmatory efficacy data -- efficacy study in the mouse model. Just because the PK/PD -- defining PK/PD

Page 62

parameters in the UTI model can be challenging.

And finally, there's not a lot of limit -- there's limited preclinical to clinical outcome correlates. So, hopefully, after this study, we can talk about ways to try and optimize some of the variables I highlighted in this presentation. Next slide, please.

I'd like to acknowledge Dr. Nicolau and Dr. Kuti and all the members of the Center for Anti-Infective Research and Development in Hartford, Connecticut for help putting this together. Thank you.

DR. KIM: Great. Thanks, Dr. Asempa for a wonderful talk about really the considerations of translating PK/PD from a laboratory animal to humans for dose support and things like that. Our next talk is going to cover considerations of non-clinical invitro infection model efficacy data to support translations to humans. So, we'll hear a pre-recorded presentation by Jason Roberts and Iain Abbott. I'd like to note that they will be available for the panel discussion.

Page 63

Now, Dr. Roberts is a clinical pharmacist at Royal Brisbane and Women's Hospital and an Australian National Health Medical Research Council Leadership Fellow at University of Queensland. He also leads the Center of Research Excellence Respond, which aims to develop optimized and biotic dosing regiments to improve patient outcomes and minimize the emergency of anti-biotic resistance super bugs.

Dr. Abbott is an infectious disease physician and clinical microbiologist at the Alfred Hospital Central Clinical School of Monash University in Melbourne, Australia. He leads the pharmacology research group within the Department of Infectious diseases and examines the optimization of antimicrobials using dynamic antimicrobial PK/PD in vitro models. Iain sits on the Australian Antimicrobial Susceptibility Testing Committee. With that, I'll turn it over.

DR. ROBERTS: Thanks very much, Dr. Abbott for that excellent review of the previous in vitro UTI models, as well as the key in vitro considerations when simulating UTIs. I'm briefly

Page 64

going to talk about the comparability of these in vitro models to animal models and the correlation with clinical outcomes. Clearly, there's not a lot of data on this topic because otherwise, there would be more time left in this presentation for this.

So, compared to in vitro models, animal models do have some shortcomings as has been very well described in the presentation from Dr. Asempa. Of course, challenges associated with sampling depending on the animal itself, the challenges on which inoculant to use are all important considerations, which are limitations for animal models.

Unfortunately, there's not much data which compares animal and in vitro models directly to help understand what correlations between these may exist. But in vitro models, of course, have the advantage over animal models because they are able to allow changing the permutations of each of the settings to align with a desired scenario, be that a low urine output or a high urine output or a high or a low inoculum. So, that's an advantage that the in vitro models have.

Page 65

The can, obviously, test many different pathogens. The urodynamics, as I mentioned, can be different as well as the pharmacokinetics. And probably most importantly, in some ways, anyways, in vitro models can run for much longer durations. So, this can allow for assessment of the application of resistant sub populations over time. This can be very valuable data for urinary tract infections.

So, again, there aren't much data which correlate clinical outcomes or clinical observations without seeing in the in vitro models. Part of this is related to the difficulty of sampling in the clinical situation, particularly for uncomplicated urinary tract infections and then being able to match up what is observed in the in vitro model.

But of course, this highlights one of the limitations for in vitro models, is that they aren't able to consider, in some cases anyway, the physiology of the host, immunological factors as well as the effective pathology. That can have, at a systemic level for the patient or the human host. So, there's, obviously, various factors that are listed

Page 66

there which in vitro models just can't account for.
However, to improve the clinical correlation, a clearer picture of the human urine antibiotic concentrations in the variability in this is quite important. Most importantly, I think, is the selection and testing of contemporary clinical uropathogen islets. This includes multi drug resistant strains. But many of you all know clinical trials are commonly done in uncomplicated urinary tract infections. This provides the ultimate correlation and support for dosing regimens that initially developed, at least, in vitro infection models.
We would like to conclude there. Thank you very much for the opportunity to contribute to this excellent meeting. We'd just like to highlight that there are unique in vitro considerations when simulating the treatment of urinary tract infections. We think that in vitro models can be very flexible and can provide robust antimicrobial PKP data, potentially to a better extent than what animal models can. These can also compliment and inform other models which

Page 67

include animal models, as well, which has been presented by Dr. Asempa.
Beyond their use in preclinical evaluation, in vitro models can also be used to provide valuable insights through different phase studies that can help be used to understand what dosing needs may be present for currently used antibodies to further optimize their usage. And of course, to inform UTI specific clinic susceptibility breakpoints. So, thanks again on behalf of Dr. Abbott and myself. Good luck for the rest of the meeting.
DR. ABBOTT: Hello, my name's Iain Abbot and on behalf of Jason Roberts, thank you for the opportunity to discuss the role of dynamic in vitro simulations to inform treatment decisions in uncomplicated UTIs. This talk will be split in two. I will start the talk off by reviewing the previous UTI in vitro models and outline the key in vitro considerations. And Jason will complete the talk by talking about the comparability to animal models and the correlation with clinical outcomes.
So, what do preclinical in vitro models

Page 68

offer? Well, mainly, they quantify the fire code dynamic index. By simulating known human pharmacokinetics, we can optimize dosing schedules, we can perform dose fractionation experiments, and test combination therapies. Really, in vitro models have the capacity for long duration experiments with multiple sampling time points. This really generates a dense data set. We can identify which pathogens are the best targets for antimicrobial therapy. We can inform the sitting of clinical susceptibility breakpoints and details and characterize the emergence of resistance.
The classification of in vitro models is important. Really, it comes down to two very simple questions. Do antimicrobial concentrations change over time? And is there bacterial loss in the system? Now bacterial loss within an in vitro model is usually considered as unintended or a potential source of bias. And this has been overcome by the use of the hollow-fiber and friction model, which I have an image hereof.
However, UTI simulations have the

Page 69

additional consideration of urodynamics. In fact, bacteria actively diluted during bladder filling in humans and then are also cleared during the voiding process. So, these experimental kinetics are important to simulate.
UTI specific PK/PD models aim to simulate antimicrobial exposure that's expected in the human bladder. They examine the antimicrobial affect specifically against uropathogens. And they want to test this under humanized conditions. So, that's urodynamics and withing urinary environment. And the dynamic nature of a UTI in vitro model, in this sense, can refer to both the changing of antimicrobial concentrations over time and the volume changes that are reflective of bladder filling and voiding.
Bladder infection in vitro models have been around for a very long time. And in fact, the first in vitro model in this setting was first published in 1966. Here O'Grady and all used a 400-mil inverted glass vessel which had a stirrer and was enclosed within a water bath. The bacterial density was measured by a photometer. Here, inflowing broth

Page 70

was infilled one mil a minute during the day. This was slowed during the night.

Now even without antibiotics introduced into the system, you can see with this glass that bacterial density slowly declined with the inflowing media and then simply declined with the following void. That was continued until you did reach a steady state. This really demonstrated the impact of urodynamics on bacterial density and was able to be reproduced in an in vitro model.

In the following decades, this model was adapted. You can see this is a picture of the model as it sat on the bench back there. You can see it was quite a large model and really incorporates a lot of glassware and hardware. Now, this model was used throughout and up to the 1990s and predominantly by Grenwood et al and enable the study of a wide range of beta lactams, co-trimoxazole, fluoroquinolones, and Fosfomycin.

In a slightly different design of a model, an open one compartment dilution model was originally published by Grasso et al in 1978. The

Page 71

slight difference between this and previous UTI models was that this really lacks the bladder voiding simulations. But it did enable the accurate representation of urinary pharmacokinetics. This model was further adapted by Satta in the ‘80s, Drobot in the 1990s and repeated again in the -- in the late 2000s.

A more complex but still a dilutional multi-compartmental model was designed by a Japanese research group. And here they looked the activity of quinolones against pseudomonas and enterococci. They used a flow rate of half mil per minute into the bladders. They did intermediate voiding every two hours during the day and had a 10-hour night phase without any voiding. One of the complexities of this model was this area where they enabled a large post void residual volume of 10 mils after each void.

Equally, in other iterations of this model, the research group looked at the activity against biofilms. And they did this by introducing glass beads into the bladder. Again, the testing was a variety of different antimicrobials against a

Page 72

variety of different pathogens.

More recently, a continuous flow dilution model has been run with a variety of different -- with Fosfomycin (inaudible) against a variety of different uropathogens. And to step you through this model, essentially, it’s run by a fresh media reservoir. Compartment A and Compartment B, which can simulate antimicrobial absorption from the intestinal tract and distribution to the circulatory system. But then most importantly, generating urinary pharmacokinetic concentration time curbs in 16 bladder compartments all run in parallel.

These bladder compartments were controlled by a fourth parasitic pump which did the voiding schedule. In this set up, voiding occurred every four hours during the experimental period. Any drug distribution exposure curve can be generated in this model by just adjusting the antibiotic dose, the flow rate in the compartment. The real benefit of this model is the use of synthetic human urine throughout and also generating data of 16 different uropathogens with a single pharmacokinetic exposure.

Page 73

Some more novel in vitro models apply the use of human cell-based technologies. And in this sense, they recreate the human bladder environment in the uroepithelium cellular structure. Most commonly, they use mono layer of cell lines. But there are also 3D structures in use. And the authors of this review paper highlight the four key factors which should be incorporated into these rather novel UTI models. And they are the tissue architecture, the apical urinary exposure, the simulation of dynamic fluid flow, and also the dynamics of uroepithelium cells stretch as the bladder increases in size.

One of the key interests in this area is how does each of these factors impact on bacterial behavior. In fact, bacterial behavior and potentially facilitating invasion into the cells.

This is another example of one of these novel models. This is a bladder on a chip UTI model. And here, the authors can recapitulate the physiology of bladder filling and voiding and also have an experimental protocol which includes infection, addition of neutrophils by a vascular channel. And

Page 74

then two cycles of antibiotic treatment interspersed by two bacterial growth cycles.

So, these two more novel models highlight some of the complexities that can go into examining the effectiveness of antibiotic therapy in uroepithelium infections.

So, what are the key in vitro factors to consider when designing your bladder infection model? Well, there's a list here and I'll go through some in more details. This is not an exhaustive list. And I've listed down here the extras which some of these more micro models have incorporated such as uroepithelium cells, the host immune response, and that specific environment of the bladder.

So, first thing on the media, specifically, urine is a nutritionally depleted and naturally antimicrobial. But it also an incredibly complex biological waste product. It's hypertonic. It has a low PH, low oxygen contract, high in nitrates and urea, which inhibit a lot of bacterial growth. So, therefore, uropathogens have specific adaptations in order to replicate in this environment.

Page 75

Now, we know that standard laboratory media like (inaudible) and broth does not really reflect bacterial growth kinetics in urine. However, working with human urine is largely impractical, even though you can pull human urine from multiple volunteers, there's going to be variability person to person, batch to batch. There's a short shelf life and no sterilization for this.

The other thing to consider is when running a complex model which uses 10 liters of media a day, the amount of urine that you would need to run, say a 96-hour experiment would be significant. There are, therefore, a variety of customized synthetic alternatives. And these aren't always easy to prepare. Some of them are 18 different chemicals which need to be individually weighed out and added in order.

There is other complexities in the preparation, the risk of precipitation, and incompatibility with some antibiotic formulations. The other thing to consider is that different pathogens can have different growth capacities in

Page 76

different synthetic media. For example, enterococcus faecium grows very poorly in synthetic human urine, despite additions of the yeast extract and peptone.

Secondly, the thing to consider with in vitro models is simulating in vitro urodynamics. Now, normal human urine output is roughly one mil per kilogram per hour. A patient should void at least every six hours. Now, high urine output and large volume, frequent voiding, can reduce the bacterial density without antimicrobial exposure. And this often something that is harnessed clinically in the treatment of UTIs.

So, therefore, the simulation of humanized in vitro flow rates within an in vitro model and a matching voiding schedule can actually provide a surrogate fitness challenge for your introduced uropathogens into the model. This is in such that pathogens added to the model must replicated faster than they are diluted. And they must maintain a bacteria population density that tis not eliminated by voiding.

Another aspect is the actual choice of

Page 77

strains and deciding inoculum that are added to the model. Really, in general, testing should preference E. coli clinical islets from a urinary source and then expand it to additional uropathogen spaces. This is because 34 uropathogenic E. coli remains the most common uropathogen in clinical infections.

Islets should also reflect the full range of the susceptibility profile of the test antimicrobial. This ranges from fully susceptible wild type populations to those islets with low level and high-level resistance. Ideally, they should be the addition of a control anti-disease strain.

Now the starting inoculum added at the beginning of the experiment should reflect the total number of bacteria expected in human infections. However, that number is not certain. Even though the traditional clinical definition of infection is greater than 10 to 5 cfu per mil in a mid-stream urine. But we do know that E. coli counts as low to 10 to the 2 have been shown to be the causes of infection in symptomatic women.

Alternatively, to test resistance

Page 78

suppression, the total number of bacteria added is required to be one log higher than the inverse of the mutation frequency. So, here there is a difference between bacterial density, so CFU per mil, and total bacterial number, which is the CFU count.

When considering your sampling of the model and considering your pharmacodynamic assessments, these are classically quantitative cultures on antibiotic free agar where antibiotic carryover is addressed. Now, modern methodologies may help efficiency in this. There are a range of different methodologies. But these have not really made it into the mainstream published literature in these types of PK/PD dynamic models.

And really, your endpoint assessments are usually the change in bacterial density from your starting point. You can assess the affect over the entire experiment. You can look at the area under the bacterial kill curve. We can look at the emergence of phenotypic resistance and also look at the genomic mechanism of resistance. But also need to consider bacterial persistence and tolerance are important

Page 79

factors in regrowth populations.

Regarding your urinary pharmacokinetic targets, while there is a much larger variability in human urinary antibiotic concentrations compared to plasma concentrations. And this is because there's important human behavioral variables that can greatly impact on antimicrobial concentrations. This is as simple as the amount of fluid intake, urine output, and even the voiding patter. And all of this is above and beyond the normal and more standard predictable PK variance such as absorption, distribution, and elimination.

Therefore, there are inherent challenges to know what specific urinary PK targets should be simulated in a bladder infection model. And ultimately, testing a range of exposures will help cover the expected normal human variation.

In the same that we take PD samples, PK samples should also be collected from the model and use that to quantify the in vitro antimicrobial concentration, peak concentrations, rate of decline, prof measurements. These really enable us to

Page 80

establish the area under the curve that peak concentration and the time of MIC.

Ultimately, these levels, and they can be representative samples, really ensure that the in vitro variables, such as the flow rate and volume have been maintained to achieve these targets. Ultimately, the drug stability needs to be confirmed before these experiments, such as -- and if not stable, then various calculations need to be made to address that.

Now the method of quantification really depends on the availability of resources, HVLC and LCM mess methods are preferable, but bioassays are also commonly used.

At this point, I'd like to hand over to Jason, who will discuss the comparability to animal models and the correlation with clinical outcomes. Thank you.

DR. TRAUTMAN: All right, I will be introducing our next speaker who is Dr. Keith Rodvold. Dr. Rodvold is a distinguished professor at the University of Illinois, Chicago. He is also a professor of pharmacy in medicine at the College of

Page 81

Medicine at University of Illinois, Chicago. Dr. Rodvold's research interests is in the areas of clinical pharmacokinetics and pharmacodynamics of anti-infective agents for infectious disease. Dr. Rodvold has authored more that 180 original research and review publications, 80 book chapters, and has edited six textbooks. And we're giving him 10 minutes to share his expertise. Dr. Rodvold?

DR. RODVOLD: Hi, good morning. As you can see on the style slide, I'm going to taking into consideration the PK/PD that you might consider in drug development if you're going for the indication of uncomplicated UTIs. Next slide, please.

These are my disclosures. I consult for most everyone in the industry at some place and time. These are the last 12 months in Janssen. Safety board has nothing to do with UTIs. Next slide.

So, we're going to look at both clinical and nonclinical information and trying to make decision making for the indication, particularly dose selection and breakpoint setting. And then consideration evidence of plasma versus urine specific

Page 82

breakpoints. I'll kind of slip between these a little bit at different times the way the outline goes. Next slide.

So, if you take a look at first, the industry guidance for uncomplicated UTI and focus in on the PK/PD and dose selection section, you'd see this as the major outline that's included. In fact, it's the complete outline. So, PK should be considered, not surprisingly, particularly secretion in the urine. Urinary concentrations are important when bacterial infections are limited to the lower urinary tract infections. Notice that serum is not emphasized here. They recommend doing a Phase 2 study, which in drug development these days, we like to try to avoid Phase 2 at time. But if you're really trying to get drugs through for resistance cases. And also, sponsor should also consider sampling in Phase 3 studies. Next slide.

In comparison -- next slide, please. In comparison, this is the outline for complicated UTIs. I just show you the contrast here. Here they emphasize evaluating in vitro models and animal

Page 83

models, which you didn't see in the previous slide and two previous speakers have outlined information for you there. Adequate urine concentrations, again, and serum concentrations, just because bacterium may be involved and/or renal parenchymal involved so you're getting the upper track.

And then a lot of more information about PK/PD issues, what other studies may need to do in Phase 1 and Phase 2, particularly for renal impairment because of the likelihood is you're going to have a wider range of patients than what you might see in uncomplicated UTIs. And then the aspect of Phase 2 and Phase 3 in dose ranging studies. Next slide.

Well, how did we get to urinary concentrations? This is an old, old study. You can see this is published in Medicine in 1965 by the Hopkins group. Stamey is the lead author here. Remember the date of this. This is back in 1965. So, the antibiotics look old. They were new at that time. I give you the doses they recommended. Note that no column has average serum concentrations, which are

Page 84

relatively low throughout the whole list.

Then the average urinary concentrations. And then finally on the final column here is in vitro test concentrations. This is actually, you know, give you kind of an MIC data for this information that they had at that time or what they used for a marker. And you can see that the serum concentrations against the in vitro susceptibility concentrations are dramatically different. 100, maybe 1000 times difference. Versus urinary concentrations, really kind of are in line with potential efficacy.

I highlight to you like nitrofurantoin has serum less than one and urine concentrations of 100. So, if you use the serum, you might say, "Jeez, it might not work." But if you use the urine, you say, "Well, there should be adequate amount of drug there." Next slide.

This is one of four studies that have commonly quoted about urinary antibiotic concentrations for UTIs, both uncomplicated and a little bit of complicated. The Gould study and the

Page 85

McCabe Jackson study are really emphasize patients with pyelonephritis. But as you saw, some people would consider some of the pyelonephritis in males that also might be considered uncomplicated UTIs.

The Stamey study really looked at more urinary tract infection of mainly uncomplicated, again. The nice thing about these studies is they give a lot of detail, more than what you maybe see in current studies. So, they're worth going back to look at. All of them emphasize urinary concentrations are important. That's the key. That's how that information really got going. Next slide.

Well, when you look at PK/PD in development, in clinical development, we're really combining here (inaudible) no flavor. We're doing preclinical and clinical pharmacology, the PK part of it. The PD is really coming from microbiological. So, we tried to create PK/PD. The ultimate is here is to get dose optimization. And also, the aspect of the -- when I say dosage I'm talking about not only the dose but also the duration of therapy.

The goal is to maximize the efficacy.

Page 86

We have not done this very well historical, but also try to do resistance suppression. And then you have to balance it against toxicity issues that are associated with the agent that you're monitoring. Next slide, please.

When you look at drug development here, if we can look at some characteristics, the FDA is very interested in this. In fact, they have an RFP out now in clinical pharmacology. Bacteria characteristics and growth, you've already from pervious speakers that you have to account for that information and understand the pathogen and pathogens you're testing. And whether or not urinary parameters have an influence upon the agents that you're going to test, both the agent that you may be comparing it to as well as the agent that you're interested in developing.

Applications of this has to be done to new agents in clinical development or if you're bringing an agent that has not been approved previously in the United States and you're trying to bring it now into the United States, it probably needs

Page 87

to go back and make sure that you've looked at this information so that you can look at the aspect of understanding the drug better compared to maybe when it was earlier developed 10, 20 years ago. I'll show you some examples in a moment. Next slide.

This is data from Fosfomycin. Most of it's coming from either Dr. Abbott which previously presented or our own lab. This is Fosfomycin that occurs on the left-hand side, as showing you the aspect of log colony forming units against time. This is actually urine concentrations from healthy volunteers in a study that was sponsored by NIH and ARLG.

And what you see here, real briefly to give you the overview, is that the E. coli kills very well. It struggles with proteas and in Klebsiella pneumonia. What is important for all these studies is Fosfomycin has its activity influenced by PH. Again, the previous slide, the characteristics of knowing. Discriminating between E. coli and Klebsiella is very important, particular the data from Abbott's lab and others has resistance of sub populations.

Page 88

High level resistance sub population in E. coli, that's not usually identified by MIC testing. The presence of glucose-6-phosphat that is often important in the testing and including in part of testing for serum concentration or serum activity for bacteria isn't really present in the urine. So, it is a difference between in vivo activity in the sense of lacing G-6-P, which is figure A here, versus in figure B when it is present.

And then finally, challenges on dosing and clinical breakpoint in particular questions the use of it against Klebsiella and pneumonia at all. I think oftentimes people get mixed up by looking at the oral use of Fosfomycin, which is this data reflecting, versus the IV use of it where you're using doses that are sixfold, you know, 18 grams a day, maybe 24 grams a day for multidrug resistant pathogens. You've got to bring it back and focus on what you're doing. You've got to bring it back and focus on site of the infection. Next slide.

The other issues that are important in drug development is the activity and microbial agent,

Page 89

so understanding how does it kill, what does it take to suppress resistance in the presence of the bacteria you're talking about. You know, traditional PK/PD parameters are usually serum related, have been utilized here. But also, you can use urinary PD parameters such (inaudible) inhibitory concentration or (inaudible) tighter concentrations, which we used in the study I previously showed you.

PK/PD parameters for treatment of complicated UTI may not necessarily come back to be appropriate for uncomplicated UTIs. Again, we lack data here. In fact, a lot of things in PK and PD development for uncomplicated urinary tract infections really hasn't been implemented and looked at like what we've done for bacterial concentrations for serum, using it for pneumonia, respiratory tract, other respiratory fact infections, bacteremia.

And finally, exposure response approach to define urinary specific breakpoints, which I'll come back to, probably needs a little bit of the in vitro data, but also the in vivo animal models here to maybe quantify what is the most important part here.

Page 90

Again, as you already heard, it's difficult in the animal models to determine breakpoints. So, it's a chronic accumulation of all this information. Next slide, please.

One of the important things, though, is to find out what causes efficacy. In other words, what's the endpoint. Normally, when you think of UTIs, you think of net bacterial stasis because it's clinical efficacy, lower margin. And that's defined for you on the top part of it. One log CFUs is usually considered where clinical efficacy on the upper margin or this higher inoculum lack of source control and great morbidity and mortality potentially associated with it.

You notice, finally, the 2-log is in here. That's really resistance prevention or suppression. So, you have this wide range. We specifically don't know necessarily which is the best here for uncomplicated UTIs. As you've heard previously, some people start with the one log method in a complicated UTI model and then bring it back to uncomplicated UTI. Many other people would argue I

Page 91

don't really want to do that experiment. And maybe net bacterial stasis is the best thing I can use here because the high concentrations in urine.

You know, we don't have established relationships to prove that, at least in my interpretation of the literature and other drug development. Next slide.

The final part of this is when you're doing a TKD PD parameters, when you're trying to use them, you're going to have to add all these pieces together. And that includes the models, the aspect of modeling it against kill curves, and then analysis of it, both in the beginning of preclinical, clinical, and even what comes out of the Phase 3 studies, to get to the point of being able to optimize dosing regiments and succenting breakpoints.

I think what's different here compared to say PKP development for other indications is that what Jason Roberts and his colleague presented previously, you have these PK/PD bladder infection levels, which is a new avenue here to evaluate, particularly for uncomplicated UTIs. Now most of

Page 92

that's been done in a limited number of labs. So, probably needs more standardization across the board. More validation so that we understand it better. What has been done has been done very eloquently at this point.

But there's ins and outs, as they showed you, in these studies in how to use them exactly at drug development is still to be timed. Next slide.

When you look at the development of nonclinical -- of modern days drugs for uncomplicated UTIs and geptotidacin is one of the few examples I can give you. This is a nice paper that was published in the March of AAC. It shows the preclinical information and non-clinical information of in vitro against a lot of islets, including some resistant islets. The animal model, here in the bladder data, I'm showing you just like what was shown you previously. It confirmed the dosing regime that they wanted to use here.

And then finally, they did prevention of resistance in the hollow-fiber model, noting that

Page 93

you had to get way up to the right before you kept depression down. Next slide.

Then from a clinical point of view, they did a lot of different human clinical trials, both Phase 1 and Phase 2. In the Phase 2, they did an uncomplicated, small uncomplicated UTI study. They confirmed the urinary concentration time profile here, which is very important. Which means you have to sample often and count for the variability. These are concentrations are much greater than what you see in serum. So, it's kind of again, this low, low serum concentrations which are actually not low. They're six to eight micrograms to mil. But against the urine, you're seeing a range of between 200 and 1,000.

And then finally, tying all that together, PK/PD targets, and in this case, it was area of the curved AMIC rations that what it took for one log reduction, what it took for suppression. And then looking against urinary exposure. And in those cases, they used a higher MIC value of four here to account for resistant to other agents. You can see they can hit both of those targets. I think that's a very

Page 94

important step that needs to be always done in these studies in the future. Next slide. Next slide please.

This is more of a reference for you to look at other places where you can summarize PK/PD data as well modeling and consideration that needs to be done. This needed to be put in context to uncomplicated UTIs. Next slide, please.

Now, can we use this information to get to exposure response approaches to define urinary specific breakpoints. Next slide.

This is EUCAST on the left-hand side and CLSI on the right-hand side, creating breakpoints. You can see if you look at both the figure here but also the scripters on the right-hand side, is that there's a lot of things they're considering to developing breakpoints these days, including different databases, interpretation from different places worldwide in public health, PK/PD correlations to affect.

So, with this, this is how differs compare to what historically, initially, comes out in

Page 95

a package insert from the FDA. Next slide.

Now, in looking at exposure relationships, this is important here. But the problem is we lack this data in many cases. Both in uncomplicated UTIs, but also in other infections. It's very hard to collect, particularly in different types of trials. Again, urine concentrations here may not be able to be collected as easily in a big Phase 3 study. But it needs to be considered here in this aspect of uncomplicated UTIs. Next slide.

This is Group U from CLSI. This is actually reporting of antimicrobial agents, primarily used for UTIs. This what they would consider for interbacterial, staphorsius and species, and enterococcal species of the pathogens that a lab should consider. Next slide.

This slide here, I put together as MIC breakpoints for uncomplicated UTIs only. This is really reflected for interbacterial, only. I'm comparing the CLSI to EUCAST. Some notes here is that you see here some subtitles like A, B, and C. The As mean this is really only a reflection for E. coli.

Page 96

Be is telling you that is only reflection that this is a different agent is used as the prototype to define the MIC here for pivmecillinam. And then cephalexin, while it's listed here, actually cefazolin, which I'll come back to is used as the marker.

You do see differences in the groups, particular Fosfomycin here, much lower breakpoints in the -- urinary specific breakpoints here than compared to CSLI. And that's really what's influenced by the data of Abbott. In our lab, it showed there's significant difference in that even the urinary concentrations that were once thought of for an oral Fosfomycin were far much lower than what we now see. Next slide.

This is cefazolin. This is the difference between what you'd used for that of systemic infections and then uncomplicated infection. It used to be cephalexin. Cefazolin is not the marker used. It's used for oral antibiotics, oral cephalosporins, particular. And specific notes about how you can use it and which antibiotics it would include as well as when you may have to look at other

Page 97

overall resistance.

Again, notice the differences here. This is not measuring in urine. It's still a serum breakpoint that's used here to account for this high urine concentrations. Next slide.

When you implement this, this is data from our own institution, when you do implement, this is what you do, you see a higher incident of percent susceptibility and you start to see a shuffle of who's more susceptible. But that doesn't change, necessarily, clinically how you think of it. This is still a second line agent, the cephalosporins. And that gets confusing for users. If you say it's more susceptible, people then say, "Well, then I should use that one compared to other agents that might be the better choice."

And so, there's an interpretation here of doing this and understanding it in respect to what you get from the laboratory. Next slide.

Finally, as I alluded to, exposure relationships are difficult to characterize here. One of the things is that if you do the PK/PD right in the

Page 98

beginning, you'll have high success rates, so you don't have failure rates that are significant. Then it's hard to sort out what is really needed at that point. This was taken from the EMA guidelines. It gives you good ideas and considerations that need to be considered to do those exposure response relationships. Next slide.

Finally, what I've tried to show you in a very short period of time here is that clinical and nonclinical needs to be incorporated for both old and new agents for this indication. Urine specific points need to be incorporated with the efficacy data that's coming from those models, but also PK/PD analysis, which will be quite complex in using simulations.

The advantage of doing this is, I think, again, as it was emphasized in various things, you're minimizing risk in developing a trial, so you don't get a failure, or you don't get develop that are resistance during it. I'd emphasize the importance of finding the target, finding the suppression rate, and combining those two against what the concentrations are at the site, which is urinary at this point.

Page 99

Final slide, please.

Thank you.

DR. KIM: Great. Thank you, Dr. Rodvold. Really appreciate the presentation describing the application of the clinical and nonclinical PK/PD considerations in drug development decision making for uUTI, both selection as well as breakpoints.

Our next speaker is Janice Tufte. She will be giving us a talk from the patient perspective. We will hear Janice is based in Seattle, Washington and is an involved patient partner in health system research, visual evidence generation, quality improvement, clinical person-centered guidance improvement, clinical person-centered guidance and measurement. She currently serves on an IDSA AIR measurement to EP as an uncomplicated UTI antibiotic stewardship subject matter expert. She previously helped prioritize patient outcomes for an IDSA UTI guideline. With that, I'll turn it over to Janice.

MS. TUFTE: Hi. Thank you for having me here today. My name is Janice Tufte, as was

Page 100

mentioned. I'm going to share a little bit about patient centered considerations and care and lived experience with uUTI as well as complicated UTIs. That's my website. I added this picture because I think UTIs are kind of confusing, sort of a mosaic. And people have similar symptoms but often their outcomes are different or the treatments. This was taken at a quality conference in San Francisco a few years ago. Next slide, please.

So, I added this because this is very important to patients. Really, not may patients, people I know, talk about it other than talking to other women about it or perhaps their spouses or partners. But the truth is it's not something like we would sit around at a dinner conversation and talk about it unless it was clinicians or pathologists or something. So, subject matter people don't talk about. There is a stigma and stress around it, even though it's nothing we should be ashamed of. But there still is.

So, how can we change that discourse from more open conversations on preventative health

Page 101

and treatments for UTIs. Next slide, please.

So, patients wonder, when talking about uncomplicated UTIs, I guess I've been diagnosed with them. And no, you don't need antibiotics. This is a question patients like myself will ask and how can we best treat an uncomplicated UTI? I would prefer choices, at home treatments, prescription options, if deemed necessary, and perhaps more than one prescription option, right, to be personalized as others were talking about.

What can we do to prevent future UTIs? And patients really appreciate answers back by evidence. Next slide, please.

So, UTIs and quality of life. Anybody that has had a UTI knows how uncomfortable they are. It is no walk in the park. This is a park near my home. And truthfully, I wouldn't even want to walk over there because I would feel uncomfortable. So, they do impact individuals' daily activities. And the treatment options have changed. Patients wonder why no antibiotics. Informed shared decision making is very important. I think it's a priority to develop

Page 102

and utilize patient (inaudible) educational materials with visuals. Now plain language for individuals that are English Second Language and/or don't have high health literacy.

And understandable handout so that individuals with UTIs understand more about uncomplicated or complicated UTIs and antibiotics stewardship. Next slide.

So, I was -- You know, I actually do a lot of research on my own. I've co-authored a number of papers, mostly on equity in healthcare. But I did come across this paper, and I wrote to the authors and said could I use this graphic because, really, it's all about communication. And barriers to effective communication in UTI consultation and optimal prescribing, right. This is very important. You know, you have a lack of time, you're limited, it could be telehealth.

There might be an issue, I expect a lot of people would prefer having a same-sex clinician that might understand more about what they're going through. And there often, I'd say, could be

Page 103

miscommunication or misunderstanding regarding the clinician and the patient. And lack of skills and material, right? There just isn't a lot out there.

I mean, I come from very advanced system where we have (inaudible) materials and other things. But I don't see much about UTIs. I have now and then but I think there should be more out there about them and the history of prescribing it. And people will be confused. This is the article that I found. So, it's barriers, communication is very important. How can we break those down? Next slide, please.

So, what are our options when we have those UTI symptoms? I added the person with the bat because I would like to bat that UTI right out of the ballpark within a day. I've learned about new medications today. I wasn't aware of the one day. I actually brought that up in the guideline outcome. Why don't we have one day opportunities, right. So, I'm going to talk to my clinicians about it next time.

They're symptomatic with urge frequency and pain, as Dr. Trautner and others have mentioned.

Page 104

Bloated stomach, urine incontinence, change in stream. But the first time someone has a UTI, they do not know what's going on. They end up in the ED. There's high utilization rates. I work with QIO, QIMs. I do know that there's high utilization rats for UTIs.

So, how can we do something to get information out there early. And peers, family, or internet are usually first line advisors, and they need to know how to be proactive to avoid UTIs. And as I mentioned co-designing and developing and have easily available public facing educational materials really is a must. And there are overprescribed antibiotics can result in antibiotic resistant infections later. You know, you've shared some of that with the 20 percent with the different medications and I've experienced it myself.

And being able to recognize, if at all possible, between a complicated or uncomplicated UTI, but still, I know, myself, I'm wondering is this really uncomplicated or is it complicated? So, it's a strange call. So, over the counter drugs, patients will talk about versus prescriptions. But I think

Page 105

consulting nursers can play a very big line a place here and should be widely used as far as when somebody should go to a clinician. Next slide, please.

So, I first had UTI when I was young. And I was given antibiotics. I didn't know what it was. I had hematuria, we don't know why I had that, either. I had it throughout my life. I didn't pain. I didn't realize that often accompanied it. But when I was older, I was working at a hotel in Montpelier, Vermont, and all of my coworkers were drinking cranberry juice a lot. I was like, "Wow, why do you drink that?" They said, "Oh, to stop urinary tract infection." I had never heard that. My mother was a nurse. And out in the west coast it wasn't as prominent as it was on the east coast.

So, I actually picked that up and I do believe cranberry tablets and capsules have helped to prevent it. I know the research is kind of out there on that. I was prescribed antibiotics. I had them, actually, in my formulary. And I could just get a prescription whenever I felt like it because I had so many when I was in my middle -- you know in my 20s and

Page 106

30s -- 30s, 40s, actually.

And I want to say when I was looking for, researching for stuff, like recent data, like Barbara Trautner had mentioned, there's not a lot out there. But I did find this, "Worldwide Urinary Tract Infection Treatment Industry Expected to reach $39 billion by 2027." The report cost $2,500 for a single PDF. That's way out of line for myself. But I think right now, it's over a $10 billion industry. So, this is not even talking about the people that are impacted, just economic factors. Next slide, please.

So, what do we hear? Everybody knows drink lots of water. But as time goes on, even here in the United States, we have areas that are similar to third world countries where the water is not drinkable and it's not clean to bathe in, actually. I mean, you could acquire UTI from it. So, it's also expensive for bottled water. I have traveled quite a bit. And I do know I buy bottled water in some states, and this is very expensive. The average family, under inflation, I don't know how they can really manage this. This is something else we need to

Page 107

deal with at a holistic level. Next slide, please.

So, antibiotic resistance strains and stewardship, I love this picture. It's exactly how you feel. I mentioned I have prescriptions on file. But one time I had a very serious strain that was resistant. They did a lab work on it. Then the antibiotics didn't respond. I had another lab done. Those antibiotics -- I end up having three different types of antibiotics over a period of weeks. I was very uncomfortable. We found out, my clinician told me that there was a cluster in Seattle and downtown, people that worked downtown, that lived downtown. So, we're not really sure where it came from, but it was a cluster of antibiotic resistant strain. Next slide, please.

So, what do I as a patient -- Oops, next slide. What do I want? So, I think we're conductors in our own healthcare. The doctors -- oops, back one slide. Anyway -- I'll go to UTI lifecycle stages. Well, here. Here, clinicians look at UTIs holistically. This is what patients want. What can I and other patients due to prevent symptoms?

Page 108

You really want to know that. Over the counter or home remedies. The one with the dye doesn't make a difference. They still dye and they can stain. People aren't aware of that.

Appropriate prescriptions, if found necessarily, for uncomplicated UTIs. At home tests, possible, for uUTIs, that would be great. This is a patient lifestyle process. A few people have brought this up. I saw life stages somewhere. Different reasons and treatments for UTIs at different stages in life. But I want my treatment preferences, values, and goals respected and documented. Next slide, please.

That would be patient centered care. I kind of made some of this up, but it's from experience and from what I know in looking up. The infant to adolescence, obvious, there's many reasons that infants can, we've mentioned some today. It could be diapering, weakened immune system, urinary surgery history, you know, bath water. And then as you go young adulthood and childbearing years, pregnancy -- Well, first of all, the honeymoon disorder, which

Page 109

might be the time when most people actually discover this UTI, if they haven't been told about it before and how they can mitigate it.

I just comment on some of the issues there. Pregnancy and any -- pregnancy can cause UTI feeling symptoms, as well as, perhaps, a higher propensity. I'm not really sure about that. I'm an older adult now. So, as we age, we have diminished capacity to care for oneself, bladder obstruction, enlargement of the prostate. This is where you see more men with UTIs. Lack of estrogen in the urogenital track, vagina apathy, and many reasons as mentioned earlier.

And the estrogen is really a big deal. And I learned about this from a doctor at a physicians meeting and she was mentioning about the cost of it. I ended up needed it later, having multiple UTI like symptoms. But you know, I was not aware of that before. So, the word isn't out there about how people can prevent it and prevent going to their clinicians over and over by something as simple as estrogen. Next slide, please.

Page 110

So, I just want to thank you. I use to monitor hummingbirds because I believe this patient partners working with scientists like you and the FDA, that we can take what we learn here and carry it forward to our clinicians, to other patient partners and community. And the same, you know, we can bring to you what our community and other patients are talking about. Thank you very much. I look forward to questions if you have any.

DR. TRAUTMAN: Thank you very much, Janice, particularly taking the time today and preparing your perspectives to share with us. I appreciate that. We all appreciate that.

I'll be introducing now Valerie Price, also a patient representative. Valerie Sarah Price is a Canadian diplomat from Quebec City, Canada. She has lived with her current urinary tract infections for over 40 years. And this is her own words, has been diagnosed with every type of bacteria under the sun, including ESPLs and multi-drug resistant pathogens. Due to her work as a diplomat, she's lived overseas and travelled extensively. As a result, has been

Page 111

treated for UTIs in over a dozen countries on three continents.

This is her first experience as a patient representative. Also, she -- because of her work as a diplomat has been called out of the country to somewhere very remote without wi-fi, so her presentation has been prerecorded for today.

MS. PRICE: Good afternoon, my name is Valerie Sarah Price. First of all, I would like to thank the organizers for inviting me today. It's not often that patients are given the chance to share their perspectives. So, I jump on the opportunity. I'm sorry I cannot be there in person or virtually live. I am currently in Southeast Asia for work amongst my suitcases. So, not at all on the same time zone for this. (inaudible) for the same reasons I wasn't able to put my slides together, so apologies for that.

I should mention here that it is my very first experience acting as a patient representative. So, please bear with me. I'm not sure if my views will be relevant or useful to you but

Page 112

I'll do my best. I want to emphasize that the views that I share with you today are solely my own. I don't represent any organization or group of patients or institution.

I also acknowledge that the experience is really my own experience and, to a certain extent, comes from a position of privilege. Most notably, I'm Canadian. So, I've always had access to universal healthcare. Certainly not perfect or always efficient, but healthcare all the same. A bit of background on myself. I'm Canadian from Quebec City. I'll pass on disclosing my age, but let's just say I'm middle-aged. I've lived with UTIs for as long as I can remember.

One thing you should know about me and UTIs is I have an underlying neurological condition since birth, hydronephrosis, for which I've had five major surgeries as well as nephrostomies during childhood and my pregnancies. So, even though this workshop focuses on uncomplicated UTI, full disclosure, often my UTI are considered complicated. This being said, they are not chronic. 95 percent of

Page 113

the time, they remain lower UTIs.

Something that is important for me to say is despite my condition, I've managed to live, so far, a full life. I'm married, I have two children. Though the pregnancies were very difficult with numerous UTIs, pyelonephritis, and nephrostomies. I've given birth to two healthy children. In fact, my 18-year-old son is just arrived in Greece for a weeklong vacation with his friends with no parents. So, little bit nervous about that.

I'm physically active. I've climbed mountains. As a diplomat and humanitarian, I've lived and worked on three continents, including in conflict zones. However, this condition can be very debilitating. I have had a lot of UTIs in my life. On average, on a good year, I'll have four or five. But on a bad year, I can get 12 to 15 UTIs. I've been infected by literally every bacteria. Of course, the usual suspects like E. coli and (inaudible), but also Klebbsiella, Pseudomonas, Stephioca. I've had ESVL producing bacteria, as well as multi-drug resistant pathogens.

Page 114

Since I've lived in several countries for work, I've been able to notice how the environment affect the kind of bacteria I'm infected with. For instance, when I worked in East Africa, I picked up a lot of drug resistant infections, notably because of the wide availability of antibiotics over the country and ensuing resistance. I've been treated with majority of existing antibiotics, both in pill form and intravenous, in the case of ESBL or multi-drug resistant, depending on the severity of the infection, the type of bacteria.

I've been given the same antibiotics for courses of either three, five, seven, ten days. The duration of treatment was based on the treatment guidelines, but also depended on the individual assessment of the doctor. And sometimes, me pushing a little bit. There's so much I could say and had I been there in person, I might have been able to better gauge what information is useful to this particular group. But in the absence of this, I will just focus on three key messages.

Number one, treatment of UTIs, I'll

Page 115

start with an accurate diagnosis. So, when discussing this presentation with the organizers and other people, I raised the issue of diagnostic tools and how unreliable they can be. I was told this workshop focuses on the development of new antibiotic treatments and doesn't deal with diagnostic tools. But from the perspective of patient, these are two very, very closely linked.

I'll describe to you something that had happened to me a gazillion times, as well as thousands of women out there and me. I feel symptoms of a UTI. I know I have a UTI. I go to the doctor. The doctor does a culture. Two days later it comes back negative. So, the doctor tells me, "Well, you don't have an infection, so I can't treat you with the antibiotics." Well, I know that I do have an infection. So, I go back home, and I spend the next few days suffering greatly. And my condition deteriorates.

So, sure enough, a week later, I find myself in the same doctor's office. Does a culture, comes back positive, and I'm given a treatment.

Page 116

There's a problem with the diagnostic tools. I'm not a microbiologist, but the conclusion I've come to is that the threshold for positive culture is often too high. And thus, it fails to detect real, active infections. The culture as we know it today is certainly an invaluable tool and is good enough. But is failing too many patients.

When you don't treat an infection early, it gets worse. This means more suffering for the patient and more damage to the bladder and urinary tract infections -- sorry, organs.

Number two, be your patient's ally. This means, one, listening to your patient, and two, educating your patient. Very often as patients, we feel so isolated and alone. So, please take the time to really listen to your patient. They are your primary and best source of information to develop a treatment plan. I've already mentioned the issues of diagnostic tools. But the same goes for the choice of antibiotics. A culture might say that a bacteria is sensitive to a particular antibiotic, but it's too often happens that in the next few days, my symptoms

Page 117

don't improve, they actually get worse. I'm still sick.

Yet, I've had doctors who will say, "Well, you know, it's sensitive in the culture, so I'm not changing." So, second way to be your patient's ally is to educate your patients. I know the doctors don't have much time for each patient. In the Canadian system, for instance, a GP will have five, six minutes to see one patient. But please try to use this time to treat your patient with intellectual dignity and educate them.

For instance, why are you prescribing this specific antibiotic? What are the common side effects? If there are side effects, what is their actual likelihood? Are they potentially serious but as likely as being hit by thunder? Listening to your patient and educating your patient makes such a difference.

I know this because last year I was lucky enough to meet an infectious disease specialist who literally changed my life. I won't say her name, but she knows who she is. She can't cure UTIs, or she

Page 118

can't cure me anymore than any other doctor did. But because she took the time to really listen to me and to educate me on the latest resource -- For instance, she told me about phages, which I never heard about and explained to me intracellular bacterial communities. Although I'm a pretty well-informed patient, she taught me so much about my condition and, thus, I was better able to interpret my symptoms.

IK now that not every patient is interested in this. But take the time to gauge the interest of your patient and use little opportunities to educate them. So, thanks to this doctor, for the first time in my life, I felt less alone. It's priceless. It's really changed my life. So, I take this opportunity for this doctor, she knows who she is, thank you again so much.

I see I'm running out of time, so I'll go very quickly for number three. Just stop the silos, please. In the same way that diagnostic tools are not entirely separate from treatment options, you cannot make a clearcut distinction between uncomplicated UTIs and chronic UTIs, for instance.

Page 119

Often one leads to the other.

You may have heard of a growing community of patients and doctors who subscribe to the theory of embedded UTIs. These are patients who have spent decades doing trial and error, short courses of different antibiotics that actually go nowhere. They are desperate. There is so much suffering. So, they end up going to see doctors who will prescribe full dose antibiotics and really hardcore antibiotics for years. It's a bit of a rogue movement at the moment but it is gaining strength simply because the UTI establishment is continuing to use the same approaches and not addressing the suffering of so many people out there.

Anyway, I will leave it at this. I want to thank you again for giving me this opportunity. I wish you a successful workshop and greetings from Northern Thailand.

DR. KIM: Thank you to both Valerie and Janice for sharing their patient perspective with us. At this time, we're going to have our public comment speaker, Dr. Cornelius Clancy. And he is presenting

Page 120

on behalf of IDSA. Dr. Clancy is professor of medicine and an associate chief of infectious disease at the University of Pittsburgh. He's also a vice chair of the Infectious Disease Society of the American Committee on Antimicrobial Resistance. He is an infectious disease physician who also conducts clinical and laboratorial research on antimicrobial resistance among bacteria and fungi. With that, I'll turn it over to you, Dr. Clancy.

DR. CLANCY: Great, thank you. Looks like everyone can hear me, at least according to my computer. I am presenting on behalf of the Infectious Disease Society, or IDSA, this morning. Thank you for the opportunity for us to offer some public commentary on the extremely important issue of antibiotic development. I'll add that I'm chief of infectious diseases in the VA Pittsburgh Healthcare system. So, to give an acknowledgement of the important role of the VA in providing healthcare to our veterans. Next slide, please.

So, here are some of the care points I'll talk about, focusing primarily on the urgent need

Page 121

for novel antimicrobials to treat the ongoing and what will be increasing problem of antimicrobial resistant bacterial infections for UTIs and, of course, other indications. I'll make the point that it's important for us to study UTIs because of their own impact on human health, as made clear in the previous presentations, but also because UTI studies offer a path forward for the approval of antibiotics that will be useful in other settings.

And then I'll talk about the IDSA's society feelings about the importance of clinically meaningful endpoints in studies, the roles of stewardship and guidelines in improving care and outcomes. And then efforts that, I think, as a community, we need to undertake to help the antibiotic development pipeline. Next slide, please.

So, Dr. Trautner, Janice Tufte, Valerie Price did a terrific job, I think, giving a sense of the lay of the land on the clinical treatment of UTIs and some of the shortcomings and knowledge gaps that currently exist. We agree on the need for well designed clinical trials and other research to

Page 122

identify and address these important knowledge gaps. We need to identify effective new drugs for the treatment of uUTIs. We need information on optimal duration of treatment, including short-course therapy that might provide excellent care while also improving stewardship endpoints.

We agree on the need for data in populations that have been historically understudied in this space, including pregnant women, diabetics, transgender individuals, and UTIs in me. We agree on the need for advancing understanding of endpoints like asymptomatic bacteriuria and intermittent culture positivity in the urinary tract. I think as really made clear in the last two talks, the IDSA is well aware of the need for patient focused and patient directed treatment algorithms. And also, on the need for involving patients in our research and in our practices and being partners in care with them. Next slide, please.

One of the top priorities of the IDSA, of course, is to partner with other constituencies in ensuring that we have a robust, healthy, viable, and

Page 123

sustainable pipeline for the development of new antibiotics, other antimicrobials, against antimicrobial resistant pathogens. I probably don't need to tell people participating in this meeting, the last FDA antibiotic approval was in 2019, November 2019. In 2019, that year, five million people died with drug resistant antimicrobial infections. And over a million of these deaths were directly caused by the AMR infection.

The lack of antibiotic options worsens outcomes for patients, really, across the whole sweep of medicine. Everything from uncomplicated urinary tract infections in people living, working in the community, to patients undergoing high end medical care, cancer, chemotherapy, transplant patient, hip and joint replacement. And emergent public health threats are linked to antimicrobial resistant and the need to be able to treat super infections as we've seen with diseases like COVID, as we see an awful lot with opioid abuse and the challenges that presents throughout much of our country.

So, we need drugs against all flavors

Page 124

of antimicrobial resistant bacteria and fungi. And particularly relevant to the urinary tract infections, we particular need agents against gram negative bacteria. And in addition to urinary tract infections, these are problems in ventilator and hospital associated pneumonia, blood stream infections, sepsis.

So, a point we'd like to make and reiterate is that trials of uncomplicated urinary tract infections are important for the insights they provide into optimally managing these problems specifically. But from a regulatory perspective, uUTI trials are the pathway to getting drugs against AMR pathogens approved and available for use in potentially other clinical settings, as well. So, urinary tract infections and research on urinary tract infections is absolutely crucial to multiple aspects of not only health care delivery but antibiotic development. Next slide, please.

So, along these lines, obviously, the recent news with tebipenem was a disappointment to the ID community and to the medical and public health

Page 125

communities more broadly. People here are aware tebipenem was an oral carbapenem with activity, among other things, against extended spectrum beta-lactamase producing, or ESBL, enterobacterial. Valerie alluded to the challenges these have presented in her own life. These are particularly problematic pathogens in that ESBL E. coli has increased by 50 percent as a cause of disease in the United States over the course of the teens.

And community acquired infections due to ESBL pathogens really have very few treatment options. In many cases now, we're reduced to the use of parenteral antibiotics to treat these infections. So, the regulatory challenges faced by tebipenem as potential oral option to treat ESBL infection, including in with people with uncomplicated community acquired infections, is really a blow to our potential treatment options.

As you know, Spero has reduced its workforce by 75 percent over the past couple of weeks. One of our asks, I think, as a society would be for greater transparency and communication in episodes

Page 126

like this as to what has happened and what are the events transpiring that have led to regulatory hurdles or Snafus, particularly after the publication of data and promising new drugs that offer treatment options.

And we're concerned, not only for the direct impact on the treatment of the infections that drugs like this are designed to attack, but also potential downstream affect it may have on developers considering trying to develop drugs in this space. We already face enough challenges with this, as is. So, more transparent, and open communication between all constituencies would be desirable. Next slide, please.

Another ask in clinical trials and other studies is to focus on clinically meaningful endpoints for urinary tract infections. The society feels endpoints should take a particular focus on clinical improvement and not necessarily on microbalactic eradication. Some of the challenges presented by Dr. Trautner and interpreting and understanding the meaning of things like asymptomatic bacteriuria or culture positivity following courses of

Page 127

treatment are areas that should be priorities for ongoing and future studies.

Clearly, these are areas that fuel a lot of the inappropriate antibiotic use that we have, which in turn leads to more antimicrobial resistance. Next slide, please.

And we also support measures to promote the optimal use of new, as well as existing, agents. And particularly for the novel anti-gram-negative agents that might be coming down the pipe, which will be used for urinary tract and other infections. We support the post approval studies that can gather clinically relevant data, particularly infections of which there is not enough data to support an indication upon approval.

We support studies to understand and promote stewardship programs around the optimal use of new agents as well as measures that will improve funding and staffing for stewardship programs nationally and the key to expansion of stewardship programs to all healthcare settings. Along these lines, the PASTEUR Act currently being considered by

Page 128

the United States Congress has specific measures within there to support stewardship within the United States. And the IDSA supports the PASTEUR Act's endeavors in this area.

IDSA also realizes some responsibility in more timely dissemination of more clinically relevant society guidelines. Dr. Trautner spoke about the earlier and now what will be updated UTI guidelines. IDSA recognized that a decade between interactions of our guidelines is really unacceptable for guiding clinicians in their treatment decisions. But also, for drug developers and other people bringing new product online, there needs to be more timely and clinically relevant recommendations about how to fold these into treatment armamentariums in a rational and responsible way.

And measures have been taken, including with recent guidance documents, for example, on the treatment of multi-drug resistant gram-negative infections that IDSA has put out and will be updating on an annual basis in sort of a more real time effort to have guidance and guidelines in place. Next slide,

Page 129

please.

I'll just conclude by saying the IDSA does recognize the fragility of the antimicrobial development pipeline. It's important to the whole of medicine. The challenges faced by drug development are well known to a large number of people on this call. But absent sustainable and viable pipeline, the whole of modern medicine really faces major, major challenges. Along these lines, we do support the PASTEUR Act, which will provide something of a subscription model for antibiotic development, as well as stewardship and AMR surveillance measures.

So, this in front of Congress right now. We encourage everyone, society members and not, to press Congress and their representatives to pass PASTEUR this year. So, with that, I'll close on behalf of the IDSA. Thank you for putting this most important forum together and for having us provide some public commentary on it. Thank you.

DR. KIM: Thank you, Dr. Clancy for the public comments. At this time, I'm in your way for the lunch break. I have just a few short words and

Page 130

then get out of your way. So, Trautner and I want to thank all the speakers this morning for their excellent presentation. They were very comprehensive, informative, and thoughtful, which is no small feat with the time restrictions you all faced. It is now time for the lunch break. So, please rejoin us at 12:20 for Session 2.

(Break)

DR. NATARAJAN: All right. I think we can get started. Welcome to Session 2 of today's workshop which will be about trial design challenges and considerations. My name is Mukil Natarajan. I work here at the FDA. And co-moderating with is Kalpana Gupta from Boston University. So, I think we'll just go ahead and get started. So, I'll turn it over to her to introduce the first speaker.

DR. GUPTA: Great. Thank you. Hi, everybody. So, I'm Kal Gupta. I'm the chief of infectious diseases at VA Boston and also the associate chief of staff there. And it's a pleasure to co-moderate this session. And our first speaker is Dr. Natarajan, actually. He joined the FDA in 2018

Page 131

and is a medical officer in the Division of Anti-infectives in the Center for Drug Evaluation and Research at the FDA.

He received his MD from Duke University and completed internal medicine residency training at the University of Michigan and his ID fellowship at NIAID. And we're really thrilled to have him speak with us today. So, thank you.

DR. NATARAJAN: Great. Can I have my first slide, please? All right. Thank you. So, today, I'm going to be speaking about the FDA's perspective on uUTI trial design. Next slide, please. So, to introduce the talk, I'm going to provide an overview of our division's current thinking on the development of drugs for uncomplicated urinary tract infections.

We have a pub -- We do have a published guidance for industry on this topic from August of 2019. So, please refer to that for additional details. I've included the link with the guidance here in the slide. We also recommend discussing the plan for any specific drug with the division early in

Page 132

the development process. Next slide, please. So, some background, first with the definition, as we've heard several definitions for uncomplicated urinary tract infection.

For the purposes of this talk, it's defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen and culture along with local signs and symptoms such as lower abdominal discomfort and dysuria. uUTIs, also known as acute cystitis, occur in women with normal anatomy and are not accompanied by systemic signs or symptoms such as fever or costovertebral angle pain.

UTIs in males are characterized as complicated UTIs in this definition, because these infections occur in association with urological abnormalities such as instrumentation or bladder outlet obstruction including benign prosthetic hyperplasia. Next slide, please. So, some words on appropriate trial design for a uUTI. We would want randomized, double-blind, controlled trials in female patients with uUTI.

And these studies could have an active

Page 133

control, and in which case, most likely they'd use a noninferiority design, or they could have a superiority design, or they could have a placebo control. And in which case, they would have a superiority design. Regardless of the study design, the safety of patients should be insured in the design of the studies, especially when a placebo is used.

And in general, we would want two adequate and well controlled. However, a single trial may be acceptable if it's supported by confirmatory evidence such as a trial in another indication, for example, complicated UTI. Next slide, please. So, I'm going to spend a moment on the active comparator for noninferiority studies. This active comparator should be considered standard of care for treatment for uUTI in the United States.

And when we make this determination, we consider several things including recommendations by authoritative scientific bodies, for example, the IDSA, that are based on clinical evidence and other reliable information that reflects current clinical practice.

Page 134

In general, the active comparators should be approved by the FDA for uUTI. I've included some possible active comparators here, including trimethoprim-sulfamethoxazole and nitrofurantoin. However, other comparators may be considered, and that would have to be in discussion with the division. Next slide, please.

So, what are the appropriate patient entry criteria for studies with uUTI? So, it should include women with uUTI who have at least two of the following signs or symptoms as mentioned earlier today. They include dysuria, urinary frequency, urinary urgency, and suprapubic pain. Patients should not have signs and symptoms of systemic illness such as fever and chills or other manifestations that would suggest a complicated UTI.

In addition, the urine culture baseline should grow at least -- should grow a single pathogen

at greater than or equal to 10 colony forming units or CFUs per millileter. Next slide, please. Okay. So, now, I'm going to move on to the primary efficacy endpoint, which we recommend be the overall response,

Page 135

which is a composite of clinical and microbiological response that is assessed at a fixed timepoint after randomization.

And this fixed timepoint will depend on the dosing of the drug and the half-life. And this overall response includes the clinical response, by which we mean the resolution of the symptoms of the uUTI that were present at trial entry and the development of no new symptoms.

And the microbiological response is the demonstration that the bacterial pathogen founded

entry has been reduced at less than 10 CFU per mL on urine culture. Next slide, please. So, I'm going to just spend a moment to describe our thinking on the importance of the microbiological response.

So, we acknowledge that urine cultures are rarely obtained at entry and even less so at follow-up in the treatment and management of patients with urine -- with uUTI.

However, in the context of a clinical trial, we believe having a negative follow-up culture ensures that the drug has microbiological activity

Page 136

against the target organisms in an actual human infection, and these data will allow clinicians to be confident that the drug actually will work for their patients and eradicate the organism even if they do not obtain cultures in clinical practice. Next slide, please.

All right. So, moving on to recommended secondary endpoints. So, we'd recommend continued clinical and microbiological response at a later fixed timepoint, approximately 21 to 28 days following randomization. And this will help evaluate sustained response. In addition, we would recommend clinical and microbiological responses be assessed separately at each fixed timepoint assessment, which... If you'd please go to the next slide, I'll cover that next.

So, the study visits, we would recommend a baseline or entry into the study visit, a nontherapy or end-of-therapy visit, and then the post-treatment visits as I've noted. 1.) For the primary endpoint assessment after the end of treatment that would depend on the dosing of the drug, and then a

Page 137

later visit 21 to 28 days after randomization for continued response. Next slide, please.

So, now, I'm going to move on to the appropriate analysis populations for these studies. So, the intend-to-treat or ITT population includes all patients who are randomized in a study. In a subset, is the microbiological intend-to-treat or micro-ITT population which is patients who have a growth of bacterial pathogens on the culture of urine at baseline that is susceptible to the active control drug. And this micro-ITT population should be the primary efficacy population.

And then, lastly, the safety population is all patients who received at least one dose of the drug. Next slide, please. So, touching again on the noninferiority margin for a noninferiority trial. So, we believe that this margin should be 10 percent, and it's supported by historical evidence, which I'll get to later.

However, this noninferiority margin should not be applicable or would not be applicable in a trial where the analysis includes infections that

Page 138

are resistant to the comparative drug. Next slide, please.

I'm going to talk about, overall, the historical data, and I'd like to thank Dan Rubin who's a statistical team leader at FDA for these slides. So, these historical data include two studies from the literature in which patients with uUTI were randomized to receive an active antibacterial drug or a placebo.

And their overall response rates, including clinical and micro response is noted here. And the difference is also noted and was 61 percent or 43.7 percent. And then, these data were used to create a random effects meta-analysis, and that showed the overall response difference of 49 percent with a 95 percent confidence interval of 33 to 65.6 percent. Next slide, please.

So, these data were used to determine the noninferiority margin. So, the lower bound of that confidence interval of 33 percent was discounted 50 percent to account for uncertainties and generalizability issues translating historical treatment effect to a current active control.

Page 139

So, we would conservatively estimate the M1 or treatment difference between active antibacterial treatment and placebo to be 16 percent. And then, considering the clinical acceptable noninferiority margin that preserves the treatment, we came to an M2 or a noninferiority margin of 10 percent for the overall response. Next slide, please.

Now, I'm going to touch on just some possible sample size considerations for a noninferiority trial. So, the micro-ITT population, we estimate should have at least 310 patients per arm.

That's based on the following assumptions: That the active drug and the drug of study of interest or patients are randomized to those arms one to one; the MI margin of 10 percent, as noted previously; success rate of 80 percent; two-sided alpha of 0.05; and 90 percent power.

So, if those assumptions were to change, then the sample size would also change as well. And then, we also note that not all patients would have a bacterial pathogenic baseline. And so, if one assumed 80 percent did, that would result in

Page 140

needing more patients in the ITT population, approximately 388. Next slide, please. So, that concludes my presentation. Thank you for your time.

And now, I'm going to move on to the next speaker, and we will -- who will discuss the regulatory perspectives from the European Medicines Agency. So, I'd like to introduce the speaker, Dr. Botgros. Dr. Botgros is an infectious disease specialist that holds the position of senior scientific officer for the Office of Biological Health Threats and Vaccine Strategy at the European Medicines Agency.

He worked as an ID clinician for 10 years before joining the agency in 2009, a scientific administrator on the pediatric team. From there, he moved to the anti-infectives and vaccine team where he worked with the efficacy and safety-related pre- and post-authorization aspects of centralized marketing authorization applications for the treatment and prevention of infectious diseases. So, I'll now turn it over to Dr. Botgros.

DR. BOTGROS: Thank you very much. I

Page 141

hope you can hear me well, and thanks for having invited me to speak at this public workshop where I'm going to present to you the regulatory perspective from the EMA and our guidance to developers on uncomplicated UTI trials. If I can have the next slide, please.

We've heard today already from previous speakers that the clinical definitions of uncomplicated urinary tract infections in both here and the U.S. are largely coming from clinical practice guidelines. And just to say that the most recent one in Europe is the guideline of the European Association of Urology from earlier this year.

And in this document, uncomplicated UTIs are clearly defined as an acute sporadic upper and/or lower UTI, meaning uncomplicated pyelonephritis and uncomplicated cystitis limited to nonpregnant women with no relevant anatomical and functional abnormalities within the urinary tract.

And on the righthand side of the slide, we see, and we've heard already before from previous speakers that a similar definition is present also in

Page 142

the U.S. IDSA guidance from 2010, the one which is currently being updated. Next slide, please.

It's worth mentioning that the regulatory definition of uUTI for the EMA differs a little bit from the clinical definition, including the one that you see here on the lefthand side of this slide from the guiding of the urologists in which you see that uncomplicated UTI incorporates cystitis, pyelonephritis, and recurrent UTI -- all of them uncomplicated, obviously.

The regulatory definition does not include pyelonephritis, which is always considered complicated, and you see that on the righthand side of the slide. And the same is true for UTIs that occur in man. So, our guidance specifies that urinary tract infections in males are considered to be complicated because these infections occur in association with urologic abnormalities such as instrumentation or blood outlet obstruction.

So, I think these are important things to mention. And obviously, the regulatory definition that we use in Europe defines the UTI as a clinical

Page 143

syndrome characterized by pyuria and documented microbial pathogen in urine culture accompanied by local silent symptoms such as lower abdominal discomfort in dysuria. So, you see that the European definition is quite close to what you have just heard from our FDA colleagues.

In fact, uncomplicated urinary tract infections for EU regulators, it is synonym for acute cystitis in women, and it's clarified that this occurs in females with normal anatomy of the urinary tract without being accompanied by systemic signs and symptoms. Next slide, please. I think before the slide moves, just to mention, I think that here, both agency are quite well aligned, I must say.

The EMA overarching guideline on the evaluation of medicines indicated for the treatment of bacterial infections has recently been adopted. We're talking about a week ago. It can be now found published on the EMA website.

And just to tell you that this version actually has revised and has added to the previous version of this guideline based on a number of

Page 144

reflections that we made on important things like scientific advice that was given on development of antibacterial agents, and obviously previous decision taken during regulatory procedures and alignments on clinical trial requirements that resulted from discussions with the FDA and with the Japanese agency.

We had those tripartite discussions a number of times where we were trying to align whatever is possible to be aligned and knowing that this one drug development could be really an incentive to developing new drugs and contribute to the fight against antimicrobial resistance.

And I must say that this is one of the things that we may wish to discuss in the panel discussion, because I think this is also an important bit whenever it comes to alignment of requirements. And in this particular indication, this alignment is there.

So, come back to the guideline and this slide. We have in this guidance revised recommendations for primary endpoints, primary analysis, population, noninferiority margin, for

Page 145

trails, and all of them, obviously, and supporting infection size specific indication for use. And what's very relevant for the present workshop is the addition of a section on clinical trials that supports treatment of uncomplicated UTI and uncomplicated gonorrhea. Next slide, please.

As I already mentioned, the guidance document is overarching. Therefore, we have the nonclinical part with the nonclinical recommendations for development treated in the general part of the document. And here, among the salient points, I think it's important to mention the fact that the mechanism of action should be elucidated whenever the tested antibiotic is new.

For previously unlicensed antibiotics and for combinations of beta-lactam with a beta-lactam as incubator, there is a need to determine the activity against clinical isolates that are obtained within five years prior to filing. Obviously, the activity of any major metabolite should be assessed, and MBC and time-kill studies should be conducted.

And then, for new BLIs, the mechanism

Page 146

of action and the enzyme kinetics should be investigated, and it should be clear whether the BLI has antibacterial activity on its own at clinically achievable plasma exposures. For these BL/BLI combinations, there is a need to test against BL-resistant strains.

And it's also important that in the application, the developer makes a recommendation on using either a fixed concentration of the BLI or a fixed BL/BLI ratio. Development of resistance definitely should be investigated, and there is work that is conducted for establishing the breakpoints in collaboration with the EUCAST, and this should be also part of the dossier. Next slide, please.

When it comes to the clinical part of the development program, there are a number of considerations that the guideline makes, among other things, about the patient selection, which obviously should be done such that the likelihood of patients that have the type of bacterial infection on the study is maximized, and that enrollment of patients with infections that are likely to resolve rapidly without

Page 147

an antibiotic is minimized.

Then again, when it comes to the microbiological evidence of infection at the enrollment, the findings required for patients to be eligible for enrollment should be part of the study protocol. There needs to be a limit set on the duration and number of doses of prior antibiotic given for infections to be treated in the study, which should normally not be longer than 24 hours.

And then, when it comes to causative pathogens, urine specimens should be obtained, a baseline from all patients, and the pathogens should be confirmed by culture. And then, there should be a list of pathogens that may be considered causative which should be part of the study protocol. Only patients with one baseline pathogen, with that pathogen being part of the list of pathogens, should be included in the m-ITT and ME populations. Next slide, please.

When it comes to the selection of the test antibacterial agent, we recommend -- we mentioned that those clinical dose finding studies are not

Page 148

required if the PKPD analysis can provide adequate support for the dose regimen selected.

And the proposed duration of therapy that is allowed should be supported by a combination of either treatment guidelines and the PK of the test antibacterial agents. When selecting the dose regimen, there is also a need to look at the in vitro PDE models to quantify the risk of selection of resistance in residual organisms. Next slide, please.

Now, in terms of the efficacy trial, you will find that our recommendations are very similar to those of our FDA colleagues. Essentially -- - not identical, but essentially what we say is that a noninferiority trial is acceptable when there's a licensed treatment for uncomplicated UTI for which the magnitude of the treatment effect of a placebo is known, or it can be estimated from existing data.

And in the U.S., we accept a noninferiority margin of 10 percent for these kind of studies, but we also mention that alternative noninferiority margins may be acceptable if adequately justified. In terms of comparative regimens, we

Page 149

acknowledge the fact that the choice of the comparator, including the dose, the dose interval, the duration, all those things are critical to the overall validity of the study. Next slide, please.

And when it comes to patient selection, we recommend that female patients with acute cystitis are included in the trial, and that they should have a minimum number of symptoms such as frequency, urgency, and dysuria. And they may be enrolled before microbiological culture results are available based only on documented pyuria, but patients eligible for

the m-ITT populations should have more than 10 CFU per (inaudible) of a single relevant pathogen in the baseline urine sample.

And so, as I said, all pathogens should be identified at the specious level. We mention that the comparator regimen should be one of the best available treatment based on clinical trials, medical opinion, infection by specific treatment guidelines, and undissipated prevalence of resistance. And I think we will have a discussion later on as to which these treatment regimens might be, but we don't

Page 150

mention in our guidance any example. Next slide, please.

Another point that may be of importance is the use, the potential use of a comparator that includes an antibacterial agent or a dose regimen that is not licensed in some or all the EU member states. Here, we must say that this is not the preferred options for us, although it may sometimes be acceptable to have such a comparator if adequately justified.

So, here, we recommend that the developer comes and discuss the comparator with us if the situation is like this early in the development.

And we recommend that the single comparative regimen is used, and that a substitution of antibacterial agent in the regimen is allowed if culture and susceptibility testing are available based on criteria that are prespecified and that are included in the study protocol. Obviously, the pivotal efficacy at trials are recommended to be double-blind. Next slide, please. Next slide. Thank you.

Page 151

The test of cure visit should occur within a predefined window of days after randomization. And here, we recommend for safety further follow-up to be conducted. And the primary analysis as you see is the combined and clinical and microbiological success in the m-ITT population at test of cure with a delta of 10 percent. Our view here is very much similar to that of our FDA colleagues that you just heard.

We should not forget that an antibiotic actually acts on the pathogen. It's not a symptomatic medication, after all. So, we therefore believe that for regulatory approval, the microbiological success cannot be ignored. We, at the same time, recognize that in clinical practice, this is not the case. But here, we are talking about trials aimed at approving a new antibiotic.

And obviously, this is something that we may wish to discuss further. Now, any patient with any baseline pathogen that is resistant to the comparative regimen needs to be removed from the primary analysis population before unblinding the

Page 152

database to treatment assignment. Next slide, please.

The last point that our guidance touched bases on for uUTI is the issue of a single pivotal trial. Our guidance identifies here two situations that are given as an example.

The first one is about the circumstances in which infection sites, specific infections for use may be supported by single pivotal studies with standard levels of alpha, which is two-sided 0.05. And that is either single trials in each of complicated urinary tract infections and uncomplicated urinary tract infections, or single trials in cUTI or uUTI and single trials in uncomplicated gonorrhea. So, these are combinations in which we would obviously be happy with a single pivotal trial.

Now, what's important is that applications based on other combinations of a single infection site specific trials may need to be discussed with an EU regulator, because they may be acceptable subject to justification that evidence of efficacy of one body site is relevant to efficacy at

Page 153

the other body site.

Then we have a second situation, which is the one in which the test antibiotic addresses an unmathematical need. So, here in this case, if our main scientifical (inaudible) considers that the total evidence is sufficient to support a pathogen specific indication in patients with limited treatment options, then additional infection site specific indications may be granted based on a single pivotal trial per indication provided that they meet additional criteria, which are discussed in the guidance.

I will stop here in the interest of time. I will thank you very much, and I give the floor back to you. Thank you.

DR. GUPTA: Excellent. Thank you so much for that perspective from the EMA. Very important for us. And I will introduce our next speaker, and that is Dr. Nadia Kadry. Dr. Kadry completed her undergraduate training at the University of Maryland and her doctorate at the University of Pennsylvania School of Medicine.

She is currently a postdoctoral fellow

Page 154

in the FDA Office of the New Drugs Division of Anti-infectives and has been with the FDA since July. She will be speaking with us today on the discordance of clinical and microbiological endpoints in clinical trials for complicated UTI. So, thanks very much for joining us, Dr. Kadry.

DR. KADRY: Thank you. So, thank you for the intro. As she said, today, I'll be briefly talking to you all about some work we've done looking at the discordance of the clinical and micro endpoints in clinical trials for cUTI. Next slide, please.

So, while the focus of today's workshop is primarily on uncomplicated UTI, a cUTI is still a really closely related condition that we think we can draw a lot of insight from. Much like an uncomplicated UTI, cUTIs are characterized by pyuria and a documented pathogen on culture. Importantly cUTIs must have both local and systemic signs and symptoms, and there must be some functional or anatomical abnormality in the urinary tract.

Some of the most common complications that we see that constitute a cUTI include a catheter,

Page 155

an urgent bladder, any kind of obstructive uropathy, renal disease, and urinary retention. Notably, because of the male anatomy, it's generally considered protective against UTI. For the purposes of this talk, infections in men are considered complicated. The FDA also considers acute pyelonephritis complicated, again, regardless of urinary tract anatomy.

Of note, women with uncomplicated infections without any systemic symptoms are excluded here, because they would not have cUTI. So, it is a slightly different population that I'm looking at.

And I do want to highlight that we're looking at cUTI primarily due to the availability of patient level data. Because FDA hasn't seen many recent submission for uUTI, and we don't have the same level of data available for the analyses I'm going to show you, but we're hoping the insights from cUTI can still be informative. Next slide, please.

So, the FDA's recommended primary efficacy endpoint is pretty similar to what we've seen used for the UTI. But just to briefly review the

Page 156

definitions, success in these trials is a composite endpoint. It requires both clinical and microbiological responses, where clinical (inaudible) refers to the resolution of symptoms at entry.

And microbiological eradication refers to reduction of the pathogen to under 1,000 CFU per mil. Failure on either one of those criteria will cause failure in the trial. Next slide.

So, before I show you how these outcomes appear in our patients, I want to talk briefly about the data you'll be seeing. So, we pulled data from new drug applications submitted to FDA between 2011 and 2019. These were all applications for antibiotics looking for cUTI indication with or without acute pyelonephritis.

So, these data come from 13 Phase 3 trials. WE looked at patients that were in the micro modified intend-to-treat population. So, they had at least one qualifying pathogen in their urine and received at least one dose of a certain drug. And we looked at outcomes based on the FDA's recommended endpoint, which is the test-of-cure visit, which is

Page 157

typically seven to 10 days after therapy. Next slide.

So, if we look at the patient data, we see a significant number of people who have achieved clinical success at the primary endpoint, but still have microbiological persistence in their urine. Because they're considered clinically cured, they don't appear to need further treatment. And so, we consider them to be discordant, and this discordant outcome is actually the most common form of clinical trial failure.

Across about 4,800 patients that were included in our cohort, 18 percent were this form of discordant failure. And so, this just really raised questions about the importance of achieving microbiological eradication and the necessity of the micro component of the endpoint. And so, our goals have been to try to understand why this outcome occurs and whether there's actually any risk of microbiological persistence in these patients. Next slide.

So, a natural question about these people is, what do they look like compared to the rest

Page 158

of the patient population? And does anything jump out as a risk factor for a discordant outcome? And so, we looked at a lot of baseline demographic, micro, and clinical data. I'm just showing you a very small amount of that here. I don't have time today to go too in depth into all the data and all the analyses that we did.

But the point that I want to make here is that when we look across baseline patient factors, we don't see a whole lot that distinguishes our discordant group, highlighted here in blue, from the patients who end up in any other outcome group. You can see that with basic data like age, sex, race, BMI, but also in basic info about their pathogens including the uropathogen they had at culture. Next slide.

And so, beyond the patients and what bugs they had for their infection, we also wanted to look at the bacterial densities. Just to quickly

5

remind you, a uropathogen has to be found at 10 CFU per mil at entry, and eradication is dependent on

3

reduction to under 10. And so, this raises a question of whether these people are discordant due to

Page 159

relative bacterial densities and perhaps some association of the bacterial density with symptoms.

And so, we can look at the mean bacterial density at randomization right at the end of therapy and then at the test of cure which, once again, our primary analysis timepoint. What I first want to highlight is that if we compare starting densities across all different kinds of outcome groups, there aren't really any notable differences. Everyone's pathogen starts out around that 5-log threshold for density.

Moreover, by the test-of-cure visit, there doesn't seem to a big difference in density among those who have micro persistence with clinical cure and those who have micro persistence with clinical failure, which remains true when we look at the changes in density assorted by actual pathogen.

And so, our discordant group is still no different from a concordant failure, suggesting that bacterial density doesn't really seem to correlate with the presence of symptoms at the test-of-cure visit. Next slide.

Page 160

So, we next wanted to ask if there were any -- It's a bit of a risk of having this bacterial resistance in the urine given that there's clinical success. And so, to do this, we looked at what happens to these patients beyond their test-of-cure visit. So, what I'm showing you here are the average study days from randomization in all studies that we evaluated. So, the end of therapy was on average Study Day 10 from randomization.

The test-of-cure visit was about a week later on Study Day 18. And the final visit, the late follow-up, occurred after a slightly longer period, which was on average Study Day 32. So, to assess the risk of bacterial persistence, we can assess whether there's an increased relapse of cUTI symptoms by that late follow-up visit. Next slide.

So, we find that patients with these discordant outcomes do appear to be more likely to have symptom relapse by that later visit. So, if you look at people who are concordant successes -- so, clinical cure with micro eradication -- you see a relatively low rate of clinical failure by that later

Page 161

visit.

But if you look at our discordant population, the risk of late clinical failure goes up significantly, and this remains true when we adjust for different causes of clinical failure and focus just on symptom worsening. The discordant population is more likely to report worsening or new development of most core UTI symptoms.

The most common one that we saw get worse or newly appear was dysuria. And so, this pretty strongly suggests that the persistent bacteria after antibiotic therapy is increasing the risk of a slight clinical failure. Next slide.

Now, because the patient pool in the cUTI trials includes both the cUTI and acute pyelonephritis patients, we wanted to see how true this was across these diagnostic groups. So, if we wake patients up, we feel that discordants are pretty consistently at increased odds of late clinical failure relative to someone who's a concordant success.

To try and see how this might extend to

Page 162

a population that's a little bit closer to an uncomplicated UTI, we separated out the uncomplicated AP population by gender to focus only the women with AP and no other complicating factors. And even in that population, we see this increased risk of late failure created by a discordant outcome. Next slide.

So, an important facet of looking at the late follow-up is the timing of when it actually happened.

On average, as I mentioned, the late follow-up visit was on an average Day 32, but across all the studies in our cohort, it actually varied in distribution from about one week after test of cure to as far as four weeks after test of cure. So, we can see how these late clinical failures appear when people are evaluated earlier relative to test of cure versus later.

And so, if you look at people who have their late follow-up visit closer to test of cure, we see about four percent of concordant successes will have late clinical failure, and about 14 percent of discordants. But if you look at people who went through a longer period between the two visits, we see

Page 163

increases in late failure in both groups, but the amount of discordants who clinically fail jumps up significantly, up to about 44 percent.

So, there's two important points to this observation. First, again, we're seeing that across the entire observation period between test of cure and late follow-up, the risk of late clinical failure is higher in people who are discordant with that bacteria compared to someone who's a concordant success. But second, the likelihood of clinical failure goes up the further we look out.

And so, this suggests that with enough time, even more of these discordants could become clinical failures because of that increased risk. Next slide.

Now, while we do see an increased risk of late clinical failure in our discordant group, there are still many of them who remain discordant through that late follow-up. And while part of this might be explained by the timing of that visit, we wanted to see if there were any other factors that could influence the risk of late clinical failure in

Page 164

this group.

So, we looked at the participants who were discordant at test of cure and looked for baseline factors that might distinguish those who developed clinical failure at the LFU from those who do not. And we found that when we adjust for the actual study they were in and the time for the late follow-up visit, the clinical failure appears to associate with older age and having diabetes. So, there may be a patient component to this as well. Next slide.

So, just to summarize what I've shown you today, we've seen that in clinical trials for cUTI, a clinical cure with microbiological persistence is the most common reason for patient failure at the primary endpoint. Microbiological persistence at the test of cure appears to consistently increase the risk of cUTI relapse at later visits, and this risk appears to increase over time when we account for other patient factors.

And so, collectively, these data suggest that microbiological persistence is probably

Page 165

an important consideration for the composite endpoint. And so, with that, I'd like to thank you for your time today.

DR. NATARAJAN: All right. Thank you, Nadia. That was a great talk, and I think it'll be very helpful in our panel discussion later this afternoon. So, now, I'd like to introduce our next speaker, Dr. Stapleton, who will be speaking about the investigator's perspective. So, Dr. Ann Stapleton is an attending physician and infectious diseases fellowship program director at Eisenhower Health, Rancho Mirage, California, and professor emeritus at the University of Washington in Seattle.

And she has maintained a UTI clinic for the past decade, and her current UTI researches focuses on treatment and prevention of UTI and lower urinary tract symptoms in women. So, please go ahead. Thanks.

DR. STAPLETON: Okay. Next slide, please. So, these are my disclosures. Next slide. So, here's an outline of what I'm going to try to talk about today. I'll start with the choice of

Page 166

comparators from complicated UTI noninferiority trials, then talk about challenges with recruiting and retaining participants in clinical trials for uncomplicated UTI, and then, finally, stewardship concerns for drugs targeting resistant pathogens. Next slide, please.

So, just some background of clinician perspective. And throughout the talk, I'm going to talk about what are the challenges. We don't have that much time, and I think we need to focus on challenges in order to see our way forward in designing and conducting future trials in an uncomplicated UTI.

So, as a clinician, right now, we don't have very many first-line therapy options. In our current guidelines, diagnosis is not covered. I think that will be addressed, but it's not an issue for infectious disease doctor. But for us interfacing with people in other disciplines, it can be difficult, particularly in older women, to distinguish UTI from other symptoms. And I think that was spoken of by one of our patient advocates.

Page 167

Then definitions of uncomplicated versus complicated UTI, we'll probably talk about this a bit more in the panel, but Dr. Trautner alluded to changes that have come through the up-to-date chapters on this and things that will probably carry over into the new guidelines being developed at IDSA. Then of course, there's always a disconnect between clinical care and the requirements of clinical trials. Next slide, please.

So, how about investigator perspectives? What are the issues there? Well, again, in a few recent clinical trials for uncomplicated UTI, and in particular issues related to delivery of care for UTI, and I'll talk a lot more about this as we go on in the brief talk here. So, earlier, we had some challenges with telephone protocols and self-start therapy, but that kind of therapy was, in most health systems, fairly well-defined.

What we're coming up against in the last decade or so is there's a lot more use of telehealth or electronic health record messaging for

Page 168

the identification and care of patients with UTI. And the remote health delivery sphere has really increased during the pandemic across many disciplines. I've even seen papers in the literature about diagnosing atrial fibrillation with Apple iWatches. Apple Watches, I guess it is. Next slide, please.

So, how about diving into the talk here? So, what would be our choice of comparators? Actually, this is not my most -- this is not my updated slides. So, this should talk about placebo right here. Could someone look into that for me?

DR. GUPTA: Yes. One moment. We'll take a look.

DR. STAPLETON: Okay, thanks. Do you want me to email them to you?

DR. GUPTA: If you have them handy, you can go ahead and email them now, and we'll get them up right after you email them.

DR. STAPLETON: Okay. To you?

DR. GUPTA: Sure.

DR. STAPLETON: Okay. I hope I'm not making typing noises. Maybe I should mute myself.

Page 169

Okay. Okay. I'm sending it right now. Sorry about this. So, when you get it, we'll go straight to Slide 6.

DR. GUPTA: It should be just another moment.

DR. STAPLETON: Okay. Thank you.

DR. GUPTA: I'm not sure why they did not upload, but it'll just be one more minute.

DR. STAPLETON: Okay, there we go. That's right.

DR. GUPTA: I think that's it.

DR. STAPLETON: That looks correct. Okay, great. So, I think I'll briefly -- I'll briefly speak about placebos. So, there are a few recent studies that have used a placebo in any UTI trial, in fact, anything where there's an infection, when you have an effective therapy available. So, it's very difficult to get IRB approval on most settings when this kind of thing is proposed.

And if participants are not that interested in not receiving active therapy, it becomes controversial for recruitment. Next slide, please.

Page 170

Next slide, please. There we go.
So, for intimate comparators -- I think this was mentioned a bit earlier -- our first-line agents looking at those -- Oh, previous slide, please. Well, is it...? There we go. Okay. So, for trimethoprim-sulfamethoxazole, right now, most communities, the resistance rates are so high that almost any agent would win over Bactrim or Septra.
So, that's basically pretty much a nonstarter for most study design -- for most studies most might wish to propose. Fosfomycin will not have as high of a resistance rate for the most part, but the sachet formulation actually makes for a more complex and costly study design, because you're probably to going to want to use a double dummy, and then that will cost more money. And the other thing that can happen is people can get diarrhea fairly commonly with fosfomycin.
So, even if you don't have a comparison of sachets versus tablets -- so, everyone knows there's not really randomization happening -- there often can be a emergence of diarrhea among the people

Page 171

who are on the fosfomycin arm, and it becomes fairly obvious who is getting what.
I just saw you sent me an email. Is there anything? Can you hear me okay, and is everything okay?
DR. GUPTA: Yes, yes.
DR. STAPLETON: I don't want to check my chat.
DR. GUPTA: Please continue.
DR. STAPLETON: Okay. Fine, sorry.
DR. GUPTA: No, you're fine. Thank you.
DR. STAPLETON: All right. So, next slide, please. The next slide would say nitrofurantoin, I think. There we go. So, previous slide now. There we go. So, for E. coli I know Barbara showed -- Dr. Trautner showed a slide with increasing resistance rates. But if you break it down to E. coli they're still relatively low. And looking in my own current local antibiogram, the resistance rates are fairly low. Can you go the slide after this, please? Next slide.

Page 172

DR. FARLEY: So, Dr. Stapleton, you have a delay. So, the folks showing the slides, Dr. Stapleton needs the nitrofurantoin slide, and just (inaudible).
DR. STAPLETON: Exactly. Yes. I could just talk about it. I have them in the background here, if it'll make it easier.
DR. FARLEY: It's up now. Nitrofurantoin, the audience is seeing that.
DR. STAPLETON: Okay, great. Thank you. So, there's relatively fewer adverse effects and collateral damage. And of course, we're looking for that in the drugs that we're studying. We would prefer to maintain that kind of thing in anything we're studying.
So, it's a better comparator in that sense, in terms of you're looking for noninferiority, of course. Tablet form in my formulation makes it no need for a double dummy type of design, and it also treats only cystitis, which also lends itself to a simplicity of the trial design. Next slide, please.
Okay. So, I think my phone is going

Page 173

faster than my computer. So, in terms of delivery of care, I do not see that yet, except for my phone. So, I think I'll just --
DR. GUPTA: We are seeing the slide that says --
DR. STAPLETON: You are?
DR. GUPTA: "Delivery of Care for uUTI (inaudible)." Yeah.
DR. STAPLETON: Okay. I think I'll just my... I'll use my PowerPoint on my computer screen and just look at my phone to make sure you're on the right slide from here, because we keep saying, "Go back and forth," and all that sort of thing. So, the delivery of care for UTI, that really affects the study recruitment. The main point is identifying potential participants.
What do we need for a successful study? The most important thing is to identify potential participants before they're prescribed antimicrobials in their clinical care setting. So, next slide, please. Okay.
So, hold on a second. So, I mentioned

Page 174

that we need to catch people before they receive treatment. So, in the previous methods of UTI care delivery, often patients presented in person. And we, in particular, were able to recruit at the point of care in person or via some type of provider referral. One of the ways that this is often done that doesn't require a great deal of IRB complexity is to have the clinical schedule.

Even if it is an electronic record, it can be available to the study coordinator or whoever's doing the screening, and it often shows the reason for the visit. If the visit is scheduled in advance, or the presumptive diagnosis such as UTI symptoms, and you can fairly readily obtain IRB permission to review this kind of schedule.

So, the study coordinator could just watch the schedule in real time, and then ask the provider to offer a study referral and go on from there. So, in current methods, we have increasing use of telehealth or electronic health record messaging for UTI diagnosis and treatment. Very often, this type of encounter is going to be a message or a phone

Page 175

call to whomever is receiving those at the end of the healthcare system, usually the nurse or the provider, in some cases, and the patient.

The diagnosis will be based on symptoms. Many systems do have protocols for empiric treatment similar to old phone protocols, and they will have some eligibility criteria that may not be met. But particularly in pandemic times, most often patients get a prescription fairly quickly, and that's actually the goal of the healthcare system is to get rapid orders for treatment out to the patient.

So, why is it difficult to intercept patients in this setting? It's just very hard, practically speaking, in my systems, to get them before they get a prescribed therapy. When we used to be have people looking at these schedules, they could be there in real time in business hours, and they could either contact the clinic phone or actually be present in the background checking on who's coming in and then speak with the providers very quickly. And it generally does not disrupt the provider workflow.

And the IRB issues, as I mentioned

Page 176

earlier, are fairly simple for that. In the telehealth model, you have individual phone calls or messages coming in from patients who believe that they have a UTI. And depending upon your system, there may be multiple gatekeepers. They can even change throughout the day in some systems based on workflows and workloads. Sometimes, it comes to the provider.

Some of them are -- Some are during the business day, but I'm sure any of you who do clinical care familiar with what Epic calls pajama time, which is where you get a message at 10:00 p.m. at night or some other off-hour time, and you have to figure out how to appropriately and promptly respond to that.

The workflows and then to pick up that message or any other message is often, according to institutional guidelines or provider guidelines -- And you don't know whether or not your study criteria will even be considered as they are going forward with trying to come up with some sort of prescription for the patient.

So, the flow and timing of these messages is not scheduled in particular, and many

Page 177

places, including the University of Washington when we tried to do this in my own UTI clinic, felt that the interception of these messages would disrupt the workflows too much for the nurses taking the phone calls. In that particular setting, it would be RNs. In some settings, it's a medical assistant who doesn't have much licensing ability to make many decisions, so will look at a protocol.

You can try to do some things to overcome these challenges. So, for example, have a UTI alert in your record. But as I have found out in more than one system, when you make an adaptation to electronic records such as Epic, the company charges you for everything. So, you have to account for that. And sometimes, particularly in the pandemic times when everyone is having staffing difficulties, it can be difficult to change any workflow or anything in the electronic record.

Another thing is that if you try to buy a dedicated platform, those are very costly. And then, there's very different privacy issues that come into play when you end up having to try to get into a

Page 178

individual chart versus looking at a clinic schedule, which is at a higher level and is easier to get a HIPAA waiver, that kind of thing, from your IRB.

So, there was one study I thought was interesting. This study did not even talk to potential participants or actual participants or anyone who would be thinking as a patient about becoming a participant and what are the issues there. This was just interviews with providers trying to do clinical trials.

So, they raised issues such as trust, credibility, and establish relationships that might be disrupted. Research efficiency, I just talked about that for about five slides. But also validity, because there can be selection bias when you're having people present in all different ways, and there are -- As I mentioned, the messages come in fairly randomly at times, and how they're handled may not be completely standardized.

Privacy and autonomy are an issue. The intersection between research and clinical care, that can be hard to maintain the appropriate boundaries for

Page 179

that provider if they are serving as the patient's physician as well. And similarly, the physician, researcher, and physician-patient relationships may be affected by the interaction of trying to recruit people into a clinical trial.

Then there's the issue of retention. It's always a problem, but this is likely impacted as well by electronic record-based management of complicated UTI.

I was not able to find any data on this, but one can readily imagine, and I have experience to some degree that it will select for patients who have more available time and also those who are more able to use their electronic record just to be recruited into the trial. And it could lend itself to having longer protocols. Next slide, please.

So, now, we should say about stewardship concerns. I'm sorry. I forgot to say to advance the slides. So, stewardship concerns. To me, the most important issue is the use of fluoroquinolones. Essentially, our goal should be to

Page 180

try to keep them out of just about everything we do, whether it be clinical care or designing a trial. They are still frequently used in uncomplicated UTIs, Dr. Trautner sadly described in one of her slides.

And of course, we all know they cause quite a bit of collateral damage. How many black box warnings has the FDA issued for that? And including specific advice not to use in this clinical entity when there are other antimicrobial options.

I'll make a quick comment about -- next slide, please -- about ESBL. So, it's a growing problem even in uncomplicated UTIs, as other speakers have mentioned previously. There are some factors that can stem from the presence of ESBLs that effect the conduct and design of a UTI study. So, for one thing, if you're trying to target ESBL, or if your ESBL is -- if ESBL is more prevalent in your population than the rest of the United States.

So, if you're targeting an ESBL, what would happen then in your study design? Well, it does change the patients who may be eligible as participants, potentially, in particular because there

Page 181

can be quite an overlap between definitions of complicated UTI and risk factors for ESBL. And hopefully, I'm on the next slide. Now, I am. Sorry about that.

Then as was raised by other speakers previously, if we're talking about targeting ESBL, essentially uncomplicated UTI -- And some day, probably it will be. Now, we're still somewhat in that overlap between people who would fall int a current definition of complicated and those who have risk factors for ESBL. There's likely going to be different recruitment procedures.

Because when you're just recruiting for a trial on the basis of symptoms, you don't know what the organism is going to be. But if you're going to try to target ESBL, you will probably be looking at a recurrent UTI population. Agents used as comparators are also an issue. You're going to have to stick to nitrofurantoin and fosfomycin because they cover ESBL. Otherwise, you really can't design a reasonable trial in the current world in the United States. Next slide.

Page 182

I think that's my last one saying thank you. And my apologies for the slide problem. I did try to work that out in advance, and I think -- I'm not sure exactly what happened, but we hopefully were able to get across what I was hoping to say. And thank you very much for your attention and for the opportunity to speak today.

DR. GUPTA: Wonderful. Thank you so much, Dr. Stapleton. That's a really insightful presentation on the investigator perspective. And we're now going to move to developer perspective, and we have a series of talks regarding that. We will start with Mr. Tom Hadley. Mr. Hadley is the president and chief commercial officer of UTILITY Therapeutics.

He has 30 years of experience commercializing drugs and devices with both multinational and startup pharmaceutical companies. He has extensive experience in preparing and executing numerous high successful commercial launches across multiple therapeutic areas spanning both primary care and specialty markets in the U.S. and globally.

Page 183

We're very pleased to have him here, and he will be talking with us on the developer's perspective on inclusion criteria and endpoints for uncomplicated UTI clinical trials. Welcome.

MR. HADLEY: Thank you, Dr. Gupta. Really want to say thank you to the FDA for putting this together as well as the panelists and participants who we've heard from so far. I also want to thank my colleagues from Iterum and GSK in working very collaboratively together to ensure we have a consistent viewpoint from industry for you today.

As was mentioned, I'm with UTILITY Therapeutics, and we are trying to bring to market in the U.S. a product that's been available in Europe for over 40 years for the treatment of uUTI. I think as we -- Yeah, you can leave it on that for now. We all know resistance is a huge issue. And regardless of therapeutic area, there is a need for new products to fill this gap.

And as Dr. Clancy mentioned, the last antibiotic was approved three years ago, but the last product approved for uncomplicated UTI is over 20

Page 184

years ago. And I'm not sure that necessarily speaks to the value of the therapeutic area to industry, but I do know there are a number of companies that are working feverishly to try and bring products to market specific to this area.

I think one of the things that I've heard come out throughout all of these talks has been the fact that there needs to be maybe a little bit closer alignment between what's happening in clinical practice and what the guidelines, and whether that be the inclusion criteria or the end measurement of clinical or microbiologic success. And I'm just happy that the FDA's open to discussing this. And so, when you look at the guidelines -- and this is another thing.

Many of the guidelines haven't been updated in a number of years, and I know we have the IDSA coming with an update, which is just fantastic. But if you look at the European guidelines, they're 3 talking about 10 with some symptomatic diagnosis in 5 women, and utilizing 10 more for the complicated.

And I think it's been mentioned time

Page 185

and time again that there is a close correlation between uncomplicated and complicated, but I think we also have to do a better job of distinguishing between the two of them. If you could, go to the next slide.

I think one of the areas that UTILITY is rather unique in identifying is because we have been looking back at all of the clinical studies that have been done for Pivmecillinam over the years. And we have reanalyzed those studies according to the 2019 guidance. And so, we have a unique view into what the 3 5 impact is of 10 versus 10 as inclusion criteria.

And I think what you can see is whether we're talking about overall response, the clinical success, or microbiologic success, the differences in terms of the percentages really don't vary that much. What tends to vary most is the number of patients, the actual ends that are included in each of these. And so, it doesn't matter if it's Pivmecillinam or the comparator norfloxacin, you still see that those overall measurements tend to be roughly about the same. So, if you could, go to the next slide.

What this really highlights is what the

Page 186

real impact is. And so, this is from the Nicolle study that was done in 2002, and the importance of this -- And I think this goes back to actually something Dr. Natarajan was mentioning was that the expectation is that you would have about 80 percent of your patients qualified for the study. When you use 5 10, it's actually closer to 40 percent.

So, you start with 483. Another 418 are actually included in it. But the difference 5 3 between a 10 and 10 is somewhat dramatic. The impact that has -- And again, you can see it for Pivmecillinam. You can see it for norfloxacin. The impact is the size of the study. And from a commercial point of view, from an industry point of view, what that means is this study's going to cost a whole lot more for me to be able to demonstrate the same thing.

And so, when we're looking at it from industry perspective, that's certainly something that comes into account. If you could, go to the next slide.

One of the -- One of the other

Page 187

perspectives is what the clinical outcomes are. And when you're looking at a score of zero for clinical outcomes, not only is that a very high bar, but that is a bar that is not necessarily used a lot in clinical practice. I think what we've seen in some other guidelines around the globe is that looking at significant improvement, and so looking at an alternative clinical success of a zero or a one, if you look at the studies themselves.

And this was a study that Dr. Natarajan highlighted as well. And what they used from the guidelines from the Ferry study, you don't see, again, a very large difference when you're looking at Pivmecillinam versus placebo. The difference is still within one percentage point. And so, when looking at that and looking at the clinical studies, having to try and develop an end to account for complete symptom score is nothing short of increasing the size of these studies.

And again, going back to the need for these products on the market, there is an urgent, unmet need. And the fact that there hasn't been new

Page 188

products in 20 years I think is a huge issue. And you can go to the next slide, if you don't mind.

So, really -- And my colleagues from Iterum and from GSK will certainly talk about some other aspects. But simply, when you're looking at the 5 3 inclusion criteria of 10 versus 10, the inclusion for the higher cutoff really represents an increase in the size of the study without any real increase in the 3 5 differentiation between the 10 and 10. And I think the same can be said when you're looking at what the clinical outcome is.

I think it's important that we build studies to reflect what is being done in clinical practice so that they're easily applied to the doctors that are using the guidelines as well. And I don't think that having 100 percent symptom resolution is necessarily what may be happening in clinical practice today. So, thank you again for the time. Thank you for putting this meeting together. I hope I've offered up a different perspective. Thank you.

DR. NATARAJAN: All right. Thank you for your perspective and your talk and your time for

Page 189

presenting. So, we're going to move on now to our second developer's perspective. From Iterum Therapeutics, we have Dr. Sailaja Puttagunta. Her talk is on the developer's perspective on the primary endpoint in uUTI trials and lessons learned.

She is the chief medical officer of Iterum Therapeutics and a board-certified infectious disease physician with more than 20 years of clinical, academic, and research experience in medicine and in infectious diseases. Thank you.

DR. PUTTAGUNTA: Thank you. Good afternoon, everyone. If you can, please, go to the next slide. So, firstly, I'd like to start by thanking the FDA for this opportunity to provide our perspective on the current time of the endpoint for uUTI trials.

My primary focus today is to discuss the current primary endpoint in uUTI trials, its relevance to real world clinical practice, and to share some pertinent data from a recently conducted Phase 3 uUTI trial that compared oral Sulopenem to ciprofloxacin.

Page 190

In addition, because of the extensive amount of data collected as part of this trial, there is an opportunity to assess any correlation between asymptomatic bacteriuria and future clinical relapse allowing a better understanding of the contribution of ASB to the overall assessment of outcomes in uUTI. We also have data to assess the impact of ASB on the development of antimicrobial resistance from this trial, which I will share it at the end of my presentation. Next slide, please.

So, let's start with (inaudible) reviewing the current standard of care for managing patients with uUTI. uUTI patients often have significant discomfort that affects their daily life.

Pain, need for frequent urination, and incontinence have major impacts on quality of life, and studies have documented increased rates of depression in women with recurrent UTIs. In order to provide them with immediate symptomatic relief, the current standard of care is (inaudible) treatment with a short course of antibiotics. Following treatment, many patients will achieve a full clinical cure with

Page 191

resolution of symptoms.

But for those that don't respond, a clean catch urine specimen is sent for (inaudible) susceptibility, and the results obtained in two days generally guide subsequent antibiotic selection. Typically, a second short-course antibiotic will resolve the symptoms and result in a clinical cure. Next slide, please.

Per the current FDA guidance, though, the primary endpoint for uUTI trials is the proportion of patients with an overall response of success at test-of-cure visit. Overall response of success is a composite of all clinical success and microbiologic eradication. So, patients need to have complete symptom resolution and a urine culture with less than

3

10 colony forming units per mil with no rescue antibacterial therapy.

This is inconsistent with real-world practice where resolution or significant improvement of uUTI symptoms is considered sufficient for a cure. Next slide, please.

To shed some light on the relevance of

Page 192

the current FDA primary endpoint, I'd like to share some data from a large uUTI trial we conducted recently. Study 301 was a Phase 3 randomized, multicenter, double-blind, active control study in women with uncomplicated UTI. This study was conducted under special protocol agreement and designed in collaboration with the FDA.

Sixteen-hundred and seventy-one women with uUTI, aged 18 years or older, were randomized in a one-to-one fashion to receive either oral Sulopenem twice daily for five days or oral cipro twice daily for three days with matching placebos for each regimen. Urinalysis and urine cultures were done at baseline, Day 3, Day 5, Day 12, which was the test-of-cure visit, and at the end of study on Day 28. Next slide, please.

Presented here are the primary endpoint results of overall success at Day 12 in the micro m-ITT R population comprised of uUTI patients with the baseline pathogen not susceptible to cipro. Point estimates to the right of zero favor oral Sulopenem.

Oral Sulopenem achieved statistical

Page 193

superiorities to cipro with 62.6 percent of patients, compared with 36 percent of cipro-treated patients responding to treatment. The treatment difference was 26.6 percent. The 95 percent confidence interval on the difference in outcomes did not include zero, and the p-value was less than 0.001. Next slide, please.

In the population of patients with a baseline pathogen susceptible to cipro, oral Sulopenem did not achieve the prespecified noninferiority margin for overall response compared with cipro at Day 12. Overall success was seen in 67 percent of patients receiving oral Sulopenem compared with 79 patients receiving cipro, and the lower limit of the 95 percent confidence interval in the difference in outcomes was less than minus 10 percent. Next slide, please.

The difference in response between the two treatment groups was driven primarily by a higher rate of asymptomatic bacteriuria in patients treated with oral Sulopenem. Thirteen percent of patients treated with oral Sulopenem compared to four percent on Cipro achieved completed symptom resolution but had

3

a urine culture with greater than or equal to 10 CFU

Page 194

per mil of the baseline pathogen.

The contribution of asymptomatic bacteriuria to overall response can be assessed by examining the clinical outcome with each regimen shown on the next slide. Next slide, please.

So, clinical success at Day 12 was similar on each regimen. Eighty-one percent of patients treated with oral Sulopenem compared with 84 percent of cipro-treated patients achieved clinical success with the low bound of the 95 percent confidence interval of the treatment difference greater than minus 10 percent. Similar rates of clinical success across treatment groups were also observed at all other study visits.

But does asymptomatic bacteriuria signal the potential for clinical failure at a later timepoint? In other words, maybe patients with ASB will relapse at a subsequent visit. That would be important to know and may make ASB more relevant to the overall success definition. As you will see in the next two slides, however, that did not happen in this study. Next slide, please.

Page 195

So, if the patients with ASB on Day 12 were on a path to clinical failure, you would expect to see a lower clinical response rate at the Day 28 visit in Sulopenem-treated patients. In fact, however, the results at Day 28 are consistent with what we've seen at Day 12. ASB at Day 12, on a population basis, did not predict recurrence of baseline symptoms and treatment failure at the end-of-study visit 16 days later. These observations derive from a population of patients.

The outcomes of individual patients that had either ASB or the overall responders would also be informative. So, let's look at that data in the next slide. I'm not sure why the data is not being visible here. But please, let's go to the next slide. Oh, there they are.

So, as you can see here... okay. As you can see here, the presence of asymptomatic bacteriuria does not predict the clinical failure rate at subsequent visits relative to patients who achieve both microbiologic and clinical cure. I'll walk you through the data here. Two hundred and forty patients

Page 196

had overall success at Day 5, end-of-treatment visit. Twenty-two of those 240 had a clinical failure at Day 12, one week later.

Only 11 patients have ASB at Day 5, and one of those had a clinical failure at Day 12. So, having ASB at Day 5 did not predict clinical failure one week later at Day 12. Similarly, 247 patients had overall success at the Day 12 test-of-cure visit. And of those, 15 patients had clinical failure at Day 28, 16 days later. Forty-seven patients had ASB at Day 12.

And of those, four had clinical failures at Day 28, resulting in a rate of clinical failure very similar to that of patients who had previously achieved both clinical and microbiologic success. Asymptomatic bacteriuria is not a surrogate marker for subsequent clinical failure for patients who receive oral Sulopenem.

As asymptomatic bacteriuria does not reflect how a patient feels, functions, or survives and is not a surrogate marker for subsequent clinical failure, its role as a component of the assessment of

Page 197

overall response should probably be reconsidered. Next slide, please.

The current IDSA guidelines also indicate that screening or treatment for ASB should only occur if a patient is pregnant or undergoing and an endourologic procedure. Not ordering cultures on asymptomatic uUTI patients outside these two situations is strongly endorsed by the clinical ID community. Similarly, obtaining proof-of-cure cultures after resolution of uUTI symptoms post-treatment is strongly discouraged in clinical practice. Next slide, please.

Before I conclude my presentation, I want to talk about one other aspect of our study results. From a stewardship perspective, we must understand whether a higher rate of ASB, as seen in the Sulopenem treatment group, selects for penem-resistant organisms. The graph shows cultures isolated from patients treated with oral Sulopenem broken down by their Sulopenem MIC both at baseline shown in light blue, and test of cure shown in dark blue.

You can see that the distribution

Page 198

before and after treatment is very similar. In addition, the MIC50 and MIC90 were also similar pre- and post-treatment. Oral Sulopenem did not select for Sulopenem-resistant organisms in this study, despite having a higher proportion of patients with ASB at the test-of-cure visit. Next slide, please.

On the other hand, looking at resistance development in patients treated with cipro, the findings are different. Despite having a lower rate of ASB at the test-of-cure visit, resistant isolates emerged as little as two weeks after treatment with cipro, and none of these patients had evidence of a gene associated with quinolone resistance at baseline. Next slide, please.

In conclusion, we feel that asymptomatic bacteriuria should not be a component of the assessment of overall response to treatment in uUTI trials as it is not only inconsistent with the patient-focused drug development guidance under PDUFA V regarding how a patient feels, functions, or survives, but it is also inconsistent with current, real-world clinical practice.

Page 199

As indicated by our clinical trial data, ASB is not a surrogate marker for clinical failure and, moreover, it reduces the sensitivity for measuring efficacy in a trial. Clinical response is a more appropriate primary endpoint in UUTI trials as it is a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives.

It is consistent with the current standard of care for uUTI patients, and it increases the sensitivity for measuring efficacy in a clinical trial. With that, I'll stop here, and thank you for your attention.

DR. GUPTA: Excellent. Thank you so much. That was a really provocative talk and data. So, thank you for that. And I will introduce our last speaker for this session. And introducing Ms. Scangarella-Oman who is the scientific director in the infectious diseases research unit at GSK.

She has over 20 years of experience in the pharmaceutical industry supporting nonclinical and clinical microbiology for GSK antibacterials, and she will be talking to us today giving us the developer's

Page 200

perspective on urinary breakpoints for uncomplicated UTI. Thanks so much and welcome.

MS. SCANGARELLA-OMAN: Thanks so much, Dr. Gupta. And thank you to the FDA and organizers of this workshop for the excellent opportunity to present a developer's perspective on urinary breakpoints and how guidance and harmonization on deriving breakpoints using urine PK for agents being used to treat uUTI are greatly needed for both the fostering of new agent development and also for antimicrobial stewardship.

I also want to say many thanks to the previous speakers who touched on some of the same concepts that I'll be discussing in this presentation in earlier presentations. Next slide, please.

In full disclosure, I am an employee and shareholder of GlaxoSmithKline. And in partnership with BARDA, we do have a novel class antibacterial, Gepotidacin, which is currently in two Stage 3 clinical trials for the treatment of uncomplicated UTI. Next slide, please.

So, what are breakpoints? And why is the topic of urine PK for breakpoint so important? In

Page 201

brief, breakpoints are used to interpret a numerical result from the lab susceptibility test to define whether the infection caused by a particular bacterial strain or isolate is likely to be treatable in a patient.

Because breakpoints are based on pharmacologically and clinically-rich data sets, they are considered robust predictors of likely clinical outcomes. It's also mentioned earlier, when determining breakpoints for an antibacterial, current guidelines incorporate PK/PD, but primarily focus on applying plasma PK. And breakpoints from many agents currently used to treat uncomplicated UTIs were not determined using current PK/PD standards.

As previously also mentioned, it is scientifically accepted that drug levels at the site of infection -- for example, the bladder -- for uncomplicated UTI are clinically relevant to antibacterial efficacy.

The next slides will discuss how applying plasma PK, per current standards, would not support the breakpoints for some agents currently and

Page 202

widely used to treat uncomplicated UTI, but how applying urine PK for these agents would support their breakpoint. This helps illustrate that using urine PK to derive breakpoints where it is appropriate would allow the use of effective agents for the treatment of uncomplicated UTIs.

If the breakpoints for these same effective agents were based on only on plasma PK, they likely would not have been approved or used clinically. Next slide, please. I think we went one ahead. Yes.

First, some background on what currently exists in guidance regarding the use of urine PK to support breakpoints. As shown on this slide and also mentioned previously, there's not a whole lot. While there is some information on the importance of understanding PK at various body sites, there is little guidance on when or how this information is applied to or integrated into breakpoint settings. Next slide, please.

Currently, there are a number of antimicrobials with breakpoints specific for the

Page 203

treatment of urinary tract infections. It should be noted that the data available or that which was used to determine many of these breakpoints vary significantly. And as you can see by all the footnotes in the table, which was also shown in a similar slide by Dr. Rodvold, the breakpoint's notes and comments also vary between agencies. Next slide, please.

IDSA guidelines recommend nitrofurantoin and fosfomycin therapies for the treatment of acute, uncomplicated cystitis or uncomplicated UTI. As will be shown on the next few slides, when applying contemporary PK/PD analyses, the plasma PK for nitrofurantoin and fosfomycin does not support their susceptible clinical breakpoints for Enterobacterales, which are shown in the table on this slide.

However, for these antimicrobials, adequate PK/PD data to support their breakpoints is achieved when applying urine drug levels, which is turn is supported by their efficacy in the treatment of uncomplicated UTI. Next slide, please.

Page 204

The first example is for fosfomycin. A recent study determined the PK/PD index and targets associated with fosfomycin efficacy against Enterobacterales. Then for isolates with different fosfomycin MICs, they calculated the probability of attaining the PK/PD target with a fosfomycin three-gram oral dose. Greater than or equal to 90 percent target attainment at given MIC is generally considered acceptable for dose selection for breakpoint settings.

In the figure on the right, when applying serum drug levels, fosfomycin only achieved the 90 percent target attainment threshold for MICs up to less than or equal to four. This MIC value is much lower than the CLSI susceptible breakpoint of 64, which was shown on the prior slide. This data helps illustrate that plasma PK does not support the fosfomycin breakpoint for E. coli. Next slide, please.

When applying the same PK/PD target for fosfomycin, but now looking at urine drug levels, the figure on the right shows that a single three-gram oral fosfomycin dose achieves the 90 percent target

Page 205

attainment threshold for MICs up to and including 64. This is the same MIC value as fosfomycin CLSI susceptible breakpoint that was shown earlier. Therefore, in contrast to the serum data presented earlier, the urine PK does support the fosfomycin breakpoint for E. coli. Next slide, please.

When applying similar PK/PD concepts to nitrofurantoin, you come to a similar conclusion in that nitrofurantoin requires urine PK to adequately support its susceptible breakpoint. And this is based on data showing the nitrofurantoin plasma levels are often a hundredfold lower than those in urine and do not exceed one microgram per mil, which leads to a time above MIC of zero in plasma at the CLSI susceptible breakpoint of 32.

Therefore, similar to fosfomycin, nitrofurantoin also requires urine PK to adequately support its susceptible breakpoint for Enterobacterales. Next slide, please.

And one final example, currently, CLSI recognizes separate breakpoints for cefazolin against Enterobacterales specific for the treatment of

Page 206

uncomplicated UTIs. However, for the FDA's susceptibility test interpretative criteria website, separate susceptibility test criteria for uncomplicated UTI are not recognized at this time. It is not entirely clear why the FDA does not recognize separate cefazolin breakpoints specific to the treatment of uncomplicated UTI. Next slide, please.

So, to summarize, breakpoints derived using urine PK where appropriate will allow the use of effective agents for the treatment of uncomplicated UTI, especially in situations where breakpoints based only on plasma PK would preclude the effective agent's approval or clinical use. And this is evident by the first-line agents, fosfomycin and nitrofurantoin, which both require urine PK for efficacy and alignment with their current breakpoint.

Some current challenges for agents used to treat uncomplicated UTI are inconsistent breakpoints and comments and minimal guidance available for using urine PK to support breakpoint. Possible solutions to these challenges would be guidance on situations and criteria of when it is

Page 207

appropriate to use urine PK, guidance on studies and required for breakpoint determination, a uniform approach to existing and future agents, and harmonization of agency recommendations.

So, in conclusion, you heard earlier from my other industry colleagues from Iterum and UTILITY about the challenges of uncomplicated UTI at clinical trials, such as the inclusion criteria and the stringency of the primary endpoint.

So, hopefully, this presentation helped illustrate another hurdle we face even after the clinical trials end, and that guidance and harmonization on deriving breakpoints using urine PK for agents being used to treat uncomplicated UTI are greatly needed, both for fostering new agent development and also for antimicrobial stewardship. Thank you so much for the time and for your attention.

DR. NATARAJAN: Great. Thank you for your presentation and your perspective. And thank you to all the speakers in Session 2. So, that's the conclusion of Session 2. So, before we move on to the moderated panel discussion, we'll have a short break.

Page 208

So, let's plan to meet back here at 2:10 Eastern Time. That's a little bit more than 10 minutes, and we'll see you the. Thanks.

(Break)

DR. KIM: Good afternoon, everyone. Just give me one second. So, this is Peter Kim, again. I'm here with Dr. Hooton and we will be moderating the panel discussion. I will also be introducing Dr. Hooton. Dr. Thomas Mack Hooton is a voluntary professor of clinical medicine at the University of Miami, Miller School of Medicine and has recently retired as the chief of medicine at the Miami VA.

He has dedicated his professional career to the clinical care and research in infectious diseases and has focused his research on the epidemiology pathogenesis treatment and prevention of UTI in women. And has published hundreds of journal articles, book chapters, and abstracts on UTI, as well as on antimicrobial stewardship, sexually transmitted infections, and HIV/AIDS. So, thank you, Dr. Hooton for joining us this afternoon.

Page 209

Before we begin, I will go over a few ground rules. For each question, we have a set amount of time for discussion. As you can see in your agenda, we want to try and stay on time so we can adequately address each question. Second, we are hoping to have a wide representation of viewpoints on this issue. So, panelists, please raise your hand and we will call on you in the order you raise your hand.

Given the limited amount of time and the interest in hearing from as many panelists as possible, and depending on the number of raised hands, we apologize in advance, but if there are a lot of people that want to provide an opinion, we may have to interrupt individuals after a few minutes in order to allow others the chance to speak. With that, Dr. Hooton, would you like to introduce question one? Um, Dr. Hooton, if you're trying to talk, you may be on mute.

DR. HOOTON: I guess I am, yes.

DR. KIM: Welcome.

DR. HOOTON: I thought all this was being handled centrally but I guess I had to do

Page 210

something here. Thank you very much for the intro. You can hear me now?

DR. KIM: Yes.

DR. HOOTON: Okay, good. So, we have three questions here. I'm going to take the first one. Peter will take the second one. The first question for our panel is please discuss the pros and cons of the currently recommended composite, clinical plus microbe primary endpoint for uncomplicated UTI studies. What we've done here is for each of the three questions is to have a person lead off the discussion just to get it going. Calpana is going to get us going down that right path.

People, please chime in, raise your hand, we'll call on you in the order that you raise your hand. To answer Barbara's question, if you have a question about anything related to this topic, raise your hand, whether it's been discussed for or not, if you have something new to say. Kal, can you lead us off please.

DR. GUPTA: Sure. Thanks very much, first of all, for putting together this really

Page 211

interesting discussion. I will start up by saying for this specific question about a composite endpoint, I have a couple of points I'd like to throw out there and get some feedback from the panel.

First of all, probably need to acknowledge that we've heard some interesting and maybe even conflicting data this morning in terms of endpoints and what their relevance is for our patients with UTI. But also, the importance of having some consistency across different regulatory agencies and also guidelines. And also, the need to understand the microbiological effect of the anti-infectives that are being approved by these agencies. So, all of that needs to be taken into account.

But I think in terms of the question about a composite endpoint, it's easier for me to talk a little bit about what I think the challenges are with the composite endpoint and then we can go from there. One issue is that when you use a composite endpoint, you end up limiting the ability to really see the clinical affect of the therapeutic that's being studied given that the microbiological rates

Page 212

tend to be relatively low in terms of success rates.

That's true to the comparator, typically, as well. But I do think that we have heard, again, this morning that there's probably some area for real growth in our ability to understand the microbiology of uncomplicated UTI. We know that somewhere in the range of 25 to 50 percent of women who come in with symptoms of acute uncomplicated UTI may not have a positive urine culture, at least the way that it's measured in the laboratory in terms of having a significant number of CFU per mil.

And then the question is can we really then exclude all those women from uncomplicated UTI trials and then rely on the people who did have a positive urine culture. And then, once again, have this positive endpoint at the test of cure and also follow-up visit that requires them to have complete clinical resolution and typically a reduction, not necessarily an absence of pathogens in their urine.

So, that's number one, is are we using appropriate inclusion criteria? Or should we be keeping these women who come in with classic symptoms

Page 213

of uncomplicated UTI and doing modified, intense treat analysis, including those women. Number two, in terms of the outcome, do we keep the clinical and micro-outcome together? Or can we separate them to really help us understand what is happening with the patient on both levels but not creating this mixed outcome, which may be hiding, perhaps, a potential clinical benefit of an agent, even if you don't see the microbiological eradication.

I think, thirdly, since we've been given some conflicting data, what is the relevance of that persistence microbiology at the end of treatment? Does it really have relevance? And do we need to have a slightly longer follow-up of our patients in these studies so that we can understand not what happens at 14 days, but maybe what happens at 30 or 60 days after end of treatment.

And then a third question is when we talk about clinical outcome, we know when we take care of these patients, there's such a diverse presentation for uncomplicated UTI in terms of the clinical symptoms. To require all of those symptoms to be

Page 214

completely resolved in order to call it a clinical success, for me, at least in practice but also as an investigator, becomes a little bit artificial because many women will continue to have some small symptom present. Often it will be improving. It's not clinically significant, meaning not requiring additional therapy. I've often wished that we could use something like requiring additional therapy as the barometer of whether someone has clinical success or failure. Those are a couple of things that I'd really like to hear from others on the panel about. We can start with those questions. I see some hands. I'll turn it back to you, Dr. Hooton.

DR. HOOTON: Excellent points. Very good points. I see no raised hands. Peter, if I'm not seeing hands that are raised, please help out here. Do people have comments?

DR. KIM: I'm seeing raised hands. I think -- I'm not seeing the order, though. I don't know if someone from AV knows the order.

WOMAN 1: The order of the panelists you see listed are the ones that raised their hands

Page 215

first.

DR. HOOTON: So, I can't see any -- Peter, I can't see any raised hands, so you're going to have to handle this. There are no raised hands on my screen.

DR. KIM: No problem. No problem. Dr. Salim Janmohamed, please go ahead with your question or your comment.

DR. JANMOHAMED: Thank you very much. I'm working with Nicole on the clinical development program for (inaudible). And I think we've heard a number of points made. Perhaps I could just formulate on the back of Cal's commentary as follows.

I think the pro of the endpoint, theoretically, seems sound. We're looking at measures that we would utilize in clinical practice. I think the question is whether they are validated, whether the stringency of their definition is perhaps set too high. We've heard mention that looking for complete eradication of bacteria, some people have views on that. We've heard about whether it's cogent to expect complete resolution of symptoms.

Page 216

It's the combination of those two, without necessarily knowing whether they vary in time, in parallel. And setting a threshold at a level which might give you specificity, but the performance characteristics of that measure may be suboptimal and could potentially underestimate treatment effect.

I think just from a clinical practice point of view, if I see a patient, for whatever condition, in general, and they say, "Do, I'm 95 percent better," according to the criteria that we use in here for symptom change, that would be counted as a failure. Of course, particularly, if they've not required additional intervention in the form of additional antibiotic therapy. Certainly, in clinical practice, that would be a success.

So, I think it goes to the point about what is a reasonable expectation, does it conform to clinical practice. I think exploring the performance of different thresholds of what is considered an adequate clinical response, I think would be very helpful to all concerned. It's not to say that if you have persistent symptoms forever,

Page 217

that's a good thing. But, of course, there's lots of confounders. Someone maybe have been encouraged to drink a lot of fluid. They may be continuing to drink a lot of fluid. They may have some further urinary symptoms. There's also not enough distinction made between the different symptoms. It may not be appropriate to weight them equally, particularly in people who got baseline symptoms, which have been clouded by the acute episode. We know post-menopausal women do have urogenital atrophy. And some of them may well have baseline urinary symptoms which will never disappear. I think in a pragmatic clinical trial, you would like to think you've excluded those patients, but they do creep in.

I think again, it reflects on the sensitivity and specificity of the definition of the endpoint. We've heard about discordance from the micro point of view. But I think the same thing could be said. We don't really know for sure whether there is discordance the other way around. And of course, somebody's got very sever blood and mucosal inflammation may have a

Page 218

microbiological eradication, but they may just be slower to improve their symptoms.

I think I would say in terms of the definitions of what is considered an adequate therapeutic response, that ought to be investigated. We've heard from Cal just now that looking in the longer term to see how that pans out might be helpful.

I think the counterpoint is that these trials can be quite burdensome for a short treatment. This has been highlighted particularly during the pandemic to have a visit, a baseline, to have one on therapy, to have one at test of cure, and then potentially one at 28 days. I mean, they're all justifiable from an academic intellectual point of view. But as we heard from others, we need to foster and encourage clinical development.

I think given that medical practices change so much, that we have remote consultation, some way of accommodating the changes in practice with remote visits, some way of being able to mold clinical development around the new reality, I think is important to consider.

Page 219

One thing I want to highlight, also, is the presumed evaluability rate. I just want to echo the comments that were made earlier, is that in practice, these are substantially lower than might be expected. That has a commiserate affect on the sizing reprogram and the practicability of completing a program. So, I'll stop there.

Just in brief, I think the primary endpoint definition looking at performance characteristics with different thresholds, particularly symptoms, as well as microbiology, I think would be an enormous step forward. Because we're all interested in knowing what predicts a successful outcome. I think the current definition is worthy in the sense that it's very stringent. The question is it overly stringent and actually negating development or possibility of development. Thank you.

DR. HOOTON: Okay. We have several hands up. Dr. Natarajan, you first, I guess.

DR. KIM: Actually, I think it's actually, the next person is Dr. Dimitri Drekonja. I apologize if I'm mispronouncing your name.

Page 220

DR. DREKONJA: No worries, Drekonja. I'll be brief. I would just echo the thoughts -- Thanks for having this conference. It's really great to hear this perspective from so many folks. I would just say that including a micro endpoint as part of the composite primary endpoint, to me seems problematic until we have a clear and consistent data set that is a relevant endpoint.

It's great to collect as a secondary endpoint. But to mandate it as a primary one when we have conflicting date seems misguided, to me.

The second point is it really generates confusion. I'm at a teaching hospital and our clinicians tend -- You know, they're trained to emulate clinical trials. Here we have to tell them that no -- yes the trial will do this, but you shouldn't do this. It generates confusion.

Lastly, as someone who just completed a pragmatic trial, extra visits make it really hard to recruit. If someone is coming in for a 60-mile drive for a visit, sometimes more, especially now with the price of gasoline, it is a burden to say

Page 221

that if you're going to do this, you need to come back in several times. We did most of our recruitment virtually. And I'd really encourage that.

I think having that micro endpoint makes it much more difficult. And I'll leave it at that. Thank you.

DR. KIM: Thank you. Mac, I think the next person in line is Dr. Trautner.

DR. TRAUTNER: I think it's Dr. Natarajan, but I'm not picky either. I don't think we're too worked up about it. We're all going to get to speak.

So, you know, we're hearing a lot of consensus for what we care about is the clinical outcome. I do want to add a few caveats around that. It has to be in a blinded trial, of course, because clinical outcome is subjective. You know, people are going to feel better if they know they got something, so it definitely has to be in a blinded trial. But I think we're all most interested in the clinical outcome because we don't really know where bacteria becomes symptomatic UTI.

Page 222

That said, as an investigator, when I'm reading a clinical trial, I definitely want to see the microbiologic outcomes. I think those need to be included because they're going to tell me, you know, in a sense, in the human model, does this antibiotic decrease the number of bacteria in the human bladder? I think that's important data. I don't know that it should be the primary outcome. But I definitely would like to see it. And I would like to see it in the majority of people that are in the trial.

That brings me to my last point here is that there are issues with the urine culture and the threshold for the urine culture. I think we've all seen that woman that had a "positive" -- had a "negative" urine culture. But really she has 10 to the 4th organisms. And the lab's cutoff is 10 to the 5th. Anyone who's been studying this clinically knows that because you're doing your own urine cultures and you're streaking them. And you're seeing there are bacteria there, they just aren't meeting that 10 to the 5th threshold.

I suspect in the human bladder that the number of

Page 223

counts of bacteria goes up and down all the time, just in the course of a day, depending on hydration status and voiding. Just like in those dynamic bladder models that we saw. So, it's hard to determine what threshold really matters.

And then another problem with the urine culture threshold of 10 to the 5th is I do think there are uncultivable organisms that can cause symptoms. It is unequivocally true that there are uncultivatable organisms in the bladder. We know that from 16-S sequencing studies. Aracocus comes up a lot, as well as well as actinobacillus. And neither of those will spoil on a standard plate.

Whether or not those are accounting for the symptoms in some of the culture negative patients, that I can't tell you. But I do know that it is possible that there are organisms there that we are not catching with our standard culture techniques. So, to me, those are all arguments against making the microbiology an essential part of the primary outcome. But I would definitely want to continue to see the microbiology results. Thank you.

Page 224

DR. KIM: Thank you. Dr. Natarajan, sorry for skipping over you, initially.

DR. NATARAJAN: It's all right. It's no problem. Thanks. This is Mukil Natarajan from the FDA. So, I think Dr. Trautner kind of covered what I was going to say already, a little bit. I just want to make a couple points. One is that we do look at both the clinical and micro endpoint data separately, in addition to them as a composite. The current recommendation is that the composite is the primary endpoint. But we definitely would be interested in those individually, so those data are not ignored.

So, the real question is what should be the primary endpoint. And, you know, at the end of the day, we are evaluating an anti-bacterial drug. As far as I know, there hasn't been a lot of effort in other kind of mechanisms that would potentially treat an uncomplicated urinary tract infection, perhaps immune based, you know, symptom -- directed at symptoms.

So, we know that that's the mechanism of action and the goal of treatment, obviously, is

Page 225

clinical improvement. We are very interested in the micro data. If a drug doesn't, you know, doesn't appear to have micro activity as mentioned earlier, it really raises questions about how well it is effective, even if it has clinical efficacy in the short term. I'll stop there. Thanks.

DR. HOOTON: Peter, if I may, I don't think anyone is arguing that micro shouldn't be considered as an outcome. Just that it not be part of the primary act up.

DR. KIM: Thanks, Mac. Understood. I believe, Mac correct me if I'm wrong, I think Janice Tufte is next.

DR. HOOTON: Yes, looked like it on my screen.

MS. TUFTE: Hi. Thank you for having me here today. I just want to say it's been very interesting as a patient, and I've learned a lot of words. You know, I really hadn't thought about break point. Endpoint I understand. So, it's been a bit of a challenge learning.

What I know personally, what a number

Page 226

of you have brought up in this discussion, is that like my test might turn negative. And recently I discovered, you know, they were doing two or three tests on me for UTIs and that there was bacteria. I was able -- it wasn't showing up in my chart. But I did find out that in a number of the organisms that we've discussed today, at various points were in it. But evidently, I did not reach the, you know, the threshold to take endobiotic. Although, I was taking them anyway for another reason at the time.

But I think it's very important when we're talking about clinical trials, this is a side note because I'm very involved with equity, that we really reach out to individuals from different backgrounds and be sure to include them in this. Because, you know, if some of the important clinical trials are from years ago, it's very important to reach people that aren't normally involved.

And regarding the elders, like myself, who do take, you know, Estradiol, whatever, is a careful to try to figure out where it's -- it's a balancing act, kind of, not to take too much. Because

Page 227

if you take too much, you can have UTI like symptoms. Or if you take too little. But I have had UTIs even under this treatment.

So, you know, we can exclude them, but we have to be very careful because people can certainly still get a UTI even though they're on certain treatment. I just wanted to add that.

And I think a good point somebody else brought up, when the patient feels better, right. Somebody said shared decision making. You know, if patient feels it's resolved, then you don't need another antibiotic, then that's something to think about. But there's a lot of -- I think it's very, very personalized. And somehow that has to be built in. Thank you.

DR. KIM: Thank you. I believe that Dr. Stapleton is next with her hand raised.

DR. STAPLETON: Hold on a second. Let me -- So I may get an echo. Are you guys getting an echo?

DR. KIM: Yes.

DR. STAPLETON: I think what I'm going

Page 228

to have to do is -- because my microphone is connected to my phone. Any AV suggestions for this?

MAN 1: Could you unmute your -- could you mute your computer mic if you have your phone on? Or your computer speakers, could you lower it?

DR. STAPLETON: It's already muted. I can try again.

MAN 1: It's not horrible.

DR. STAPLETON: Is that better?

MAN 1: Or just try to turn down your computer speakers itself, just a little bit.

DR. STAPLETON: Okay, how's that?

MAN 1: Kind of the same.

DR. STAPLETON: I could drop -- I could leave the meeting on the computer. Maybe that will work. Let me try that. Okay, can you hear me now? It's more normal? Okay. It was just easier to see the slides, but I can make the phone bigger from here on in.

I was thinking because of struggling with Paxlovid rebound in the last few days and the rest of my life as an infectious disease doctor, we're

Page 229

thinking a lot about what are the consequences of still having the organism around in these patients who are, you know, obviously a viral pathogen. Then also thinking about newer concepts that the bladder is never really sterile.

I think these guidelines about completely getting rid of symptoms and completely getting rid of bacteria have a sort of a feel, to me, of predating information that we have gathered over the last decade or two that the bladder's never really sterile. There are gradation of bacteriuria and, of course, viral shedding in the case of -- what made me think of this, a Paxlovid rebound situation that many are dealing with.

If we could, I think as has been mentioned by several people, have a better understanding of what happens. Since we all know, I think, we recognize that clinically, we don't completely eradicate symptoms, usually. We don't completely eradicate uropathogens. If we do, we often end up against, coming up against collateral damage, such as C. Diff. or other things. Even using

Page 230

antimicrobials that are not associated with that kind of outcome.

So, studies that would look at how good does it have to be in terms of symptoms. And if it isn't perfect, what happens a month later? And how does it have to be (inaudible) reduction of bacterial counts. What is a threshold, if there is one, that is associated with not getting a recurrence or not requiring a retreatment in the near future and, I guess, the far future?

What is the far future that is appropriate? Because there are other changes that would impact the risk of UTI that could confound that question, as well. I'll put myself back on mute.

DR. KIM: Thank you, Dr. Stapleton. Dr. Brittain, I think you're next.

DR. BRITTAIN: Hi, yeah. This is Erica Brittain from NIAID. I'm a statistician at NIAID. So, I'm probably going to say a lot of things people have already said. But just quickly, it certainly bothers me about the composite endpoint that two drugs could look the same on that, when in fact, one could

Page 231

look -- one could be better on a clinical endpoint, that those two things can happen at once.

And to have the approval based on the composite when, in fact, there's a difference on the clinical seems problematic. But I understand the appeal of the composite endpoint. And wonder if it should be more of kind of a joint endpoint, whether it's officially co-primary or one is like a key secondary or something on that order.

And I also want to make the point that -- I haven't heard anybody talk about this, but I would still think you'd want, even if you went to a clinical endpoint, you would still want the primary population to be in the micro, for the primary analysis to be in the micro positive population because it is a non-inferiority trial, we want to make sure people really do have the infection.

Now, you could have a larger study where you include people, the many people who don't actually have positive cultures, but not for the primary. Yeah, I think that was it. Thank you.

DR. KIM: Thank you. Dr. Evans, I

Page 232

think you're next.

DR. EVANS: Thank you. I thank the sponsor, the FDA, and the other speakers for their thoughtful presentations. I understand the complexities associated with today's proceedings. I appreciate the efforts to understand the challenges and the data.

The current primary efficacy endpoint is really a composite of what you might think of as the short -- the shorter-term response, which you're able to measure through the clinical response component focusing on symptoms. But the other part of it is the longer-term response, measured by microbiological component, as a surrogate, essentially, for relapse.

Now, there are some questions, really, about the relative importance of the microbiological response component, particularly relative to the clinical response component. The current endpoint treats them of similar importance because if you fail on either one, it implies overall failure.

So, it could be argued that the

Page 233

clinical outcome is the most immediate importance for patients, as it reflects immediately on impacts, patient symptoms. Yet, there's this, also -- you know, this important evidence that says microbiological response would predict -- is predictive of relapse and longer-term outcomes.

So, in absence of following patients for longer term outcomes, one idea might -- or one question might be might there be a compromise that, one, prioritizes the immediate and most important clinical response component? And two, recognizes the important increased risk for relapse and longer-term outcomes with a failed microbiological response.

So, for example, for each patient, when you consider clinical response and microbiological responses, there's four possible outcomes for a patient. The patient either has clinical response with or without microbiological response or clinical failure with or without the microbiological response. So, there's an ordinal nature to those four possible patient outcomes.

And so, a patient centric sort of

Page 234

desirability of that outcome ranking could be defined with four levels, the most desirable level is the -- is there's appropriate response in both. The least desirable is the failure on both.

There are two levels in between. And if you prioritize the immediate clinical response, the second most desirable outcome for the patient is a clinical success but a microbiological failure. And below that would be a microbiological success but with a clinical failure.

Analysis can then be conducted recognizing finer gradations of these responses through evaluating and comparing the distribution of this patient level outcome based on the desirability of what's happening. I'll stop there. Thanks.

DR. KIM: Thanks Dr. Evans. I just want to doublecheck, Dr. Botgros, I saw your hand up. I'm not seeing you at the moment. I just wanted to make sure that –

DR. BOTGROS: Thank you very much, Dr. Kim. I don't know if you can see and hear me. Actually, indeed, I had my hand up. I just lowered it

Page 235

because many of the points I was trying to make were already expressed.

I think, you know, what I'm a little bit puzzled about, having heard some of the comments is the fact that some of the speakers were speaking -- were talking about total eradication in the micro endpoint. Whereas here, we are actually looking for a reduction of CFUs (inaudible). And, you know, antibiotics are working on pathogens. That's reality. And therefor, I think for us as regulator, it's important to understand in how far they have activity on the bug.

It's very interesting what we just heard from the previous speaker with regard to the four possible outcomes. I'm really wondering for an antibiotic, if you would -- I mean, how often, really, you would see situations in which the micro-outcome would be a failure. So, that, essentially, the antibiotic would not reduce the burden of pathogens but then the patient would be a clinical success.

I can't understand that there will be such situations. But I would imagine that in order to

Page 236

make sure the drug is working on what it's supposed to work, we would need to see, also, some activity at the microbiological level. Obviously, what I'm saying now is not as a regulator.

But I've seen on one of the presentations there were -- I think there was some wet banner saying this is the entry point for important drugs that can be used for other indications. And I'm not advocating for, obviously, off-label use. But frankly, even more so, we need to make sure the drug is working on the bug or the bugs that are in the antimicrobial spectrum. I'll stop here. Thank you very much.

DR. HOOTON: Peter, we have three more minutes this session.

DR. KIM: Thanks, Mac. And welcome back. Thank you. I know you were having some weather issues. I thought I saw Dr. Iarikov's hand up. I just want to make sure that I'm not missing him on my hands up list.

DR. IARIKOV: No, Peter, you're not. I lowered my hand because a point I wanted to bring up

Page 237

(inaudible). I'm good. Thank you.

DR. KIM: Okay. Next, I believe, Dr. Trautner, again.

DR. TRAUTNER: Yes, sorry I don't want to take up all the time. We're having an interesting discussion about bacterial eradication. People are studying non antibiotic approaches to treating UTI. And some of that may involve leaving -- modifying the virulence of the organisms. It doesn't necessarily mean they won't be in the bladder. It's just that they won't be causing as much inflammation and tissue destruction.

So, that may be for trials of the future as a consideration, particularly for bacteriophage as it comes along.

And then, of course, someone mentioned desirability of different outcomes, I think that's called the DOOR strategy, desirability of outcome ranking. And it's becoming an increasingly popular strategy in infectious diseases clinical trials. But I could not speak to the details of that study design.

DR. KIM: Mac, I'm checking with you.

Page 238

Do you see any other hands up?
DR. HOOTON: No, I think it's 2:50, about. So, I think we go to the next topic, Peter.
DR. KIM: All right. Thanks everyone. Excellent discussion on this issue. We'll move on to the next question, which is Question NO. 2. Please discuss what would be acceptable active comparators in uncomplicated UTI, non-inferiority studies. And for this question, we were interested in having Dr. Stapleton kick off the response.
DR. STAPLETON: Okay. I am going to be fairly brief because this is a shorter discussion, and we have lots of questions from the last one. So, I'll go back to -- You don't have to see the slide, I've got it here, about nitrofurantoin and why did I say among the first line therapies that we have right now for UTI this would be our best comparator.
Well, the resistance rates are relatively low. And they've been pretty durable over the last several decades. So, we wouldn't be likely to have, using nitrofurantoin in a middle of a trial, starting to have local rates to change and become

Page 239

higher. There is minimal adverse effects and collateral damage, which is what we would like to have in our study drugs. While we hope that we're not introducing more problematic agents as much as possible into the armamentarium.
It has the tablet formulation, which makes it easier to study it. And it does treat only cystitis, which is not a huge issue. But is nice to know that if you have the emergence of, say, a protractor or non-bladder symptoms or signs, that that would be potentially already present at the time, or at least -- not necessarily that, but it gives you the opportunity to think about your definitions of eligibility and ineligibility when you put people into the trial.
And so, you would be able to tell how many people failed because the upper tract wasn't being covered when you're using nitrofurantoin as your comparator drug. And I think that's all I'll say. Others can make comments.
DR. KIM: Anybody have comments?
DR. HOOTON: Well, I have a comment

Page 240

while we're waiting on hands. Ann, how about suplisforance -- we don't want to use floquidalonce (inaudible). But how about suplisforance?
DR. STAPLETON: Well, as you know, we published two trials showing that in comparison with -- I think both times it was floquidolon, unfortunately, that we saw higher rates of recurrence after the trial and more rapid recurrence. I would have to say in my UTI clinics, this is what I see as my most common consult, which is people who give more and more courses of typically something like Keflex, cephalexin and sometimes even longer.
So, it's the idea of well, we have to hit it harder, or we have to treat longer. And perhaps, it irradicate bacteria from this person or irradicate all symptoms, which is, of course, a separate issue. But I commonly see that presumably because of both vaginal and gut, microbiome disruptions and changes, that people have long clusters of recurrence, often of the same organism, even with the same antibiogram.
So, I do not advocate using beta-

Page 241

lactams in clinical trials, mostly because of the -- our previous data and my anecdotal experience as a care provider for UTI patients.
DR. KIM: Thanks, Dr. Stapleton. Dr. Trautner, I see your hand is up.
DR. TRAUTNER: Yes. So, I didn't realize I guess until this meeting, the FDA wanted the active comparator to be one of the guidelines recommended drug. I think what's interesting is to look at what people are actually using because that's what is considered the active drug in that setting.
For example, at my hospital, what's recommended for uncomplicated UTI is Cefpodxime, followed by ciprofloxacin. And that's based on the local resistance of antimicrobial resistance at our facility.
DR. HOOTON: You mean for uncomplicated UTI, you don't use -- (inaudible) is not your first line?
DR. TRAUTNER: It is not. I didn't like the recommendations, locally. But it's driven by what is the resistance profile of the organisms that

Page 242

are in the urine of the patients that walk into our clinic, male and female.

DR. HOOTON: Well, we're talking about uncomplicated UTI, here. Most people are using that term for women only. So, for women with uncomplicated cystitis, you would use a fluoroquinolone or cefpodoxime. That's really surprising to me.

DR. TRAUTNER: No, my preference is (inaudible). But I'm just saying, there are -- you can look at (inaudible) does something similar, which is our public health system in Houston. So, I think given that the current guidelines are 12 years old and it's going to be a little while before we have new guidelines, we might be wanting to broaden our choice of active comparators.

DR. KIM: Thanks, Dr. Trautner. I believe MR. Hadley, you're next with your hand up.

MR. HADLEY: Thank you, I appreciate it. And I completely understand the desire to move towards nitrofurantoin because of the resistance. But does anybody see any issues using nitro with its low susceptibility for anything other than E. coli?

Page 243

Especially if you're trying to look at a number of different bacteria through the study.

DR. Hooton: Well, luckily, with uncomplicated cystitis, the E. coli is the -- is the main pathogen. So, it's not a huge concern. The other thing about uncomplicated UTI that we haven't discussed today is it's a very mild disease, by definition. If it's more serious than that, it shouldn't be considered an uncomplicated UTI. So, if you fail therapy, it's not that big a deal.

So, what you want to try to do is minimize the collateral damage, I think, which is why we try to avoid fluoroquinolones in general.

MR. HADLEY: Agreed. But doesn't that beg the question, then, why not do placebo-controlled studies if it's such a short course of therapy?

DR. HOOTON: I certainly have no problem with that. I think Ann raised some good points about just the practical difficulties of doing a placebo-controlled trial. If you look to complete a trial, in the United States, anyway, I think you're going to have a little trouble.

Page 244

MR. HADLEY: Agreed, yes.

DR. KIM: Dr. Natarajan, I think you're next with your hand raised.

DR. NATARAJAN: Thanks. Thank you for everyone else's comments, too. I just wanted to make a point about, not specifically about the active comparator. But people are talking about resistant data driving what to use for uncomplicated UTI and I just wanted to, you know, point as usually, as has been mentioned several times today, that urine cultures are rarely obtained in clinical practice for UTI.

So, I don't know if we really know the real micro -- the resistance spectrum of uUTI if we're not getting cultures. And usually, cultures are obtained when patients aren't doing well. So, we may be skewed towards more resistance than what's actually out there, at least when we look at larger studies, you know, out in the community. Obviously, clinical studies might be a little bit more representative. Thanks.

DR. KIM: Thanks Dr. Natarajan. Dr.

Page 245

Gupta, I think you're next.

DR. GUPTA: Great, thanks. So, I guess what I'm hearing is the question is do we have to have one answer? I hear some really good rational for nitrofurantoin. I don't disagree with the concept that Dr. Trautner brought up, which is using something that a lot of clinicians use, even if they're not number one on the current guidelines, but just suplusforin.

And it may depend on, you know, the therapeutic that's being tested. It wouldn't be fair, I don't think, to use a suplusforin as your comparator if you are looking at something that has activity against ESBL. But potentially, if you're looking at something more narrow, then a suplusforin might be a good idea. And then if you do have something that has activity against an ESBL, then nitrofurantoin might be your choice.

I don't really like the idea of placebo-controlled trials for UTI because I think it underestimates the burden of UTI in women when they have even uncomplicated UTI. There is a burden of

Page 246

symptoms that affects their lifestyle. And there's a rate in placebo-controlled trials that we already have in our hands of a higher rate of pyelonephritis. I don't think that we need to go to that extent.

I think we can find an active antibiotic comparator for people who truly have UTI based on their symptoms. And yes, also including the microbiology. So, those are my comments. Thank you.

DR. KIM: Thank you, Dr. Gupta. Dr. Trautner?

DR. TRAUTNER: Yes, I'll second that. I don't agree with a placebo control. Many people, when talking about women with uncomplicated UTI are suffering actively. We don't want to not treat them. There's the risk of pyelonephritis, which is two to five percent. We know that from placebo-controlled trials. There's the need to shorten the duration of suffering, which we also know from placebo-controlled trials, can be done with antibiotics.

I was going to comment on the very astute mention that we don't know what's in urine culture of people with uncomplicated UTI because we

Page 247

haven't looked at that. Three groups kind of have now. One was a large national study where they had everyone with UTI symptoms get a urine culture. We did a small one locally. We actually found very high resistance. In Houston, Texas, we have a lot of international patients and ESBL was, I think, about eight percent in our uncomplicated UTI urine cultures in people that would not normally have had a urine culture.

In terms of what bug is nitrofurantoin right for us, only 56 percent of those cultures grew E. coli, 21 percent would be strep. And then after that, you had your kleb and your proteus accounting, combined for about 10 percent. So, nitrofurantoin would have worked except for that about 10 percent klebsiella and proteus. That's why our guidelines actually have, let's see -- Our county guidelines recommend nitrofurantoin followed by septinere, followed by Bactrim for uncomplicated cystitis in women.

Again, I didn't write those, either. But that's just the reality of what's being used in

Page 248

Houston, Texas.

DR. KIM: Thanks, Dr. Trautner. Next, I believe, Dr. Janmohamed has the hand raised up.

DR. JANMOHAMED: Yeah, I thought it might be opportune to ask, as we're talking about nitrofurantoin in the context of global studies, given that you don't have complete harmony with CLSI, the data and (inaudible) kind of getting older now. Where there might be some need to try and get some harmonization of what is a nitrofurantoin susceptible organism. Because they're not, as far as I know, exactly the same, according to the definitions.

Is there some possibility of getting some convergence to facilitate global studies?

DR. HOOTON: Good point.

DR. KIM: So, Dr. Janmohamed, are you talking about CLSI versus UCAL?

DR. JANMOHAMED: Yeah, I mean, having singular definition what is considered nitrofurantoin susceptible organism according to a singular break point, yeah. Or definition of susceptibility. I mean, you know, you can cut the data according to

Page 249

different definitions, but it does complicate things. We're talking about a comparative like nitrofurantoin. That seems to, you know, number one in terms of guidance and in terms of covering (inaudible) or at least E. coli.

Just opportunistically, I wondered if there's -- some consideration might be given to it. I'm not expecting a solution today. But as we have our EMA colleague here and you're here, whether, in terms of fostering global development, that might be something to – you know, that might help.

DR. HOOTON: You know, there's no one drug that's perfect for a comparator for a trial like this. So, nitrofurantoin -- and I have no stock in nitrofurantoin. It seems like a reasonable drug.

And Barbara, to your point, nitrofurantoin probably should have activity against Group B strep. So, it has activity for some bugs, not all bugs. And you showed before 22 percent susceptibility in that national survey. But E. coli is still resistance is still quite low.

The probably, certainly with the

Page 250

fluoroquinolone and resistance. And with the beta lactam. Beta lactam may be fine. I have no problem with that, either. It's just that Beta lactam generally haven't performed as well. So, we don't have a perfect drug to use as the active drug in these trials.

But nitrofurantoin has a lot of attributes. And it has activity against ESBL. So, that's -- in your area, that would make sense, to me, unless these bugs are resistant to nitrofurantoin. Eight percent is very high for ESBL in uncomplicated cystitis.

DR. KIM: Thanks, Mac. And then, Dr. Janmohamed, we would likely need to include members from CSLI and New Cast as well in order to reach alignment on break points beyond FDA and EMA. But point well taken. Thank you.

Mac, I'm not seeing any other hands. Are you seeing any other hands?

DR. HOOTON: I thought I saw Barbara's. Barbara, did you -- No? Okay. No, nothing on my screen, Peter.

Page 251

DR. KIM: Okay.

DR. HOOTON: Shall we go to the next one?

DR. KIM: Yes, please.

DR. HOOTON: Okay. I'm going to start out. But again, the hand raising, I'll leave to you because it's not clear who raised their hand first on my screen.

Okay, so the third topic is please discuss the pros and cons regarding the use of urine specific break points for the development of antibacterial drugs for uncomplicated UTI. Please also comment on what studies would be helpful to evaluate urine specific break points. Dr. Rodvold is our leadoff speaker on this one.

DR. RODVOLD: Thank you. What I presented, as well as my colleague from GSK presented, I think we're in agreement that we think this is very important for drugs that have a high concentration in the urine for uncomplicated urinary tract infections versus their serum concentration. What exactly is high concentration that meets this has probably got a

Page 252

little bit of debate.

Historically, you go back, and you see statements made that high concentrations in urine, the drugs is going to be efficacy. And you can't really fake it that way, I think, anymore, with what we know about PK and PD.

The second thing is that while the concentrations are above the MCI, so that should be drug effective. It goes back to understanding the drug you have, the drug you're developing and what it's PK and PD driver is, as I showed you. So, is it turning on the curve AMIC, the time above AMIC, what is it?

And getting a parameter that gives you what you think you need. Again, we don't have a clear definition of what stasis is the most important or is one-fold CFU decrease. There's debate about that within the literature. I think in uncomplicated, it's probably statis but I don't have a lot of data to back that up and tell you that.

And as I had mentioned, too, so that's a -- so, those are studies preclinically you could

Page 253

sort out. I think the suppression of resistance is also important so that these drugs do have a longevity to it. As I showed you with the GSK data with jepto didiosin that, you know, they had done nicely where they showed you what it took to kill it in that one log and then also what suppression is. And then showed you the uranic concentrations using a higher MIC in the range that reflected not only susceptible E. coli but also some resistant E. coli so that you have adequate enough coverage of that.

So, I think there's a pro to do it as long as you have these high concentrations that are present. But at the same time, you have the aspect of you need the pharmacodynamics to be defined for you and as well as PK. PK in the urine has got high variability use off of my colleague speakers. And doing these studies myself, I can tell you that we do a lot of penetration studies. I'm more in lung penetration but urine is no different. You know, you have variability that's 100 percent at times.

So, you have to act -- you have to accurately collect urine concentrations to reflect

Page 254

those values. The Glaxo data that I showed you, they collected every two hours over a 12-hour period, which was their sampling -- which was their dosing interval. And a lot of times, historically, PK studies that have urine collection, they're only really doing to get the recovery of how much drug is there.

So, you know, you'd have to do the trial that reflects, that gives you a good balance of urine concentration to understand that profile to be able to go against those kinetic dynamic markers.

I think other studies you could do pre-clinically is that, as was shown by the Australians, is the models that are being used for urine now in vitro that allow you to do a lot of things. They have a very complex model that you can do multiple pathogens with multiple susceptibilities. You have urine voiding going on that isn't a model and is illustrated.

Again, doing these studies is that, you know, even when you do it Phase 1, you have healthy volunteers in the study that you control. You almost need a Phase 2 study to have patients to see do they

Page 255

match up the same things that you have with healthy controls. Again, the GSK data, they did a nice small study to confirm what they got out of Phase 1, what their in vitro showed, as well in vivo studies had showed to take them there in place.

Those are the -- those are the drug development issues, you know, that are here. There's a practical issue after this, though. You know, I talk to people in COSI in prepping for this meeting. While COSI and UKS has this data, they're emphasizing a lot because they're hard to implement. For the lab tech, they don't know whether or not this is an uncomplicated or a complicated urinary tract infection. Or is it even a urinary tract infection.

You're potentially talking about that needs a urinary break point. Remember, those urinary break points that you see on the slide I illustrated as well as my colleague presented, that's for only uncomplicated urinary tract infections. And so, they don't know which break point. If there's a set for serum versus a set for UTIs, they've got to know the set for UTI and is the tech going to be able to

Page 256

interpret that right.

In addition to that, automated panels are already loaded with how many MIC testing they can do, even per drug. So, like the Cefazolin model that we showed you, you know, there was two break points -- three break points because there was an intermediate for that of serum. And then you had two different break points for urine. So, that's five points that you're bringing up.

So, there's implementation issues that come after this in how to interpret that information, if that was going to be used clinically. Now, that's the -- you know, an issue whether or not that's even practically needed and/or to do.

The final -- a couple final comments I talk to you about, as well, is that -- is looking at this kind of information and sorting through what it all means is that so far we've gotten to this point because people said these drugs work. And they've got these high concentration, so let's elevate it. With really no outcome data, necessarily.

And so, we need outcome data that

Page 257

probably matches whatever MIC that you're using. If it's a urinary MIC, which we're kind of assuming it's going to be, does that correlate with what you see in the clinical trial of outcome. And does it, you know, fairly well work to do it. So, you need initially finding what it is, finding out what the PD marker is, simulate what your dosages are, and then see does it work in the clinical trial in relationship to outcomes.

You know, you've had discussion going on before this, do you need microbiological data? Well, yeah, you kind would need it for this, too, to see that you actually -- these break points work against the pathogen or not. But that's, you know, that's a different fold than what you're looking at it as an efficacy marker for approving a drug.

So, those are some comments. I'm sure there's plenty more that could be made on this issue that are both considerations of what we have and then what we could do and then the kind of trials. Every drug would have to be, you know, coming through the agency, would probably have to be individualized

Page 258

because they all have their own PK, PD characteristics. The type of trial you can and can't do because of the issues of the models you're using. And to get to this urinary break points. So, I'll stop there and let others chime in.

DR. HOOTON: Good points. Any questions or comments? So, Nicole? Nicole Scangarella?

MS. SCANGARELLA-OMAN: Can you hear me okay? Just trying to come off of mute. Just want to completely agree with everything that Dr. Rodvold said. Really our key goal with depotitozine was to do a lot of the work, non-clinically, to really help inform our dose selection and then move into the clinical program, which is obviously still ongoing.

So, the hopeful outcome will be demonstrating the clinical efficacy to tie all those together. But just wanted to echo many of the points that he made. As you saw between our two presentations, we had similar views on a lot of these aspects. But some guidance documented in, you know, guidance documents and COFI documents on what can be done around urine break

Page 259

points would be helpful to sponsors, especially those that may not be as familiar with this area as others.

DR. HOOTON: Great. Dmitri?

DR. IARIKOV: Thanks. I was just going to agree with Dr. Rodvold that the process of sort of getting that pre-clinical data and then getting clinical outcome data is really important. And then I think the final point that needs to happen is implementation, how to communicate to practicing clinicians, not just ID docs of what this means. What does it mean when you have a drug that has a urinary break point?

We're used to communicating this with nitrofurantoin and Fosfomycin, already. If there's more out there, it's still a concept that some people really struggle with, when can you use a urine only drug and when can you not. So, figuring a good way to communicate that to people on a broader scale is going to be really important if we do this. Thank you.

DR. HOOTON: Nicole, your hand is still up. You've got another question?

DR. SCANGARELLA-OMAN: No, apologies, I

Page 260

haven't put it down yet, thanks.

DR. HOOTON: Any other questions, comments? I don't know how you pronounce your name. Grace, you're up.

DR. DANIELSEN: Hi, Grace Danielson, pharmacology at FDA. I just want to comment on the use of urine concentration in the (inaudible) or break point determination. We certainly recognize the relevance of the urine concentration to support the UTI indication. However, we have some specific concerns. For example, as others have pointed out, urine concentration carries large (inaudible), so that can significantly affect the accuracy of the PTA prediction.

And secondly, in order to use the urine concentration quantitatively in the PT analysis, we would need a specific PK, PD parameters. And we have limited experience with that approach. And using the urine concentration, (inaudible) urine concentration to reach a plasma target from a fly model, as shown in some of the presentation, there is some concern.

So, how relevant is the target from a

Page 261

pharm model using (inaudible) concentration rather than for UTI indication? So, as the previous presenters mentioned, there's multiple (inaudible) models for new UTI. And each carries some strengths and limitations. I think for a robust PK, PD package will include the non-clinical models to see how to better align with each other.

At this point, we need to see more data to feel more confident using the different non-clinical models to support the urinary break point. Thanks.

DR. RODVOLD: I don't disagree with anything you said, to be honest with you. I'm trying to emphasize that a lot of this is in its infancy at this point. When I inherited this topic from the agency, I thought I'll find all this stuff in the literature. There's hardly anything in the literature to go on. Like I said, I talk to CLSI people. Even within CLSI, there's debate about the how important -- what the importance is and how to interpret it depending on who you're talking to.

And then you get into the

Page 262

implementation problems I talked to you about with a micro lab. In the development, I totally agree with you. We haven't modeled urine concentrations to a great degree. So, I think we need to take slow steps. In doing this, we're going to have to learn how to handle that, maybe physiological modeling would be a value to us in this situation.

But again, we haven't do a lot of that with urine. Again, once you move away from plasma, we start to struggle with other matrices. And this is not going to be any different here. I think there's a lot to be gained. You have an RFP out for looking for studies and trying to help define this. I think you need to look at some of the data that came out of Abbot's group and others that have done some of this to try to put these pieces together at this point.

I think you're going to have to take it one by one. I think the Glaxo data and their outcome will give you an idea of maybe an initial way of doing. But that can always improved again. And again, drug specific depending on what's coming through the agency at this point.

Page 263

The other problem is the comparator drug will likely not have a lot of information, either. And so, that will always be sitting there of understanding what it is. That may not be the major issue in the development yet. But that's up to you guys.

DR. HOOTON: Peter, I went off again. I missed the conversation.

DR. KIM: No problem, Mac. Dr. Rodvold was responding to Dr. Danielsen. For the most part in agreement that we all need more experience with the non-clinical model in development of urinary break point. Dr. Danielsen, it looked like you were about to –

DR. DANIELSEN: Yeah. I had one comment to point out. I understand it is very difficult to collect this PK, PD data for uUTI. And also considering the difficulty to collect accurate urine samples and determining the urine PK, PD parameters, I'm wondering whether we can use a plasma PK as a surrogate for urine concentration. Similarly, as what we do for like lung infection model for split

Page 264

pneumonia.

We can (inaudible) use the human plasma PK to match the plasm target determined in the relevant animal infection model for uUTI. We would have to consider the potential species difference in the renal equation between the animal species and the human. Thanks.

DR. HOOTON: Hand up, Tomefa Asempa. Tomefa?

DR. ASEMPA: Yes.

DR. HOOTON: Are you on?

DR. ASEMPA: I am on. Let's see. Can you see me?

DR. HOOTON: Yup, you're good.

DR. ASEMPA: Great. I'd like to echo a lot of what Dr. Rodvold and Grace have spoken about. It is very challenging setting up these models and trying to wrap our heads around what urine specific break points actually mean.

To Grace's point, what we try to do is establish the PK/PD parameters in plasma. And then do efficacy studies in the UTI model. And that's

Page 265

because, like the reasons that have spoken about, getting urine concentration in vivo is a challenge. So, we do that in plasma.

But it seems from this session that we're going to have a lot of data from GSK and from Adverum because they've done a lot of work in Phase 1 and Phase 2. So, if we could somehow collaborate and essentially, from the ground up, work up a new -- a new platform for understanding urine specific break points in vivo, I think that would be great and do us a lot of justice in trying to rethink how to do this because we've not had a lot of data previously.

So, this has all come out in the last two, three years. So, I think this is certainly a good avenue to do that. I know the FDA has put out an RFP on that. So, I'm just trying to reach across the aisle so we can work on that. Because it's a tremendous gap in our knowledge because we just don't have our hands on clinical urine data to try to replicate that in the Mouse or Porcine model. Thanks.

DR. HOOTON: Good point. Other comments? As a clinician, it's not clear how you

Page 266

train clinicians to provide the laboratory with clinical data or to be able to interpret what the laboratory sends you in terms of whether you should be using -- what break points you should be using. That's a chronic, ongoing problem. I don't know how to fix that.

It would seem simple that physician knows that if he's treating a UTI, he should be using the urine break points when they're available. But that is not always simple to do, I guess.

Anyway, any other comments? Peter, we're a little early. Do you want to take any comments on the other topics?

DR. KIM: Sure. We have a few minutes. If people have additional comments on either of the other comments or additional thoughts in general.

DR. HOOTON: I think they're worn down. It's a good session.

DR. KIM: A robust discussion. Thank you, everyone. And thank you, Mac, for being a co-moderator.

All right, so at this point, I am going

Page 267

to summarize the discussion that we had. And then we'll close the day out. So, here I go.

At the beginning of this morning, Dr. Trautner provided an overview of the current state of clinical care for uncomplicated urinary tract infections in the United States. She discussed how the definition of uncomplicated UTI has evolved over time, past, present, and future. As we await the new IDSA guidelines, as well as uUTI epidemiology issues with bacterial resistance and patient risk factors for resistance, treatment recommendations.

She also highlighted the results from recent trials and their outcomes. Dr. Trautman noted the several knowledge gaps in the field, such as the relevance of asymptomatic bacteriuria.

Next we heard from Dr. Mobley. He discussed virulence factors and other properties of bacterial strain that cause uncomplicated UTI. And noted that horizontal gene transfer generates a variety of E. coli pathotypes, uropathogenic E. coli or upac are genetically diverse. And virulent gene expression may vary between patients.

Page 268

DR. Mobley noted that the mouse model recapitulates gene expression in women with uncomplicated UTI. It has been observed that during infection, core genome expression is conversed, but ribosomal genes are over expressed, and amino acid transporters are up regulated, which is associated with rapid growth in the urinary tract.

Next we heard from Dr. Asempa, who discussed the current state of antibacterial PK/PD in uncomplicated UTI animal models, including the utility and limitation of each of the models, such as the porcine and murine models. He also noted that urinary break points -- urinary end points and break points may be challenging to ascertain in rodent studies and robust in vivo studies defining PK and PD are yet to become available.

He also noted that the use of preclinical studies may help to de-risk clinical development.

Next we heard from Drs. Roberts and Abbot who discussed the role of dynamic in vitro simulations to inform treatment decisions in

Page 269

uncomplicated UTI. They provided an extensive review of previous UTI in vitro models, outlined key considerations when simulating UTIs. Discussed comparability to animal models and correlation with clinical outcomes.

They noted that there are unique in vitro considerations when simulating the treatment of UTIs. That the in vitro models can be flexible and provide robust and microbial PK/PD data. That they can compliment and inform in vivo models. And beyond their use in preclinical use evaluation, in vitro models can potentially provide insight throughout the clinical development program. Help to optimize currently used antibiotics and inform UTI specific clinical susceptibility break points.

Then we heard from Dr. Rodvold. He discussed how clinical and nonclinical PK/PD information can be used in drug development decision making for uUTI. For example, in dose selection and break point setting. And considerations regarding plasma versus urine specific break points for drugs for uncomplicated UTI. He noted that nonclinical and

Page 270

clinical PK/PD programs need to be individualized for the specific agents that are being developed for uncomplicated UTI.

And that urine specific break points should incorporate clinical efficacy data and PK/PD analysis. And that PK/PD consideration may help to minimize risk in clinical development.

We then heard from the patient perspectives from two individuals. We heard from Ms. Tufte who provided patient perspective on her experiences with UTI. And noted the need for patient centered considerations in care, that clinicians should look at UTI holistically. That patients, she reminded us that patients want to understand what they can do to prevent further UTIs and to understand treatment options and to have their values and goals respected and documented.

We then heard from Ms. Price, who discussed her experiences with UTIs throughout her life. She's had UTIs that ranged in years from four to five to 12 to 15 per year, including UTIs due to ESBL and MDR pathogens. She's been treated with both

Page 271

oral and IV antibiotics based on the pathogen. She noted that there have been times when she, symptomatically, have developed a UTI. But the initial culture was perceived as negative. And she called out for the threshold for positive cultures may be currently too high.

She also noted her concerns regarding poor communication about her condition from prior physicians. However, more recently, she was thankful for an IG physician that she met who was able to explain her condition and possible other treatment options. She disagreed with the silos of uncomplicated UTI and recurrent UTI and noted that many patients like her are suffering with current UTI.

Next, we heard from Dr. Clancy, who discussed the urgent need for novel agents to treat antibiotic resistant bacterial infections, including uncomplicated UTI. That there may be potential use of the uncomplicated UTI indication as a gateway indication to developing drugs for indications with great unmet need. He highlighted the role of clinically meaningful endpoints, the role of

Page 272

stewardship, and the importance of guideline development and revision in a timely manner, as well as the need for economic incentives to support anti-bacterial drug development.

We then heard from Dr. Natarajan, who provided an overview of the FDA's current thinking on the development of drugs for uncomplicated UTI, including trial design considerations, active comparators for non-inferiority trials, patient entry criteria, primary efficacy, end point considerations, the importance of assessing the microbiological response in the end point, analysis population, and non-inferiority margin considerations.

We then heard from Dr. Botgros, who provided an overview of the European Medicine Agency's current thinking on the development of drugs for uncomplicated UTI. He discussed the recently revised EMA guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections, including uncomplicated UTI. He noted alignment between the EMA and FDA on many design considerations for uncomplicated UTI, including but not limited to

Page 273

the use of a composite primary end point for uncomplicated UTI studies, as well as the use of a 10 percent NI margin.

We next heard from Dr. Kadry, who discussed discordance of clinical and microbiological endpoints in clinical trials for complicated UTI. She noted that she analyzed data from 13 Phase 3 complicated UTI trials that had been submitted to the FDA as part of new drug applications. And the primary analysis population was the micro modified intent to treat population. She noted that in this database, 18 percent or 871 patients were identified as clinical cures with microbiological persistence.

And noted that compared to those with concordant success on both clinical and microbiological end points, those patients with discordant results clinical cure microbiologic persistence had more bacteria remaining in urine immediately following the end of therapy. Also, these patients with discordant results were more likely than successes to become clinical failures by the long-term follow-up end point.

Page 274

That discordance became clinical failures by developing symptoms. It would suggest that persistent bacteriuria post treatment of a complicated UTI may increase the risk of late symptom development in cUTI, acute pyelonephritis and acute pyelonephritis in women.

She also noted that the risk of late clinical failure increased with time. And that microbiologic eradication appears to be an important consideration for the composite end point.

Next we heard from Dr. Stapleton who provided a clinician, investigator's perspective on the development considerations for anti-microbial drugs for the treatment of uncomplicated UTI. She discussed comparators for uncomplicated UTI in non-inferiority trials. The challenges with recruiting and retaining participants in clinical trials as well as stewardship concerns for drugs targeting resistant pathogens.

Regarding choice of comparators, she noted that a case could be made for nitrofurantoin as a reasonable comparator among the current first-line

Page 275

therapies. Regarding challenges with recruiting and retaining participants in clinical trials, she noted that electronic health record-based management of uUTI may impact both recruitment and retention of patients with more telehealth related visits, less face time with patients. Protocols with multiple visits may be in person visits may be difficult in this situation.

She also noted the challenges associated with enrolling patients with antibiotic resistant pathogens, such as ESBL producing enterobacterial. And that targeting patients with ESBL pathogens blends issues of participant eligibility and practical aspects of comparator agent consideration.

Next we heard from MR. Hadley, from Utility Therapeutics. He provided a developer's perspective on including criteria and end points for uncomplicated UTI trials. And noted that increasing the colony forming unit counts from 10 to the 3rd to 10 to the 5th for inclusion into uncomplicated UTI studies reduces the pool of eligible participants for these studies, essentially making the studies more

Page 276

expensive to conduct.

He also asked for consideration in the adoption of overall response to include significant clinical improvement instead of complete absence of symptoms.

Next we heard from Dr. Puttagunta from Iterum Therapeutics. She provided a developer's perspective on the primary end point in uncomplicated UTI trials and lessons learned. She discussed Iterum's experiences with bacteriuria in participants post treatment and noted that asymptomatic bacteriuria did not lead to clinical failures at later time points.

She also noted that higher rates of ASB in participants treated with sulopenem were not associated with election of penin resistant organisms. She also discussed that in Iterum's uUTI study oral sulopenem was statistically superior to ciprofloxacin for overall response among participants with organisms resistant to ciprofloxacin. The micro MITTR population. And that oral sulopenem was not inferior to ciprofloxacin for overall response among

Page 277

participants with organisms susceptible to ciprofloxacin, the micro-MITTS population.

The difference in overall response in the micro-MITTS population was driven by ASB. Clinical success rates in the micro-MITTS population were similar between oral sulopenem and oral ciprofloxacin arms. And that higher rates of ASB did not lead to lower clinical success rates of (inaudible).

DR. Puttagunta concluded her talk by noting that ASB should not be a component of the assessment of overall response to treatment in uUTI trials. And that clinical response would be a more appropriate primary end point.

We next heard from Ms. Scangarella-Oman from GSK. She provided a developer's perspective on urinary break point. She noted that guidance and harmonization on deriving break points using urine PK for agents being used to treat uncomplicated UTI are greatly needed for new agent development and antimicrobial stewardship.

She noted the drug levels at the site

Page 278

of infection, in this case the bladder, are clinical relevant to the demonstration of antibacterial efficacy in the treatment of uncomplicated UTI. That the application of plasma PK would not support the break points for some agents currently used to treat uncomplicated UTI. However, application of urine PK for these agents would support the break points, such as for nitrofurantoin and (inaudible).

Regarding consideration to support the utility of urine PK for break point for agents used to treat uUTI, she pointed out the need for guidance on situations and criteria for when is appropriate to use urine PK and on the studies required for break point determination. She also noted that a uniform approach for existing and future agents by current and updated standards and also the importance of harmonization of agency recommendations.

From there, we moved on to the panel discussion. Okay, so regarding Question 1 in the composite end point, there was a lot of discussion about the use of a clinical only end point, how there should be consistency across guidelines, as well, and

Page 279

whether it would be possible to separate the clinical from the microbiological response.

There was a thought that more work may be needed to understand the relevance of clinical response. That if we were using a clinical only end point, there may be a need for longer follow-up, out to 30 or 60 days. There was then a discussion on whether clinical symptoms would need to be completely resolved or mostly resolved to the point where no further antibiotic treatment would be needed.

We also had further discussion on different ways to assess the clinical and microbiological end point, such as potentially DOOR type of end point where we potentially separate out clinical and micro into clinical success-micro success, clinical success-micro failure, etc. And to evaluate the gradation of overall response.

In addition, there was further discussion regarding the threshold for enrollment based on urine culture in clinical trials. That perhaps 10 to the 5th may be too high and that further discussion may be needed from that perspective.

Page 280

Let's see. All right, then we moved on to Question 2 and acceptable comparators. Dr. Stapleton lead off the discussion and noted that nitrofurantoin may still be an appropriate comparator agent in clinical trials given, in general, the relatively low rates of resistance, the minimal side effects, the fact that it can be given in tablet form, and that it is focused on treating cystitis.

There was a discussion about whether beta lactam would be used as comparators. There was concern with higher rates of recurrence with beta lactam. We also heard from Dr. Trautner that in some regions, particularly in her hospital system, current uUTI therapies are, at least, leading therapies are Cefpodxime, followed by ciprofloxacin.

Let's see. There was also a discussion on the utility or whether or not to use placebo-controlled trials. There was concern about the use of placebo-controlled trials due to the wanting to reduce symptom burden and to prevent the potential for the development of pyelonephritis, given that there has been noted to be a risk, two to four percent, in prior

Page 281

placebo-controlled studies of pyelonephritis.

We also heard about the need for harmonization of susceptibility test interpretive criteria between CLSI and Newcast for nitrofurantoin.

Regarding Question 3 and the pros and cons of urine specific break points, Dr. Rodvold led off the discussion and noted the importance of understanding each individual drugs' PK/PD drivers. There was a discussion on whether the targets should be statis versus, at least, a one log drop in colony forming units, the importance of suppression of resistance. And the fact that in order to get a sense of urine specific break points, there is a need to collect many samples of urine concentrations to understand the profile of a drug.

There was also further discussion on the fact that urinary break points are of interest, but they may be difficult to implement given the automated panels are already quite loaded. And also, discussion on how to best educate healthcare practitioners about when to use a urinary susceptible interpretive criterion versus plasma.

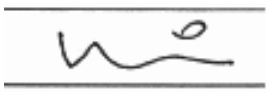
And that there's a need for further guidance on urinary break point development. There was also further discussion on how preclinical work is important ahead of the clinical trials to further define urine break points.

All right. With that, I'd like to thank everyone for their participation. And I'd also like to thank the AV staff, as well as the amazing amount of help that we received from Sunita and also from the Office of Infectious Diseases. So, with that, once again, thank you for a robust discussion. I wish you a good afternoon. And with that, we'll close out the workshop. Thank you.

(Whereupon, at 3:45 p.m., the proceeding was concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, IRENE GRAY, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



IRENE GRAY
Notary Public in and for the
DISTRICT OF COLUMBIA

CERTIFICATE OF TRANSCRIBER

I, SONYA LEDANSKI HYDE, do hereby certify that this transcript was prepared from the digital audio recording of the foregoing proceeding, that said transcript is a true and accurate record of the proceedings to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

/s/ Sonya Ledanski Hyde
SONYA LEDANSKI HYDE

0

0.001. 193:6
0.05 139:17
0.05. 152:10
0.75 55:9
0.75. 55:14

1

1 5:15,18 6:6 7:6 20:14 29:18,20 36:18 37:12 83:9 93:5 135:1 136:20 149:1 185:1 214:21 228:3,8,10 228:13 254:20 255:3 265:6 278:19
1,000 31:21 93:14 156:6
1,500 29:11
1.4 24:5
10 22:14 25:13 29:10,20 30:17 33:11 39:11 45:18 45:19 47:1,1 57:12,13,16 71:14 71:17 75:10 77:18 77:20 81:7 87:4 106:9 134:19 135:10,12 137:17 139:6,15 140:13 148:19 149:10,12 151:7 157:1 158:19,21 160:9 184:20,21 185:10 185:11,11 186:7 186:10,10 188:6,6 188:9,9 191:16 193:15,22 194:12 208:2 222:15,16 222:20 223:7 247:14,15 273:2 275:19,20 279:21
100 14:9 20:16 25:11 30:15 35:2 84:10,15 188:16 253:20
1000 84:10
108 31:22
10:00 176:11
11 26:1 135:11 149:11 185:11 196:4
12 34:9 37:11 81:16 113:17 135:12 149:12 185:12 192:14,18 193:10 194:6 195:1,6,6 196:3,5 196:7,8,11 242:12 254:2 270:21
128 59:9
12:20 130:7
13 135:13 149:13 156:16 185:13 273:7
14 19:18 20:3,7,9 20:10,11 22:8,12 22:15,16,19,20 23:4 39:21 40:1 41:4,5 57:20,21 135:14 149:14 162:20 185:14 213:16
14799 283:17
15 113:17 135:15 149:15 185:15 196:9 270:21
16 72:11,21 135:16 139:3 149:16 185:16 195:9 196:10 223:10
17 35:12 39:13 135:17 149:17 185:17
18 59:15 75:15 88:16 113:8 135:18 149:18 157:12 160:11 185:18 192:9 273:11
180 43:13 81:5
19 135:19 149:19 185:19
1965 83:17,19
1966 69:19
1978 70:22
1982 35:8
1984 31:20
1990s 70:16 71:6
1b 59:15,15

2

2 14:2 21:1 58:21 59:15,17 77:20 82:13,15 83:9,13 90:15 93:5,5 130:7,10 135:2 149:2 185:2 207:20,21 238:6 254:22 265:7 280:2
2,500 106:7
2,600 29:2
2,653 40:1
2.5 25:14
20 16:4,7,12 17:11 21:14 87:4 104:15 135:20 149:20 183:22 185:20 188:1 189:8 199:19
200 93:14
2000 13:10 14:1
20001 1:11
2000s 71:7
2001 13:1
2002 186:2
2004 27:12
2007 13:2,4
2009 140:14
2010 8:10 9:16 12:6 17:3 19:13 142:1
2010s 16:11
2011 156:13
2015 18:16 19:4
2017 18:22
2018 15:15 130:22
2019 9:22 12:6 18:19 19:4 27:12 123:5,6,6 131:19 156:13 185:9
2020 15:15
2021 10:4 12:8
2022 1:7
2027 106:7
20s 105:22
21 135:21 136:10 137:1 149:21 185:21 247:12
22 16:7,8,8 135:22 149:22 185:22 249:19
22.4 45:12
224 22:11,14
23 20:14 22:14 27:9
24 32:2 88:16 147:9
240 196:2
247 196:7
25 21:13 212:7
26,000 29:9
26.6 193:4
27 42:5
28 20:12 21:10,21 22:10,18 136:10 137:1 192:15 195:3,5 196:9,13 218:13
2:10 208:1

2:50 238:2

3

3 1:7 58:19 60:7 82:17 83:13 91:14 95:8 135:3,12 149:3 156:16 158:20 184:19 185:3,11 186:9 188:5,8 189:21 191:15 192:3,14 193:21 200:19 273:7 281:5
30 23:9 30:15 35:2 55:9,14 182:16 213:16 279:7
301 192:3
30s 106:1,1
310 139:11
315n 35:18
32 160:13 162:10 205:15
33 138:15,19
34 77:5
36 193:2
388 140:2
39 106:6
3:45 282:14
3d 73:6
3rd 275:19

4

4 5:6 20:14 45:15 135:4 149:4 185:4
4,800 157:11
4.64 28:21
40 110:18 183:15 186:7
400 69:19
40s 106:1
418 186:8
43.7 138:12
44 163:3
483 186:8
49 138:14
4th 45:18 222:16

5

5 45:15 77:18 134:18 135:5 149:5,12 158:18 159:10 184:20 185:5,11 186:6,9 188:5,8 192:14 196:1,4,6
5.16 28:22
50 13:18,19 14:9 41:18,19 125:7 138:20 212:7
500 29:1 46:3
5073507 1:13
531 18:3
56 247:11
57 57:17
5th 45:19 222:17 222:21 223:7 275:20 279:21

6

6 88:3,8 135:6 149:6 169:3 185:6
6.3 14:1
60 213:16 220:21 279:7
61 138:11
62.6 193:1
64 204:14 205:1
65.6 138:15
67 193:11
6th 57:13

7

7 19:18 42:3 135:7 149:7 185:7
7.5 55:9,14
70,000 29:12
70s 49:9
75 18:22 125:20
79 193:12

8

8 135:8 149:8 185:8
8.6 13:4
80 45:18 81:6 139:16,22 186:5
80s 71:5
84 194:8
86 39:7
87 59:17
871 273:12
88 39:15 43:11 58:21
8th 33:11

9

9 135:9 149:9 185:9
9.2 42:17
90 14:1 51:12 139:17 204:7,12 204:22
95 112:22 138:15 193:4,13 194:10 216:9
96 75:12
9:00 1:8
9th 57:13

a

a.m. 1:8 47:1
aac 92:14
abbot 67:13 268:21
abbott 2:2 62:21 63:9,20 67:10,12 87:7 96:10
abbott's 87:21
abbot's 262:15
abdominal 132:8 143:3
ability 52:4 177:7 211:20 212:5 283:10 284:7
able 6:15 47:16 50:17 54:4,19 56:5 60:21 64:17 65:14,18 70:9 91:15 95:8 104:17 111:17 114:2,18 118:8 123:18 174:4 179:10,14 182:5 186:16 218:20 226:5 232:11 239:16 254:10 255:22 266:2 271:10
abnormalities 9:20 132:16 141:19 142:18
abnormality 10:19 154:20
absence 11:14 114:20 212:19 233:7 276:4
absent 129:7
absolutely 124:17
absorption 72:8 79:11
abstracts 208:19
abuse 123:20
academic 189:9 218:14
accept 148:18
acceptable 4:20 133:10 139:4 148:14,21 150:9 152:21 204:9 238:7 280:2
accepted 201:16
access 112:8
accommodating 218:19
accompanied 105:8 132:11 143:2,11
account 66:1 86:11 93:20 97:4

138:20 164:19 177:14 186:20 187:17 211:14
accounting 223:14 247:13
accumulation 90:3
accuracy 260:13
accurate 71:3 115:1 263:18 283:9 284:5
accurately 253:22
achievable 146:4
achieve 80:6 190:22 193:9 195:20
achieved 50:17 59:1 157:3 192:22 193:21 194:9 196:15 203:20 204:11
achieves 204:22
achieving 56:10 157:14
acid 40:17 41:9 46:10 268:5
acids 38:17,21,21 40:18 46:12
acknowledge 62:8 112:5 135:16 149:1 211:6
acknowledged 58:9
acknowledgement 120:18
acquire 106:17
acquired 35:3,13 125:10,17
acquisition 34:17
act 127:22 129:10 225:10 226:22 253:21
acting 111:20
actinobacillus 223:12
action 145:13 146:1 224:22 283:12,16 284:8 284:12
activate 30:6
active 4:21 32:19 113:11 116:4 132:22 133:13,14 134:1,3 137:10 138:8,22 139:2,13 169:21 192:4 238:7 241:8,11 242:15 244:6 246:5 250:5 272:8
actively 69:2 246:14
activities 101:19
activity 71:10,19 87:18 88:5,7,22 125:2 135:22 145:18,20 146:3 225:3 235:11 236:2 245:13,17 249:17,18 250:8
acts 151:11
actual 57:15 76:22 117:15 136:1 159:17 164:7 178:6 185:17
act's 128:3
acute 10:14,15 18:2 35:7 45:20 132:9 141:15 143:8 149:6 155:6 156:15 161:15 203:11 212:8 217:9 274:5,5
adaptation 177:12
adaptations 74:21
adapted 70:12 71:5
add 91:10 120:16 221:15 227:7
added 75:16 76:18 77:1,13 78:1 100:4,10 103:14 143:21
addition 73:22 77:12 124:4 134:17 136:12 145:4 190:1 198:2 224:9 256:2 279:18
additional 69:1 77:4 131:19 153:8 153:10 214:7,8 216:13,13 266:15 266:16
additions 76:3
address 6:15,19 8:10 80:9 122:1 209:5
addressed 78:10 166:17
addresses 153:3
addressing 119:13
adequate 5:11 83:3 84:17 133:9 148:1 203:19 216:20 218:4 253:10
adequately 148:21 150:9 205:9,17 209:5
adherence 34:10
adhesins 36:1
adjust 161:4 164:6
adjusting 72:18
administered 60:2
administration 1:1 56:6
administrator 140:15
admittedly 25:17
adolescence 108:17
adopted 143:17
adoption 276:3
adult 10:1 12:7 13:16 21:4 109:8
adulthood 108:21
adults 12:8 24:6
advance 174:12 179:20 182:3 209:12
advanced 26:9,21 103:4
advancing 122:11
advantage 64:17 64:21 98:15
adverse 172:11 239:1
adverum 265:6
advice 8:20 144:2 180:8
advisors 104:8
advocate 240:22
advocates 166:22
advocating 236:9
aeruginosa 30:21
afebrile 19:21 21:4
affect 52:11,12 69:8 78:17 94:20 114:3 126:8 211:21 219:5 260:13
affiliations 5:7
africa 114:4
afternoon 6:17 27:3 111:8 165:7 189:12 208:5,22 282:12
agar 78:9
age 13:17,19,21 14:1 109:8 112:12 158:13 164:9

aged 112:13 192:9
agencies 203:7 211:10,13
agency 4:8 140:7 140:12,14 143:14 144:6 207:4 257:22 261:16 262:22 278:17
agency's 272:15
agenda 5:6 209:4
agent 16:17 19:2 48:18 86:4,15,16 86:20 88:22 96:2 97:12 147:21 150:5,16 170:8 200:9 207:15 213:8 275:13 277:20 280:5
agents 4:21 17:4,8 19:10 20:4 23:13 47:12 81:4 86:14 86:19 93:21 95:12 97:15 98:11 124:3 127:8,10,18 144:3 148:6 170:4 181:17 200:8 201:12,22 202:2,5 202:8 206:10,14 206:17 207:3,14 239:4 270:2 271:16 277:19 278:5,7,10,15
agent's 206:12
ago 87:4 100:9 143:18 183:21 184:1 226:17
agree 8:18 121:21 122:7,10 246:12 258:11 259:5 262:2
agreed 243:14 244:1
agreement 8:17 192:6 251:18 263:11
agrees 8:21
ahead 130:15 165:17 168:17 202:11 215:7 282:4
aids 58:21 208:21
aim 69:6
aimed 151:16
aims 63:6
air 99:16
aisle 265:17
al 70:17,22
alert 177:11
alfred 63:10
algorithms 122:16
align 64:19 144:8 261:7
aligned 10:6 143:14 144:9
alignment 144:16 144:17 184:9 206:15 250:16 272:20
alignments 144:4
allocate 41:12,13
allotted 5:10
allow 57:2 64:18 65:6 136:2 202:5 206:9 209:15 254:14
allowed 148:4 150:16
allowing 48:12 190:5
allows 48:17
alluded 97:20 125:4 167:3
ally 116:12 117:6
alpha 139:17 152:9
alternative 148:20 187:8
alternatively 77:22
alternatives 75:14
amazing 282:8
ambulatory 13:2
america 7:10 8:6 9:17 13:12
american 120:5
amic 93:17 252:12 252:12
amino 38:17,21,21 40:17,18 41:9 46:10,12 268:5
amount 48:22 75:11 79:8 84:17 158:5 163:2 190:2 209:2,9 282:9
amr 123:9 124:13 129:12
anabolic 42:8
analyses 155:17 158:6 203:13
analysis 91:12 98:13 137:4,22 138:13 144:22 148:1 151:5,22 159:6 213:2 231:15 234:11 260:16 270:6 272:12 273:10
analyzed 273:7
anatomic 10:19
anatomical 141:18 154:20
anatomy 50:5 52:1 132:10 143:10 155:3,8
ancestral 28:3
anecdotal 241:2
angela 21:2 22:2
angle 9:6 132:12
animal 31:14 47:20 48:1,11 50:22 56:2,14 57:4 60:21 62:15 64:2,6,10,12,14 64:17 66:21 67:1 67:20 80:15 82:22 89:21 90:2 92:17 264:4,6 268:10 269:4
ann 3:9 23:6 165:9 240:1 243:18
annual 128:21
answer 210:16 245:4
answered 52:7
answers 101:12
anti 4:3 47:8,12,19 48:2,7,9 62:9 63:8 77:12 81:4 127:9 131:1 140:16 154:1 211:12 224:15 272:3 274:13
antibacterial 5:1 138:8 139:3 144:3 146:3 147:21 148:6 150:5,16 191:17 200:18 201:10,19 251:12 268:9 278:2
antibacterials 199:21
antibiogram 16:18 17:12 171:20 240:21
antibiotic 7:8 14:15,21 18:22 19:2 22:16 30:10 66:4 72:18 74:1,5 75:20 78:9,9 79:4 84:20 99:17 104:13 107:2,14 115:5 116:21 117:13 120:15 121:15 123:5,10 124:18 127:4

129:11 145:14 147:1,7 151:10,17 153:3 161:12 183:21 191:5,6 216:14 222:5 227:12 235:16,19 237:7 246:6 271:17 275:9 279:10
antibiotics 11:10 23:17 70:3 83:20 96:19,21 101:4,21 102:7 104:13 105:5,19 107:7,8 107:9 114:6,8,12 115:16 116:20 119:6,9,9 121:8 123:2 125:13 145:15 156:14 190:21 235:9 246:19 269:14 271:1
antibodies 67:8
antigens 34:12
antimicrobial 1:3 4:10 63:15,17 66:20 68:9,15 69:7,8,13 72:8 74:17 76:10 77:9 79:7,20 95:12 120:5,7 121:2 123:3,7,17 124:1 127:5 129:3 144:12 180:9 190:8 200:10 207:16 208:20 236:12 241:15 277:21
antimicrobials 63:15 71:22 121:1 123:2 173:19 202:22 203:18 230:1
anybody 101:14 231:11 239:21 242:21
anymore 118:1 252:5
anyway 38:13 65:18 107:19 119:15 226:10 243:21 266:11
anyways 65:4
ap 162:3,4
apathy 109:12
apical 73:9
apologies 111:17 182:2 259:22
apologize 209:12 219:22
app 3:3
appeal 231:6
appear 156:10 157:7 160:18 161:10 162:14 225:3
appears 164:8,17 164:18 274:9
apple 168:5,5
applicable 49:21 137:21,21
application 65:6 99:5 146:8 278:4 278:6
applications 86:18 140:19 152:18 156:12,14 273:9
applied 188:14 202:19
apply 73:1
applying 201:12 201:21 202:2 203:13,20 204:11 204:19 205:7
appreciate 99:4 101:12 110:13,13 232:6 242:18
approach 11:5 89:18 207:3 260:18 278:14
approaches 4:17 6:4 94:10 119:12 237:7
appropriate 61:11 89:11 108:5 132:19 134:8 137:4 178:22 199:5 202:4 206:9 207:1 212:21 217:7 230:12 234:3 277:14 278:12 280:4
appropriately 176:13
approval 121:8 123:5 127:12,15 151:13 169:18 206:13 231:3
approved 47:11 48:10 86:20 124:14 134:2 183:21,22 202:9 211:13
approving 151:16 257:16
approximately 136:10 140:2
aracocus 223:11
architecture 73:9
area 9:11 31:5 71:16 73:13 78:18 80:1 93:16 128:4 183:18 184:2,5 212:5 250:9 259:2
areas 8:14,15 81:2 106:14 127:1,3 182:21 185:5
aren't 65:9,18 75:14 108:4 159:9 222:20 226:18 244:16
argue 90:22
argued 232:22
arguing 225:8
arguments 223:19
arlg 87:13
arm 139:11 171:1
armamentarium 239:5
armamentariums 128:15
arms 139:15 277:7
arrived 113:8
article 26:9 103:9
articles 208:19
artificial 214:3
arwen 43:7
asb 26:11,17,18 190:6,7 194:17,19 195:1,6,12 196:4 196:6,10 197:4,16 198:5,10 199:2 276:14 277:4,7,11
ascend 31:6 32:3
ascended 33:3
ascending 31:15 31:17 50:11
ascertain 61:15 268:14
asempa 2:3 47:6,7 47:13,14 62:13 64:8 67:2 264:8 264:10,12,15 268:8
ashamed 100:19
asia 111:14
asked 276:2
asks 125:21
aspect 76:22 83:12 85:19 87:2,10 91:11 95:10 197:14 253:13
aspects 7:5 124:17 140:18 188:5 258:20 275:13

assay 37:4
assemble 17:19
assess 56:5 60:15 78:17 160:13,14 190:3,7 279:12
assessed 135:2 136:13 145:20 194:3
assessing 272:11
assessment 65:6 114:16 136:14,21 190:6 196:22 198:17 277:12
assessments 25:5 78:8,15
assignment 152:1
assistant 177:6
associate 47:7 120:2 130:20 164:9
associated 8:22 28:15,16 30:13 40:16 42:4 61:5 64:9 86:4 90:14 124:6 198:13 204:3 230:1,8 232:5 268:6 275:9 276:16
association 132:15 141:12 142:17 159:2
assorted 159:17
assume 47:4
assumed 139:22
assuming 257:2
assumptions 139:13,18
astute 246:21
asymptomatic 8:12 25:12,19 26:14 29:15 30:8 122:12 126:21 190:4 193:18 194:2,15 195:18 196:16,19 197:7 198:16 267:15 276:11
atrial 168:5
atrophy 217:10
attack 126:7
attain 48:20
attaining 204:6
attainment 204:8 204:12 205:1
attending 39:8 165:10
attention 27:2 46:17 58:4 182:6 199:12 207:17
attorney 283:14 284:10
attributes 250:8
audience 172:9
audio 283:8 284:4
august 131:18
australia 63:12
australian 63:3,16
australians 254:12
author 10:11,12 83:18
authored 81:5 102:10
authoritative 133:19
authorization 140:18,19
authors 10:8 55:22 58:9 73:6 73:19 102:12
automated 256:2 281:19
autonomy 178:20
av 214:20 228:2 282:8
availability 80:11 114:6 155:14
available 17:8 46:12 62:21 104:11 124:14 149:10,18 150:17 155:17 169:17 174:10 179:13 183:14 203:2 206:20 266:9 268:16
avenue 91:21 265:15
average 28:20,22 45:10 83:22 84:2 106:20 113:16 160:6,8,13 162:9 162:10
avian 49:20
avoid 82:15 104:9 243:13
avoided 17:8
await 267:8
aware 14:10 103:17 108:4 109:18 122:15 125:1
awful 123:19
axis 55:17

b

b 3:3,3 72:7 88:9 95:21 249:18
back 13:1,8 26:16 33:1 38:22 59:19 70:13 83:19 85:9 87:1 88:18,19 89:10,20 90:21 96:5 101:12 107:19 115:13,17 115:22 144:19 153:14 173:13 185:7 186:3 187:20 208:1 214:13 215:13 221:1 230:14 236:17 238:14 252:2,9,19
background 6:3 112:11 132:2 166:7 172:6 175:19 202:12
backgrounds 226:15
backing 50:10
bacteremia 29:10 32:4 89:17
bacteria 24:16,16 26:14 27:16 28:6 29:15 30:9,13 32:3 33:11,18 36:6,8 38:15 40:19 41:3,11 42:6 43:15 44:1 44:10 45:7,19 46:2,11 50:12 52:5 53:11,19 54:1 56:10 57:18 57:21 58:2 60:4 69:2 76:20 77:15 78:1 86:9 88:6 89:2 110:19 113:18,21 114:3 114:11 116:20 120:8 124:1,4 161:11 163:9 215:20 221:21 222:6,20 223:1 226:4 229:8 240:15 243:2 273:18
bacterial 27:21 31:2 43:21 47:12 47:19 48:2,7 56:6 59:12 68:16,17 69:21 70:5,9 73:14,15 74:2,20 75:3 76:9 78:4,5 78:16,19,22 82:11 89:15 90:8 91:2 118:5 121:3

135:11 137:9 139:21 143:17 146:20 158:18 159:1,2,4,20 160:2,14 201:3 224:15 230:6 237:6 267:10,18 271:17 272:4,19
bacteriophage 237:14
bacterium 32:16 83:4
bacteriuria 8:13 11:17 22:3,15,17 22:18,20 23:2,4 24:22 25:12,19 26:3,15 27:16 39:15 50:19 122:12 126:22 190:4 193:18 194:3,15 195:19 196:16,19 198:16 229:11 267:15 274:3 276:10,11
bactrim 15:20,21 16:7,12 17:10 170:8 247:19
bad 13:7 25:9 44:2 113:17
balance 86:3 254:8
balancing 226:22
balb 57:17
ballpark 103:16
banner 236:7
bar 60:16 187:3,4
barbara 3:10 5:15 7:1 106:4 171:17 249:16 250:21
barbara's 210:16 250:20
barda 200:17
barely 19:6
barometer 214:9
barriers 102:14 103:10
bars 41:15,17
base 28:21,21,22
based 73:2 99:11 114:14 133:20 139:12 143:22 149:10,18 150:17 152:18 153:9 156:21 175:4 176:6 179:8 201:6 202:8 205:10 206:11 224:19 231:3 234:14 241:14 246:7 271:1 275:3 279:20
baseline 134:17 136:18 137:10 139:21 147:12,16 149:14 151:20 158:3,9 164:4 192:14,20 193:8 194:1 195:8 197:20 198:14 217:8,11 218:11
bases 152:3
basic 158:13,14
basically 170:9
basis 128:21 181:14 195:7
bat 103:14,15
batch 75:7,7
bath 69:21 108:20
bathe 106:16
battling 29:13
baylor 5:16 7:2
bcps 2:20
beads 71:21
bear 111:21
bearing 22:3
beautiful 43:7 53:2 55:10
becoming 178:8 237:19
becton 15:12
beg 243:15
beginning 77:14 91:13 98:1 267:3
behalf 67:10,13 120:1,12 129:17
behavior 73:15,15
behavioral 79:6
believe 11:5 58:11 105:17 110:2 135:21 137:17 151:12 176:3 225:12 227:16 237:2 242:17 248:3
bench 70:13
benefit 72:19 213:8
benign 132:17
benjamin 5:17
bensman 2:4 5:15 5:19,21
best 13:10 23:17 52:16 68:9 90:18 91:2 101:6 112:1 116:17 149:17 238:17 281:20 283:9 284:6
beta 17:6 23:14 70:18 125:3 145:16,16 240:22 250:1,2,3 280:10 280:11
better 66:21 87:3 92:3 97:16 114:18 118:8 172:16 185:3 190:5 216:9 221:18 227:9 228:9 229:16 231:1 261:7
beyond 11:11 12:9 67:3 79:10 158:16 160:5 250:16 269:10
bias 68:19 178:15
big 19:19 95:8 105:1 109:14 159:13 243:10
bigger 228:18
billion 106:7,9
bind 36:11,12
bioassays 80:12
biofilms 71:20
biological 74:18 140:10
biomarkers 24:10
biotic 63:6,8
birds 28:17
birth 112:17 113:7
bit 5:8 6:14 32:10 33:20 34:18 35:15 36:17 49:8 50:14 82:2 84:22 89:20 100:1 106:19 112:10 113:10 114:17 119:10 142:5 144:16 160:2 162:1 167:3 170:3 180:6 184:8 208:2 211:17 214:3 224:6 225:20 228:11 235:4 244:20 252:1
bl 146:4,5,10
black 34:3 44:1 180:6
bladder 9:1,18 10:16 11:11,13 12:9 24:12 31:6 32:19 33:12 45:22 50:10,18 52:1 53:14,19 56:7 57:19 69:2,8,15 69:16 71:2,21 72:11,13 73:3,12

73:18,20 74:8,14 79:15 91:20 92:17 109:9 116:10 132:16 155:1 201:17 222:6,22 223:3,10 229:4 237:10 239:10 278:1
bladders 52:11 58:17 59:12 71:13
bladder's 229:10
blends 275:12
bli 146:2,4,9,10
blind 132:20 150:21 192:4
blinded 20:6 221:16,19
blis 145:22
bloated 104:1
blocks 35:10
blood 25:5 35:6 50:12 124:6 142:19 217:22
bloodstream 46:1
blow 125:17
blue 15:22 33:17 41:15 158:11 197:21,21
bmi 158:13
board 59:19 81:17 92:2 189:7
bodies 133:19
body 152:22 153:1 202:17
bombarded 28:3
book 81:6 208:19
boston 130:14,19
botgros 2:5 140:8 140:8,21,22 234:17,20 272:14
bothers 230:21
bottled 106:18,19
bottom 36:13 44:1 44:3 55:13,18
bounce 26:16
bound 36:11 138:18 194:10
boundaries 178:22
box 6:18,19 36:21 180:6
boxes 41:5
break 5:1 46:22 47:1,3 103:11 129:22 130:6,8 171:18 207:22 208:4 225:19 248:20 250:16 251:11,14 255:16 255:17,20 256:5,6 256:8 257:13 258:4,22 259:12 260:7 261:10 263:12 264:19 265:9 266:4,9 268:13,13 269:15 269:20,21 270:4 277:17,18 278:5,7 278:10,13 281:6 281:13,17 282:2,5
breaking 42:8
breakpoint 81:21 88:11 97:4 200:22 202:3,20 204:9,14 204:17 205:3,6,10 205:15,18 206:16 206:20 207:2
breakpoints 61:14 67:10 68:11 82:1 89:19 90:2 91:16 94:11,13,17 95:18 96:7,8 99:8 146:12 200:1,6,7 200:21 201:1,6,10 201:12,22 202:4,7 202:14,22 203:3 203:15,19 205:21 206:6,8,11,19 207:13
breakpoint's 203:6
brief 167:15 201:1 219:8 220:2 238:12
briefly 8:10 23:6 30:13 63:22 87:14 154:8 155:22 156:11 169:13,13
bring 36:14 86:22 88:18,19 90:21 110:6 183:13 184:4 236:22
bringing 40:18 86:20 128:13 256:9
brings 24:20 43:14 222:11
brisbane 63:2
brittain 2:6 230:16,17,18
broaden 242:14
broader 259:18
broadly 125:1
broken 38:21 197:19
broth 69:22 75:2
brought 38:20 103:18 108:8 226:1 227:9 245:6
bsc 2:16
bug 60:18,20 235:12 236:11 247:10
bugs 57:8 63:8 158:17 236:11 249:18,19 250:10
build 188:12
building 42:9
built 227:14
burden 54:1 56:6 57:18 60:4 220:22 235:19 245:21,22 280:20
burdensome 218:9
business 175:17 176:9
buy 106:19 177:19

c

c 2:1 4:1 49:19 57:17,17 95:21 229:22
cal 218:6
calculate 45:6
calculated 204:5
calculations 80:9
california 165:12
call 9:15 20:16 35:1 104:21 129:7 175:1 209:8 210:15 214:1
called 34:10 111:5 237:18 271:5
calls 176:2,10 177:5
calpana 210:12
cal's 215:13
canada 110:16
canadian 110:16 112:8,11 117:8
cancer 123:15
canine 49:10
can't 11:21 31:16 66:1 115:15 117:22 118:1 181:20 215:2,3 223:16 235:21 252:4 258:2
capacities 75:22
capacity 68:6 109:9
capsule 34:15
capsules 105:17
capture 36:10
carbapenem 125:2

carbohydrates 46:13
carbon 38:17
card 39:11
care 4:14 7:13 11:8 14:11 24:15 100:2 108:14 109:9 120:21 121:13 122:5,18 123:15 124:18 133:15 167:8,14 168:1 173:2,7,14 173:20 174:2,5 176:10 178:21 180:2 182:21 190:12,20 199:9 208:15 213:19 221:14 241:3 267:5 270:12
career 208:15
careful 226:21 227:5
carries 260:12 261:4
carry 35:11 36:4 110:4 167:5
carryover 78:10
case 16:14 58:11 93:16 114:9 133:1 133:4 151:15 153:4 229:12 274:21 278:1
cases 11:18 18:8 25:16 26:5,6 65:18 82:16 93:19 95:4 125:12 175:3
cast 250:15
catabolic 42:7
catabolism 40:20
catch 47:18 174:1 191:3
catching 223:18
categories 28:9
catheter 30:13 154:22
catheterization 30:14
catheterized 11:20 12:13 30:14
causative 147:10 147:14
cause 8:4 28:6,10 28:11 29:10,16 30:8 32:3 50:12 50:13 52:5 109:5 125:8 156:8 180:5 223:8 267:18
caused 20:22 123:8 201:3
causes 77:20 90:6 161:5
causing 12:15 14:16 27:16,22 31:10 54:14 237:11
caveats 221:15
cba 31:18
cd 56:11
cdc 13:3
cdi 56:12
cefazolin 96:4,15 96:18 205:21 206:6 256:4
cefepime 60:3,8,9
cefpodoxime 23:7 23:10 242:7
cefpodxime 241:13 280:15
ceftazidime 35:5
cell 36:17 73:2,5
cells 25:5 31:9,9 31:10 52:2,2 73:11,16 74:13
cellular 73:4
center 4:5 7:4 47:8 62:9 63:5 131:2
centered 99:14,15 100:2 108:14 270:12
central 63:11
centralized 140:18
centrally 209:22
centric 233:22
cephalexin 96:3 96:18 240:12
cephalosporins 96:20 97:12
certain 29:3 48:20 77:16 112:6 156:20 227:7
certainly 51:22 112:9 116:6 186:19 188:4 216:14 227:6 230:20 243:17 249:22 260:8 265:14
certificate 283:1 284:1
certified 189:7
certify 283:3 284:2
cft73 32:16 35:4
cfu 33:21 34:1 54:1 77:18 78:4,5 135:12 149:12 156:6 158:19 193:22 212:11 252:17
cfus 90:10 134:20 235:8
chair 27:10 120:4
challenge 54:21 56:2 76:16 225:21 265:2
challenges 64:9,10 79:14 88:10 123:20 125:5,14 126:10,19 129:5,9 130:11 166:2,9,11 167:16 177:10 206:17,21 207:7 211:17 232:6 274:16 275:1,8
challenging 52:16 57:8 61:14 62:1 264:17 268:14
chance 30:15 46:22 111:11 209:15
change 10:12,13 19:3 61:8 68:16 78:16 97:10 100:21 104:1 139:19,19 176:5 177:17 180:21 216:11 218:17 238:22
changed 101:20 117:21 118:14
changes 15:22 69:14 159:17 167:4 218:19 230:12 240:19
changing 64:18 69:13 117:5
channel 73:22
chapters 81:6 167:4 208:19
characteristics 86:7,10 87:19 216:5 219:9 258:2
characterize 39:19 68:11 97:21
characterized 132:6,13 143:1 154:16
charges 177:13
chart 178:1 226:5
chat 171:8
check 171:7
checking 175:19 237:22

chemicals 75:15
chemotherapy 123:15
cheng 43:8
chicago 80:21 81:1
chief 120:2,16 130:18,20 182:14 189:6 208:12
childbearing 108:21
childhood 112:19
children 113:4,7
chills 9:5 134:15
chime 210:14 258:5
chip 73:18
choice 17:9 18:17 23:17,22 24:1 76:22 97:16 116:19 149:1 165:22 168:8 242:14 245:18 274:20
choices 101:7
choose 16:6 24:10
choosing 16:16,22
chose 15:14
chromosome 35:4 35:12 43:19,21
chronic 90:3 112:22 118:22 266:5
cipro 23:10 192:11,20 193:1,2 193:8,10,13,21 194:9 198:8,12
ciprofloxacin 20:2 23:7 189:22 241:14 276:18,20 276:22 277:2,7 280:15
circle 35:21 43:20
circuited 35:4
circulatory 72:9
circumstances 152:7
cited 35:8
citrate 36:15
city 110:16 112:11
clancy 119:22 120:1,9,10 129:20 183:20 271:15
clarified 143:9
class 200:17
classic 9:16 59:3 212:22
classically 78:8
classification 68:13
clean 106:16 191:3
clear 7:22 12:4 15:15 121:6 122:14 146:2 206:5 220:7 251:7 252:15 265:22
clearcut 118:21
cleared 69:3
clearer 66:3
clearly 5:9 64:3 127:3 141:15
client 1:9
climbed 113:11
clinic 24:7 25:9 26:4 37:15 67:9 165:14 175:18 177:2 178:1 242:2
clinical 4:14,15,16 4:17 5:21 6:1,3 7:11,13 10:3,6 11:17 20:8,17 21:10,19,21 22:10 22:12,17 23:9,11 24:20,21 48:5,5 49:2,5 58:7 59:14 60:20 62:3,18 63:1,10,11 64:3 65:10,10,13 66:2 66:6,8 67:21 68:10 77:3,6,17 80:16 81:3,19 85:14,16 86:9,19 88:11 90:9,11 91:13 92:15 93:3 93:4 98:9 99:5,14 99:15 120:7 121:19,22 124:15 126:14,18 132:6 133:20,21 135:1,6 135:20 136:5,9,13 138:10 139:4 141:8,10 142:5,22 144:5 145:4,18 146:15 147:22 149:18 151:5,15 154:4,4,10,11 156:2,3 157:4,9 158:4 159:14,16 160:3,21,22 161:3 161:5,13,19 162:14,20 163:7 163:10,14,17,22 164:5,8,13,14 166:3 167:7,8,12 173:20 174:8 176:9 178:10,21 179:5 180:2,8 183:4 184:9,12 185:7,13 187:1,2 187:5,8,16 188:11 188:13,17 189:8 189:19 190:4,22 191:7,13 194:4,6 194:9,13,16 195:2 195:3,19,21 196:2 196:5,6,9,12,13 196:15,17,21 197:8,11 198:22 199:1,2,4,10,21 200:19 201:8 203:15 206:13 207:8,12 208:10 208:15 210:8 211:21 212:18 213:3,7,19,21 214:1,9 215:10,16 216:7,14,18,20 217:13 218:15,20 220:15 221:14,16 221:20 222:2 224:8 225:1,5 226:12,16 231:1,5 231:13 232:11,19 233:1,11,15,17,18 234:6,8,10 235:20 237:20 241:1 244:11,19 257:4,8 258:15,17 259:6,7 261:6,10 263:12 265:19 266:2 267:5 268:18 269:5,13,15,17 270:1,5,7 273:5,6 273:12,15,17,21 274:1,8,17 275:2 276:4,12 277:5,8 277:13 278:1,21 279:1,4,5,8,12,15 279:15,16,20 280:5 282:4
clinically 22:9 26:12 56:15 76:11 97:11 121:11 126:15 127:13 128:6,14 146:3 157:6 163:2 199:6 201:7,18 202:10 214:6 222:17 229:18 254:12 256:12 258:13 271:22
clinician 7:2 102:20 103:2 105:3 107:10

140:13 166:7,14 265:22 274:12
clinicians 8:19 10:14 18:11 100:16 103:20 107:20 109:20 110:5 128:11 136:2 220:14 245:7 259:10 266:1 270:12
clinics 240:9
close 14:2 21:13 129:16 143:5 185:1 267:2 282:13
closely 11:3 41:21 115:8 154:14
closer 13:22 162:1 162:18 184:9 186:7
clouded 217:9
clsi 94:13 95:11,20 204:14 205:2,14 205:20 248:7,17 261:18,19 281:4
clue 9:10
cluster 107:11,14
clusters 240:20
coast 105:14,15
cochairing 7:9
cochairs 5:14
code 68:1
coefficient 42:16 42:18
cofi 258:21
cogent 215:21
cohort 157:12 162:11
coli 15:1,4,7 27:14 27:21 28:2,9,10 28:12,14,16,19 29:2,4,6,7,13,15 30:20 32:1,13 34:7 35:4 38:16 38:17 39:3,16 41:15 43:5 45:15 46:3 77:3,5,19 87:15,20 88:2 95:22 113:19 125:7 171:16,19 204:17 205:6 242:22 243:4 247:12 249:5,20 253:9,9 267:20,20
collaborate 265:7
collaboration 146:13 192:7
collaboratively 183:10
collateral 172:12 180:6 229:21 239:2 243:12
colleague 91:19 249:9 251:17 253:16 255:18
colleagues 31:20 43:8 143:6 148:12 151:9 183:9 188:3 207:6
collect 54:22 55:2 95:6 220:9 253:22 263:17,18 281:14
collected 33:11 37:8 39:11 79:19 95:8 190:2 254:2
collection 40:4 254:5
collective 52:17
collectively 164:21
college 5:16 7:3 80:22
colonel 34:14
colonic 31:4
colonization 24:12 50:18 52:4,12 57:3
colonize 32:2
colony 30:17 33:13 87:10 134:19 191:16 275:19 281:10
color 15:22
columbia 283:20
column 83:22 84:3
combination 68:5 148:4 216:1
combinations 42:14 145:16 146:5 152:14,18
combined 151:5 247:14
combining 85:15 98:21
come 25:9,11 26:3 89:10,20 96:5 102:12 103:4 116:2 144:19 156:16 167:4 176:19 177:21 178:17 184:7 205:8 212:8,22 221:1 256:11 258:10 265:13
comes 13:22 15:1 68:14 91:14 94:22 112:7 115:13,22 144:16 146:15 147:2,10,20 149:5 150:12 176:7 186:20 223:11 237:15
coming 85:17 87:7 98:13 127:10 141:10 167:20 175:19 176:3 184:18 220:20 229:21 257:21 262:21
commensal 28:2,3 28:20 46:3
commensally 32:1
comment 109:4 119:21 180:10 215:8 239:22 246:20 251:13 260:6 263:16
commentary 120:14 129:19 215:13
comments 129:21 203:7 206:19 214:17 219:3 235:4 239:20,21 244:5 246:8 256:15 257:17 258:7 260:3 265:22 266:11,13 266:15,16
commercial 182:14,20 186:14
commercializing 182:17
commiserate 219:5
committee 7:10 63:17 120:5
common 13:16 25:17 29:16 30:19 48:1 51:1 61:3 77:6 117:13 154:21 157:9 161:9 164:15 240:10
commonly 66:9 73:4 80:13 84:20 170:18 240:17
communicate 259:9,18
communicating 259:13
communication 102:14,15 103:10 125:22 126:11 271:8

communities 52:5 118:6 125:1 170:7
community 110:6 110:7 119:3 121:15 123:14 124:22 125:10,16 197:9 244:19
comorbidities 9:20
companies 24:14 182:18 184:3
company 177:13
comparability 64:1 67:20 80:15 269:4
comparative 138:1 148:22 150:15 151:21 249:2
comparator 4:21 133:13,14 149:2 149:17 150:4,9,12 172:16 185:19 212:2 238:17 239:19 241:8 244:7 245:12 246:6 249:13 263:1 274:22 275:13 280:4
comparators 134:1,3,5 166:1 168:8 170:2 181:17 238:7 242:15 272:9 274:15,20 280:2 280:10
compare 42:13,19 94:22 159:7
compared 40:12 43:8 59:18 64:6 79:4 87:3 91:17 96:8 97:15 157:22 163:9 189:21 193:2,10,12,20 194:8 273:14
compares 64:14
comparing 51:8 86:15 95:20 234:13
comparison 82:19 82:20 170:19 240:5
compartment 70:21 72:7,7,19
compartmental 71:9
compartments 72:12,13
compile 17:19
complete 67:19 82:8 187:17 191:14 212:17 215:19,22 243:20 248:7 276:4
completed 131:5 153:19 193:21 220:19
completely 178:19 214:1 229:7,7,19 229:20 242:19 258:11 279:8
completing 219:6
complex 34:16 71:8 74:18 75:10 98:14 170:14 254:15
complexities 71:15 74:4 75:18 232:5
complexity 174:7
complicate 249:1
complicated 10:4 54:3,5 61:10 82:20 84:22 89:10 90:21 100:3 102:7 104:18,20 112:21 132:14 133:12 134:16 142:13,16 152:11 154:5 155:5,7 166:1 167:2 179:9 181:2 181:10 184:21 185:2 255:13 273:6,8 274:4
complicating 162:4
complications 154:21
compliment 66:22 269:10
component 157:16 164:10 196:22 198:16 232:12,14 232:18,19 233:11 277:11
composite 135:1 156:1 165:1 191:13 210:8 211:2,16,18,19 220:6 224:9,10 230:21 231:4,6 232:9 273:1 274:10 278:20
compounds 36:14
comprehensive 130:3
comprised 192:19
compromise 233:9
compromised 10:20
computer 120:12 173:1,10 228:4,5 228:11,15
concentration 48:18 55:11,12,13 72:11 79:21 80:2 88:5 89:6 93:7 146:9 251:19,21 251:22 254:9 256:20 260:7,9,12 260:16,19,19 261:1 263:21 265:2
concentrations 66:4 68:15 69:14 79:4,5,7,21 82:10 83:3,4,16,22 84:3 84:4,8,9,11,14,21 85:10 87:11 89:7 89:15 91:3 93:10 93:12 95:7 96:12 97:5 98:21 252:3 252:8 253:7,12,22 262:3 281:14
concept 245:5 259:15
concepts 200:13 205:7 229:4
concern 243:5 260:21 280:11,18
concerned 9:9 126:5 216:21
concerns 166:5 179:19,20 260:11 271:7 274:18
conclude 66:14 129:2 197:13
concluded 277:10 282:15
concludes 140:3
conclusion 51:17 116:2 198:15 205:8 207:5,21
concordant 34:4 159:19 160:20 161:20 162:19 163:9 273:15
condition 112:16 113:3,14 115:18 118:7 154:14 216:8 271:8,11
conditions 26:12 45:16 69:10
conduct 57:3 180:15 276:1

conducted 39:7 40:5 145:21 146:12 151:4 189:20 192:2,6 234:11
conducting 166:12
conductors 107:18
conducts 120:6
conference 100:8 220:3
confidence 138:15 138:19 193:4,14 194:11
confident 136:3 261:9
confined 10:15
confirm 255:3
confirmatory 61:21 133:10
confirmed 80:7 92:19 93:7 147:13
conflict 113:13
conflicting 211:7 213:11 220:11
conform 216:18
confound 230:13
confounders 217:2
confused 103:9
confusing 97:13 100:5
confusion 220:13 220:17
congress 128:1 129:13,15
conjugation 28:4
connected 228:1
connecticut 62:11
cons 4:22 210:8 251:10 281:6
consensus 8:15 9:3,11 56:9 61:13 221:13
consent 39:10
consequences 229:1
consequently 33:21
conservatively 139:1
conserve 46:9
conserved 42:11 51:12
consider 12:12 13:20 65:18 74:8 75:9,21 76:4 78:21 81:11 82:17 85:3 95:13,16 133:18 157:8 218:22 233:15 264:5
consideration 69:1 81:11,22 94:6 165:1 237:14 249:7 270:6 274:10 275:14 276:2 278:9
considerations 1:3 4:9,15,18,20 6:4 62:14,17 63:22 64:11 66:17 67:19 98:5 99:6 100:2 130:12 139:9 146:17 257:19 269:3,7,20 270:12 272:8,10,13,21 274:13
considered 17:7 68:18 82:9 85:4 90:11 95:9 98:6 112:21 127:22 133:15 134:5 142:12,16 147:14 155:3,5 157:6 176:18 191:20 201:8 204:8 216:20 218:4 225:9 241:11 243:9 248:19
considering 78:6,7 94:16 126:9 139:4 263:18
considers 153:5 155:6
consistency 211:10 278:22
consistent 183:11 195:5 199:8 220:7
consistently 161:19 164:17
constituencies 122:21 126:12
constitute 154:22
consult 81:14 240:10
consultation 102:15 218:18
consulting 105:1
contact 175:18
contaminate 31:5
contemporary 66:6 203:13
contend 52:17 53:18
content 54:9
context 94:7 135:20 248:6
continents 111:2 113:13
continue 171:9 214:4 223:21
continued 70:7 136:9 137:2
continuing 119:12 217:3
continuous 58:13 72:2
continuum 26:12
contract 74:19
contrast 82:21 205:4
contribute 66:15 144:11
contribution 190:5 194:2
control 14:5,9 19:12 77:12 90:13 133:1,4 137:10 138:22 192:4 246:12 254:21
controlled 36:19 72:14 132:20 133:9 243:15,20 245:20 246:2,16 246:18 280:18,19 281:1
controls 255:2
controversial 169:22
convergence 248:14
conversation 100:15 263:8
conversations 6:9 100:22
conversed 268:4
convert 44:22
coordinator 174:10,16
copies 44:16,20
core 29:1 39:19,22 41:18 43:3,4 46:5 46:8 161:8 268:4
cornelius 119:22
correct 169:12 225:12
correlate 56:17 65:10 159:21 257:3
correlated 32:9
correlates 48:5 58:7 62:4

correlation 42:16 42:17 43:11 64:2 66:3,11 67:21 80:16 185:1 190:3 269:4
correlations 64:15 94:19
cosi 255:9,10
cost 106:7 109:16 170:16 186:15
costly 170:14 177:20
costovertebral 9:6 132:12
costs 61:4
council 63:3
counsel 283:10,13 284:7,10
count 16:17 57:20 78:5 93:9
counted 216:11
counter 104:21 108:1
counterclockwise 49:19
counterpoint 218:8
countries 106:15 111:1 114:1
country 111:5 114:6 123:21
countrywide 16:18
counts 77:19 223:1 230:7 275:19
county 247:17
couple 125:20 211:3 214:10 224:7 256:15
course 10:10 18:18,21 20:17 27:20 37:21 64:9 64:16 65:16 67:9 113:18 121:3 122:4,21 125:8 167:7 172:12,18 180:5 190:21 191:6 216:12 217:1,21 221:16 223:2 229:12 237:16 240:16 243:16
courses 19:1 114:13 119:5 126:22 240:11
cover 8:1 62:17 79:17 136:16 181:19
coverage 253:10
covered 45:8 166:16 224:5 239:18
covering 7:16 249:4
covid 7:15 123:19
coworkers 105:10
cows 28:15
cranberry 105:11 105:17
crash 27:20
create 54:19 85:18 138:13
created 162:6
creates 42:17
creating 94:13 213:6
credibility 178:12
creep 217:14
crew 20:4
cristina 2:20
criteria 22:13 134:9 150:18 153:11 156:7 175:7 176:17 183:3 184:11 185:11 188:6 206:2,3,22 207:8 212:21 216:10 272:10 275:17 278:12 281:4
criterion 281:22
critical 36:19 149:3
crucial 124:17
csli 96:9 250:15
cultivatable 20:22
culture 18:7,8 20:14 21:11,15 22:7,8 25:6,10 30:3 40:13 41:3 115:13,21 116:3,5 116:20 117:4 122:12 126:22 132:7 134:17 135:13,21 137:9 143:2 147:13 149:10 150:17 154:17 158:15 191:15 193:22 212:9,15 222:12 222:13,15 223:7 223:15,18 246:22 247:3,9 271:4 279:20
cultured 39:14 41:2,16 42:12,15
cultures 21:17 29:22 78:9 135:16 136:5 192:13 197:6,10,18 222:18 231:20 244:11,15,15 247:7,11 271:5
culture's 18:10
curbs 72:11
cure 18:6,10 22:3 23:9,11,11 24:13 58:22 117:22 118:1 151:1,7 156:22 159:5,12 159:15,22 160:5 160:10,21 162:12 162:13,15,18 163:7 164:3,14,17 190:22 191:7,12 191:20 192:15 195:21 196:8 197:9,21 198:6,10 212:16 218:12 273:17
cured 157:6
cures 273:13
current 4:14 8:5 17:1 25:2 85:9 110:17 131:14 133:21 138:22 165:15 166:16 171:20 174:19 181:10,21 189:15 189:18 190:12,20 191:9 192:1 197:3 198:21 199:8 201:10,14,21 206:16,17 219:13 224:9 232:8,19 242:12 245:8 267:4 268:9 271:14 272:6,16 274:22 278:15 280:13
currently 7:9 17:22 58:20 67:7 99:16 111:14 121:21 127:22 142:2 153:22 200:18 201:13,22 202:13,21 205:20 210:8 269:14 271:6 278:5
curve 44:12,13,22 45:5 72:17 78:19 80:1 252:12
curved 93:17
curves 91:12

customized 75:13
cut 248:22
cuti 152:13 154:11 154:13,22 155:11 155:14,18 156:14 160:15 161:15,15 164:14,18 274:5
cutis 154:16,18
cutoff 188:7 222:16
cycle 31:10 37:22 38:1,2,2,11 39:1
cycles 74:1,2
cystitis 8:19 9:1 9:18 10:2,15 12:7 12:8 17:3 18:2 35:20 36:2 39:9 53:22 58:12 59:7 132:10 141:17 142:8 143:9 149:6 172:20 203:11 239:8 242:6 243:4 247:19 250:12 280:8
cytokines 32:6 34:3

d

d 4:1
daily 25:5 101:19 190:14 192:11,11
damage 50:7,12 116:10 172:12 180:6 229:21 239:2 243:12
dan 3:6 138:4
danielsen 2:7 260:5 263:10,13 263:15
danielson 260:5
dark 197:21
data 7:19,21 12:21 13:3,9 14:19 16:15 18:15,19 22:1,5,10 23:19 23:21,22 25:11 37:6 41:1 47:16 48:22 52:14,15 58:20 59:4,14 61:18,21 62:18 64:3,13 65:8,9 66:20 68:8 72:21 84:5 87:6,21 88:14 89:12,21 92:17 94:6 95:4 96:10 97:6 98:12 106:3 122:7 126:3 127:13,14 136:2 138:4,6,12,17 148:17 155:15,17 156:11,12,16 157:2 158:4,6,13 164:21 179:10 189:20 190:2,7 192:2 195:13,14 195:22 199:2,14 201:7 203:2,19 204:15 205:4,11 211:7 213:11 220:7 222:7 224:8 224:12 225:2 232:7 241:2 244:8 248:8,22 252:19 253:3 254:1 255:2 255:10 256:21,22 257:11 259:6,7 261:8 262:14,18 263:17 265:5,12 265:19 266:2 269:9 270:5 273:7
database 152:1 273:11
databases 94:18
date 1:7 10:4,8,13 11:3 12:7 49:14 83:19 167:4 220:11
day 18:5 20:4 21:9 22:8,12,15,16,18 22:19,20 23:4 25:22 26:2 33:12 49:5 70:1 71:14 75:11 88:16,17 103:16,17,19 160:9,11,13 162:10 176:6,9 181:7 192:14,14 192:14,15,18 193:10 194:6 195:1,3,5,6,6 196:1,2,4,5,6,7,8 196:9,10,13 223:2 224:15 267:2
days 18:3,4 19:18 20:3,6,7,9,10,10 20:11,12 21:6,9 21:10,20,22 22:10 23:8,9 25:14,16 25:18,18 30:15 57:20,21 82:14 92:11 94:17 114:13 115:13,18 116:22 136:10 137:1 151:2 157:1 160:7 191:4 192:11,12 195:9 196:10 213:16,16 218:13 228:21 279:7
dc 1:9,11
de 49:5 268:18
deal 107:1 109:14 115:6 174:7 243:10
dealing 229:14
deaths 123:8
debate 252:1,17 261:19
debilitating 113:15
decade 128:9 165:15 167:21 229:10
decades 7:5 70:11 119:5 238:20
deciding 77:1
decision 24:20 81:20 99:7 101:21 144:3 227:10 269:18
decisions 67:15 128:11 177:7 268:22
decline 79:21
declined 70:5,6
decrease 222:6 252:17
decreasing 19:5
dedicated 50:21 177:20 208:14
deemed 101:8
defects 13:21 38:11
define 89:19 94:10 96:2 201:2 262:13 282:5
defined 9:18 11:13 25:8,13 90:9 132:6 141:15 167:19 234:1 253:14
defines 142:22
defining 8:14 9:22 61:22 268:15
definitely 146:11 221:19 222:2,8 223:21 224:11
definition 8:2 9:12 9:16,21 10:5,8,13 10:17,22 11:3,6 11:10 12:10 77:17 132:2,14 141:22 142:4,5,11,21 143:5 181:10 194:20 215:18 217:17 219:9,14 243:8 248:19,21

252:16 267:7
definitions 9:15 12:4,11 132:3 141:8 156:1 167:1 181:1 218:3 239:13 248:12 249:1
degree 179:12 262:4
delay 172:2
deliver 60:19
delivered 53:7 55:9 57:12 58:13 59:7
delivering 53:14 53:19
delivery 124:18 167:14 168:2 173:1,7,14 174:3
delta 151:7
demographic 158:3
demonstrate 186:16
demonstrated 60:11 70:8
demonstrating 258:16
demonstration 135:11 278:2
dense 68:8
densities 158:18 159:1,8
density 69:21 70:5 70:9 76:10,20 78:4,16 159:2,4 159:11,13,17,20
department 27:7 27:10 63:13
depend 135:4 136:22 245:10
depended 114:15
dependent 48:18 48:18 158:20
depending 64:9 114:10 176:4 209:11 223:2 261:21 262:21
depends 80:11
depicted 36:8 40:15
depicts 6:6
depleted 74:16
depotitozine 258:12
depression 93:2 190:18
depth 158:6
derive 195:9 202:4
derived 206:8
deriving 200:7 207:13 277:18
describe 115:9 135:14
described 9:16 64:8 180:4
describing 99:5
design 4:18 26:10 70:20 130:11 131:12 132:19 133:2,3,5,5,6 170:10,14 172:19 172:21 180:15,20 181:20 237:21 272:8,21
designed 71:9 121:22 126:7 192:7
designing 74:8 104:10 166:12 180:2
desirability 234:1 234:14 237:17,18
desirable 50:4 126:12 234:2,4,7
desire 242:19
desired 64:19
desperate 119:7
despite 76:3 113:3 198:4,9
destruction 237:12
detail 37:7 85:8
details 68:11 74:10 131:20 237:21
detect 116:4
deteriorates 115:19
determination 133:17 207:2 260:8 278:14
determine 24:10 37:5,7 90:2 138:17 145:17 203:3 223:4
determined 201:14 204:2 264:3
determines 26:20
determining 23:19 201:10 263:19
develop 26:14 49:4 61:18,20 63:6 98:18 101:22 116:17 126:9 187:17
developed 31:3,19 36:9 37:4 49:9,12 66:12 87:4 164:5 167:6 270:2 271:3
developer 146:8 150:12 182:11
developers 126:8 128:12 141:4
developer's 183:2 189:2,4 199:22 200:6 275:16 276:7 277:16
developing 24:14 86:17 94:17 98:17 104:10 144:11 252:10 271:20 274:2
development 1:3 4:9,22 6:5 47:8 48:8,12 62:10 81:12 82:14 85:14 85:14 86:6,19 88:22 89:13 91:7 91:18 92:8,10 99:6 115:5 120:16 121:16 123:1 124:19 129:4,5,11 131:15 132:1 135:9 144:2,10 145:10 146:10,16 150:13 161:7 190:8 198:8,19 200:10 207:16 215:10 218:16,21 219:16,17 249:10 251:11 255:7 262:2 263:5,12 268:19 269:13,18 270:7 272:2,4,7 272:16 274:5,13 277:20 280:21 282:2
deviations 55:19
devices 24:14 182:17
devoted 36:16
diabetes 10:20 24:4 164:9
diabetics 122:9
diagnosed 19:22 101:3 110:19
diagnosing 168:4
diagnosis 115:1 166:16 174:13,21 175:4 184:20
diagnostic 115:3,6 116:1,19 118:19 161:17

diagram 53:2 57:7 57:7
diagrams 40:7
diameter 35:21
diapering 108:19
diarrhea 28:6,10 28:11 170:17,22
diary 25:7
dickinson 15:12
didiosin 253:4
didn't 25:19 60:13 60:14 83:1 105:5 105:7,8 107:7 241:6,20 247:21
died 123:6
diff 229:22
difference 14:4 15:16 19:19 41:22 71:1 78:3 84:10 88:7 96:11,16 108:3 117:18 138:11,14 139:2 159:13 186:9 187:13,14 193:3,5 193:14,16 194:11 231:4 264:5 277:3
differences 51:22 96:6 97:2 159:9 185:14
different 10:7 14:18 28:5 30:18 34:9 35:15 36:9 37:11 40:8 42:22 44:11,11 51:11 54:12 56:19 65:1 65:3 67:5 70:20 71:22 72:1,4,5,21 75:15,21,22 76:1 78:12 82:2 84:10 91:17 93:4 94:17 94:18 95:6 96:2 100:7 104:15 107:8 108:9,10 119:6 155:12 159:8,19 161:5 177:21 178:16 181:12 188:20 198:9 204:4 211:10 216:19 217:6 219:10 226:14 237:17 243:2 249:1 253:19 256:7 257:15 261:9 262:11 279:12
differentiation 188:9
differs 94:21 142:4
difficult 32:22 90:1 97:21 113:5 166:19 169:18 175:12 177:17 221:5 263:17 275:7 281:18
difficulties 177:16 243:19
difficulty 65:12 263:18
digital 283:8 284:3
dignity 117:11
diluted 69:2 76:19
dilution 70:21 72:3
dilutional 71:8
diminished 109:8
dimitri 2:8 19:15 219:21
dinner 100:15
diplomat 110:16 110:21 111:5 113:12
dipstick 21:5,17
direct 126:6
directed 122:16 224:19
directing 17:17
direction 26:20 37:2
directional 44:2
directly 26:18 45:8 64:14 123:8 199:6
director 4:3 47:7 165:11 199:17
disagree 245:5 261:12
disagreed 271:12
disagreement 8:15
disappear 217:12
disappointment 124:21
disciplines 166:19 168:3
disclosing 112:12
disclosure 112:21 200:15
disclosures 7:14 7:17 47:21 81:14 165:20
discomfort 132:9 143:4 190:14
disconnect 167:7
discordance 154:3 154:10 217:18,20 273:5 274:1
discordant 157:8 157:8,13 158:2,11 158:22 159:18 160:18 161:2,6 162:6 163:8,17,18 164:3 273:17,20
discordants 161:18 162:21 163:2,13
discounted 138:19
discouraged 197:11
discourse 100:21
discover 109:1
discovered 226:3
discriminating 87:20
discuss 9:14 54:11 56:21 67:14 80:15 140:5 144:14 150:12 151:19 189:17 201:20 210:7 238:7 251:10
discussed 152:20 153:11 210:18 226:7 243:7 267:6 267:17 268:9,21 269:3,17 270:19 271:16 272:17 273:5 274:15 276:9,17
discussing 115:1 131:21 184:13 200:13
discussion 4:19 5:12 6:7,16,20 27:3 62:22 134:6 144:15 149:21 165:6 207:22 208:8 209:3 210:12 211:1 226:1 237:6 238:5 238:12 257:10 266:19 267:1 278:19,20 279:7 279:11,19,22 280:3,9,16 281:7 281:9,16,20 282:3 282:11
discussions 4:9 6:8 12:1 144:6,7
disease 5:22 8:5 9:5 10:18 63:9 77:12 81:4 117:20 120:2,4,6,13 125:8 140:8 155:2

166:18 189:8 228:22 243:7
diseases 4:4 7:2,10 9:17 13:12 63:14 120:17 123:19 130:19 140:20 165:10 189:10 199:18 208:16 237:20 282:10
disorder 108:22
dispensable 38:15
disrupt 175:21 177:3
disrupted 178:13
disruptions 240:19
dissemination 128:6
distinct 26:12
distinction 118:21 217:6
distinguish 164:4 166:20
distinguished 27:6 80:20
distinguishes 158:10
distinguishing 185:3
distribution 57:5 72:9,17 79:11 162:12 197:22 234:13
district 283:20
diverse 28:20 57:6 213:20 267:21
diving 168:7
division 4:3 5:22 131:1,22 134:6 154:1
division's 131:14
dmitri 2:15 259:3
dna 28:1 35:2 41:8
docs 259:10
doctor 5:20 109:15 114:16 115:12,12,14 118:1,12,15 166:18 228:22
doctorate 153:20
doctors 107:18 117:3,6 119:3,8 188:14
doctor's 37:9 115:21
document 141:14 145:8,11
documented 108:12 132:7 143:1 149:11 154:17 190:17 258:21 270:17
documents 128:18 258:21,22
doesn't 40:19,21 97:10 108:2 115:6 159:13,20 174:6 177:6 185:18 225:2,2 237:9 243:14
dog 49:9
doing 8:7 10:7 17:2 39:3,5 53:8 82:13 85:15 88:18 91:9 97:18 98:15 119:5 174:11 213:1 222:18 226:3 243:19 244:16 253:17 254:5,19 262:5,20
dominant 49:14
don't 15:2 16:11 17:10,14 24:1,9 26:19 30:7,7 37:14 38:16 43:12 57:8 90:18 91:1,4 98:2,18,18 100:17 101:4 102:3 103:6 103:19 105:6 106:21 112:3 115:14 116:8 117:1,7 123:3 149:22 155:16 157:7 158:5,10 166:9,14 170:19 171:7 176:17 181:14 185:15 187:12 188:2,15 191:2 213:8 214:19 217:19 221:10,21 222:7 225:7 227:11 229:18,19 231:19 234:21 237:4 238:14 240:2 241:18 244:13 245:5,12,19 246:4 246:12,14,21 248:7 250:4 252:15,19 255:12 255:20 260:3 261:12 265:18 266:5
door 237:18 279:13
dorsal 32:15
dosage 85:20
dosages 257:7
dose 21:7 48:13 55:8 59:4,8,11,20 60:3 61:20 62:16 68:4 72:18 81:21 82:6 83:13 85:19 85:21 119:9 137:14 147:22 148:2,6 149:2,2 150:5 156:20 204:7,9,22 258:14 269:19
doses 49:4 58:13 58:16 60:20 83:21 88:15 147:7
dosing 63:6 66:11 67:7 68:3 88:10 91:15 92:19 135:5 136:22 254:3
dossier 146:14
double 132:20 150:21 170:15 172:19 192:4
doublecheck 234:17
doubling 33:17,19 45:12 46:11
doudoroff 38:4,14
downregulate 42:6
downregulated 40:19 41:9
downstream 126:8
downtown 107:11 107:12,12
dozen 111:1
dr 4:2 5:15,15,19 6:2,11,13 7:1 27:4 27:4,5,5,9,13,17 27:18 46:19,19 47:4,6,7,13,14,16 47:21 51:6 62:8,9 62:13,13 63:1,9 63:19,19 64:8 67:2,10,12 80:18 80:19,20 81:1,4,8 81:9 87:7 99:3,3 103:22 110:10 119:19,22 120:1,9 120:10 121:17 126:20 128:7 129:20,20 130:9 130:17,22 131:9 140:7,8,21,22 153:15,18,18 154:6,7 165:4,8,9 165:19 167:3

168:12,14,16,19
168:20,21 169:4,6
169:7,9,11,12
171:6,7,9,10,11
171:13,17 172:1,1
172:2,5,8,10
173:4,6,7,9 180:4
182:8,9 183:5,20
186:4 187:10
188:21 189:3,11
199:13 200:4
203:6 207:18
208:5,7,9,9,21
209:15,17,19,20
209:21 210:3,4,21
214:13,14,18
215:2,6,6,9
219:18,19,20,21
220:1 221:7,8,9,9
224:1,1,3,5 225:7
225:11,14 227:16
227:17,18,21,22
228:6,9,12,14
230:15,15,16,17
231:22,22 232:2
234:16,16,17,20
234:20 236:14,16
236:18,21 237:2,2
237:4,22 238:2,4
238:9,11 239:21
239:22 240:4
241:4,4,4,6,17,20
242:3,8,16,16
243:3,17 244:2,2
244:4,22,22,22
245:2,6 246:9,9,9
246:11 248:2,2,3
248:4,15,16,16,18
249:12 250:13,13
250:20 251:1,2,4
251:5,14,16 258:6
258:11 259:3,4,5
259:20,22 260:2,5
261:12 263:7,9,9
263:10,13,15
264:8,10,11,12,14
264:15,16 265:21
266:14,17,19
267:3,13,16 268:1
268:8 269:16
271:15 272:5,14
273:4 274:11
276:6 277:10
280:2,12 281:6
dramatic 186:10
dramatically 84:9
draw 154:15
drawing 59:19
drekonja 2:8
19:15 219:21
220:1,1
drill 16:19
drink 105:12
106:13 217:3,3
drinkable 106:16
drinking 105:10
drive 220:21
driven 193:17
241:21 277:4
driver 252:11
drivers 281:8
driving 244:8
drobot 71:5
drop 228:14
281:10
drs 5:17 268:20
drug 1:1 4:5,9 6:4
16:13,21 18:17
54:17 55:12,21
56:6 60:16 66:7
72:17 80:7 81:12
82:14 84:17 86:6
87:3 88:22 91:6
92:8 99:6 110:20
113:21 114:5,9
123:7 128:12,19
129:5 131:2,22
135:5,22 136:3,22
137:11,15 138:1,8
139:13,13 144:10
156:12,20 198:19
201:16 203:20
204:11,20 224:15
225:2 236:1,10
239:19 241:9,11
249:13,15 250:5,5
252:9,10,10 254:6
255:6 256:4
257:16,21 259:11
259:17 262:21
263:2 269:18
272:4 273:9
277:22 281:15
drugs 1:4 4:10 5:2
16:5 48:10 82:16
92:11 104:21
122:2 123:22
124:13 126:4,7,9
131:15 144:11
154:1 166:5
172:13 182:17
230:21 236:8
239:3 251:12,19
252:4 253:2
256:19 269:21
271:20 272:7,16
274:14,18
drugs' 281:8
due 107:22 110:21
125:10 155:14
158:22 270:21
280:19
duke 131:4
duly 283:5
dummy 170:15
172:19
durable 238:19
duration 68:6
85:21 114:14
122:4 147:7 148:3
149:3 246:17
durations 65:5
dye 61:19 108:2,3
dynamic 63:15
67:14 68:2 69:12
73:10 78:14 223:3
254:10 268:21
dynamics 73:11
dysentery 28:6
dysuria 8:21
132:9 134:12
143:4 149:9
161:10

e

e 2:1,1,3 4:1,1
15:1,3,6 27:14,21
28:1,9,10,12,14
28:16,19 29:1,4,6
29:7,13,15 30:20
32:1,13 34:7 35:4
38:16,16 39:3,15
41:15 43:5 45:15
46:3 77:3,5,19
87:15,20 88:2
95:22 113:19
125:7 171:16,19
204:17 205:6
242:22 243:4
247:12 249:5,20
253:9,9 267:20,20
earlier 34:16 87:4
109:13 128:8
134:11 141:13
162:15 167:16
170:3 176:1
200:14 201:9
205:3,5 207:5
219:3 225:3
early 33:16 104:7
116:9 131:22
150:13 266:12
easier 172:7 178:2
211:16 228:17
239:7

easily 95:8 104:11 188:14
east 105:15 114:4
eastern 47:2 208:1
easy 51:5 75:14
echo 219:2 220:2 227:19,20 258:18 264:15
economic 106:11 272:3
ed 104:3
edited 81:7
editorial 26:8
educate 117:6,11 118:3,12 281:20
educating 116:14 117:17
educational 102:1 104:11
effect 138:22 148:16 180:14 211:12 216:6
effective 65:20 102:14 122:2 169:17 202:5,8 206:10,12 225:5 252:9
effectiveness 74:5
effects 117:14,14 138:13 172:11 239:1 280:7
efficacy 48:2 49:2 54:6 56:4 59:3 60:15 61:12,21,21 62:18 84:12 85:22 90:6,9,11 98:12 134:21 137:12 140:17 148:10 150:20 152:22,22 155:21 199:4,10 201:19 203:21 204:3 206:15 225:5 232:8 252:4 257:16 258:17 264:22 270:5 272:10 278:3
efficiency 78:11 178:13
efficient 112:10
effort 128:21 224:16
efforts 5:4 121:14 232:6
eight 45:7 93:13 247:7 250:11
eighty 25:21 194:7
eisenhower 165:11
either 20:1,19 21:6,8 23:8 54:10 54:17 87:7 105:7 114:13 146:9 148:5 152:10 156:7 175:18 192:10 195:12 221:10 232:21 233:17 247:21 250:3 263:3 266:15
elders 226:19
election 276:16
electronic 167:22 174:9,20 177:13 177:18 179:8,14 275:3
elegans 49:19
element 36:20
elevate 256:20
elevated 37:13
elicited 32:6
eligibility 175:7 239:14 275:13
eligible 147:5 149:11 180:21 275:21
eliminated 76:20
elimination 79:12
eloquently 92:4
else's 244:5
elucidated 145:13
ema 98:4 141:4 142:4 143:15,19 153:16 249:9 250:16 272:18,21
email 168:15,17 168:18 171:3
embedded 119:4
emerged 198:11
emergence 68:11 78:19 170:22 239:9
emergency 63:8
emergent 123:16
emeritus 165:12
emitting 32:16
emphasize 82:22 85:1,10 98:19 112:1 261:14
emphasized 82:13 98:16
emphasizing 255:10
empiric 16:17 17:22 23:17 175:5
empirically 16:6 16:11,14
employed 283:11 283:14 284:8,11
employee 200:15 283:13 284:10
emulate 220:15
enable 70:17 71:3 79:22
enabled 71:16
enclosed 69:21
encoded 35:1
encounter 174:22
encourage 129:14 218:15 221:3
encouraged 217:2
endeavors 128:4
ended 109:17
endobiotic 226:9
endorsed 197:8
endourologic 197:6
endpoint 4:20 48:20 56:5,14,18 56:18 60:10 78:15 90:7 134:22 136:21 155:21 156:2,22 157:4,16 164:16 165:1 189:5,15,18 191:10 192:1,17 199:5,6 207:9 210:9 211:2,16,18 211:20 212:16 215:14 217:17 219:8 220:5,6,8 220:10 221:5 224:8,11,14 225:20 230:21 231:1,6,7,13 232:8,19 235:7
endpoints 48:21 49:1 61:14 121:12 122:6,11 126:16 126:17 136:8 144:21 154:4,10 183:3 211:8 271:22 273:6
ends 185:17
energy 36:17
english 102:3
enjoy 46:20
enlargement 109:10
enormous 219:11
enroll 19:20
enrolled 21:4 25:3 149:9
enrolling 275:9

enrollment 22:7 146:21 147:4,5 279:19
ensuing 114:7
ensure 5:11 80:4 183:10
ensures 135:22
ensuring 122:22
enter 31:9
enterobacterales 203:16 204:4 205:19,22
enterobacterial 125:4 275:11
enterococcal 95:15
enterococci 71:11
enterococcus 76:1
entire 44:10 78:18 163:6
entirely 118:20 206:5
entity 180:8
entner 38:4,14
entry 134:9 135:8 135:12,17 136:18 156:4 158:20 236:7 272:9
environment 69:11 73:3 74:14 74:22 114:2
enzyme 41:13 146:1
enzymes 38:5
ep 99:17
epic 176:10 177:13
epidemiology 208:17 267:9
episode 53:2 217:9
episodes 125:22
epithelial 31:8 50:18
equal 134:19 193:22 204:7,13
equally 71:18 217:7
equation 264:6
equity 102:11 226:13
eradicate 136:4 229:19,20
eradication 126:19 156:5 157:15 158:20 160:21 191:14 213:9 215:20 218:1 235:6 237:6 274:9
erica 2:6 230:17
error 119:5
es 283:4
esbl 114:9 125:4,7 125:11,15 180:11 180:16,17,17,19 181:2,6,11,16,19 245:14,17 247:6 250:8,11 270:22 275:10,12
esbls 180:14
especially 18:10 48:11 133:7 206:11 220:21 243:1 259:1
espls 110:20
essential 223:20
essentially 72:6 148:12,13 179:22 181:7 232:15 235:18 265:8 275:22
establish 80:1 178:12 264:21
established 91:4
establishing 146:12
establishment 119:12
estimate 13:4 139:1,11
estimated 148:17
estimates 192:21
estimating 43:17
estradiol 226:20
estrogen 109:11 109:14,21
esvl 113:20
et 70:17,22
eu 143:8 150:6 152:20
eucast 94:12 95:20 146:13
europe 141:12 142:22 183:14
european 4:8 140:6,11 141:12 143:4 184:19 272:15
evaluability 219:2
evaluable 22:7,9
evaluate 91:21 136:11 251:14 279:17
evaluated 160:8 162:15
evaluating 82:22 224:15 234:13
evaluation 4:5 22:13 67:4 131:2 143:16 269:11 272:18
evans 2:9 231:22 232:2 234:16
events 26:1 126:2
everybody 27:19 106:12 130:18
everyone's 5:7 159:10
evidence 17:19 23:15 81:22 99:13 101:13 133:11,20 137:18 147:3 152:21 153:6 198:13 233:4
evident 206:13
evidently 226:8
evolved 9:13 29:16 267:7
exactly 39:14 92:8 107:3 172:5 182:4 248:12 251:21
exaggerated 45:9
examine 69:8
examines 63:14
examining 74:5 194:4
example 15:18 33:2,9 73:17 76:1 128:18 133:12,19 150:1 152:5 177:10 201:17 204:1 205:20 233:14 241:12 260:11 269:19
examples 87:5 92:12
exceed 17:11 205:13
excellence 63:5
excellent 43:11 45:5 51:6 63:20 66:16 122:5 130:3 153:15 199:13 200:5 214:14 238:5
exclude 10:21 212:13 227:4
excluded 155:10 217:14
executing 182:19
exhaustive 74:10
exist 50:16 64:16 121:21

existing 114:8 127:8 148:17 207:3 278:15
exists 202:13
exotoxins 34:18
expand 34:17 77:4
expansion 127:20
expec 29:10
expect 102:19 195:2 215:21
expectation 186:5 216:17
expected 69:7 77:15 79:17 106:6 219:4
expecting 249:8
expensive 50:21 106:18,20 276:1
experience 100:3 108:15 111:3,20 112:5,6 179:12 182:16,19 189:9 199:19 241:2 260:18 263:11
experienced 104:16
experiences 270:11,19 276:10
experiment 75:12 77:14 78:18 91:1
experimental 69:4 72:16 73:21
experiments 68:4 68:6 80:8
expert 99:18
expertise 50:22 81:8
explain 40:9 271:11
explained 118:5 163:20
explicitly 18:6
exploring 216:18
exponential 44:13
exposure 48:14,20 54:17 55:16 69:7 72:17,22 73:10 76:10 89:18 93:19 94:10 95:2 97:20 98:6
exposures 79:16 146:4
expressed 34:7 37:17,19 46:9 235:2 268:5
expression 32:8 36:18 37:12 39:20 41:15 42:1,7,9,11 42:13,20 43:5,9 46:4,6 51:11,13 51:14 267:22 268:2,4
expressions 43:3 46:8
extend 161:22
extended 125:3
extensive 182:19 190:1 269:1
extensively 110:22
extent 11:11 66:21 112:6 246:4
extra 29:1 220:19
extract 36:13 76:3
extraordinarily 46:14
extrapolate 45:11
extras 74:11
extremely 120:15

f

f1810 10:11
face 36:22 126:10 207:11 275:5
faced 125:14 129:5 130:5
faces 26:10 129:8
facet 162:7
facilitate 248:14
facilitating 73:16
facility 50:21 241:16
facing 104:11
facp 3:9
fact 18:8 34:19 53:22 69:1,17 73:15 82:7 86:8 89:12,17 113:7 143:7 145:12 149:1 169:16 184:8 187:22 195:4 230:22 231:4 235:5 280:7 281:12,17
factor 29:18 34:22 158:2
factors 16:16 17:18,20 23:19 34:6,10,20 35:11 35:14 36:5 51:14 65:19,22 73:7,14 74:7 79:1 106:11 158:9 162:4 163:21 164:4,20 180:13 181:2,11 267:10,17
factory 42:2
faecium 76:2
fail 163:2 232:20 243:10
failed 233:13 239:17
failing 116:7
fails 116:4
failure 22:12,17 60:21 98:2,18 156:7,8 157:10,13 159:16,19 160:22 161:3,5,13,20 162:6,20 163:1,8 163:11,17,22 164:5,8,15 194:16 195:2,8,19 196:2 196:5,6,9,14,17 196:22 199:3 214:10 216:11 232:21 233:19 234:4,8,10 235:18 274:8 279:16
failures 162:14 163:14 196:13 273:21 274:2 276:12
fair 56:22 245:11
fairly 167:18 170:17 171:1,21 174:14 175:9 176:1 178:17 238:12 257:5
fake 252:5
fall 181:9
familiar 176:10 259:2
family 104:7 106:21
fantastic 184:18
far 12:2 49:13 51:3 96:13 105:2 113:4 162:13 183:8 224:16 230:10,11 235:11 248:11 256:18
farley 172:1,8
farther 13:8
fashion 36:20 192:10
fast 33:16 43:15 44:5
faster 33:18 76:18 173:1
fastest 45:15
favor 192:21
favorable 59:16
fccp 3:5
fda 4:5 5:15 6:1 9:21 12:6 48:9

86:7 95:1 110:3 123:5 130:13,22 131:3 134:2 138:5 143:6 144:6 148:12 151:8 154:1,2 155:6,15 156:13 180:7 183:6 189:14 191:9 192:1,7 200:4 206:5 224:5 232:3 241:7 250:16 260:6 265:15 272:21 273:9
fda's 131:11 155:20 156:21 184:13 206:1 272:6
feat 130:4
fecal 35:20,22
federick 27:6
feedback 211:4
feel 6:17 29:5 101:18 107:4 115:11 116:15 161:18 198:15 221:18 229:8 261:9
feeling 109:6
feelings 121:11
feels 126:17 196:20 198:20 199:7 227:9,11
fellow 4:7 63:4 153:22
fellowship 131:6 165:11
felt 25:9 105:21 118:13 177:2
female 31:18 132:20 149:6 242:2
females 143:10
fembrey 57:2
ferry 187:12
fever 9:5 11:15 132:12 134:15
feverishly 184:4
fewer 172:11
fi 111:6
fiber 68:20 92:22
fibrillation 168:5
fidsa 3:5,9
field 267:14
fifth 25:13 30:17
fight 36:6 144:11
figure 12:17 13:6 41:12 88:8,9 94:14 176:12 204:10,21 226:21
figures 15:18
figuring 259:17
file 107:4
filing 145:19
fill 183:19
filling 69:2,15 73:20
filter 40:13
fimbriae 29:18,18 29:20,21 34:10 36:18 37:1,12
fimbriated 36:1
final 84:3 91:8 99:1 160:11 205:20 256:15,15 259:8
finally 32:8 57:11 62:2 84:3 88:10 89:18 90:15 92:21 93:15 97:20 98:8 166:4
financially 283:15 284:11
find 15:5 19:16 90:6 106:5 115:20 148:11 160:17 179:10 226:6 246:5 261:16
finding 23:10 45:17 98:20,20 147:22 257:6,6
findings 147:4 198:9
fine 171:10,11 250:2
finer 234:12
fire 68:1
first 6:3,12,14,22 17:4,9 19:14 49:8 49:11 52:20 53:3 55:8 58:8 69:18 69:18 74:15 82:4 104:2,8 105:4 108:22 111:3,9,20 118:13 130:16,21 131:10 132:2 152:6 159:6 163:5 166:15 170:3 202:12 204:1 206:14 210:5,6,22 211:5 215:1 219:19 238:16 241:18 251:7 274:22
firstly 189:13
fisac 3:4
fitness 38:12 76:16
five 18:3 20:19 21:6,9,20 33:5 34:12 52:2 112:17 113:16 114:13 117:8 123:6 145:19 178:14 192:11 246:16 256:8 270:21
fix 266:6
fixed 135:2,4 136:10,14 146:9 146:10
flagella 32:17 34:15 41:9
flank 9:6 11:15
flavor 85:15
flavors 123:22
flexible 66:19 269:8
flip 37:2
floating 31:13
floor 153:14
floquidalonce 240:2
floquidolon 240:6
flow 71:12 72:2,19 73:10 76:14 80:5 176:21
fluid 73:10 79:8 217:3,4
fluoroquinolone 242:6 250:1
fluoroquinolones 16:8 17:6 18:17 18:19 23:13 70:18 179:22 243:13
fluroquinolone 19:4
fly 260:20
focus 12:6 14:22 16:15 47:9 82:5 88:18,19 114:20 126:15,17 154:12 161:5 162:3 166:10 189:17 201:11
focused 4:9 7:17 12:7 40:2 122:15 198:19 208:16 280:8
focuses 27:13 112:20 115:5 165:16
focusing 120:22 232:12

fold 128:15 252:17 257:15
folks 5:9 172:2 220:4
follow 11:2 33:9 47:16 58:22 135:18,21 151:4 160:12,16 162:7 162:10,18 163:7 163:19 164:8 212:17 213:14 273:22 279:6
followed 33:12 241:13 247:18,19 280:15
following 20:5 70:6,11 126:22 134:11 136:11 139:12 190:21 233:7 273:19
follows 215:13
food 1:1
footnotes 203:5
foregoing 283:3,4 284:4
forehead 15:3
forever 216:22
forget 17:13 38:2 151:10
forgot 17:14 179:19
forks 43:19
form 39:9 114:8 157:9,12 172:18 216:13 280:7
formal 59:10,21
formation 31:1
forming 30:17 33:13 87:10 134:19 191:16 275:19 281:11
formulary 105:20
formulate 215:12
formulation 170:13 172:18 239:6
formulations 75:20
forth 26:16 173:13
fortunate 26:8
fortunately 43:4
forty 195:22 196:10
forum 129:18
forward 4:18 27:2 110:5,8 121:8 166:11 176:18 219:12
fosfomycin 15:7 17:5 18:5 19:7,9 21:3,7,21 55:9 70:19 72:4 87:6,8 87:18 88:14 96:7 96:13 170:11,18 171:1 181:19 203:10,14 204:1,3 204:5,6,11,17,20 204:22 205:2,5,16 206:14 259:14
foster 218:15
fostering 200:9 207:15 249:10
found 5:7 16:3 20:10 29:1,4 31:12 35:17 38:10 103:10 107:10 108:5 143:18 158:19 164:6 177:11 247:4
founded 135:11
four 9:14 12:4,11 14:10 20:20 29:7 30:18 33:3 44:15 52:2 72:16 73:7 84:19 93:20 113:16 162:13,19 193:20 196:12 204:13 233:16,20 234:2 235:15 270:20 280:22
fourth 72:14
fractionation 68:4
fragility 129:3
francisco 100:8
frankly 236:10
free 6:17 42:5 51:7 78:9
freeman 49:12
frequency 8:22 78:3 103:21 134:12 149:8
frequent 76:9 190:15
frequently 180:3
fresh 72:6
frick 43:7
friction 68:20
friends 113:9
front 129:13
fshp 3:3
fuel 39:1 127:3
full 5:5 77:7 112:20 113:4 119:8 190:22 200:15
fully 77:9
functional 141:18 154:19
functions 196:20 198:20 199:7
funding 7:15 127:19
fungi 120:8 124:1
further 67:8 71:5 151:4,19 157:7 163:11 217:4 270:15 279:10,11 279:18,21 281:16 282:1,3,4 283:12 284:9
fusions 32:16
future 6:9 94:2 101:11 127:2 166:12 190:4 207:3 230:9,10,11 237:13 267:8 278:15

g

g 4:1 88:8
gained 262:12
gaining 119:11
gap 14:12 56:17 183:19 265:18
gaps 8:11 23:15 121:20 122:1 267:14
gasoline 220:22
gastrointestinal 28:13
gatekeepers 176:5
gateway 271:19
gather 127:12
gathered 229:9
gauge 114:19 118:10
gazillion 115:10
gender 162:3
gene 32:8 35:3 41:15 42:1,7,8,10 42:13,19 43:3,4 46:4,6 51:13 198:13 267:19,21 268:2
genentech 7:15
general 16:3,18 77:2 133:8 134:1 145:10 216:9 243:13 266:16 280:5
generalizability 138:21
generally 155:3 175:21 191:5 204:8 250:4

generated 28:1 72:17
generates 68:7 220:12,17 267:19
generating 72:10 72:21
generation 99:13
generous 21:11
genes 29:1,1,2,4,6 29:9,12,18 32:17 35:1,17 36:22 37:20 39:21 40:1 40:11,15,20 41:18 41:19 42:3 43:3,9 46:3,9 268:5
genetic 42:22
genetically 28:20 267:21
genome 35:13 39:19 40:1 44:10 46:5,8 268:4
genomes 39:20
genomic 45:7 78:20
gepotidacin 58:8 58:19 200:18
geptotidacin 92:12
getting 21:9 83:6 124:13 171:2 227:19 229:7,8 230:8 244:15 248:8,13 252:14 259:6,6 265:2
gi 53:12
give 22:2 27:20 28:5 59:4 83:21 84:5 85:8 87:15 92:13 120:18 153:13 208:6 216:4 240:10 262:19
given 105:5 111:11 113:7 114:12 115:22 144:2 147:7 152:5 160:3 204:8 209:9 211:22 213:11 218:17 242:12 248:6 249:7 280:5 280:7,21 281:18
gives 98:5 239:12 252:14 254:8
giving 81:7 99:10 119:16 121:18 199:22
glad 47:16
glass 69:20 70:4 71:21
glassware 70:15
glaxo 254:1 262:18
glaxosmithkline 200:16
global 7:19 248:6 248:14 249:10
globally 182:22
globe 29:8 187:6
gluconeogenesis 38:3,11 39:1
glucose 38:12 40:21 88:3
glycolysis 38:3,13
go 12:5 13:8 26:20 33:21 37:6 38:22 38:22 40:6 44:18 45:18 49:17 74:4 74:9 87:1 105:3 107:19 108:20 115:12,17 118:18 119:6 130:15 136:15 158:5 165:17 167:15 168:17 169:2,9 170:1,5 171:15,16 171:21 173:13 174:18 185:4,21 186:20 188:2 189:12 195:15 209:1 211:18 215:7 238:3,14 246:4 251:2 252:2 254:10 261:18 267:2
goal 47:18,22 49:3 56:5,9,22 85:22 175:10 179:22 224:22 258:12
goals 108:12 157:16 270:16
goes 82:2 106:13 116:19 161:3 163:11 186:3 216:16 223:1 252:9
going 5:13 6:15 8:1,2,3,5,8 9:14 11:2,12,16,21,22 12:15,21 13:9 14:14 16:18 17:18 19:11 21:1 22:6 22:11 35:15 40:9 43:19 46:22 47:17 49:18 53:5,7,20 54:22 62:17 64:1 75:6 81:10,12,18 83:10 85:9,12 86:14 91:10 100:1 102:21 103:20 104:3 109:20 119:8,21 131:11 131:13 133:13 134:21 135:13 137:3 138:3 139:8 140:4 141:3 155:17 165:21 166:8 170:15 172:22 174:22 176:18 181:11,15 181:15,18 182:11 186:15 187:20 189:1 210:5,12,12 210:13 215:3 221:1,11,17 222:4 224:6 227:22 230:19 238:11 242:13 243:22 246:20 251:5 252:4 254:17 255:22 256:12 257:3,10 259:4,18 262:5,11,17 265:5 266:22
gonorrhea 145:6 152:14
good 4:2 5:20 43:12 47:14 48:22 49:1 54:22 56:10 57:9 67:11 81:9 98:5 111:8 113:16 116:6 189:11 208:5 210:4 214:15 217:1 227:8 230:3 237:1 243:18 245:4,16 248:15 254:8 258:6 259:17 264:14 265:15,21 266:18 282:12
gosh 24:3
gotten 256:18
gould 84:22
gp 117:8
grace 2:7 260:4,5 264:16
grace's 264:20
gradation 229:11 279:17
gradations 234:12
gram 15:17 16:3 27:15 34:11 124:3 127:9 128:19 204:7,21
grams 88:16,16
grande 2:10

granted 153:9
graph 55:8 60:16 197:18
graphic 34:8 102:13
graphical 26:10
graphicly 33:1
grasso 70:22
gray 1:12 36:21 283:2,18
great 5:19 24:2 46:22 49:16 57:16 62:13 90:13 99:3 108:7 120:10 130:17 131:9 165:5 169:13 172:10 174:7 207:18 220:3,9 245:2 259:3 262:4 264:15 265:10 271:21
greater 31:21 36:3 77:18 93:10 125:22 134:19 193:22 194:12 204:7
greatly 79:6 115:18 200:9 207:15 277:20
greece 113:8
green 41:10
greetings 119:18
greibling 13:11
grenwood 70:17
grew 247:11
gross 33:22
ground 209:2 265:8
group 46:21 63:13 71:10,19 83:18 95:11 112:3 114:20 158:11,12 159:18 163:17 164:1 197:17 249:18 262:15
groups 13:22 96:6 159:9 161:17 163:1 193:17 194:13 247:1
grow 45:16 46:14 134:18,18
growing 33:16,18 43:15,16 44:1,5 44:21 119:2 180:11
grown 44:10
grows 76:2
growth 20:15,16 20:17 29:22 42:2 43:18,20 44:2,12 44:13 45:2,6,11 46:10 60:17 74:2 74:20 75:3,22 86:10 137:8 212:5 268:7
growths 44:14,14
gsk 183:9 188:4 199:18,21 251:17 253:3 255:2 265:5 277:16
guarantee 11:22
guess 101:3 168:6 209:19,22 219:19 230:10 241:7 245:2 266:10
guidance 9:22 82:5 99:14,15 128:18,22 131:18 131:20 141:4 142:1,15 144:20 145:7 150:1 152:2 152:4 153:11 185:10 191:9 198:19 200:7 202:13,18 206:19 206:22 207:1,12 249:4 258:20,21 277:17 278:11 282:2
guide 11:6 23:21 23:22 191:5
guided 11:10 18:11
guideline 99:20 103:18 141:12 143:15,22 144:19 146:17 272:1,18
guidelines 7:8,11 8:6,9,20 9:17 10:11,22 11:1 12:9 14:8 16:11 17:3,21 18:6,13 19:10,14 23:20 98:4 114:15 121:13 128:7,9,10 128:22 141:11 148:5 149:19 166:16 167:6 176:16,16 184:10 184:14,16,19 187:6,12 188:15 197:3 201:11 203:9 211:11 229:6 241:8 242:12,14 245:8 247:16,17 267:9 278:22
guideline's 11:4
guiding 128:11 142:7
gupta 2:11 10:9 10:10 130:14,17 130:18 153:15 168:12,16,20 169:4,7,11 171:6 171:9,11 173:4,7 182:8 183:5 199:13 200:4 210:21 245:1,2 246:9
gut 240:18
guys 227:19 263:6

h

hadley 2:12 182:13,13 183:5 242:17,18 243:14 244:1 275:15
hadn't 225:19
hagberg 31:19
half 17:17 18:17 29:2,19,19 39:14 39:15 71:12 135:5
hand 80:14 87:9 94:12,13,15 198:7 209:7,8 210:15,16 210:18 227:17 234:17,22 236:18 236:22 241:5 242:17 244:3 248:3 251:6,7 259:20 264:8
handle 51:5 215:4 262:6
handled 178:18 209:22
handout 102:5
hands 209:11 214:13,15,16,18 214:22 215:3,4 219:19 236:20 238:1 240:1 246:3 250:18,19 265:19
handy 168:16
happen 170:17 180:20 194:21 231:2 259:8
happened 9:13 14:20,21 115:10 126:1 162:8 182:4
happening 170:21 184:9 188:17 213:5 234:15
happens 116:22 160:5 213:15,16 229:17 230:5

happy 47:6 152:15 184:12
hard 14:20 23:16 57:9 95:6 98:3 175:13 178:22 220:20 223:4 255:11
hardcore 119:9
harder 240:14
hardware 70:15
harmonization 200:7 207:4,13 248:10 277:18 278:16 281:3
harmony 248:7
harnessed 76:11
harry 2:21 27:5
hartford 47:9 62:10
harvest 54:1
hasn't 89:14 155:15 187:22 224:16
haven't 45:9 109:2 184:16 231:11 243:6 247:1 250:4 260:1 262:3,8
heads 54:2 264:18
health 39:8 46:17 63:3 94:19 99:12 100:22 102:4 121:6 123:16 124:18,22 140:10 165:11 167:18,22 168:2 174:20 242:11 275:3
healthcare 13:3 14:13 102:11 107:18 112:9,10 120:17,19 127:21 175:2,10 281:20
healthy 87:11 113:7 122:22 254:20 255:1
hear 4:13 62:19 99:11 106:12 120:11 141:1 171:4 210:2 214:11 220:4 228:16 234:21 245:4 258:9
heard 90:1,19 105:13 118:4 119:2 132:3 141:7 141:21 143:5 151:9 183:8 184:7 207:5 211:6 212:4 215:11,19,21 217:17 218:5,14 231:11 235:4,14 267:16 268:8,20 269:16 270:8,9,18 271:15 272:5,14 273:4 274:11 275:15 276:6 277:15 280:12 281:2
hearing 46:20 209:10 221:13 245:3
helicobacter 27:15
hello 67:12
help 6:8 24:10 49:4 62:11 64:15 67:6 78:11 79:16 121:15 136:11 213:5 214:16 249:11 258:13 262:13 268:18 269:13 270:6 282:9
helped 99:19 105:17 207:10
helpful 15:5 24:18 165:6 216:21 218:7 251:13 259:1
helps 202:3 204:15
hematuria 105:6
heme 36:12,13
hemolytic 28:7
hereof 68:21
hereto 283:14 284:11
here's 33:8 165:21
heterogeneous 43:1,2 46:2
he's 120:3 266:8
hi 81:9 99:21 130:17 225:16 230:17 260:5
hiding 213:7
high 14:8 42:16 64:20,20 74:19 76:8 77:11 88:1 91:3 97:4 98:1 102:3 104:3,5 116:4 123:14 170:7,12 182:20 187:3 215:19 247:4 250:11 251:19,22 252:3 253:12,15 256:20 271:6 279:21
higher 13:15 16:6 16:12 44:17 78:2 90:12 93:20 97:8 109:6 163:8 178:2 188:7 193:17 197:16 198:5 239:1 240:7 246:3 253:7 276:14 277:7 280:11
highlight 54:10 66:16 73:7 74:4 84:13 155:13 159:7 219:1
highlighted 62:6 158:11 187:11 218:10 267:12 271:21
highlights 65:16 185:22
highly 32:9 35:8 37:19 41:6 43:1,2 50:3 51:15 55:2 60:18
hip 123:15
hipaa 178:3
hiruy 2:13
histopathology 32:4
historical 86:1 137:18 138:4,6,21
historically 94:22 122:8 252:2 254:4
history 49:8 103:8 108:20
hit 93:22 117:16 240:14
hiv 208:21
hiwot 2:13
hold 173:22 227:18
holds 140:9
holistic 107:1
holistically 107:21 270:13
hollow 68:20 92:22
home 61:1,5 101:7 101:17 108:2,6 115:17
honest 261:13
honeymoon 108:22
honored 7:12
hons 3:3
hooked 58:12
hooton 2:14 10:9 10:12 23:6 25:1 208:7,9,9,21 209:16,17,19,21

210:4 214:13,14 215:2 219:18 225:7,14 236:14 238:2 239:22 241:17 242:3 243:3,17 248:15 249:12 250:20 251:2,5 258:6 259:3,20 260:2 263:7 264:8,11,14 265:21 266:17
hope 141:1 168:21 188:19 239:3
hopeful 258:16
hopefully 62:4 181:3 182:4 207:10
hoper's 31:7
hoping 155:18 182:5 209:6
hopkins 83:18
horizontal 28:1 35:3 267:19
horrible 228:8
hospital 47:9 63:2 63:11 124:6 220:13 241:12 280:13
hospitalize 11:9
hospitalized 35:7
host 36:7,8 65:19 65:21 74:13
hosts 43:2
hotel 105:9
hour 71:14 75:12 76:7 176:12 254:2
hours 32:2,7,14 33:2,3,5,6,19 34:4 44:13,16,19 71:14 72:16 76:8 147:9 175:17 254:2
housekeeping 5:8 6:14
houston 7:3,4 242:11 247:5 248:1
how's 228:12
huge 50:9 53:18 56:17 183:17 188:1 239:8 243:5
hugely 49:5
human 31:17 32:5 37:8 40:13 41:16 42:5 45:8 51:8,15 51:18,20 53:10,10 56:15 65:21 66:3 68:2 69:8 72:20 73:2,3 75:4,5 76:2 76:6 77:15 79:4,6 79:17 93:4 121:6 136:1 222:5,6,22 264:2,7
humanitarian 113:12
humanized 59:5 60:3 61:20 69:10 76:14
humans 30:4 31:16 32:9 50:5 52:3 56:18 62:16 62:19 69:3
hummingbirds 110:2
hundred 192:8 195:22
hundredfold 205:12
hundreds 29:3 208:18
hurdle 207:11
hurdles 126:2
huttner's 21:2
hvlc 80:11
hyde 284:2,18,19
hydration 55:3 223:2
hydronephrosis 112:17
hyperplasia 132:18
hypertonic 74:18

i

iain 2:2 62:20 63:16 67:12
iarikov 2:15 236:21 259:4
iarikov's 236:18
idea 233:8 240:13 245:16,19 262:19
ideally 77:11
ideas 18:2 98:5
identical 43:3 148:13
identification 168:1
identified 88:2 149:16 273:12
identifies 152:4
identify 24:6 68:8 122:1,2 173:18
identifying 173:15 185:6
idsa 8:9 10:11,22 12:5,9 16:11 17:3 17:20 19:13 99:16 99:19 120:1,13 122:14,20 128:3,5 128:9,20 129:2,17 133:20 142:1 167:6 184:18 197:3 203:9 267:9
idsa's 121:10
ig 271:10
ignored 7:18 151:14 224:12
ik 118:9
illinois 80:21 81:1
illness 11:12,15 134:14
illustrate 55:6 202:3 204:16 207:11
illustrated 254:18 255:17
image 68:21
imagine 179:11 235:22
imaging 32:12
immediate 190:19 233:1,10 234:6
immediately 37:9 39:12 40:4 52:10 233:2 273:19
immune 10:20 30:6 50:5 74:13 108:19 224:19
immunocompet... 59:8
immunological 50:6 65:19
immunology 27:8 27:11
impact 70:8 73:14 79:7 101:19 121:5 126:6 185:11 186:1,10,13 190:7 230:13 275:4
impacted 106:11 179:7
impacts 190:16 233:2
impaired 38:12
impairment 83:10
implement 97:6,7 255:11 281:18
implementation 7:7 18:14 256:10 259:9 262:1
implemented 89:14
implies 232:21
importance 98:19 121:11 135:15

150:3 157:14 186:2 202:17 211:9 232:17,20 233:1 261:20 272:1,11 278:16 281:7,11
important 7:19 8:12,12 9:10 14:12 26:11 31:15 38:6 42:2 49:5 54:16 56:13 58:4 64:11 66:5 68:14 69:5 78:22 79:6 82:10 85:11 87:17 87:21 88:4,21 89:22 90:5 93:8 94:1 95:3 100:11 101:22 102:16 103:11 113:2 120:15,18 121:4 122:1 124:10 129:4,18 142:20 144:1,15 145:12 146:7 152:17 153:17 162:7 163:4 165:1 173:18 179:21 188:12 194:19 200:22 218:22 222:7 226:11,16 226:17 233:4,10 233:12 235:11 236:7 251:19 252:16 253:2 259:7,19 261:19 274:9 282:4
importantly 39:10 65:4 66:5 72:10 154:17
impractical 75:4
improve 63:7 66:2 117:1 127:18 218:2
improved 262:20
improvement 99:14,15 126:18 187:7 191:19 225:1 276:4
improving 121:13 122:5 214:5
inactivated 38:8
inappropriate 127:4
inaudible 26:11 28:21 30:9,19 31:8 34:13,21 35:5,11,17 36:10 36:11,22 38:22 40:4,7 43:19 45:19 53:6 58:22 72:4 75:2 85:15 89:6,7 102:1 103:5 111:16 113:19 149:13 153:5 156:3 172:4 173:8 190:11,20 191:3 215:11 230:6 235:8 237:1 240:3 241:18 242:9,10 248:8 249:4 260:7,12,19 261:1,3 264:2 277:9 278:8
incentive 144:10
incentives 272:3
incident 97:8
include 11:19 22:5 28:6 57:4 67:1 96:22 134:10,12 138:6 142:12 154:22 193:5 226:15 231:19 250:14 261:6 276:3
included 82:7 131:20 134:2 147:18 149:7 150:19 157:12 185:17 186:9 222:4
includes 66:7 73:21 91:11 135:6 137:5,22 150:5 161:15
including 10:16 17:13 28:13 29:18 30:9 57:17 88:4 92:16 94:17 110:20 113:13 122:4,9 125:16 128:17 132:17 133:18 134:3 138:10 142:5 149:2 158:14 177:1 180:7 205:1 213:2 220:5 246:7 268:10 270:21 271:17 272:8,20 272:22 275:17
inclusion 183:3 184:11 185:11 188:6,6 207:8 212:21 275:20
incompatibility 75:20
inconsistent 191:18 198:18,21 206:18
incontinence 104:1 190:16
incorporate 201:11 270:5
incorporated 73:8 74:12 98:10,12
incorporates 70:14 142:8
increase 57:22 164:17,19 188:7,8 274:4
increased 125:7 160:15 161:19 162:5 163:14,16 168:2 190:17 233:12 274:8
increases 73:12 163:1 199:9
increasing 16:1 121:2 161:12 171:18 174:19 187:18 275:18
increasingly 237:19
incredibly 41:22 74:17
incubator 145:17
index 48:17 68:2 204:2
indicate 197:4
indicated 35:21 143:16 199:1 272:19
indication 81:12 81:20 98:11 127:15 133:11 144:17 145:2 153:7,10 156:15 260:10 261:2 271:19,20
indications 91:18 121:4 153:8 236:8 271:20
individual 23:19 42:20 114:15 176:2 178:1 195:11 281:8
individualized 257:22 270:1
individually 75:16 224:12
individuals 102:2 102:6 122:10 209:14 226:14 270:9
individuals’ 101:19

induced 38:18
industry 4:7 9:22 81:15 82:5 106:6 106:9 131:18 183:11 184:2 186:14,19 199:20 207:6
ineligibility 239:14
inexpensive 51:5
infancy 261:14
infant 108:16
infants 50:9 108:18
infect 32:1 45:22 52:21
infected 57:16 113:18 114:3
infection 6:5 7:6 7:21 9:1,16,19 11:11 12:9 30:15 31:15 32:19 36:19 37:21 38:6,7,19 43:16 50:13 51:9 51:16,18,20 52:6 52:21 54:3,5,13 54:14,18 55:4 56:11 61:7,9,19 62:18 66:12 69:16 73:21 74:8 77:17 77:21 79:15 85:6 88:20 91:20 96:17 105:13 106:6 114:10 115:15,17 116:8 123:9 125:15 132:4 136:2 145:2 146:20 147:3 149:19 152:7,19 153:8 158:17 169:16 201:3,17 224:18 231:17 255:14,14 263:22 264:4 268:4 278:1
infections 4:11 28:16 30:16 33:9 53:10,11 56:12 65:8,14 66:10,18 74:6 77:6,15 82:11,12 89:13,17 95:5 96:17 104:14 110:17 114:5 116:5,11 121:3 123:7,13,18 124:2 124:5,7,10,16,17 125:10,13,17 126:6,16 127:11 127:13 128:20 131:16 132:15 137:22 141:9 142:16,17 143:8 143:17 146:22 147:8 152:8,11,12 155:5,10 203:1 208:21 251:20 255:19 267:6 271:17 272:19
infectious 4:4 5:22 7:2,10 8:5 63:9,13 81:4 117:20 120:2 120:4,6,12,16 130:19 140:8,20 165:10 166:18 189:7,10 199:18 208:15 228:22 237:20 282:10
infective 47:8 62:10 81:4
infectives 4:4 48:9 131:2 140:16 154:2 211:12
inferior 276:21
inferiority 4:21 231:16 238:8 272:9,13 274:16
infilled 70:1
infiltration 32:7 34:5
inflammation 30:7 217:22 237:11
inflation 106:21
inflowing 69:22 70:5
influence 86:14 163:22
influenced 87:18 96:9
influential 48:11
info 158:14
inform 66:22 67:9 67:15 68:10 258:14 268:22 269:10,14
information 13:11 81:19 83:2,7 84:6 85:12 86:12 87:2 90:3 92:15,15 94:9 104:7 114:19 116:17 122:3 133:21 202:16,19 229:9 256:11,17 263:2 269:18
informative 130:4 155:19 195:13
informed 6:7 101:21 118:6
inherent 79:13
inherited 261:15
inhibit 74:20
inhibitory 89:6
initial 57:19 262:19 271:4
initially 58:3 66:12 94:22 224:2 257:5
initiate 44:2
innate 30:6
inoculant 64:11
inoculated 32:13 32:20 33:11
inoculum 56:22 57:12,17 64:21 77:1,13 90:12
inpatient 14:20 15:16
ins 92:6
insert 95:1
insertion 35:11
insight 154:15 269:12
insightful 182:9
insights 67:5 124:10 155:18
instance 13:22 114:4 117:8,12 118:3,22
institutes 46:16
institution 97:7 112:4
institutional 176:16
instrumentation 132:16 142:18
insured 133:6
int 181:9
intake 79:8
integrated 202:19
intellectual 117:10 218:14
intend 137:5,7 156:18
intense 213:1
intent 273:10
interaction 179:4
interactions 128:10
interbacterial 95:14,19
intercept 175:12
interception 177:3
interest 118:11 139:14 153:12 209:10 281:17

interested 37:16 86:8,16 118:10 169:21 219:12 221:20 224:11 225:1 238:9 283:15 284:12
interesting 7:19 19:9 25:11,22 36:20 39:2 178:5 211:1,6 225:18 235:13 237:5 241:9
interests 73:13 81:2
interfacing 166:18
intermediate 71:13 256:6
intermittent 122:12
internal 131:5
international 247:6
internet 104:8
interpret 118:8 201:1 256:1,11 261:20 266:2
interpretation 91:6 94:18 97:17
interpretative 206:2
interpreting 126:20
interpretive 281:3 281:22
interrupt 209:14
intersect 57:8
intersection 178:21
interspersed 74:1
interval 138:15,19 149:2 193:4,14 194:11 254:3
intervention 216:13
interviews 178:9
intestinal 72:9
intimate 170:2
intracellular 52:5 118:5
intraurethral 53:1
intravenous 114:9
intravesical 58:1
intrigued 20:13
intro 154:8 210:1
introduce 6:11,21 47:5 130:16 131:13 140:7 153:17 165:7 199:15 209:16
introduced 70:3 76:16
introducing 47:6 71:20 80:19 110:14 199:16 208:9 239:4
invaluable 116:6
invasion 73:16
inverse 78:2
inverted 69:20
invertible 36:20
investigated 146:2 146:11 218:5
investigational 47:11
investigator 7:2 167:10 182:10 214:3 222:1
investigators 50:17
investigator's 165:9 274:12
invited 141:2
inviting 111:10
invitro 29:22 30:3 40:14 41:2,3 62:18
involve 237:8
involved 19:15 31:1 83:5,5 99:12 226:13,18
involving 122:17
irb 169:18 174:7 174:14 175:22 178:3
irene 1:12 283:2 283:18
iron 34:16 36:2,7 36:7,8,10,11,13 36:17
irradicate 240:15 240:16
islets 66:7 77:3,7 77:10 92:16,17
isn't 59:2 88:6 103:3 109:19 230:5 254:17
isolate 201:4
isolated 35:5 39:17 40:3 43:10 43:10 116:15 197:18
isolates 29:8 145:18 198:11 204:4
issue 102:19 115:3 120:15 152:3 166:17 178:20 179:6,21 181:18 183:17 188:1 209:7 211:19 238:5 239:8 240:17 255:8 256:13 257:18 263:5
issued 180:7
issues 83:8 86:3 88:21 109:4 116:18 138:21 167:11,13 175:22 177:21 178:8,11 222:12 236:18 242:21 255:7 256:10 258:3 267:9 275:12
iterations 71:18
iterum 183:9 188:4 189:2,7 207:6 276:7
iterum's 276:10 276:17
itt 137:5,7,11 139:10 140:1 147:18 149:12 151:6 192:19
it'll 35:8 165:5 169:8 172:7
it's 9:13 10:7 12:7 13:17 15:5,14 19:9 23:1,16 30:4 30:9 31:21 32:22 35:8,18 36:19,21 37:17 42:3,11 47:4 51:1,4,5 54:8 54:21 55:2,7,17 55:18 56:11,13,22 57:9 58:4 59:3 72:6 74:18 82:8 87:7 90:1,2,8 93:11 95:6 96:4 96:19 97:3,13 98:3 100:14,19 101:22 102:13 103:10 104:20 106:9,16,17 107:3 108:15 111:10 116:21 117:4 118:13,14 119:10 121:4 129:4 130:20 132:5 133:10 137:18 143:9 145:12 146:7 151:11 155:3 160:2 169:17 172:8,16 175:13 177:6

179:7 180:11 184:22 185:18 186:7 188:12 201:9 211:16 212:10 214:5 215:21 216:1,21 219:14,20 220:3,9 221:9 223:4 224:3 224:3 225:17,20 226:11,17,21,21 227:11,13 228:6,8 228:17 231:8 235:10,13 236:1 237:10,19 238:2 240:13 241:21 242:13 243:5,7,8 243:10,16 250:3 251:7 252:11,18 257:2,2 259:15 265:22 266:18
iv 11:9 58:13 88:15 271:1
iwatches 168:5
i'd 62:8,21 80:14 98:19 102:22 138:4 140:7 165:2 165:7 189:13 192:1 211:3 214:11 221:3 264:15 282:6,7
i'll 7:22 8:10 23:5 27:16 32:9 34:17 40:8 43:17 48:3,4 50:1,14 58:6 63:18 74:9 82:1 87:4 89:19 96:4 99:20 107:19 110:14 112:1,12 113:16 114:22 115:9 118:17 120:8,16,22 121:4 121:10 129:2,16 130:15 136:15 137:18 140:20 154:8 165:22 167:14 169:13,13 173:3,9,10 195:21 199:11 200:13 214:13 219:7 220:2 221:5 225:6 230:14 234:15 236:12 238:13 239:19 246:11 251:6 258:4 261:16
i'm 4:3 5:13,21 7:1,1 8:2,3,5,8 9:14 15:10 16:5 16:21 19:11 21:1 22:5 26:7 27:2 35:3 40:9,10 41:14 47:16 63:22 81:10 85:20 92:18 95:19 100:1 103:20 104:19 109:7,7 111:13,21 112:7,11,12 113:4 113:11 114:3 115:22 116:1 117:1,4 118:6,17 120:16 129:21 130:18,18 131:11 131:13 133:13 134:21 135:13 137:3 138:3 139:8 140:4 141:2 155:12,17 158:4 160:6 165:21 166:8 168:21 169:1,7 176:9 179:19 181:3 182:3 183:12 184:1,12 195:14 208:7 210:5 214:15,18,19 215:10 216:9 219:22 220:13 221:10 222:1 225:12 226:13 227:22 230:18,19 234:18 235:3,15 236:3,8,19 237:1 237:22 242:9 245:3 249:8 250:18 251:5 253:18 257:17 261:13 263:20 265:16
i've 7:5,17 40:15 45:21 74:11 98:8 101:3 102:10 103:16 104:16 112:8,13,17 113:3 113:7,11,12,17,20 114:1,2,7,12 116:2,18 117:3 131:20 134:2 136:20 164:12 168:3 184:6 188:19 214:7 225:18 236:5 238:14

j

j 2:2 31:18
jackson 85:1
jalal 3:8
janice 3:11 99:9 99:11,20,22 110:11 119:20 121:17 225:12
janmohamed 2:16 215:7,9 248:3,4 248:16,18 250:14
janssen 81:16
japanese 71:9 144:6
jason 3:3 62:20 67:13,19 80:15 91:19
jeez 84:15
jepto 253:3
job 1:13 27:19 121:18 185:3
joined 4:7 130:22
joining 140:14 154:6 208:22
joint 123:16 231:7
journal 208:18
judge 45:5
juice 105:11
july 154:2
jump 111:12 158:1
jumps 163:2
june 1:7
justice 265:11
justifiable 218:13
justification 152:21
justified 148:22 150:10

k

kadry 2:17 153:18 153:18 154:6,7 273:4
kal 130:18 210:19
kalpana 2:11 130:14
kalpna 10:9,10
keep 173:12 180:1 213:3
keeping 212:22
keflex 240:11
keith 3:5 80:19
kenan 49:12
kept 25:6 93:1
kerian 2:10
key 17:21 29:17 48:12 63:21 67:18 73:7,13 74:7 85:11 114:21 127:20 231:8 258:12 269:2
kick 6:12 238:10

kidney 33:3,6 45:22 50:11,13 54:14 56:7 58:2 61:7,9
kidneys 32:3 33:7 53:20 54:1 58:17 59:12 60:4
kill 78:19 89:1 91:12 145:21 253:5
kills 87:15
kilobases 35:2
kilogram 59:9,10 76:7
kim 2:18 4:2,3 5:20 27:4 62:13 99:3 119:19 129:20 208:5,6 209:20 210:3 214:18 215:6 219:20 221:7 224:1 225:11 227:16,21 230:15 231:22 234:16,21 236:16 237:2,22 238:4 239:21 241:4 242:16 244:2,22 246:9 248:2,16 250:13 251:1,4 263:9 266:14,19
kind 82:1 84:5,11 93:11 100:5 105:18 108:15 114:3 148:19 155:1 167:17 169:19 172:14 174:15 178:3 224:5,17 226:22 228:13 230:1 231:7 247:1 248:8 256:17 257:2,12 257:20
kinds 159:8
kinetic 254:10
kinetics 69:4 75:3 146:1
kleb 247:13
klebbsiella 113:20
klebsiella 15:4 87:16,20 88:12 247:16
knew 21:8
know 16:2 23:16 24:1,9 26:19 37:14 39:4,18 53:7,10 66:8 75:1 77:19 79:14 84:5 88:16 89:3 90:18 91:4 100:12 102:9 102:17 104:2,4,9 104:14,19 105:5,6 105:18,22 106:19 106:21 108:1,16 108:20 109:18 110:6 112:15 115:12,16 116:5 117:4,6,19 125:19 171:16 176:17 180:5 181:14 183:17 184:3,17 194:19 212:6 213:19 214:20 217:9,19 220:14 221:13,17,18,21 222:4,7 223:10,16 224:14,16,19,21 225:2,19,22 226:3 226:8,16,20 227:4 227:10 229:3,17 233:4 234:21 235:3,8 236:17 239:9 240:4 244:9 244:13,13,19 245:10 246:16,18 246:21 248:11,22 249:3,11,12 252:5 253:4,19 254:7,20 255:7,8,12,20,21 256:5,13 257:4,10 257:14,21 258:21 260:3 265:15 266:5
knowing 37:16 87:19 144:9 216:2 219:12
knowledge 8:11 14:12 23:16 56:17 121:20 122:1 265:18 267:14 283:9 284:6
known 4:11 17:11 68:2 129:6 132:9 148:17
knows 101:15 106:12 117:22 118:15 170:20 214:20 222:17 266:8
kuti 62:9

l

l.t. 2:21
lab 31:7,22 43:8 51:7 54:3 60:1 61:18 87:8,21 95:15 96:10 107:6 107:7 201:2 255:11 262:2
label 21:8 236:9
laboratorial 120:7
laboratory 20:18 30:1 41:16 42:12 42:21 45:16 46:8 46:16 62:15 75:1 97:19 212:10 266:1,3
labs 15:12 92:1
lab's 222:16
lacing 88:8
lack 10:17 89:11 90:12 95:4 102:17 103:2 109:11 123:10
lacks 71:2
lactam 145:16,16 250:2,2,3 280:10 280:12
lactamase 125:3
lactams 17:6 23:14 70:18 241:1
land 121:19
language 102:2,3
large 31:11 35:10 49:13 50:22 51:3 54:22 70:14 71:16 76:8 129:6 187:13 192:2 247:2 260:12
largely 75:4 141:10
larger 79:3 231:18 244:18
lasted 25:15
lastly 137:13 220:18
late 71:6 160:11 160:16 161:3,19 162:5,7,9,14,18 162:20 163:1,7,7 163:17,19,22 164:7 274:4,7
latest 118:3
launches 182:20
lay 121:19
layer 73:5
lcm 80:11
lead 10:11 25:19 61:9 83:18 210:11 210:19 276:12 277:8 280:3
leader 138:5
leaders 4:7
leadership 63:4
leading 280:14

leadoff 251:15
leads 61:6 63:5,12 119:1 127:5 205:13
leakage 53:6
learn 13:14 37:22 38:1 110:4 262:5
learned 103:16 109:15 189:5 225:18 276:9
learning 225:21
leave 46:1 119:15 183:16 221:6 228:15 251:6
leaving 237:8
led 19:15 126:2 281:6
ledanski 284:2,18 284:19
left 32:19 34:9 40:10 41:14 43:20 44:12 57:18 64:5 87:9 94:12
lefthand 142:6
lend 179:15
lends 172:20
lenient 20:15
lessons 189:5 276:9
lest 10:6
let's 10:22 40:6 112:12 190:11 195:13,15 208:1 247:17 256:20 264:12 280:1,16
level 16:16 37:12 65:21 77:10,11 88:1 107:1 149:16 155:15,17 178:2 216:3 234:2,14 236:3
levels 51:11,13,14 80:3 91:21 152:9 201:16 203:20 204:11,20 205:11 213:6 234:2,5 277:22
levo 58:16
lfu 164:5
li 2:19
licensed 148:15 150:6
licensing 177:7
life 75:7 101:14 105:7 108:9,11 113:4,15 117:21 118:13,14 125:6 135:5 190:14,16 228:22 270:20
lifecycle 107:20
lifespan 13:17
lifestyle 108:8 246:1
lifetime 13:15
light 32:16 37:2 191:22 197:20
lighter 16:1
lights 32:22
likelihood 16:20 83:10 117:15 146:19 163:10
limit 62:2 147:6 193:13
limitation 54:11 268:11
limitations 14:19 48:4 64:12 65:17 261:5
limited 34:20 56:14 58:20 62:3 82:11 92:1 102:17 141:17 153:7 209:9 260:18 272:22
limiting 211:20
line 17:4,7,9 23:12 31:8 33:17 34:3 84:11 97:12 104:8 105:1 106:8 166:15 170:3 206:14 221:8 238:16 241:19 274:22
linear 55:17
lines 73:5 124:20 127:22 129:9
link 5:7 131:20
linked 115:8 123:17
list 5:5 74:9,10 84:1 147:14,17 236:20
listed 47:22 65:22 74:11 96:4 214:22
listen 116:16 118:2
listening 116:13 117:16
literacy 102:4
literally 113:18 117:21
literature 19:18 58:7 78:13 91:6 138:7 168:4 252:18 261:17,17
liters 39:13 75:10
little 6:14 14:20 23:21,22 33:20 34:17 35:15 49:8 50:14 82:1 84:22 89:20 100:1 113:10 114:17 118:11 142:5 162:1 184:8 198:11 202:18 208:2 211:17 214:3 224:6 227:2 228:11 235:3 242:13 243:22 244:20 252:1 266:12
live 28:12 32:12 111:14 113:3
lived 100:2 107:12 110:17,21 112:13 113:12 114:1
living 123:13
loaded 256:3 281:19
local 11:13 132:8 143:3 154:18 171:20 238:22 241:14
locally 241:21 247:4
location 1:9
log 45:4 55:18 56:11,12 78:2 87:10 90:10,15,20 93:18 159:10 253:6 281:10
london 29:11
long 18:1,21 19:17 24:2,9 26:17 30:13 48:22 68:6 69:17 112:13 240:19 253:12 273:21
longer 19:1 24:5 65:5 147:9 160:12 162:22 179:16 213:14 218:6 232:13 233:6,8,12 240:12,14 279:6
longevity 253:2
look 9:12 10:22 14:8 15:10 18:15 18:21 19:6 22:11 28:2 32:11 35:16 37:10,11,22 41:21 42:1 48:9 55:16 55:18 56:7,8 78:18,19,20 81:18 82:4 83:20 85:9 85:13 86:6,7 87:2

92:10 94:5,14 96:22 107:20 110:8 148:7 157:2 157:22 158:9,18 159:3,16 160:20 161:2 162:17,21 163:11 168:11,13 173:11 177:8 184:14,19 187:9 195:13 224:7 230:3,22 231:1 241:10 242:10 243:1,20 244:18 262:14 270:13
looked 15:16 20:8 23:7 25:2 35:19 39:20 71:10,19 85:5 87:1 89:14 156:17,21 158:3 160:4 164:2,3 225:14 247:1 263:13
looking 4:18 12:10 18:18 27:2 41:5 48:16 51:7 56:15 88:13 93:19 95:2 106:2 108:16 154:9 155:12,14 156:14 162:7 170:4 171:19 172:12,17 175:16 178:1 181:16 185:7 186:18 187:2,6,7,13,15 187:16 188:5,10 198:7 204:20 215:15,19 218:6 219:9 235:7 245:13,14 256:16 257:15 262:12
looks 15:6 120:10 169:12
loss 68:16,17
lot 8:17 9:3 14:17 14:22 15:6,9 24:14 25:18 52:14 61:17 62:2 64:3 70:15 74:20 83:7 85:8 89:12 92:16 93:4 94:16 102:10 102:19 103:3 105:11 106:4 113:15 114:5 123:19 127:4 154:15 158:3,10 167:14,21 186:16 187:4 202:16 209:12 217:3,4 221:13 223:11 224:16 225:18 227:13 229:1 230:19 245:7 247:5 250:7 252:19 253:18 254:4,14 255:11 258:13,20 261:14 262:8,12 263:2 264:16 265:5,6,11 265:12 278:20
lots 53:7 106:13 217:1 238:13
love 107:3
low 35:22 64:20 64:21 74:19,19 77:10,19 84:1 93:11,11,12 160:22 171:19,21 194:10 212:1 238:19 242:21 249:21 280:6
lower 20:17 33:17 34:2 82:11 90:9 96:7,13 113:1 132:8 138:18 141:16 143:3 165:16 193:13 195:3 198:9 204:14 205:12 219:4 228:5 277:8
lowered 234:22 236:22
lps 34:11
luck 67:11
luckily 243:3
lucky 117:20
lunch 42:5 129:22 130:6
lung 28:16 253:18 263:22
lux 32:16

m

m 147:18 149:12 151:6 192:18
m1 139:2
m2 139:6
mac 10:9,11 23:6 221:7 225:11,12 236:16 237:22 250:13,18 263:9 266:20
machinery 40:17 41:8
mack 208:9
macro 42:8,9
magnitude 48:19 148:16
main 7:17 153:5 173:15 243:5
mainstream 78:13
maintain 76:19 172:14 178:22
maintained 80:6 165:14
major 82:7 112:18 129:8,8 145:20 190:16 263:4
majority 26:6 114:8 222:10
making 38:12 81:20 99:7 101:21 168:22 223:19 227:10 269:19 275:22
male 14:13 19:15 155:3 242:2
males 85:3 132:13 142:16
man 142:15 228:3 228:8,10,13
manage 106:22
managed 1:9 113:3
management 135:18 179:8 275:3
managing 124:11 190:12
mandate 220:10
mandatory 11:18
manifestations 10:3 134:15
manner 272:2
map 15:21
march 92:14
margin 90:9,12 137:16,17,20 138:18 139:5,6,15 144:22 148:19 193:9 272:13 273:3
margins 148:21
marker 84:7 96:5 96:18 196:17,21 199:2 257:6,16
markers 254:10
market 183:13 184:4 187:21
marketing 140:18
markets 182:22
married 113:4
maryland 27:9 153:20
mastitis 28:16
match 65:14 255:1 264:3

matches 257:1
matching 20:5 76:15 192:12
material 103:3
materials 102:1 103:5 104:11
matrices 56:19 262:10
matter 23:20 99:18 100:17 185:18
matters 223:5
maximize 85:22
maximized 146:21
mbbs 2:2,16
mbc 145:21
mccabe 85:1
mci 252:8
md 2:5,8,11,13,14 2:15,18,22 3:2,9 3:10 131:4
mdr 270:22
mean 8:19 22:4 23:1,3 36:7 41:3 45:12,14,17 52:9 95:22 103:4 106:17 135:7 159:3 218:13 235:16 237:10 241:17 248:18,22 259:11 264:19
meaning 51:12 126:21 141:16 214:6
meaningful 121:12 126:15 199:6 271:22
means 20:19 22:9 36:21 93:8 116:9 116:13 186:15 256:18 259:10
meant 22:7 26:1
measure 45:5 216:5 232:11
measured 37:18 45:3 60:4 69:22 212:10 232:13
measurement 99:16,17 184:11
measurements 79:22 185:20
measures 127:7 127:18 128:1,17 129:12 199:7 215:15
measuring 97:3 199:4,10
mechanism 78:21 145:12,22 224:21
mechanisms 224:17
media 70:6 72:7 74:15 75:2,10 76:1
medical 7:4 27:8 27:11 63:3 123:14 124:22 131:1 149:18 177:6 189:6 218:17
medication 151:12
medications 103:17 104:16
medicinal 272:18
medicine 5:16 7:3 80:22 81:1 83:17 120:2 123:12 129:5,8 131:5 153:21 189:9 208:10,11,12 272:15
medicines 4:8 140:6,11 143:16
meet 117:20 153:10 208:1
meeting 66:16 67:11 109:16 123:4 188:19 222:20 228:15 241:7 255:9
meets 251:22
mega 28:21
melbourne 63:12
member 150:6
members 46:16 62:9 129:14 250:14
men 9:10 10:16,16 13:7,13,16,17,19 13:21 14:4,9,12 19:17,21 20:13,20 21:13 23:22 24:2 109:11 155:5
meningitis 28:7,15
menopausal 217:10
mention 23:6 60:13 111:19 142:21 143:13 145:12 148:20 149:16 150:1 215:19 246:21
mentioned 47:18 54:20 61:16 65:2 100:1 103:22 104:10 106:4 107:4 108:18 109:13 116:18 134:11 145:7 147:21 162:9 170:3 173:22 175:22 178:17 180:13 183:12,20 184:22 201:9,15 202:15 225:3 229:16 237:16 244:10 252:21 261:3
mentioning 109:16 142:3 186:4
meropenem 60:11
mess 80:12
message 174:22 176:11,15,15
messages 114:21 176:3,22 177:3 178:17
messaging 167:22 174:20
met 22:12 60:9 175:8 271:10
meta 138:13
metabolic 38:5 41:13 51:14
metabolite 145:20
method 53:5 80:10 90:20
methodologies 78:10,12
methods 80:12 174:2,19
mi 139:15
miami 208:11,12
mic 57:5 80:2 84:5 88:2 93:20 95:17 96:3 197:20 204:8 204:13 205:2,14 228:4 253:8 256:3 257:1,2
mic50 198:2
mic90 198:2
mice 32:9,12 33:10 54:14,20,22 55:4,7 57:16 59:8 60:4
michigan 27:8,11 131:6
micro 74:12 137:7 137:11 138:10 139:10 154:10 156:17 157:16 158:3 159:14,15 160:21 192:18 213:3 217:18 220:5 221:5 224:8

225:2,3,8 231:14 231:15 235:6,17 244:13 262:2 273:10 276:20 277:2,4,5 279:15 279:15,16
microbalactic 126:19
microbe 210:9
microbial 30:16 88:22 132:7 143:2 269:9 274:13
microbiologic 21:22 23:11 184:12 185:14 191:13 195:21 196:15 222:3 273:17 274:9
microbiological 49:2 56:16 59:1 59:16 85:17 135:1 135:10,15,22 136:9,13 137:7 147:3 149:10 151:6,13 154:4 156:3,5 157:5,15 157:19 164:14,16 164:22 211:12,22 213:9 218:1 232:14,17 233:5 233:13,15,18,19 234:8,9 236:3 257:11 272:11 273:5,13,16 279:2 279:13
microbiologically 22:6
microbiologist 63:10 116:2
microbiology 4:16 27:7,10 199:21 212:6 213:12 219:11 223:20,22 246:8
microbiome 240:18
microgram 205:13
micrograms 93:13
microphone 228:1
microscope 56:8
mics 204:5,12 205:1
mid 77:18
middle 105:22 112:13 238:21
miglis 2:20
mil 33:14,21 69:20 70:1 71:12 76:6 77:18 78:4 93:13 156:7 158:20 191:16 194:1 205:13 212:11
mild 243:7
mile 220:21
miller 208:11
milligram 59:9,9
milligrams 55:9
millileter 134:20
million 13:4 14:1 14:3 24:6 28:22 123:6,8
mils 71:17
mimic 51:20
mimics 31:17
mind 188:2
mindful 6:10
minimal 206:19 239:1 280:6
minimize 63:7 243:11 270:7
minimized 147:1
minimizing 98:17
minimum 149:8
minivan 39:13
minus 193:15 194:12
minute 47:1 70:1 71:12 169:8
minutes 45:13,15 45:18 81:7 117:9 208:2 209:14 236:15 266:14
mirabilis 27:14 30:20
mirage 165:12
miscommunicat... 103:1
misguided 220:11
mispronouncing 219:22
missed 263:8
missing 236:19
misunderstanding 103:1
mitigate 109:3
mittr 276:20
mitts 277:2,4,5
mixed 88:13 213:6
ml 135:12
mnemonic 18:2
mobley 2:21 27:5 27:6,9,17,18 46:19 47:16 267:16 268:1
mobley's 27:13 51:7
mode 52:20
model 30:4 31:2 31:14,17 32:1,5 38:9 43:6 46:5 47:20 48:3 49:9 49:10,11,12,13,14 49:22 50:3,16,20 51:2,3,9,15,16,18 51:18 52:8,19 53:13,22 54:4,5,7 54:18,20 55:7 56:2,9,15 57:1,4 57:10 58:9,10,12 59:7,22 60:2,12 60:21 61:3,6,7,9 61:19,22 62:1,18 65:15 68:17,20 69:12,18 70:10,11 70:13,14,15,21,21 71:5,9,16,19 72:3 72:6,18,20 73:18 74:9 75:10 76:14 76:17,18 77:2 78:7 79:15,19 90:21 92:17,22 129:11 176:2 222:5 254:15,17 256:4 260:20 261:1 263:12,22 264:4,22 265:20 268:1
modeled 262:3
modeling 91:12 94:6 262:6
models 48:2,4,11 49:17,20 50:1 52:6 54:11,13 61:2,2,19 63:16 63:21 64:2,2,6,7 64:12,14,16,17,22 65:5,11,17 66:1 66:13,19,21,22 67:1,4,18,20,22 68:5,13 69:6,16 71:1 73:1,8,18 74:3,12 76:5 78:14 80:16 82:22 83:1 89:21 90:2 91:11 98:13 148:8 223:4 254:13 258:3 261:4,6,10 264:17 268:10,11 268:12 269:2,4,8 269:10,12
moderate 130:21
moderated 207:22
moderating 6:2 130:13 208:8

moderator 6:11 266:21
modern 78:10 92:11 129:8
modified 156:18 213:1 273:10
modifying 237:8
mold 218:20
molecules 42:8,9
moment 29:14 87:5 119:10 133:13 135:14 168:12 169:5 234:18
monash 63:11
money 170:16
monitor 110:2
monitoring 86:4
mono 73:5
month 230:5
months 17:16 25:4 81:16
montpelier 105:9
morbidity 90:13
morganella 30:22
morganii 30:22
morning 4:2 5:20 47:14 81:9 120:13 130:2 211:7 212:4 267:3
mortality 90:13
mosaic 100:5
mother 105:13
motile 34:15
mountains 113:12
mouse 30:3 31:17 31:18 32:5,5,11 38:9 43:6,10 46:5 49:12,13 51:15,17 52:1,8,8,9 53:13 57:15 58:5 59:7 60:2,12 61:3,22 265:20 268:1
move 32:21 33:20 34:1 52:18 134:21 137:3 140:4 182:11 189:1 207:21 238:5 242:19 258:14 262:9
moved 33:7 49:10 140:16 278:18 280:1
movement 33:5 119:10
moves 143:13
moving 31:13 47:5 136:7
mph 2:11
mucosal 217:22
mukil 2:22 130:12 224:4
multi 66:7 71:9 110:20 113:21 114:9 128:19
multicenter 192:4
multidrug 88:17
multinational 182:18
multiple 68:7 75:5 109:17 124:17 176:5 182:21 254:15,16 261:3 275:6
murine 51:3 268:12
mutants 38:7,9,10
mutation 78:3
mutations 29:17
mute 168:22 209:18 228:4 230:14 258:10
muted 228:6

n

n 2:1 4:1
nadia 2:17 153:18 165:5
name 99:22 111:8 117:21 130:12 219:22 260:3
named 27:10
name's 5:20 67:12
narrow 245:15
natarajan 2:22 130:9,12,22 131:9 165:4 186:4 187:10 188:21 207:18 219:19 221:10 224:1,3,4 244:2,4,22 272:5
national 12:22 46:16 63:3 247:2 249:20
nationally 127:20
natural 157:21
naturally 74:17
nature 69:12 233:20
nausea 9:6
near 101:16 230:9
nearly 43:2
necessarily 10:20 23:3 89:10 90:18 97:11 108:6 126:18 184:1 187:4 188:17 212:19 216:2 237:9 239:12 256:21
necessary 101:8
necessity 157:15
need 11:9 24:3,4 40:19 49:6 50:21 53:18 54:2,8,10 54:19,22 57:4 75:11,16 78:21 80:9 83:8 98:5,12 101:4 104:9 106:22 120:22 121:15,21 122:2,3 122:7,11,15,16 123:4,18,22 124:3 145:17 146:5 148:7 152:19 153:4 157:7 166:10 172:19 173:17 174:1 183:18 187:20,22 190:15 191:14 211:5,11 213:13 218:15 221:1 222:3 227:11 236:2,10 246:4,17 248:9 250:14 252:15 253:14 254:22 256:22 257:5,11,12 260:17 261:8 262:4,14 263:11 270:1,11 271:16 271:21 272:3 278:11 279:6,8 281:2,13 282:1
needed 18:9,10 94:7 98:3 109:17 200:9 207:15 256:14 277:20 279:4,10,22
needing 140:1
needle 52:18
needs 52:7 67:7 80:7 86:22 89:20 92:2 94:1,6 95:9 98:10 128:13 147:6 151:21 172:3 184:8 211:14 255:16 259:8
negating 219:16
negative 15:17 21:14,17 27:15 115:14 124:3 127:9 128:19 135:21 222:15 223:15 226:2

271:4
negatives 16:3 34:12
neither 223:12 283:10 284:7
neonatal 28:15
nephrostomies 112:18 113:6
nervous 113:10
net 90:8 91:2
neurologic 9:19 13:12
neurological 112:16
neuropathogenic 27:14 28:14,19 43:5
neutropenic 60:3
neutrophil 32:6
neutrophils 34:5 73:22
never 105:13 118:4 217:12 229:5,10
new 83:20 86:19 91:21 98:11 103:16 115:5 122:2 123:1 126:4 127:8,18 128:13 135:9 144:11 145:14,22 151:17 154:1 156:12 161:7 167:6 183:18 187:22 200:9 207:15 210:19 218:21 242:13 250:15 261:4 265:8,9 267:8 273:9 277:20
newcast 281:4
newer 229:4
newly 161:10
news 12:20 13:7 43:12 124:21
ni 273:3
niaid 131:7 230:18 230:18
nice 85:7 92:13 239:8 255:2
nicely 253:4
nicolau 47:21 62:8
nicole 3:7 215:10 258:7,7 259:20
nicolle 186:1
night 70:2 71:14 176:11
nih 87:12
nine 22:19
nitrates 74:19
nitro 242:21
nitrofurantoin 16:8 17:4 18:3 21:3,7,20 59:18 84:13 134:4 171:15 172:3,9 181:19 203:10,14 205:8,9,11,17 206:14 238:15,21 239:18 242:20 245:5,17 247:10 247:14,18 248:6 248:10,19 249:2 249:14,15,17 250:7,10 259:14 274:21 278:8 280:4 281:4
noises 168:22
non 4:15,21 15:20 20:22 21:4 22:20 25:22 29:11 62:17 92:15 231:16 237:7 238:8 239:10 258:13 261:6,9 263:12 272:9,13 274:15
nonclinical 81:19 92:11 98:10 99:6 145:9,9 199:20 269:17,22
noninferiority 60:10 133:2,14 137:16,16,20 138:18 139:5,6,10 144:22 148:14,19 148:21 166:1 172:17 193:9
nonpregnant 141:17
nonstarter 170:10
nontherapy 136:19
norfloxacin 185:19 186:12
normal 76:6 79:10 79:17 132:10 143:10 228:17
normally 90:7 147:9 226:18 247:8
northern 119:18
notable 159:9
notably 112:7 114:5 155:2
notary 1:12 283:1 283:19
note 12:11 56:13 62:21 83:21 139:20 155:9 226:13
noted 31:1 56:1 136:20 138:10,11 139:15 203:2 267:13,19 268:1 268:12,17 269:6 269:22 270:11 271:2,7,13 272:20 273:7,11,14 274:7 274:21 275:2,8,18 276:11,14 277:17 277:22 278:14 280:3,22 281:7
notes 95:20 96:20 203:6
notice 82:12 90:15 97:2 114:2
noting 92:22 277:11
novel 7:6 73:1,8 73:18 74:3 121:1 127:9 200:17 271:16
november 123:5
novy 27:6
nowadays 8:7
number 26:13 31:6 33:8 34:9,20 39:20 43:18 44:16 44:19 54:22 55:1 57:9 77:15,16 78:1,5 92:1 102:10 114:22 116:12 118:18 129:6 143:22 144:8 146:16 147:7 149:8 157:3 184:3,17 185:16 202:21 209:11 212:11,20 213:2 215:12 222:6,22 225:22 226:6 243:1 245:8 249:3
numbers 22:21
numerical 201:1
numerous 113:6 182:20
nurse 105:14 175:2
nursers 105:1
nurses 177:4
nutritionally 74:16

o

o 4:1
observation 163:5 163:6
observations 65:10 195:9
observed 65:15 194:14 268:3
obstruction 109:9 132:17 142:19
obstructive 155:1
obtain 136:5 174:14
obtained 39:10 135:17 145:18 147:11 191:4 244:11,15
obtaining 197:9
obvious 108:17 171:2
obviously 13:15 65:1,22 124:20 142:10,21 144:3 145:1,19 146:18 150:19 151:18 152:15 224:22 229:3 236:3,9 244:19 258:15
occur 12:19 132:10,15 142:14 142:17 151:1 197:5
occurred 72:15 160:12
occurring 10:1
occurs 87:9 143:9 157:17
odds 161:19
offer 68:1 120:14 121:7 126:4 174:18
offered 188:20
office 4:4 6:1 14:1 14:3 37:9 115:21 140:10 154:1 282:10
officer 131:1 140:10 182:14 189:6 283:2
officially 231:8
oftentimes 88:13
oh 105:12 170:4 195:16
okay 12:17 23:5 26:7 27:4 34:12 60:1 134:20 165:19 168:14,19 168:21 169:1,1,6 169:9,13 170:5 171:4,5,10 172:10 172:22 173:9,21 195:17 210:4 219:18 228:12,16 228:17 237:2 238:11 250:21 251:1,5,9 258:10 278:19
old 83:16,16,20 98:10 113:8 175:6 242:12
older 12:21 105:9 109:8 164:9 166:20 192:9 248:8
omadacycline 59:6,17,20
oman 3:7 199:17 200:3 258:9 259:22 277:15
once 32:20 96:12 159:5 212:15 231:2 262:9 282:11
ones 40:2,8,11 214:22
oneself 109:9
ongoing 55:4 58:20 121:1 127:2 258:15 266:5
online 128:13
oops 107:16,19
open 21:8 70:21 100:22 126:11 184:13
opinion 7:21 149:19 209:13
opioid 123:20
opportune 248:5
opportunistically 249:6
opportunities 103:19 118:11
opportunity 7:12 47:15 66:15 67:14 111:12 118:15 119:17 120:14 182:7 189:14 190:3 200:5 239:13
opposite 37:2
optimal 45:16 102:15 122:3 127:8,17
optimally 124:11
optimization 63:14 85:19
optimize 52:18 59:20 61:8 62:5 67:8 68:3 91:15 269:13
optimized 49:4 63:6
option 101:9 125:15
options 101:7,20 103:13 118:20 123:10 125:12,18 126:4 150:8 153:7 166:15 180:9 270:16 271:12
oral 88:14 96:12 96:19,19 125:2,15 189:21 192:10,11 192:21,22 193:8 193:12,19,20 194:8 196:18 197:19 198:3 204:7,22 271:1 276:17,21 277:6,6
order 74:22 75:17 166:11 190:18 209:8,14 210:15 214:1,19,20,21 231:9 235:22 250:15 260:15 281:12
ordering 197:6
orders 175:11
ordinal 233:20
organism 16:21 20:22 21:19 35:8 136:4 181:15 229:2 240:20 248:11,20
organisms 8:4 15:6,17 20:16 25:11,13 31:4,12 136:1 148:9 197:18 198:4 222:16 223:8,10 223:17 226:6 237:9 241:22 276:16,19 277:1
organization 112:3
organizers 111:10 115:2 200:4
organs 116:11
origin 43:21 44:16 44:17,20 45:1
original 81:5
originally 70:22
ought 218:5
outcome 21:9,20 23:9,14 62:3 103:18 157:9,17

158:2,12 159:8 162:6 188:11 194:4 213:3,4,6 213:19 219:13 221:14,17,20 222:8 223:20 225:9 230:2 233:1 234:1,7,14 235:17 237:18 256:21,22 257:4 258:16 259:7 262:18 283:15 284:12
outcomes 47:13 63:7 64:3 65:10 67:21 80:16 99:19 100:7 121:14 123:11 156:10,21 160:18 187:1,3 190:6 193:5,14 195:11 201:9 222:3 233:6,8,13 233:16,21 235:15 237:17 257:9 267:13 269:5
outcompetes 30:3
outlet 132:17 142:19
outline 67:18 82:2 82:7,8,20 165:21
outlined 83:2 269:2
outpatient 14:3,16 14:21 15:16 19:8 19:21
output 64:20,20 76:6,8 79:8
outs 92:6
outside 28:12 197:7
overall 25:14 97:1 134:22 135:6 138:3,9,14 139:7 149:3 185:13,20 190:6 191:11,12 192:18 193:10,11 194:3,20 195:12 196:1,8 197:1 198:17 232:21 276:3,19,22 277:3 277:12 279:17
overarching 143:15 145:8
overcome 68:19 177:10
overlap 55:15 181:1,9
overly 219:15
overprescribed 104:12
overseas 110:21
overview 87:15 131:14 267:4 272:6,15
oxygen 74:19
ozone 27:19
o'grady 69:19

p

p 2:1,1 4:1 22:20 29:18,21 88:8 193:6
p.m. 176:11 282:14
package 95:1 261:5
packages 48:9
page 5:6
pain 8:22 9:6,9 11:15 103:22 105:7 132:12 134:13 190:15
pair 35:13
pairs 28:22
pajama 176:10
pandemic 168:3 175:8 177:15 218:10
panel 6:8,17,20 27:2 33:10 34:2 41:14,22 62:22 144:14 165:6 167:3 207:22 208:8 210:7 211:4 214:11 278:18
panelists 5:4,6 11:5 183:7 209:7 209:10 214:21
panels 41:2 256:2 281:19
pans 218:7
paper 55:22 73:7 92:13 102:12
papers 13:1 53:21 102:11 168:4
parallel 72:12 216:3
parameter 252:14
parameters 62:1 86:13 89:4,6,9 91:9 260:17 263:20 264:21
parasitic 72:14
parenchymal 83:5
parenteral 125:13
parents 113:9
parita 23:6
park 101:16,16
part 17:10 37:12 65:11 85:16 88:4 89:22 90:10 91:8 145:9,10 146:14 146:15 147:5,15 147:17 163:19 170:12 190:2 220:5 223:20 225:9 232:12 263:10 273:9
participant 178:8 275:12
participants 164:2 166:3 169:20 173:16,19 178:6,6 180:22 183:8 274:17 275:2,21 276:10,15,19 277:1
participating 123:4
participation 282:7
particular 4:13 19:2 30:2 87:21 88:11 96:7,20 114:19 116:21 124:3 126:17 144:17 167:13 174:4 176:22 177:5 180:22 201:3
particularly 43:12 65:13 81:20 82:9 83:9 91:22 95:6 110:11 124:2 125:6 126:3 127:9 127:13 166:20 175:8 177:15 216:12 217:8 218:10 219:10 232:18 237:14 280:13
parties 283:11,14 284:8,11
partner 99:12 122:21
partners 100:14 110:3,5 122:18
partnership 200:17
pass 112:12 129:15
pasteur 127:22 128:3 129:10,16
path 121:8 195:2 210:13
pathogen 60:17 86:12 132:7 134:18 135:11

143:2 147:16,17 149:13 151:11,20 153:6 154:17 156:6,19 159:10 159:17 192:20 193:8 194:1 229:3 243:5 257:14 271:1
pathogenesis 31:3 46:21 49:18 53:16 208:17
pathogenic 139:21
pathogenistides 35:2
pathogens 14:15 53:16 57:5 60:7 65:2 68:8 72:1 75:22 76:18 86:12 88:17 95:15 110:20 113:22 123:3 124:14 125:6,11 137:9 147:11,12,14,17 149:15 158:14 166:5 212:19 235:9,19 254:16 270:22 274:19 275:10,12
pathologists 100:16
pathology 65:20
pathophysiology 4:16
pathotypes 28:2,5 267:20
pathway 38:4,4,7 38:8 124:13
pathways 38:3,6 38:14
patient 11:7 15:1 16:16,17,20 17:16 17:18,20 18:9 24:19 25:14 35:7 41:4,17 42:12,16 42:20 43:10 47:13 63:7 65:21 76:7 99:10,12,19 100:2 102:1 103:2 107:16 108:8,14 110:2,5,15 111:4 111:20 115:7 116:10,13,14,16 117:7,9,10,17,17 118:7,9,11 119:20 122:15,15 123:15 134:8 146:18 149:5 151:19 155:15 157:2 158:1,9 161:14 164:10,15,20 166:22 175:3,11 176:20 178:7 179:3 196:20 197:5 198:19,20 199:7 201:5 213:5 216:8 225:18 227:9,11 233:3,14 233:17,17,21,22 234:7,14 235:20 267:10 270:8,10 270:11 272:9
patients 11:20 12:8,13 14:11,13 19:20 20:6 21:8 30:14 37:14 42:7 42:11 43:4,13 46:4 58:21 59:15 83:11 85:1 100:11 100:11 101:2,5,12 101:20 104:21 107:21,22 110:7 111:11 112:3 116:7,14 117:6 119:3,4 122:17 123:11,14 132:21 133:6 134:13 135:18 136:4 137:6,8,14 138:7 139:11,14,20 140:1 146:19,21 147:4,12,16 149:6 149:11 153:7 156:10,17 157:11 157:19 158:12,16 160:5,17 161:16 161:18 168:1 174:3 175:9,13 176:3 179:13 180:21 185:16 186:6 190:13,13 190:22 191:11,14 192:19 193:1,2,7 193:11,12,18,19 194:8,9,17 195:1 195:4,10,11,20,22 196:4,7,9,10,14 196:17 197:7,19 198:5,8,12 199:9 211:8 213:14,20 217:14 223:15 229:2 233:2,7 241:3 242:1 244:16 247:6 254:22 267:22 270:13,14 271:14 273:12,16,20 275:4,6,9,11
patient's 18:12 116:12 117:5 179:1
patter 79:9
pattern 35:16 42:13
patterns 8:4
paxlovid 228:21 229:13
pay 58:4
pcr 37:4
pd 47:19 48:2,8,8 48:10,12,17,20,21 49:3,18,22 50:2 51:1 52:15 54:20 55:7 57:4 59:3,10 59:21 61:18,18,22 61:22 62:15 63:15 69:6 78:14 79:18 81:11 82:6 83:8 85:13,17,18 89:3 89:5,9,12 91:9,20 93:16 94:5,19 97:22 98:13 99:6 201:11,14 203:13 203:19 204:2,6,19 205:7 252:6,11 257:6 258:1 260:17 261:5 263:17,19 264:21 268:9,15 269:9,17 270:1,5,6 281:8
pde 148:8
pdf 106:8
pdufa 198:19
peak 33:15,19 45:1,9 79:21 80:1
peaks 32:7 34:3
pearson 42:17
pediatric 140:15
peers 104:7
pelvic 9:9
penem 197:17
penetration 253:18,19
penin 276:16
pennsylvania 153:21
pentose 38:3,13
people 8:7 10:7,17 17:2,13 18:22 24:4 49:16 51:4 52:21 53:3,4,8 85:2 88:13 90:20 90:22 97:14 100:6 100:12,17 102:20 103:9 106:10 107:12 108:4,8 109:1,19 115:3

119:13 123:4,6,13 125:1,16 128:12 129:6 157:3,22 158:22 160:20 162:15,17,21 163:8 166:19 170:17,22 174:1 175:16 178:16 179:5 181:9 209:13 210:14 212:14 214:17 215:20 217:8 221:17 222:10 226:18 227:5 229:16 230:19 231:17,19,19 237:6 239:14,17 240:10,19 241:10 242:4 244:7 246:6 246:12,22 247:8 255:9 256:19 259:15,18 261:18 266:15
peptide 38:18
peptides 38:20 40:18 46:12
peptone 76:3
perceived 271:4
percent 16:4,7,7,8 16:9,12 17:11 18:22 19:8 20:15 21:14,14 22:14,18 22:19 25:14,21 29:20 30:15 34:12 35:13 39:15 41:18 41:19 42:3,5 51:10,12 58:21 97:8 104:15 112:22 125:7,20 137:17 138:11,12 138:14,15,15,19 138:20 139:3,6,15 139:16,17,22 148:19 151:7 157:12 162:19,20 163:3 186:5,7 188:16 193:1,2,4 193:4,11,13,15,19 193:20 194:7,9,10 194:12 204:7,12 204:22 212:7 216:9 246:16 247:7,11,12,14,15 249:19 250:11 253:20 273:3,12 280:22
percentage 36:1,4 187:15
percentages 185:15
perfect 112:9 230:5 249:13 250:5
perform 68:4
performance 216:4,19 219:9
performed 59:17 250:4
perineal 9:9
period 32:15 33:13 72:16 98:9 107:9 160:12 162:22 163:6 254:2
periurethral 31:5 53:1,12
permission 174:14
permits 6:21
permutations 64:18
persist 32:1
persistence 78:22 157:5,19 159:14 159:15 160:14 164:14,16,22 213:12 273:13,18
persistent 50:18 161:11 216:22 274:3
person 11:9 75:6,7 99:14,15 103:14 111:13 114:18 174:3,5 210:11 219:21 221:8 240:15 275:7
personalized 101:9 227:14
personally 225:22
perspective 99:10 115:7 119:20 124:12 131:12 141:3 153:16 165:9 166:8 182:10,11 183:3 186:19 188:20,22 189:2,4,15 197:15 200:1,6 207:19 220:4 270:10 274:12 275:17 276:8 277:16 279:22
perspectives 110:12 111:12 140:6 167:11 187:1 270:9
pertinent 189:20
pervious 86:11
peter 2:18 4:3 208:6 210:6 214:15 215:3 225:7 236:14,21 238:3 250:22 263:7 266:11
ph 74:19 87:18
phages 118:4
pharm 3:3 261:1
pharm.d. 3:5
pharmaceutical 182:18 199:20
pharmacist 63:2
pharmacodynamic 78:7
pharmacodynam... 47:11 81:3 253:14
pharmacokinetic 72:11,22 79:2
pharmacokinetics 47:10 65:3 68:3 71:4 81:3
pharmacologica... 201:7
pharmacology 4:17 5:21,22 6:1 63:12 85:16 86:9 260:6
pharmacy 80:22
pharmd 2:3,4,20
phase 36:21 44:18 58:19,20 59:15,15 59:15,17 60:7 67:5 71:14 82:13 82:15,17 83:9,9 83:13,13 91:14 93:5,5,5 95:8 156:16 189:21 192:3 254:20,22 255:3 265:6,7 273:7
phd 2:2,4,6,7,9,10 2:13,15,17,19,21 3:3,6,8,10
phenotypic 78:20
phone 26:7 172:22 173:2,11 174:22 175:6,18 176:2 177:4 228:2,4,18
phosphat 88:3
phosphate 38:4,14
photometer 69:22
phrase 17:9,17
physically 113:11
physician 63:10 120:6 165:10 179:2,2,3 189:8 266:7 271:10

physicians 109:15 271:9
physiological 262:6
physiology 50:5 65:19 73:19
pick 52:9 176:14
picked 105:16 114:4
picky 221:10
picture 66:3 70:12 100:4 107:3
pieces 91:10 262:16
pili 34:10 57:2
pill 114:8
pipe 127:10
pipeline 49:6 121:16 123:1 129:4,7
pittsburgh 120:3 120:17
pivmecillinam 96:3 185:8,18 186:12 187:14
pivotal 150:20 152:4,8,16 153:9
pk 47:19 48:2,8,8 48:10,12,17 49:3 49:18,22 50:2 51:1 52:15 54:16 54:20 55:7 57:4 59:3,10,21 61:18 61:18,22,22 62:15 63:15 69:6 78:14 79:10,14,18 81:11 82:6,8 83:8 85:13 85:16,18 89:3,9 89:12 91:20 93:16 94:5,19 97:22 98:13 99:6 148:5 200:8,22 201:11 201:12,14,21 202:2,3,8,14,17 203:13,14,19 204:2,6,16,19 205:5,7,9,17 206:9,12,15,20 207:1,13 252:6,11 253:15,15 254:4 258:1 260:17 261:5 263:17,19 263:21 264:3,21 268:9,15 269:9,17 270:1,5,6 277:18 278:4,6,10,13 281:8
pkp 66:20 91:18
pkpd 148:1
place 81:15 105:1 128:22 255:5
placebo 20:5 133:3,7 138:8 139:3 148:16 168:10 169:15 187:14 243:15,20 245:20 246:2,12 246:16,18 280:17 280:19 281:1
placebos 169:14 192:12
places 94:5,18 177:1
plain 102:2
plan 116:18 131:22 208:1
planktonically 31:12
plasm 54:18 264:3
plasma 55:10,17 55:22 79:5 81:22 146:4 201:12,21 202:8 203:14 204:16 205:11,14 206:12 260:20 262:9 263:20 264:2,21 265:3 269:21 278:4 281:22
plate 223:13
platform 177:20 265:9
play 52:4 105:1 177:22
please 5:17 6:17 7:14 8:1,13,16 9:2 9:10 12:3,11,14 12:16,17 13:6 14:14,17 16:22 18:1,13 19:2 20:9 24:22 26:7,22 27:22 28:8,18 29:14 30:12 31:2 31:14,16 32:10 33:7 34:5,7,22 35:16 36:6,18 37:10,19 38:9 39:2,6,18 41:11 42:10 43:4,13,18 44:9,21 45:6,21 47:20,22 48:6 49:7,15 50:2,15 50:19 51:2,21 52:13,19 53:8 54:15 55:5 56:3 56:20 57:13 58:5 58:14,18 59:5,13 59:22 60:5,22 62:7 81:13 82:19 86:5 90:4 94:3,8 99:1 100:9 101:1 101:13 103:12 105:3 106:11 107:1,15 108:13 109:22 111:21 116:15 117:9 118:19 120:20 121:16 122:19 124:19 126:13 127:6 129:1 130:6 131:10,12,19 132:1,18 133:12 134:7,20 135:13 136:6,15 137:2,15 138:2,16 139:7 140:2 141:6 142:2 143:12 145:6 146:14 147:19 148:9 149:4 150:2 150:21 152:1 154:11 155:19 165:17,20 166:6 167:9 168:6 169:22 170:1,4 171:9,14,22 172:21 173:21 179:17 180:11 189:12 190:10 191:8,21 192:16 193:6,15 194:5,22 195:15 197:2,12 198:6,14 200:14 200:20 202:10,20 203:8,22 204:18 205:6,19 206:7 209:7 210:7,14,20 214:16 215:7 238:6 251:4,9,12
pleased 183:1
pleasure 6:2 130:20
plenty 257:18
plot 40:10
plus 210:9
pneumonia 7:15 87:17 88:12 89:16 124:6 264:1
point 5:13 24:13 24:15 33:18 43:14 55:1 78:17 80:14 91:15 92:5 93:3 98:4,22 121:4 124:8 150:3 152:2 158:8 173:15 174:4 186:14,14 187:15 192:20

216:7,16 217:18 218:14 220:12 222:11 225:20 227:8 231:10 236:7,22 244:6,9 248:15,21 249:16 250:17 255:16,20 256:18 259:8,12 260:8 261:8,10,15 262:16,22 263:13 263:16 264:20 265:21 266:22 269:20 272:10,12 273:1,22 274:10 276:8 277:14,17 278:10,13,20,21 279:6,9,13,14 282:2
pointed 260:11 278:11
points 5:1 61:1 68:7 98:11 120:21 145:11 163:4 211:3 214:14,15 215:12 224:7 226:7 235:1 243:19 250:16 251:11,14 255:17 256:5,6,8,8 257:13 258:4,6,18 259:1 264:19 265:10 266:4,9 268:13,13,13 269:15,21 270:4 273:16 275:17 276:13 277:18 278:5,7 281:6,13 281:17 282:5
polysaccharide 34:15
pool 161:14 275:21
poor 271:8
poorly 59:18 76:2
popular 237:19
population 76:20 88:1 137:5,8,11 137:12,13 139:10 140:1 144:22 151:6,22 155:12 156:18 158:1 161:3,6 162:1,3,5 180:18 181:17 192:19 193:7 195:7,10 231:14 231:15 272:12 273:10,11 276:21 277:2,4,5
populations 65:7 77:10 79:1 87:22 122:8 137:4 147:18 149:12
porcine 49:22 50:3,16,20 51:2 265:20 268:12
position 37:6,17 37:18 112:7 140:9
positive 21:5,11 21:17 22:7 30:22 47:13 115:22 116:3 212:9,15,16 222:14 231:15,20 271:5
positivity 122:13 126:22
possibility 219:16 248:13
possible 21:1 23:4 104:18 108:7 134:3 139:9 144:9 206:21 209:11 223:17 233:16,20 235:15 239:5 271:11 279:1
post 71:16 127:12 136:19 140:18 197:10 198:3 217:10 274:3 276:11
postdoctoral 153:22
potency 47:10
potential 68:18 84:12 125:15,17 126:8 150:4 173:16,18 178:6 194:16 213:7 264:5 271:18 280:20
potentially 66:20 73:15 90:13 117:15 124:15 180:22 216:6 218:12 224:17 239:11 245:14 255:15 269:12 279:13,14
power 139:17
powerful 46:7
powerpoint 173:10
practicability 219:6
practical 53:4 243:19 255:8 275:13
practically 175:14 256:14
practice 7:11 8:20 10:6 11:17 133:22 136:5 141:10 151:15 184:10 187:5 188:14,17 189:19 191:19 197:12 198:22 214:2 215:16 216:7,14,18 218:19 219:3 244:11
practices 122:18 218:17
practicing 259:9
practitioners 281:21
pragmatic 217:12 220:19
pre 48:5 62:19 140:17 198:2 254:11 259:6
precipitation 75:19
preclinical 6:4 58:6 62:3 67:3,22 85:16 91:13 92:14 268:18 269:11 282:3
preclinically 252:22
preclude 206:12
predating 229:9
predefined 151:2
predict 23:2 195:7 195:19 196:6 233:5
predictable 79:10
prediction 260:14
predictive 25:20 233:6
predictors 201:8
predicts 219:13
predominantly 70:16
predominately 52:21
prefer 101:6 102:20 172:14
preferable 80:12
preference 77:2 242:8
preferences 108:11
preferentially 46:13
preferred 150:7

pregnancies 112:19 113:5
pregnancy 9:20 108:21 109:5,5
pregnant 12:12 21:4 24:1 30:11 122:9 197:5
premenopausal 9:19 12:6
preparation 75:19
prepare 75:15
prepared 284:3
preparing 5:4 17:14 110:12 182:19
preponderance 31:11
prepping 255:9
prerecorded 111:7
prescribe 119:8
prescribed 20:1 105:19 173:19 175:15
prescribing 102:16 103:8 117:12
prescription 101:7,9 105:21 175:9 176:19
prescriptions 104:22 107:4 108:5
presence 57:2 88:3 89:2 159:21 180:14 195:18
present 22:6 24:16 24:16 25:14 27:1 40:1 47:15 67:7 88:6,9 135:8 141:3,22 145:3 175:19 178:16 200:5 214:5 239:11 253:13 267:8
presentation 6:16 7:18 12:18 48:1 62:6,20 64:5,8 99:4 111:7 115:2 130:3 140:3 182:10 190:10 197:13 200:13 207:10,19 213:20 260:21
presentations 121:7 200:14 232:4 236:6 258:19
presented 23:15 67:2 87:8 91:19 125:5 126:20 174:3 192:17 205:4 251:17,17 255:18
presenters 261:3
presenting 7:20 15:11 25:3 119:22 120:12 189:1
presents 123:20
preserves 139:5
president 182:14
prespecified 150:18 193:9
press 129:15
presumably 240:17
presumed 219:2
presumptive 174:13
pretty 8:21 21:11 118:6 155:21 161:11,18 170:9 238:19
prevalence 17:11 35:17,19,21 149:20
prevalent 180:17
prevent 7:7 23:4 101:11 105:18 107:22 109:20,20 270:15 280:20
preventative 100:22
prevention 90:16 92:21 140:20 165:16 208:17
previous 17:16 63:20 67:17 71:1 83:1,2 87:19 121:6 141:7,21 143:21 144:3 170:4 171:15 174:2 200:12 235:14 241:2 261:2 269:2
previously 86:21 87:7 89:8 90:20 91:20 92:19 99:18 139:16 145:15 180:13 181:6 196:15 201:15 202:15 265:12
price 3:1 110:14 110:15 111:8,9 121:18 220:22 270:18
priceless 118:14
primarily 95:12 120:22 154:13 155:14 193:17 201:11
primary 4:19 21:9 23:9 38:17 47:9 60:10 116:17 134:21 136:20 137:12 144:21,21 151:4,22 155:20 157:4 159:6 164:16 182:21 189:4,17,18 191:10 192:1,17 199:5 207:9 210:9 219:8 220:6,10 222:8 223:20 224:10,14 225:10 231:8,13,14,21 232:8 272:10 273:1,9 276:8 277:14
principally 27:21 28:9 38:16 40:22
prior 18:15 25:18 145:19 147:7 204:15 271:8 280:22 283:5
priorities 122:20 127:1
prioritize 99:19 234:6
prioritizes 233:10
priority 101:22
privacy 177:21 178:20
privilege 112:7
pro 215:14 253:11
proactive 104:9
probability 204:5
probably 16:19 23:1 30:16,19 65:4 86:22 89:20 92:2 123:3 164:22 167:2,5 170:15 181:8,16 197:1 211:5 212:4 230:19 249:17,22 251:22 252:19 257:1,22
problem 50:9 55:15,20 95:4 116:1 121:2 179:7 180:12 182:2 215:6,6 223:6 224:4 243:18 250:2 263:1,9 266:5

problematic 125:6 220:7 231:5 239:4
problems 124:5 124:11 262:1
procedure 197:6
procedures 144:4 181:12
proceed 26:18 44:3
proceeding 282:15 284:4
proceedings 232:5 283:3,4,6,8 284:6
process 44:6,7 48:12 69:4 108:8 132:1 259:5
produce 34:9,11 34:14,18,19
produced 34:20 38:5
producing 113:21 125:4 275:10
product 74:18 128:13 183:14,22
production 41:14 42:4
products 183:18 184:4 187:21 188:1 272:18
prof 79:22
professional 208:14
professor 27:7 35:9 80:20,22 120:1 165:12 208:10
profile 55:11,13 77:8 93:7 241:22 254:9 281:15
profiles 57:6
program 5:14 42:22 146:16 165:11 215:11 219:6 258:15 269:13
programs 127:17 127:19,21 270:1
project 13:12
prominent 105:15
promising 126:4
promote 127:7,17
promoter 36:22
promptly 176:13
prompts 39:2
pronounce 260:3
proof 197:9
propensity 109:7
properties 27:21 267:17
proportion 191:10 198:5
propose 170:11
proposed 148:3 169:19
pros 4:22 210:7 251:10 281:5
prostate 109:10
prostatitis 9:9
prosthetic 132:17
proteas 87:16
protective 155:4
protein 42:2
proteins 41:7
proteus 27:14 30:19 247:13,16
protocol 73:21 147:6,15 150:19 177:8 192:6
protocols 167:17 175:5,6 179:16 275:6
prototype 96:2
protractor 239:10
prove 91:5
provide 66:20 67:5 76:15 122:5 124:11 129:10,18 131:13 148:1 189:14 190:19 209:13 266:1 269:9,12
provided 5:6 22:8 22:10 25:4 39:9 153:10 267:4 269:1 270:10 272:6,15 274:12 275:16 276:7 277:16
provider 14:11 20:1,21 174:5,18 175:2,21 176:7,16 179:1 241:3
providers 14:13 175:20 178:9
provides 66:10
providing 120:19
provocative 199:14
pseudomonas 30:21 71:11 113:20
pt 260:16
pta 260:13
ptr 45:5
pub 131:17
public 1:5,12 4:6 94:19 104:11 119:21 120:14 123:16 124:22 129:19,21 141:2 242:11 283:1,19
publication 13:13 13:13 16:2 126:3
publications 8:20 13:11,14 14:18 81:6
publish 12:1
published 8:9 10:5 10:12 13:3 19:13 22:1 31:22 60:8 69:19 70:22 78:13 83:17 92:13 131:17 143:19 208:18 240:5
publishing 54:10
pull 53:21 75:5
pulled 156:12
pump 72:14
pumps 58:13
purposes 132:5 155:4
pushing 114:16
put 12:4 15:8 94:7 95:17 111:17 128:20 230:14 239:14 260:1 262:16 265:15
puttagunta 3:2 189:3,11 276:6 277:10
putting 62:11 129:17 183:6 188:19 210:22
puzzled 235:4
pyelonephritis 35:6,7,20 36:3 50:7 58:9 60:2 85:2,3 113:6 141:16 142:9,12 155:6 156:15 161:16 246:3,15 274:5,6 280:21 281:1
pylori 27:15
pyuria 10:2 25:20 25:21 26:3 132:6 143:1 149:11 154:16
pyurial 11:16

q

qims 104:4
qio 104:4
qualified 186:6 283:7
qualifying 156:19

quality 14:8 99:13 100:8 101:14 190:16
quantification 80:10
quantify 68:1 79:20 89:22 148:8
quantitative 78:8
quantitatively 260:16
quebec 110:16 112:11
queensland 63:4
question 6:20 22:22 24:13,21 39:3 52:3,6,10 53:9,15 61:10 101:5 157:21 158:22 209:2,5,16 210:7,16,17 211:2 211:15 212:12 213:18 215:7,17 219:15 224:13 230:14 233:9 238:6,6,9 243:15 245:3 259:21 278:19 280:2 281:5
questions 6:15,18 52:13 68:15 88:11 110:9 157:14 210:5,11 214:12 225:4 232:16 238:13 258:7 260:2
quick 180:10
quickly 45:20 118:18 158:18 175:9,20 230:20
quinolone 198:13
quinolones 71:11
quite 31:18 34:14 36:17 39:1 54:21 66:5 70:14 98:14 106:18 143:5,14 180:6 181:1 218:9 249:21 281:19
quoted 84:20

r

r 2:1 4:1 192:19
rabbits 49:11
race 158:13
radu 2:5
raise 209:7,8 210:14,15,17
raised 115:3 157:13 178:11 181:5 209:11 214:15,16,18,22 215:3,4 227:17 243:18 244:3 248:3 251:7
raises 22:22 24:12 158:21 225:4
raising 251:6
rancho 165:12
random 138:13
randomization 135:3 136:11 137:1 151:3 159:4 160:7,9 170:21
randomized 14:5 14:9 19:12 20:3 21:13 23:8 24:3 132:20 137:6 138:7 139:14 192:3,9
randomly 178:17
range 70:17 77:8 78:11 79:16 83:11 90:17 93:14 212:7 253:8
ranged 270:20
ranges 77:9
ranging 55:8 57:12 59:8,11 83:13
ranking 234:1 237:19
rapid 44:14 45:12 46:10,14 175:11 240:8 268:7
rapidly 146:22
rarely 15:7 135:17 244:11
rat 58:8
rate 16:7,13 33:22 42:3 43:18,20 45:6,11 71:12 72:19 79:21 80:5 98:20 139:16 160:22 170:12 193:18 195:3,19 196:13 197:16 198:10 219:2 246:2,3
rates 29:22 45:2 58:12 76:14 98:1 98:2 104:4 138:9 170:7 171:18,21 190:17 194:12 211:22 212:1 238:18,22 240:7 276:14 277:5,7,8 280:6,11
ratio 45:2,9 146:10
rational 128:16 245:4
rations 93:17
rats 49:11 59:4 104:5
reach 70:7 106:6 226:8,14,18 250:15 260:20 265:16
reaches 44:8
readily 174:14 179:11
reading 222:1
real 72:19 87:14 116:4 128:21 174:17 175:17 186:1 188:8 189:19 191:18 198:22 212:5 224:13 244:13
reality 8:7 17:2 18:14 218:21 235:9 247:22
realize 105:8 241:7
realizes 128:5
really 11:8 12:12 12:22 14:12 19:3 19:19 20:12 24:1 24:9 26:7,9,19 33:15,16 46:20 49:3,21 52:18 60:15 62:14 68:5 68:7,14 70:8,14 71:2 75:2 77:2 78:12,15 79:22 80:4,10 82:15 84:11 85:1,5,12 85:14,17 88:6 89:14 90:16 91:1 95:19,22 96:9 98:3 99:4 100:11 101:12 102:13 104:12,20 106:22 107:13 108:1 109:7,14 112:6 116:16 118:2,14 119:9 122:13 123:11 125:11,17 128:10 129:8 131:7 144:10 154:14 157:13 159:9,20 168:2 170:21 173:14 181:20 182:9 183:6 185:15,22 188:3,7 199:14

210:22 211:20 212:12 213:4,13 214:11 217:19 220:3,12,20 221:3 221:21 222:15 223:5 225:4,19 226:14 229:5,10 231:17 232:9,16 235:15,16 242:7 244:13 245:4,19 252:4 254:5 256:21 258:12,13 259:7,16,19
reanalyzed 185:9
reason 11:4 53:4 164:15 174:11 226:10
reasonable 23:1 181:20 216:17 249:15 274:22
reasons 108:10,17 109:12 111:16 265:1
rebound 228:21 229:13
recapitulate 73:19
recapitulated 43:6 60:12
recapitulates 46:6 51:18 268:2
receive 20:3 138:8 174:1 192:10 196:18
received 21:6 22:15 131:4 137:14 156:20 282:9
receiving 20:7 169:21 175:1 193:12,13
receptors 36:2,11 36:12
recipients 12:13
recognize 104:17 129:3 151:14 206:5 229:18 260:8
recognized 128:9 206:4
recognizes 205:21 233:11
recognizing 234:12
recombinase 37:1
recommend 82:13 131:21 134:22 136:8,12,18 147:21 149:6 150:11,14 151:3 203:9 247:18
recommendation 17:12 146:8 224:10
recommendations 128:14 133:18 144:21 145:9 148:11 207:4 241:21 267:11 278:17
recommended 17:1,7 18:8,18 19:1,10 30:10 83:21 136:8 150:20 155:20 156:21 210:8 241:9,12
reconsidered 197:1
reconvene 47:1
record 167:22 174:9,20 177:11 177:18 179:8,14 275:3 283:9 284:5
recorded 62:20 283:6
recording 283:8 284:4
records 177:13
recovered 57:21 58:2
recovery 254:6
recreate 73:3
recruit 174:4 179:4 220:20
recruited 179:15
recruiting 166:2 181:13 274:16 275:1
recruitment 169:22 173:15 181:12 221:2 275:4
recurrence 20:11 195:7 230:8 240:7 240:8,20 280:11
recurrent 142:9 181:17 190:18 271:13
red 33:13 41:6,17 43:22
reduce 76:9 235:19 280:19
reduced 125:12,19 135:12 283:6
reduces 199:3 275:21
reduction 48:22 56:12,16 58:15 59:12 60:6 93:18 156:6 158:21 212:18 230:6 235:8
refer 13:1 69:13 131:19
reference 15:11 94:4
references 13:1 15:9 19:18
referral 174:5,18
refers 156:4,5
reflect 75:3 77:7 77:14 188:13 196:20 253:22
reflected 95:19 253:8
reflecting 88:14
reflection 95:22 96:1
reflections 144:1
reflective 69:15
reflects 10:13 133:21 217:16 233:2 254:8
reflex 31:10
reflux 50:8,9 53:17,20
refresher 48:7
regard 235:14
regarding 4:22 79:2 103:1 182:12 198:20 202:13 226:19 251:10 269:20 271:7 274:20 275:1 278:9,19 279:19 281:5
regardless 133:5 155:7 183:17
regime 92:19
regimen 148:2,7 149:17 150:5,15 150:16 151:21 192:13 194:4,7
regimens 66:11 148:22 149:22
regiments 63:7 91:16
region 31:5
regions 280:13
regrowth 79:1
regulated 268:6
regulator 152:20 235:10 236:4

regulators 4:8 143:8
regulatory 8:20 124:12 125:14 126:2 140:6 141:3 142:4,11,21 144:4 151:13 211:10
reiterate 124:9
rejoin 130:6
relapse 160:15,19 164:18 190:4 194:18 232:15 233:6,12
relate 53:10
related 4:19 6:20 7:16 13:20 55:3 65:12 89:4 140:17 154:14 167:13 210:17 275:5 283:11 284:7
relationship 48:13 257:8
relationships 91:5 95:3 97:21 98:7 178:12 179:3
relative 58:16 159:1 161:20 162:15 195:20 232:17,18 283:13 284:10
relatively 15:14 51:4 84:1 160:22 171:19 172:11 212:1 238:19 280:6
relevance 189:19 191:22 211:8 213:11,13 260:9 267:15 279:4
relevant 111:22 124:2 127:13 128:7,14 141:18 145:3 149:13 152:22 194:19 201:18 220:8 260:22 264:4 278:2
reliable 133:21
relief 190:19
rely 212:14
remain 113:1 163:18
remaining 273:18
remains 77:5 159:16 161:4
remedies 108:2
remember 83:19 112:14 255:16
remembers 17:10
remind 158:19
reminded 270:14
remote 1:9 111:6 168:2 218:18,19
removed 151:21
renal 12:12 50:7 83:5,9 155:2 264:6
repeated 71:6
replacement 123:16
replicate 74:22 265:20
replicated 76:18
replication 40:16 43:19,22 44:4,6,8 44:16,17 45:1
report 106:7 161:7
reported 1:12 15:7
reporting 95:12
represent 35:12 41:18 112:3
representation 71:4 209:6
representative 32:11 80:4 110:15 111:4,21 244:20
representatives 57:10 129:15
represented 34:13
represents 41:7 188:7
reproduced 70:10
reprogram 219:5
require 11:16 174:7 206:15 213:22
required 37:20 38:5,19 48:20 78:2 147:4 148:1 207:2 216:12 278:13
requirements 144:5,16 167:8
requires 156:2 205:9,17 212:17
requiring 214:6,8 230:9
rescue 191:16
research 4:5 18:15 27:13 47:8 54:9 62:10 63:3,5,13 71:10,19 81:2,5 99:13 102:10 105:18 120:7 121:22 122:17 124:16 131:3 178:13,21 189:9 199:18 208:15,16
researcher 179:3
researches 165:15
researching 106:3
reserve 56:11
reservoir 72:7
residency 131:5
residual 71:17 148:9
resistance 8:4 14:15,22 15:21 16:1,5,7,13,16 17:11 57:6 63:8 68:12 77:11,22 78:20,21 82:16 86:2 87:22 88:1 89:2 90:16 92:22 97:1 98:19 107:2 114:7 120:5,8 127:5 144:12 146:10 148:9 149:20 160:3 170:7,12 171:18 171:20 183:17 190:8 198:8,14 238:18 241:15,15 241:22 242:20 244:14,17 247:5 249:21 250:1 253:1 267:10,11 280:6 281:12
resistant 16:21 24:17 60:18,20 65:7 66:8 88:17 92:16 93:21 104:13 107:6,14 110:20 113:21 114:5,10 121:2 123:3,7,17 124:1 128:19 138:1 146:6 151:20 166:5 197:18 198:4,10 244:7 250:10 253:9 271:17 274:18 275:10 276:16,20
resolution 20:8,11 21:21,22 135:7 156:4 188:16 191:1,15,19 193:21 197:10 212:18 215:22
resolve 26:16 146:22 191:7
resolved 18:12 25:16 26:6 214:1 227:11 279:9,9

resource 118:3
resources 41:12 80:11
respect 97:18
respected 108:12 270:17
respiratory 89:16 89:17
respond 63:5 107:7 176:13 191:2
responders 195:12
responding 193:3 263:10
response 21:10 30:6 48:14 59:16 74:13 89:18 94:10 98:6 134:22 135:2 135:6,6,10,15 136:9,12 137:2 138:9,10,14 139:7 185:13 191:11,12 193:10,16 194:3 195:3 197:1 198:17 199:4 216:20 218:5 232:10,11,13,18 232:19 233:5,11 233:13,15,17,18 233:19 234:3,6 238:10 272:12 276:3,19,22 277:3 277:12,13 279:2,5 279:17
responses 136:13 156:3 233:16 234:12
responsibility 128:5
responsible 128:16
rest 67:11 157:22 180:18 228:22
restarting 44:3
restrictions 130:5
result 104:13 110:22 139:22 191:7 201:2
resulted 144:5
resulting 196:13
results 60:9 149:10 191:4 192:18 195:5 197:15 223:22 267:12 273:17,20
retaining 166:3 274:17 275:2
retention 155:2 179:6 275:4
rethink 265:11
retired 208:12
retract 43:13
retreatment 230:9
review 49:16 63:20 73:6 81:6 155:22 174:14 269:1
reviewer 5:21
reviewing 32:13 67:17 190:12
revised 23:20 143:21 144:20 272:17
revision 272:2
rfp 86:8 262:12 265:16
ribosomal 41:7 42:1 46:9 268:5
ribosome 42:4 43:14
ribosomes 40:17
rich 201:7
rid 229:7,8
right 7:1 12:14 19:6 23:16 26:19 32:21 33:6 36:12 38:20 39:22 40:9 40:11 41:1 47:14 61:1 80:18 93:1 94:13,15 97:22 101:9 102:16 103:3,15,19 106:9 129:13 130:9 131:10 136:7 159:4 165:4 166:14 168:11,18 169:1,10 170:6 171:13 173:12 188:21 192:21 204:10,21 210:13 224:3 227:9 238:4 238:16 247:11 256:1 266:22 280:1 282:6
righthand 141:20 142:13
rigors 9:5
rigs 41:19
risk 13:15 17:18 17:20 23:19 49:5 75:19 98:17 148:8 157:18 158:2 160:2,14 161:3,12 162:5 163:7,14,16 163:22 164:17,18 181:2,11 230:13 233:12 246:15 267:10 268:18 270:7 274:4,7 280:22
rna 40:3,5 43:9
rnaprotect 39:12
rns 177:5
roberts 3:3 23:6 25:1 62:20 63:1 63:19 67:13 91:19 268:20
robust 4:19 52:14 57:3 61:17 66:20 122:22 201:8 261:5 266:19 268:15 269:9 282:11
roche 2:10
rodent 49:22 61:15 268:14
rodvold 3:5 80:19 80:20 81:5,8,9 99:4 203:6 251:14 251:16 258:11 259:5 261:12 263:9 264:16 269:16 281:6
rodvold's 81:2
rogue 119:10
role 27:12 67:14 120:18 196:22 268:21 271:21,22
roles 121:12
roughly 76:6 185:20
row 36:10
royal 63:2
rubin 3:6 138:4
rules 209:2
run 65:5 72:3,6,12 75:11
running 75:10 118:17

s

s 2:1 4:1 223:10 284:18
sachet 170:13
sachets 170:20
sadly 180:4
safety 81:17 133:6 137:13 140:17 151:3
sailaja 3:2 189:3
salient 145:11
salim 2:16 215:7
sample 93:9 139:9 139:19 149:14
samples 39:14 41:4 79:18,19

80:4 263:19 281:14
sampling 54:16 64:9 65:12 68:7 78:6 82:17 254:3
san 100:8
sarah 110:15 111:9
sat 70:13
satta 71:5
saw 58:15 59:11 59:16 60:6 85:2 108:9 161:9 171:3 223:4 234:17 236:18 240:7 250:20 258:19
saying 25:9 129:2 173:12 182:1 211:1 236:3,7 242:9
says 15:2,3 173:5 233:4
sc 3:3
scale 55:18 259:18
scangarella 3:7 199:17 200:3 258:8,9 259:22 277:15
scenario 64:19
schedule 72:15 76:15 174:8,15,17 178:1
scheduled 174:12 176:22
schedules 68:3 175:16
school 27:9,12 63:11 153:21 208:11
scientific 133:19 140:10,14 144:2 199:17
scientifical 153:5
scientifically 201:16
scientists 110:3
scope 29:5
score 187:2,18
scott 2:9 31:7
screen 173:11 215:5 225:15 250:22 251:8
screening 174:11 197:4
script 59:2
scripters 94:15
seattle 99:11 107:11 165:13
second 17:7,17 23:12 41:22 97:12 102:3 117:5 153:2 163:10 173:22 189:2 191:6 208:6 209:5 210:6 220:12 227:18 234:7 246:11 252:7
secondary 136:8 220:9 231:9
secondly 76:4 260:15
secretion 82:9
section 82:6 145:4
see 15:2,18 17:16 19:6 26:9 32:18 32:22 33:1,1,2,13 33:15 34:2 35:22 36:16 37:16 40:11 41:17,22 42:15,21 43:11,21 44:12,15 44:19 45:4,9,20 47:2 48:10 53:22 55:10,14 57:18,22 58:3 60:16,20 70:4,12,13 81:10 82:6 83:1,12,17 84:7 85:8 87:14 93:10,21 94:14 95:21 96:6,13 97:8,9 103:6 109:10 117:9 118:17 119:8 123:19 141:21 142:6,8,13 143:4 151:5 154:22 157:3 158:10,13 160:21 161:16,22 162:5,14,19,22 163:16,21 166:11 173:2 185:12,19 186:11,12 187:12 194:20 195:3,17 195:18 197:22 203:4 208:3 209:3 211:21 213:8 214:12,15,22 215:2,3 216:8 218:7 222:2,9,9 223:21 228:17 234:21 235:17 236:2 238:1,14 240:9,17 241:5 242:21 247:17 252:2 254:22 255:17 257:3,7,13 261:6,8 264:12,13 280:1,16
seeing 65:11 93:14 156:11 163:5 172:9 173:4 214:16,18,19 222:19 234:18 250:18,19
seen 40:8 123:19 155:15,21 164:13 168:4 187:5 193:11 195:6 197:16 222:14 236:5
select 179:12 198:3
selected 44:11 148:2
selecting 148:6
selection 66:6 81:21 82:6 99:7 146:18 147:20 148:8 149:5 178:15 191:5 204:9 258:14 269:19
selects 197:17
self 167:17
sending 169:1
sends 266:3
senior 140:9
sense 41:20 69:12 73:3 88:8 121:18 172:17 219:14 222:5 250:9 281:12
sensitive 116:21 117:4
sensitivity 199:3 199:10 217:16
sent 171:3 191:3
separate 118:20 205:21 206:3,6 213:4 240:17 279:1,14
separated 162:2
separately 136:14 224:8
sepsis 124:7
septinere 247:18
septra 170:8
seq 40:5
sequence 39:18 44:10
sequences 45:7
sequencing 223:11
sequesters 36:7,8
series 182:12

serious 107:5 117:15 243:8
serum 82:12 83:4 83:22 84:8,14,15 88:5,5 89:4,15 93:11,11 97:3 204:11 205:4 251:21 255:21 256:7
served 52:16
serves 47:7 99:16
service 39:8
serving 27:12 179:1
session 5:14,18 6:3,6,16 130:7,10 130:21 199:16 207:20,21 236:15 265:4 266:18
set 6:8 68:8 72:15 147:6 209:2 215:18 220:8 255:20,21,22
sets 201:7
setting 69:18 81:21 173:20 175:13 177:5 216:3 241:11 264:17 269:20
settings 64:19 121:9 124:15 127:21 169:18 177:6 202:20 204:9
seven 20:3,4,5,7 20:10 33:12 44:19 52:2 114:13 157:1 196:10
seventeen 22:18
seventy 29:7 34:12 192:8
sever 217:21
severity 11:12 114:10
sex 102:20 158:13
sexually 208:20
shape 52:11
share 81:8 100:1 110:12 111:11 112:2 189:20 190:9 192:1
shared 22:2 101:21 104:14 227:10
shareholder 200:16
shares 50:4
sharing 119:20
shed 191:22
shedding 229:12
sheikh 3:8
shelf 75:7
she's 110:21 270:20,22
shockingly 38:13
short 75:7 98:9 119:5 122:4 129:22 187:18 190:21 191:6 207:22 218:9 225:6 232:10 243:16
shortcomings 64:7 121:20
shorten 246:17
shorter 232:10 238:12
shouldn't 220:17 225:8 243:9
show 32:10 34:8 41:2 50:17 54:1 60:19,21 82:21 87:4 98:8 155:18 156:9
showed 34:16 51:9 51:13 89:8 92:7 96:10 138:13 171:17,17 249:19 252:11 253:3,5,7 254:1 255:4,5 256:5
showing 35:4 41:14 49:1 51:20 53:2 58:21 87:9 92:18 158:4 160:6 172:2 205:11 226:5 240:5
shown 31:7 44:9 77:20 92:18 164:12 194:4 197:20,21 202:14 203:5,12,16 204:15 205:3 254:12 260:20
shows 15:19 19:3 92:14 174:11 197:18 204:21
shuffle 97:9
sick 117:2
side 32:14,15,18 36:12 39:22 40:11 41:1 87:9 94:12 94:13,15 117:13 117:14 141:20 142:6,13 226:12 280:6
sided 139:16 152:10
sides 10:2 33:4
sights 35:10
signal 22:22 194:16
signals 33:22
signature 283:17
significance 24:21
significant 22:21 58:15 59:11 60:6 75:12 96:11 98:2 157:3 187:7 190:14 191:19 212:11 214:6 276:3
significantly 36:3 51:11 161:4 163:3 203:4 260:13
signs 8:18 9:4,8 10:17 11:13,14 132:8,11 134:11 134:14 143:11 154:18 239:10
silent 143:3
silos 118:19 271:12
similar 12:10 14:1 32:4 41:1 50:4 51:15 100:6 106:14 141:22 148:12 151:8 155:21 175:6 194:7,12 196:14 198:1,2 203:6 205:7,8,16 232:20 242:10 258:19 277:6
similarities 51:6
similarly 179:2 196:7 197:9 263:21
simple 68:15 79:8 109:21 176:1 266:7,10
simplicity 172:21
simply 70:6 119:11 188:5
simulate 69:5,7 72:8 257:7
simulated 79:15
simulating 63:22 66:18 68:2 76:5 269:3,7
simulation 73:10 76:13
simulations 67:15 68:22 71:3 98:14 268:22

simultaneously 30:18
single 38:8 44:8 72:22 106:7 133:9 134:18 149:13 150:14 152:3,8,10 152:12,13,15,18 153:9 204:21
singular 248:19 248:20
sit 100:15
site 88:19 98:22 152:19,22 153:1,8 201:16 277:22
sites 152:7 202:17
sits 63:16
sitting 68:10 263:3
situation 65:13 150:13 153:2 229:13 262:7 275:7
situations 152:5 197:8 206:11,22 235:17,22 278:12
six 28:10 32:7,14 33:6,19 34:3,4,13 44:19 51:10 76:8 81:7 93:13 117:9
sixfold 88:16
sixteen 192:8
size 28:21 73:12 139:9,19 145:2 186:13 187:18 188:8
sizing 219:5
skewed 244:16
skills 26:10 103:2 283:10 284:6
skipping 224:2
slide 6:6,22 7:14 8:1,13,16 9:1,10 11:1 12:3,14,17 13:6 14:14,17 15:9,10 16:22 17:2 18:1,13 19:2 19:7,11,14 20:9 21:1,12,22 23:5 23:14 24:22 26:6 26:22 27:22 28:8 28:8,18 29:14 30:12,12 31:2,14 31:16 32:10 33:7 34:5,7,22 35:16 36:6,18 37:10,19 37:21 38:9 39:2,6 39:18 40:6 41:11 42:10 43:4,13,18 44:9,21 45:6,21 47:20,22 48:6 49:7,15 50:2,14 50:19 51:2,21 52:13,19 53:8 54:15 55:5 56:3 56:19 57:13 58:5 58:14,18 59:5,13 59:22 60:5,22 62:7 81:10,13,17 82:3,18,19 83:1 83:14 84:18 85:12 86:5 87:5,19 88:20 90:4 91:7 92:9 93:2 94:2,2,8 94:11 95:1,10,16 95:17 96:14 97:5 97:19 98:7 99:1 100:9 101:1,13 102:8 103:11 105:3 106:11 107:1,14,17,19 108:12 109:22 120:20 121:16 122:19 124:19 126:12 127:6 128:22 131:10,12 131:21 132:1,18 133:12 134:7,20 135:13 136:5,15 137:2,15 138:1,16 139:7 140:2 141:6 141:20 142:2,7,14 143:12,13 144:20 145:6 146:14 147:19 148:9 149:4 150:1,21,21 152:1 154:11 155:19 156:8 157:1,20 158:15 159:22 160:16 161:13 162:6 163:15 164:11 165:19,20 166:6 167:9 168:6 169:2 169:22 170:1,4 171:14,14,16,17 171:21,22 172:3 172:21 173:4,12 173:20 179:16 180:11 181:3,22 182:2 185:4,21 186:21 188:2 189:13 190:10 191:8,21 192:16 193:6,15 194:5,5 194:22 195:14,16 197:2,12 198:6,14 200:14,20 202:10 202:15,20 203:6,7 203:17,22 204:15 204:17 205:6,19 206:7 238:14 255:17
slides 50:1 56:8 111:17 138:5 168:10 172:2 178:14 179:20 180:4 194:21 201:20 203:13 228:18
slight 71:1 161:13
slightly 70:20 155:12 160:12 213:14
slip 82:1
slow 33:20 262:4
slowed 70:2
slower 29:22 45:15 218:2
slowly 44:1,21 70:5
small 22:21 39:13 93:6 130:4 158:4 214:4 247:4 255:2
smiley 26:10
snafus 126:3
society 7:10 8:6 9:17 120:4,13 121:11 125:21 126:16 128:7 129:14
sole 35:9
solely 112:2
solution 249:8
solutions 206:21
somebody 105:2 227:8,10
somebody's 217:21
somewhat 9:22 181:8 186:10
somnolescent 34:18
son 113:8
sonya 284:2,18,19
soon 26:18
sorry 16:5 26:5,7 40:10 111:13 116:11 169:1 171:10 179:19 181:3 224:2 237:4
sort 14:20 98:3 100:5 128:21 173:13 176:19 229:8 233:22 253:1 259:5
sorting 256:17

sound 215:15
source 68:19 77:3 90:12 116:17
sources 13:10 35:14 38:17
southeast 111:14
space 122:9 126:9
spaces 77:4
spanning 182:21
speak 5:9 7:12 47:19 131:7 141:2 169:14 175:20 182:7 209:15 221:12 237:21
speaker 6:12 27:5 80:19 99:9 119:22 130:16,21 140:5,7 153:18 165:8 199:16 235:14 251:15
speakers 5:3 6:7 47:5 83:2 86:11 130:2 141:8,22 180:12 181:5 200:12 207:20 228:5,11 232:3 235:5 253:16
speaking 131:11 154:3 165:8 175:14 235:5
speaks 184:1
special 192:6
specialist 117:20 140:9
specialty 182:22
species 27:16 29:6 30:8,18 31:18,19 95:14,15 264:5,6
specific 5:1 17:18 17:20 67:9 69:6 74:14,21 79:14 81:22 89:19 94:11 96:8,20 98:11 117:13 128:1 131:22 145:2 149:19 152:7,19 153:6,8 180:8 184:5 202:22 205:22 206:6 211:2 251:11,14 260:10,17 262:21 264:18 265:9 269:14,21 270:2,4 281:6,13
specifically 15:1 69:9 74:16 90:18 124:12 244:6
specificity 216:4 217:16
specifies 142:15
specimen 11:18 191:3
specimens 147:11
specious 149:16
spectrum 125:3 236:12 244:14
speed 33:22
spend 115:17 133:13 135:14
spent 119:5
spero 125:19
sphere 168:2
split 67:16 263:22
spoil 223:13
spoke 128:7
spoken 166:21 264:16 265:1
sponsor 61:20 82:17 232:3
sponsored 87:12
sponsors 59:19 259:1
sporadic 141:15
spouses 100:13
spread 29:8
spreading 32:21
st131 29:7
stability 80:7
stabilized 37:10 39:12 40:3
stable 80:8
staff 130:20 282:8
staffing 127:19 177:16
stage 6:8 200:19
stages 107:20 108:9,10
stain 108:3
stamey 83:18 85:5
standard 21:11 44:22 45:5 55:19 75:1 79:10 133:15 152:9 190:12,20 199:9 223:13,18
standardization 92:2
standardized 178:19
standards 201:14 201:21 278:16
staphorsius 95:14
stapleton 3:9 23:7 25:2 165:8,9,19 168:14,19,21 169:6,9,12 171:7 171:10,13 172:1,3 172:5,10 173:6,9 182:9 227:17,18 227:22 228:6,9,12 228:14 230:15 238:10,11 240:4 241:4 274:11 280:3
starbucks 39:11
stark 14:4
start 9:15 26:14 44:7 67:17 90:20 97:9 115:1 165:22 167:17 182:13 186:8 189:13 190:11 211:1 214:12 251:5 262:10
started 5:9 130:10 130:15
starting 34:8 77:13 78:17 159:7 238:22
startling 42:4 45:17
starts 159:10
startup 182:18
stasis 48:21 56:10 90:8 91:2 252:16
state 4:14 18:11 70:8 267:4 268:9
stated 18:6
statements 252:3
states 7:14,18 12:16,19 13:5 15:13,21 16:3 19:18 24:5 86:21 86:22 106:14,20 125:8 128:1,3 133:16 150:6 180:18 181:21 243:21 267:6
stationary 44:18
statis 252:19 281:10
statistical 138:5 192:22
statistically 276:18
statistician 230:18
status 55:3 223:2
stay 5:10 209:4
stayed 22:9
steady 70:7
stem 180:14
step 31:4 72:5 94:1 219:11
stephioca 113:20
steps 262:4

sterile 229:5,11
sterilization 75:8
sterilized 40:13
stewardship 7:8 99:18 102:8 107:3 121:13 122:6 127:17,19,20 128:2 129:12 166:4 179:19,20 197:15 200:10 207:16 208:20 272:1 274:18 277:21
stick 5:10 181:18
sticker 15:3
stigma 100:18
stirrer 69:20
stock 249:14
stomach 104:1
stone 31:1
stop 105:12 118:18 153:12 199:11 219:7 225:6 234:15 236:12 258:5
store 54:21
stow 52:9
straight 53:14 169:2
strain 28:2,3 29:4 30:2 35:15 42:13 42:14 43:9 57:15 58:5 77:12 107:5 107:14 201:4 267:18
strains 27:21 28:4 28:14,20 29:3,9 29:10,11,16,19,19 29:21,21 30:5 31:22 34:13,19 35:18,20,22 36:1 36:3,4 37:11 39:17,21,22 40:1 41:4 42:20 43:1 51:10 57:16,22 66:8 77:1 107:2 146:6
strange 104:21
strategies 7:6
strategy 140:11 237:18,20
streaking 222:19
stream 77:18 104:1 124:6
strength 119:11
strengths 48:3 61:4 261:4
strep 247:12 249:18
stress 100:18
stretch 73:11
stretching 52:11
stringency 207:9 215:18
stringent 219:15 219:15
strong 33:5
strongly 161:11 197:8,11
structural 13:21
structure 73:4
structures 73:6
struggle 259:16 262:10
struggles 87:16
struggling 228:20
studied 27:15 211:22
studies 4:20 14:22 27:20 29:6 31:22 40:5 49:5,6 50:6 50:22 51:19,19 61:15 67:6 82:18 83:8,13 84:19 85:7,9 87:17 91:14 92:7 94:2 121:7,12 126:15 127:2,12,16 132:22 133:7,14 134:9 137:4 138:6 145:21 147:22 148:20 152:9 160:7 162:11 169:15 170:10 185:7,9 187:9,16 187:19 188:13 190:17 207:1 210:10 213:15 223:11 230:3 238:8 243:16 244:18,20 248:6 248:14 251:13 252:22 253:17,18 254:4,11,19 255:4 262:13 264:22 268:14,15,18 273:2 275:21,22 275:22 278:13 281:1
study 4:21 7:15 15:6,12 19:3 21:1 21:2 22:1,10 25:1 25:8,12 29:11 32:12 35:5 39:7 40:3 43:7 50:7 51:6 55:7 57:16 59:3,3,21 61:21 62:4 70:17 82:14 83:16 84:22 85:1 85:5 87:12 89:8 93:6 95:9 121:5 133:5 136:17,18 137:6 139:14 146:20 147:5,8,15 149:4 150:19 160:7,9,11,13 164:7 170:10,14 173:15,17 174:10 174:16,18 176:17 178:4,5 180:15,20 186:2,6,13 187:10 187:12 188:8 192:3,4,5,15 194:14,22 195:9 197:14 198:4 204:2 231:18 237:21 239:3,7 243:2 247:2 254:21,22 255:3 276:17
studying 7:5 172:13,15 222:17 237:7
study's 186:15
stuff 106:3 261:16
style 81:10
sub 65:7 87:22 88:1
subclinical 26:1 26:15,17
subject 99:18 100:17 152:21
subjective 221:17
submission 155:16
submitted 156:12 273:8
suboptimal 216:5
subscribe 119:3
subscription 129:11
subsequent 23:2 191:5 194:18 195:20 196:17,21
subset 137:6
substantially 219:4
substitution 150:15
subtitles 95:21
subunit 42:1
succenting 91:16
success 59:1 98:1 139:16 151:6,13 156:1 157:4 160:4 161:21 163:10 184:12 185:14,14

187:8 191:11,12 191:13 192:18 193:11 194:6,10 194:13,20 196:1,8 196:16 212:1 214:2,10 216:15 234:8,9 235:20 273:15 277:5,8 279:15,16,16
successes 160:20 162:19 273:21
successful 119:17 173:17 182:20 219:13
suffering 115:18 116:9 119:7,13 246:14,18 271:14
sufficient 153:6 191:20
sugar 40:20,20
sugars 40:22
suggest 134:16 164:22 274:2
suggested 43:15
suggesting 46:10 159:19
suggestions 228:2
suggests 161:11 163:12
suitcases 111:15
sulfamethoxazole 15:19 17:5,15 18:4 20:2 134:4 170:6
sulopenem 189:21 192:10,21,22 193:8,12,19,20 194:8 195:4 196:18 197:17,19 197:20 198:3,4 276:15,18,21 277:6
summarize 45:21 94:5 164:12 206:8 267:1
sun 110:19
sunita 282:9
super 63:8 123:18
superior 21:20 23:10,13 276:18
superiorities 193:1
superiority 60:11 133:3,5
suplisforance 240:2,3
suplusforin 245:9 245:12,15
support 46:17 62:16,19 66:11 127:7,12,14,16 128:2 129:9 148:2 153:6 201:22 202:2,14 203:15 203:19 204:16 205:5,10,18 206:20 260:9 261:10 272:3 278:4,7,9
supported 133:10 137:18 148:4 152:8 203:21
supporting 145:1 199:20
supports 128:3 145:4
supposed 236:1
suppress 89:2
suppression 78:1 86:2 90:17 93:18 98:20 253:1,6 281:11
suprapubic 8:22 134:13
sure 87:1 107:13 109:7 111:22 115:20 168:20 169:7 173:11 176:9 182:4 184:1 195:14 210:21 217:20 226:15 231:17 234:19 236:1,10,19 257:17 266:14
surgeries 112:18
surgery 108:19
surprising 242:7
surprisingly 36:5 82:9
surrogate 76:16 196:16,21 199:2 232:14 263:21
surrogates 49:2
surveillance 129:12
survey 13:3 249:20
surveyed 35:18
surveys 12:22
survives 196:20 198:21 199:7
susceptibilities 254:16
susceptibility 15:20 63:17 67:9 68:10 77:8 84:9 97:9 150:17 191:4 201:2 206:2,3 242:22 248:21 249:20 269:15 281:3
susceptible 77:9 97:10,14 137:10 192:20 193:8 203:15 204:14 205:3,10,15,18 248:10,20 253:8 277:1 281:21
suspect 222:22
suspects 113:19
sustainable 123:1 129:7
sustained 136:12
sweden 30:5
sweep 123:11
switch 37:3,5,7,17
sworn 283:5
symptom 20:11 25:6 160:19 161:6 187:17 188:16 191:15 193:21 214:4 216:11 224:19 274:4 280:20
symptomatic 24:12 26:19 77:21 103:21 151:11 184:20 190:19 221:22
symptomatically 271:3
symptoms 8:18,22 9:4,7 10:3,18 11:13,14 18:12 19:22 20:9,12 21:5,17 24:19 26:2,15 30:8 39:9 45:20 100:6 103:14 107:22 109:6,18 115:11 116:22 118:8 132:8,11 134:11 134:14 135:7,9 143:3,12 149:8 154:19 155:10 156:4 159:2,21 160:15 161:8 165:17 166:21 174:13 175:5 181:14 191:1,7,20 195:8 197:10 212:8,22 213:22 213:22 215:22 216:22 217:5,6,8 217:11 218:2 219:10 223:8,15

224:20 227:1 229:7,19 230:4 232:12 233:3 239:10 240:16 246:1,7 247:3 274:2 276:5 279:8
syndrome 28:7 132:6 143:1
synonym 143:8
synthesis 41:8
synthetic 72:20 75:13 76:1,2
system 50:5 68:17 70:4 72:10 99:12 103:5 108:19 117:8 120:17 175:2,10 176:4 177:12 242:11 280:13
systemic 9:5 11:15 65:21 96:17 132:11 134:14 143:11 154:18 155:10
systems 34:17 36:9 167:18 175:5 175:14 176:6

t

table 12:4 203:5 203:16
tablet 172:18 239:6 280:7
tablets 105:17 170:20
take 5:18 45:18 46:22 56:8 61:1,5 79:18 82:4 89:1 110:4 116:15 118:10,14 126:17 168:13 210:5,6 213:19 226:9,20 226:22 227:1,2 237:5 255:5 262:4 262:17 266:12
taken 98:4 100:8 128:17 144:4 211:14 250:17 283:3,12 284:9
talk 8:2,3,5,8 12:15 14:14 19:11 21:1 23:15 28:13 29:15 47:18 50:14 57:15 62:5,14,17 64:1 67:16,17,19 99:10 100:12,15 100:17 103:20 104:22 120:22 121:10 131:13 132:5 138:3 155:5 156:10 165:5,21 166:2,8,9 167:2 167:14,15 168:7 168:10 172:6 178:5 188:4,22 189:4 197:14 199:14 209:17 211:16 213:19 231:11 255:9 256:16 261:18 277:10
talked 178:13 262:1
talking 53:21 54:9 67:20 85:20 89:3 100:12 101:2,10 106:10 110:8 143:18 151:16 154:9 181:6 183:2 184:20 185:13 199:22 226:12 235:6 242:3 244:7 246:13 248:5,17 249:2 255:15 261:21
talks 122:14 182:12 184:7
tan 16:1
taniborbactam 60:3,8,9
target 48:19 98:20 136:1 180:16 181:16 204:6,8,12 204:19,22 260:20 260:22 264:3
targeting 166:5 180:19 181:6 274:18 275:11
targets 68:9 79:3 79:14 80:6 93:16 93:22 204:2 281:9
taught 118:7
tca 37:22 38:1,1,2 39:1
tch 38:11
teaching 18:3 220:13
team 25:2 138:5 140:15,16
team's 21:2
tebipenem 124:21 125:2,14
tech 255:12,22
techniques 223:18
technologies 73:2
teens 125:9
telehealth 102:18 167:22 174:20 176:2 275:5
teleost 49:20
telephone 167:16
tell 14:18 15:8 24:15,19 32:20 43:17 123:4 143:20 220:15 222:4 223:16 239:16 252:20 253:17
telling 16:15 96:1
tells 115:14
ten 114:13
tend 185:20 212:1 220:14
tends 185:16
term 30:13 218:6 225:6 232:10,13 233:6,8,12 242:5 273:21
terminus 43:22 44:18,20 45:2
terms 14:21 20:11 21:19,21 51:13 52:1,4 148:10,22 172:17 173:1 185:15 211:7,15 212:1,10 213:2,21 218:3 230:4 247:10 249:3,4,10 266:3
terrific 6:13 121:18
test 18:6,10 21:5 39:5 58:22 65:1 68:4 69:10 77:8 77:22 84:4 86:15 146:5 147:21 148:5 151:1,7 153:3 156:22 159:5,12,21 160:5 160:10 162:12,13 162:15,18 163:6 164:3,17 191:12 192:14 196:8 197:21 198:6,10 201:2 206:2,3 212:16 218:12 226:2 281:3
tested 38:8 145:13 245:11
testifying 283:5
testing 15:7 24:14 63:17 66:6 71:21 77:2 79:16 86:13 88:3,4,5 150:17 256:3

tests 108:6 226:4
texas 7:3 247:5 248:1
textbooks 81:7
thailand 119:18
thank 5:3,16,18 5:19 6:13 27:1,4 27:18 46:15,18,19 47:15 62:11 66:14 67:13 80:17 99:2 99:3,21 110:1,8 110:10 111:10 118:16 119:16,19 120:10,13 129:17 129:19,20 130:2 130:17 131:8,10 138:4 140:3,22 150:21 153:13,14 153:15 154:7,7 165:2,4 169:6 171:11 172:10 182:1,6,8 183:5,6 183:9 188:18,18 188:20,21 189:10 189:11 199:11,13 199:15 200:4 207:17,18,19 208:21 210:1 215:9 219:17 221:6,7 223:22 224:1 225:16 227:15,16 230:15 231:21,22 232:2,2 234:20 236:12,17 237:1 242:18 244:4 246:8,9 250:17 251:16 259:19 266:19,20 282:7,8,11,13
thankful 271:9
thanking 189:14
thanks 27:18 62:13 63:19 67:10 118:12 141:1 154:5 165:18 168:14 200:2,3,11 208:3 210:21 220:3 224:4 225:6 225:11 234:15,16 236:16 238:4 241:4 242:16 244:4,21,22 245:2 248:2 250:13 259:4 260:1 261:11 264:7 265:20
that's 9:11 10:5 14:12 16:1,14 17:12 18:14 19:19 26:22 34:4 35:2 36:11 37:15 40:12 40:20 42:2 45:14 50:4 52:6 53:7 57:1,12 60:14 61:15,18 64:21 69:7,10 82:7 85:11,11 88:2 90:9,16 92:1 93:22 96:9 97:4 98:12 100:4 106:8 139:12 162:1 169:10,11 170:9 175:9 182:1,9 183:14 186:19 207:20 208:2 211:21 212:2,20 217:1 222:7 224:21 227:12 235:9 237:17 239:19 241:10,14 242:7 245:11 247:16,22 249:13 250:9 252:21 253:20 255:18 256:8,12,13 257:14,15 263:5 264:22 266:5
theoretically 215:15
theory 119:4
therapeutic 182:21 183:18 184:2 211:21 218:4 245:11
therapeutically 30:5
therapeutics 182:15 183:13 189:3,7 275:16 276:7
therapies 68:5 203:10 238:16 275:1 280:14,14
therapy 23:8 68:9 74:5 85:21 122:4 136:19 148:3 157:1 159:5 160:8 161:12 166:15 167:17,18 169:17 169:21 175:15 191:17 214:7,8 216:14 218:11 243:10,16 273:19
therefor 235:10
there's 8:17 9:3 14:19 16:6,12,13 18:14 23:21 28:10 33:5 42:5 48:22 52:14,22 53:1,15 56:16 57:11 58:20 59:14 61:17 62:2 62:3 64:3,13 65:22 74:9 75:6,7 79:5 92:6 94:16 96:10 97:17 104:3 104:5 106:4 108:17 114:17 116:1 148:14 157:18 160:3,15 163:4 167:7,21 169:16 170:21 172:11 177:21 179:6 181:11 202:15 212:4 213:20 217:1,5 227:13 231:4 233:3,16,20 234:3 246:1,15,17 249:7 249:12 252:17 253:11 255:7,20 256:10 257:18 259:14 261:3,17 261:19 262:11 282:1
there've 12:22
they'd 133:1
they'll 34:3 44:6,7
they're 24:17 32:21 33:16,19 34:15 37:13,19 39:4 40:8 41:19 42:15,21 44:5,21 56:19 85:9 93:12 94:16 102:21 103:21 157:6 171:19 173:19 178:18 184:19 188:14 218:13 220:14 222:4 227:6 245:7 248:11 254:5 255:10,11 266:9 266:17
they've 22:15 32:20 33:4,7 35:13 36:16 216:12 238:19 255:21 256:19 265:6
thick 52:2,3
thing 74:15 75:9 75:21 76:4 85:7 91:2 112:15 169:19 170:16 172:14 173:13,18

177:19 178:3 180:16 184:15 186:17 217:1,19 219:1 243:6 252:7
things 37:22 40:18 40:19 42:7 47:17 48:16 62:16 89:12 90:5 94:16 97:22 98:16 103:6 125:3 126:21 133:18 142:20 144:1,14 146:18 149:3 167:5 177:9 184:6 214:10 229:22 230:19 231:2 249:1 254:14 255:1
think 10:7 11:21 15:2,5 17:21 23:2 25:10 26:11 30:4 36:19 37:11 39:5 56:13,22 59:1 61:5 66:5,19 88:13 90:7,8 91:17 93:22 97:11 98:16 100:5 101:22 103:7 104:22 106:8 107:17 121:14,18 122:13 125:21 130:9,14 142:20 143:12,13 144:15 145:11 149:21 154:14 165:5 166:10,16,21 169:11,13 170:2 171:15 172:22 173:3,9 182:1,3 183:15 184:6,22 185:2,5,12 186:3 187:5 188:1,9,12 188:16 202:10 211:15,17 212:3 213:10 214:19 215:11,14,16 216:7,16,18,20 217:12,13,15,18 218:3,8,17,21 219:8,11,13,20 221:4,7,9,10,19 222:3,7,13 223:7 224:5 225:8,12 226:11 227:8,12 227:13,22 229:6 229:13,15,18 230:16 231:12,21 232:1,9 235:3,10 236:6 237:17 238:2,3 239:13,19 240:6 241:9 242:11 243:12,18 243:21 244:2 245:1,12,20 246:4 246:5 247:6 251:18,18 252:5 252:15,18 253:1 253:11 254:11 259:8 261:5 262:4 262:11,13,17,18 265:10,14 266:17
thinking 10:14 16:10,21 131:14 135:14 178:7 228:20 229:1,4 272:6,16
third 18:20 23:5 106:15 213:18 251:9
thirdly 213:10
thirteen 193:19
thomas 2:14 208:9
thought 4:7 20:21 30:9 52:15 96:12 178:4 209:21 225:19 236:18 248:4 250:20 261:16 279:3
thoughtful 130:4 232:4
thoughts 220:2 266:16
thousand 29:7
thousands 115:10
threats 123:17 140:11
three 8:8 17:4,16 18:4 19:10,12 23:8 25:4 30:17 30:22 31:7 33:2 44:15 51:10 52:2 107:8 111:1 113:13 114:13,21 118:18 183:21 192:12 204:6,21 210:5,11 226:3 236:14 247:1 256:6 265:14
threshold 116:3 159:11 204:12 205:1 216:3 222:13,21 223:5,7 226:9 230:7 271:5 279:19
thresholds 20:18 216:19 219:10
thrilled 131:7
throw 211:3
thunder 117:16
tie 258:17
tighter 89:7
tim 5:20 27:18
time 1:8 5:10,11 5:11 6:10,20 9:14 10:14 12:5 13:8 18:9 25:3 26:17 32:15 33:9,17,19 45:12 47:2,4 48:18 55:1,11,13 61:7,9 64:5 65:7 68:7,16 69:14,17 72:11 80:2 81:16 82:15 83:20 84:6 87:10 93:7 98:9 102:17 103:20 104:2 106:13 107:5 109:1 110:11 111:15 113:1 116:15 117:7,10 118:2,10 118:13,17 119:21 128:21 129:21 130:5,6 140:3 145:21 151:14 153:13 158:5 163:13 164:7,19 165:2 166:10 174:17 175:17 176:10,12 179:13 184:22 185:1 188:18,22 189:15 205:14 206:4 207:17 208:1 209:3,4,9 216:2 223:1 226:10 237:5 239:11 252:12 253:13 267:8 274:8 275:5 276:12
timed 92:8
timely 128:6,14 272:2
timepoint 135:2,4 136:10,14 159:6 194:17
times 44:11 82:2 84:10 115:10 144:8 175:8 177:15 178:18 221:2 240:6 244:10 253:20 254:4 271:2
timing 162:8 163:20 176:21
timothy 2:4 5:15

tis 76:20
tissue 56:14,18 73:9 237:11
tkd 91:9
today 4:19 5:5,11 6:9 7:11,17 8:1 27:1 28:14 45:22 99:22 103:17 108:18 110:11 111:7,10 112:2 116:5 131:8,11 134:12 141:7 154:3,8 158:5 164:13 165:3,22 182:7 183:11 188:18 189:17 199:22 225:17 226:7 243:7 244:10 249:8
today's 130:10 154:12 232:5
told 45:21 107:10 109:2 115:4 118:4
tolerance 78:22
tom 2:12 182:13
tomefa 2:3 47:6 264:8,9
tool 46:7 116:6
tools 4:17 115:3,6 116:1,19 118:19
top 19:6 32:19 33:10 34:8 36:10 38:20 43:22 55:8 55:17 90:10 122:20
topic 15:10 24:3 64:4 131:18 200:22 210:17 238:3 251:9 261:15
topics 266:13
topline 60:9
total 29:9 41:18 77:14 78:1,4 153:5 235:6
totally 262:2
touch 47:17 48:1,3 50:1 58:6 139:8
touched 51:19 52:16 152:3 200:12
touches 49:17
touching 137:15
toxicity 86:3
toxins 36:2
track 83:6 109:12
tract 4:11 6:5 7:6 7:21 9:4,7 10:18 11:14 28:13 31:15 43:16 46:15 53:12 54:3,5,7,13 65:8 65:14 66:10,18 72:9 82:12 85:6 89:13,16 105:12 106:5 110:17 116:11 122:13 123:13 124:2,4,10 124:16,16 126:16 127:11 131:15 132:4 141:9,19 142:15 143:7,10 152:11,12 154:20 155:7 165:17 203:1 224:18 239:17 251:20 255:13,14,19 267:5 268:7
traditional 34:6 77:17 89:3
trails 145:1
train 266:1
trained 220:14
training 131:5 153:19
transcending 53:13
transcriber 284:1
transcript 284:3,5
transcriptionist 283:7
transcriptomes 51:7
transduction 28:5
transfer 28:1 35:3 267:19
transform 45:4
transformation 28:4
transgender 24:6 24:7 122:10
transient 25:15
transitional 31:8
translate 61:11
translating 62:15 138:21
translation 40:16 41:8 47:12
translations 62:19
translocate 50:13
transmitted 208:20
transparency 125:22
transparent 126:11
transpiring 126:2
transplant 12:13 123:15
transporters 36:14 38:18 40:17 40:21 41:9 46:10 268:6
transurethral 52:22 53:3
transurethraly 59:7
trautman 47:4 80:18 110:10 267:13
trautner 3:10 5:16 5:17 6:2,11,13 7:1 27:5 46:19 103:22 106:4 121:17 126:20 128:7 130:1 167:3 171:17 180:4 221:8,9 224:5 237:3,4 241:5,6 241:20 242:8,16 245:6 246:10,11 248:2 267:4 280:12
traveled 106:18
travelled 110:22
treat 7:7 16:17 18:2 19:17 24:2,7 54:5 58:11,11 101:6 115:15 116:8 117:10 121:1 123:18 125:13,15 137:5,7 156:18 200:8 201:13 202:1 206:18 207:14 213:1 224:17 239:7 240:14 246:14 271:16 273:11 277:19 278:5,11
treatable 201:4
treated 19:8 24:4 111:1 114:7 145:10 147:8 193:2,18,20 194:8 194:9 195:4 197:19 198:8 270:22 276:15
treating 11:7,19 14:6 18:9,16,22 19:12 237:7 266:8 280:8
treatment 1:4 4:10 8:6,8,13 9:17 11:5 14:10 17:22 20:14 22:16 23:3

24:22 25:4 30:10 66:18 67:15 74:1 76:12 89:9 101:20 106:6 108:11 114:14,14,22 115:22 116:18 118:20 121:19 122:3,4,16 125:11 125:18 126:4,6 127:1 128:11,15 128:19 133:15 135:18 136:20,21 138:22 139:2,3,5 140:19 143:16 145:5 148:5,15,16 149:18,19,22 152:1 153:7 157:7 165:16 174:2,21 175:6,11 183:15 190:20,21 193:3,3 193:17 194:11,13 195:8 196:1 197:4 197:11,17 198:1,3 198:12,17 200:19 202:5 203:1,11,21 205:22 206:7,10 208:17 213:12,17 216:6 218:9 224:22 227:3,7 267:11 268:22 269:7 270:16 271:11 272:19 274:3,14 276:11 277:12 278:3 279:10

treatments 17:1 100:7 101:1,7 108:10 115:6

treats 172:20 232:20

tremendous 48:8 58:3 265:18

tremendously 28:19 50:21 55:19

trial 4:17 19:15,16 23:5 24:3 98:17 119:5 130:11 131:12 132:19 133:9,11 135:8,21 137:16,22 139:10 144:5 148:10,14 149:7 152:4,16 153:9 156:8 157:10 169:15 172:21 179:5,15 180:2 181:14,20 189:21 190:2,9 192:2 199:1,4,11 217:13 220:16,19 221:16,19 222:2 222:10 231:16 238:21 239:15 240:8 243:20,21 249:13 254:8 257:4,8 258:2 272:8

trials 8:9 14:5,8 14:10,10 19:12 66:9 93:4 95:7 121:22 124:9,13 126:14 132:20 141:5 145:4 149:18 150:20 151:16 152:10,13 152:13,19 154:5 154:11 156:1,17 161:15 164:13 166:2,3,12 167:8 167:12 178:10 183:4 189:5,16,18 191:10 198:18 199:5 200:19 207:8,12 212:14 218:8 220:15 226:12,17 237:13 237:20 240:5 241:1 245:20 246:2,17,19 250:6 257:20 267:13 272:9 273:6,8 274:16,17 275:2 275:18 276:9 277:13 279:20 280:5,18,19 282:4

tried 85:18 98:8 177:2

trigger 32:6

trimethoprim 15:19 17:5,15 18:4 20:2 134:4 170:6

trimoxazole 70:18

tripartite 144:7

trouble 243:22

trough 45:1,9

true 142:14 159:16 161:4,16 212:2 223:9 283:9 284:5

truly 246:6

trust 178:11

truth 100:14

truthfully 101:17

try 6:19 7:22 59:19 62:5 82:15 86:2 117:9 157:17 161:22 165:21 177:9,19,22 180:1 181:16 182:3 184:4 187:17 209:4 226:21 228:7,10,16 243:11,12 248:9 262:16 264:20 265:19

trying 17:19 19:16 50:8 52:18 55:15 55:20 56:17 61:11 81:19 82:16 86:21 91:9 126:9 144:8 176:19 178:9 179:4 180:16 183:13 209:17 235:1 243:1 258:10 261:13 262:13 264:18 265:11,16

tube 39:5

tufte 3:11 99:9,21 99:22 121:17 225:13,16 270:10

turn 5:13 6:10 27:17 32:22 36:22 37:3 63:18 99:20 120:9 127:5 130:15 140:20 203:21 214:13 226:2 228:10

turned 25:20

turning 252:12

twenty 196:2

twice 192:11,11

two 7:5,5,22 10:2 10:8 12:22 15:15 20:4 23:12 25:16 28:9 29:6 32:14 41:2 48:16 52:6 56:11 57:22 58:13 58:16 59:9 67:16 68:14 71:13 74:1 74:2,3 83:2 98:21 113:4,7 115:7,13 116:12,13 122:14 133:8 134:10 138:6 139:16 152:4,9 162:22 163:4 185:4 191:4 193:17 194:21 195:22 196:2 197:7 198:11 200:18 213:2 216:1 226:3 229:10 230:21 231:2 233:11 234:5 240:5 246:15 254:2

256:5,7 258:19 265:14 270:9 280:22
tying 93:15
type 6:18 17:12 29:18,20 31:7 36:18 37:12 40:7 77:10 110:19 114:11 146:20 172:19 174:5,22 258:2 279:14
types 28:10 34:13 78:14 95:7 107:9
typewriting 283:7
typical 44:12
typically 25:15 157:1 191:6 212:3 212:18 240:11
typing 168:22

u

u 95:11
u.s. 141:10 142:1 148:18 182:22 183:14
ucal 248:17
uks 255:10
ultimate 66:10 85:18
ultimately 61:6 79:16 80:3,6
um 209:16
unable 56:1
unacceptable 128:10
unanswered 52:13
unblinding 151:22
uncertainties 138:20
uncomfortable 101:15,18 107:10
uncommon 13:17
uncomplicated 1:4 4:11 6:5 7:13 8:3,11,14 9:12,18 10:1,5,15,21 11:4 11:6,12,19,20 12:14,16,19 13:20 17:1 18:7,16 19:5 19:13 23:18 27:22 39:4 46:7 47:20 54:6,13 61:2,6,12 65:13 66:9 67:16 81:13 82:5 83:12 84:21 85:4,6 89:11,13 90:19,22 91:22 92:11 93:6 93:6 94:8 95:5,10 95:18 96:17 99:17 101:3,6 102:7 104:18,20 108:6 112:20 118:22 123:12 124:9 125:16 131:15 132:3 141:5,9,14 141:16,17 142:8 142:10 143:7 145:5,5 148:15 152:12,14 154:13 154:16 155:9 162:2,2 166:4,13 167:1,13 180:3,12 181:7 183:4,22 185:2 192:5 200:1 200:20 201:13,18 202:1,6 203:11,12 203:22 206:1,4,7 206:10,18 207:7 207:14 210:9 212:6,8,13 213:1 213:21 224:18 238:8 241:13,17 242:4,5 243:4,6,9 244:8 245:22 246:13,22 247:7 247:19 250:11 251:12,20 252:18 255:13,19 267:5,7 267:18 268:3,10 269:1,22 270:3 271:13,18,19 272:7,17,20,22 273:2 274:14,15 275:18,20 276:8 277:19 278:3,6
uncultivable 223:8
uncultivatable 21:19 223:9
underestimate 216:6
underestimates 245:21
undergoing 123:14 197:5
undergraduate 153:19
underlining 46:21
underlying 112:16
understand 48:13 48:17 49:17,21 50:8 54:19 55:16 55:20 64:15 67:6 86:12 92:3 102:6 102:21 127:16 157:17 197:16 211:11 212:5 213:5,15 225:20 231:5 232:4,6 235:11,21 242:19 254:9 263:16 270:14,15 279:4 281:15
understandable 102:5
understanding 47:10 54:4,17 87:3 89:1 97:18 122:11 126:21 190:5 202:17 229:17 252:9 263:4 265:9 281:8
understood 225:11
understudied 122:8
undertake 121:15
undissipated 149:20
unequivocally 223:9
unfortunately 50:20 54:12,20 57:3,6 64:13 240:7
unheard 13:18
uniform 207:2 278:14
unintended 68:18
unique 29:3 66:17 185:6,10 269:6
unit 199:18 275:19
united 7:14,18 12:16,19 13:5 15:13,21 16:2 24:5 86:21,22 106:14 125:8 128:1,2 133:16 180:18 181:21 243:21 267:6
units 30:17 33:13 87:10 134:19 191:16 281:11
universal 112:8
university 27:6,8 27:11 39:8 63:4 63:11 80:21 81:1 120:3 130:14 131:4,6 153:19,20 165:13 177:1 208:11
unlicensed 145:15
unmathematical 153:4

unmet 187:22 271:21
unmute 228:3
unreliable 115:4
unstable 9:8
upac 267:21
update 7:11 10:22 11:2 12:10 17:21 184:18
updated 9:21 128:8 142:2 168:10 184:17 278:15
updating 23:18 128:20
upec 28:19,22 29:17 30:3 31:3 31:22 32:8 34:9 43:16 45:22
upfront 14:19
upload 169:8
upper 9:4 10:18 11:14 44:12 83:6 90:12 141:15 239:17
upregulated 40:12 41:6,6 46:11
upsell 38:22
uranic 253:7
urea 30:22 74:20
uremic 28:7
ureter 33:3
ureters 31:13
urethra 31:6 50:11 52:22
urge 103:21
urgency 8:21 134:13 149:8
urgent 120:22 155:1 187:21 271:16
urinalysis 192:13
urinary 4:11 6:5 7:6,21 9:7 11:14 21:5,16 24:19 26:2 31:15 43:16 46:15 54:3,5,7,13 61:14 65:8,14 66:9,18 69:11 71:4 72:10 73:9 77:3 79:2,4,14 82:10,12 83:15 84:2,11,20 85:6 85:10 86:13 89:5 89:13,19 93:7,19 94:10 96:8,11 98:22 105:12 106:5 108:19 110:17 116:10 122:13 123:12 124:2,4,9,16,16 126:16 127:11 131:15 132:3 134:12,13 141:9 141:19 142:15 143:7,10 152:11 152:12 154:20 155:2,7 165:17 200:1,6 203:1 217:4,11 224:18 251:20 255:13,14 255:16,16,19 257:2 258:4 259:11 261:10 263:12 267:5 268:7,12,13 277:17 281:17,21 282:2
urination 190:15
urine 5:1 11:18 14:15 16:4 18:7,8 18:10 20:14 21:11 22:8 25:6,6 29:22 30:3 31:12 33:14 35:6 37:8 38:18 39:11 40:13 41:2 41:3,4,16 42:3,15 46:12 50:10 52:9 54:18,21 55:1,2 55:13,16 56:1,2,7 56:16 58:17 59:13 64:20,20 66:3 72:20 74:16 75:3 75:4,5,11 76:2,6,8 77:19 79:8 81:22 82:10 83:3 84:14 84:16 87:11 88:6 91:3 93:14 95:7 97:3,5 98:11 104:1 134:17 135:13,16,19 137:9 143:2 147:11 149:14 156:19 157:5 160:3 191:3,15 192:13 193:22 200:8,22 202:2,3 202:14 203:20 204:20 205:5,9,12 205:17 206:9,15 206:20 207:1,13 212:9,15,19 222:12,13,15,18 223:6 242:1 244:10 246:21 247:3,7,8 251:10 251:14,20 252:3 253:15,19,22 254:5,9,13,17 256:8 258:22 259:16 260:7,9,12 260:15,19,19 262:3,9 263:19,19 263:21 264:18 265:2,9,19 266:9 269:21 270:4 273:18 277:18 278:6,10,13 279:20 281:6,13 281:14 282:5
urodynamics 65:2 69:1,11 70:9 76:5
uroepithelium 73:4,11 74:6,13
urogenital 109:12 217:10
urologic 142:18
urological 132:15
urologists 142:7
urology 141:13
uropathogen 57:1 60:19 66:7 77:4,6 158:15,19
uropathogenic 77:5 267:20
uropathogens 51:8 57:7 69:9 72:5,22 74:21 76:17 229:20
uropathogins 60:14
uropathy 155:1
usage 67:8
use 5:1 12:21 16:12,13 17:10,14 18:19 19:4,7 24:10 33:8 38:16 38:16 40:21 50:2 51:4 56:1 57:1,10 60:14,14 64:11 67:3 68:19 72:20 73:2,5,6 79:20 84:15,16 88:12,14 88:15 89:5 91:2,9 92:7,20 94:9 96:21 97:14 102:13 110:1 117:9 118:11 119:12 124:14 125:12 127:4,8,17 133:1 142:22 145:2 150:4,4 152:8 167:21 170:15 173:10 174:19 179:14,21 180:8 186:6 202:5

202:13 206:9,13 207:1 211:19 214:8 216:10 236:9 240:2 241:18 242:6 244:8 245:7,12 250:5 251:10 253:16 259:16 260:7,15 263:20 264:2 268:17 269:11,11 271:18 273:1,2 278:12,21 280:17,18 281:21
useful 51:20 111:22 114:19 121:9
users 97:13
uses 31:18 75:10
usual 113:19
usually 30:16 68:18 78:16 88:2 89:4 90:11 104:8 175:2 229:19 244:9,15
ut 61:2
uti 1:4 7:7,8,11,13 7:18 8:3,4,11,14 9:12,17,18 10:1,4 10:5,15,21 11:4,6 11:12,19,20 12:4 12:14,16 13:5,14 13:15,20,22 14:2 14:3,6,16 15:2 16:6 17:1,15,20 17:22 18:7,16 19:5,13,14,15,17 19:21 20:1,12,20 20:21 21:3,18 23:2,4,18,20 24:2 24:8,11 25:3,4,8 25:10,18,20,22 26:1,15,17,19,21 27:22 28:7 31:17 31:17 37:8 38:12 39:3,4 40:12,20 42:5 45:8 46:7,21 47:20 49:9,11,14 51:9 55:7 56:9 57:1 59:21 61:2,6 61:11,12 62:1 63:21 67:9,18 68:22 69:6,12 71:1 73:8,18 82:5 89:10 90:21,22 93:6 99:17,19 101:6,15 102:15 103:14,15 104:2 104:18 105:4 106:17 107:19 109:2,5,17 112:20 112:21 115:11,12 119:11 121:7 128:8 133:12 134:16 141:5,16 142:8,9,22 145:5 148:15 154:5,13 154:16 155:4,22 161:8 162:2 165:14,15,16 166:1,4,13,20 167:2,13,14 168:1 169:15 173:14 174:2,13,21 176:4 177:2,11 179:9 180:15 181:2,7,17 183:4,22 192:5 200:2,20 201:18 202:1 203:12,22 206:4,7,11,18 207:7,14 208:18 208:19 210:9 211:9 212:6,8,13 213:1,21 221:22 227:1,6 230:13 237:7 238:8,17 240:9 241:3,13,18 242:4 243:6,9 244:8,12 245:20 245:21,22 246:6 246:13,22 247:3,7 251:12 255:22 260:10 261:2,4 264:22 266:8 267:7,18 268:3,10 269:1,2,14,22 270:3,11,13 271:3 271:13,13,14,18 271:19 272:7,17 272:20,22 273:2,6 273:8 274:4,14,15 275:18,20 276:9 277:19 278:3,6
utility 182:14 183:12 185:5 207:7 268:10 275:16 278:10 280:17
utilization 104:4,5
utilize 102:1 215:16
utilized 89:5
utilizing 184:21
utis 12:19 19:8 63:22 67:16 76:12 81:13,17 82:21 83:12 84:21 85:4 89:11 90:8,19 91:22 92:12 94:8 95:5,10,13,18 100:3,5 101:1,3 101:11,14 102:6,7 103:6 104:5,9 107:21 108:6,10 109:11 111:1 112:13,16 113:1,6 113:15,17 114:22 117:22 118:22,22 119:4 121:3,5,19 122:10 132:13,14 141:15 142:14 180:3,12 190:18 201:13 202:6 206:1 226:4 227:2 255:21 269:3,8 270:15,19,20,21
uti's 13:16
uuti 4:12,15,20 5:2 48:3 99:7 100:3 124:12 131:12 132:19,21 133:16 134:2,9,10 135:8,19 138:7 142:4 152:3,13 155:16 173:7 183:15 189:5,16 189:18,21 190:6 190:13,13 191:10 191:20 192:2,9,19 197:7,10 198:18 199:5,9 200:8 244:14 263:17 264:4 267:9 269:19 275:3 276:17 277:12 278:11 280:14
uutis 108:7 122:3 132:9

v

v 198:20
va 7:4 14:11 120:17,19 130:19 208:13
vacation 113:9
vaccine 140:11,16
vagina 53:11 109:12
vaginal 240:18
valerie 3:1 110:14 110:15 111:9 119:19 121:17 125:4
validated 215:17
validation 92:3
validity 149:4 178:14

valuable 65:8 67:5
value 22:20 24:13 93:20 184:2 193:6 204:13 205:2 262:7
values 108:11 254:1 270:16
variability 57:11 57:19,20 58:3 66:4 75:6 79:3 93:9 253:16,20
variable 53:18 55:2 56:4,21 57:14
variables 52:16 61:16 62:6 79:6 80:5
variance 79:11
variation 79:17
varied 162:11
varies 36:21
variety 15:17 28:1 35:14 71:22 72:1 72:3,5 75:13 267:20
various 27:20 35:14 65:22 80:9 98:16 202:17 226:7
vary 43:20 46:4 185:15,16 203:3,7 216:2 267:22
vascular 73:22
ven 57:6,7
ventilator 124:5
ventral 32:14,18
vermont 105:10
version 30:20 143:20,22
versus 52:2 53:13 56:18 81:22 84:10 88:8,15 104:22 162:16 167:2 170:20 178:1 185:11 187:14 188:6 248:17 251:21 255:21 269:21 281:10,22
vesicoureteral 50:8,9 53:17,20
vessel 69:20
veterans 120:19
viable 122:22 129:7
vice 120:3
view 93:3 151:7 185:10 186:14,15 216:8 217:18 218:14
viewpoint 183:11
viewpoints 209:6
views 111:22 112:1 215:20 258:20
viral 229:3,12
virialized 35:17
virtual 1:5 4:6 27:19
virtually 111:13 221:3
virulence 34:6,20 34:22 35:11 36:4 37:20 46:4 49:18 49:21 51:14 237:9 267:17
virulent 28:4 29:17,17 267:21
visible 195:15
visit 136:18,19 137:1 151:1 156:22 159:12,22 160:6,10,11,16,19 161:1 162:10,18 163:20 164:8 174:12,12 191:12 192:15 194:18 195:4,9 196:1,8 198:6,10 212:17 218:11 220:21
visits 13:5,7 14:2,3 136:17,20 162:22 164:18 194:14 195:20 218:20 220:19 275:5,6,7
visual 99:13
visually 32:11
visuals 102:2
vital 9:8
vitro 47:10 48:15 63:16,21,21 64:2 64:6,14,16,22 65:5,11,15,17 66:1,12,17,19 67:4,15,18,18,22 68:5,13,17 69:12 69:16,18 70:10 73:1 74:7 76:5,5 76:14,14 79:20 80:5 82:22 84:4,8 89:21 92:15 148:7 254:14 255:4 268:21 269:2,7,8 269:11
vivo 38:15 43:18 48:14 52:15 59:21 61:17 88:7 89:21 255:4 265:2,10 268:15 269:10
void 52:10 70:7 71:17,17 76:7
voiding 69:3,15 71:2,13,15 72:15 72:15 73:20 76:9 76:15,21 79:9 223:3 254:17
volcano 40:10
volume 57:18 61:8 69:14 71:17 76:9 80:5
voluntary 208:10
volunteers 75:6 87:12 254:21
vomiting 9:7
vs 20:3,7 21:3 22:19 23:7 35:5 43:10

w

waiting 240:1
waiver 178:3
wake 161:18
walk 101:16,17 195:21 242:1
want 12:17 13:6 60:13 69:9 91:1 101:17 106:2 107:17,21 108:1 108:11 110:1 112:1 119:16 130:1 132:19 133:8 155:13 156:10 158:8 159:7 168:15 170:15 171:7 183:6,8 197:14 200:11 209:4,13 219:1,2 221:15 222:2 223:21 224:6 225:17 231:10,12,13,16 234:17 236:19 237:4 240:2 243:11 246:14 258:10 260:6 266:12 270:14
wanted 4:6 39:18 39:19 60:15 92:20 158:17 160:1 161:16 163:21 227:7 234:18 236:22 241:7 244:5,9 258:18
wanting 242:14 280:19
warnings 180:7
washington 1:11 99:11 165:13

177:1
wasn't 60:18 103:17 105:14 111:17 226:5 239:17
waste 74:18
watch 174:17
watches 168:6
water 69:21 106:13,15,18,19 108:20
way 28:11 31:4 44:3,9 82:2 93:1 106:8 117:5 118:19 128:16 129:21 130:1 166:11 212:10 217:20 218:18,20 252:5 259:17 262:19
ways 33:8 62:5 65:4 174:6 178:16 279:12
weakened 108:19
weaknesses 61:4
weather 236:17
webex 1:10
webpage 5:8
website 100:4 143:19 206:2
week 115:20 143:18 160:10 162:12 196:3,7
weeklong 113:9
weeks 107:9 125:20 162:13 198:11
weighed 75:16
weight 217:7
welcome 4:6 27:19 130:10 183:4 200:2 209:20 236:16
went 22:17 162:21 202:10 231:12 263:7
west 105:14
wet 236:6
we'd 16:19 20:16 66:16 124:8 136:8
we'll 6:19 9:15 34:8 45:21 62:19 130:15 167:2 168:12,17 169:2 207:22 208:2 210:15 238:5 267:2 282:12
we're 6:14 7:16 11:1,2,16,21,22 12:10,15 13:9 14:14 17:18 22:11 29:12,13 37:15 41:5 46:21 47:16 47:17 60:21 81:7 81:18 85:14,15 107:13,17 119:21 125:12 126:5 131:7 143:17 155:13,18 163:5 167:20 172:12,13 172:15 181:6,8 182:11 183:1 185:13 186:18 189:1 215:15 219:12 221:11,11 221:13,20 226:12 228:22 237:5 239:3 240:1 242:3 244:14 248:5 249:2 251:18 257:2 259:13 262:5 265:5 266:12
we've 32:15 33:10 33:10,11 37:4 45:2 89:15 108:18 123:18 132:2 141:7,21 154:9 155:21 164:13 183:8 187:5 195:6 210:10 211:6 213:10 215:11,19 215:21 217:17 218:5 222:13 226:7 256:18 265:12
what's 9:13 12:15 26:11 31:14 41:5 46:20 90:7 91:17 96:9 104:3 145:3 152:17 184:9 234:15 241:9,12 244:17 246:21 247:22 262:21
whilst 56:15
white 25:5
whoever's 174:10
who's 97:9 138:4 161:20 163:9 175:19 222:17
wi 111:6
wide 55:19 57:5 70:17 90:17 114:6 209:6
widely 105:2 202:1
wider 83:11
wild 77:10
wimpy 30:20
win 170:8
window 151:2
wish 119:17 144:14 151:19 170:11 282:12
wished 214:7
withing 69:11
witness 283:4
woman 9:19 10:1 22:5 24:7 214:21 222:14
women 10:16 12:6 12:7,12 13:7,13 13:15,16,21 14:2 14:7 18:2,16 21:3 21:4,6,12,16 22:12,14 23:8,18 24:1 25:2,9,21 26:2,13 30:11 39:4,5,7,14 40:12 43:5 46:6 77:21 100:13 115:11 122:9 132:10 134:10 141:18 143:9 155:9 162:3 165:17 166:20 184:21 190:18 192:5,8 208:18 212:7,13,22 213:2 214:4 217:10 242:5,5 245:21 246:13 247:20 268:2 274:6
women's 63:2
wonder 101:2,20 231:6
wondered 249:6
wonderful 62:14 182:8
wondering 104:19 235:15 263:20
won't 24:19 37:6 117:21 237:10,11
word 11:22,22 109:19
words 15:20 90:6 110:18 129:22 132:18 194:17 225:19
work 7:3 31:16 46:20 60:1 84:16 104:4 107:6 110:21 111:5,14 114:2 130:13 136:3 146:11

154:9 182:3 228:16 236:2 256:19 257:5,8,13 258:13 265:6,8,17 279:3 282:3
worked 20:10 107:12 113:13 114:4 140:13,17 221:11 247:15
workflow 175:21 177:17
workflows 176:6 176:14 177:4
workforce 125:20
workhorse 49:14
working 11:2 23:18 75:4 105:9 110:3 123:13 183:9 184:4 215:10 235:9 236:1,11
workloads 176:7
workshop 1:5 4:6 5:5,5,8 112:20 115:4 119:17 130:11 141:2 145:3 154:12 200:5 282:13
world 51:1 106:15 181:21 189:19 191:18 198:22
worldwide 94:19 106:5
worn 266:17
worries 220:1
worse 55:4 58:10 116:9 117:1 161:10
worsening 161:6,7
worsens 123:10
worth 85:9 142:3
worthy 219:14
wouldn’t 101:17 238:20 245:11
wow 16:10 105:11
wrap 48:4 54:2 264:18
write 247:21
written 59:2
wrong 225:12
wrote 102:12

x

xianbin 2:19

y

y 55:16
yan 2:7
yeah 173:8 183:16 230:17 231:21 248:4,18,21 257:12 263:15
year 12:20 13:5,10 14:1 29:10 113:8 113:16,17 117:19 123:6 129:16 141:13 270:21
years 15:15 27:9 31:3 87:4 100:9 108:21 110:18 119:10 140:14 145:19 182:16 183:15,21 184:1 184:17 185:8 188:1 189:8 192:9 199:19 226:17 242:12 265:14 270:20
yeast 76:3
yielded 29:11
yielding 28:22
young 105:4 108:21
you’d 82:6 96:16 136:15 231:12 254:7
you’ll 98:1 156:11
you’re 9:8 11:7 12:21 16:10 53:5 53:6,13 54:4,9,21 56:15 81:12 82:15 83:5,10 86:4,13 86:14,16,19,21 88:15,18 89:3 91:8,9,10 93:14 98:17 102:17 170:14 171:11 172:17 173:11 178:15 180:16,19 181:13,15,18 187:2,13 188:5,10 209:17 215:3 221:1 222:18,19 222:19 230:16 232:1,10 236:21 239:18 242:17 243:1,21 244:2 245:1,14 249:9 252:10 255:15 256:9 257:1,15 258:3 260:4 261:21 262:17 264:14
you’ve 40:8 86:10 87:1 88:17,19 90:19 104:14 217:13 257:10 259:21
yup 264:14

z

zero 187:2,8 192:21 193:5 205:14
zhixia 2:7
zone 111:16
zones 113:14
zoom 6:18

’

’21 10:13
’67 49:12