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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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MICROBIOLOGY DEVICES PANEL

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November 10, 2016
8:00 a.m.

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PANEL MEMBERS:

ANGELA M. CALIENDO, M.D. Ph.D.	Panel Chair
KATHLEEN G. BEAVIS, M.D.	Non-Voting Member
KIMBERLY E. HANSON, M.D., M.H.S.	Non-Voting Member
CATHY A. PETTI, M.D.	Non-Voting Member
DAVID F. WELCH, Ph.D., D(ABMM)	Non-Voting Member
DANIEL B. JERNIGAN, M.D., M.P.H.	Temporary Non-Voting Member
STEVEN J. SKATES, Ph.D.	Temporary Non-Voting Member
BERNHARD L. WIEDERMANN, M.D., M.A.	Temporary Non-Voting Member
CHRISTOPHER F. CARPENTER, M.D.	Temporary Non-Voting Member
THOMAS A. MOORE, M.D.	Temporary Non-Voting Member
DEAN FOLLMANN, Ph.D.	Temporary Non-Voting Member
DANIEL J. BRACCO, RAC	Industry Representative
THOMAS G. SIMON	Consumer Representative
BARBARA D. BERNEY, B.A.	Patient Representative
SHANIKA CRAIG, M.H.A., M.B.A.	Designated Federal Officer

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Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

STEVEN GITTERMAN, M.D., Ph.D.
Deputy Director, Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health

KRISTIAN ROTH, Ph.D.
Chief, Bacterial Respiratory and Medical Countermeasures Branch
Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health

FDA PRESENTERS:

BRITTANY GOLDBERG, M.D., M.S.
Division of Microbiology Devices
Office of In Vitro Diagnostics and Radiological Health

QIN LI, Ph.D.
Division of Biostatistics
Office of Surveillance and Biometrics

GUEST SPEAKER:

EBBING LAUTENBACH, M.D., M.P.H., MSCE
Professor of Medicine and Epidemiology
Chief, Division of Infectious Diseases
Perelman School of Medicine
University of Pennsylvania
Antibacterial Resistance Leadership Group (ARLG)

SPONSOR PRESENTERS:

MARK MILLER, M.D.
Chief Medical Officer
bioMérieux

SAM BOZZETTE, M.D., Ph.D.
Vice President, Medical Affairs-Americas
bioMérieux

NOAM KIRSON, Ph.D.
Vice President
Analysis Group, Inc.

PHILIPP SCHUETZ, M.D., M.P.H.
Chief Physician of Endocrinology and Internal Medicine
University of Basel
Kantonsspital Aarau, Switzerland

SPONSOR ADVISOR:

ALEXANDER KRAUSE
bioMérieux

OPEN PUBLIC HEARING SPEAKERS:

SEAN-XAVIER NEATH, M.D., Ph.D.
Associate Clinical Professor
Department of Emergency Medicine
University of California, San Diego

MICHAEL BROYLES, B.S.Pharm., RPh, PD, Pharm.D.
Director of Pharmacy and Laboratory Services
Five Rivers Medical Center

H. BRYANT NGUYEN, M.D., M.S.
Chief, Division of Pulmonary & Critical Care Medicine
Director, Medical Intensive Care Unit
John E. Peterson Professor of Medicine and Emergency Medicine
Loma Linda University

VOLKER LEIBENBERG, M.D.
Director, Global Medical Affairs
Clinical Diagnostics Division
Thermo Fisher Scientific

JAMES NEWTON, M.D., FACP
Washington Regional Medical Center

DEVENDRA AMIN, M.D., FCCM, FCCP
Assistant Professor of Medicine
Medical Director of Critical Care
USF School of Medicine at Morton Plant Hospital
BayCare eCARE

LANCE PRICE, Ph.D.
Director, Antibiotic Resistance Action Center
Milken Institute School of Public Health

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M E E T I N G

(8:08 a.m.)

DR. CALIENDO: I would like to call the meeting of the Microbiology Devices Panel to order.

I'm Angela Caliendo. I'm the Chairperson of this Panel. I am an adult infectious disease clinician with experience in clinical microbiology. I am currently at Brown University.

At this meeting, the Panel will discuss and make recommendations regarding the premarket notification 510(k) submission for a new indication for bioMérieux's VIDAS B·R·A·H·M·S PCT test to add an indication to the use as an aid in the antibiotic management of patients with suspected lower respiratory tract infection, an indication for use as an aid in antibiotic management of patients being treated with antibiotics for confirmed or documented sepsis or both.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And thank you for joining us.

DR. HANSON: Good morning. My name is Kim Hanson, and I'm an adult infectious diseases physician and medical microbiologist. I'm an Associate Professor of Medicine and Pathology at the University of Utah in the ARUP labs.

DR. WELCH: David Welch. I'm a clinical microbiologist from Dallas, Texas. I direct the clinical microbiology laboratories of an 800-bed hospital in North Dallas.

DR. WIEDERMANN: Bud Wiedermann, a pediatric infectious disease physician at Children's National Health System and Professor of Pediatrics at the George Washington University School of Medicine in D.C.

DR. CARPENTER: Chris Carpenter. I'm an infectious disease specialist at Beaumont

Hospital in Royal Oak, Michigan and also a Professor of Medicine at the Oakland University William Beaumont School of Medicine.

MR. SIMON: Tom Simon, Atlanta, Georgia, associated with the St. Joseph's Cancer Survivors Network and a Consumer Representative for the FDA.

MS. BERNEY: I'm Barbara Berney. I'm the Patient Representative, and I'm on the disease side of things.

MR. BRACCO: Good morning. My name is Dan Bracco. I'm the Industry Rep, and I'm with Roche Diagnostics.

DR. GITTERMAN: I'm Steve Gitterman. I'm the Deputy Director for the Division of Microbiology Devices in the Office of In Vitro Diagnostics and Radiological Health at the Center for Devices and Radiological Health at FDA.

DR. FOLLMANN: I'm Dean Follmann, head of biostatistics at NIAID.

DR. SKATES: Steven Skates. I'm a biostatistician at Massachusetts General Hospital and Harvard Medical School.

DR. MOORE: Tom Moore. I'm an infectious disease physician in Wichita, Kansas, and a clinical professor at the University of Kansas.

DR. JERNIGAN: I'm Dan Jernigan. I'm the Director of the Influenza Division at CDC, and I'm a physician.

DR. PETTI: Cathy Petti. I'm an adult infectious diseases physician and medical microbiologist. I am a Professor of Medicine and Pathology at the University of South Florida Morsani School of Medicine.

DR. BEAVIS: Good morning. I'm Kathleen Beavis. I am a pathologist, and I concentrate in medical microbiology, and I'm the Interim Director of Laboratories at the University of Chicago.

DR. CALIENDO: Thank you, everybody.

If you have not already done so, please sign the attendance sheets on the table by the doors.

Ms. Shanika Craig is our Designated Federal Officer for the Microbiology Devices Panel, and she will be making some introductory comments.

MS. CRAIG: Good morning. I will now read the Conflict of Interest Statement dated November 8th, 2016. FDA Conflict of Interest Disclosure Statement, particular matter involving specific parties, Microbiology Devices Panel of the Medical Devices Advisory Committee, November 10th, 2016.

The Food and Drug Administration is convening today's meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of the Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at U.S. Code 18 Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that the members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under U.S. Code 18 Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is deemed that the Agency's need for a particular individual's services outweighs his or her potential financial conflicts of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened

for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purpose of U.S. Code 18 Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the premarket notification 510(k) submission for a new indication for bioMérieux's VIDAS B·R·A·H·M·S PCT test to add an indication for use as an aid in the antibiotic management of patients with suspected lower respiratory tract infections, and an indication for use as an aid in the antibiotic management of patients being treated with antibiotics for confirmed or documented sepsis or both.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with U.S. Code 18 Section 208.

Mr. Daniel Bracco is serving as an Industry Rep, acting on behalf of all related industry, and is employed by Roche Diagnostics Corporation.

The Agency would like to note for the record that Mr. Ebbing Lautenbach, who is an invited guest speaker with us today, has acknowledged a financial interest in the form of a grant in which an affected firm is a part in.

We would like to remind members and consultants that if the discussion involves any other product or firm that is not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the Panel of any financial relationships that they may have with any firm at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

For the duration of the Microbiology Devices Panel meeting on November 10th, 2016, Drs. Christopher Carpenter, Dean Follmann, Thomas Moore, and Bernhard Wiedermann have been appointed to serve as Temporary Non-Voting Members. For the record, Drs. Carpenter, Moore, and Wiedermann serve as consultants to the Antimicrobial Drugs Advisory Committee in the Center for Drug Evaluation and Research, and Dr. Follmann serves a regular Government employee to the Antimicrobial Drugs Advisory Committee for CDER. These individuals are special Government employees or regular Government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

These appointments was authorized by Dr. Janice Soreth, Acting Associate Commissioner for Special Medical Programs, on November 8th, 2016.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

Before I turn the meeting back over to Dr. Caliendo, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is (410) 974-0947.

Information on purchasing videos for today's meeting can be found on the table in the meeting room.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. Artair Mallett at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and all other electronic devices at this time. Thank you very much.

Dr. Caliendo.

DR. CALIENDO: Okay. Thank you, Shanika.

We're now going to hear a brief introduction from Dr. Kristian Roth.

DR. ROTH: Thank you, Dr. Caliendo.

Thank you. My name is Kris Roth. I am a Branch Chief in the Bacterial Respiratory and Medical Countermeasures Branch in the Division of Microbiology. That's in the Office of In Vitro Diagnostics and Radiological Health, the Center for Devices at the FDA. And I want to just extend to everyone on the Panel and from the public, your time commitment and interest in this meeting, because this is a very important meeting to us for a number of different reasons, and these deliberations and your advice is a critical part of the decision-making process, and your input is highly valued. This is all about public service, and you all have exhibited a very high level of commitment to helping FDA make these decisions. And really, this is how FDA moves forward. It's meetings like this that we ask experts in the field, like yourself, to weigh in on these difficult matters, and it allows us to kind of make these groundbreaking and potentially controversial public health decisions and really impact public health on a national scale.

So, with that, I would like to just kind of focus the discussion here. Today's meeting is about a 510(k) submitted by bioMérieux for expanding the current intended use for

procalcitonin. So the current intended use for this particular peptide, you can see it here. There's that little bit of a preamble discussing what the specimen type is and what the use setting is, but the real meat of the intended use is to aid the risk assessment -- and this was first cleared back in the early 2000s -- is to aid in the risk assessment of critically ill patients on the first day of ICU admission for progression to severe sepsis and septic shock. Just recently, within the past year, another claim was added, and this was for an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with sepsis or septic shock in the ICU or other locations related to the ICU, and this was a change in PCT level over time. So the first indication was a single-point measurement, and the second indication is a change over time.

What we're talking about today is adding two new intended use claims. The first will be an aid in the decision making on antibiotic therapy for patients or outpatients with suspected or confirmed LRTI, and the definition of LRTI is either community-acquired pneumonia (CAP), acute bronchitis, or acute exacerbation of chronic obstructive pulmonary disease (AECOPD); and also to aid in the decision-making process on antibiotic discontinuation for patients with suspected or confirmed sepsis.

Now, this intended use statement does have some legalese in it, and it's there for a good reason. So let's just kind of strip that away and just kind of look at, you know, what is the task at hand today, and really, today we're talking about validation of new claims. Is the submitted evidence sufficient to make a determination of safety and effectiveness for these new claims? And again, for LRTI, it's antibiotic initiation and discontinuation; and for sepsis, it's discontinuation alone. So those are kind of a summation of the new claims, and these will also be covered in great detail in further presentations.

So just briefly: procalcitonin, 10 years since the first FDA clearance, a number of citations in the literature, including a recent IDWeek special symposium discussing the pros

and cons of using PCT in clinical practice. However, despite these efforts, the clinical utility of PCT is subject to diverging opinions. And also this is not the last word on PCT. There are active investigations going forward that we'll also hear about today.

So the topics for discussion are the expansion of the claims for procalcitonin. Also, this is somewhat of a novel and atypical meeting for us. Usually, we have fit-for-purpose studies that are designed and executed to substantiate specific claims. In this case, we're talking about a meta-analysis of current literature to establish new claims, and ultimately the question is, is this approach safety -- is this approach sufficient to determine safety and effectiveness?

Kind of a third goal, maybe, is to discuss the uncertainty which persists even after maybe safety and effectiveness has been determined or not determined. What other kind of mitigating factors could be discussed to put into the labeling or otherwise surrounding the use of procalcitonin for these new claims?

This is a brief outline of the agenda. There will be some presentations by both FDA, industry, and other folks, comments and concerns related to the Sponsor, and then there will be an open public comment, a very active open public comment portion discussing PCT-guided management, and then a Panel discussion and then ultimately, you'll be asked to weigh in on this particular question of PCT-guided management.

I'm sure you have all the detailed agenda with you. And again, thank you again for your commitment to public health and to the Sponsor, bioMérieux, for bringing in this novel and ultimately very interesting 510(k). And also, we have a very large team of FDA participants who have worked very hard on this mission.

And I'll hand it back to you, Dr. Caliendo.

DR. CALIENDO: Thank you, Dr. Roth.

So now we'll hear a presentation from Dr. Ebbing Lautenbach from the Antibacterial

Resistance Leadership Group, or the ARLG, a presentation on Challenges in Studying Rapid Diagnostic Tests in Outpatient Respiratory Tract Infections. At the conclusion of this presentation, there will be time for questions from the Panel.

Take it away.

DR. LAUTENBACH: Great. Thank you, Dr. Caliendo. And thank you for the opportunity to speak here today. Uh-oh, I think I might have messed something up here. How do I advance the slides?

(Pause.)

DR. LAUTENBACH: Got it. So I wanted to organize my presentation today around a couple of areas, first, to talk very briefly about antibiotic use and antibiotic resistance. I'll then spend some time talking about the need for rapid diagnostic tests as an avenue to better inform antibiotic use. I'll spend, then, some time talking about the Antibacterial Resistance Leadership Group's TRAP-LRTI study, and I realize there are a lot of acronyms up here, and I'll describe them all in much more detail coming up. Then I'd like to spend a little bit of time talking about newer methods in the evaluation of antibiotic use trials.

So obviously, the landscape of antibiotic resistance continues to evolve. It's a major problem as evidenced by a recognition from the CARB initiative, from a recent UN assembly, a problem that has been in existence for a good number of years and continues to get worse.

So the number of healthcare-associated infections that are resistant to a first-line therapy and often multi-drug resistant continues to increase. That is also true for community-associated infections as well, all of these resulting in a marked clinical and economic impact, both at the healthcare level and societal.

I think one of the challenges for those of us who do a lot of infection prevention and antibiotic stewardship is that with continued emergence of antibiotic resistance, it's really

resulted in a loss of confidence in our healthcare systems to be able to deal with these issues.

And these are data from the CDC that demonstrate the number of illnesses and deaths estimated to result from antibiotic resistance on the top; and then, obviously, as we talk about the impact of antibiotic overuse, *Clostridium difficile* numbers on the bottom, the numbers of *C. diff* illnesses and number of deaths as a result is demonstrated in CDC data.

So the primary driver, I think most people recognize, of resistance is antibiotic use, and the antibiotic era, now not even 100 years old, continues to demonstrate the pattern of development of new antimicrobials and fairly rapid emergence of resistance to those same antimicrobials. So if the primary driver of resistance is antibiotic use, efforts to better use antibiotics under the construct of antimicrobial stewardship is urgently needed. Antimicrobial stewardship is a concept as programs optimize how we use antibiotics. It's really been primarily focused on the inpatient setting and primarily on large tertiary care settings where there has been demonstrated to be significant improvements in antibiotic use when directed within the confines of a stewardship program.

The question is, recognizing that a lot of antibiotic use happens in the outpatient setting, can we think about efforts to optimize antibiotic use in outpatients in the same way that we've at least had early gains in the inpatient setting?

There are a lot of antibiotics that are used in the outpatient setting, so upwards of 260-plus million courses of outpatient antibiotics. These are now 5-year-old data. A lot in adults, a lot in pediatrics. The studies that have looked at how frequently these courses of antibiotics fall within accepted guidelines suggest that somewhere between 50 and 65% of outpatient antibiotic courses are unnecessary. Most of those are focused on respiratory tract infections, typically bronchitis, sinusitis, things of that nature. And there's a fair amount of variation from prescriber to prescriber. So prescribers who find themselves in

the highest deciles in terms of antibiotic overuse tend to drive a lot of this over-prescribing. That said, across the board, there is a lot of inappropriate antibiotic prescribing in the outpatient setting.

This is the distribution of antimicrobial use by specialty. Not surprisingly, given who mostly sees patients in the outpatient setting, family practice, internal medicine, pediatrics tends to drive this use of antibiotics in the outpatient setting.

And when you look across the United States, there's a fair amount of variability in the rate of antibiotic prescribing per thousand patients, suggesting again that not only is there variability from clinician to clinician, there's also variability from region to region in ways that aren't explained by differences in case mix of patients across providers or across geographic regions.

So with that backdrop, I think there's an urgent need for more -- for better tests to inform antibiotic use in the outpatient setting. It's well recognized, especially historically, that patients who come in with an upper respiratory tract infection, adults or the parents of kids who come in with upper respiratory tract infections, often expect to receive a prescription for an antibiotic as part of that visit.

That said, most clinicians, when surveyed, suggest that at least in their practice, most of the time those cases don't require prescribing. There's been some more work more recently in better defining the attitudes of both patients and their parents and clinicians and their expectations in these sort of interactions that suggests that there are more nuanced aspects of those interactions that aren't just the desire for an antibiotic on the part of the patients, but there's still much that we don't understand about those behavioral dynamics of antibiotic prescribing in the outpatient setting.

But it's impractical oftentimes to think about, in the context of a very busy outpatient practice, spending 20 to 30 minutes explaining to a patient why they don't need

an antibiotic, but rather it's much easier to prescribe antibiotics. And when surveyed, that's often -- those time pressures are cited frequently by physicians as one of the reasons why antibiotics are prescribed often unnecessarily.

So there have been a number of strategies that have been attempted to try to improve antibiotic use in the outpatient setting, and those include benchmarking, in which prescribers are compared against their peers to identify best practices, often using a positive deviance approach identifying those prescribers that do better in terms of prescribing and trying to benchmark for them. There have been a number of educational interventions that have been rolled out and a number of other studies using different aspects of communication skills, training, clinical decision support, and so forth. Most of these have had either no effect or a fairly modest effect, and especially for those interventions that have emphasized educational interventions. When those educational interventions are taken away, typically prescribing goes back to baseline fairly quickly.

So what are the potential roles of rapid diagnostics? If one of the challenges is in the information that's available to clinicians or to patients at the time that they may be seeking or thinking about prescribing an antibiotic, then more information to help inform that decision would seem to be important. And there is some evidence from past diagnostics, rapid strep tests, for example, that have demonstrated the ability of these sorts of tests to inform antibiotic use.

The challenges in developing these tests are that new studies to develop new diagnostics and to test them in the clinical setting are time prohibitive, especially in the context of continued emergence of antibiotic resistance, especially in the outpatient setting. And the development of novel diagnostics is challenging given that when you talk about respiratory tract infections, the ability to come up with a clear microbiologic diagnosis to better distinguish, in a given patient, bacterial versus viral etiologies is often

very challenging, again making the ability to define a gold standard for a new diagnostic test very difficult.

There are really two strategies to think about, or a number of targets to think about, in terms of development of rapid diagnostics. One, which was alluded to in the prior presentation, would be to either inform the decision to initiate therapy or the decision to decrease the duration of therapy. In my estimation, in the landscape of outpatient respiratory tract infections, it's really the decision to initiate therapy that is the most informative. By the time somebody leaves the office, the emergency department with a prescription, the likelihood of informing the cessation of antibiotic use, recognizing that antibiotic durations are often not the lengthiest, at least when compared to the in-hospital setting, the ability to decrease duration, I think, is much less compelling as a way of informing antibiotic use.

Now, the other question is how do you potentially target this? So do you emphasize the ability to distinguish bacterial from viral or non-infectious causes as a way of informing antibiotic use, or do you focus on identification of the organism? Given the fact that we recognize that most acute respiratory infections in the outpatient setting are viral in nature, in my opinion, the ability to distinguish bacterial causes from non-bacterial or non-infectious causes likely has the most upside in informing antibiotic use because that's really the decision point the clinicians are making in the outpatient setting.

To get back to the notion of diagnostic uncertainty, these are data, and these have been -- there are other studies that have shown the same thing, but I'll use this as an example. These are data from the CDC's EPIC study that focused on the conducted population-based surveillance to look at community-acquired pneumonia to determine how often a true pathogen diagnosis could be made with a robust approach to culturing, serologic testing, molecular approaches to identify the causative pathogen. And even with

this robust approach, which is not all what typically happens in the outpatient setting, pathogens were identified only 38% of the time. So again, this is the landscape in which one would think about developing a novel diagnostic when you only have, even with the best approaches available, the ability to diagnose a pathogen 38% of the time. The ability to then use those data to construct a gold standard against which a diagnostic would be based would be incredibly challenging.

So let me now talk about the TRAP-LRTI study as one that is going to be getting under way shortly, which addresses some of these issues, but I think also points out the complex nature of doing these sorts of studies because this is a study that has not started yet and will take several years to complete.

By way of background, since I'm representing the Antibacterial Resistance Leadership Group, I'll tell you a little bit about that for those who may be less familiar with it. The ARLG is an NIAID-funded collaborative that is based at Duke University and is co-led as co-PIs by Vance Fowler at Duke and Chip Chambers at UCSF, the goal of which is really to conduct transformative trials addressing the problem of antibiotic resistance, trials that couldn't otherwise be done.

And there are several focus areas for ARLG, and they focus on multi-drug resistant gram-negatives, multi-drug resistant gram-positives, antibiotic stewardship and infection prevention, and diagnostics and devices. And again, within each of these areas, the focus is on identifying novel strategies to inform efforts to curtail antibiotic resistance. So for purposes of the discussion today, this really falls within two categories: diagnostics and devices, and antimicrobial stewardship and infection prevention. There are several other special emphasis panels within ARLG that focus on pediatrics, pharmacokinetics, and other special populations, mostly immunocompromised patient populations.

So the TRAP-LRTI study: TRAP-LRTI is targeted reduction of antibiotics using

procalcitonin in outpatients for suspected lower respiratory tract infection, is a joint collaboration between NIAID, ARLG, and bioMérieux.

The overall goal of this study is to identify a patient population in which there's no clear benefit of antibacterial therapy in the outpatient setting, and I'll tell you briefly the way that this study is set up.

So this is a randomized, placebo-controlled, double-blind, non-inferiority trial that compares azithromycin to placebo. Operationally, the way that it works is that adults present as outpatients with a suspected LRTI, and under screening on this slide, you see the characteristics of both symptoms and vital signs that would get you into the study. When patients present meeting criteria for LRTI, if they choose to enroll, a procalcitonin level is sent. If that procalcitonin is less than 0.1, patients would be considered eligible for this study and would then be randomized to azithromycin versus placebo. This is being conducted at a number of sites shown here.

I think I've actually talked about this already, so in the interest of time I'll move on from this slide.

There are several times during which outcomes are going to be assessed, and the primary outcome is at Day 5, in which there's an assessment of the initial presenting signs and symptoms that originally got the patient into the study, an assessment of clinical improvement at that point. There's also follow-up, and that's done both in person and via phone. There's also a telephone follow-up at Day 3, a telephone follow-up at Day 11 and Day 28, all of those seeking not only to look at resolution of clinical signs and symptoms but also other important endpoints, so a return to a physician's office, return to an emergency department and so forth.

The primary objective here is really to determine, within this patient population defined by a procalcitonin level of less than 0.1, how do patients who receive azithromycin

versus placebo compare, and again using a non-inferiority approach with the hypothesis being that the outcomes in people who don't receive an antibiotic therapy are going to be comparable or non-inferior to those who do.

There are several secondary study objectives, as I described before, so antibiotic use, recognizing that not only are people getting the antibiotics that are dictated by the trial but may, in fact, get other antibiotics subsequently as well, depending on the progression of their clinical signs and symptoms, return visits to a physician's office, emergency department visits, and so forth.

As part of this trial, though it's not the primary assessment of outcomes, we'll be using some novel methods, which I'll describe in the subsequent slides, that will use a superiority approach that I think will give us some really valuable information in this study.

So we plan to enroll about 420 patients in the study with the non-inferiority margin of 12.5% in comparing the two groups. We'll do both the intention-to-treat analysis and a per-protocol analysis.

So let me talk about the DOOR and RADAR methods, and I will wrap it up with this. So these are the novel approaches that we'll be employing as part of the TRAP-LRTI study, as a secondary approach to evaluating the outcomes. And before I describe what DOOR and RADAR are, let me tell you sort of how these evolved. And before I do this, let me say that the brains behind the operation of development of the novel methods is Scott Evans, who's at Harvard, so I want to make sure that they understand that these are really -- this is really his work in thinking very carefully about how we've done antibiotic use trials in the past and how we might think about doing them differently to address exactly the issues that I'll bring up here.

So there's often an issue of competing risks when we compare one strategy to another. We're certainly interested in decreasing antibiotic use, but we don't want to do

that at the expense of clinical outcomes. So in people who die -- as an extreme example, in people who die early, they're going to use fewer antibiotics than people who survive. That's not what we're looking to do in any trial. So there really is an issue of competing risk and a lot of important things to consider beyond antibiotic use. And these can be challenging when you look at these outcomes separately in clinical trials.

There are also well-recognized issues with non-inferiority studies. There are inherent biases and potential manipulation of data that can occur in non-inferiority studies that superiority studies are less susceptible to. There's also the question of how you define the non-inferiority margin, who you select as a control group, and whether, in fact, that control group, given advances in medical care, may change over time.

Finally, there's a question of individual versus group assessment. So in any trial, you look to see what the risks and benefits are of the potential therapies. What often isn't answered is, is that the same group of people who are getting both the benefit and the adverse events, or are they different groups? And the approach, if you look at it in that way, can be very different. So if there's a certain subset of the study population that's getting all the benefit and none of the adverse events, then the approach would be to better define who that patient population is and limit the therapy to them. If it's the same group of people who tend to be getting the benefits and the risks, then it really becomes a risk-benefit decision in treating those patients.

So let me describe, very briefly to wrap up, the DOOR and RADAR methodologies. So DOOR stands for Desirability of Outcome Ranking, and as Scott has designed these methods, what this really does is to rank trial participants based on their overall outcome, and it's really the designation of an ordinal scale in which you define potential clinical outcomes. The example here is that you have a particular therapy, and you look at whether the patient had clinical benefit without any adverse events. That would be the best.

Clinical benefit with some adverse events, that's not quite as good but still okay. Worse than that would be at least you survived but you had no clinical benefit or adverse events. Even worse, you survive but you had no clinical benefit and you had adverse events. And the worst would be death. And again, depending on sort of what the study question is that you're looking at, there needs to be a very careful discussion and delineation of exactly how this ordinal ranking is designated, and there has to obviously be consensus that these are designations that make sense.

RADAR is really one component of DOOR. So RADAR standards for Response Adjusted for Duration of Antibiotic Risk, and this really now looks not only at clinical outcomes but also at antibiotic use outcomes. So within each of those clinical categories that I defined on the slide previously, what was the antibiotic use for those patients in that category? So clinical outcome is always going to trump antibiotic use. So if you do worse by categorization of clinical outcomes but you use fewer antibiotics, that's not good. But within each clinical category, those who used fewer antibiotics are going to be ranked higher than those who used a greater number of antibiotics.

And the idea behind this approach is to say let's take into account -- back to the notion of competing risks, let's take into account both the clinical outcomes and the antibiotic use outcomes, include those as part of an ordinal outcome, compare the proportion or the ranking of patients in one group versus the other to really get a more complete picture of exactly what happened to these patients. Typically, this is volume of antibiotic use when, at least in its limited history so far, that's been used; but it could also look at various other components of antibiotic use, broad versus narrow spectrum, oral versus intravenous and so forth. But I think this really -- although still very early on in its development and use, I think this really offers a very novel strategy for thinking about how we might consider doing antibiotic use trials and evaluating them in the future.

And I think I've already talked about all of this as part of the prior slide.

So let me conclude by emphasizing that resistance continues to be an important problem that's driven by antibiotic use. Much of the antibiotic use in the outpatient setting, especially when focused on respiratory tract infections, is inappropriate. And I will argue that the interventions that have been used so far, typically educational interventions, haven't worked in really moving the needle considerably in decreasing the rates of inappropriate antibiotic use. So strategies to use greater data, better diagnostics, or to use diagnostics to help inform these decisions in the outpatient setting, I think, are urgently needed. And I think novel methods, as I've described, developed by Scott, I think will help us as we do further studies to evaluate these interventions.

Let me stop there, and I'm happy to take questions.

DR. CALIENDO: So I'd like to thank Dr. Lautenbach for his presentation.

Does anyone on the Panel have a brief clarifying question? Remember that you will also have time to ask questions during our Panel deliberations. So I'm going to open it up for questions.

DR. FOLLMANN: You didn't really address this directly --

DR. CALIENDO: When you speak, please introduce yourself.

DR. FOLLMANN: Oh, yeah. I'm Dean Follmann.

You didn't really address this directly in your presentation, but in the materials there was talk about an ARLG-guided use trial where you compare use of PCT to guide therapy versus, I guess, usual care. Are you going to discuss that? Are there any details about that trial you want to go over today, or is that sort of not on the table?

DR. LAUTENBACH: So the only ARLG study that's focusing on procalcitonin is the one that I described here, which is using procalcitonin to define the patient population in which we evaluate placebo versus antibiotic.

DR. FOLLMANN: Just a comment about this: I like this trial because it's comparing placebo versus a drug. Some of these use trials will compare Strategy A versus usual care, and with Strategy A versus usual care, patients in both arms can both receive drugs, so it's not such a pure, clean comparison because some in both arms are getting the same intervention.

DR. LAUTENBACH: If I can comment on that, I think the other challenge of those is that it very much depends on the local prescribing culture of the institutions in which it's done and whether they have a robust stewardship infrastructure or not. I think those have been the challenges of those studies that have been done in the past.

DR. CALIENDO: Go ahead, Tom.

DR. MOORE: Yeah. So a question about the --

(Off microphone comment.)

DR. MOORE: I'm sorry. This is Tom Moore. That's a habit I'm going to have to get into. I'm sorry.

With regard to the study that's being executed at Baylor, what's the turnaround time on it? Just a practical question, what's the turnaround time on the procalcitonin assay? I presume it's at the point of care. But my point is there's a tremendous amount of antibiotic use and frankly misuse in my state, and it depends on where you are. And this is true for a lot of states in the Midwest, where you are, whether you're rural versus urban. But anyway --

DR. LAUTENBACH: Yeah, so great points. So the turnaround time designated in the trial is 2 hours or less, so it is a point-of-care test. And I agree with you, one of the challenges in an emergency department, in particular, is they want to make the decision on what to do with the patient, you know, as quickly as possible. And so having a test that requires a significant amount of time, I think, would've been a non-starter, and ultimately it

would have been a non-starter for the trial, it would be a non-starter for implementing this. And so I think that's key.

DR. CALIENDO: Go ahead, Tom.

MR. SIMON: Tom Simon.

Did I understand you to say that in an outpatient setting, that the relationship of the physician and the patient and the time allowed is basically the biggest problem with prescribing antibiotics?

DR. LAUTENBACH: I think there are a lot of problems with how antibiotics are prescribed in the outpatient setting. So I think time is one. So as there's an emphasis to try to see patients, especially in large academic centers, as quickly as possible, I think the challenges for clinicians are it takes longer to explain to a patient or to a parent why they don't need an antibiotic than it does to write a script, and that's, I think, been pretty well documented in a variety of studies.

I think the other challenges are that there is -- there's really no objective data. When somebody comes in with a respiratory tract infection, unlike, for example, rapid strep tests, there's no objective information that a clinician can point to and say here's why I believe you don't have a bacterial infection and you don't need an antibiotic, and I think that could go a long way to better informing those sort of discussions.

I think there's a lot of interesting work that's being done in better understanding sort of the socio-behavioral determinants of how both patients and physicians go into these relationships with -- we've typically thought that patients go in demanding antibiotics and they're upset if they don't get antibiotics and perhaps they'll go see another physician, which is another potential driver of inappropriate prescribing. It turns out that when more recent studies have been done, what patients are really looking for is information; they want to know what the physician thinks and what he or she recommends in terms of their

therapy. But again, those sort of discussions, especially in the absence of any objective information, take time. And so it's not necessarily the patients or parents are demanding antibiotics, but they want to know, if they're not getting an antibiotic, why.

MS. BERNEY: Barbara Berney.

I understand all of what you just said, but supposing I just go to my doctor, who may not be -- may or may not be part of a larger clinic and is affiliated with a health system, as is my case. If you are not done in 5 minutes, they be done, okay? So supposing they decide to do some sort of test. First of all, if you are an independent practitioner, a solo practitioner, are you going to have this in your office? It's a lot of equipment, and it's an expense. Plus it takes a lot of time. Is the patient going to sit for 2 hours waiting to find out whether they need it or not? These are just questions I have. I understand why this would be great in a large clinical setting. I'm having a lot of difficulty understanding how this can apply to solo practitioners or small groups.

DR. LAUTENBACH: Yeah, I think those are great questions and are probably more sort of operational questions. If the general notion is that this is an approach that makes sense, I think those are exactly the right questions to be asking. So maybe this makes sense in an emergency department setting or in a large multi-practice group, and it has a lot to do with the infrastructure to be able to bring something like this on board and how quickly it would take to turn around the test result. So 2 hours. Depending on the setting in which you're practicing, maybe 2 hours is too long. But I think those are operational questions that I think are really important.

MS. BERNEY: Trust me, 2 hours is too long to sit around waiting when you're sick.

DR. LAUTENBACH: Yeah. So I would agree that in the -- you know, in the outpatient practice setting, that's a long time. I think the TRAP-LRTI study is being done primarily in the emergency department setting where I think, for right or wrong, patients tend to sit

around for a little bit longer. But I would agree with you that the ability to make these decisions as quickly as possible and to have information back as quickly as possible would be key.

DR. CARPENTER: Chris Carpenter, Beaumont Health.

Just if you could comment on a couple of things: One is the threshold of Point 1 that was used -- is going to be used for the study and why that decision was made, and then the second is the choice of azithromycin as the comparator arm to no antibiotic. And obviously, there are issues with resistance there; there's anti-inflammatory activities with azithromycin that may muddy the water, so to speak.

DR. LAUTENBACH: Yeah. So let me handle the second question first, because I've temporarily forgotten the first one. So the choice of the comparator we spent a long time thinking about, and we wanted a drug that is in general use, that's used frequently for these sorts of indications, that has a well-recognized efficacy and safety profile. We shied away from fluoroquinolones for obvious reasons and ended up deciding that, you know, based on sort of consensus discussion within ARLG, that azithromycin made the most sense, recognizing that there is emerging resistance to azithromycin. Exactly what the clinical implications of the resistance is, I think, remain somewhat less clear, but I think that was the -- that seemed to be -- at least in terms of current practice of use of antibiotics, tended to be the one which we felt had the most face validity. And now I've forgotten the first question.

DR. CARPENTER: Chris Carpenter again. I'll clarify.

So the threshold of Point 1 -- and I'm just wondering, epidemiologically in this population, are most of these people with values below 0.1, because obviously inpatient, the studies look at 0.25 and above that for suggesting bacterial infection.

DR. LAUTENBACH: Yeah. So I mean, as you know, there have, both in the outpatient

literature and in the sepsis literature, been all kinds of different thresholds used. So we wanted to use a very conservative threshold of 0.1 to really identify that population of patients that we really felt would be of very little likelihood of having a bacterial infection. Even if you look at data, both published and unpublished, in people who have what clinically would be described as community-acquired pneumonia, many of them have levels that are well below 0.25 and 0.1 as well, suggesting that perhaps much of what we're treating is community-acquired pneumonia, which I think would be a much harder sell in a study like this. Many of those people probably don't have bacterial infections either, especially for this population.

And I should have clarified, in case it wasn't clear. People who have what's identified by the treating clinician to likely be community-acquired pneumonia wouldn't be included in the TRAP-LRTI study because we felt that that would be a slightly sicker patient population that certainly, as a first pass, wouldn't be the one that we would focus on.

DR. CALIENDO: So Angie Caliendo.

Ebb, are you going to enroll older people, people with chronic kidney disease, people who you might expect to have an elevated procalcitonin level at baseline, or are they going to be excluded?

DR. LAUTENBACH: Yeah, people in whom -- and these are actually still discussions that we're having currently. People in whom there is some evidence that procalcitonin levels may not be the most reliable or may be elevated simply because of their underlying diseases would be excluded from this.

DR. SKATES: Steven Skates.

This trial uses PCT as an eligibility criteria. In terms of assessing whether PCT is helpful or not with managing antibiotic use, shouldn't there be a comparison with PCT and without PCT to look at that contrast and an endpoint of antibiotic use and safety?

DR. LAUTENBACH: Yeah. So I think those are sort of the two, you know, types of trials to envision. Those are much more consistent with the European literature, in which there has been sort of the usual care arm in which procalcitonin isn't involved in the decision-making process, and a procalcitonin arm in which somebody who presents has procalcitonin measured and, based on an algorithm that's defined as part of the study, either has antibiotics initiated or not initiated. I think the challenges with that, as Dr. Follmann, I think, highlighted earlier, are that that not only assesses the impact of procalcitonin, it also assesses the prescribing culture of the institution in which you're studying and also incorporates some sense of antibiotic stewardship, depending on sort of how well established that is at the institution or not.

What we really chose to do as part of this one is take out those sort of elements of what already exists in terms of antibiotic prescribing practice or stewardship at the intervention to really use procalcitonin not to inform therapy, but rather to define a patient population that, based on the randomized controlled trial, we believe doesn't require antibiotics. So it's slightly nuanced differences, but I think important ones.

DR. SKATES: So it's Steven Skates again.

What is the logic, then, for saying PCT is helpful with this setting, clinical setting? What's the contrast here that you're going to end up highlighting to show that PCT is useful?

DR. LAUTENBACH: So I think the goal of this trial is to say we are using this trial to identify a certain subset of patients who have procalcitonin of less than 0.1, who come in with LRTI signs and symptoms. If the RCT demonstrates what we hypothesize and shows that people who get azithromycin do no better or do -- or at least the non-inferiority criteria are met, suggesting that people -- there's no difference whether you get an antibiotic or not, that then the implications, I think, are that procalcitonin can be used to define a

patient population in which antibiotics are needed.

DR. PETTI: Cathy Petti.

Dr. Lautenbach, thank you very much. I very much appreciate your expertise. I realize in the interest of time you didn't go into deep details about case definitions for LRTI and perhaps absence of other symptoms. But as a diagnostician, I'm very curious, when we're trying to determine the added value of procalcitonin, how you will manage the use of other diagnostic tests that would perhaps give you the diagnosis within 2 hours.

DR. LAUTENBACH: You mean standard sort of diagnostic tests like chest x-ray or things of --

DR. PETTI: Influenza, you know, PCR. There are a lot of point-of-care tests that are currently available or soon will be that are CLIA waived and used in the outpatient setting, and in order, again, to determine the added value of procalcitonin, I think knowing your thoughts on that would be very helpful.

DR. LAUTENBACH: Sure. The evaluation of the patient that's seen in the outpatient setting for LRTI will be up to the caring clinician. And so whatever they choose to send, they may send them for a chest film, they may send them for a white count, they may do a flu test depending on the season, that would all be part of the clinician's evaluation of that patient. And so the expectation is that these are patients in whom the clinician is considering use of antibacterials.

And so procalcitonin really becomes -- let's say a patient, at least when they're initially seen, has a procalcitonin that's sent and we don't know the value of it yet, they also get sent for a chest film which shows a lobar infiltrate. The clinician at that point says you know what, I think this person's got community-acquired pneumonia, I don't feel comfortable randomizing them to a trial in which they may not get antibiotics, so they would be out of the trial. And the same thing would happen if, let's say, there's a rapid flu

test that shows -- that suggests influenza, in which case the clinician could at that point say this isn't somebody that I would choose to randomize to the trial.

DR. CALIENDO: All right, I think -- I'm sorry, one more question. Okay, this will be our last. Go ahead.

DR. BEAVIS: Kathleen Beavis.

I'm a little confused about the entry point in terms of consent for the study. You mentioned that it's patients who are included who have less than 0.1 ng/mL for procalcitonin, but can I assume they're going to be consented and informed about the study before the level is drawn and a test sent?

DR. LAUTENBACH: That's correct.

DR. BEAVIS: Thank you.

DR. CALIENDO: Thank you. This has been very helpful. I'm sure we'll have more questions for you later in the day.

DR. LAUTENBACH: Great, thank you.

DR. CALIENDO: So we're going to move on now to hear a presentation from bioMérieux, and at the conclusion of the presentation, and there's going to be a series of them, we'll have time again for some questions. So we're going to hear from Dr. Mark Miller, who's the Chief Medical Officer of bioMérieux; followed by Dr. Sam Bozzette, who's the Vice President of Medical Affairs-Americas for bioMérieux; Noam Kirson, the Vice President for the Analytics Group; and Philipp Schwartz or Schuetz, sorry, Chief Physician of Endocrinology and Internal Medicine at the University of Basel.

So, Dr. Miller, please start us off.

DR. MILLER: Good morning. My name is Mark Miller, and I'm the Chief Medical Officer at bioMérieux, a global company that is 100% dedicated to diagnostics. I am a board-certified internist with subspecialty training in infectious disease, microbiology, and

epidemiology. I would like to thank the FDA and the Advisory Committee for your time to discuss the urgent need for biomarkers to aid clinicians in the appropriate use of antibiotics and to help reduce antibiotic resistance. Today we will present one of these biomarkers, procalcitonin, or PCT, and its value in improving patient care and promoting the appropriate use of antibiotics without compromising patient safety. We will begin today's presentation with a brief discussion of antibiotic misuse and the global crisis of antimicrobial resistance. We will then describe our procalcitonin assay, the VIDAS B·R·A·H·M·S PCT, and its two current FDA-cleared indications. And then we will discuss two proposed uses for this biomarker and the meta-analyses which were used to assess and support these claims.

Today we are discussing what has become one of the most serious and growing threats to U.S. and global public health: the overuse of antibiotics, including inappropriate initiation and prolonged use. This misuse poses a safety risk to patients and has contributed to the rise of antibiotic resistance both here in the United States and elsewhere in the world, a crisis that the CDC links to the cause of 2 million illnesses and approximately 23,000 deaths each year here in the United States alone. This has become such a serious problem that many countries, as well as the United Nations, have recently convened high-level meetings to draw attention to the matter and to brainstorm for solutions.

However, properly diagnosing a bacterial infection that would require an antibiotic is a difficult task. Diagnosing bacterial infections is often performed using cultures, which can take 2 to 3 days or more. These cultures often give false negative results. As well, they may not differentiate colonization from infection, leading to false positive results.

Clinicians and patients themselves need faster, more accurate indicators of the presence of a bacterial infection in order to make critical antibiotic decisions. Giving the right antibiotic to the right patient at the right time is at the heart of antimicrobial stewardship, and appropriate diagnostic tests can help achieve this objective.

To put this in perspective, out of the 69 million prescriptions for acute respiratory conditions annually in the United States, 34.3 million of these prescriptions, or 50%, are unnecessary because a bacterial infection is not the cause.

As essential as antibiotics are in fighting true bacterial infections, when used inappropriately, they carry all of the risks of an antibiotic but without any of the benefits. Unnecessary exposure to antibiotics is associated with side effects and toxicity, such as allergic reactions, diarrhea, and other intestinal problems; collateral damage such as *Clostridium difficile* infections, which have significant morbidity and mortality; the induction of antibiotic resistance, which may produce multi-drug resistant bacteria with few treatment options; and the subsequent propagation of drug-resistant pathogens within the hospitals and into the community at large.

The increasing number of drug-resistant infections such as MRSA, VRE, and CRE are associated with more serious illness and disability, a higher death rate compared to antibiotic-susceptible infections, the need for more complex therapeutic options, which are often more toxic, and extended hospitalizations.

Today we are here to present the data that demonstrates the safety and effectiveness of the VIDAS B·R·A·H·M·S PCT assay as a tool to guide the appropriate use of antibiotics in two specific common clinical syndromes.

The first is the use of the VIDAS B·R·A·H·M·S PCT assay to assist in whether to start and when to stop antibiotics in patients with suspected lower respiratory tract infection. The second is the use of the VIDAS B·R·A·H·M·S PCT assay to assist in deciding when to stop antibiotics in patients diagnosed with suspected sepsis.

In order to illustrate these clinical challenges, let's look at two actual patient examples where symptoms, signs, and usual lab tests were not sufficient to guide antibiotic treatment decisions.

First, let's consider a 78-year-old male who arrived in the emergency room complaining of fever, cough, and chest pain. On examination, he was found to have a low-grade fever, abnormal chest sounds, a slightly elevated white cell count, and an abnormality on the right side of his chest x-ray. The clinician is suspecting a community-acquired pneumonia, but the clinical characteristics are not specific and cannot definitively determine whether he, in fact, has an infection. And if he is indeed infected, it is unclear if the cause is bacterial or viral and if he requires an antibiotic. A reliable diagnostic tool is needed to help the clinician in this decision making. Often in these cases, physicians will prescribe antibiotics just in case.

Now, let us look at someone with suspected sepsis. Rapid initiation of antibiotics is recommended by current sepsis guidelines; however, the timing of antibiotic discontinuation is much less clear. Here is a case of a 50-year-old female with a history of mild heart failure who was admitted to the intensive care unit with shock of undetermined origin. On exam, she was also found to have fever and the presence of multiple lung abnormalities on an x-ray and CAT scan of her chest. She was diagnosed with probable sepsis from pneumonia, but heart failure and sepsis from another source were also possibilities. The patient was started on antibiotics and placed on mechanical ventilation. Routine cultures and diagnostic tests did not reveal the source of her condition, as is frequently the case unfortunately. For her, it remains unclear if she is benefiting at all from antibiotic treatment and when it can be safely discontinued.

In both of these cases, a reliable biomarker of bacterial infection would provide additional valuable information for making rational antibiotic treatment decisions.

Based on these two serious needs highlighted by actual patient examples, we are here to discuss the bioMérieux VIDAS B·R·A·H·M·S PCT assay and its role in helping to guide appropriate antibiotic use. At the present time, there are two FDA-cleared uses for this

assay. Firstly, it is intended to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock. Additionally, it is used to aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock, using a change in the PCT levels over time.

In our presentation, we will review scientific documentation that the VIDAS B·R·A·H·M·S PCT assay can be used safely and effectively for two new proposed indications. The first new proposed indication is the following: Used in conjunction with other laboratory findings and clinical assessments, VIDAS B·R·A·H·M·S PCT aids in decision making on antibiotic therapy for inpatients or outpatients with suspected or confirmed lower respiratory tract infections defined as community-acquired pneumonia, acute bronchitis, and acute exacerbation of COPD.

The second new proposed indication is the following: Used in conjunction with other laboratory findings and clinical assessments, VIDAS B·R·A·H·M·S PCT aids in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

For the purposes of this entire presentation, we will be referring to each of these conditions respectively as simply LRTI and sepsis.

In the last decade, nearly two dozen randomized controlled trials have evaluated the safety and effectiveness of PCT guidance for antibiotic therapy for LRTI and sepsis. Given the wealth of existing scientific evidence, bioMérieux worked through interactive discussions with the FDA to develop a comprehensive evaluation of the published literature and meta-analyses to support the two new proposed indications for use. We reviewed with the FDA the details of our plan to conduct rigorous meta-analyses with a goal to determine whether antibiotics could be safely reduced in these two conditions without compromising patient safety. We are here today to present these results.

In our presentation, we will review the biology of procalcitonin, or PCT, and its role

as a host response biomarker whose production by the body is stimulated by the presence of a bacterial infection. We will then present results from our meta-analyses showing that for patients with two common clinical conditions, suspected or confirmed LRTI and suspected or confirmed sepsis, PCT-guided treatment decisions can reduce antibiotic use without any compromise in patient safety. We will close with a benefit-risk analysis that will summarize the clinical evidence supporting the benefits of the VIDAS B·R·A·H·M·S PCT test in improving the appropriate use of antibiotics with no additional risk.

Turning now to our agenda, Dr. Sam Bozzette, bioMérieux's Vice President of Medical Affairs, will discuss the biology and diagnostic utility of procalcitonin, or PCT. Dr. Noam Kirson, Vice President of the Analysis Group in Boston, will describe the methods of our multiple in-depth analyses. Dr. Philipp Schuetz, Chief Physician of Endocrinology and Internal Medicine at the University of Basel and a leader in the field of infectious disease, will present the findings of both the study- and patient-level analyses of PCT-guided therapy in both LRTI and sepsis. Finally, I will conclude with an overview of the positive benefit-risk profile of PCT-guided therapy in these two conditions. Dr. Bozzette will then return to moderate the question and answer period.

All external experts and speakers have been compensated for their time and travel expenses for today's meeting.

And I will now invite Dr. Bozzette to the podium.

DR. BOZZETTE: Good morning. My name is Sam Bozzette. In addition to my role at bioMérieux, I am a member of the American College of Physicians and of the Infectious Diseases Society of America and the Association of American Physicians. This portion of our presentation will focus on the use of PCT as a diagnostic tool.

Procalcitonin, a precursor of the hormone calcitonin, is a host response biomarker that is stimulated by the presence of bacterial infection. In the C cells of the thyroid gland,

PCT is produced and converted to calcitonin under endocrine control. It is also produced at low levels by neuroendocrine cells around the body. As a consequence, most healthy people have measurable concentrations of PCT, but these are less than 0.05 ng/mL. Bacterial infection stimulates the production of PCT in essentially any tissue. This results in concentrations that are typically above 0.25 ng/mL and can rise 1,000-fold in patients with septic shock.

PCT levels are significantly higher in influenza patients with bacterial co-infection. In these box-and-whisker plots, the median value is shown by the black line within the boxes. As we see on the left, patients with only viral infection had much lower PCT levels than patients with microbiologically confirmed bacterial co-infection, seen on the right.

Now, to assist in decision making, a biomarker should increase rapidly following bacterial insult and decline as the patient continues to improve. PCT has just these properties.

This graph shows PCT concentrations from the unfortunate case of a 76-year-old woman who developed sepsis after accidentally receiving an *Acinetobacter*-contaminated infusion. Her PCT levels rose dramatically in the first few hours after infection. But after control of infection, her PCT levels concentrated -- PCT concentrations, pardon me, declined with a half-life of about 23 hours. This is consistent with what we see in general. PCT levels rise within 4 to 6 hours of a bacterial insult and decline with a half-life of about 24 hours after control of infection.

PCT levels correlate with disease severity. This graph shows that even on a log scale, the progressive rise in median values is obvious, with the median in septic shock, the box on the far right, being more than 10 times higher than in the systemic inflammatory response syndrome seen on the far left. Such data underpin our existing intended uses and aid in the risk assessment of critically ill patients. Indeed, it has been shown that patients with

suspected sepsis and lower levels of PCT are at much lower risk for severe sepsis or septic shock.

Changes in PCT have prognostic significance. This graph depicts data from a 13-center U.S. study of patients admitted to the ICU with sepsis. Patients whose PCT levels did not drop by more than 80% at 4 days, represented by the red line, had a twofold higher risk of death at 28 days than patients who did have an 80% drop, represented by the black line. These data are the basis for our existing intended uses and aid in assessing the risk of mortality and sepsis. These findings also have implications for our proposed intended uses and aid to decision making on antibiotic discontinuation in sepsis.

PCT adds unique information to clinical judgment. On this ROC curve, higher into the left is better. It shows that PCT plus clinical judgment, the blue line, is superior in the diagnosis of sepsis than a clinical model alone, the orange line. However, even when used alone, which is not our recommendation, PCT levels have a high negative predictive value, or NPV. The NPV is the probability that a condition is absent given a negative test, and this is something you're going to want to be confident of if you are going to withhold antibiotics.

For example, Rodriguez found an NPV of 92% for confirmed bacterial co-infection in flu patients. This means one can be 92% confident that co-infection is absent based on the PCT level alone. And Stolz found an NPV of 94% for LRTI clinically requiring antibiotics, meaning one can be 94% confident that a need for antibiotics is absent based on the PCT level alone.

However, PCT is an aid to clinical judgment, not a substitute. Accordingly, the bioMérieux antibiotic management algorithms have two components: First, they incorporate guidance based on PCT levels; second, the algorithms incorporate clinical judgment such as close monitoring of patients with severe pneumonia. The result is improved antibiotic decision making.

So now let me show you our algorithms, starting with the PCT component. The PCT cutoffs are based on the most common cutpoints used in clinical trials as well as in clinical practice. For the initiation of antibiotics in LRTI, antibiotics are strongly discouraged for PCT levels less than 0.1 ng/mL and discouraged for levels between 0.1 and 0.25. Antibiotics are encouraged for PCT levels between 0.26 and 0.5 and strongly encouraged for levels above 0.5. The clinical guidance that is integral to the algorithm provides context and acts as a safety measure.

For inpatients, we recommend repeating a PCT determination within 6 to 24 hours and regularly thereafter as needed. For outpatients, we also recommend reassessing if symptoms persist or worsen. In all cases, we recommend that antibiotic therapy be considered regardless of PCT level if the clinical context indicates that this is warranted. This could, for example, be a patient with a local infection that is not severe enough to raise PCT levels.

For patients who have initiated antibiotics, follow-up determination should be made at regular intervals and antibiotic therapy adjusted using the following guidance: For patients with LRTI, the algorithm recommends that antibiotics are discontinued once PCT drops to below 0.25 ng/mL or lower, or drops by more than 80% from peak. For patients with sepsis, the algorithm recommends that antibiotics are discontinued once PCT levels drop to 0.5 ng/mL or lower, or drops more than 80% from peak.

The discontinuation algorithms also incorporate clinical guidance. We recommend that continuing therapy be considered if clinical instability or disease progression are present and that treatment value be considered if PCT levels remain high.

The diagnostic utility of PCT has led to wide use since the first test became available 10 years ago. It is estimated that about 50% of U.S. acute care hospitals already use PCT. Moreover, PCT guidance is already incorporated into several international treatment

guidelines and in clinical practice in several U.S. healthcare systems.

More than 36 million PCT determinations were performed worldwide in 2015, and indeed, the VIDAS B·R·A·H·M·S PCT is used around the world. It is an automated and individual test used on the VIDAS family of instruments. The assay takes 20 minutes to run. The device has two components: the VIDAS B·R·A·H·M·S PCT kit and the VIDAS instruments. These automatically perform all the steps of the enzyme-linked fluorescent immunoassay.

Performed on serum or lithium heparin plasma, the VIDAS PCT assay produces accurate results. The assay has a detection limit of 0.03 ng/mL and a quantitative linear range of 0.05 to 200 ng/mL.

In summary, PCT is a useful and reliable biomarker for detecting bacterial infection. Levels rise rapidly after bacterial insult, decline rapidly with controlled infection, and correlate with severity of disease. PCT is an effective aid in assessing the risk of disease progression and prognosis.

PCT has a high negative predictive value for bacterial infection and adds unique information to clinical judgment. These factors make PCT a useful tool for antibiotic decision making. In fact, the use of PCT guidance is widely accepted and cited in international treatment guidelines. And we have demonstrated that the VIDAS system measures PCT levels with accuracy and precision.

Now that we have fully described PCT as a biomarker for bacterial infection, we'll move into the results of our extensive meta-analysis on the safety and effectiveness of PCT-guided therapy. We'll begin with Dr. Noam Kirson, who will review the methods of the meta-analyses.

DR. KIRSON: Good morning. My name is Noam Kirson, and I am a consultant with the Analysis Group. I am a Ph.D. health economist with advanced training in statistics.

The Analysis Group worked with bioMérieux in the development and execution of

the study-level meta-analyses which will be presented here today. My presentation will describe the methodology used in both the patient-level and study-level literature reviews and meta-analyses.

bioMérieux worked closely with the FDA to develop the meta-analysis approach to evaluate safety and effectiveness of PCT-guided therapy compared to standard of care in patients with LRTI or sepsis.

The two primary goals of these meta-analyses were to evaluate the extent of reduction in antibiotic use, as well as evaluate the potential impact of PCT guidance on the safety outcomes.

As meta-analysis methods may be less familiar to some, let me provide a short introduction. Meta-analysis is a quantitative tool that summarizes the state of the published literature for a particular intervention. By combining the results of multiple randomized controlled trials, meta-analyses provide greater precision in estimating effects than individual trials. Since different randomized clinical trials may vary in key clinical factors, their outcomes will also vary. The idea, then, is to leverage that variation to best capture an intervention's effect.

At the study level, a meta-analysis essentially averages the effect of an intervention across studies, accounting for within- and between-study variability. A related issue is how to interpret the variation across studies. We accounted for the variation by using a random effects model. Different researchers, different settings, different patients, or any other study characteristic can result in differences in the treatment effect. Therefore, confidence intervals need to appropriately account for the variability that stems from these various factors.

For the current meta-analyses, we included randomized trials where patients with LRTI or sepsis were randomized to one of two treatment arms. In the control group,

antibiotic treatment was based on clinical judgment under standard of care. In the PCT group, antibiotic treatment was based on clinical judgment plus the additional information provided by the PCT assay.

There were two types of meta-analyses performed, one at the study level and one at the patient level. The study-level meta-analysis aggregates study-level information, such as the overall mean differences or odds ratios for each study. With this approach, there is limited ability to account for patient-level characteristics such as age or gender.

The patient-level meta-analyses combine individual-level information from the raw datasets of each trial. This allows for greater flexibility to address heterogeneity in patient characteristics.

The first step in the process was establishing predefined methodologies for the systematic literature review, data extraction, and meta-analyses. Distinct methodologies were used for the study-level and patient-level literature searches, and within the study-level literature search, LRTI and sepsis searches were handled separately.

The methods for these steps were conducted in accordance with the recognized standards for conduct and reporting as outlined by the Cochrane Collaboration, which is the gold standard for this type of research.

At the study level, we conducted a systematic literature review for LRTI and sepsis using the PubMed database and the Cochrane database of systematic reviews. Key words were prospectively identified, and publications were selected based on predefined criteria. Two reviewers independently screened articles for eligibility.

The patient-level literature review was identified in a prior systematic review and a meta-analysis conducted in 2011 to evaluate the safety and effectiveness of PCT-guided therapy for patients with acute respiratory infection. The results of this meta-analysis were published in 2012. The literature search was conducted using the Cochrane Controlled

Trials Registry, Medline, and Embase. Publications were selected on predefined criteria, which can be found in your panel pack. As with the study-level search, all articles were independently screened by two reviewers.

For the LRTI literature review, 263 articles were screened for inclusion in the meta-analysis. The screeners followed a process to screen out articles. The primary reasons for exclusion were that they did not have original data, PCT was not measured for the intended purpose or was not measured in the target population. This resulted in 11 articles representing 4,090 patients reporting findings from prospective, randomized clinical trials that were retained for meta-analysis.

For the sepsis literature review there were 340 articles screened. After review, 10 articles representing 3,489 patients were retained for reporting RCT data on sepsis for any cause.

The literature review conducted in 2011 for patient-level data identified 327 articles. The primary reason for exclusion were because the trials were either not RCTs or ongoing or were duplicate publications. Of the 14 trials retained for meta-analysis, 13 were used for LRTI, representing more than 3,000 patients. Five were retained for sepsis, representing 598 patients.

The next step was data extraction. For the study-level analysis, data on study characteristics and outcomes were extracted from relevant publications, independently by two reviewers, into a standardized data form. Discrepancies between reviewers were resolved by consensus.

The patient-level data were extracted from the original acute respiratory infection dataset created for the previously published meta-analysis. The ability to conduct this type of patient-level meta-analysis is a unique opportunity because all the individual study investigators provided their patient-level datasets. This allows us to look at subgroups

across trials.

For the LRTI dataset, we selected individuals with community-acquired pneumonia, acute bronchitis, or acute exacerbation of COPD. For the sepsis dataset, data were only available for patients treated in the intensive care unit with sepsis due to pulmonary infections.

The patient-level meta-analyses were conducted by Dr. Philipp Schuetz, an expert in this area, who was the first author on the publications of the original patient-level meta-analysis. The study-level meta-analyses were conducted by myself and my colleagues at the Analysis Group.

This chart summarizes the effectiveness endpoints that were extracted for analysis. Effectiveness measures included the proportions of patients initiating antibiotics, duration of therapy, and overall exposure. Duration reflects the amount of time a patient who was initiated on antibiotics remained on them. Exposure reflects the amount of time on antibiotics, regardless of whether or not the patient was initiated. For sepsis, duration and exposure are essentially the same endpoint because nearly all patients initiate antibiotics.

Let me show you the difference between duration and exposure with a simple example. Take five patients, two of whom were never initiated and three patients who took antibiotics for 4, 5, and 6 days. The duration is calculated as the average time on antibiotics among the three patients who were initiated, which is the average of 4, 5, and 6 days, resulting in 5 days. With exposure, we take the average of all the patients regardless of whether or not they were initiated, which in this example would be 3 days because those two zeros are included as well.

Because duration only reflects the time on antibiotics among those who initiated, that measure is more relevant to the individual patient's benefit. Exposure, on the other hand, looks at total antibiotic burden in the population and is more relevant to the public

health benefit.

This chart summarizes the safety endpoints that were extracted for analysis. For LRTI, mortality and hospital length of stay were evaluated in both study- and patient-level analyses. Complications could be assessed at the patient level. For sepsis, we analyzed mortality and ICU length of stay in both types of meta-analyses, and total hospital length of stay at the patient level.

Our random effects models report point estimates, 95% confidence intervals, and p-values for all results. Models for the study level did not adjust for any covariates. The models for the patient-level analyses were adjusted for age.

In response to requests from the FDA, multiple subgroup analyses and stratifications were performed. For the study-level analyses, we performed analyses by type of LRTI, risk of bias, and level of adherence. For the patient-level analyses, we performed analyses by type of LRTI, PCT level, age, gender, and inpatient versus outpatient setting.

We also assessed the risk of bias following the Cochrane Handbook recommendations and evaluated the potential impact on our findings. Overall, we found no evidence that bias had a substantive impact on our primary conclusions.

Another methodological definition to keep in mind is adherence. The PCT algorithm is comprised of both the PCT level and clinical judgment. However, for the purposes of our analyses, we defined adherence as strictly following the PCT level only. This is how we're able to measure adherence in the published studies, and it does not reflect additional clinical considerations. For example, consider an LRTI patient admitted with a PCT level of 0.12 ng/mL. If the physician decided to initiate antibiotics due to other clinical factors, this decision would be considered non-adherent in our analyses.

All together, the methodologies used in the systemic literature reviews and meta-analyses were performed according to the highest standards of evidence synthesis.

Thank you. I would now like to invite Dr. Philipp Schuetz to present the results of the meta-analyses.

DR. SCHUETZ: Good morning. My name is Philipp Schuetz. I'm the Chief Physician of Endocrinology and Internal Medicine at the University of Basel in Kantonsspital Aarau in Switzerland. For the last 10 years, I have focused my clinical and research interests in the use of procalcitonin and other biomarkers on antibiotic therapy. During that time, I gained considerable experience using PCT in clinical practice in the United States and in Europe and conducting several research studies in this area. I also had the unique opportunity to get clinical and statistical training at the Harvard School of Public Health in Boston.

I will be presenting the results from the study- and the patient-level meta-analyses. My presentation will follow this outline. I will first review the baseline characteristics, effectiveness, and safety results from the LRTI meta-analyses, followed by the results for sepsis. For the sake of time, I will be covering only the key results. We performed several additional sensitivity and subgroup analyses, which can be found in your panel pack.

I'll start by reviewing the baseline characteristics of the patients in the patient-level meta-analysis. As expected with randomized trials, the baseline characteristics are similar between the PCT and control groups and were similar to the target population. There were 1,536 patients in the PCT group and just over 1,600 patients in the control group. The median age was 66 years old, and about half of the patients were female. Approximately two-thirds of patients were diagnosed with community-acquired pneumonia; 20% of patients were diagnosed with acute bronchitis or acute exacerbation of COPD, respectively. The median PCT levels at study initiation were also similar between the groups.

The first finding I will review is the effectiveness of PCT guidance for reducing antibiotic initiation. This slide shows results from both the study-level and patient-level meta-analyses. Results demonstrated that PCT-guided therapy significantly reduced the

likelihood of antibiotic initiation.

I'll be showing several charts like this, so please let me orient you. Each line in this table represents the pooled results from either the study-level or the patient-level meta-analyses. The next column shows the number of trials included in the study-level analyses and the summary statistics for the patient-level meta-analysis.

So, for example, the study-level analyses aggregated data from 10 trials. In the patient-level analysis, 71% of patients in the PCT group were initiated on antibiotics compared to 88% in the control group. The right side of the table shows the odds ratios. Results to the left of 1 favor the safety or effectiveness in the PCT group. Results to the right of 1 favor the control group. The study-level meta-analyses produced a statistically significant odds ratio of 0.26; similar results were found in the patient-level meta-analysis.

Well, perhaps the most relevant clinical interpretation of these results is the relative reduction. Patients in the PCT group were 19% less likely to be initiated on antibiotics than those in the control group.

Another way to consider results for the study-level analysis is by looking at the results for each of the individual studies. So the blue diamond at the top shows the overall estimate from the study-level analyses that I have just showed you on the last slide. Each of the individual study results are plotted below as gray diamonds. As you can see, nearly all the study favored the PCT group.

For the sake of time, I will only be showing the overall study estimates for the rest of our analyses. Complete forest plots like these can be found in the appendix in your panel pack.

Next I'll show the results demonstrating the effectiveness of PCT guidance for reducing antibiotic duration and overall exposure. Results at both the study and the patient level demonstrated that PCT-guided treatment significantly reduced the duration and total

exposure to antibiotics.

Starting with duration, in the study-level analysis, the duration of antibiotics among patients who initiated therapy was 1.3 days shorter on average in the PCT group. The results did not reach statistical significance due to the large confidence interval. In the patient-level analysis, the median duration was reduced from 10 days to 7 days for an average duration that was 2.9 days shorter in the PCT group. This was a statistically significant result.

In terms of total exposure among all patients, the study-level analysis pooled data from five trials and found an average reduction in exposure of 2.8 days in the PCT group. In the patient-level analysis, the median exposure was reduced from 9 days to 5 days for an average reduction of 3.6 days. The larger treatment differences in exposure compared to duration account for the fact that PCT-guided therapy also reduced the number of patients initiating antibiotics.

Another way to assess these trends is to look at the percentage reduction in overall exposure. Let's start with the clinical setting, inpatients on the left versus outpatients. These slides show the percentage of patients on antibiotics over follow-up in both groups. At Day 0 in the inpatient setting, 91% of patients in the control initiated antibiotics compared to 79% in the PCT group. When we look at the cumulative difference over follow-up, shaded in light blue, there was a 38% reduction in antibiotic exposure among inpatients. For outpatients, 82% of control patients initiated antibiotics compared to 50% in the PCT group. This resulted in an overall 51% reduction in exposure to antibiotics.

We performed the same analyses by type of LRTI. So for community-acquired pneumonia, nearly all patients in the control group started on antibiotics compared to 90% in the PCT group. Ultimately, there was an overall 37% reduction in antibiotic exposure in the PCT group.

For bronchitis, two-thirds of patients in the control were initiated on antibiotics compared to 24% in the PCT group. There was an overall 65% reduction in antibiotic exposure for patients with bronchitis using the PCT algorithm.

For acute exacerbation of COPD, 73% of patients in the control group were initiated on antibiotics compared to 48% in the PCT group. Overall, there was a 49% reduction in antibiotic exposure in the PCT group.

While reducing unnecessary antibiotic use is an important clinical and public health goal, we need to be confident that the strategy to reduce antibiotics does not adversely affect patient outcomes. To this end, we conducted several analyses of safety outcomes, which found a favorable safety profile for PCT.

I'll start with the mortality data. Overall, we did not see any adverse mortality signal associated with PCT-guided therapy in the treatment of LRTI. One important point to note is that the patient-level data was based on 30-day mortality, but there were several durations of short-term mortality reported at the study level. In both analyses, we observed odds ratios or risk ratios very close to 1, with confidence interval above and below 1. This suggests that PCT-guided therapy did not negatively impact mortality. This was despite the shorter duration of antibiotic use.

These Kaplan-Meier survival curves further illustrate that mortality rates were very similar between the PCT and control groups over time.

For the patient-level analysis, we were also able to assess the incidence of complications. These were defined as death, ICU admission, hospitalization or rehospitalization, acute respiratory infection-specific complications, or recurrent or worsening infection. Eighteen percent in the PCT group experienced a complication compared to 21% in the control group. The upper bound of the confidence interval for the odds ratio is just less than 1, suggesting that the incidence of complications was significantly

lower in the PCT group.

We also looked at subgroup analyses at the patient level to ensure that the favorable safety profile of PCT guidance was consistent. We observed that the 30-day mortality and complication profile of the two groups were similar across the three types of LRTI. This can be seen clearly in the forest plot where the point estimates are relatively close to 1, with confidence intervals that fall below and above 1. The only significant finding among these analyses was the lower rate of complications for patients with community-acquired pneumonia in the PCT group.

We also examined the total length of hospital stay and found no evidence of an adverse safety signal here either. The median duration of hospital stay was 7 days in PCT group and 6 days in the control group. Both the study- and patient-level analyses found no significant difference between the groups in regard to length of hospital stay. This finding was also consistent across the three types of LRTI.

In summary, the findings of the LRTI meta-analyses demonstrated the following:

First, PCT guidance was associated with an approximate 19% relative reduction in antibiotic initiation. Second, it resulted in a 1- to 3-day mean reduction in the duration of therapy. And third, we saw an overall 3- to 4-day mean reduction in total exposure to antibiotics. Across the three types of LRTI, these results translated into overall reduction in exposure that ranged from 37% in community-acquired pneumonia to 65% for acute bronchitis.

Now, importantly, PCT-guided treatment did not adversely affect patient outcomes. Mortality rates, complications rates, and hospital lengths of stay were not increased in the PCT group compared to the control group. Furthermore, we observed that the safety and effectiveness findings were consistent across subgroups. This suggests that the results are broadly generalizable.

The totality of the effectiveness and safety results from these meta-analyses demonstrate that PCT-guided therapy is a safe and effective strategy for antibiotic stewardship in the clinical context of LRTI.

Next I'll turn to the meta-analyses for sepsis, again starting with the patient characteristics. Approximately 300 patients were enrolled in both groups, which were balanced in demographics and PCT levels. The median age was 62 years, approximately 30% of patients were female, and the median PCT values at initiation were 1.2 to 1.4 ng/mL.

In terms of effectiveness, it is standard practice for patients admitted with sepsis to be started immediately on antibiotics. So our meta-analyses focused on determining whether PCT guidance could reduce antibiotic duration and exposure after the initiation of antibiotics. And since nearly all patients initiate antibiotic therapy, there is essentially no distinction between duration and exposure for the sepsis population.

The results demonstrate that PCT guidance significantly reduced the average use of antibiotics for patients with sepsis. The study-level analyses found a significant mean reduction of 1.5 days of antibiotic use in the PCT group. In the patient-level analyses, antibiotic use was reduced from a median of 12 days in the control group to 8 days in the PCT group.

Now, when we look at the trend over the course of follow-up, we see that patients in the PCT group discontinued antibiotics earlier than patients in the control group. Overall, the PCT group had a 24% reduction in overall antibiotic exposure.

Finally, I will turn to the safety results for the sepsis analysis. We observed no adverse signal with regard to mortality. The odds ratios or risk ratios for mortality are below 1 in the study-level and patient-level analyses, with confidence intervals that overlap with 1. This suggests no significant difference between the groups.

This Kaplan-Meier plot further illustrates the similarity in mortality of the two groups

over time.

In addition to mortality, we also evaluated length of ICU and hospital stay. On this forest plot, we found no difference between the groups with regard to length of ICU stay. The confidence interval for the difference between the groups overlap with 1 -- excuse me, with zero. In the patient-level analysis, the median duration of ICU stay was 12 days in both groups. In terms of the total hospital length of stay, the median stay was 21 days in the PCT group and 23 days in the control group. This difference was not statistically significant.

So, in summary, our meta-analyses for sepsis demonstrated that PCT-guided treatment was associated with an approximate 1.5- to 3-day or overall 24% reduction in antibiotic use compared to control patients. Mortality rates, length of ICU stay and hospital stay were not increased in the PCT-guided patients. Mirroring the results with LRTI, the results of the sepsis meta-analyses support that PCT-guided treatment is safe and effective.

That concludes my presentation. I will now turn the lectern over to Dr. Miller to provide a benefit-risk assessment. Thank you.

DR. MILLER: Thank you, Dr. Schuetz.

I am pleased to conclude with a summary of today's presentation and the clinical benefit-risk assessment of PCT-guided therapy using the VIDAS B·R·A·H·M·S PCT assay.

Antimicrobial resistance is a global public health emergency that has been recognized around the world. From the United Nations to the United Kingdom's Office of the Prime Minister to the White House, government and public health leaders are calling for ways to improve antibiotic prescribing practices across all healthcare settings. One key focus is the development and use of rapid diagnostic tests for curbing unnecessary antibiotics on a patient-by-patient basis. We've seen today that PCT has been thoroughly studied in suspected LRTI and sepsis.

Now, let us look back at the two patients we presented earlier but with the added

information of PCT levels.

Recall the 78-year-old male diagnosed with possible community-acquired pneumonia. Rather than prescribing antibiotics, just in case, his physician asked for a PCT level, and the result showed it to be very low at 0.11 ng/mL. Based on the added information provided by this result and the extremely low probability of a bacterial infection, the physician decided to perform a CAT scan of the chest. The scan revealed blood clots leading to bilateral pulmonary emboli as the cause of his symptoms. For this patient, initiating antibiotics would not have conferred a benefit and would have put him at unnecessary risk of antibiotic-related side effects such as allergic reactions, diarrhea, fungal infection, and even a *C. difficile* infection.

Now, let's go back to the 50-year-old female in the intensive care unit with suspected sepsis. After being started on antibiotics as per the guidelines and standard of care, no clear diagnosis was established. The principal question then became when the antibiotics could be safely stopped. The patient's initial PCT level was low, 0.15 ng/mL, leading the ICU team to consider a diagnosis of heart failure rather than sepsis. After her first 4 days of antibiotic treatment, her PCT level dropped even lower to 0.05 ng/mL. The treating physician discontinued her antibiotic therapy on the fourth day, and she had a good clinical outcome.

In both of these cases, PCT levels provide additional clinical insight which assists with rational antibiotic decision making, thereby improving the individual and overall appropriate use of these important medications. By rapidly determining a patient's PCT level, the VIDAS B·R·A·H·M·S PCT assay can help guide clinicians on ways to significantly and safely reduce unnecessary antibiotic use. And with PCT levels, along with other critical assessments, a clinician can make a more informed decision regarding the initiation or continuation of antibiotic therapy.

We have leveraged the existing knowledge base of 23 randomized controlled trials in LRTI and sepsis, with more than 7,000 patients, to demonstrate the safety and effectiveness of PCT-guided antibiotic decision making. Given the number of high-quality randomized controlled trials, this meta-analysis study design is robust and appropriate. Meta-analyses like the ones we presented today give us the opportunity to benefit from many studies, aggregating different results across many settings. This approach provides greater external validity and generalizability than any single study, which may reflect the experience of only one clinical location.

In addition, the design has allowed us to respond urgently to the public health need for improved antimicrobial stewardship as a means of improving individual patient care and curbing overall antibiotic resistance.

This overview of the meta-analyses for LRTI demonstrates the effectiveness of PCT guidance for reducing antibiotic initiation, duration, and exposure. We observed no adverse safety signal in mortality, complications, or length of hospitalization. In fact, the only notable trend seen was in a single measure which actually demonstrated a decrease in complications in the PCT-guided group in the patient-level analysis.

Furthermore, we saw no safety signal in any of the five key subgroup analyses performed, which took into account age, gender, initial PCT level, inpatient and outpatient settings, and type of LRTI. Similar safety was seen in other subgroups, which you can find in the panel pack.

The consistency of the safety profile across these subgroups provides additional confidence that the PCT guidance can be used safely in the full range of patients who present with LRTI.

In patients with sepsis, PCT guidance significantly reduced overall antibiotic use, even in this heavily antibiotic-treated group. We found no adverse safety signal for

mortality, length of ICU stay or length of overall hospital stay, even in the three key subgroup analyses applicable to this population, which included age, gender, and initial PCT level.

The ultimate goal of antimicrobial stewardship is to ensure that antibiotics are given to the right patients at the right time and for the right duration. The data presented today demonstrate that the VIDAS B·R·A·H·M·S PCT assay would be a valuable tool for achieving this important outcome.

We have shown that PCT-guided therapy can safely reduce antibiotic use in presumptive LRTI patients and presumptive sepsis patients with no increased risk to them.

The White House national action plan for combating antimicrobial-resistant bacteria calls for a reduction in antibiotic prescribing of 20% in inpatients and 50% in outpatients. Just looking at our LRTI data, this shows that using a PCT-guided algorithm may actually exceed these goals with a reduction of 38% in inpatients and 51% in outpatients.

In summary, the VIDAS B·R·A·H·M·S PCT assay, along with other clinical information, provides healthcare professionals with a tool for making better evidence-based antibiotic decisions which may ultimately prevent and slow the emergence of resistant bacteria and avoid the side effects of unnecessary antimicrobials. This approach not only benefits individual patients but the entire healthcare system as well.

Thank you very much. And I'm pleased to now welcome Dr. Bozzette back to the podium to take your questions.

DR. CALIENDO: Okay, I'd like to thank bioMérieux for their presentation.

Does anyone on the Panel have any questions, remembering that we will have time this afternoon during our Panel discussions also?

Go ahead, Dan.

DR. JERNIGAN: Just actually a quick question to FDA. Can you comment on how

frequently meta-analyses are being used for a new claim?

DR. GITTERMAN: I certainly can't answer that question. Frequently we are presented with meta-analyses, and again, the exact number I couldn't say, but I'd just say we have a commitment to look into any valid approach. So I don't think the issue is whether, in fact, we do this or not, but more so is this a valid approach for demonstrating safety and efficacy for the proposed use? But it has been used, and I suspect some of the people with drugs, more commonly, would be able to comment on that because it's not infrequent in that center.

DR. CALIENDO: Go ahead, Steve.

DR. SKATES: Steven Skates.

Can you comment on if there was any overlap between the studies that were included in the study-level meta-analysis and the patient-level meta-analysis or whether they were completely separate? And then I have a second question.

DR. BOZZETTE: Certainly. May I have the overlap slide, please? Yes, in the meta-analysis for the LRTI, there were five RCTs that were only at the patient level, eight in both, and three only at the study level. For sepsis, there was one RCT only at the patient level, four overlapped, and six were only at the study level.

DR. SKATES: And so, for example, in this slide here, why was the patient level, on the left, not included in the study level analysis? Is there a reason for excluding it?

DR. BOZZETTE: Sure. If one has patient-level data, access to the raw patient-level data, it's possible to subset relevant patients from a larger study. Say, for example, you're doing a study of LRTI, you're doing a meta-analysis of LRTI, and you have before you a study of hospitalized patients. With patient-level data, you can pull out those LRTI patients and put them in the meta-analysis, whereas it would not be appropriate to include that particular study at the study level.

DR. SKATES: Steven Skates again.

In terms of the differences in which the PCT rule was applied between the different studies, can you comment on how consistent that rule was or how variable it was, to give us a sense of what we're averaging over?

DR. BOZZETTE: The cutoffs were remarkably similar across studies. May I have the LRTI study cutoffs, please? Here we can see, for LRTI, that the crucial cutpoint between antibiotics discouraged and antibiotics encouraged, all of the studies used 0.25 with the only differences being whether or not it was 0.25 inclusive or greater than 0.25. At the strongly discouraged and strongly encouraged line, not all studies had those, but again, the figures were quite consistent. The blue line are what is contained in our algorithms and is a reasonable consensus of the ones above. Oh, did you want that slide up? I'm sorry.

DR. WIEDERMANN: Yes. Bud Wiedermann.

Thank you for that presentation. I had two, I hope, quick questions. One is, in your patient-level analysis for sepsis, all of those patients had LRTI, correct?

DR. BOZZETTE: Yes.

DR. WIEDERMANN: In your study level, it could be sepsis of any cause --

DR. BOZZETTE: Yes.

DR. WIEDERMANN: -- or any source. Okay. And then I may have missed it, but I didn't see any mention of assessment of publication bias. Was that performed?

DR. BOZZETTE: Yes. And I can turn to Dr. Kirson to discuss the publication bias issue.

DR. KIRSON: Thank you, Dr. Bozzette. Noam Kirson from the Analysis Group.

As we noted in our methodological overview, we conducted an assessment of bias, both along the Cochrane Handbook recommendations and a separate analysis of publication bias. For the publication bias assessment, we used a standard visual tool of funnel plots. I have to caution that in our setting here we have 10 and 11 studies; that's

right on the cusp of what is recommended for that. I will bring up here, for example, a funnel plot for our mortality in LRTI and show this result. We conducted a similar type of assessment for all the relevant endpoints, and when I say relevant, those are some of the binary endpoints that lend themselves to this type of assessment.

DR. FOLLMANN: Yeah, I like the patient-level --

DR. CALIENDO: Introduce yourself.

DR. FOLLMANN: Oh, right. Sorry. Dean Follmann, NIAID.

The patient-level analysis was very nice because, as you pointed out, you can look at subsets and do more sensitive kinds of analyses. My impression was that was sort of a dataset of opportunity where there was a patient-level analysis done up to 2012, and so you just reused that for your purposes to focus on this issue. Would there be an advantage, or how many additional patients or subjects or studies would you have if you could include studies from 2012 to 2016?

DR. BOZZETTE: Yeah, we have that information. Could I have the combined overlap slide for sepsis and LRTI? It will just take a second. If you look across both -- for meta-analyses, you see that there were nine RCTs that were published after 2011 and included in one of our study-level meta-analyses.

DR. FOLLMANN: So, in theory, you could get some number of those, some subset of those nine, presumably, maybe get patient-level data and do more expansive patient-level meta-analysis?

DR. BOZZETTE: Yeah, I can talk to -- I'll have Dr. Schuetz discuss his future plans in that respect.

DR. SCHUETZ: Philipp Schuetz.

So, yes, it is a unique opportunity to get individual data from trials, because the trialists need to be encouraged to share this data. And so for the 2012 analyses, we were

able to obtain all the 14, at this point, published studies. Now, with the new trials, we are now approaching these trialists and asking for data, but it's hard to predict whether they will be sharing their data.

MR. BRACCO: In response to your earlier -- oh, Dan Bracco. Sorry.

In response to your earlier question about the FDA's acceptance of meta-analysis data, I just want to say, from personal experience, I have used the process, and it actually works. I had it for a PMA supplement. What is rare, however, is for a meta-analysis to actually get the actual patient data. I think that makes for a more robust dataset and makes it more scientifically valid.

So I also want to comment or add on to Dr. Skates' question about the PCT-guided therapy that was used. In one of your slides, you had mentioned that there are several treatment guidelines available right now.

DR. BOZZETTE: Yes.

MR. BRACCO: And I was wondering if they were incorporated into the PCT-guided therapy, if they're common, and also whether or not your new indications basically mimic those guidelines that are currently being used anyway in the field.

DR. BOZZETTE: To discuss the question of guidelines, I'll ask Dr. Krause to the podium.

DR. KRAUSE: So good morning. My name is Alexander Krause. I'm Medical-France manager at bioMérieux.

So it's true that in these guidelines for LRTI and also for sepsis, PCT would be used to discontinue in the case of sepsis or to initiate in the case of LRTI. However, in those guidelines, there is no kind of determination given. It says, for example, low PCT levels could be used in addition to clinical information to stop antibiotic treatment, but there's no notion of guidelines whatsoever.

DR. WELCH: David Welch.

Dr. Bozzette, from your presentation, I'm referring to Slide 23, and it's about predictive values. In that study that you cite from 2016, it shows a negative predictive value of 92%. So is it fair to say that among those that had a negative procalcitonin, 8% of them might have been misdirected?

DR. BOZZETTE: Let me answer that in two ways. The first is, as pointed out in the FDA's panel pack, nailing the operating characteristics of a test like this is very difficult because of the gold standard problem. All the tests we have to establish a gold standard are either not sensitive enough or not specific enough.

Having said that, let me say that yes, these high negative predictive values are not 100%, but no laboratory test has 100%. The point is that PCT is an aid to be used in the context of the clinical situation. And so the combination of the high NPV and the safety margin provided by the clinical element of the algorithm makes us confident that, you know, missed therapy would be rare.

DR. WELCH: And then on positive predictive values, in that one study the positive predictive value of 25% is real low.

DR. BOZZETTE: Yes.

DR. WELCH: I presume, since the endpoint was confirmed bacterial co-infection, that those might've been just viral infections.

DR. BOZZETTE: Yeah.

DR. WELCH: And I was also wondering whether you've ever wondered about the seasonality of viral infections. In other words, if you use this test during the influenza season, you know, with presentations in the emergency departments mostly uncomplicated respiratory virus infection, are you not going to get a lot of false positives?

DR. BOZZETTE: Well, I mean, I think again we would emphasize the negative

predictive value because the usual question here is whether to withhold the antibiotics, and that's the most relevant operating characteristics for making that decision. Now, in terms of the positive predictive value in the Rodriguez study, if we could see that again -- well, let me just say that --

DR. WELCH: Yeah, the positive predictive value --

DR. BOZZETTE: Yeah.

DR. WELCH: -- is 25%.

DR. BOZZETTE: Yeah. This turns out to be yet another manifestation of the gold standard problem. It turns out Rodriguez had very strict criteria for calling a bacterial infection, so it's pretty clear that there were some test-positive/disease-negative patients that were in the wrong box, and if those were moved to disease-positive, the predictive value would have been higher. We contrast that with Stolz, which had a looser criteria, and you can see there that the positive predictive value is all the way up at 93%. So again, I think it's the gold standard problem.

DR. CALIENDO: I'm going to ask a question that I would like for you to answer this afternoon because I think you're probably going to have to go get some data. The bucket of LRTI, to me, it's very diverse. Community-acquired pneumonia is very different than an acute exacerbation of COPD than bronchitis. And you showed us a little bit of breakout data, but I was wondering if you could show us more details of breakout, particularly for acute exacerbations of COPD and how many of these patients were in the inpatient setting and how many were in the outpatient setting. So we'll come back to that when we have our Panel discussion, but I just wanted to give you that information. So if you can -- any more details that you could pull for us, I think it would be very helpful.

DR. BOZZETTE: We could show you the subgroup analyses by respiratory diagnosis now, if you'd like.

DR. CALIENDO: And inpatient and outpatient?

DR. BOZZETTE: We have inpatients and outpatients, and we have subcategories of the diagnosis, but not both, because the numbers were too small.

DR. CALIENDO: I think that's getting at my point. So let's hold that for this afternoon --

DR. BOZZETTE: Okay.

DR. CALIENDO: -- because I want to get to the break so that we can all take a few minutes before the next presentation. But I want to thank you very much for your presentation. For the Panel, we'll have plenty of time this afternoon to ask more questions.

I want to make a few comments. One is, if you are presenting at the public hearing and you want to have slides, you need to give those to someone over in the AV area so that they can get those loaded up for you.

For people on the Panel, please fill out your lunch form and give it to the FDA outside at the desk there.

So we're going to take a 10-minute break now, and I would like to remind Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience, and we'll resume back here promptly at 10:30.

(Off the record at 10:21 a.m.)

(On the record at 10:33 a.m.)

DR. CALIENDO: Okay, welcome back, everybody. So we're going to move on and hear a presentation from the FDA. At the conclusion of this presentation, there will be time for questions from the Panel. We're going to have two presenters, Dr. Brittany Goldberg from the Division of Microbiology Devices and Dr. Qin Li from the Division of Biostatistics.

Take it away.

DR. GOLDBERG: Good afternoon, everyone. So in the following presentation, I'll be

reviewing the clinical considerations associated with procalcitonin-guided evaluation and management of lower respiratory tract infections and sepsis. So I'm one of the medical officers in the Division of Microbiological Devices.

So as we've already heard today, procalcitonin is currently approved as an aid in the risk assessment for the progression to severe sepsis and septic shock, and as an aid in assessing the cumulative 28-day risk of all-cause mortality in patients with sepsis or septic shock.

However, we're here today to talk about the proposed expansions to the indications for use, in which procalcitonin would be used as an aid in decision making for antibiotic therapy, so meaning both initiation and discontinuation, for both inpatients and outpatients with suspected or confirmed lower respiratory tract infections, which bioMérieux has defined as community-acquired pneumonia, acute bronchitis, and acute exacerbations of chronic obstructive pulmonary disease. bioMérieux has also proposed that procalcitonin can be used as an aid in decision making for antibiotic discontinuation in patients with suspected or confirmed sepsis.

So when considering diagnostic approaches for pneumonia and sepsis, there are kind of two different approaches. You can go at this from the microbiological approach, in which you're looking for a culture confirmation, targeted PCRs, or other laboratory evidence of a microbiological cause of the patient's signs and symptoms of disease. On the other hand, you have non-microbial biomarker, so this is a laboratory test in which you're assessing the host response, which is thought to be secondary to an infectious cause of some kind.

However, as we've talked again today, many of the clinical trials suffer from the lack of a gold standard, and this really complicates our clinical trial design because we can't really get down to the microbiological truth associated with the patient's signs and symptoms of disease.

So this has already been brought up once before. Back in 2015, the CDC conducted their EPIC study. And I agree, this is probably a more exhaustive microbiological workup than most patients get as inpatients and outpatients, and despite all of that, we were unable to find a pathogen in roughly two-thirds of the patients. And these were, again, patients with signs and symptoms of pneumonia and radiographic confirmation of infection.

There's normally not a comparative study for sepsis. Most of the sepsis epidemiological data dates back to the early 2000s with the activated protein C clinical trials. But when you do happen to get an infection or find a bug, it's mostly lung, with some abdomen and urinary tract infections. However, you should keep in mind that you only get a culture confirmation of infection in about 20 to 30% of patients, and up to 50% of the time you may not ever find a microbiological cause of infection.

I think it's also important to keep in mind that we don't have really great outcome studies from these microbiological assays either. So this was a 2010 review of antibiotic use in patients who were admitted to the hospital with respiratory symptoms, who then received a diagnosis of viral respiratory tract infection within 48 hours of their admission. So about 200 patients were enrolled, and these were adults who were found to have influenza, adenovirus, RSV, or parainfluenza. And despite having a microbiological cause for their infection, 64% of them continued to receive antibiotics after the viral diagnosis for a median of 8 days. And you might say, well, we have a hard time diagnosing pneumonia, but about two-thirds of them had a normal chest x-ray. Troublingly, 6% of them went on to develop *C. difficile* diarrhea, and there was an association with increased length of stay. So the pilot study was not powered for mortality or readmission, but patients who did get antibiotics tended to be in the hospital longer than those who did not.

On the other hand, we have non-microbial biomarkers. So these are not biologically tied to a specific microorganism or a family of microorganisms. They are associated with

the various aspects of the host response to infection and are generally hypothesized to distinguish between colonization, contamination, and true infection. However, the diagnostic accuracy with these non-microbial biomarkers is very variable due to our lack of an imperfect comparator method.

So procalcitonin, this has been around for quite a while and has been pretty exhaustively studied in the literature. So there are presently more than 3,000 peer-reviewed articles looking at procalcitonin across a variety of infections. So for just about everything somebody has done a procalcitonin study; dengue, malaria, Kawasaki's, meningitis, somebody has looked at it with procalcitonin.

Since 2009 there have been more than 25 meta-analyses conducted, many of them covering similar ground to what we're reviewing today. There's been more than 300 review articles and commentaries on this topic. I'm just going to say there's been many prospective randomized clinical trials. I'm not going to try to bin those.

So this brings us to one of the core questions: How good was the bioMérieux literature evaluation? So FDA conducted a literature evaluation in parallel with bioMérieux, and we looked at between 2,000 and 3,000 articles, and I can say that I don't feel that there's any duplicity in the bioMérieux literature evaluation. They seem to have done a good job in selecting articles without any signs of selection bias. I can't really speak to publication bias in which negative studies may not been published.

So this kind of was reached on earlier. So what are the current professional society recommendations for the use of procalcitonin? So the Agency for Healthcare Research and Quality reviewed the available literature back in 2012 and felt that procalcitonin could be recommended for both initiation and discontinuation in lower respiratory tract infections and that there is high-quality evidence supporting sepsis discontinuation.

The IDSA, which includes recommendations from the Surviving Sepsis Campaign and

SHEA, recommended that procalcitonin could be applied for discontinuation in both lower respiratory tract infections and sepsis but didn't feel that the evidence met -- was sufficient for lower respiratory tract infection initiation.

The UK's NICE organization looked at the data as well and felt that it was sufficient for both initiation and discontinuation for lower respiratory tract infections, but felt that there was more research needed for sepsis discontinuation.

So in looking through the professional society recommendations, again and again a few things come up. So there's always this question about the generalizability of benefit. So in facilities in which you have an existing robust stewardship program or those in which you just have a low baseline duration of antibiotic treatment, will you see the same magnitude of benefit as in the clinical trials? I think it's also important to keep in mind that most of these trials were conducted in Europe, and we have relatively little U.S. clinical trial data, which may be important when we're thinking about treatment norms or patient demographics.

Some societies also discuss the appropriate patient population, so this is probably not a test that you need to order when you feel that you're very confident of the diagnosis. So if you're certain that your patient has a bacterial pneumonia, this is not the patient population for this test. And if you're very certain that it's not viral, you're also probably -- this doesn't add much to your workup. However, in those patients in which you're not sure what's going on, that there's some degree of lingering diagnostic uncertainty, that appears to be the appropriate population.

And then I'd just reiterate that a lot of -- some of the societies brought up the question of diagnostic accuracy and felt that if you couldn't meet an a priori goal for sensitivity and specificity, they weren't going to make a recommendation.

So this kind of brings us to our first question. So can we establish an accurate

measurement of sensitivity and specificity for non-microbial biomarkers in the absence of an appropriate comparator method? And I would argue that probably the answer to this question is no.

So there are a lot of factors that run into diagnostic accuracy. So low culture yield, poor quality or absent specimens, patient population characteristics, all of these are going to make it difficult to measure diagnostic accuracy and will complicate your comparisons between different studies.

So what is the appropriate clinical trial approach to answer the question of is procalcitonin-guided management safe and effective?

So our kind of options are on the table. So in a diagnostic accuracy study, you might end up with an estimation of diagnostic accuracy. You could probably look at potential clinical limitations, so how does the test function in specific patient subpopulations? And some physicians may feel this is important for their clinical decision making. However, you're going to have a problem comparing between studies, and the variable reference method will maybe complicate this.

A clinical outcome trial, on the other hand, evaluates the impact of the diagnostic on the patient's management and the patient outcomes. But you may not have a great estimate of the accuracy of the test.

So I think the question before the Panel this afternoon is can we use pragmatic clinical trial evidence to establish the safety and effectiveness of procalcitonin-guided management?

So this is taken from the bioMérieux package insert, and this is how they are proposing to implement the literature recommendations for PCT. So they have identified the four cutoff values. In inpatients, they recommend that you repeat a procalcitonin measurement within 6 to 24 hours. For outpatients, they kind of just recommend that

we're going to reassess and repeat tests if the symptoms persist or worsen. It's unclear how that would be implemented. For discontinuation, the cutoff has been identified as 0.25 or a percent decrease of 80%.

For sepsis initiation, it's off the table, and the cutoff has changed from 0.25 to 0.5 or a percent decrease of 80%, and this really mirrors what the current equation for calculating PCT in the labeling is.

So what are some known limitations of procalcitonin? Certainly we know that localized infections may not trigger a robust PCT rise, so emphysemas, cellulitises, abscesses, you might not see the same degree of increase. If you measure your procalcitonin too early, you may miss the peak. Steroid use has been shown to blunt the PCT response, which may be important in COPD patients who might be on chronic steroids for their underlying condition. There's some evidence that atypical bacteria, so *Chlamydophila* and some of the other atypicals, may not a trigger a robust rise in PCT. On the other hand, false positives have been shown to occur. Some oncological processes may falsely elevate your PCT. Pancreatitis, heat stroke, trauma, burns, surgery, all of these seem to cause a robust rise. And there's some evidence that certain strains of influenza or viral respiratory tract infections may also cause a rise in PCT.

I think it's also important to keep in mind that there are some understudied populations, so we don't have a lot of data in pediatrics, for children and babies. There is some evidence that patients with chronic renal failure may have increased baseline normals of PCT. And then most studies exclude the immunocompromised, so they are just not included in the studies, but they certainly are at increased risk for sepsis or respiratory tract infections.

So when it comes down to what are the risks and benefits of PCT-guided management, from looking at the data, it does seem to indicate that patients will

experience benefit from PCT-guided management in the form of decreased antibiotic duration, decreased antibiotic initiation, and potentially decreased antibiotic side effects. The question mark next to the antimicrobial resistance, that is more of a public health question, and I'm not sure that any of the studies have really looked at will we see a concrete decrease in resistance with the magnitude of benefit from PCT-guided management?

But one of the questions before the Panel this afternoon is, is the clinical data sufficient to determine if the reduction in antibiotic duration or initiation will increase risk to patients in terms of mortality, length of stay, recurrence of infection, or does it prolong symptoms or decrease quality of life?

And when thinking about the risks, we also have to consider how did the adherence affect our evaluations of safety and effectiveness for PCT-guided care? So when I say adherence, I mean adherence to the recommendations from the PCT level.

So I think, on one hand, adherence probably underestimates the efficacy. Probably you might see a little bit better decrease in antibiotic duration. If the physicians were more strictly adhering to the algorithm, then their hand is going to complicate our evaluations of safety. Are we overestimating our safety? But you could consider that is reflective of clinical practice, and I don't think anybody is ever going to go to a physician and say you're not allowed to give the patient antibiotics because of a lab test.

I think it also might complicate our extrapolations to the outpatient populations and some of the other patient subgroups. But then you also have to consider can we demand better adherence in studies? And this has ethical implications. Again, you can't force clinicians not to give antibiotics if they feel the patient needs them. So it's not clear that even with a different study population, we would answer this question.

So this is the data presented by bioMérieux, looking across the different subgroups.

So we have certainly CAP, bronchitis, and AECOPD separately, but we don't really have the breakouts for the outpatients amongst these groups, but there doesn't appear to be a mortality difference in these subpopulations.

So has the safety of PCT-guided management been established for all of our subpopulations, for the outpatients in these subpopulations, for antibiotic initiation, and for discontinuation? And I think, again, another question before the Panel today is additional limitations for certain patient groups needed based on the available data.

But then what are some of our potential risk mitigations? So this is meant to be an aid in the diagnosis of sepsis or lower respiratory tract infections, and it's meant to be used in association with other imaging and laboratory tests. Right now, that means healthcare facilities with a moderate to high-complexity lab. Certainly, if we would look into the outpatient physician offices in a CLIA-waiver setting, I think the risk-benefit would shift. And this is really meant to be used in association with clinical judgment.

It also should be kept in mind that as hospitals incorporate PCT into their practices, antimicrobial stewardship programs will be expected to develop internal policies and procedures about how they intend to implement this test.

And then this is also not the end. So this is the ProACT trial. So this is a 5-year multicenter trial that is going on right now in the United States to look at the effect of procalcitonin on antibiotic use. So the primary and secondary outcomes mirror the studies that we're examining today.

This is taken from the site, so they are using the same procalcitonin algorithm that's been studied in the other -- in the meta-analyses. They have a 1-hour turnaround goal for the procalcitonin result in the emergency room. And I think it's important to think that, you know, this is very similar to the European studies, so it may help us determine magnitude of value in the United States, but I think there still will be some lingering questions between

these two trials.

So, in summary, procalcitonin does appear to correlate with bacterial infections in sepsis or lower respiratory tract infections. However, the diagnostic accuracy of procalcitonin is difficult to assess precisely because of the imperfect comparator method.

It does seem apparent that use of antibiotics is reduced when procalcitonin is utilized as proposed by bioMérieux.

We have not seen any significant differences in the adverse outcomes. However, our algorithm adherence and aspects of the clinical trial design complicate our safety analysis in that our subpopulation analysis was performed on smaller patient subsets.

In conclusion, the FDA generally concurs that PCT-guided therapy reduces antibiotic use with the proposed diagnostic algorithm. The submission seems to reflect an accurate description of the current data available regarding procalcitonin-guided therapy. However, certainly limitations from the current data are well recognized, and results from additional prospective clinical trials may not be available for several years and may not answer all of our questions. So we still have significant concerns regarding the safety and conditions of use of PCT.

So the question to the Panel, again, will just be to discuss the potential advantages and disadvantages of using this test as proposed. We would be particularly interested in hearing from the Panel any risks that they foresee with the new use and what those risks might be, both for the lower respiratory tract infections and as an aid in diagnosis for sepsis discontinuation.

References. And then thank you, everybody from the FDA who helped out with this. And I think that's all I have. Yes.

DR. CALIENDO: Do you want to take questions now, or do you want to do the second presentation?

DR. GOLDBERG: It doesn't make any difference to me.

DR. CALIENDO: Let's get the second presentation in, and then that way we won't -- we'll make sure we get both of them done.

DR. GOLDBERG: Okay.

DR. LI: Good morning. My name is Qin Li. I'm the statistical reviewer for this submission, from the Division of Biostatistics in FDA CDRH. Today I'm going to present statistical considerations for procalcitonin-guided evaluation and management of lower respiratory tract infections and sepsis.

In my presentation, I will start with an overview of how to evaluate diagnostic tests. And then I will briefly describe the meta-analysis results conducted by the Sponsor, followed by several limitations and concerns FDA has identified during our review. In the next part, I will discuss some alternative study design and analysis considerations for evaluating PCT as a biomarker in antibiotic stewardship trials. I will conclude my presentation with summary remarks from a statistical point of view.

Diagnostic tests can be evaluated on many levels. In their seminal paper, Fryback and Thornbury identified six levels on which diagnostic tests may be evaluated.

Diagnostic tests submitted to FDA are evaluated for analytical and clinical validity, which usually encompasses Level 1 and Level 2. Level 1 is the technical efficacy, which refers to the quality of the test measurement. It is evaluated through analytical performance studies. Most commonly, clinical validation of a diagnostic test submitted to FDA involves an evaluation at Level 2, diagnostic accuracy. In very general terms, diagnostic accuracy is the association of the diagnostic test results with a reference diagnosis of the clinical condition of interest. It usually is to be done as treated in a clinical performance study.

However, for this submission, as a few speakers mentioned earlier, diagnostic

accuracy of PCT for bacterial infection can be difficult to assess because of the biological and technological difficulties in identifying the truth.

In fact, in our review of the literature, we have found that the reported sensitivities, specificities, positive predictive values, and negative predictive values vary greatly between studies. And I want to point out here that PPV and NPV are also dependent on the prevalence, which can be varied across studies.

The Sponsor presented two publications in reporting the sensitivity and specificity of PCT for diagnosing bacterial infection for the LRTI population. They are the circled points in this plot. FDA briefly reviewed four additional studies in addition to the Sponsor's search. The results are summarized on this summary ROC plot where x-axis is 1 minus specificity and y-axis is the sensitivity. The connecting lines are the points for different cutoffs considered in the same study. Note that the pairs of sensitivity and specificity do not line up very well to form a single ROC curve but instead have a wide spread above our identity line, indicating some heterogeneity in the diagnostic accuracy estimates.

In lieu of diagnostic accuracy, a diagnostic test may be evaluated for patient outcome efficacy. In this submission, randomized controlled trials were combined in a meta-analysis to evaluate patient outcome efficacy at Level 5, which evaluates the ability of the diagnostic test to improve clinical outcomes. The meta-analysis was also used to evaluate the therapeutic efficacy at Level 4, that is, the frequency by which the diagnostic test results help the physician plan the management of the patient.

In the next few slides, I will briefly describe meta-analyses conducted by the Sponsor.

The Sponsor conducted a meta-analysis to compare PCT guidance group versus standard care in antibiotic use. The proposed effectiveness endpoints included antibiotic initiation, duration, and exposure, which can be regarded as a Level 4 evaluation of

therapeutic efficacy. The Sponsor also proposed to evaluate the safety endpoints, including mortality, complications, length of hospital stay and ICU stay, which can be regarded as a Level 5 evaluation of patient outcome efficacy.

For the endpoint of antibiotic use, a pre-specified hypothesis was that antibiotic use should be lower for the PCT group than that in the standard care group. For the safety endpoints, no study success criteria were pre-specified, such as non-inferiority of the PCT-guided group to the standard care group based on a non-inferiority margin.

The Sponsor performed four meta-analyses, study-level and patient-level analyses for two populations, LRTI and sepsis. The study-level analysis extracted summary-level information from the included studies. The patient-level analysis used the raw dataset from the included studies.

At the study-level analysis, there were 11 studies with 4,090 subjects for LRTI population and 10 studies with 3,489 subjects for sepsis population. At the patient-level analysis, there were 13 studies with 3,142 subjects for LRTI and 5 studies with 598 subjects for sepsis. Please note that the study-level and patient-level publications have some overlap but not exactly the same.

Randomized controlled trial was one of the publication selection criteria for meta-analysis. It is observed that the selected randomized controlled trials all used this so-called marker strategy design. With this design, patients are randomized to the PCT-guided group or not. For patients in non-PCT guided group, antibiotic therapy follows the standard of care. For patients in PCT group, the test results of PCT will be used in conjunction with standard of care to inform antibiotic treatment decisions. The effect of interest is compared between non-PCT-guided group and PCT-guided group.

The Sponsor's main findings from the meta-analysis suggested a statistically significant reduction in effectiveness endpoints, such as antibiotic initiation rate, duration

for both LRTI and sepsis, comparing PCT guidance to the standard care group.

In the meantime, the significant difference in safety endpoints, such as mortality and hospital stay, were not observed for both LRTI and sepsis, comparing PCT guidance to the standard care group.

Using the patient-level data, the Sponsor also performed several subgroup analyses. These subgroup analyses include analysis by the type of LRTI, by inpatient versus outpatient, also by initial PCT values and some other subgroup analyses.

Overall, it is recognized that the Sponsor conducted the meta-analyses appropriately, according to a well-accepted guideline, Cochrane Handbook. The process of literature search and publication selection appear appropriate. Hypotheses and analyses were pre-specified and a statistical analysis plan was followed. Potential bias of meta-analysis was examined through quality assessment tools. Publication bias was examined using funnel plots. Also, study heterogeneity was incorporated into meta-analysis by treating studies as random effect in addition to a fixed effect.

For the meta-analysis results, FDA's interpretations are, for effectiveness endpoints, PCT algorithm is designed to reduce antibiotic initiation, duration, and exposure. Antibiotic use will be reduced if PCT recommendation is followed for some patients. So statistical significance of reduction is not an issue. However, magnitude of reduction can be an important assessment for clinical significance.

On the other hand, it is also important to consider safety, in this case, for the study success. For safety analysis, no significant difference in mortality or length of hospital stay or ICU stay was observed between PCT group and control group. Lack of significant differences in safety may be due to the PCT assay is actually selecting patients for whom antibiotic use may be reduced. However, it may also be due in part to the following reason: Patients for whom PCT algorithm recommends the same antibiotic use as control arm dilute

the difference between arms in safety endpoints, making the two arms appear similar. In addition, because of the nature of meta-analyses, it may be subject to several biases, and the study heterogeneity included in the analysis also created difficulties to interpret the results. In the next several slides I will discuss these limitations.

The Sponsor performed quality assessment of the included publications for potential biases using guidelines from Cochrane Handbook. This assessment examined the following biases: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each publication was designed as low risk, high risk, or unclear risk for each domain after examination. As you can see from the reported table for both LRTI and sepsis, that the lack of blinding is a common domain that receives high risk from many publications, and there are some other unclear risks for several publications.

Although lack of blinding of participants and personnel was to be expected, as many physicians who know in advance whether to perform PCT tests to their patients, knowing the treatment arm may cause physicians to consciously or unconsciously manage subjects differently in the PCT arm than the control arm, apart from the PCT results. This potential bias could be characterized as a type of Hawthorne effect for physicians.

Meta-analyses can be subject to publication bias. For example, significant treatment effects in favor of PCT-guided management may be more likely to be published. Combining only the published studies may lead to an overoptimistic conclusion. A funnel plot is a visual method to examine if publication bias exists in a meta-analysis. In these plots, treatment effect, odds ratio or risk ratio is plotted on the x-axis, and the precision of estimated treatment effect is plotted on the y-axis. In the absence of publication bias, the treatment effect should scatter symmetrically about a mean effect size, with the scatter narrowing with the increasing precision of the effect size estimate. If publication bias is in favor of the device or present, the precision would correlate positively with the effect size.

As shown in these funnel plots, for some endpoints such as antibiotic initiation for LRTI and mortality for sepsis, the top two plots -- the three least precise studies are all scattered to the left side of the mean effect size, which favors the device. The number of studies is small, so the interpretation needs to be careful. Upon FDA request, the Sponsor performed Egger's tests for testing the symmetry, and according to the tests, none of the plots exhibited significant publication bias.

Missing data are another concern that can result in a biased estimation of treatment effect. One common reason for missingness is loss of follow-up. In the current meta-analysis, follow-up time varied across studies, ranging from 5 days, 1 month to 6 months. Follow-up rates varied from 83% to 99% for the LRTI studies and 67% to 98% for sepsis studies. In the patient-level analysis for the safety endpoints, patients lost to follow-up were assumed not to have experienced the events. Also, there may be other reasons for missingness that were not described in the publications.

It can be argued that since clinical methodological diversity always occur in the meta-analysis, statistical heterogeneity is inevitable. However, it is still important to know to what extent the results of the studies are consistent. A useful statistic for quantifying inconsistency is I^2. I^2 is ranged from 0 to 100 with a rough guide with that I^2 above 75% indicates considerable heterogeneity. For each endpoint, the Sponsor constructed a forest plot and also calculated I^2. For some of the endpoints, I^2 are bigger than 75%, which indicates considerable heterogeneity.

In reviewing the analysis, we observed several differences among selected studies, which may explain some of the heterogeneity in the analysis results. It is noticed that not all studies used VIDAS B·R·A·H·M·S PCT, as in fact many studies used B·R·A·H·M·S sensitive KRYPTOR assay in measuring PCT values. This slide shows the details of devices used in the selected studies for four meta-analyses.

The Sponsor performed concordance study between VIDAS and KRYPTOR assays. The results showed some amount of disagreement between two assays around cutoff 0.1 and 0.25. This discordance may be one source of uncertainty for the meta-analysis conclusion.

Another source of heterogeneity among selected studies is that different thresholds were used to guide the antibiotic therapy. This slides shows the PCT guidance used in each study. The Sponsor proposed to use the majority thresholds. The highlighted ones are the ones matched with the claimed device. It is observed that the PCT guidance used in the selected publications for meta-analyses are not necessarily well aligned with the claimed device.

The other issue I want to point out is the proposed thresholds used to define the device. In the PCT group for LRTI, the initiation of antibiotic therapy was guided -- was based on a single cutoff, which is to start the antibiotic if PCT value is above 0.25 and do not start antibiotic if PCT value is below 0.25. The additional cutoffs such as 0.1 and 0.5 for antibiotic initiation were not evaluated.

The meta-analysis results show that no significant difference of adverse event rates were observed between PCT group and the standard care group. However, please be reminded that the physicians can disregard and override the PCT level recommendation. The subgroup in which physicians did not adhere to the PCT recommendation may dilute the effect of interest. Adherence to the PCT recommendation in treating patients in the PCT treatment group was reported in 8 out of 11 studies for LRTI and 4 out of 10 studies for sepsis. It ranged from 59% to 91% for LRTI and 47% to 93% for sepsis studies.

Also, as Dr. Goldberg mentioned earlier, there is very limited studies from U.S. sites. The generalizability of the results using non-U.S. studies needs to be considered when evaluating the device.

Next, I would like to discuss some study design and analysis considerations for PCT biomarker studies.

As I mentioned earlier, it is noticed that the selected randomized controlled trials in meta-analysis all used the so-called marker strategy design, where patients are randomized to the PCT-guided group or not. For non-PCT guided group, antibiotic therapy follows the standard of care. For PCT-guided group, the PCT levels will be used in conjunction to the standard of care to guide the antibiotic treatment. The endpoint of interest will be compared between PCT versus standard care group.

The marker strategy design appears to evaluate the effect using the marker of PCT on patient outcomes. However, the marker typically only impacts the management of a subset of the subjects. As a result, differences in patient outcomes between the treatment groups, for example, the PCT and standard care group, are diluted by patients for whom management would have been the same in either group. Physicians who did not adhere to the PCT recommendation may also affect the safety difference, which can impair interpretability of the study results.

The marker strategy design compares PCT and control arms on the whole study population as opposed to just the subgroup for whom PCT changed the treatment decision. A useful design should focus on subgroups in whom the treatment decision is likely to change, which is illustrated in the following -- in this table, where standard of care -- associates the standard of care arm and plus PCT is the PCT guidance arm. The highlighted two diagonal cells are the subgroups in whom PCT suggests different treatment than the standard of care adjunctively. And when visible, this subgroup should be the focus of the analysis when evaluating the PCT for the outcome, patient outcome efficacy.

In marker strategy design, a difference in safety outcomes between PCT and control groups can depend on one or more of the following factors:

- Treatment effect on outcome
- Diagnostic accuracy of PCT for bacterial infection
- Adherence to PCT level recommendation
- Proportion of the subjects for whom PCT and standard of care indicate the same treatment decision
- Any differential between the arms in management of subjects apart from the influence of PCT levels

It can be shown that diagnostic accuracy on differences cannot be separated from the other factors using marker strategy design. This can make the obtained difference between groups hard to interpret.

Let's go back to take a look at the safety analysis results conducted by the Sponsor. In most of the endpoints, the estimated odds ratio is less than 1, and the difference is less than zero, indicating PCT guidance improved the safety endpoints. Although not statistically significant, these results may not have been expected.

So FDA took a closer look at the patient-level data for LRTI. The patient-level meta-analysis contains 13 studies for LRTI. Line data from each study was combined for this analysis. This table presents a cross-tabulation between antibiotic initiation levels and PCT group stratified by the baseline PCT category.

The number and the percentage of deaths in each combination is provided in parentheses. Among patients who did not get antibiotics, five deaths were observed. Note that all of them are from the PCT group. Four of the deaths are in the group that PCT levels recommends no antibiotic initiation. This data tells a different story from the previous meta-analysis results when collapsing the treatment of antibiotics and no antibiotics, as well as baseline PCT categories. Please be noted that in this analysis, patients lost to follow-up are assumed to have not experienced any events here.

In addition, FDA performed analysis on examining the conditional independence controlling -- yeah, controlling for the baseline PCT categories. The association of death and PCT group within two levels of antibiotic use were examined using Cochran-Mantel-Haenszel test. The tests were performed for all patients and also for patients with PCT value lower than 0.25. Where the PCT recommendation is no antibiotic initiation, no significant association was observed.

Different designs can be used to avoid some of the marker strategy design limitations. One design called marker enrichment design is useful when convincing evidence such as that the potential treatment benefit is limited to a certain biomarker defining the patient subgroup. In this design, a subgroup of patients defined by the diagnostic test value, for example, initial PCT value is less or equal to 0.25, are randomized to receive either treatment therapy or control. In Dr. Lautenbach's presentation earlier, the design used in the TRAP-LRTI trial was actually this enrichment design with PCT value less than 0.1.

As an alternative to evaluate each of the endpoints separately, a composite endpoint at the patient-level data can be used in the overall evaluation of a device. A composite endpoint may increase the power to detect significant differences between treatment group compared with evaluating endpoints separately.

In Dr. Lautenbach's presentation this morning, he mentioned the DOOR/RADAR approach by Evans et al. in 2015. In this approach, a Desirability of Outcome Ranking (DOOR) is constructed based on the clinical endpoints. For antibiotic stewardship trials, a version of DOOR called Response Adjusted for Duration of Antibiotic Risk (RADAR) break ties between patients in a clinical outcome ranking based on duration of antibiotic use. Trial arms may be compared with DOOR composite endpoint using statistical methods for rank data, such as Mann-Whitney significance test for location difference in the distribution

of ranks.

In conclusion, the meta-analyses were conducted to demonstrate comparative safety of using PCT for the intended indications versus standard of care, and the effectiveness of using PCT to reduce antibiotic use compared to standard of care.

The meta-analyses have demonstrated that the use of antibiotics is reduced when PCT is utilized in the patient management for the proposed indications.

No statistical significant difference in adverse outcomes were observed between patients whose treatment was managed with the input from PCT levels in conjunction with the standard of care compared with those treated according to the standard of care alone.

However, limitations are inherent to the studies in the available literature, including heterogeneity in the study design and study conduct and patient populations.

The lack of precise data on diagnostic accuracy of the device made interpretations of safety results less clear.

The benefit of reducing antibiotic use could outweigh the risk of mistreating some patients based on PCT-guided therapy if that subset were small enough, but the risk to the patients of using PCT to guide their therapy is difficult to estimate precisely based on the available data and the current meta-analyses.

With that, that's all I have.

DR. CALIENDO: Thank you for those presentations.

So we're going to open up for questions from the Panel to both of our FDA speakers.

Go ahead, Tom.

DR. MOORE: Yeah. Tom Moore.

So I have a question for Dr. Li and then a question for Dr. Goldberg. Dr. Li first. On Slide 37, would you be able to tell me the -- or would you be able to share with the Panel the causes of those mortalities?

DR. LI: I'm not able to tell the cause of the death. That's just the opposite issue from the data.

DR. MOORE: Okay. So we don't know whether they died of sepsis or not?

DR. LI: Yeah, yeah. I guess maybe the Sponsor can have more information on that.

DR. MOORE: Okay.

DR. LI: Yeah.

DR. MOORE: And a question for Dr. Goldberg. You mentioned that it will be several years before these randomized clinical trials on procalcitonin are complete. Does the FDA have a position on whether they are recommending, you know -- and I guess what I'm saying is I know that the FDA is soliciting comment and feedback from this Panel, but I guess the question is does the FDA have a recommendation about whether to go forward or not with this indication?

DR. GITTERMAN: To address that question, we may at the end of the day.

DR. MOORE: Okay, thank you. Thank you.

(Laughter.)

DR. MOORE: That's what I needed, thank you.

DR. FOLLMANN: Thanks. This is Dean Follmann.

I had a couple questions for Dr. Li. The first one had to do with the lack of success criteria for the safety endpoints.

DR. LI: Um-hum.

DR. FOLLMANN: You know, if this was a prospectively defined study, we would think about having a non-inferiority margin for, say, mortality and duration of hospitalization, those being the two sort of safety endpoints, but you chose not to do that. Could you comment on why that was?

DR. LI: You mean I didn't choose to use a non-inferiority margin when we

designed --

DR. FOLLMANN: Right, you didn't have -- there wasn't a pre-specified non-inferiority margin.

DR. LI: I would say this is not an FDA decision, not choosing --

DR. FOLLMANN: Uh-huh.

DR. LI: -- a non-inferiority margin, yeah.

DR. FOLLMANN: Okay. So effectively, I guess the Panel will think about what margin we might like to think about.

DR. LI: Yeah, I think there will be a discussion to see what is the margin for non-inferiority.

DR. FOLLMANN: The other comment I had, had to do with Slide 38. So I appreciated your comments about really if you have this kind of design and the usual care and then the guided therapy, some patients will both get antibiotics for a long duration and they will have similar outcomes, and so it can dilute the treatment effect.

DR. LI: Um-hum.

DR. FOLLMANN: And so I appreciate trying to get at subgroups where there will be a difference in duration of antibiotics or initiation.

DR. LI: Um-hum.

DR. FOLLMANN: This slide, though, it seems a little problematic, in a way, to me. So if we look at antibiotic initiation, no or yes --

DR. LI: Um-hum.

DR. FOLLMANN: -- that's sort of a post-randomization variable. It's going to be very different in the two groups.

DR. LI: Right.

DR. FOLLMANN: And so if we look at the first two rows, there are 120 in the control

who didn't initiate and 254 in the PCT group which didn't initiate.

DR. LI: Right.

DR. FOLLMANN: This would be expected, there's less reason to initiate antibiotics there. But those two are not sort of balanced by randomization, the numbers are very different, the kinds of patients that there might be could be very different.

DR. LI: Right.

DR. FOLLMANN: So looking at like the odds ratio on the bottom is -- I think it has the potential to be misleading because it's not using a baseline variable to look at the effect of the treatment.

DR. LI: Um-hum.

DR. FOLLMANN: It's using something post-randomization. We no longer really have a randomized trial, and so in my mind, there are better ways to try and get at this dilution effect, and maybe we can talk about that more in the afternoon.

DR. LI: Yeah. Yeah, I agree. Yeah, that will be -- um-hum.

DR. SKATES: This is Steven Skates.

A question for Dr. Goldberg. Your last conclusion slide, the end statement, there was -- this is Slide 33 from your deck -- significant concerns exist regarding safety and conditions of use. I'd really appreciate you elaborating on that statement because the Sponsor's study or meta-analysis showed fairly tight confidence intervals for the mortality comparison between PCT use and no PCT use. And this gets to Dean's question about margin for error or margin for adverse events. So if you could elaborate on that and say whether that margin is involved in that conclusion of significant concern, I'd appreciate it.

DR. GOLDBERG: So I mean, I think this is more in reference to our concerns regarding the impact of adherence on our estimates of safety and if the safety was extrapolated across all of the different patient subgroups, inpatient, outpatients, questions

along those lines. So I think a lot of the mortality estimates are the data as a whole.

DR. SKATES: So the concern is that with patient subgroups, the sample size is small, and therefore the confidence interval gets wide, and therefore for certain subgroups, there is a concern as to whether the mortality actually could be increased in the PCT group. Is that the --

DR. GOLDBERG: Well, that and I think the adherence question as well. For some studies we didn't have adherence estimates, so it's hard to say if you do strictly adhere to the guideline for the recommendations for the PCT-guided therapy, will you see a difference in your safety outcomes?

DR. SKATES: And you expect, if you do adhere strictly, that risk could increase; is that the --

DR. GOLDBERG: Yeah, I think the concern would be that if you kind of arrive at your clinical judgment, that it's hard to say how many people would do that. But certainly I think that as, you know, clinicians get more experience with the algorithm, the adherence may change.

DR. SKATES: Okay, thanks.

DR. HANSON: Hi. Kim Hanson.

A question on the study inclusion criteria for many of the studies that were included in the meta-analysis. I see many of these excluded immunocompromised patients. Were there any other vulnerable or high-risk groups that were excluded, for instance, in the lower respiratory tract studies, excluding cystic fibrosis patients or other groups that we should be aware of? And will there be an opportunity, potentially in the labeling, for conditions of use that specifically exclude high-risk immunocompromised pediatric patients, for instance?

DR. GOLDBERG: Yeah. Certainly, the inclusion/exclusion criteria vary across the different studies. Generally, cystic fibrosis patients were excluded, pregnant patients were

excluded, children were excluded. It kind of varied from study to study, about what they felt was a high-risk group. In terms of limitations, yeah, I think that if the patient wasn't studied, there would be an opportunity to include that as a limitation in the labeling.

DR. HANSON: And another question on subgroup analyses. I was interested to see that actually different procalcitonin assays were used in some of these studies and that there was variability in those assays and their ability to quantitate at the lower range. Was subgroup analysis done for studies that used the assay that we're talking about today, specifically with the algorithm that we're talking today, and were there any differences noted there relative to other studies?

DR. GOLDBERG: Yeah, that may be a good question for bioMérieux because I believe that they did do those analyses, but I don't have the data on hand at the moment.

DR. CALIENDO: Okay, so we can get to that during the Panel deliberation.

UNIDENTIFIED SPEAKER: I have two questions. You mentioned that taking steroids can dampen the PCT response. What about nonsteroidal anti-inflammatories, common ones that could be used like ibuprofen?

DR. GOLDBERG: I'm not aware of any data regarding the patient nonsteroidal anti-inflammatory PCT value.

DR. CALIENDO: Angie Caliendo.

The same question with azithromycin. How do we sort out the anti-inflammatory part versus the antibiotics? I think that was brought up earlier. Maybe, Chris, I think you brought it up. Any way to get our heads around that?

DR. GOLDBERG: Yeah. Well, presumably when you're first having your PCT level drawn, you won't have an anti-inflammatory on board at that moment, but in terms of --

DR. CALIENDO: Well, I mean some chronic lung disease --

DR. GOLDBERG: Yeah.

DR. CALIENDO: -- are on it for that purpose, particularly COPD. So there's no way to get to the bottom --

Okay.

DR. SKATES: Hi, it's Steven Skates.

One of your slides was a presentation of the scales balancing risk and benefits, and it's helpful to assist the worst-case scenario of risk to the benefits that are being observed here. So for the effectiveness endpoint, on your Slide 11 there's an odds ratio of 0.26. So presumably that means initiation was reduced by a fairly substantial fraction, 74 -- you know, 0.74. And sorry, this is Dr. Li's slide, actually No. 11. So 0.74, I take that roughly as saying that three-quarters -- going from odds to a probability, but about three-quarters of the time we had a reduction in initiation of antibiotic therapy because you used PCT.

I want to contrast that with the safety and trying to get that on the same scale and you -- and Dr. Li's Slide 36, there was an odds ratio of 0.94 for mortality, but it could go from 0.69 to 1.28, so potentially a worst-case scenario of increasing mortality by 0.28. And what I want to try and do is understand whether that's on the same scale as the 0.76 reduction for reducing antibiotic use. What is the balance there? Is 0.28, which is the potential increase in mortality, comparable to a 0.74 reduction in antibiotic use? So that's what I wanted to try and grapple with. What's the appropriate weighting to compare the risk and benefits?

DR. GOLDBERG: I mean, that's a very difficult question, and I think that's partially why we've convened the Panel today. So a lot of the studies did not look at the magnitude in reduction of like antibiotic-associated side effects, so a lot of times you see a duration, and the presumption is that you're going to see a decrease in *C. diff* colitis and some of the side effects with these. And certainly, anybody who's had *C. diff* colitis knows that this can be a very, very life-changing event. But again, I don't know that I can really answer that.

DR. CALIENDO: Go ahead, Steve.

DR. GITTERMAN: I apologize, but if I could just partially address that concern in the earlier slide that you had asked about from Dr. Goldberg. One of the reasons is -- and again, bioMérieux can respond, is there actually is not a tremendous amount of data from the United States. And again, certainly I don't mean this as a comment, this is something that bioMérieux can respond to, but these are studies -- you know, these are practical studies in use, and there's a lot more experience with, as Dr. Li had shown very clearly, lack of adherence. Again, bioMérieux can break this down, but it reflects a lot of factors, which of course is clinical intuition, other relationships. And a lot of these are not quantifiable in the sense that were there to be an FDA promoteur in this country, it would be part of the reasons we believe risks exist, is because you're translating something again -- and bioMérieux can contact these academic medical centers, etc. -- different conditions of use, which may not directly translate to the same scenarios as in the United States.

And I believe that was a point you had made, Dr. Goldberg.

DR. GOLDBERG: I think it's also important to know that we don't really know why the patients died either. So there's a lot of uncertainty. Would they have lived if they got antibiotics? I don't know.

DR. CALIENDO: Angie Caliendo.

Can we pull up Dr. Li's Slide No. 24? So if you look at -- so knowing that most of these studies were not done with the VIDAS assay, and that most of the variability between the two assays is under 0.25 -- so if you go down and look at positive and negative percent agreement, it's very good once you get to 0.25. If we look at the proposed algorithm at 0.1, would it be safer to have a 0.25 cutoff for initiation of antibiotics in the lower respiratory tract rather than 0.1, in light of these data? How do we balance that?

DR. GOLDBERG: Yeah, as part of the application process, they'll have to demonstrate

that they can measure around all of the claimed cutoffs.

DR. CALIENDO: But that's not the point; the point is it doesn't agree. They can't do what the comparator did that was used in most of these studies, right? There are differences between their assay and the assay that was used in most of these studies. So is it just safer to say don't use a 0.1 cutoff, use a 0.25 cutoff or not? Is it safer to do the 0.1? Anyone on the Panel have --

DR. GITTERMAN: Angie, there are technical reasons, actually, why these assays may, in fact, be more similar than just random assays, and I suspect that would be a very good question to ask bioMérieux. This is a somewhat unique situation in a lot of ways because, for lack of a better way to describe it, all the assays have a very similar heritage.

DR. CALIENDO: Right. Angie Caliendo.

Correct, but there are clear differences in what they do at the lower end. And so I guess, in my mind, I'm trying to figure out what's the least risk, using the 0.1 cutoff or using a 0.25 cutoff?

DR. GITTERMAN: That's also a question to the Committee.

(Laughter.)

DR. SKATES: This is Steven Skates.

Can I just comment on that? Isn't the difference between the two levels strongly discourage use of antibiotics and then discourage? So it doesn't seem to me -- there's a rather subjective difference between the 0.1 and the 0.25, so both of them say discourage. It doesn't seem to me that there's a huge difference there.

DR. CALIENDO: So Angie Caliendo.

So I'm looking at this algorithm, and I'm thinking of primary care docs who -- and even ED docs. How can we simplify it? You know, one of the issues that I have with these algorithms is how easy are they to use, and does that contribute sometimes to the lack of

adherence? And if we simplified the number of categories, would that just make it easier? I mean, ultimately the goal, you could envision this being out in primary care practices, and how easy can we make it for people to just interpret the test and use it?

DR. CARPENTER: Chris Carpenter.

You know, to piggyback on that, it was ironic, you were talking about safety, and I would have thought you'd be talking in the other direction because you look at a lower threshold. Obviously, we're not going to go below 0.1, but in terms of safety, you'd be thinking that might be the safer direction to go. So when you're saying to expand to a higher level, I thought that was a little bit ironic.

What I have a question for, and it wasn't really kind of detailed in here, is I understand the levels may be higher in patients with chronic renal failure, and I'd be interested in more information on that and if we need to expand into the afternoon.

The other question I have, there's a lot of our patients with lower respiratory tract infections in the hospital, and especially the ones who are septic in the intensive care unit develop renal failure, and I don't know if the biomarker has been looked at over that period of time. You could come in, and your renal failure is normal based on blood tests, and 5 days later your creatinine is 6, and you're not making urine, and if we're trying to track it through that process, are we going to be able use this marker for that?

DR. GOLDBERG: I think that's a really interesting point. I'm not aware of any studies that look at the effect of chronic renal failure on your longitudinal estimate of PCT values, so if you're less likely to decline or something. There were a handful of studies, mostly in the elderly, that suggested that elderly patients with chronic renal failure have a higher baseline level of PCT, but there's not a ton of evidence really looking at that in depth.

DR. CALIENDO: Angie Caliendo.

But what we're talking about is a difference between acute kidney injury --

DR. GOLDBERG: Um-hum.

DR. CALIENDO: -- and someone who may come in with a normal creatinine and bump to 2, 2½, and somebody with chronic kidney disease. Are there data out there on acute kidney injury?

DR. GOLDBERG: Not that I'm aware of.

DR. CALIENDO: Okay.

MR. SIMON: Tom Simon.

My viewpoint as a consumer and patient, it appears that everything I've heard from the FDA and the company is that everything hinges on the relationship of a doctor and the patient, and I don't know what is being done with regard to that. I know that it's been mentioned. I also had a question with regard to what caused the deaths. But also, could you explain a little further what adverse events took place and how that affects, in your mind, the test going forward? And also, is there a difference between outpatient and inpatient with regard to adverse events and mortality?

DR. GOLDBERG: Um-hum. So bioMérieux may be able to talk about if they saw anything in terms of adverse events in the outpatients. The subgroup analysis doesn't seem to suggest that there is a difference in mortality between inpatients and outpatients, but that is kind of for all outpatients as a whole.

With regards to your first question, so can you --

MR. SIMON: The patient relationship with the doctor.

DR. GOLDBERG: Yeah, yeah.

(Off microphone comment.)

DR. GOLDBERG: Sure. Well, I mean, I think the patient relationship with the doctor is always critical because -- but it kind of comes back to some of the discussions early on. If you have a lot of time to sit down, you know, this is a family that you have a great

relationship with, and they're going to call you if anything happens, you may feel more comfortable withholding antibiotics in that case. But, you know, if you're in an outpatient situation in like an urgent care clinic where you've never seen this patient before and you might never see them again, you might be more inclined to give antibiotics because you don't know them well. But this is more of an additive supportive tool.

MR. SIMON: So that I understand, do you anticipate or does the company anticipate the use of the standard of care and the PCT --

DR. GOLDBERG: Um-hum.

MR. SIMON: -- right, together?

DR. GOLDBERG: Yes, I believe it's been proposed as an additional supplemental lab test.

MR. SIMON: Okay.

DR. JERNIGAN: Just to your point about sort of making the algorithms simpler. I mean, these certainly are algorithms that have been used, I think, in a lot of places and by microbial stewardship programs. But if you're below 0.25, you're essentially not doing anything different than you are the 0.1, so the recommendation is the same for either one. So to me, there could be a simplification because this 0.1, maybe you'll feel better about it, but you're not actually asked to do anything different.

My question, I guess, is about in the RCTs or in the patient-level studies, if somebody had a viral diagnosis they were continued in the trial, right, they weren't removed from that? Or is there any sub-analysis on those that did have a viral diagnosis and how they handled the procalcitonin result?

DR. GOLDBERG: I don't believe that we have any information about the microbiological diagnosis and how that would have affected the management. Some of the studies excluded certain diagnoses, so if it was a patient that they felt was going to need

long-term antibiotics, they ruled them out. But to my knowledge, nothing for viruses.

DR. GITTERMAN: If I could just perhaps slightly address Mr. Simon's question. I expect that everybody realizes that this would be a moderately complex test and would be done only at facilities that have, you know, turnaround time. Right now, the issue of a CLIA waiver is not on the table, and it's not a discussion; it's this is an aid in the use, but that very likely is going to be only places that can do moderately complex tests with a rapid turnaround and that practically -- and again, we're looking to the Committee to say that. But it isn't a case where there will be -- there's likely to be other information.

If I could just make a comment. The question of viral diagnoses is very, very good, and it's only fairly recently that sponsors are looking at biomarkers or are routinely using rapid diagnostic tests that are affordable. Perhaps before 2012 or maybe 2014, it would not have at all been practical. But the tests or sponsors that are doing this now would very commonly use something like the biovar or similar tests to do that.

And one last editorial comment is the issue of balancing adverse events in every way, shape, and form is, you know, part of the reason Dr. Lautenbach spoke. There are attempts to -- you know, the DOOR is really -- again, I'm not saying that it's been successful, but it's certainly a very promising intuitive way to address this, and part of the question facing the Committee is, is this enough to make these decisions now, or is it the more responsible thing? But believe me, I'm not even intimating anything to wait the amount of time that it will be to get really what we might consider definitive information. There's a tremendous amount of information out there, but does it answer the questions enough to make exactly the judgment that you are requesting?

DR. CALIENDO: Angie Caliendo.

Just to add, Dan, to what you had asked, there are data out there, there are studies that have looked at when you have the definitive diagnosis of a virus and a negative PCT

and the compliance with the algorithm, the confidence that physicians have in stopping the antibiotics is remarkably low, even though they know they have flu or RSV and they know they have a procalcitonin of 0.1. And there is some data out there. I don't think that it's necessarily in the studies that were presented, but it's a very important point, and it gets back to kind of the complexities of how are we going to get people to change management and use the data.

But I think, Steve, you had a question?

DR. SKATES: Yeah. Steven Skates.

I'd like a little bit of context here in terms of size. There's an application here for expanding the use of PCT. And I think there are three groups or three settings where it's going to be expanded, LRTI inpatient and outpatient and sepsis inpatient. Compared to the current approved use, how much of an expansion is that in terms of patient numbers? Are we doubling the patient numbers, or are we doing it 20-fold, or is it a 10% increase? So can you give us some rough judgment as to what that expansion might entail in terms of just patient numbers?

DR. GOLDBERG: Yeah, that's kind of a tough question because it's hard to say, you know, what's the current baseline use as a mortality assessment or a risk assessment claim. I imagine it would encourage uptake, but in terms of the magnitude, I'm not sure that I can give you a number.

DR. SKATES: I guess I'm trying to get a sense of, for the current indications that are already approved, there's a patient population out there. Whether PCT is used or not, that's not my question. My question is that's a certain subgroup of patients.

DR. GOLDBERG: Um-hum.

DR. SKATES: The expanded use goes to another group of patients. What's the ratio of those two groups? Are we talking -- roughly.

DR. GOLDBERG: Yeah.

DR. SKATES: And maybe the --

DR. GOLDBERG: Yeah.

DR. SKATES: You know, because that gives context of how crucial this issue is.

DR. GOLDBERG: I doubt you would see much change on the sepsis side, so that's basically the same patient population. For lower respiratory tract infections, it's probably more common than sepsis, but really I don't think I can give you a magnitude and --

DR. SKATES: Yeah, I would have thought this is a huge expansion.

DR. GOLDBERG: Yeah.

DR. CALIENDO: Okay, so last question. Tom, did you have a question?

DR. MOORE: No. Sorry, Tom Moore.

I just had a comment that there are data available on a number of outpatient visits, as well as hospitalizations for LRTI released from the CMS database. What you would expect is essentially a 1 to 10 ratio in terms of sepsis versus evaluation for LRTI, which is very common. Of course, it's seasonal, but averaged over the years, it's a very common condition.

UNIDENTIFIED SPEAKER: You said 10-fold.

DR. MOORE: Yeah, it's essentially 10-fold. I mean, there are regional variations and seasonal variations, but on average it's about 10-fold.

DR. PETTI: And one quick question.

DR. CALIENDO: Go ahead.

DR. PETTI: This is a very specific FDA question. When we're evaluating the feasibility of an expanded use, does the Panel have the ability to request, I hate to use this word, a postmarket surveillance special control?

DR. GITTERMAN: That's a very, very interesting question.

(Laughter.)

DR. GITTERMAN: As a 510(k), the answer is no. I would say the Panel's recommendations make them, but there's -- how would I describe it? There are different scenarios, and if the Panel were to decide that the question could be answered only in the setting of certain additional studies that would be performed, we can make this happen, but not under the 510(k) paradigm.

DR. CALIENDO: Okay, so we're going to take a break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room promptly at 12:45. Please take any personal belongings with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

And anybody who's giving a public comment after lunch, could you please give your material to the audiovisual people?

Thank you.

(Whereupon, at 11:48 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:50 p.m.)

DR. CALIENDO: Okay, let's get started here. So it is -- oh, my goodness, it's 12:50, and we're going to resume the Panel meeting. We will proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Craig will read the Open Public Hearing disclosure process statement.

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

FDA has received 10 requests to speak prior to the final date published in the *Federal Register*.

DR. CALIENDO: Okay, we will now begin the Open Public Hearing. Our first speaker is Sean-Xavier Neath. Please come forward to the microphone. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings

of the meeting. At the conclusion of all of the Open Public Hearing presentations, there will be time for questions from the Panel members.

DR. NEATH: Good afternoon. Thanks for having me. In my 7 minutes in the postprandial slot, I will try to keep you awake with some gentle views and opinions from the role of procalcitonin in improving medical decisions from the emergency department. I am an Associate Professor of Emergency Medicine from the University of California, San Diego systems. We see both very high-acuity patients and sometimes we're primary care doctors, even for the people with insurance who can't get in to see their own. So you'll see a little bit of a mix.

The reality of emergency department care -- there's probably a high probability that almost all of you have experienced something like this with a loved one or a family member. It's a loud, over-stimulating environment. Those of you who are internists might be embarrassed by the fact that I probably haven't heard an S3 in over 10 years. We have multiple comorbidities of the typical ED patient that puts them at much higher risk for evolving to serious bacterial infection. And so in a risk-aversive environment, that oftentimes leads towards a prophylactic administration of antibiotics.

There's also a high patient expectation for antibiotic therapy for a suspected infection. Educating why not to take antibiotics takes 10 minutes out of my 5 minutes with someone. Prescribing those antibiotics takes less than 1 minute. And this was referred to by multiple speakers earlier in the day; it's a very complex situation that we're in.

One of the more important advances in sepsis care has evolved into a CMS bundle, which, in itself, if you look at the spirit of it, is quite good. In the end, it has, of course, created a whole intricate web of things that we now need to document for our sepsis patients, and the absence of the administration of broad-spectrum antibiotics has to be carefully noted. For instance, if I have an undergraduate student with streptococcal

pharyngitis who actually has the research criteria and low blood pressure, I need to justify why I only gave penicillin. And so we kind of -- we're between a rock and a hard place with doing the right thing and then either underperforming or overperforming.

So where PCT has a value in this is that if you see on the left side of this slide, my patients don't come in with a problem list like the left side. I had to dig around in EPIC to find that one. Most of my 70-year-old patients have the problem list on the right side. So I'm looking at this in the context of multiple comorbidities and a decision of whether they come in with dyspnea, confusion, fever, whether this represents a serious bacterial infection.

I think this is strongly supported in my institution. There's a very good evolution in the dataset for procalcitonin that we now have enthusiasm for integration into our existing sepsis pathways with multidisciplinary support from the emergency department, infectious disease, hospital medicine, especially in critical care. And the review of the existing data, in our opinion, support the utility of identifying a serious bacterial infection of broad patient populations.

Part of my personal research interest has been historically in identifying the subset of CHS patients who have superimposed pneumonia or in whom are missing the diagnosis of pneumonia. This was a large multinational center trial a few years ago that I had the good fortune of being a part of. I'll just show you one piece of data from there.

Basically, this was an all-comer study for patients with dyspnea presenting with shortness of breath. There were analyses for heart failure and analyses for pneumonia. The prevalence in this all-comers population -- it is multinational, both Europe and the U.S. as well as Australasia -- was roughly 10%. Interestingly, a separate figure, the number of heart failure patients ultimately diagnosed with superimposed bacterial pneumonia by final adjudicated pulmonary diagnosis was also 10%.

So PCT, for us, in a high-acuity patient, is useful in determining whether bacterial infection is either the cause or part of the cause of the patient's presenting symptom complex. I think we've also realized, from our hospital physician colleagues, that there's a great deal of downstream utility for them to guide management. So when I have emergency physician colleagues who say why do I need to order procalcitonin, I don't really do much for it, I really know what's going on with the patient, I actually reply to them, well, why do you order blood cultures? You don't actually ever get an actionable result in the emergency department on blood cultures, but you are doing them for your colleagues' downstream management of that patient.

And finally, there's a very useful negative predictive value for us that can use -- that we can use to avoid some harmful or unnecessary therapies in patients who look like pneumonia but actually are pure heart failure or COPD.

So what about PCT in the less sick ED patient? And this was a topic of conversation when we talked about outpatient/inpatient. ED divides that gap. So you come in the emergency department as an outpatient, and you remain an outpatient until you're admitted or sent to ED observation or an acute care home, and a large number of our patients are treated as outpatients.

The fear of patient complaints and dissatisfaction are perennial. Internists know this, pediatricians know this, we know this. And now our patient satisfaction is part of the reimbursement model, very well ingrained now.

More than half of the outpatient lower respiratory tract infection with viral etiologies inappropriately receive antibiotics. We've seen that data multiple times in different slices through this day. And then an adult/pediatric ED study shows that antibiotics are prescribed inappropriately for about almost 70% of patients with acute bronchitis. So this is a huge issue.

So my doctor, my pit doctor's perspective of PCT is that it's useful in both high- and low-acuity patients where some clinical indecision exists about the presence or absence of serious bacterial infection. It does reduce unwarranted antibiotic exposure, the data support that, and in a less sick patient, it can give both the clinician and the patient confidence in foregoing unnecessary antibacterial agents. That conversation, that 10-minute conversation with a mom about why the kid's not getting the antibiotic, or with the patient, can actually become a quicker conversation when I say I have this tool, in addition to your negative chest x-ray and my exam, to support the fact that this is a viral etiology.

So I came in under time, and thank you.

DR. CALIENDO: Thank you.

I think what we'll do is we'll do all the public comments, and then we'll have time for questions at the end. So thank you.

Next is Dr. Broyles from the Five Rivers Medical Center.

DR. BROYLES: Thank you, panelists. I am a Pharm.D. I specialize in infectious diseases and have worked in that area for a little over 25 years. What I'd like to share with you is how we've been able to apply procalcitonin use in the management of sepsis and respiratory tract infections and then show you some outcomes from our study.

So as far as disclosures, I have participated in advisory boards for Thermo Fisher and Roche Diagnostics, and I'm frequently paid to speak on sepsis and on procalcitonin and those types of topics that are infectious disease related.

As far as how we came about the implementation of procalcitonin, some years back, when the ProHOSP/ProRESP papers came out, I found them very useful, and even though it was European data, the concept behind it seemed very solid to me. And so with that, that data, the application of the sensitivity and the specificity and the kinetics of procalcitonin, it seemed very likely that it could be a very useful tool for us. We already had the bioMérieux

instrument in house; we were using the VITEK instrument or the VIDAS instrument. And so the application of procalcitonin, that was very straightforward, so it allowed us to bring that in.

Initially, one of the things that I knew would be a great problem was the education piece. If this was going to be successful, there was so much to know about it, as you discussed today over and over again, that the education was going to be a key component. And so we structured many programs around that education piece, which I'll talk a little bit more in a moment.

So we took the ProHOSP data and the PRORATA data, and we derived where we are at now from that data initially. And so when we began that program, one of the things, as you discussed, is safety. We were always concerned about safety. And so since this was new, because we'd been doing this for over 6½ years, we decided that we would enroll every patient in that first year into a study, and we would look at outcomes, we would look to see was there a change in any type of outcome. That would be to have adverse drug events, all of those things that are centered around those patients.

And so to mitigate any concerns, we monitored those patients for the first year. After that it wasn't necessary, but we did that for our physicians and our clinicians to make sure they were comfortable.

Our process is this: On admission, a procalcitonin is drawn, and then we repeat a procalcitonin every 24 hours up to the 72-hour time frame, and we will do it more often as needed, but that's our baseline. We place procalcitonin in all of our order sets and then everywhere that we could to make sure that we have procalcitonin essentially in place and it was ordered. We use procalcitonin for all infections, okay? It is going to be a rule in/rule out, and it's going to help us with the management of our therapy. More about that in just a moment.

So with this process, along with education, the other component that became very, very necessary was somebody has to own a process, and one of the things you guys talked about over and over again was adherence. You said we want to make sure that people adhere. And so for that to happen, because physicians see only a group of patients, a group of patients, a group of patients, pharmacy was the one that was seeing everyone, okay? So we made it such that we reviewed all procalcitonin orders. If an order was missed, we picked it up, and then we communicated with physicians and worked in this team approach so that there was a comprehensive net to make sure that the procalcitonin orders were followed up on.

In the study that we did, we brought in all patients regardless of age. We looked at anybody that had an infectious disease diagnosis that required administration of parenteral antibiotics. So if they got an IV antibiotic, they were enrolled in our study. We excluded those patients who received antibiotics for surgical prophylaxis or who were transferred to another facility. Obviously, that would skew your data.

So in this retrospective analysis that we did, we looked at 4 years' worth of patients before our procalcitonin implementation. We were fully implemented in March of 2010. We let that be our washout time frame, and then we looked at 4 years' worth of data post-procalcitonin. So we had 985 patients in the pre-group, our control group. We had 1,167 patients in our post-group. The typical respiratory tract -- the typical infections we saw were lower respiratory tract infection, sepsis, COPD, biliary, and so on. And in relation to what we're talking about today, those are the respiratory tract infections. Of this number, 2,152 patients, over 1,500 patients met those criteria. So we're talking about a very large number of patients.

As far as comparison of the two, we selected a 4-year time frame because we wanted to make sure the two groups were very similar. And indeed if you look, you can see

that the mean age for both groups was 70 years of age, which is similar, statistically similar, percentage male 42 to 43, statistically similar. And when we looked at the diagnosis as far as sepsis, respiratory tract infections, we looked at every one of those, and each one was analyzed to see if they were statistically similar, and the answer is yes.

Now, very important, at least in my opinion, is this one thing we see right here at the bottom, antimicrobial days of therapy per patient. We're looking at exposure of the patient to antibiotics; this is huge. In our control group, we had 16.4 days of exposure to antibiotics per patient, and in our control group -- excuse me, our pre-group, 16.4, our post-group, 9.5. That's a huge decrease in antibiotic exposure, and it was statistically significant.

So if you look at all of the outcomes across the board based on our process that we put in place, we actually were able to show -- because we had a very high level of adherence, we had a 42% reduction in antimicrobial days of therapy. And of note, this is antimicrobial days of therapy, which is a much more accurate measure than daily defined doses. So this is the real deal. And you can see that that was statistically significant.

In addition, we actually were to show a reduction in mortality. Now, of note, many of the studies that were done were in the ICU. This is hospital-wide, but we were able to show a 57.6% reduction in mortality. And also those patients who went to a general med/surg floor who were transferred to the ICU, that was reduced by 60%. Thirty-day readmissions were decreased by 42.7%. *Clostridium difficile* infection, the one thing that we are trying to avoid over and over again, 64.6% reduction, and then a 50% reduction in adverse drug events. All of those were statistically significant.

As far as our algorithm, we made it very simple. We consider cessation of therapy whenever the patient reaches 80 to 90% of the peak PCT or when the absolute value is 0.5 or less. We do exclude patients who are being treated for skin and skin structure infections, osteomyelitis, and endocarditis.

The keys to success is education, education, education. There are two things: education and ultimate ownership of the program.

So in the education component, the one thing that we found to be most successful is that of the initial PCT pathophysiology; you have to understand the process, and the way that everyone learns is through case studies. And we shared case studies, and we had luncheons with our physicians, we had grand rounds and those types of things.

The other component is ultimate program ownership. It has to be in your order sets. You have to ensure that the procalcitonin is ordered, that it's followed up on. And so oftentimes in a test lab, what happens? We get a result, and nobody looks at it. Or we look at it the next day. As we did, it was looked at in a timely fashion, meaning within the next 30 minutes, because it alerted us on our computer system, very, very important.

So, in summary, we found that this process with procalcitonin use has led us to decreased antibiotic use. We've had a significant decrease in mortality, 30-day readmissions, *Clostridium difficile* infections, and adverse drug events. And at this point, based on our quality data, because the outcomes have been so successful and we followed up with our physicians and this has taken place over like 6½ years, we actually have essentially 100% compliance with our algorithm, as far as being able to stop early and those types of things.

DR. CALIENDO: Thank you.

DR. BROYLES: Thank you.

DR. CALIENDO: Just to remind people to please stick to your time as our first two speakers have done. It might come as a surprise, but I, in fact, will cut you off.

Bryant Nguyen is our next speaker from Loma Linda University Medical Center.

DR. NGUYEN: Yes, my name is Bryant Nguyen. I'm the Chief of Pulmonary Critical Care at our institution, also the Medical Director for the ICU. Clinically, I am board certified

in emergency medicine, internal medicine, and critical care. So I do split my time both in the ED and the ICU. So my purpose is to share with you our own real-world experience at our institution with the use of PCT. I do have several disclosures to share.

At Loma Linda, we've used procalcitonin for the last 4 years. It's truly a multidisciplinary approach, house-wide, mainly inpatient. We do not use it in the outpatient setting yet. So it involves the ED, the ICUs, the general ward, the infectious disease physicians, and obviously, our central lab. We do use the KRYPTOR from B·R·A·H·M·S, and we do have a 1-hour turnaround time. But we also, a priori, decided not to collect utility data based on the large amount of data that's already out there. We just started using the marker.

How do we use it? Basically really to guide therapy. So number one is the decision to give antibiotic or not, and number two is, especially in the ICU with sepsis patient, when can we stop antibiotic? Fortunately, I'm pretty confident that not many of our clinicians are aware of the current indications, which is to aid in the risk assessment of critically ill patients on their first day of ICU admission, and also the percent change in PCT level over time also aids in the prediction of cumulative 28-day mortality. For me, unfortunately it doesn't help me guide therapy. If I can predict their mortality, I may put them in a high-risk group, a lower-risk group, but so what?

So we use it to really base on our guidelines. So these are the two guidelines. Being an intensivist, these are critical care guidelines. Number one is to use the procalcitonin level for discriminating infection as a cause for fever or sepsis, and number two is that the use of low levels can assist the clinician in the discontinuation of empiric antibiotics. So that's basically why we do what we do, is based on these guidelines.

So I just want to share with you -- you know, these are true scenarios; one is in the ED. So this is a 28-year-old male with a history of asthma, presented here with a complaint

of shortness of breath for 3 weeks now. The patient went to urgent care a week ago, a chest x-ray was normal, and was discharged home. Now he comes back to the ED, symptoms do not improve on inhaler, but also added with a cough for the last 3 days. Vital signs slightly tachycardic, however, truly unremarkable. A physical exam did show a continued wheeze but no crackles.

We obtained a chest x-ray, pretty normal actually. I don't see any consolidation in infiltrate and pleural effusions. So we decided to order only one test, just a procalcitonin, no CBC, no electrolytes, nothing else, and it was pretty low. So based on that decision, we gave him -- continued the med nebs and added, you know, steroids, and the patient had no repeat ED in the last 6 months. Now, for me, as an emergency physician, no return to the ED is actually a success. So that was a very nice illustration of how we use just a single test to help with clinical care.

The next indication is really to stop antibiotic, and this is just, you know, another way of looking at the algorithm, and you know that 0.5, you know, for sepsis patient, greater than 0.5 suggests there is still ongoing infection versus less than 0.5. So we use this in our clinical care of the sepsis patient in the ICU.

So this is another scenario. It's a 74-year-old female now in the hospital for 33 days, presented to me for the first time in the ICU on Day 1. She does have a history of renal transplant rejection and now on dialysis; atrial fibrillation, hypertension, diabetes, coronary bypass surgery, and *C. diff* as well. Over the last month, during this hospital course, she's had a perforated chole that required a cholecystectomy, pneumonia, fungal UTI, and also viremia. So at my first evaluation of her, she's now in the ICU for acute respiratory failure, she's on vancomycin, pip/tazo, levofloxacin, fluconazole, and metronidazole. I don't know what else we can do as far as antibiotic. And she's been on these actually for the last several weeks.

So our coach isn't here, so my resident actually said, well, we need to either change antibiotic or consult ID to add something else. I said, well, why don't we just get a procalcitonin, and it's actually slightly greater than 1. So based on the clinical judgment, number one, the patient has renal insufficiency; number two, she's been in the hospital for 4 weeks now, so the PCT must have been much higher than this; and thirdly, this is my only level, so I need to make a clinical judgment, and it was really to D/C the antibiotic, especially when all cultures have been negative. And the patient actually just had a transudative pleural effusion and needed some drainage and then doing pretty well.

So obviously, my resident said, well, let's call ID consult to make sure that we did the right thing. So our chief of ID has a very nice way of incentivizing de-escalation. So she would give us, you know, a nickel if we gave appropriate antibiotic. She'll give us a quarter if we deescalate. I actually had a dollar because I was bold enough to just discontinue them all. So that's our experience, you know, that's one clinician experience, but really representing how we do this at our institution.

This is now the real-world data. So this is a paper in print in *Chest*, by Bob Balk out at Rush Medical University, and basically he's looking at the Premier healthcare database. It's a database of, I would say, close to 700 hospitals in the United States, and they have data on billing costs, medical treatment, device use, procedures. And what he did was basically look at the patient who had procalcitonin over the last, you know, 3 years, in January to May of '14 -- January '11 -- in 550 hospitals, and to the left is a patient who had one or two measures of PCT during their first day of ICU admission versus those that did not have PCT at all. And as you see, consistent with the previous meta-analysis, the data is very similar in real-world practice. On the left, decreased hospital days, decreased ICU length of stay, decreased total cost, decreased antibiotic cost -- even though not significant -- decreased antibiotic exposure, and also increased number of patients that we're able to

discharge home successfully. Similarly, to the mortality of the meta-analysis, there was no difference in mortality.

Recently, at the IDSA annual meeting just a few months ago, the same group presented this -- also another paper looking at the use of procalcitonin compared to C-reactive protein in the United States, and basically the red graph there is CRP. There is increase over time, but a slow increase compared to PCT, which is the blue graph, a significant increase in the last 5 years compared to the trend of increase of CRP.

And in the last year, 2014 and 2015, he estimated in the nation -- so this is basically the graph shows 568 hospitals, but if you estimate it in the United States completely, he showed that there's actually 1.5 out of 29 million patients actually receive PCT measurement while they're in the hospital.

So, in summary, I believe usage of PCT has increased significantly over the last decade in the United States, and we use it -- at least I know I do -- really to use PCT to guide our clinical decision making based on guidelines recommendation and mainly non-U.S. data. So I think having an indication for PCT use to guide therapy in patients with infections definitely would be valuable.

Thank you so much.

DR. CALIENDO: Thank you.

Our next speaker is Dr. Sakoulas from the University of California School of Medicine.

UNIDENTIFIED SPEAKER: Uh-uh.

DR. CALIENDO: No, but he used his 15 minutes.

UNIDENTIFIED SPEAKER: No.

DR. CALIENDO: No, I'm sorry.

(Off microphone comment.)

DR. CALIENDO: No. Who's keeping track of time? Did he do 15 minutes?

(Off microphone response.)

DR. CALIENDO: Yeah, 7 minutes. Okay, sorry. This is Dr. Leibenberg from Thermo Fisher Scientific. Sorry about that, sir.

DR. LEIBENBERG: Thank you, Dr. Caliendo.

Panel members, thank you for the opportunity to comment on this subject matter here. My name is Volker Leibenberg. I'm Global Medical Director at the Clinical Diagnostics Division at Thermo Fisher Scientific. I'm a physician by training, and I'm working IVD in the industry for more than 10 years now. I'm having global responsibility for the B·R·A·H·M·S PCT product family that we've been talking here all day, and you have seen the many different assays in the various studies.

Over the last years, PCT has been widely adopted into clinical routine across the world, showing an exponential growth. This year, and we heard the numbers before, we expect more than 36 million tests to be used worldwide. At the same time, more than 3,800 publications make PCT one of the best-studied biomarkers in clinical science.

The use of PCT is well established in LRTI and sepsis, across Europe especially. The meta-analysis presented by bioMérieux shows a robust positive effect of PCT for the key parameters of antibiotic stewardship. Several other speakers today provided convincing real-world data from the U.S., in addition to what we've seen this morning.

For several years, PCT has been included in many national and international clinical guidelines. To understand the current low level of recommendation, it's important to consider the slow uptake of new evidence into such guidelines. The benefit of reducing antibiotics is well known for years. Newer data will take time.

The SAPS study, or Stop Antibiotics on guidance of Procalcitonin, published earlier this year, was the first to show a significant mortality benefit in the PCT treatment arm of more than 5%. The interventional trial enrolled more than 1,500 patients, making it the

biggest prospective interventional study in the ICU to date. And as you can expect from the epidemiology, a majority of patients had a respiratory tract infection. The power of the SAPS study was sufficient to show a statistically significant mortality benefit despite the rather moderate adherence to the algorithm. The effect of the algorithm adherence on safety and efficacy is of specific interest to this Panel and the FDA, and we talked about this, this morning. The lack of a good comparator for determining diagnostic performance make outcome data key to assess efficacy and safety.

I really want to congratulate Dr. Broyles on his brave approach he just presented, maximizing adherence with a strict protocol and the impressive results he showed us. The tremendous outcome improvement confirms the value of PCT for guiding decisions in patients with suspected infection. It strongly advocates for a strict use of a simple algorithm which is in line with the established cutoffs.

Today we are here because there is still controversy about the efficacy and safety of procalcitonin. History in medicine tells us that such controversy will take time to resolve. The clinical assessment of patients with suspected infection and multiple comorbidities is, and will remain, a complex challenge. Let's not forget that the information available in time for decision making is limited and often desperately needed, and we saw cases of this today, too. There is no proper gold standard to compare to, making it really difficult to create a yes/no answer and actually trust it.

The established PCT algorithm contains several cutoffs due its risk-based approach and alignment with clinical judgment. This might not be as straightforward as we wish. Yet it's comparable to other well-established and FDA-cleared biomarkers, like BNP or troponin, using multiple cutoffs, gray zones, repeat measurements for decision making.

The excellent correlation of a B·R·A·H·M·S assay around the clinically relevant cutoffs allows us to compare the results from clinical studies and routine use across the complete

B·R·A·H·M·S product family.

So let me conclude. Overall, PCT has been shown to be a clinically useful and robust tool to guide antibiotic treatment decisions. It adds valuable information in time to remove uncertainty and has been shown to reduce mortality. There are several studies ongoing, and we talked about this, as well, to provide additional evidence in the future. Nevertheless, the benefit of improvement in PCT as a tool for antibiotic stewardship outweighs the associated risks already to date. It's time to implement it.

Thank you for your attention.

DR. CALIENDO: Thank you.

Okay, so our next speaker will be Dr. Sakoulas from the University of California School of Medicine.

DR. NEWTON: I am not Dr. Sakoulas. My name is Buddy Newton. I'm reading his written statement and it says:

"Good afternoon. My name is George Sakoulas. I am currently a physician-scientist at San Diego, California. I spend about 70% of my time as an active infectious disease clinician in the Sharp HealthCare system and the remainder as a translational research scientist at the University of California, San Diego School of Medicine. My current positions offer me the unique opportunity to practice medicine and medical research on a daily basis.

"In the past several years, the VIDAS PCT assay has been integrated into the clinical decision-making process regarding antibiotic prescribing in our hospital system. It is available as an in-house assay that is used daily by my hospital's critical care and infectious disease colleagues when evaluating patients with suspected lower respiratory tract infection or systemic infections. I believe that the VIDAS PCT assay would have an important role in integrating the art of clinical impression into the expanding data-driven practice of medicine. It adds a supportive piece of laboratory data to the clinical

assessment of patients to help guide judicious antibiotic use.

"Currently, every day in every hospital around the country, clinicians are prescribing, perhaps over-prescribing, antibiotics to patients who may not need them or continuing antibiotics when they are no longer necessary. This practice is speeding up the rates of emergence of various forms of antibiotic resistance. It's driving up costs of healthcare directly by usage of drugs that are not necessary, but more importantly, indirectly by increasing complications due to adverse consequences of antibiotics.

"Duration of antibiotic therapy is perhaps the area where there's greatest room for improvement in antibiotic stewardship. When I was in training, the majority of infections were treated with 14 days of antibiotics. As a trainee, my attempts to get a specific answer from my mentors as to how this duration was chosen proved unsuccessful. It was only recently, in preparation for a research lecture, that I realized that these durations likely originated from case reports on the first use of antibiotics from the 1940s. Many of us have read the story of a 4-year-old girl whose life was saved from a severe group A strep infection by 14 days of penicillin in 1943 in the Mayo Clinic. While miraculous, these fairly arbitrary treatment paradigms from 70 years ago are the basis for much of our practice today. However, with a dwindling supply of antibiotics and the use of these precious resources, we need a reevaluation.

"The VIDAS PCT assay is an important step in helping us guide duration of antibiotic therapy on a case-by-case basis rather than the arbitrary standard set decades ago. In the past, clinicians lived and died by clinical impression, but treatment decisions are now moving to be driven by objective data, data to support actions taken and actions not taken. PCT may offer tangible evidence for or against treatment in some patients when the traditional markers, like elevated white blood counts and fever, are unreliable. A clinical impression supported by objective data is the ideal combination for the practice of

medicine. Downstream, the benefits are clear and critical, lowering patient treatment costs, reducing antibiotic resistance, reduced rates of complications from antibiotic use, such a *C. difficile* colitis.

"I believe that combining clinical judgment with PCT will offer doctors the best possible opportunity of appropriately treating LRTI, or lower respiratory tract infections, and sepsis patients.

"Sincerely, George Sakoulas."

DR. CALIENDO: Thank you.

Our next speaker is Dr. Amin, Medical Director of BayCare eCARE.

DR. AMIN: Good afternoon, and thank you for the opportunity to speak. We've been using procalcitonin since it first was available in 2008 in the community setting.

For disclosure, I have been a speaker and consultant to bioMérieux prior to this, not including this project, and I'm being expensed for this trip up here from Florida.

So this is an interesting statement I saw in an early quote from '61, from an infectious disease consultant, 1961. It says, "Antimicrobial therapy saves thousands of lives and relieves much suffering, yet...untoward effects, harm and death may occur after logical, but especially after indiscriminate, prescription. The proper use of antimicrobics can be attained by comprehension of their place, value, and proper dosage in amount and time. Empiric and experimental therapy is justified if properly controlled. The Hippocratic injunction 'first do no harm' or the question 'Is this drug really necessary?' are pertinent. Much needless expense, untoward effect, harm and disappointment can be prevented by better judgment in the use of antimicrobics for prophylaxis and therapy." That was in 1961. At that point, only the UK had MRSA, developed in '60 and then in the U.S. in 1968, very farsighted.

So we've discussed previously the rationale for antibiotic stewardship, and I won't go

through all of this again, but we see these complications every day: antibiotic-related diarrhea, *C. difficile*, renal failure. One article struck out. In the mid-1970s, 72 to 85% of patients being given antibiotics for respiratory tract infection is probably unnecessary. Those numbers have improved somewhat, but still we see a large number of patients getting unnecessary or prolonged use of inappropriate antibiotics.

So what are the barriers to utilization in a community hospital setting? I didn't introduce myself properly. I'm board certified in critical care, pulmonary medicine, and internal medicine. Community hospital system, we have a nonprofit system, so 11 hospitals. In my hospital, it's got 450 beds. I'm Medical Director of ICU and also the eCARE system. And through that, we see a lot of patients and see what's being done, and we've been managing patients either through eICU or on the floor daily.

So the lack of guidelines, formal guidelines, has been a barrier. So when we start educating them with how to use PCT using the algorithms you've all seen, adherence is not dramatic, it's not great, and you need everyday education and reeducation. They're easy to use, and they're often a crutch. Well, 1 or 2 more days, just give an antibiotic, it's not a problem. Well, we all know it is a problem. It creates patient satisfaction, as has been iterated before. It takes me twice as long to say why it's really not a good idea to have an antibiotic versus "Here, just have a prescription and I'll see you later."

A rapid diagnostic test may hold the key to development of rational strategies for antimicrobial stewardship in the hospital setting and in the ICU.

This is an early study from Beat Müller's research group, and what it showed was that the dark blue circles on the far left-hand side had a much better sensitivity and specificity when you did multiple PCTs in the first 72 hours and one at discharge, compared to lactic acid, which is a standard for sepsis and differentiating SIRS from sepsis.

A lot of the studies that have been done before, when we talk about sensitivity and

specificity, especially the positive predictive values being done on single one-point-in-time testing, nobody comes to the emergency room with chest pain and walks out with a single troponin; they all get serial troponin, and individual troponin sensitivity and specificity is not great in that clinical setting. You do a second one at 6 hours, a third one at 12 hours, and your sensitivity and specificity goes up dramatically, as you can see.

We do this in our system now; it's on our sepsis protocol and pneumonia protocol. So we do a 0, 12, 24 if they're septic, and 0 and 24 if it's a respiratory tract infection, LRTI. That helps us with diagnosis. It also helps us with stewardship.

But again, a single point-in-time PCT may be helpful early on, but certainly the repeat testing is very helpful, and the negative predictive value is not elevated at discontinuation of antibiotics. And here, you can't read the numbers, they're in the 90s, so positive predictive value and negative predictive value, when you do multiple testing in a short period of time, compared to lactic acid, which is in the 30 to 40% range.

There have been some recent guidelines, as has been pointed out, in microbiology, and it says biomarkers can guide treatment duration by an application of predefined stopping rules for antibiotics. It has been shown that such rules work even in the most severe patients, in the septic patients. The Surviving Sepsis Campaign guidelines said we suggest the use of low PCT to assist the clinician in discontinuation of empiric antibiotics when no evidence of infection is found, so look for something else.

More recently, the IDSA guidelines for healthcare-associated pneumonia or hospital-associated pneumonia, the question was what is the optimal duration of antibiotic therapy for hospital-acquired pneumonia or non-VAP patients? The recommendation was the patients with HAP, we recommend a 7-day course of antimicrobial therapy, a strong recommendation with very low-quality evidence. And they also added to that, use clinical information, of course. Another question in that same section in XXIV: Should

discontinuation of antibiotic therapy be based upon PCT levels plus clinical criteria or clinical criteria alone in patients with HAP/VAP, healthcare-associated pneumonia or ventilator-associated pneumonia. The recommendation was that patients with an HAP or VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy rather than clinical criteria alone. And that was a weak recommendation with low-quality evidence. Slightly better than the previous one, but a lot of this is empiric 7, 14, 10 days, but you have a test now that allows us to do this more personally for the patient.

You've seen some of this data from ProREAL. I'll move on quickly here. But the community-acquired pneumonia, bronchitis, COPD exacerbations, asthma, there's a significant reduction in using antibiotics if the initial PCT was negative. And that's with starting or not starting antibiotics. Multiple studies have shown, whether it's in the home setting, ED setting, or in-hospital setting, as we've seen -- it's not moving -- to reduce duration of antibiotics.

We were the one U.S. site in the ProREAL study, in conjunction with French and Swiss sites, showing that the utilization varied based on the experience of the centers and type of infection or problem that was available. So things like bronchitis, there's a big reduction in antibiotics. COPD, not so big, but duration was reduced and total antibiotic exposure was reduced. The U.S. site, our site, had a 30% compliance rate compared to other European centers because we were kind of naive to the test, and it was hard to get physicians to stop using antibiotics even if they had a negative or low PCT. That was in 2012. I think we're much better right now, and that's being done.

We used the same algorithms everybody else has talked about, a cutoff point of 0.25 for LRTI or 0.5 for sepsis. If we see two negative or low PCTs in the first 24 hours on patients with an LRTI presentation, we'll stop antibiotics at that point, but collecting data.

This, I think, is probably the single most powerful tool we have in education. This is from the electronic medical record, a patient with sepsis from pneumonia. This is a dynamic test. Infection, lower respiratory tract infection or sepsis is a dynamic process. A one-point-in-time test helps a little at the front end, but see how it goes up dramatically and then comes down with treatment of intervention with antibiotics, fluids, resuscitation. When you see that procalcitonin-time level come down with appropriate therapy over a period of time, very predictably, even in patients with renal failure on administrations, we'll see the elevation and we'll still see the drop with appropriate therapy. That is very compelling evidence to tell the other clinicians that this patient is getting better. And when we show this on the medical record, people are convinced that clinicians are getting better. Plus, if we're seeing this, it may be a reason to stop antibiotics when the levels drop by 80%. Just seeing a number in isolation isn't that compelling.

And here's one quick case study. This is an elderly female who came in -- this was in 2008 December -- with an upper lobe infiltrate, treated for pneumonia and went home feeling a little better but not dramatically. We didn't see her on that admission. After Christmas, she came back in the following year in 2009 January. She still has a big left upper -- right upper lobe infiltrate and had some more infiltrate in the right lower lung field and on the left side. We were consulted that time because she was getting hypoxic, getting sicker, not responding to antibiotics. I did the PCT. We were able to get one from the day before because the blood sample was stable, had negative PCTs.

Looking back at her admission in December, she had negative PCTs, but having, too, the antibiotics -- because, as somebody said, there's no point in doing a test if you don't look at the result and act on it. So we acted on this, saying, look, we don't think she's got a bacterial infection; we need to do something more aggressive. We got a CAT scan done that showed significant dense infiltrates and effusion. No heart failure; the echo was fine.

Did a bronchoscopy biopsy; she had a diagnosis of bronchiolitis obliterans organizing pneumonia. This was not bacterial pneumonia. So the negative predictive value to allow us to move forward more quickly within 2 or 3 days rather than a week or two of trying antibiotics is very powerful.

We talked about starting antibiotics and de-escalation, which is all great data, but this is a great example of when antibiotics can actually be harmful because they stop you from looking for other things for a period of time, which could be potentially fatal.

We feel, in our system, when we have it in our order sets to use PCT in LRTI and sepsis, it's helpful in diagnosis, initiation. Probably most importantly is de-escalation, which is a huge problem and not taken appropriately, but I think it has very valuable value there.

Thank you.

DR. CALIENDO: Okay, thank you.

Our next speaker is Dr. Newton, speaking on his own behalf this time, I assume, from Washington Regional Medical Center.

DR. NEWTON: Yes, I'm still Dr. Buddy Newton.

(Laughter.)

DR. NEWTON: I am being reimbursed for this trip by bioMérieux, but no other compensation has been given.

Speaking on my own behalf, this is where I work. We're a 366-bed community hospital, going to 425 next week. We're a Level 2 trauma center, and we have a 40-bed ICU staffed by full-time board-certified intensivists. We're also a center of neurology, a center of excellence for endovascular neurosurgery and stroke.

Our procalcitonin experience: We began using the test in October of 2012. We've opened it to all providers for any indication. About 75% of our initial procalcitonin orders are entered in the ED. I've tested about over 14,000 patients for a variety of diagnoses

since that time. We've had serial procalcitonin testing available in about 25% of our patients in a retrospective analysis, and we have used PCT for antibiotic initiation as well as de-escalation and discontinuation.

A little more about me: I am a board-certified infectious disease doc. I am the Director of Antibiotic Stewardship for our hospital. I am the Department of Antibiotic Stewardship for our hospital.

(Laughter.)

DR. NEWTON: Right now, people are writing antibiotics willy-nilly because I'm not there.

(Laughter.)

DR. NEWTON: But have we seen an impact of procalcitonin? You can see our length of stay has dropped significantly over that time. I've only looked at this for about the past year, as far as length of stay, and you can see that we're approaching a 3-day length of stay difference in those who use procalcitonin guidance in combination with our stewardship advice.

The impact on length of treatment: Unfortunately, we don't have software that will calculate DOT, so I do the next best thing, and I just count up number of antibiotic days, and you can see that we've had significant declines in our antibiotic length of therapy in approximately 2 days on the average of less antibiotic use. And more importantly is we've been avoiding antibiotic use in up to almost 40% of our patients across the board.

One study we did, we took 857 cases from May of 2013 to April of 2014. These were patients who all received PCT analysis. They also received antibiotic advice through the stewardship program. What I did is divided out those who were compliers with antibiotic advice versus those who weren't and basically showed that we had a significantly shorter length of antibiotic use in that group, comparing the compliers and non-compliers, in both

the advice to give total antibiotic use as well as antibiotic use after the advice was given. We did not show a difference in length of stay between those two groups. That study is currently under -- it has been submitted for publication.

So, summarizing, we have a wealth of PCT experience treating multiple diagnoses. We've learned through experience that there are certain things that it doesn't do well for us, specifically cystitis, cellulitis, localized infections, but things it works very well for, including respiratory tract infection, sepsis, septic arthritis, meningitis. It's very helpful for determining the difference between aseptic and bacterial meningitis, which I don't know why we need to a test to tell us that since the CSF analysis should tell you that without the test. But for some reason, our younger doctors can't get that right.

We have had a shorter length of stay when we have procalcitonin guidance used. We also have shorter antibiotic usage times, and more importantly, we're avoiding antibiotic use in 38% of our patients when ordered through the ER.

Thank you.

DR. CALIENDO: Thank you very much.

Our next speaker is Dr. Mansour from Massachusetts General Hospital.

DR. AMIN: I'm speaking for Dr. Mansour. I didn't go to Massachusetts General Hospital, but I did stay at a Holiday Inn. Sorry.

(Laughter.)

DR. AMIN: So this is his statement that I've been asked to read. He says:

"Thank you to the FDA and this Committee for allowing me to speak you today. My name is Michael Mansour. I'm an infectious disease specialist practicing in the Massachusetts General Hospital in Boston. My clinical work has focus on care of patients, both immunocompetent as well as those who are in deeply immunocompromised states who have complex infections, including pneumonia. As an NIH-funded physician-scientist,

my research goals are to understand the host immune response to better understand why some patients often have a devastating infectious complication while others appear to do well. To answer these questions, I recently undertook a clinical study investigating the prognostic value of serial procalcitonin for patients admitted to MGH with pneumonia.

"In a 4-year study that enrolled 500 patients, we measured PCT sequentially over 4 days for each patient. The goal was to see if serial measurements of PCT could help understand each patient's clinical cause who would require ICU-level care and who came back to readmit. Based on our analysis, which was accepted for publication in the journal *Open Forum Infectious Diseases*, we have found PCT to be an incredibly useful prognostic indicator. Data suggests that serial PCT is able to stratify patients, even those patients who are at the highest risk category for mortality based on the accepted clinical scoring systems such as the PORT score. The prognostic data may have significant impact, including assigning patients to the correct hospital areas, allow for optimizing nursing care and improved and efficient utilization of hospital resources.

"Additionally, I'm a co-investigator in a multicenter NIH-funded study/clinical trial, the ProACT study. This study has two arms, one group of patients randomized to a team knowing the PCT value and another group randomized as standard care. The main outcome is antimicrobial usage after factoring in the PCT value. Based on my first-person preliminary observations from the study, which has not completed enrollment, it is obvious that clinicians allowed to integrate the PCT results have reduced initiation of antimicrobial treatment in admitted patients. Based on the confidence I have gained from working in these two studies, one focus of PCT as a prognostic indicator and the other asking if PCT can be used to guide initiation of antibiotics, I strongly support the use of procalcitonin.

"PCT used in conjunction with clinical assessment can be an invaluable additional metric in helping the physicians make informed determinations about whether to use

antibiotics or whether to continue using antibiotics for patients with LRTI or sepsis. These benefits could be substantial, reduce morbidity from antibiotic-related side effects, more optimize hospital and care resources, and potential reduction in antibiotic resistance and high-yield outcomes. I'm excited to have this product available for LRTI and sepsis.

"I have just returned from the National Infectious Diseases meeting and IDWeek in New Orleans, where a main focus is that of rising resistance rates. This biomarker is something that I could see as a must-have in our daily use and assessment of patients to help curb these alarming rates of resistance. Making decisions about antibiotic therapy is of critical importance. Having this tool to help in that decision making makes sense to me.

"Thank you very much for your time."

DR. CALIENDO: Thank you.

Okay, our next speaker is Dr. Aronoff from Vanderbilt.

(No response.)

DR. CALIENDO: Okay, it doesn't look like he is here, so we'll move on to Dr. Alterman.

(No response.)

DR. CALIENDO: A no-go there. Okay, Dr. Price from the Antibiotic Resistance Action Center.

DR. PRICE: I'm here. I was just in the back.

DR. CALIENDO: We haven't started the clock yet. Don't worry.

DR. PRICE: Thank you. I appreciate that. My name is Lance Price, and as you heard, I direct the Antibiotic Resistance Action Center at the Milken Institute School of Public Health. I started the center in 2012 to help protect the function of antibiotics for future generations.

Just as a matter of disclosure, I have attended bioMérieux-sponsored conferences in

the past, but I have no financial relationships with them. I have no stakes in PCT or their assay, that very long-named assay, and I paid for my own travel to get here today.

So I came here to speak about the urgent need of new diagnostics to aid in antibiotic stewardship. Over the past two decades or a few decades, we've seen two clashing trends; we've seen the rapid emergence of multi-drug resistant bacteria and a rapid decrease in new drug development, and the clashing of these two trends is reverberating in the form of untreatable bacterial infections, or at least very difficult to treat bacterial infections. And for the first time in our lives, we're facing a time where we do see bacteria that are dangerously close to untreatable, and this is going to dramatically change our lives from what procedures can take place in the hospital to what it feels like to take public transportation or shake somebody's hand for fear of picking up a superbug.

I think it's important to remember just where these bacteria come from, right? So a normal bacterial cell can become super or resistant just by making an error in their DNA or by picking up a resistance plasmid from another organism. And these random genetic events are taking place all the time in the background, but it's really under that selection of antibiotics that these superbugs can emerge as serious problems.

And if you think about a bacterium like *E. coli*, you know, *E. coli* can double every 30 minutes. So you can go from a single, you know, resistant cell to billions in 24 hours, and this type of real-time Darwinian evolution can take place in a Petri dish, a test tube, a herd of pigs, or a person. And people who are treated with antibiotics can become walking reservoirs of antibiotic-resistant bacteria, and they can spill these superbugs into the environments around them. So patients treated in hospitals can be sources of drug-resistant bacteria to their fellow patients, and then people who are treated in the community can become reservoirs or sources to their family members or other household contacts.

And it's not just the bacteria that are causing the infections that are affected, right? So antibiotics permeate all the tissues of the body, and they can put this selective force on the normal microbiome of those patients. So even cured patients that no longer have that specific acute infection can become asymptomatic carriers of superbugs.

Now, I'm not saying that we shouldn't treat sick people. We obviously want to treat sick people with antibiotics, and antibiotics are the best therapies for treating bacterial infections. But we have to do more to treat them, to use them more effectively or more carefully because the more we use them, the less likely they are to work. So despite widespread knowledge of this, the CDC estimates that millions of inappropriate antibiotic prescriptions are given each year. So whenever possible, we have to move away from this empiric treatment where clinicians guess at what antibiotics are needed, towards directed therapies where clinicians are treating exactly -- you know, they know what they're treating and why.

So using diagnostics to guide the start of therapy is probably intuitive. But as we've heard today, using these diagnostics to know when to deescalate is also very important. So rapid tests such as PCT can give clinicians the confidence they need to stop or deescalate antibiotic therapy sooner and stop that selective force, that drive for resistant bacteria in those patients, and more quickly move them away from being a reservoir for their fellow patients.

So, you know, the CDC and the WHO warned that we're moving towards a post-antibiotic era in medicine, but it's clear to me that we can avoid this world full of superbugs if we can quickly change the way we use antibiotics, both in human medicine and in animal production, and rapid diagnostics are among the most promising tools for doing this. So because of this, I hope that the FDA will do all that they can to bring new tools, like the VIDAS B·R·A·H·M·S PCT, to the U.S. market so that we can better protect antibiotics for

future generations.

Thank you.

DR. CALIENDO: Thank you.

Does anyone else wish to address the Panel?

(No response.)

DR. CALIENDO: Okay, then I would like to thank the Open Public Hearing speakers for their presentations.

Does anyone on the Panel have any clarifying questions for any of the speakers?

Tom.

DR. MOORE: Yes. So a question for Dr. Lautenbach, if he's still there. A quick question about, you know, it's interesting to me -- I guess I'm wondering how -- if the FDA approves the expanded use or expanded indications of this particular test, how will that affect your study going forward, the use of it in this trial?

DR. LAUTENBACH: You know, I think the -- I mean, I think that remains to be seen. I think the focus of our study is a little bit different than the clinical context in which most of the work that you've heard about in the open comments have been presented, which is more the inclusion of a procalcitonin component in what is really a stewardship intervention. Our study is really meant to identify a patient population in which we believe procalcitonin can help identify a population in which antibiotics aren't needed. So they're slightly different questions, but I think if it were to become routinely available and indicated for something like this, I think we would have to think through that.

DR. MOORE: So the other question is related to what we were talking about earlier, whether someone can explain what was the cause of death in the studies used for the meta-analysis.

DR. CALIENDO: Okay, so right now we're going to focus on the people who spoke at

the public hearing and when --

DR. MOORE: Sorry about that.

DR. CALIENDO: -- those questions are done, then we can open up to both the Sponsor and the FDA.

Are there any other questions? Does anyone on the Panel --

DR. PETTI: I have one for Ebbing before he sits down.

DR. CALIENDO: Oh, Ebbing.

DR. PETTI: Well, while you're up there, you know. I'd just like to clarify and follow up on the question that I had previously, as far as using alternative diagnostic modalities in your patient population, and you said it would be up to -- it was the prerogative of the physician whether or not to enroll the patient in the study, and if they had an alternative diagnosis based on chest x-ray or point-of-care PCR tests, they would not be enrolled. Is there any mechanism or are there plans for capturing that patient population, because they wouldn't necessarily be enrolled yet, so it's like -- right, because you're saying that the physician makes that decision.

DR. LAUTENBACH: So if I understand your question correctly, it's those patients who end up not being enrolled in the study, will we capture information on them? And the answer is yes, although the details of that in the protocol are still being worked out. The same question actually applies to those patients who initially come in with an LRTI and have procalcitonin above 0.1 who wouldn't be included in this study. And nevertheless, that's a population that, although we're not going to capture nearly the data that we would in the primary patient population, it would be an interesting population to examine as well.

DR. CALIENDO: Okay, any more questions for people who spoke in the Open Public Hearing?

Chris.

DR. CARPENTER: Yeah, I think it's Dr. Neath; is that correct? Just I wanted to follow up on your ER experience and wondering about actually if you clinically, or if you've observed clinically that you've actually made a decision on an admission based on the results of a procalcitonin test.

DR. NEATH: So one of the things working in a hospital setting is turf wars, and one of the very difficult turf wars is between hospital medicine and cardiology, and there are cases where, you know, COPD versus pneumonia or CHF versus pneumonia are very difficult to determine. I'm not saying that's an approved indication for PCT by any means, but it's one additional piece of information that buttresses the case to get the patient to the right care level, whatever appropriate level of care or appropriate service of care may be.

DR. CARPENTER: Thank you.

DR. CALIENDO: Tom.

MR. SIMON: Tom Simon.

This is a general question for any or all of the presenters. Have you ever found, in your experiences with the PCT test, that the test showed antibiotics were not necessary but in fact they were? And if so, what happened to the patient, and was their specific infection that always kept coming up that caused that?

DR. AMIN: I'll address that. Devendra Amin.

There are certainly cases where patients need antibodies and PCT level is not elevated. So patients with low-level infection, a little infection on the finger or a UTI were positive, if they do need an antibiotic, their PCT will not go up. But in the respiratory tract infection or septic patient presenting in those two scenarios, my clinical experience in the last 8 years has been no. If they're negative times two in 24 hours and they have been given antibodies, has not been -- there has not been a subsequent reoccurrence in my experience.

DR. CALIENDO: Steve.

DR. SKATES: So I had a very similar question.

DR. CALIENDO: Introduce yourself.

DR. SKATES: Sorry, Steven Skates.

I had a very similar question. We're charged here with balancing the benefits and risks of PCT, and I've heard, with all the presentations in this session, about all the benefits, and I haven't heard about any of the risks, and I want to understand where those risks came from and how they could be minimized. So can anyone, including yourself, speak to that?

So there are two risks; one is a false positive and one is a false negative. So a false positive meaning that it's elevated, PCT is elevated and you act on that, even though it's not a bacterial infection. And the other is what Tom mentioned, which is it's not elevated, and it should have been and you act on that, which is presumably not giving an antibiotic and you should have. So I want to understand how big those two risks were and can they be minimized.

DR. AMIN: Yeah, I think they're both excellent questions, and both scenarios do occur. I think the patient who has a positive PCT that subsequently we find out usually within 24 to 48 hours they probably don't have an infection have different kinetics. You don't see a big upswing and then a reduction with antibiotics occurring. If they're behaving like they're infected and their levels don't come down, then you're kind of missing the boat; you change antibiotics, better source control. We've seen patients with -- rarely, but we've seen patients with things like new endocrine cell tumors, non-small cell cancer that's been 70 or 80 and flat, no signs of infection or sepsis. So after 3 or 4 days, you say, look, this is a cancer; it's not an infection we can stop. Clinical judgment, history, physical exam are integral in using PCT as the additional tool. On the other hand, when we have patients who have negative PCTs but there is an actual infection as in subacute bacterial endocarditis or

low-level infections, again, the clinical history and exam will help you with that, the positive --

DR. SKATES: Okay, but in terms of the two indications or three indications of what we've got here, which is lower respiratory tract infection and sepsis, what's the situation there --

DR. AMIN: I think if you have --

DR. SKATES: -- in terms of false positives and false negatives?

DR. AMIN: Well, from my experience, if you have serial PCT testing in the first 24 hours, the negative predictive value is very strong in that situation to say you can stop antibiotics or you were right to have withhold antibiotics if they're negative. And the positive predictive value, again, with serial testing is very valid and very high levels in the 90% range with serial testing.

DR. SKATES: So does anyone else have evidence as to how big these risks are, which I'm calling false positives and false negatives, and how that can be minimized in these indications that we're discussing today?

Thank you.

DR. AMIN: I just want to point out that in terms of the process of getting new things in, it took 17 years for aspirin to become standard of care for MI. We shouldn't have to wait that long to get a reasonably good approach in managing bacterial infection.

DR. NGUYEN: Yes, this is Bryant Nguyen from Loma Linda.

So I think to really tease out -- number one, it's not a single marker in its own right, right? There has to be a clinical judgment in the background. So if you talk about the risks, I have maybe a case I can remember where a patient comes in with a dialysis catheter, right, has a fever and looks okay. Got a procalcitonin, and it was negative, right? But the patient is actually in shock, has vasopressor on board, and we know that patients in septic

shock, only 30 to 40% of patients actually have any culture positives. So in that patient, even though the procalcitonin is negative, I need to give antibiotic because the catheter, if I did a good -- you know. Unfortunately, a day later when we realized, you know, that's the only source of infection, we massaged the site of the catheter, and there's pus coming out. So, obviously, there's a catheter infection that if we just look at the procalcitonin alone, we would not do the right thing.

Another scenario that we alluded to in a different presentation was the use of lactate as well. So in septic shock, lactate is a sign of hypoperfusion requiring further resuscitation, whereas PCT is an infection. So a scenario could be in a patient who has high lactate but normal PCT, I need to resuscitate the patient. So if you don't check the lactate and your PCT is okay, you may not do the right thing, and in those patients, I would say we need to give them antibiotics as well.

And the converse, in a patient who has high PCT, right, and then pneumonia, for instance, those are the patients that I see but has normal lactate. Well, if we didn't check the lactate and our resident or clinician -- oh, PCT means infection, sepsis guidelines says infection, I have to give a bolus of fluids. Well, if the lactate's normal and the patient has an EF of 20%, I don't need to give fluids. Maybe, you know, very small but not a lot. So there has to be a clinical judgment in the background to avoid those risks, and I think if we have an indication, we have to have a lot of education on how to use it correctly.

Thank you.

MR. BRACCO: I just want to point out that in the labeling, the proposed labeling --

DR. CALIENDO: Introduce yourself.

MR. BRACCO: Oh, I'm sorry. Dan Bracco.

I want to just point out that it starts out by saying use in conjunction with other, you know, laboratory findings. And then also one of the key opening phrases in the bullets

beneath it is to aid in decision making. So there's no indication to me that this is an absolute test that, you know, needs to be relied on solely, and I think that's very clear in the labeling.

DR. CALIENDO: Any other questions?

(No response.)

DR. CALIENDO: Okay. So I pronounce the Open Public Hearing to be officially closed, and we will proceed with today's agenda. So we will now begin the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers. During this time, we will open up the floor to questions for the FDA, the Sponsors, guest speakers, and Open Public Hearing speakers.

We probably should start by going back to bioMérieux for the question that I had asked them this morning. So if you could be so kind as to start the presentation there.

DR. BOZZETTE: Sure. Sam Bozzette, bioMérieux.

We have the data you asked for, but before we present it, we'd ask your permission to make a couple of clarifying comments around some matters that came up this morning.

DR. CALIENDO: Sure.

DR. BOZZETTE: Okay. The first one relates to the precision of the B·R·A·H·M·S VIDAS PCT. You can see here that the repeatability and total precision values, the coefficient of variation is well within accepted standards, and at the crucial cutoffs of around 0.25 and around 0.5, the values are very good indeed.

Next, I want to mention the number of studies using VIDAS. There were five. Two for LRTI used VIDAS exclusively, and three were done for sepsis, one of which used VIDAS exclusively.

Looking at concordance, the FDA table is very big and fully informative, but what we've done is to cut to the crucial cutpoints again to try and look at agreement at those cutpoints. And once again, I'd mention that 0.25 and 0.5 are the dividing lines between recommended and not recommended. At those levels we have 97.5 and 99% overall agreement with kappas well above 9 in both of them.

So for the second clarifying point, I'd like to turn to Dr. Schuetz, who will talk about renal failure.

DR. SCHUETZ: Philipp Schuetz.

I'd like to just make a comment about chronic and acute renal failure. Could I have -- yeah. So there are actually several research studies showing that the PCT half-life is not significantly altered in patients according to renal failure, the reason for that being that renal elimination is not the major mechanism for PCT removal, but it's rather an elimination over the liver and biochemical clearance. And also I think it's important -- there was a comment about acute kidney failure. And so in the patients that were included in the sepsis trials, the majority of these patients have renal dysfunction as part of their organ failure in sepsis, and though in these patients the use of PCT was similarly effective and safe in the studies.

DR. CALIENDO: Thank you; that's helpful.

DR. KIRSON: Noam Kirson from Analysis Group on behalf of bioMérieux. Just a couple more clarifying issues before we get to your question from before.

The topic of adherence has come up repeatedly and I think was the topic of an extensive conversation, and I think it was repeatedly again referenced over the last hour. We would like to once again just reiterate, and I think this was mentioned, when we talk about the PCT algorithm and the proposed indication, we're talking about the combination of PCT level and clinical judgment. However, when we talk about the measurement of

adherence in the studies, the available data, to us, is really about that mechanical threshold; it's about the level of the PCT. That is what we can measure adherence based on. So to some degree, while we understand the questions that were raised beforehand about the effect this might have on the endpoints, we think we should just keep that in mind as we consider the results. Specifically, we wanted to probe that further in our analyses and again using this narrower definition, which we think is too narrow a definition of adherence, we looked at how adherence is measured in the studies.

Now, unfortunately it is not measured in all studies, so if you remember we had 11 LRTI studies and 10 sepsis studies. So for LRTI, you can see the eight studies for which we have it measured, and for sepsis, four studies in which it was measured. What we did in order to explore further whether this affected our results in a meaningful way was present a simple stratification where we look above and below median adherence, and median adherence is just defined based on this set of studies that we see here. You can see the median is 82% for LRTI, 72% for sepsis. What I'd like to show you is a couple of forest plots focusing on LRTI because obviously a stratification based on four studies is a little bit more limited in its information.

But starting with the LRTI and effectiveness endpoint, in this case we're talking about the duration of use; you can see that on the top half of the panel is the lower adherence studies, and the bottom half of the panel is the higher adherence studies. And while the point estimates may vary slightly, the overall picture is fairly consistent, and from a statistical perspective, one cannot reject that these are the same result.

More importantly, we would like to look at the safety endpoint, because I think this is where people with that concern came up most pointedly. So here you look at the mortality endpoint in LRTI stratified by this, again, just the measured adherence; this is not the overall algorithm. You can see the lower adherence and the higher adherence. And

again, these two subset point estimates are essentially identical, fully overlapping, and even in the eyeball test do not seem to vary in a meaningful way. And we take this to be a very encouraging finding that shows consistency with regard to this dimension.

DR. CALIENDO: Thank you. That was very helpful.

Dr. Bozzette.

DR. BOZZETTE: The last clarification we wanted to make was to address Mr. Simon's concerns. We certainly agree that physicians have an obligation to discuss the results of every lab test and the implications of every lab test with the patient, and we want to assure you that, as an organization, we're committed to giving physicians the tools they need to do that. We plan an extensive education program if these indicated uses are approved. We'll do training in laboratories. We're going to have in-services for physicians, materials, both for physicians and for patients, interpreting results, physician-to-physician education, webinars, and in-services by nurses in critical care medicine. So we hear that concern, and we're trying to be responsive.

Now, I think finally we will turn to your question.

(Laughter.)

DR. BOZZETTE: We were going to get there.

DR. KIRSON: So hello. Noam Kirson from Analysis Group again.

So this was regarding the question of the stratification, inpatient versus outpatient and then specifically by subtype of LRTI. So we were able to run those numbers over the last couple of hours, and I would like to start with the exposure metric in LRTI. Just for orientation, again, as we begin to slice this, I think you will see that some of the sample sizes are getting a little bit smaller, but in the effectiveness endpoint, we still have very precise estimates that are remarkably consistent down this column that you can look at. So the way this is organized is within every subtype of LRTI, we have inpatient separately from

outpatient, and you can see both the ends and the summary statistics that are relevant for this. So fairly consistently, if you just look down that column, those blue diamonds are lining up essentially in the same place. Similarly for mortality. Here I'll just point out that the actual event numbers are very low, as would be expected for some of these subtypes of LRTI. So we can't actually even calculate this without adding some sort of correction afterwards to account for the zeroes. And what you can see here in terms of the numbers is you can look for pneumonia at the top, we see the inpatient number and the outpatient number, which is less precisely estimated because we have many, many fewer events, of course, in an outpatient setting, but we don't see any inconsistency in the information. For bronchitis, we are unable to report an odds ratio, but if you just look at the raw event numbers that you see here, you can see here that in the outpatient setting they were zero in both arms. And in acute exacerbations of COPD, we have a single mortality event in the PCT arm and no events in the control arm.

DR. CALIENDO: Thank you, that was very helpful.

Okay, to the Panel, you're allowed to ask questions to anybody who has spoken with us so far today.

DR. HANSON: Kim Hanson.

I'll ask a question just about the subgroup analysis again. Specifically looking at the outpatient cohorts, you showed us some data on outcomes relative to antimicrobial use and mortality, but how about some of the other outcomes like had to come back to clinic, clinically getting worse, need for hospitalization? Any of those sorts of measures available for the outpatient group specifically?

DR. BOZZETTE: I'm afraid I don't think we have the complication rates broken out for inpatient versus outpatients, I'm sorry.

DR. HANSON: Okay. And do you have a sense in the -- Kim Hanson again.

In the outpatient studies, part of your algorithm suggests, you know, if patients aren't better or symptoms persist or they're worse, they need to come back for a repeat analysis, assuming the first test was low and antibiotics were withheld. In those studies, was that mandated? Was there always follow-up over the next several days? I'm trying to get to thinking about if I was practicing in an outpatient setting, how realistic -- is my patient really going to come back to get tested again?

DR. BOZZETTE: Well, again, we don't have specific data, but we would submit that this is really standard clinical practice to see a patient with an outpatient illness and prescribe or not. Unfortunately, usually it's prescribe and then have them come back as their condition warrants.

Dr. Schuetz, would you like to make a comment?

DR. SCHUETZ: Yes, sure. Philipp Schuetz.

So there were two outpatient trials, so the first one was a Swiss trial, and as part of the protocol, we demanded patients to come back just to do another test, but we realized during the trial that it was not necessary for the majority of patients. And so the second trial, which was done in Germany, they just had an initial PCT level and told the patients, in case they felt that the disease was not resolving as it should, they should come back. And so in both groups, the control groups with antibiotics or without antibiotics, there were patients not feeling better going back for another evaluation, but there was no increase in the number of hospitalization or complications or any safety issues for this.

Thank you.

DR. FOLLMANN: Dean Follmann.

So I wanted to have a question to bioMérieux. One of the things we talked about was risks and benefits, and one of the risks we're concerned about is maybe there is a subgroup of patients for which there is not -- that discontinuing antibiotics early harms

them in some way. And to get at that, I think the ideal way is to try and identify subgroups beforehand using baseline variables where one group will have a low rate of antibiotic usage and the other will have a rate of antibiotic usage. In your document you had a slide -- a figure, Figure 18, which showed mortality on the basis of baseline PCT --

DR. BOZZETTE: Yes.

DR. FOLLMANN: -- in the LRTI group. So okay, great. So it's up there. So this is, for me, a kind of important slide. So if we look at this, these categories match your treatment algorithm with the bottom -- with the top category where antibiotic use is strongly discouraged. And so for that top group, we would expect the biggest difference in antibiotic usage over the course of the study, so this is where the two groups are most different, and we see very little difference in mortality. They're also the healthiest patients in the sense of having --

DR. BOZZETTE: Right.

DR. FOLLMANN: -- you know, the lower mortality rate. And looking at that for the other groups, as well, towards the bottom, is where we would expect the two groups to be most similar in terms of antibiotic usage; they would both be strongly encouraged to start antibiotics and presumably continue for a similar amount of time. So this is, for me, a very helpful slide. I think it would be helpful, also, if you would have sort of the antibiotic exposure for the two groups stratified by this, and I think it would also be helpful to me if you had a similar kind of slide for the sepsis indication. I know that's a little different because sepsis is not where you're looking at not initiating treatment.

DR. BOZZETTE: Right.

DR. FOLLMANN: All of them initiate treatment. This here is for initiation. But as a proxy, you might look at the change in PCT over the first day or so, if that's in the database, and then you could break that by the median, the fast decliners versus the slow decliners.

DR. BOZZETTE: Sure.

DR. FOLLMANN: The fast decliners presumably would have less antibiotics, and so I'd be interested in looking at the treatment effect among that group as well. I'm concerned about like is there -- my central concern is if they're a small group that --

DR. BOZZETTE: Right.

DR. FOLLMANN: -- for whom it's harmful and it's getting washed out by the majority group where the antibiotic usage is similar. So this slide, to my mind, is encouraging, and it would be nice if there were additional slides. I don't know if you can make those today or, you know, in further discussions with the FDA.

DR. BOZZETTE: I think that it would have to be done in the future.

DR. FOLLMANN: And another comment. So that was sort of risk. The other thing that we're counterbalancing is benefit. The benefit is, in some sense, less antibiotic use, and that's very clear that that is occurring with this, as you would expect, but that isn't really a clear benefit to the patient in terms of how they feel, function, or survive necessarily. So, to me, if you had evidence that there were fewer *C. diff* infections or fewer resistant organisms in those studies that you did a meta-analysis on, that would be a tangible benefit to the patient, not just the more nebulous benefit, well, we're using fewer antibiotics, there must be a societal benefit. I understand that argument, and I think that's sort of an important argument for this. But I would also like to see evidence, if it's possible, that the individual patients are getting some kind of benefit in terms of these kind of outcomes I mentioned, *C. diff* or other adverse events.

DR. BOZZETTE: Yeah, specific complications of antibiotics, the rates were usually not reported, so things like *C. diff* and such, we really don't have those data. We do have data on overall complication rate. I think we showed you earlier, death, ICU admission, hospitalization, respiratory disease, worsening infection, and that actually favored the PCT

group. But in terms of -- I'm going to ask Dr. Miller to discuss, you know, the issues at the individual patient level of antibiotic overuse.

DR. MILLER: Yeah. I mean, there are two issues here. Obviously, there's the public health issue: the more antibiotic use, the more resistance. I think we have a slide of the country-specific antibiotic use and resistance. So we know that in countries that use a lot of antibiotics, there's increased resistance rates, and so the hypothesis and the corollary is that if we can reduce overall antibiotic use, then we'll reduce resistance rates. So that's on public health. There's a graph of the different countries with the correlation.

But public health aside, you're asking about individual patients, and we know that for individual patient level, that the duration and receiving antibiotics is correlated with VRE acquisition, with CRE acquisition, and other superbug acquisition, and it's definitely related to *C. difficile* infection. Now, in this population that you see the average age, we know that *C. difficile* itself has a mortality in those over 65-70 years of age of about 15%. So it's expected that if we can reduce antibiotics in those individual patients and reduce the *C. diff* rate in those individual patients, then we can also reduce the morbidity and mortality in them as well. And I think that's not a stretch to do that.

So I think if we just put up the first one that we're talking about, here you see that there's a very clear correlation between total antibiotic use and per population per day in countries, and it's by country, and then you see one particular proxy measure, which is penicillin non-susceptible pneumococcus, which is pen-resistant pneumococcus, and you see there's very clearly a correlation there. There are other correlations related to this as well. So I think there's enough data on the public health and on the individual side.

DR. CALIENDO: Dr. Skates, you had a question?

DR. SKATES: I had a couple questions. This gets back to Dean's question on your BF-18 slide, the bottom category which showed on the left-hand panel there, there was

13% in the PCT, where there was I guess 13% mortality, and then in the next column there's 12% in the control group. So that says to me that PCT is a little more dangerous than the control group for when PCT is greater than half. And yet, on the right-hand column, your odds ratio is less than 1. So that didn't jive.

DR. BOZZETTE: I'm going to ask Dr. Kirson to explain that.

DR. SKATES: Great.

DR. BOZZETTE: Did you have another --

(Laughter.)

DR. BOZZETTE: Did you have -- yeah, I'll get someone else to answer that.

DR. SKATES: I guess I wanted to come back to this issue of what that upper limit means of 1.13, because the FDA has highlighted, at least in my mind, safety.

DR. BOZZETTE: Yes.

DR. SKATES: With the effectiveness here, at least I don't have any problems with it. You've done an excellent analysis on multiple levels. I'm very impressed with the patient-level meta-analysis. That takes a huge amount of work, in my experience, compared to doing a study-level meta-analysis, and yet it provides so much more solid grounds for concluding that the results are substantive. So I want to be very positive about that effectiveness aspect and the patient-level meta-analysis for both effectiveness and safety. But I do want to try and push on that safety interpretation of potentially increased mortality at some subgroup here and how that weighs off against the effectiveness, the reduction in antibiotic use, because I want to try and get them on the same level --

DR. BOZZETTE: Yeah.

DR. SKATES: -- and say how many patients -- there's an increased mortality in 1 in 100 patients. Maybe that's 1%, that 13 versus 12, and yet we save 20 or 30 antibiotic uses where it wasn't needed.

DR. BOZZETTE: Right.

DR. SKATES: That gives me a balance of safety versus risk.

DR. BOZZETTE: Um-hum.

DR. SKATES: So at some point I want to get back to that --

DR. BOZZETTE: Sure.

DR. SKATES: -- quantitation. But that first odds ratio, first issue of odds ratio being 0.88 is a little disconcerting.

DR. BOZZETTE: Let me do two things. First of all, let me again remind the Panel that we took lots of cuts at mortality, Kaplan-Meier curves, odds ratios, risk ratios, subgroups, and saw no signal. Now, the confidence interval is a little wider for some than others, but in many of them the confidence interval is very narrow. And to address this specific question and perhaps walk you through some of that mortality data, I will turn to Dr. Kirson.

DR. KIRSON: Thank you, Dr. Bozzette. Noam Kirson from Analysis Group.

So a very, very pointed question about the odds ratios versus the risk ratios. What you see on the left is essentially the raw risks in each group. What you see on the right is the odds ratio from the adjusted model, which includes an adjustment for age. So that can sway it in the other direction, and the point estimate need not be identical. So these are the numbers, and we should have clarified that in the initial presentation.

Regarding the mortality data and the risk-benefit analysis, I want to first echo Dr. Bozzette's point about the consistency of the results. I think, beforehand, when you first raised that question earlier this morning about the risk-benefit analysis, I think you gravitated towards the upper end of the confidence interval on the study-level analysis, and frankly, that estimate is less precise. We gain a lot of confidence in the very clear consistency in the results between that and the patient-level analysis, and the patient-level analysis, as I bring it up over here, has a narrower confidence interval with essentially the

same point estimates. So I think when we look at this, it's not that I can fully rule out that one, but I think in this case we look at this and we see consistency, we see a narrower confidence interval, and even more so when we look at those Kaplan-Meier curves that we looked at beforehand, we really saw no daylight between those curves. So there was a very, very, very consistent finding in terms of the results and the mortality. How to put that in a risk-benefit analysis -- let me just show that, in this case, again just to remind everyone of the Kaplan-Meier curves. So I think, with the mortality data, we have approached this every which way we possibly can with the data that we have. We are encouraged by the consistency; we are very, very aware of the importance of this point, and I think our conclusion from looking at it in many ways, this way is an encouraging one. We feel comfortable with these results in terms of their consistency.

In terms of a risk-benefit analysis, it is very, very difficult to quantify these very different dimensions because -- and I'm setting aside, of course, the public health spillovers and external effects which may be very large. These sets of analyses don't lend themselves immediately to sort of an equation that I can lay out before you and say our tradeoff is X number of deaths per Y number of adverse events for overuse of these.

DR. SKATES: But one could try to get to that, right, with the data you have. I tried to do that myself using the FDA slides, and I'm wondering if we can bring up Slide No. 11 and No. 12 from Dr. Li's presentation, and maybe Dr. Li will weigh in on this. But I just want to take you through it and see if you agree with my -- in some sense a worst-case scenario, because then that sets the upper bound that we need to worry about. If you just take a look at -- and I focused on the patient-level analysis because I find that much more convincing. Let's see, that's the effectiveness, and we're changing it from 88% in the control group, at the LRTI patient-level analysis, initiation; 88% down to 71%, right? So that's a 17% difference, a reduction in initiation of antibiotics, which is very positive. Out of

those 1,536 patients in the PCT group, 17% would be about 260 patients.

Okay, so that's the benefit. There's 266 -- 260 uses of antibiotics that one may say weren't needed and is a benefit to the group. So then the question is, on the next slide, No. 12, we're looking at safety, again LRTI patient-level analysis, and we see a reduction in mortality from 119 down to 103. The denominator is a little bit different, but 7.4% down to 6.7%. But what I'm trying to do is look at that upper limit on the odds ratio of about 1.16. If we just take that as a 16% increase, that's the maximum that the confidence interval could suggest being a mortality increase -- 16% -- and an increase above the 6.7% of 1,536 turns out to be 16 increase in mortality. That's the maximum that your confidence interval could say balanced with the 260 patients. So your ratio there of 260 to 16 is about 16. So that's saying that 16 patients are saved, and there's one potential increase in mortality.

Now, that's a back-of-the-envelope calculation, and I think that's the absolutely worst-case scenario, and my guess is it's probably hundreds of antibiotic prescriptions saved that were unnecessary for potentially, at most, one mortality in the LRTI situation. What I'd like to see is what is that ratio when you do a proper analysis and you look at the proper confidence interval for that ratio? If it was, you know, something like 100 to 1, I'd be quite reassured. If it was more like 10 to 1, I'd be somewhat worried because I think that tradeoff is a little risky. So that's what I -- that's my response to the FDA's raising the issue of this safety concern and it not being as tight as I'd like. What is the upper limit that we're going to be finding reassuring?

DR. KIRSON: First, let me say that I find this line of reasoning a very important one to consider, and the area that I struggle with in trying to provide an answer is in putting those in an apples-to-apples. So when you say 1 per 16 or 1 per 100, 1 of what, per 100 of what, and what the value of those are could be dramatically different. So let me start by stating, first of all, I think even that was an overly pessimistic calculation for the simple

reason that it only accounted for number of initiators and didn't account for the decreased use, which is another very important element here. So I think the overall decrease -- probably the metric you want to be thinking about, this, again, is that public health metric of the exposure, overall. So what we need to think about is what's the conversion ratio of exposure days of antibiotics to value of mortality in order to come up with a reasonable way to do that math, and I'm not aware of a way to do that. And I do want to, however, give Dr. Miller a chance to opine on these risk-benefit issues, which I think he has given a lot of thought to.

DR. SKATES: This is really my response to the FDA's raising the conclusion that safety is a question mark here, and I wanted to try and quantify that and put it -- there was an FDA slide of scales, risk and benefit --

DR. KIRSON: Yes.

DR. SKATES: -- and you want to weigh those, too, and putting them on the odds ratio scale with different denominators clouds that weighing.

DR. MILLER: Right.

DR. SKATES: And I wanted to get back on number of patients that have the safety issue versus the benefit that you see in the effectiveness side and weigh those somehow. And you know, I think the company would be in the best situation to say here's a reasonable weighing of that and we think the benefits outweigh the harms.

DR. MILLER: So we absolutely agree, and we, again, did not anticipate any pushback on the benefits; I think it's very clear. So you get down to the benefit-risk ratio or the benefit-risk balance, and I think that we're doing this a disservice by only looking at one risk, which is mortality, and one or two benefits, which is reduction in antibiotic prescribing, because if we're going to do a true benefit-risk assessment, there are other benefits here that we are not measuring. And so to get a true benefit-risk portrayal of what's going on in

individual patients or even at the public health, we have to take into account other benefits of this program, which would be what we mentioned: reduction in return visits because of allergic reactions to the antibiotic that was inappropriately prescribed, return visits and emergency room visits because of diarrhea from antibiotics, and dehydration in the elderly, *C. difficile* rates, which kill 15% over the age of 70, and all of the other side effects of inappropriate -- and that goes on the benefit side. So we are not capturing that in our analysis; we couldn't and we're not.

But when you're looking certainly from the FDA side, as we would encourage, it would be the entire benefit-risk ratio. Now, it's very hard quantitatively because we haven't measured it, but I would encourage that when we look at the entire benefit-risk ratio, for an individual patient, as well as public health. But let's talk about the individual patient; there are other direct benefits of this program that we're not capturing here that make a difference in the balance.

DR. SKATES: Okay. I mean, that's fair enough. What I'd like to see is whatever evidence from these trials you can bring to bear on that equation. You present, in some sense, your best light to it in terms of data that summarizes that risk-benefit tradeoff, and I'm pushing on this because of the FDA's highlighting the safety concern, and we have to answer the questions do we believe it's effective and do we believe it's safe, and then do the harms outweigh the benefits. And I'm trying to do that weighing with whatever you can bring -- whatever quantitation you can bring to that balance.

DR. CALIENDO: Okay, let's see. Tom's next and then Dan.

Tom, do you have a question?

DR. MOORE: Well, no, just a follow-up from the previous -- I missed, in all of the discussion, any mention of the cause of mortality from the studies and meta-analyses.

DR. BOZZETTE: I'm afraid we don't have cause of mortality, no cause of death. It's

just not included in the databases.

DR. JERNIGAN: So just with regard to the effectiveness question and trying to find risks for the outpatient of the studies that were done, that's largely ED, is that right, for these? There are only two studies, I think, where you had outpatient information, and so one was a primary care.

DR. CALIENDO: One or two were primary care, right -- Angie Caliendo -- in the outpatient setting?

DR. BOZZETTE: Yeah, I'm going to ask Philipp Schuetz to discuss those.

DR. CALIENDO: I know the one was primary care.

DR. SCHUETZ: Yes, Philipp Schuetz.

Yeah, there were two outpatient which were multicenter primary care practices.

DR. JERNIGAN: And so I guess the question, then, is in terms of the adherence of the patients to returning because the algorithm asks for a follow-up, but I'm trying to figure out how much of the data that you had actually had this second test for the outpatient.

DR. SCHUETZ: Excuse me, could you repeat the question?

DR. JERNIGAN: I'm asking, did you repeat the measurement within 6 to 24 hours for the LRTI? And so that's part of this algorithm, and I'm trying to see, in your studies, how many patients actually came back for the follow-up.

DR. SCHUETZ: It was demanded by the protocol, so most patients did come back. I don't know the exact number, but because it was part of the protocol, so all patients were asked specifically to come back to do another test.

DR. JERNIGAN: Right. So that's what I'm trying to figure out, if that is considered some kind of risk as you try to roll this out, the actual adherence of the patients may be much lower at returning. Is that a risk that we need to account for, that you're basically not going to get the full effect of this because of the way that it's rolled out in general practice?

DR. BOZZETTE: Well, I just would point out that the automatic repeats are recommended for inpatients, and for outpatients what's recommended is routine outpatient follow-up, which is the patient is counseled to return if they, you know, worsen or do not improve. So there really isn't an issue of coming back in for a second test automatically.

DR. CALIENDO: Angie Caliendo.

But we have some inconsistencies because the clinical trials were based on them coming back, and there's a certain amount of safety involved in having them come back. If your algorithm doesn't have them come back, that's different. You're using data from trials that are designed differently than how you have intended use.

DR. BOZZETTE: We're going to have to get back, I think, to the FDA later about exactly how many trials had follow-up built in and how many didn't. I know it's not all of them, but I'm afraid I can't give you a number.

DR. CALIENDO: Yeah, okay, because I'm thinking of the outpatient. I think, Dan, you and I are stuck on the same place.

And go ahead, Cathy, you can talk, and then I have a question myself.

DR. PETTI: It's on the same theme, so I think we're all converging on similar ideas. Since our charge is really to look at it as an aid in antibiotic decision making for inpatients and/or outpatients, and again, I'm focusing on outpatients, I'm concerned about the generalizability of benefit. And I believe we need to more fully explore the role of turnaround time in these clinical trials that were done in the multicenter primary care clinics, mainly because ensuring less than 2 hours turnaround time, even in a primary care clinic that is right next door to a major regional laboratory, would be difficult to ensure, and then hence, better understanding how does that influence clinical decision making, risk to loss of follow-up, potential mortality and complications if antibiotics are not initiated. So I

would love to hear your comments on what kind of market research or lab capacity or infrastructure investigations you have done to ensure the less than or equal to a 2-hour turnaround time and how your benefits have been based on the rapidity of receiving that diagnostic result.

DR. BOZZETTE: A few things. One is that, you know, what we control is how long it takes to run the test, which is 20 minutes. Now, obviously, there's collection time and such, but the total duration from the time of draw to the time of the result is, you know, obviously a local -- it's a characteristic of the local laboratories, where they are, where they're set up. About 1,400 or 1,200 labs currently have the VIDAS. It's a CLIA moderately complex test, and so many more hospitals or clinics have access to it through there.

Now, how does that fit into clinical practice? I think that's something for the individual practices. For example, it's -- the whole delayed prescription strategy has become more and more common, where one gives the patient a prescription and tells them to fill it if they call back later. And so I think there are a number of strategies that are available that may make it a little more workable in an outpatient setting. But certainly, if you don't have that rapid access to the test, it's not going to be very helpful.

DR. PETTI: I guess my concern is as a Panel we are supposed to evaluate the scientific evidence presented to us, and is that evidence solely based on a less than 2-hour turnaround time?

DR. BOZZETTE: I don't know that. We will have to look back at the trials, specifically, around that issue.

DR. CALIENDO: Angie Caliendo.

Cathy, if I remember, the outpatient ones did have a 2-hour turnaround time. And I do have to agree with Cathy; it's just not practical. In fact, Barbara alluded to something earlier today. You know, in our primary care practices in the U.S., they're seeing patients, if

they're lucky, every 15 minutes. And so I think the benefit of this -- for me, in the outpatient setting is where I'm struggling. Someone said the benefit is clear. I don't know that the benefit is clear, if I look at your analysis of less than 50 patients with acute exacerbations of COPD in the outpatient setting. And so my question to you, and probably to Steve also, is what can I draw from -- what conclusion can I draw from either benefit or risk from 50 patients in a group? Not you, Steve. That Steve.

DR. GITTERMAN: Oh.

(Laughter.)

DR. CALIENDO: The statistician Steve. Sorry.

DR. SKATES: You're asking me?

DR. CALIENDO: Yes. And bioMérieux, too, please.

DR. SKATES: So Steven Skates.

Fifty is a small *n*. So my statement was to the LRT and to the sepsis setting and mainly inpatient. So I'd qualify that with the outpatient setting.

DR. CALIENDO: Okay. I don't know.

DR. BOZZETTE: I guess the one thing we would point out is that the disaggregated and the aggregated results are all very, very similar and very consistent when we slice them. We make big slices, we make little slices, we look overall. I think you've seen that the point estimates and the confidence intervals are all very, very similar. So yes, it's only 50 patients, but the reductions that we're seeing were in line with the overall outcomes, and the confidence intervals were quite small.

DR. CALIENDO: Yeah. And I think that was -- Angie Caliendo.

I think that was helpful, but I'm still struggling because, in my mind, acute exacerbations of COPD physiologically are different, those patients are different than people that come in with community-acquired pneumonia.

DR. BOZZETTE: Sure.

DR. CALIENDO: Or even bronchitis. And I think that's what I'm struggling to get my head around.

Chris, did you have a question? Yeah, Chris and then Barbara.

DR. CARPENTER: Thank you. Chris Carpenter.

More of a technical question, actually, regarding the assay, and I think one of the open forum speakers brought it up, and it actually alludes to what was just discussed, is a lot of times I'd like to go back in time and go back and get the blood cultures before somebody starts antibiotics. So they had said that they've used specimens that were stored and were able to go back and use them. What is the stability of procalcitonin, and how consistent is your assay if you checked it and you found out that they had blood done a day prior? Could you go back to that blood and test it, and how consistent would that result be?

DR. BOZZETTE: I'm going to call Dr. Krause to talk about these technical issues with the assay.

DR. KRAUSE: Alexander Krause.

So if I'm not mistaken, what we have data for is for storage of about 12 hours, where the CV is constant. But if you want to know about 24 hours, I can look it up. So I don't have the answer right now.

MS. BERNEY: I brought up the point about outpatient usefulness earlier, and I have a couple of things that I want to ask. First of all, the health system and the delivery of healthcare in the U.S. is significantly different than it is in other countries where everybody's covered. Regardless of Obamacare or whatever you want to call it, there's still a lot of people who are not covered. Unfortunately, when I go to the hospital where I live, unless I have insurance, they're not going to do that test because I can't pay for it. I also

live in a state that has a very large rural population, and I can pretty much guarantee you that those large clinic things where they have multiple centers don't exist. So I'm still trying to figure out the utility of this in a situation where you go to the family doctor and that's it.

Now, I also have one other observation to make, and this is in general. I have had pneumonia, bacterial pneumonia, probably six or seven times in my life, and each time I have gone to the doctor, oh, you just have bronchitis. And even with my history of almost every time I got a cold I had a bacterial infection, not always pneumonia, but you know -- and because there was no way to tell whether I actually had a bacterial infection or not until I was sick for 3 weeks, I had needless suffering. So I guess what I'm saying is how is this better than the doctor saying, well, I see you've had pneumonia over and over and it's often bacterial? Wouldn't it be better, if I lived in a rural setting, for them to initiate antibiotic therapy, because he doesn't have the tools in that setting. There is no lab that's going to turn stuff around for you that quickly.

DR. MOORE: Well, the importance -- I hear what you're saying. Often, patients who have structural lung disease or who become prone to recurrent infections, this is really the issue that I see in my practice, where we have patients who come who have had recurrent episodes may or may not have an underlying immunodeficiency, we don't know. You know, for the average person, it's the recurrent episodes that should prompt you to look at that. But be that as it may, whether they have hypogam or not, you know, you don't know. Is it a bacterial infection or is it a viral infection? This is actually, you know, the ideal situation where you'd really like to know, because for reasons which were stated earlier -- sorry, this is Tom Moore -- you know, you reduce the risk of antibiotic -- adverse effects from an antibiotic.

I mean, you know, we don't give insulin to patients who don't have diabetes, so we shouldn't be giving antibiotics to people who don't have bacterial infections, and over half

the time -- all the studies show that over half the time we do, inappropriately. So if we have a test that would -- can be verified to make that distinction, then you would save both the community at large from increasing rates of antibiotic resistance, but also the person specifically from adverse effects. That would be the ideal approach.

I hear what you're saying and I think in a rural -- what state are you in?

MS. BERNEY: Illinois.

DR. MOORE: Illinois, yeah. Well, Kansas is a similar way. We have a large -- most of the people in the state are going to be not able to or are going to be beyond the reach of this particular test at the moment but in the future perhaps could benefit from it. But certainly, in large metropolitan areas or areas where there are a lot of patients who are admitted to a Level 1 and Level 2, possibly Level 3 hospital, if this test is available, you can definitely get a reduction in antibiotic use.

DR. CALIENDO: Go ahead, Barbara. You want to --

MS. BERNEY: I'm not arguing the use in hospital and large clinic settings. I'm just having a problem with how this relates to an outpatient, somebody like me, who goes to the doctor who is a single -- a solo practitioner, and I can guarantee you, he does not have that kind of diagnostic stuff. So if you tell me, well, it's one -- don't do it, but come back tomorrow, I'm not going to drive 35 miles to go get another test.

DR. MOORE: This is Tom Moore again.

So just to finish this topic. The way I would handle this would be to say here's a prescription, I'm going to give it to you, but I don't want you to -- or I'll send it electronically. Don't pick it up or don't fill it until you hear from me and get this procalcitonin test. The other alternative would be to say go ahead and start taking the antibiotic, but stop it if you hear back from me and the procalcitonin is negative. That may be another option, but there are ways around it. It's not ideal, but there are ways of

addressing that as an outpatient.

MR. BRACCO: This is Dan Bracco.

I just want to point out that there's a certain reasonability for the physician as well. I mean, this doesn't mean that they have to follow this. If their population is somewhat remote, then they wouldn't obviously employ it.

DR. CALIENDO: Okay, are there -- oh, go ahead, Steve. Do you want to make a comment?

DR. GITTERMAN: I just wanted to make a quick comment. One is, as interesting as this discussion is, I do think perhaps it's a little bit out of scope. I mean, the test is what it is, and I think, as Dr. Bozzette said, the actual turnaround -- the test itself is not very long, and again, if people feel that the test is not adequate for their use, they don't have to use it. We're not mandating use; we're saying the Committee really, to some extent, should be focusing more on not what problems it solves as much as what -- you know, can it be labeled safe and effective? And I do want to share Dr. Moore's, you know, opinion that they are going to evolve different strategies that people use if, in fact, the 2-hour turnaround is a concern. But I have to say from my own experience, 2 hours, you know -- again, many of the tests we have in a year are, in my own experience, the nurses get them before you even hit the door.

DR. CALIENDO: Angie Caliendo.

I don't think, Steve, we're talking about the ER. We're talking about the doctor's office, and I think that's where many people are hung up.

DR. GITTERMAN: No, I agree, but I would emphasize the point before. You're a sole practitioner, and this is a moderately complex test, it's not going to be in their office.

DR. CALIENDO: In their office, right.

DR. GITTERMAN: It's not going to be done in individual offices.

DR. CALIENDO: Yeah, right.

DR. GITTERMAN: It's going to be in offices -- the reason they're moderately complex is they offer other tests as well.

DR. CALIENDO: Okay. Angie Caliendo.

I would like to make another comment that kind of, in my mind, impacts the safety and effectiveness of this test, and that's we keep bringing up antibiotic stewardship, and I will say, at our institution, we do not have the bandwidth in our stewardship program to take on procalcitonin. And I've talked to other directors of stewardship programs and said that procalcitonin stewardship could be a full-time job in a large academic medical center. So my only comment is don't assume that all the education is going to be done and all the management of this is just going to be done in stewardship programs. I don't think that that's realistic for many hospitals.

And, Sam, you did a nice job of pointing out what your education plan is, and I strongly encourage you to deliver on that because this is a lot of work, and stewardship programs are very busy now just managing other aspects of antibiotic utilization.

DR. BOZZETTE: Absolutely. We wouldn't suggest that this would, you know, supplant antibiotic stewardship at all; we'd see it as an additional tool. And I think we showed you some data that, at least in terms of discriminating the presence of infection, this adds unique information over and above clinical judgment. You know, it would seem that this would actually enhance antibiotic stewardship programs, although clearly it's one more parameter to consider.

DR. CALIENDO: Okay, are there more questions for bioMérieux or the FDA?

Steve.

DR. SKATES: I have a question for the FDA I'd like to follow up on, and this is Dr. Li's analysis. I just want to bring up -- this is getting back to the safety. I just want to bring up

her Slide 12 and then go to her Slide -- her last conclusion slide, Slide 43. So can we have her Slide 12? And so again, I want to get back to this, just as an example, the LRTI, the confidence interval for that odds ratio for the mortality at the patient level getting up to -- from 0.77 to 1.16. So it's the upper level that, I think, is a concern. So just keep that in mind. And then let's go to Slide 43, which is -- and the last sentence there. The risk to patients -- so I presume that's talking about the safety slide -- of using PCT to guide therapy is difficult to be estimated precisely. So is that upper limit, is that what you were worried about, that that odds ratio had a wide confidence interval and you wanted to see it more narrow? Or was there additional implications of that risk to patients that I'm not picking up on? So could you clarify that statement? And then I've got another question about the DOOR/RADAR issue.

DR. LI: I think the risk here is more general, not only for the mortality. It could be like other complications, and we are saying it's difficult to estimate precisely using the current literature. But there are a lot of other limitations in the current design, all the other factors that can --

DR. SKATES: Can you elaborate on what those are?

DR. LI: Like the not perfect diagnostic accuracy of the assay and the adherence rate and also the subgroup, the percent of the subgroup that should be in the study analysis and also the physician may manage the two groups of patients differently in part of the PCT results only. So there are lots of different factors that make the interpretation of the results difficult.

DR. SKATES: So is that comment in the sense of the company could revise their safety analysis to address those, or the data are simply not there to do the analysis that you would like to see?

DR. LI: Right now I think many of the limitations are inherent to the current

literature.

DR. SKATES: Okay.

DR. LI: The study design, yeah.

DR. SKATES: And then your Slide No. 41 on the DOOR/RADAR approach.

DR. LI: Um-hum.

DR. SKATES: I know Scott Evans, and I'm sure he's done an excellent job in coming up with an alternative or improved approach to infectious disease biomarker analysis. Is the thinking here that this approach could improve the safety analysis, or is this only directed at the effectiveness analysis?

DR. LI: I think this is another -- yeah, it's another alternative way to analyze the data by combining both the effectiveness endpoints, which is the reduction in antibiotic use, the duration of antibiotics, combined together with the safety endpoints, the mortality, the hospitalization, the antibiotic-related adverse events, all of those together in a composite.

DR. SKATES: And the company could do such an analysis, and it would at least try to address this issue of balance between safety and risk. Sorry, safety and effectiveness.

DR. LI: Uh-huh, probably in a future trial.

DR. CALIENDO: Yeah. Angie Caliendo.

I'm not sure they can -- I think we're a little off target here, but I don't think they can go back and get the data that they need to do a DOOR analysis retrospectively, is that correct, that it would have to have been collected prospectively.

So I think, Dr. Li, your comment --

DR. FOLLMANN: They can do it with the patient-level data. You just don't know --

DR. CALIENDO: If they have enough of the patient-level data.

DR. FOLLMANN: Right. But they have date of death and duration of antibiotics, so that's all you need to do the simplest version of the DOOR/RADAR.

DR. CALIENDO: Well, yeah, the simplest version, but --

DR. FOLLMANN: Well, you could do more complicated ones, as well, because they have, you know, patient-level data looking at duration. I guess some kinds of adverse events as well, because we saw that. They certainly have mortality. So you could do this, you know, in my estimation, for the patient-level meta-analysis.

DR. LI: Um-hum.

DR. CALIENDO: Okay. Dean, you had a question, and then we're going to have to take a break.

DR. FOLLMANN: Yeah. So I guess this goes back to the slides we've been seeing before about the confidence intervals for the patient-level data with LRTI and sepsis. Dr. Skates had a particular view on it, and he was, I think, taking a worst-case scenario. You know, straightforwardly he said that. I have a slightly different view on this, I guess. I had earlier mentioned how you didn't have a pre-specified sort of margin for a non-inferiority analysis, and that was sort of up for us to decide. I looked at that and I saw that both of those upper confidence intervals were less than 1.2 or less than 20%. The LRTI was based on 3,000 patients, which is a very large meta-analysis, and I know of other cardiovascular safety studies where they've used margins on the odds ratio of 1.3 or 1.7.

So I think if we want to look at it and analyze it more as a traditional non-inferiority trial, you would have specified a previous -- you know, you would specify a margin from the start. I think a 1.2 margin would have been a reasonable one. I sort of understand why you didn't do that; you wanted to let us opine on it. And so I wanted to comment on that.

I think if you're always going to look at the worst-case scenario, under this situation there's always going to be an upper confidence interval, and maybe it's 1.1. There will always be a concern about an excess mortality, and even if we're doing a 3,000 or larger person study, if we can't rule it out, there would be no way to proceed with this. So I think

a more standard way would be to look at this through a non-inferiority trial with a preset margin of 1.2 or something like that.

A couple other comments: You talked about diagnostic accuracy, and you thought there was a concern for the meta-analysis. I think, you know, if you're not identifying bacterial cases that can be cured by the human immunity, that's not necessarily a misclassification. So even if you don't truly identify some bacterial infections, if human immunity can correct it, maybe that antibiotic wasn't necessary. So I don't think diagnostic accuracy is the metric I'm really concerned about with this device. It's more clinical outcomes, mortality, hospitalization, duration, and antibiotic duration. That's the metric I'm more interested in here.

DR. LI: Um-hum.

DR. FOLLMANN: And then, finally, adherence rate. I mean, you mentioned that as a concern for the meta-analysis. Adherence, you know, it sounds like something you really want to comply with it. We think of that like in a drug trial where you need to adhere to the drug and you want 90% compliance to the drug and so on. That's a different setting than what we have here. This is an aid, and it's understood, in my mind, that the adherence could be less than 100% because the physician is overruling the -- well, the algorithm, based on clinical judgment. So I'm not so concerned about having what you call low adherence rate because I understand this is being used as an aid for choice of antibiotics.

DR. CALIENDO: Okay, great. Thank you.

All right, let's see, where are we? Okay, we're going to take a 10-minute break, and Panel members, please do not discuss the meeting topic during the break amongst yourselves or with other members of the audience, and we're going to resume at 3:10.

Thank you.

DR. CALIENDO: Okay, welcome back, everybody. So we're going to get ready to

address the FDA questions at this point, but as the Chair, I would like to take the prerogative to ask one question that I had on my list that I did not get to and I need somebody from bioMérieux here to help me with it. So is there anyone out there?

They left.

(Pause.)

DR. CALIENDO: I think Sam probably needs to be the person -- oh, great. Okay, Mark can probably do it, too.

Okay, so the question that I'd like to address to bioMérieux is what about atypical bacteria? So we have a test that doesn't get -- the procalcitonin, it doesn't elevate with atypical pathogens. Can you tell us what -- how many cases of this you've had in your studies? Is there a risk that patients should get antibiotics but won't get antibiotics? What data do you have; how can you help us process that?

DR. BOZZETTE: We really don't have microbiologic data in the studies that were available for the meta-analysis. There is some observational data, but I think it's mixed, and I'm really not prepared to quote it at this point.

We do have answers to two issues that came up before the break, if you'd like to see them?

DR. CALIENDO: Sure.

DR. BOZZETTE: Dr. Krause.

DR. KRAUSE: Yes, so Dr. Alexander Krause.

Dr. Carpenter, your question was about the stability of the PCT samples in the case that you wanted to retest them, so we had a quick look on our package insert, and if I can see the slide, please, which is here. So what we confirmed in our internal studies is that the sera, once that they are prepared, they are at the refrigerator 48 hours stable. Then if you need them for a longer time, they could be stored for 6 months, without any impact, in the

fridge. And you can also do three freeze-thaw cycles in case you want to look at it again.

DR. CALIENDO: Angie Caliendo.

Do you have any data on room temperature storage?

DR. KRAUSE: On room temperature?

DR. CALIENDO: Um-hum.

DR. KRAUSE We don't have it in the package --

DR. CALIENDO: Okay.

DR. KRAUSE: -- but only it's at 12 hours.

DR. CALIENDO: Okay.

DR. KRAUSE: Thank you.

DR. BOZZETTE: I'd like to announce that I was wrong, we have more data than I thought, and so Dr. Kirson is going to present some data about exposure by PCT level.

DR. KIRSON: Hello, again. Noam Kirson.

So this is just a follow-up. I think we had a brief discussion about stratified results by initial PCT level; we shared mortality data. There was a question whether there was comparable information for exposure, and we do indeed have that. This is the LRTI results. Again, this is stratified by initial PCT, and I think there are some variability in these results, but they're fairly consistent. I don't want to over-interpret some of the lower numbers on the lower groups, but these are the results as stratified by initial PCT, and then similarly, for sepsis, I think that we see very, very similar findings here. There's really no difference between these two estimates depending on whether it was below or above 0.5 initially. This is initial PCT.

DR. CALIENDO: Okay, thank you. Anything else?

DR. BOZZETTE: No.

DR. CALIENDO: Okay, great.

Okay, so what we're going to do now is address the FDA questions to the Panel, and Panel members, you're going to find a copy of the questions in your folder, and they were also in the presentation that the FDA gave earlier this morning. Someone is going to read the first question to us, and the way this is going to work is we're going to go around the table and everybody's going to comment on it. And so is someone --

UNIDENTIFIED SPEAKER: Steve.

DR. CALIENDO: Steve, are you going to read the question?

DR. GITTERMAN: Since I have the microphone, I do want to thank everyone on the Committee, as Dr. Roth did earlier. I mean, this is incredible public service, and again, we genuinely appreciate some people flew very far for this one day. And we realize, you know, given how much time it takes, we'll reserve future meetings for more challenging questions. I'd also like to point out we have backup slides, too. We just didn't need to use them.

(Laughter.)

DR. GITTERMAN: But if we can get Slide 34 of Dr. Goldberg's presentation. Slide 34 of Dr. Goldberg's presentation.

Okay, thank you. And again, I think the question should be pretty straightforward by now: Please discuss the potential advantages and disadvantages of using this test as proposed in the intended -- Indications for Use.

That's what you're actually discussing, but we want everyone's opinion. If your statement varies a little bit about recommendations, that's fine.

In your discussion, please note whether the current submission addresses any potential new risks from the modified Indications for Use, and if so, please describe those risks. Please address each of the following of the modified Indications for Use independently including:

Next slide.

a. As an aid in antibiotic decision making for inpatients or outpatients with suspected or confirmed lower respiratory tract infection defined as community-acquired pneumonia, acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease.
b. As an aid in decision making for antibiotic discontinuation for patients with suspected or confirmed sepsis.

And again, we'd appreciate all and any comment. Thank you.

DR. CALIENDO: Thank you, Steve.

So I think it will be easier to break these into two, so we'll discuss LRTI first. If people can please break them out by community-acquired pneumonia, bronchitis, and COPD, if you feel so inspired, that you don't have the same opinion on each one. And so why don't we start with Dean, and we'll just go around one at a time and give our thoughts on Question 1.

DR. FOLLMANN: Thank you.

So I'll be addressing LRTI, I guess, to start with, and then we'll go around again for sepsis. I think the potential advantages and disadvantage of using this test as, you know, an aid to clinical choice of antibiotics are pretty obvious. The advantages are less antibiotic duration, and while we don't see necessarily in the data direct benefit to the patients there, I'm willing to accept that it would have sort of a benefit to society and indirectly probably have a benefit to the patient. Even though we didn't see that directly, we know that less antibiotics should result in less C. *diff* and so on complications.

The disadvantage is, of course, in my mind, the mortality. Is there some decrement in mortality by some patients being undertreated with antibiotics, so bioMérieux looked at -- provided with us some data that I think was reassuring in that regard.

Another comment I guess I would make is to try to detect subtle effects like this in

terms of mortality; meta-analysis is a pretty good tool, in my mind, because we have the strength of numbers here for LRTI, we have 3,000 patients at the subject level, and you know, I can't really imagine doing a prospective study that large to -- and address this issue, so I'm focused on the patient level analysis, which I thought was done well and provide some reassurance.

One thing that was brought up at the end of the last session was whether DOOR/RADAR could be applied to analyze this data; I think it could, and I think that would be of help for the FDA when they make a decision about this ultimately. I think it will show an overall advantage of use of the procalcitonin readout compared to usual care, but I think that would be an important analysis to do.

And so I guess, harkening back to some comments I made earlier, to me this is essentially a non-inferiority trial question, and we're answering that with meta-analysis. We don't really expect in my -- to see an improvement on mortality or duration of hospitalization. We expect them to be similar or not unacceptably worse with the procalcitonin arm. And if I was designing a prospective study like this, I think an odds ratio margin of 1.2% would be a reasonable thing to do, maybe kind of strict, and for LRTI, we meet that margin with an upper confidence similar to 1.16. So using the conventional approach of looking at a non-inferiority trial, I would think that there's benefit to using this strategy for LRTI.

Across the different categories, CAP, acute bronchitis, and COPD, if you start looking at those individually, it was just pointed out, you have relatively small numbers, and so what I look for is consistency of effect, and I see consistency of effect across these different subgroups, and so I'm tending to go with the overall effect and apply that to each of the different subgroups, so overall I think there's a favorable risk-benefit profile --

DR. CALIENDO: Great, thank you.

DR. FOLLMANN: -- for LRTI.

DR. CALIENDO: Steve.

DR. SKATES: I don't have a lot to add to that. Much of Dean's comments take the words right out of my mouth. I would add or I would reinforce the DOOR/RADAR approach, I think, has some additional benefit to what the separate safety and separate effectiveness analysis that we were presented with provides. It combines those two and would take away my concern as to what the right upper limit is on the mortality because you want to have that mortality scale, numbers of life saved versus -- or some measure, sorry, numbers of potential additional deaths versus reduction in duration, reduction in initiation of use of antibiotics. And I think that would reassure the FDA in terms of do we have an adequate risk-benefit tradeoff.

I like the narrow confidence intervals that are provided by the patient level meta-analysis on the safety side; they are fairly narrow. I'm just in a little bit of unease to be definitive about -- sorry. They are narrow, and that's reassuring. Just how narrow, narrow needs to be is what I'm battling with, you know, why is 1.2 the right answer and not 1.3 or 1.1. And so that's where I think the DOOR/RADAR approach can be illuminating and quite -- and my guess is it's going to be quite reassuring.

In terms of breaking LRTI down by CAP and acute bronchitis and acute exacerbation of chronic COPD, I think the answer that Sam gave was right on the money, that even if you've got 50 patients in the COPD subgroup, the fact that all of the point estimates are lining up on the effectiveness side is very reassuring for the COPD subgroup, which echoes what Dean said, so in terms of small numbers for those subgroups, I'm not too worried about it because of that consistency.

DR. CALIENDO: Thank you.

Tom.

DR. MOORE: So -- sorry, this is Tom Moore.

So I came across -- I thought about this. This -- well. I guess get my thoughts together first before I speak. Chronic problem.

I looked up some of the data, obviously, on sepsis versus LRTI, and I think the best way to look at this -- I have no hesitation to use procalcitonin. I think it's going to be best used for limitation or stopping antibiotics in patients who are septic. Obviously, these patients come into the hospital, they get started on antibiotics immediately, and then the real issue is when you stop the antibiotics.

I think the data from the meta-analyses, meta-analysis of the trials that were presented, the data that were presented really support -- given even you take a limitation that these are actually slightly different tests, they didn't use the same test every time, I still think the data are pretty robust. You can reasonably infer from those data that it's probably best used -- the meta-analysis trials -- or sorry, meta-analysis of the trials supports an indication of safety and efficacy for reduction -- sorry, for use in patients who have sepsis in order to reduce antibiotics. Yes?

DR. CALIENDO: But we're on LRTI.

DR. MOORE: Right, I'm sorry. I was -- that was my next point.

(Laughter.)

DR. MOORE: So the issue then, secondly, is what about LRTIs? Well, so there are 52 million visits in the United States per year, ambulatory visits for LRTI. And obviously, that's a significant, that's a vast increase versus the 90,000 deaths -- sorry, 90,000 cases per year of sepsis in the United States. And this is what I was -- I apologize for the long rambling. This is what I was getting to, basically, that the biggest risk here is the risk of death for patients who would be, albeit small, would be missed by having a negative procalcitonin level. Now, I know the emphasis was that it should be combined with clinical judgment, but

the -- and I think that's the way it should be emphasized, but I know that there will be practitioners out there that will rely solely on this test to make a decision about a variety of things because that's the temptation; when there's a question, you go to an objective test.

I think it's reasonable, given the variability, I think it's reasonable to say that it seems safe, it's certainly efficacious when it's done correctly, and when it's -- I mean, there's limited variability. But I'm very hesitant to -- well, I think that would be -- it would be most useful in the outpatient setting for LRTIs, but it would have to be approved with that significant caveat that it has to be taken into account with other things, including clinical judgment.

DR. JERNIGAN: This is Dan Jernigan.

So I think -- I mean, I agree with the prior comments, and I think the point that in general all the estimates are in the same direction is an encouraging thing. The issue I'm having a little trouble with is if you're in the hospital where you're in the context of an antimicrobial stewardship program, I can see how that works as you go to the ED and into the outpatient setting. It gets less clear to me how the actual application of it and whether or not the effectiveness that we're anticipating that we would see with it, what exactly that would look like because the implementation, especially in a doctor's office through use of a send-out test or something, I just -- I don't know that we have the experience with that yet.

Equally, from the LRTI, from CAP, as you go down to the acute exacerbation of COPD, again, you begin to see that this, the data just -- there's not as many people there for which the experience, especially in the outpatient setting, is there and so I don't -- that's enough for it to not have that claim, per se, because I actually do, I would love to have these types of biomarkers in the community for use, but it -- you get to numbers and application of how you do this, it gets -- the clarity, to me, is just not as much as it should be.

DR. PETTI: Cathy Petti.

I certainly agree with both Dr. Moore's and Dr. Jernigan's concerns when this test is applied to the outpatient setting. I think we all have well intentioned efforts to reduce the public health threat of antimicrobial resistance, but I hope that we resist the temptation that while battling one crisis, we don't necessarily introduce another one, which is the inappropriate use of laboratory testing, and then we'll need laboratory stewardship programs.

(Off microphone comment.)

DR. PETTI: Yes. And we already do in many institutions.

And I echo what my colleagues have voiced, which is I believe that the scientific evidence presented to us today, limiting it to the outpatient setting is insufficient for me to ensure not only adequate benefit, but also safety. We really don't have a better idea of not just the subgroups of CAP, chronic bronchitis, or COPD, but also the sub-subgroup of who's immunocompromised in that population, who's on immunomodulatory agents, and what have you.

DR. CALIENDO: Angie Caliendo.

Cathy, can I ask you to clarify something? Do you feel that it's -- there's insufficient evidence because of the data presented or because of the characteristics of the test, the turnaround time of the test and how it would impact clinically? Is that driving what you're thinking or is -- are you not convinced by the data that they showed that there's actual benefit?

DR. PETTI: That's great. Thank you for asking me to clarify. It's the data. I believe that the clinical trials that were retained in the meta-analysis did not adequately address the diversity of individuals in the outpatient setting, nor did it adequately address issues of logistics when it does come with turnaround time. So it's the data and the way the trials were designed.

DR. CALIENDO: Okay.

DR. BEAVIS: Kathleen Beavis.

I also had some struggles with the data, and where I'm getting stuck is on the adherence percentages and the broad range of adherence percentages in many of the studies, and it ranged from 60 to 90%. And that makes me ask what was the relative contribution of the procalcitonin result versus the clinician judgment in the outcome of the patient, you know, and if someone is worried while coming in, concerned about lower respiratory tract infection, you know, I don't know what this test is going to add.

Anyway, I'm sorry that my words aren't better composed than that, but I think the relative contribution of this test versus clinical judgment with, you know, the widely ranging adherence rates, I'm not sure that the contribution of this test was demonstrated. So that's my concern.

DR. CALIENDO: Angie Caliendo.

Can you clarify whether you feel that way about inpatient setting, outpatient setting, all the data that we saw today?

DR. BEAVIS: So I think it's more concerning in an outpatient setting, and I'll tell you why. So if it's done in the concept of a stewardship program -- again, and I'm biased by the stewardship programs. I've had, you know, a lot of contact with both at Cook County Hospital University of Chicago where they are very aggressive; they're run by very smart infectious disease and pharmacy people. And I really felt that if there were a patient in the hospital who had a low procalcitonin but any of them felt that there was a reason for the patient to receive antimicrobials, there would be numerous people looking at this patient and arguing strongly for the patient's benefit. So I'm less concerned about its application in the inpatient setting just because I think we have so many more checks and balances on patient care. I don't know that those checks and balances exist outside, you know, in the

purely outpatient setting. And I just don't know that the data, for me, have convinced me of the contribution of this test versus clinical judgment.

DR. CALIENDO: Thank you.

Angie Caliendo.

You know, I have to say that I -- when I read all the data before I came, I was very concerned about the outpatient setting, too, and was there enough data to really show a risk, the benefit-risk to the risk. But our statisticians today, Dean and Steve, have kind of convinced me that the risk isn't really that different for -- what hung out for me was COPD. We just didn't have enough data. But I'm reassured, somewhat, by their statistical approach saying, you know, all the data kind of lines up, and so I, too, remain a little bit ambivalent about the outpatient setting. I am not ambivalent at all about the inpatient setting or the ED setting.

The one thing I do feel strongly about is that we -- it has to be very clear in the package insert what patient populations this test is not appropriate for because we talked about a lot of different patient populations today where it just doesn't fit: immunocompromised people on steroids, children, pregnant women, so all that really does need to be spelled out.

Kim.

DR. HANSON: Yeah, I agree, Angie. This is Kim Hanson.

I don't know I have much more to add on that. And I will say in the outpatient setting, one thing that reassures me a little bit is just the overall acuity and kind of risk profile of patients that are being managed in the outpatient setting is less than those that are seen in the ED or admitted to the hospital. So that, as well, I think, is reassuring for me in the outpatient setting and with the breakdown for the different forms of LRTI.

DR. WELCH: David Welch.

Well, from my perspective, it seems like quite a big step from the existing two claims which deal with risk assessment to this claim, which is basically decision making with respect to starting or not starting antibiotics, and as a microbiologist, I like to look at organisms and grow them, and these meta-analysis studies with no microbiologic data are troublesome for me, to say the least. I think that the new risks that are posed do include miscategorizing because of the performance characteristics which were not entirely clear of the procalcitonin assay. And I do have concern with -- my main concern, therefore, is that procalcitonin would become an actionable result based on this claim.

And I also have concerns about the importance of excluding certain patient populations and perhaps even something with respect to how frequent the procalcitonin assay should be repeated or a limit to the number in some way so it gives laboratories some mechanism to control usage, you know. If an order is written for procalcitonin every hour, there may be 24 done per day unless that's -- that's something that can be controlled like the -- an example would be C. *difficile* testing. The package insert says this can't be done on children under 24 years -- 24 months of age, so something that would give the laboratory a little bit of ability to control this test, I think, would be helpful, too.

DR. CALIENDO: Angie Caliendo.

Dave, just to have you clarify your concern about misclassification, is that across all inpatient/outpatient, all different diagnoses? Is there an area that you feel more less discomfortable, less discomfort?

DR. WELCH: I think it applies to both, inpatients and outpatients. I mean, the use of it at all is -- I have more of a reservation with respect to outpatients is because of accessibility, I think.

DR. CALIENDO: Okay.

DR. WIEDERMANN: Bud Wiedermann.

I figured out, as the day has progressed, that I'm the token pediatric voice on the Panel. So let me first give you some pediatric perspective to this.

First of all, I find my bias, and it's probably representative that the stewardship issue is huge, and to some extent, all of you internists and family practitioners are the enemies of children because antibiotics tend to get approved in adults considerably before they are approved in children, and by the time we're using them in children, there's significant resistance in the community, so I'm for anything that will lessen antibiotic use, but obviously, we want to be safe.

The other thing, from a pediatric perspective, getting back to something Tom was talking about in the outpatient arena, for many years now, for acute otitis media in children meeting certain low risk criteria, there is the practice of using an anticipatory prescription, so you say, you know, Mrs. Jones, I'm happy to say it looks like we can spare Johnny another exposure to antibiotics today, but we want to have close follow-up, and that close follow-up can be by the phone, so you can give them a prescription but not fill it at the time, but have monitoring, and if there's no improvement in 48 hours or worsening or something, then you go ahead and treat, and that's been around for several years now and seems to be working well. So I don't know why it wouldn't work in this situation in outpatient practices with LRTI.

Otherwise, I would have to say I was -- you know, I'm also at best an amateur statistician, and I was very pleased to see all the meta-analyses and hear the discussion on that, but I think we also need to remember it's -- they are based on bad data essentially. Not anybody's fault, but it's a feature of the illnesses that are being studied. We don't have a good gold standard. We're talking about essentially a clinical practice guideline which, by its nature, is open label. We're asking people to use clinical judgment, which is difficult to quantify. So at some point, we have to quit parsing this data because it's going beyond the

quality of the data we have to begin with. But having said that, I certainly think it would be worth a DOOR/RADAR attempt at the existing data.

And the other thing I don't think I've heard anybody mention is potentially simulating a clinical effectiveness study using different sensitivity analyses assigning, you know, as is often done in these studies, sort of point values to different outcomes, whether it's mortality or days in the hospital or time in rehab or things like that, and that would be a huge undertaking, absolutely, so I'm not sure I'd require that, but that's another way to maybe get a handle on what we're all worried about was -- which is are we missing some significant mortality signal, and we're going to harm people by approving or suggesting that these new indications be granted.

On the other hand, it also seems like the train has left the station. Procalcitonin is being used in many institutions for many uses that certainly haven't been studied, so you know, hopefully those individuals who are doing that will collect data carefully and may further inform, but that's going to take time. But for LRTI, with all those misgivings, I'm somewhat reassured that we haven't seen at least a significant mortality signal so far.

DR. CALIENDO: Great, thank you.

Chris.

DR. CARPENTER: Thank you. Chris Carpenter.

A few things: One is to get a plug in because of the timeliness of this to remind everybody that actually next week starts the Get Smart About Antibiotics Week, so I think this review is quite timely in that regard. Up front, I am supportive of LRTI. My concern is regarding COPD. I just think it's a little bit different of a beast. However, as I think Kim had said earlier, that's a lower-stakes game, I think, in the outpatient setting, so I am concerned about that. I think if we could have more comparison down the road to perhaps -- I think the gold criteria are, again, in another revision, but looking at the gold criteria and

comparing those with or without procalcitonin would be of interest because there's a huge population of people out there with COPD who are chronically on azithromycin or another macrolide, and how do you interpret this test in that setting. And also the definition of COPD is, I think, one of the other -- one of the -- the open forum speakers looked at a problem list and had 15 problem lists on one side or 15 problems on one side and zero on the other side. That zero is probably their primary care doctor, whoever didn't fill those ones in, as I suspect.

(Laughter.)

DR. CARPENTER: But unfortunately, COPD gets thrown into everybody's, you know, box in terms of a problem list because they smoked and they had a cough, you know, type of thing. So I worry about kind of the over-expansion of COPD, but I think strictly in those people who truly have COPD, I just -- I'm a little less comfortable because I think it's a different type of a process.

A few other things: So yes, I would lean towards for CAP and for regular bronchitis because I think that is 95-plus percent viral, so I don't think you're going to -- you know, you could almost flip a coin and do as good. But for COPD, I'd want kind of a deeper dive into that information.

A few other points to kind of point out because a lot of things have come up, and I think, from a practice perspective, somebody mentioned before pretest probabilities, and I struggle when people put up negative and positive predictive values because that all depends on the population of patients you're seeing. In your practice, if you're in rural Illinois versus you're in inner-city Chicago, it's going to be a different type thing, versus if you're in the ER versus primary care office versus inpatient in the ICU or someplace else, and so you've got to look at your patient and think about what their pretest probability is.

The one thing that was brought up, and I think Mr. Simon brought it up earlier, was

when you're sitting down, especially -- well, in inpatient and outpatient setting, but when you're coming in the outpatient setting and going to see that physician because you have something that you think you need an antibiotic for, they're coming in to look for a tangible exchange from you and that's the major -- not major, wrong word -- but the quick and easy way out is to write that prescription.

I would push in the direction of I think it would be a better route to go to do a test like this and not write that prescription, even with some of the concerns that have been raised because I think that would be potentially that tangible exchange, and that tangible exchange could also be that education. I understand, I think, the ER physician earlier said I've got -- takes me 10 minutes to explain when I only have 5 minutes to see the patient. That's tougher in the ER, but if you're a primary care physician working directly with the patient, I think you're in a better position to first education, the next time around is going to be a lot easier conversation, and the third time, I think, hopefully they're going to be kind of on the same thing with you.

Going to the outpatient setting, one thing I want to point out is we do have some point of care things coming up, and I'm sure, in the back of some folks at bioMérieux's minds, are could we eventually evolve this test to no point of care test, and obviously right now the technology's not there, but if you can turn this around in a primary care office just like we can now with strep tests, I think that would be a huge leap forward, so that's where I find it kind of exciting. So I think yes, right now, not really practical in the outpatient setting except for maybe in ER, but down the road I could really see this taking off and helping us out.

And the last thing I want to make -- and some of this I will not talk as much when we talk about the subsets because I'm making all my points now. But what I would encourage FDA to do here is really, you know -- I think somebody mentioned the package insert earlier.

I look at package inserts for drugs. I do not look at it for tests, for the most part, unless I need to get specific information. Here I would encourage the FDA to provide a kind of almost a boilerplate or at least a starting point comment for this test, if this gets approved for these indications; this is what we recommend you put on there so that when the less-educated clinician reads it, they've got more information and here's -- it's 0.36, what do you do with that, you know. If you got more of a kind of a target rate and don't make it that complicated, I was kind of going back and forth, should we just kind of make it one threshold versus two, I'll defer that to the folks who really know the data better than I, but I would want to encourage commenting and simplified with simple break points, if feasible.

Thank you.

DR. CALIENDO: Great. Thanks, Chris.

Go ahead, Tom.

MR. SIMON: Tom Simon.

Dr. Carpenter obviously stole my answers from my test. I have the same answers.

DR. CARPENTER: I've been looking at it, so --

(Laughter.)

MR. SIMON: Kidding.

My concern has been, from the very beginning, the doctor-patient relationship in the outpatient setting mainly. I'm also encouraged that if sufficient training and education could occur between the doctor and the patient with regard to the PCT test, that would be excellent, and obviously, you'd use the PCT test along with standard of care and clinician judgment. That, to me, has to go hand in hand. The obvious risk, the obvious risk is mortality. And the one thing that I'm concerned is that we don't know the cause of death in the number of deaths that occurred. That would be nice to know, if you will. And lastly, I believe using a PCT test as well as, as I mentioned, the clinician judgment and the standard

of care that exists, I think it will be helpful in the antibiotic decision-making process.

DR. CALIENDO: Thank you.

Barb.

MS. BERNEY: Barbara Berney.

I really don't have a lot to add. I'm listening to all of the things that are being said, and I don't have any reservations really about the hospital or ED setting, but I echo the concerns about the outpatient use of this and how that's going to be delivered and what will be the value. I would love to see technology move forward so that it could be made available to every outpatient, but that's a whole other story, so I'm comfortable with the basic safety, you know, risk-benefit analysis, but I do have reservations about the outpatient use.

DR. CALIENDO: Okay, thanks.

Dan.

MR. BRACCO: So Dan Bracco.

I'm a regulatory guy, and I'm listening to all this and I'm wondering, as I'm sure FDA is, so what do you want us to do? So we have some indications here, and I'd be interested in maybe hearing some feedback from the Panel about whether or not there's some room in these indications. It's in the FDA panel pack on page 5; I'm sure most of you have it in front of you. But is there any way we can massage the labeling, maybe tone down the outpatient claim and focus on the inpatient? Should we just say patients? So those are the kind of things that I'd like to hear some feedback on. I think FDA would as well, so that they can craft the labeling appropriately. Or not have any labeling if people feel that it's not appropriate to do this at all.

DR. CALIENDO: So Angie Caliendo.

Steve, why don't I summarize the comments, and I think some of what people said

gets to what you're bringing up, and if not, then we can discuss it further.

So for the first question on the risk-benefit profile for lower respiratory tract infections, there is not consensus on a favorable risk-benefit profile overall for LRTI. But there does seem to be near consensus for the ED and inpatient setting. I think where people have concern is in the outpatient setting, and a couple of important issues have been brought up. One is that there are few studies truly in the primary care setting. And the study design may not be ideal. And how can we clearly show advantage over clinical judgment? And then the calling out of COPD as was said by Chris, it's a different beast. So I think there's -- the concern sits mainly in the ambulatory setting.

That being said, there were some very good suggestions that I think can help the FDA. One is to apply the DOOR/RADAR analysis to the data and see if you can get a better feeling about the risk-benefit profile, making sure that it's clear that this test is used in conjunction with clinical judgment, and I think bioMérieux has done a very nice job of outlining that that's certainly their intent. We need to eliminate populations and make that very clear to clinicians, of where we do not have data, that there is safety around certain populations.

I think we've talked about several studies today that are under way, and moving forward with those studies, I think, would be very helpful. To hold up everything for the data on those two studies is not what I'm hearing from the Committee, and I don't think people are in favor of that.

Including frequency of testing in the package insert would be very helpful for laboratories and stewardship programs so that they can control this.

There needs to be information directed to clinicians. We don't usually do this with laboratory tests. It all sits in the package insert, but I think that was a very important point. This is not a straightforward algorithm, and I think that thought needs to be given to how to

simplify the patient population that it applies to and the interpretation of the data.

And so that's my summary of people's thoughts. Steve, do you have any thoughts on this? Are there gaps that you want us to fill?

DR. GITTERMAN: No, no. In fact, I think that is so spot on. I could repeat back what I heard, just to make sure we agree with that. The Committee generally, with very few exceptions, accepts the ED setting, and the outpatient setting there's much more ambivalence about. And again, I think we can approach bioMérieux and understand that better.

Clearly, the educational component, which was described better and I think is actually, given some concerns about how well that could be rolled out, in fact restricted to the ED setting would be far better. And I think it is incredibly good you brought up the point, because there are people here from NIAID and that there's very strong support for continuing TRAP-LRTI. I think the same is true for ProACT, which has not been discussed as more, but that's very clear.

The issue of limitations, so no-brainer for labeling, that was everybody's intention. And the fact that bioMérieux has committed, verbally at least, to doing such a really thorough outpatient educational role, that should, in fact, address that. I heard Dr. Carpenter say we should publish an article on this to widely disseminate it.

I think the frequency of serial measurement is a real concern, and we do have to address that in labeling, that's clear. I think everything you said was spot on.

The two issues, again, are perhaps some additional analyses from bioMérieux at this point is certainly well heard, as well as your point, and I think -- in fact, it was Dr. Wiedermann's support. I do think, though, perhaps we could clarify one thing, the use in pediatrics, and perhaps you could summarize very quickly the proposed use in pediatrics or else Dr. Goldberg could.

DR. MILLER: So there were three randomized control trials that we know of in pediatrics using PCT along the same algorithm. One of these is in Chinese and was translated into English and, because of the language, was excluded from the meta-analysis. The other two were found in the publication search, but because they were dedicated pediatric populations, we proposed to the FDA that they be analyzed separately, and so they were analyzed separately.

If we can just have the forest plots of the pediatrics in addition to -- so here we have the antibiotic exposure and duration, exposure or duration because it was measured differently, so on the top you have the adult studies, and on the bottom three in yellow are the pediatric studies, and you see that the point estimates, again, are in line and the total overall adult and pediatrics combined, which is the light blue on the bottom, is hardly different from the dark blue on top, which is the adults only.

If we then go on to the -- not the mortality, but the safety issue in pediatrics and we see the length of stay, which is the one that was measured, again, the bottom three studies are the pediatric, pure pediatric studies, and again you see consistent, again, like the adults, showing the same types of effects with the point estimates. So we believe, again, and you see the light blue is the total overall adult and pediatrics together, so we believe that these are consistent results along with the adult.

DR. GITTERMAN: Does that help at all, Dr. Wiedermann?

DR. WIEDERMANN: Well, I'm -- this would take another hour discussion. I'm very familiar with the studies, and I think there are better ways to achieve the same outcomes while we gather more information on PCT and children.

DR. CALIENDO: Okay, thanks.

So, Steve, you're good we move to the second question?

DR. GITTERMAN: Absolutely.

DR. CALIENDO: Okay.

DR. GITTERMAN: This is invaluable, and thank you all.

DR. CALIENDO: All right, so our second question is the same approach but now we're talking about discontinuing antibiotics for people with suspected or confirmed sepsis.

So Dean, why don't we start with you?

DR. FOLLMANN: Thanks. This is Dean Follmann.

I have pretty much similar comments for sepsis as I had for LRTI. I thought there was very strong and clear evidence that antibiotic duration is reduced, and then I thought of the patient-level safety analysis is a large safety study of 600 individuals, and when I looked at the odds ratio upper limit, it was < 1.2, which was sort of my working margin, and just elaborate on that a little. If you look at a 1.2 odds ratio and convert it to a death rate, the overall death rate was about 22% in the septic population, and a 1.2 odds ratio translates to a 25.3 death rate, so the difference between 25.3 and 22% is about a 3% difference in mortality.

So I'm used to comparing one anti-infective drug versus another anti-infective drug, say in the HAP/VAP setting, and there we have margins of 10% or so, so 3% is much, much smaller, and just to give some context on what Dr. Skates mentioned, how do we sort of decide if 1.2 is better than 1.3 or 1.1. We, you know, bring our experience to it, and that's sort of how I felt comfortable with this kind of safety analysis.

I don't have much more to add, I think, in the sepsis setting. We use -- the PCT will be used serially, so that gives -- be some comfort that, you know, if there's a mistake made, it's low, and you don't initiate therapy later on; it can become high and you can initiate therapy, so that's a comfort. Once again, this is an aid, not, you know, a strict algorithm. Also, DOOR/RADAR, as you mentioned, for LRTI, I think, would be good to apply here for sepsis. And that's all.

DR. CALIENDO: Okay, thank you.

Go ahead, Steve.

DR. SKATES: Steve Skates.

I don't have much difference to add. I'm reassured by additional data that I've seen from the independent presenters on the effectiveness of looking at longitudinal changes, and I'd like to -- I think that reassures me greatly. I'd like to clarify a couple of things, you know, what is the recommended frequency for looking at PCT, what is the reduction from a peak or from the initial or from some other average. So making clear what that reduction, what the denominator for that reduction is, I think, would help systematize the longitudinal algorithm across all users.

But on the whole, I see this as a good tradeoff between risk and benefit in this setting. The odds ratio on the mortality, given the level of mortality in sepsis patients, I think, is very reasonable, and I'm much less concerned in this setting about the safety/effectiveness tradeoff than I am in the previous setting.

DR. CALIENDO: Dr. Bozzette, do you want to comment?

DR. BOZZETTE: At every 24 to 48 hours and 80% from the peak.

(Off microphone comment.)

DR. SKATES: And -- I'm sorry. And that's in the package insert, that definition? The peak is. Okay, great.

DR. CALIENDO: Go ahead, Tom.

DR. MOORE: Right. So I said pretty much what I was going to say earlier.

(Laughter.)

DR. MOORE: But I will say this, you know, my earlier concerns, previously stated concerns about outpatient use of procalcitonin for LRTI notwithstanding, I really don't want to over-emphasize that. I mean, I think that's going to be an emphasis to educate the

clinician and make sure they use their clinical judgment. I do think it's a very important test that should be available for outpatient use for many reasons, but one specific reason that I'd like to emphasize, and that is that it's very difficult to do clinical trials on community-acquired pneumonia in the United States because we can keep people alive in a hospital for a long time, and that's one of the issues is that, you know, we used to use mortality as an endpoint.

If we have good biomarkers, we could use them as a substitute, and that's really been a continual point of discussion in previous FDA panels. So if the FDA does, indeed, endorse these, procalcitonin for LRTI, and extends to community-acquired pneumonia, what have you, then that could benefit both the Agency as well as facilitate drug development.

DR. CALIENDO: Okay, thanks.

Go ahead, Dan.

DR. JERNIGAN: Dan Jernigan.

On the prior one, there was some concern about controls in the community setting, the outpatient setting, but here with the estimate, the effect estimates are extremely well understood, there's numerous studies, so I'm very comfortable with the data in this particular setting. In addition, there are controls in place in the form of multiple clinicians taking care of it, there are multiple opportunities, so ASP is in place, as well, so I think in this setting, it makes a lot of sense to move forward with it.

DR. CALIENDO: Go ahead, Cathy.

DR. PETTI: Yes, I agree, it makes a lot of sense. This is just a quick question. In the original indications for use, it says, "progression to severe sepsis and septic shock," and in that indications you clearly know what syndrome we're speaking of, but now we're using just the word "suspected or confirmed sepsis." Could that be confused with just merely

bloodstream infection?

DR. GITTERMAN: I don't think we should revisit the past for the --

DR. PETTI: No, no, no. No, no. I understand in the context of the original intended use. I'm just curious about now the modified IFU is not using the modifier of "severe sepsis" or "septic shock"; it's just using "sepsis."

DR. GITTERMAN: That's exactly right. I think all of us recognize -- you know, sepsis is a phenotype. I don't want to set these folks off about, you know, how useful it is. And, you know, there's so many definitions to sepsis; the diagnosis of sepsis has gone up 10-fold over the last decade. There's so many issues that, at this point, to leave it nonspecific is really the best we can do. Everybody knows there's been a redefinition of what sepsis is for research.

DR. PETTI: Yes.

DR. GITTERMAN: Anyway, it -- you know, we just couldn't go there, but your point is incredibly insightful, and in very careful studies that people do, it's very problematic. But your point is correct; we just -- you know, I think to do that would be almost impossible at this point, but it's a very good point.

DR. CALIENDO: Go ahead, Kathleen.

DR. BEAVIS: Yeah, Kathleen Beavis.

Sometimes it's just smart to pun and just know that everybody gets the message. No, and I don't have reservations with using this for the sepsis indication, as discussed.

DR. CALIENDO: Angie Caliendo.

I don't have any reservations either. Just a comment. Again, we're going to have to list patients that this is not appropriate for. One of the things that we haven't really talked very much today is hypoperfusion and how that can lead to elevated procalcitonin levels. Septic people are often hypotensive, so I think we just need some clarification for that in

the labeling, also.

DR. HANSON: Yeah, I have nothing to add. I have no reservations in the ICU sepsis setting, and I think the risk of discontinuing antibiotics too early is mitigated by serial measurement and careful attention to a patient who's being monitored by multiple providers.

DR. WELCH: David Welch.

I have no problem with this question about the use for discontinuation of antibiotics in patients suspected or confirmed to have sepsis. They could add the advantage of having an additional data point to do that with.

DR. WIEDERMANN: Bud Wiedermann.

I don't have a lot to add. This is a marginally easier question. But we should remember the patient level dataset was just from LRTI-associated sepsis, so you know, I have a little uneasiness that it's a little narrower than the intended use.

DR. CARPENTER: Chris Carpenter.

And as per my word before, I'm just going to state that I'm in full support of this use for sepsis.

MR. SIMON: Tom Simon.

My last comments suffice, and being the age of 70, I noticed that one of the tests had my category in, so I'm happy for an additional test. Thank you.

MS. BERNEY: Barbara Berney.

I have no reservations about this test for sepsis.

DR. CALIENDO: Dan.

MR. BRACCO: Dan Bracco.

No comment.

DR. CALIENDO: Okay, Dr. Gitterman, we have consensus. Everybody on the Panel is

very comfortable with the risk-benefit analysis of sepsis for deescalating antibiotics in sepsis, and there's no concern for this indication.

Several comments: Make sure we identify which populations this can be used on and which cannot -- I'm not quite sure where you will go with pediatrics, since it sounds like there's actually no real data in children with sepsis, so -- and certainly, we talked, like I said, about immunocompromised hypotensive; to recommend the DOOR/RADAR analysis of the data, again, for sepsis; and the importance of sequential monitoring and making sure that both labs and clinicians understand the frequency of monitoring and the importance of sequential monitoring.

And we didn't talk about it specifically, but I think this is another place for provider education that would be very useful.

Any additional questions, Steve, that you have?

DR. GITTERMAN: No, but if you're planning to draw the meeting to a close, I would like the opportunity to --

DR. CALIENDO: Oh, Steve, I would never do that without giving you an opportunity to talk, but first, do you have any other questions related to sepsis?

(No audible response.)

DR. CALIENDO: So, Dr. Gitterman, you get the floor for any comments that you want to make.

DR. GITTERMAN: Well, first, of course, I thanked the Committee, so I'm not going to do that again. I would like to emphasize, though, I don't -- well, I suspect, given the consensus, which is very -- you know, it's just a great result, how important this result is. Dr. Skates had said huge. That's -- this is a really, really important step that has not been taken before, and again, I think people realize this, and for the practicing clinicians around the room, this is going to potentially impact everybody's practice, and we can't thank that

enough. And since, again, I'm in closing credits, Dr. Roth, when he spoke originally way back when, which seems like yesterday, had said this was an atypical meeting, and actually violating Dr. Caliendo's charge to the Committee, Dr. Bracco actually discussed something with me at some point during a break, I hate to say that, but his question was how often does the Committee -- does the FDA present 510(k)s to the Committee, and that's extremely unusual in many -- and I just want to say this is atypical, and I really would like to recognize the vision of our Director, Dr. Scherf; our Office Director, Dr. Alberto Gutierrez; and regarding the overall meeting, the Center Director Dr. Shuren. I think my colleagues at the FDA, it would be hard pressed to say how much work they have done. I mean, you didn't get to see their Team PCT t-shirts.

(Laughter.)

DR. GITTERMAN: That's not a joke -- which they wear to the internal meetings; unfortunately for those people who didn't get theirs, the shipping was delayed, and maybe we'll send one to bioMérieux, but the amount of effort. And just to recognize Dr. Pennello, Dr. Li, Dr. Goldberg, Dr. Shea, who's hunched over a computer because she doesn't like to be recognized, but the number of e-mails that she sent at 1:00 in the morning, which I read at 1:00 in the morning, would astound, and again, I can't go through everybody's name, but everybody's being quiet there, it was an unbelievable team effort.

And I would also be amiss if I didn't recognize the Sponsor has done an unbelievable job, you know, given the FDA vagaries; we set a date and they had to meet that date, and the effort and the professionalism and the interaction, I think, could be a model for them. And just to emphasize something, many of the people here weren't here, weren't here yesterday, but in Dr. Scherf 's introductory comments to the Committee, he said the reason we were having this meeting, which encompassed 2 days, was to promote public health and protect the public, and that really is the answer, I think everybody here has contributed to

this, and somewhat to address Dr. Bracco, why did we have this meeting, because we thought it was important to the public health. And in our own thinking, for the people there for the 2009 workshop, to us, this is the logical follow-up to the 2009 workshop. And again, I don't think -- we should be more thankful for the clarity and the really very, very high level of discussion, so we thank everyone.

And is it a rule the Committee has to end on time?

DR. CALIENDO: Only if I'm running it.

So I just want to give bioMérieux an opportunity. Do you have any additional comments, anything that you want to say before we close?

DR. MILLER: If you don't mind, I'd like to do a closing statement.

DR. CALIENDO: Sure.

DR. MILLER: So following up to Dr. Gitterman's comments, I'd be remiss to not say that an enormous bioMérieux team has devoted blood, sweat, and tears into this, and to do it within the deadline in order to have a productive discussion here today, and so I think it's something that really is truly beyond. But bioMérieux itself, as a company, would like to thank, profoundly thank the FDA and the Advisory Panel for the opportunity to present and discuss our 510(k) today and its submission and the value of PCT.

We understand the extraordinary situation of this meeting, and we truly appreciate it, as Dr. Gitterman has mentioned. We believe that safe reduction in inappropriate antibiotic use is important for patients, but also for the healthcare system in the United States. We believe that the benefit-risk balance is in favor of the two new proposed intended uses, and we appreciate the active discussion about both sides of the equation, both the benefit and the risk. The power of 23 randomized control trials with over 7,800 patients is very strong. In addition, there's tremendous value, as has been mentioned by the patient level meta-analysis, which is not always available for these types of things. The

exhaustive subgroup analyses, which all show the same results and the same direction, are very convincing, and we believe that that's very strong evidence, as well, even despite adherence to the algorithm inpatient/outpatient setting, patient groups, etc.

The true importance of PCT, as everybody realized and got, is in the additional value on top of clinical judgment. It adds value on top of what the clinician is already doing with the patient in terms of all the other tests, the history, the physical exam, and the lab tests, as has been demonstrated. And this value really is additive to standard of care, and I think everybody appreciated that, and that's very important.

The VIDAS B·R·A·H·M·S PC test, PCT test, is a 20-minute test. Getting results within an hour is possible and has been demonstrated in certain healthcare settings in the United States. We believe that if a healthcare system finds it valuable to provide that result, that they should modify the pre- and post-analytic environment to render that result within an hour or two to try to effect changes in patient management, but the test itself is 20 minutes, and it can be done, as has been evidenced. And that change in environment has already been done for troponin, for streptococcal antigen; there can be changes in a system to improve patient healthcare.

Again, we'd like to thank the FDA and the Advisory Panel for their time today and the very valuable comments. We look forward to further discussions and lots of interaction with the FDA. Thank you.

DR. CALIENDO: Thank you, Dr. Miller.

This is Angie Caliendo.

I would just say that I've been chairing these meetings for a couple of years now, and it's rare that they're done in time for me to actually say something other than the meeting's over, we got to go. But I want to take a minute and really recognize what the FDA has been doing over the last several years, which I think is showing a commitment to very creative

ways of moving the field forward. We've talked about a variety of things over the years that -- over the last couple of years that we would have never addressed 5 or 6 years ago. So I just appreciate very much your willingness to listen to clinicians and a variety of professional organizations to have a meeting like we did today, have a meeting like we did yesterday. I think these are the types of activities and decisions that are changing patient care in a very, very positive way.

So I just want to extend my appreciation, one, to the FDA. I know this was a ton of work, it was a ton of work for bioMérieux, and you made this so much easier for us. It was a lot of data to go through, but it was incredibly well presented, and I want to thank everyone on the Panel, because when I got my e-mail from Shanika and I had four inches of studies to read, I thought, oh, my god. And so I know everybody put a lot of work into this, and I think we ended up with a very, very productive day.

So thank you very much for your contributions, and the meeting of the Microbiology Devices Panel is now adjourned.

(Whereupon, at 4:18 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

MICROBIOLOGY DEVICES PANEL

November 10, 2016

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947