the effect, if you start out with 5 percent mortality rate, then you can't get any better than 5 percent treatment effect; whereas if you have a 70 percent mortality rate, you can have a 70 percent treatment effect.

DR. SINGER: That's right. It's certainly much larger in older patients, the treatment effect; the magnitude is different. I'm not sure I know how to answer that question.

ACTING CHAIR TOWNSEND: Dr. Fleming has a comment.

DR. FLEMING: That's a very intriguing issue, and you are right on target by noting that when we talk about whether there is effect modifiers or interaction it depends on the measure we use.

We in our presentation today have followed the lead for what people have done in this area, which is to look at the absolute difference. And people talk about 10 percent margins as the absolute different. Well, if

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you have a 15 percent mortality, you're allowing a 10 percent margin, you are allowing a 67 percent relative increase in mortality.

Might it be that a 67 percent relative increase in mortality on a relative risk scale could be a margin that could be used to extrapolate to younger people? The data are certainly consistent with your observation. The data are consistent with the fact that we may well still have that same level of benefit in the very young, even in non-bacteremic young people. It requires huge numbers of patients though to validate that that relative risk approach can be extrapolated to those younger patients.

But it's a very reasonable supposition that you've making. By the way if you take that approach, though, and you use the margins that many of us are advocating we could use in more higher mortality settings, 15 mortality you could use a 10 percent margin, in a 2 percent mortality, you could

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basically - in a 3 percent mortality you could use a 2 percent margin, so yes, I think there is a basis for arguing that in these very low risk people there still is an effect. It's hard to prove it because to show a relative risk of having or whatever it takes, 88 events, and 88 events are easy to get in older patients or bacteremic patients; they're really hard to get cumulative data and aiding events in younger non-bacteremic. But the data aren't inconsistent with your supposition.

But if we followed that supposition then the margin you would use in a population that had 3 percent mortality would be 2 percent; the margin you'd use in a population with 1 percent mortality would be 2/3rds of a percent.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: I just wanted to say once again, Dr. Fleming, I don't really understand - I wish I could, but I was going

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to say that we have got to talk abo9ut a proportional decrease. You can't talk about the absolute number. It just doesn't make any sense. Honestly, just as was stated, if your mortality starts out at 4 percent and you drop it to 2 percent, that is not a 2 percent decline; that's a 50 percent decline.

And that's exactly the same if it starts out at 50 percent and it goes to 25 percent.

DR. FLEMING: So you are concurring with what we are saying?

DR. MUSHER: Yes, exactly right, and I noted it as the slides were going along also.

DR. FLEMING: And we used the absolute, because that's what tradition has been in this area. But it's very fair to say that when you have a very low rate of events occurring in young children who are - in people below 30 who aren't bacteremic, the data indicate there is undoubtedly a benefit,

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but understanding what that relative benefit is is so much harder when there are so few events.

So if we extrapolate the same level of benefit, which is a big assumption, but if you do you can come up with margins.

But the point is, if you have a 10 percent margin when you have a 15 percent mortality in the control, that would be extrapolated to a 2 percent margin when you have a 3 percent mortality in control, following the relative risk concept.

ACTING CHAIR TOWNSEND: Thank you, Dr. Singer.

DR. SINGER: Thank you.

ACTING CHAIR TOWNSEND: Our next presentation will be by Dr. Nambiar, contemporary CAP trials and determination of treatment effect.

CONTEMPORARY CAP TRIALS AND DETERMINATION OF TREATMENT EFFECT

DR. NAMBIAR: Thank you, Dr.

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Townsend, and good afternoon, everybody.

An overview of my talk is as follows. I summarize the recent CAP trials that have been submitted to the agency for registration purposes. This includes both oral and IV studies.

I will make an attempt to link historical studies to contemporary CAP trials, outlining the difficulties we face in linking these two sets of patients.

I'll also review the alternate approaches we took to determining a treatment effect in CAP.

For inclusion in current CAP studies, patients should have a new infiltrate on a chest X-ray and at least two of the following signs and symptoms: a cough, sputum production, auscultatory findings, dyspnea, tachypnea, fever, elevated white count and hypoxemia.

Though microbiologic evaluation has to be performed on each patient, isolation

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of a pathogen is not required for overall evaluating. The primary endpoint in these studies was clinically cure at the test of cure visit, seven to 21 days after completion of treatment.

The primary analysis populations were the intention to treat and per-protocol population.

Clinical cure was defined as complete resolution or improvement of all signs and symptoms, and improvement or lack of progression of all abnormalities on chest radiograph, such that no additional anti-bacterial therapy was required.

Microbiologic response could be categorized as any of the following four: the pathogen was considered eradicated and the original pathogen was absent from the test of clear culture; it was categorized as being persistent if the original pathogen was still present in the test of clear culture.

Presumed eradication and presumed

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persistence were indirectly derived from the clinical outcome. So if you had a clinical cure, and there was no specimen available for culture at the test of cure visit, you were deemed to have presumed eradication. And on the contrary, if you were a clinical failure, without a culture at the test of cure visit, you were considered to be presumed persistent.

The intention to treat population included all randomized patients, the per-protocol or clinically valuable patients were those ITT patients who had no major protocol violations.

The modified or microbiologic intention to treat population includes all intention to treat patients who had a baseline pathogen including those with a positive serological diagnosis.

The microbiologically valuable populations were those patients who were in the MITT population and had no major protocol violations.

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Seven comparative studies conducted from 2000 to present were reviewed. Most of these studies were multinational. They were all randomized, double blind, non-inferiority trails that used a pre-specified, noninferiority margin of 10 or 15 percent.

About three to 500 patients were randomized per study. The active controls used in these trials are varied, and included clarithromycin, amoxicillin and clavulanate or levofloxacin.

This is a summary of the common clinical features seen in these patients. Most patients had either cough or sputum production. Interestingly, fever has generated a fair amount of discussion this morning, and fever was reported only in 19 to 33 percent of patients.

In one study 98 percent of patients were febrile, but in this study fever was a requirement to be enrolled in this particular trial.

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Other symptoms included chills, shortness of breath and chest pain. Multi-lobar disease was seen in 16 to 25 percent of patients.

This graph represents the frequency with which patients had a baseline pathogen. So the bars represent the percentage of patients who had a microbiologically documented infection. And the bars in pink represent those who had streptococcus pneumonia confirmed on culture, either from the sputum or the blood.

So as you can see in the graph streptococcus pneumonia was not identified in a large number of patients, and varied from about 6 to 20 percent of patients.

In this graph we have presented the treatment difference between the test drug and the active comparator in the intent to treat and in the per-protocol population so the vertical bars represent the 95 percent confidence intervals around the treatment -

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for the treatment difference, in the intent to treat or the per-protocol population for each of the seven studies.

And as you can see all studies would have met a noninferiority margin of 15 percent; and five studies would have met the noninferiority margin of 10 percent.

So to summarize, what we found on review of the oral CAP studies the mean age of patients was 46 years, with a range from 18 to 98 years; majority of patients had PORT scores of two or less; five to 10 percent of patients had PORT scores of three; baseline pathogens were identified in 45 to 75 percent of patients; 6 to 20 percent had streptococcus pneumoniae, and anywhere from zero to 2 percent had streptococcus pneumonia bacteremia.

More than 80 percent of patients were clinically cured in the intention to treat population, and that was 90 percent or greater in the pro-protocol population.

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Mortality in these studies was less than 2 percent.

The IV CAP studies were generally similar to those of the oral CAP studies. An important difference is that some of them were open label trials.

The endpoints and analysis populations in the IV studies was similar to those of the oral CAP studies, and the study size ranged from about 300 to 700 patients.

In summary the mean age of patients in the IV CAP studies was 56 years; 55 percent of patients had PORT scores of one or two; 20 percent of patients had PORT score three; and 20 percent has PORT score four.

Less than 5 percent of patients were enrolled with PORT scores of five. Baseline pathogens were identified in 30 to 55 percent of patients; 20 percent had strep pneumonia; and 49 percent of patients had strep pneumonia bacteremia.

Clinical cure about 80 percent in

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the intention to treat population and 90 percent in the pro-protocol population.

Mortality ranged from 2 to 4 percent.

Moving on to the second part of my talk, which is an attempt to bridge the gap between the historical studies and contemporary CAP studies.

As Dr. Singer has already summarized, all the CAP studies in the early 1900s, this is just a quick summary of those studies, they are primarily conducted in hospitalized patients. The severity of the disease in these studies is unclear, but we think it is reasonable to assume that most had moderate to severe disease.

There was no standardized classification system used across these studies. Most studies were primarily in patients with pneumococcal pneumonia, though some studies did include patients without confirmed pneumococcal etiology.

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In current CAP trials, the majority have been older CAP studies; they have all been nonferiority trials, with a prespecified margin of 10 to 15 percent.

By and large patients in these studies were otherwise healthy with mild to moderate CAP. Few patients had PORT scores of three or greater. The proportion of patients with strep pneumonia identified as etiologic agent was small, and the number of patients with bacteremia was also small.

The primary endpoint was clinical outcome. Generally success rates in these trials were high with very small differences between the tests and the active comparator. And mortality was low in most studies.

So the three major areas which I would like to highlight where we've had issues in linking historical data with current CAP trials are the patient populations, microbiology and endpoints.

And I'll give you my clinical

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perspective and the statistical implications of these uncertainties will be discussed by Dr. Valappil and his staff.

It is difficult to define a patient population identical to those seen in historical studies. So this raises some important questions.

Can patients in current CAP trials be compared to those in historical studies if matched for age?

As Dr. Singer had outlined in her presentation, a large majority of patients in the observation studies, and in the controlled historical studies were under 50 years of age.

The second question is, is it acceptable to assign a PORT score for patients in historical studies based on age alone? We only have limited data on comorbidities.

In terms of microbiology, again as Dr. Singer had outlined in her summary slide, historical data is primarily for patients with pneumococcal pneumonia. Granted there were a

few patients in whom other organisms were isolated, including staphylococcus aureus and hemolytic sterptococci, and there was also a group of patients in whom no pathogen was identified.

And as I have summarized for you from our current CAP trials, streptococcus pneumonia is isolated in only a small fraction of cases, and a smaller proportion of patients have bacteremia.

So this raises the question whether or not the treatment effect from these historical studies can be extrapolated to organisms other than streptococcus pneumonia.

Based on the treatment effect seen for mortality, we have seen the treatment effect is larger in patients older than 50 years of age and in bacteremic patients.

In current studies mortality is low. It's important to note that as risky therapy is used in patients failing treatment, mortality is prevented in many cases.

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Clinical outcome is the primary endpoint in current studies rather than mortality. Based on limited data for other endpoints that are available from historical studies, is it reasonable to extrapolate to the treatment effect in the form of clinical outcome that is assessed in present trials?

A second question that needs to be answered is, as death is included in clinical failure, is it reasonable to assume that the treatment effect for clinical outcome is likely to be greater than that seen for mortality.

Moving on to the last part of my talk which is the alternative approaches we reviewed in a further attempt to quantify the magnitude of treatment effect in patients with community-acquired pneumonia.

We reviewed studies that had looked at outcomes of discordant therapy, either based on adherence to treatment guidelines or based on in vitro susceptibility

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of the infecting pathogen.

We reviewed studies that looked at the effect of timing of antibiotic administration on outcome or mortality.

We reviewed failed active comparator studies; superiority studies; and also dose-ranging studies.

In the literature discordant therapy is defined two ways. It's discordant based on guidelines, and generally it's based on whether or not the therapy was concordant with the IDSA or ATS guidelines which were current at that point in time.

Most of these studies have been retrospective studies that have used varying definitions of discordant therapy.

The vast majority of studies have looked at concordant or discordant therapy in the first 48 hours.

The endpoints in these studies varied. Some studies looked at 48 hour mortality, while others have looked at 30-day

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mortality or in-hospital mortality.

The number of patients who received discordant therapy in these studies was generally very small.

While studies did adjust for severity of illness or other covariates using propensity scores, some other studies did not adjust for these covariants.

We also reviewed studies that looked at discordant therapy based on in vitro susceptibility of streptococcus pneumonia. Generally there was no different in mortality or clinical success was seen as reviewed in a recent metanalysis.

The recent change in penicillin breakpoints are definitions used in some of these studies may not be applicable.

We reviewed active comparator studies, and most studies that we identified in the literature have all been noninferiority studies, though some have shown superiority, and I have identified two of them here, and

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I'm sure there are others.

In one of these studies levofloxacin was compared with ceftiaxone or cefuroxene. That was the File study and the Finch study.

Moxifloxacin was compared with amoxicillin clavulanate with or without clarithromycin.

Generally on review of active comparator studies we noticed that all classes of antibacterials are effective, and summary reviews have not demonstrated superiority of one class over another.

Hence any estimate of treatment difference would be an underestimate. The fact that very few studies demonstrated superiority represent that this was likely a chance finding alone.

Studies that have looked at the timing of antibiotic administration were primarily observational studies. Most of them have been retrospective studies, but there

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have been prospective studies as well.

And time to first antibiotic dose of four hours has been associated with better outcome.

We were unable to identify any study that showed superiority of one dosing regimen over another, though there are studies that compare one regimen versus not another. And most of them again have been noninferiority studies.

One field active comparator study that has been discussed even at the workshop is the daptomycin studies. These were phase three randomized double-blind noninferiority trials in hospitalized CAP patients where intravenous daptomycin was compared to intravenous centriaxone. Results of these studies were published about two weeks ago in CID.

Of the two blind studies, the second study was stopped early based on results of the first study. These are fairly

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contemporary studies, having been conducted from 2000 to 2002.

Results in the publication are based on the full studies, so I don't have results by individual study.

Four hundred and thirteen daptomycin and 421 centriaxone-treated patients were enrolled in these two studies combined. A little over 40 percent fo patients had a PORT score of two; a third of patients had PORT scores of three; and the remainder were PORT scores of four; there was one patient with a PORT score of five.

A little less than a third of patients had a microbiologically documented infection which in this instance was either streptococcus pneumonia or staphylococcus aureus, with 28 percent of daptomycin treated patients and about 25 percent of centriaxone-treated patients.

About 7 percent of patients in each of the treatment arms had bacteremic.

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And these are the results for the pooled population. Both the intention to treat and the clinically valuable population were the co-primary analysis populations for this study.

And in both populations daptomycin was inferior to the comparator, with a treatment difference in the ITT population fo minus 6.5, and in parentheses and provided the 95 percent confidence intervals.

Twenty one daptomycin treated patients and 12 centriaxone treated patients died during the study.

Besides the inferiority of daptomycin, one other important aspect of the study, which was based on a post hoc analysis, in the pooled CE population, was that daptomycin-treated patients who received prior effective therapy for less than 24 hours had higher success rates than those who did not receive such therapy. And I think this is an important point of discussion as we discuss

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future of clinical trials in CAP.

Though daptomycin has been shown to interact with pulmonary surfactant, we feel that the daptomycin effect seen here is likely larger than what one would see with placebo.

We also reviewed studies that looked at other endpoints, such as time to resolution of symptoms.

We certainly did identify studies that have identified superiority of one regimen over another for such endpoints. However for most of these studies there were either a secondary endpoint, or were part of a subgroup analysis.

Some studies have used clinician-reported outcomes and some have used patient-reported outcomes that were not validated.

CAP-Sym is a patient-based outcome measure that was evaluated in outpatients with CAP and was published a few years ago. To the best of my knowledge, this tool has not been used to support a primary endpoint in

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registration of trials.

So to summarize the supportive data we reviewed to quantify the treatment effect in CAP. Overall the studies did support the effectiveness of anti-bacterials in CAP. The choice of anti-bacterial and its timing of administration appear to be important.

However, the supportive information we reviewed was not directly contributory to determining the magnitude of treatment effect. Alternate endpoint, such as time to resolution of signs or symptoms, maybe an option for future trials.

I would be remiss if I didn't spend a minute or so talking about pediatric CAP trials being a pediatrician myself, and I also see that it has generated a fair amount of discussion already today.

I know Dr. Nelson had to spend some time talking about pediatric studies. And a lot of what we are discussing today is

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just as relevant to the pediatric population.

As in adults historical studies in children have showed reduction in mortality after introduction of sulfonamides. In addition to the observational data that Dr. Singer had discussion, which is from Bullowa paper, we did review some other studies that looked at treatment benefit in children with sulfonamides. Most of these have been K series, and the greatest treatment difference really was seen in infants less than a year of age.

In the Raycraft series there were about 200 infants who were less than a year of age, and the mortality was 10 percent compared to 30 percent based on historical controls. There were no concurrent control trials that we were able to identify.

And Ormiston study was again a K series of about - I forget the number, but it was less than 50 children.

Most recent CAP trials in children

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have all been equivalency trials. In these studies children with severe or very severe pneumonia based on the WHO classification system was used. And this morning Dr. Nelson had reviewed some of these studies with you.

The regimens used in these trials varied. Amoxicillin was compared to either intravenous ampicillin or penicillin. Chloramaphenicol was compared to a combination of ampicillin and gentamicin.

In most studies the clinical outcomes in both treatment groups were very similar.

There was one recent study which showed that the combination of ampicillin and gentomycin was superior to chloramphenicol in children aged two to 59 months who had very severe pneumonia based on the WHO classification system.

So to summarize what I've presented thus far, I've given you an overview of recent CAP trials both oral and IV studies.

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I have briefly touched upon the study design endpoint, analysis populations, microbiology and outcomes in these studies.

It's important to note that although treatment effect was demonstrated in historical studies, there are difficulties and limitations in linking historical data to current CAP trials.

I've also provided you an overview of additional data that are supportive of anti-bacterial effect in CAP though not directly contributory to estimating a treatment effect.

So to conclude I would like to say that patient populations described in the historical studies differ from those seen in current CAP trials. In current CAP trials patients may be less ill; a small proportion have strep pneumonia, as the baseline pathogen; and very few patients are bacteremic.

The endpoints evaluated in

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historical studies are different from those used in current CAP trials. So for noninferiority trials in CAP we need to define patient populations and endpoints that are best supported by the treatment effect seen in historical studies.

This should be the end. And I would really like to acknowledge Dr. Carol Higgins, one of our statistical team leaders, who analyzed all the data on the contemporary CAP trials and had presented it at great length at the workshop in January.

Thank you.

ACTING CHAIR TOWNSEND: Thank you, Dr. Nambiar.

We have time for one or two questions. Dr. Wong-Beringer.

DR. WONG-BERINGER: I wonder if you could comment on one particular area which I haven't heard so far today, and that is specifically measuring the host-microbial interaction there.

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I think we appreciate more that antibiotics have more profound biological effects on these organisms than perhaps even up-regulating the virulence expression here, and that could play a role in confounding the treatment effect.

And secondly the polymorphisms in human susceptibility or host inflammatory response to the infection itself could also introduce a difference in treatment effect there.

Please comment on where these might fit in in the study design or alternative approach.

DR. NAMBIAR: I don't think I'm equipped to answer that question.

In terms of exposure response, I know Chris, one of our clinical pharmacologist, is certainly going to -- I think his presentation will follow later this afternoon, so you will have a better idea about exposure response.

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Your second question is in terms of host and immunomodulatory --

DR. WONG-BERINGER: Possibly.

DR. NAMBIAR: In terms of how to factor that into clinical trials?

DR. WONG-BERINGER: Well, I think, not necessarily on the immunomodulating part, but in terms of the host's response to treatment, or the driver could be the inflammatory response and host genetic difference there. In perhaps the more severe pneumonia group.

DR. NAMBIAR: But that would be in addition to the anti-bacterial effect?

DR. WONG-BERINGER: Right, and differentiating the treatment groups.

DR. NAMBIAR: I'm not quite sure how I could differentiate the two. And I suppose if you are doing a randomized controlled trial you would expect it to be balanced across arms.

So are you trying to suggest that

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there is an alternative way of looking at just that aspect separate from the anti-bacterial effect?

DR. WONG-BERINGER: I guess I would be interested in looking at the treatment groups, measuring the play, the role where genetic polymorphism could play a role in affecting the treatment response there.

DR. NAMBIAR: I'm possibly not aware of any particular polymorphism or genetic marker that identifies an outcome, but maybe there is somebody else in the audience who is better aware than I am. I do not know of any specific genetic polymorphism that I could use as a marker in patients with CAP.

DR. WONG-BERINGER: Not specifically in CAP; it's certainly a developing area. And I think in terms of going forward in the future trial design.

DR. NAMBIAR: There is a fair amount of discussion in that regard in pharmacogenetics and all that, which is -- I

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will not claim to be an expert, but I am certain there is a lot of discussion.

ACTING CHAIR TOWNSEND: Dr. Venitz.

DR. VENITZ: I just want to make sure that I understand the current registration trials. Those patients have not demonstrated sensitivity in culture to the study drug; is that correct?

DR. NAMBIAR: Well, what happens is, when they get enrolled you often don't have a microbiological pathogen documented at the time of enrollment; and there is usually a delay of 24 or 48 hours before you identify the organism.

And as was discussed this morning, by and large what happens is, if you do - once you get the culture back, and if the organism is resistant, very often if the patient is doing well, they sometimes remain in the study, but often they are taken out of the study once you identify a resistant organism.

DR. VENITZ: So what's the

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proportion of patients that would be included in the analysis, in the final ITT analysis, that would not be sensitive to the study drug?

DR. NAMBIAR: There is more than one we are analyzing. So sometimes we leave them - we do leave them in the pure intent to treat population. Because everybody stays there. And often they are considered failures. But sometimes if there is a large number we may end up doing a sensitivity analysis and looking at it more ways than one.

ACTING CHAIR TOWNSEND: Dr. Follmann.

DR. FOLLMANN: I have a brief comment and then a question.

So I thought the presentation was illuminating for me because it's showing that the current trials you're using in CAP have very low mortality rate; in fact they are not using mortality as an endpoint, but cure.

Part of our task today and tomorrow is to come up with a margin, and most

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of our discussion is focused on margin for mortality. And maybe there is some margin we're comfortable with in a study that had a fairly high mortality rate, 10, 20 percent, or 30 percent or so; but it doesn't seem like those are the kinds of trials that are being done.

Now is that because such patients don't exist? Or is it because they were designed with a cure endpoint in mind and a particular margin in mind?

Because if we come out of here and just say we have a margin for a trial where we have a population of 20, 30, 40 percent mortality, is that going to be helpful? Would such a trial be possible?

DR. NAMBIAR: I think there are two answers to your question.

One is, when patients are failing therapy they are often given rescue therapy, so in effect you are preventing mortality; so that's one reason why you don't see a high

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mortality.

And secondly a lot of our patients meet one or the other of exclusion criteria. So a lot of these very sick patients don't get enrolled in the trials.

And as I've shown in the parenteral studies too, patients with PORT scores of four are only a small fraction, and PORT scores of five are hardly ever enrolled.

So there are two reasons why you do see a low mortality.

DR. FOLLMANN: And then the other comment had to do with your brief reference to some superiority studies which you said were successful. And if you have any more details on those, I'd be curious about them, because you know one way out of this mess would be to do superiority studies in patients with extremely mild CAP if it's possible.

DR. NAMBIAR: I actually have the publications. These were studies designed as noninferiority studies. And both of them, if

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I remember correctly, were open labeled studies. So they were designed as noninferiority trials, and I thought it's a 10 percent or 15 percent margin. But at the end of the day when they got the results it happened to demonstrate superiority.

So they were not designed to be superiority studies.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: I'd like to make a few comments if I could please.

First of all, an open label study that looks at something other than mortality is not a valid study. Because if a doctor knows what's the matter -- I'm going to comment on this briefly tomorrow -- the doctor knows which drug the patient is getting; the patient knows which drug the patient is getting, and you are interpreting resolution of symptoms and other kinds of things -- ladies and gentlemen, that's no study. The FDA shouldn't encourage that, the FDA

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shouldn't accept those data. That's a series of anecdotal reports; that's not a study. I feel very strongly about that.

Now I want to comment on the -- I'm not so knowledgeable about who designs the studies. But Dr. Wunderink commented that we have too many patients in our studies who don't have severe disease. So you notice a remarkable uniformity, a 90 percent success rate in just about everybody, and just about every trial of pneumonia no matter what drug was given.

So what kind of a situation is that? Well, pick patients who -- first of all, I absolutely agree with Dr. Wunderink, we shouldn't be mixing together the so-called mild and the so-called moderate. I think his point should be listened to. These patients had mild pneumonia, most of them.

Well, I think that the pharmaceutical industry is the one that designs the studies. And they are going to

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design a study in which their drug is going to look good. And if they design one that's going to look good, then you take a bunch of people who've got mild pneumonia and put them in a study, and you can compare it with anything you want, any other kind of treatment, and they are all going to do very well. And I think that's what you see in these studies.

So I think Wunderink is on target, and if you want to compare drug A with drug B you've got to take patients who are sick enough so it's going to make a difference.

Thank you.

ACTING CHAIR TOWNSEND: Thank you very much.

DR. NAMBIAR: Thank you.

ACTING CHAIR TOWNSEND: Next presentation will be by Dr. Valappil, noninferiority margin for CAP studies.

NON-INFERIORITY ISSUES IN TRIALS OF COMMUNITY ACQUIRED PNEUMONIA

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DR. VALAPPIL: Thank you, Dr. Townsend.

Good afternoon.

The outline of my presentation is as follows: critical steps in designing a noninferiority trial; statistical uncertainties in noninferiority studies; discounting and preservation of controlled treatment of fact; historical evidence and captions; magnitude of treatment benefit. And then I will summarize my talk with future considerations.

Dr. Fleming has gone extensively discussing the noninferiority design and issues, so I'm not going to go through it again, and go into that and discuss the issues.

But primarily for custom-specific issues have led to the noninferiority trials.

What are the critical steps in designing a noninferiority trial? Determine that the historical evidence of sensitivity to

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drug effect exists. Determine the design features of the historical placebo control trials from which the drug effect has been established. Determine a scientifically justifiable noninferiority margin. And also assure the quality of the trial and its conduct.

Any kind of subjectivity or imprecision can be rewarded in an noninferiority trial, and can artificially make the treatment look similar when in fact they are not.

What are the statistical uncertainties in noninferiority studies? What are the sources of uncertainties?

Magnitude and position of the estimate of active control treatment of fact, based on historical placebo control studies. Lack of constancy assumption, that is the potential lack of comparability of historical evidence. Estimate of the size of the treatment effects in the current

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noninferiority setting.

The observed treatment effect from a single study or a collection of studies may not be reproducible, introducing bias. It shows up in the estimate of the treatment difference between the test drug and active control in the current noninferiority setting.

This scenario is to demonstrate unclear treatment of fact. As you can see, the conference results in lapse and it is difficult to differentiate the untreated effect from the active control effect. And essentially a noninferiority margin determination will be difficult.

On the other hand in this scenario you see a substantial treatment effect, of active control over untreated effect. And a noninferiority margin can be defined provided the evidence is coming from adequate and well controlled historical studies.

Now the question is, how to account for statistical uncertainties in

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estimating a noninferiority margin? Two steps involved essentially: discounting or reduction of the historical control effect size; and preservation of the control effect.

Discounting of the historical control effect size is required to account for greater sources of uncertainties. For example it could be due to lack of constancy assumption, or lack of inter-trial variability. Differences in patient population, differences in dosing, or divisional control drug.

Preservation of the discounted treatment effect size is based on the 95 percent confidence developed around the difference in treatment effect.

The proportional -- the control effect preserve these based on good clinical judgment. Smaller noninferiority margin should be chosen when treatment failure results in irreversible outcomes such as mortality.

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Now the question is, why a smaller NI margin? Let us consider an example using the endpoint clinical success or failure. So if the clinical success rate is -- note that the clinical failure also include mortality. So if you consider a clinical success rate of 95 percent, the corresponding mortality rate would be 5 percent, or the clinical failure rate would be 5 percent.

If you consider an 85 percent success rate, then the corresponding failure rate in gross mortality is 15 percent, which is almost three times compared to the first case. So there is an increased mortality. So we need to balance the mortality with the clinical success.

So the message is, how much higher mortality is clinically and ethically acceptable when moving from a more objective endpoint like mortality to a clinical endpoint?

Now let us talk about the

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noninferiority inference. Let us assume that we have established a noninferiority margin based on adequate and well controlled historical studies. What would be the statistical inference?

There are four scenarios in this outline. Please note that there is a yellow dotted line on the left side which indicates a noninferiority margin.

The first two scenarios clearly shows that the noninferiority is demonstrated. However, if you look at the second scenario, the treatment difference, the point estimate of the treatment difference was above zero, indicating a better treatment effect. However, there is a large variability associated with that.

In the scenario three it clearly fails to demonstrate noninferiority because the lower limit of the 95 percent conference limit around the treatment difference has fallen below the noninferiority margin.

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What else in scenario four? It does simultaneously demonstrate a noninferiority and superiority.

Now let us discuss on the historical evidence in CAP studies. Dr. Singer has gone in great detail on the historical studies and issues, so I'm not going to discuss that again.

However, I would like to point out some of the issues based on the historical studies.

What is the reliability of the control effect based on the historical studies? The historical data for CAP would not be considered adequate based on the current standard for adequate and well controlled studies.

There are several design issues which were introduced by us. All cause mortality rate were evaluated in these historical studies. There was limited information on the resolution of clinical

signs and symptoms, as measured in the current CAP studies.

No true placebo controlled studies were conducted. However studies which use no specific treatment, for example, symptomatic therapy, were considered as untreated or placebo.

There are major limitations in the historical studies, including but not limited to the following.

These studies were not blinded. Some were observation studies, while some were controlled, though not randomized for current standards.

Majority of patients were hospitalized with pneumococcal or lobar pneumonia.

Subjects were assigned to anti-bacterial drugs including penicillin, sulfonamide, and tetracycline. There was significant variability and mortality rates across studies.

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The difference in overall mortality based on point estimates, in pneumococcal or lobar pneumonia, from the control studies it was in the range of 10 to 19 percent, and it gets higher if you look at the bacteremic patients.

However, there is significant variability in these estimates, and therefore, it lacks reliability.

This diagram indicates and first of all this is based on the controlled clinical trials, looking at the variability in mortality rates.

As you can see, Dr. Singer has pointed out that there is - sorry - 10 to 19 percent of treatment difference between the point estimates. However if you look at the variability around that estimate it is quite high. There is large variability.

Also note that this study, the Agranat, has a small number of patients. Probably that might explain the large

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variability around those estimates.

But again there is a lot of uncertainty in the point estimates.

Now if I may go back to the historical evidence and talk about the control effect, whether it is reproducible or not.

There appears to be a mortality benefit in hospitalized CAP patients that seem to have moderate to severe pneumococcal or lobar pneumonia.

However, there is significant variability and associated uncertainties in the estimated historical mortality rates. The magnitude of effect may not be reliable and reproducible in all CAP patients who appear to have less severe disease.

Now the question is, can we control the constants of a control effect based on the historical studies? Does the control effect remain constant over time? How do historical trials compare to the current trials? Difference in the patient population,

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this is definition, outcome criteria; those durational control and timing of the outcome assessment.

What is the internal variability of the effect size in the historical studies? As I said earlier, the anti-bacterials used in these studies included sulfonamides, penicillin and tetracycline, and we have lot more options in the current studies.

The mortality rates in the current studies are not very high, probably close to four percent, again, depending on which patient population you look at. If we look at the high risk population probably it is much higher than that.

The lack of -- although it may -- if I may just go back -- current studies don't have that many. I'm just hypothetically saying that if you could identify the high risk patient population, probably the mortality rates could be higher.

The lack of comparability between

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historical CAP studies and the current studies raise concerns in determining a precise estimate of the treatment effect.

This can be due to any number of sources including differences in patient population; advances in standard of care; differences in the endpoints; mortality or clinical failures; or emerging drug resistance issues.

How about the study quality and conduct, based on the historical studies? The historical CAP studies were not randomized per current standards, blinded or controlled for potential biases. Therefore in general when using historical studies the following issues can undermine its ability to reliably estimate the treatment benefit.

For example that includes subjective endpoints, lack of specificity in the diagnosis of patients, spontaneous resolution of signs and symptoms, treatment noncompliance, contribution of therapies, or

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misclassification of outcomes.

So if I may summarize the historical evidence, the historical data may be primarily limited to those with moderate to severe disease, due to streptococcus pneumonia. Historical studies do not provide quantitative estimates of clinical benefit other than all-cause mortality.

The microbiological etiology in historical studies, the first one, recent CAP studies.

Thus far I have summarized the historical evidence and its limitations. Given all the issues in the historical studies, the interpretation of the data can probably vary.

However, hence, our interpretation of the historical data is different from the IDSA position paper, and therefore I would like to make a few general comments.

This presentation focused only on controlled trials, while the IDSA position

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paper has also included or considered remaining studies.

IDSA's position paper reported absolutely mortality rate in the controlled studies by pooling studies, and did not take into consideration the lack of internal consistency in the mortality rates approach to this.

As you are aware, pooling studies makes several strong assumptions, including similarity in the patient population; disease characteristics; treatment duration. And it may be difficult to meaningfully interpret the results.

Now I would like to make a few comments on the Kingston paper, tetracycline versus placebo was studied in 290 healthy Marine recruits between age 17 to 22 years with mild communicative pneumonia. Mycoplasma pneumonia was the etiology in only 133, that was 46 percent of the subject, of the total number of subjects, which is only a subgroup

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of patients.

There are several endpoints being looked at, for example, mean time to defervescence, normalized chest X-ray, resolution of cough, and a few other endpoints.

There are potential multiple pressing issues and inflation of overall type rates based on this exploratory analysis.

Duration of fever is based on cumulative percent and it is not clear how missing values were accounted, and it has the potential for overestimating the treatment effect.

These findings are based on a single study, and subgroup analysis, and therefore, these results cannot be generalized.

Now if I may go back to the magnitude of treatment benefit based on historical studies. There appears to be a treatment benefit based on all-cause mortality

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in the historical studies. In hospitalized CAP patients with pneumococcal or lobar pneumonia, although the estimates lack precision as it explained.

However, mortality is lower in current studies due to availability of alternative therapies which could rescue patients and prevent death, as Dr. Nambiar has mentioned.

The question is, can we translate the mortality benefit observed in historical studies to a clinical benefit as measured in current studies, or will it be misleading?

The margin chosen for a noninferiority trial cannot be greater than the smallest effect size that active drug would be reliably expected to have compared with the placebo in the setting of the planned trial.

A noninferiority trial design is possible if you use mortality as the endpoint, because we have historical data to back up.

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Or scientifically justified extrapolation of the mortality benefit seen in historical studies to another clinically meaningful endpoint, probably clinical failure.

Dr. Nambiar has already discussed the results based on the current CAP studies, and the clinical cure rates were higher than 80 percent in the ITT population.

Now let us consider a 15 percent clinical failure rate which includes mortality in this hypothetical example. The main purpose here is to show that all failures are not the same.

So as you can see here, the red indicates the mortality rate, and the green indicates the rescue rate, and the white indicates failure rate other than mortality.

The first figure, you can see a clear mortality difference, whereas in the second figure you see the mortality as well as the rescue therapy being given, but they are

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balanced across the treatment arms plus that has less control.

Now again if I may remind you, this is only based on the 15 percent mortality rate. I'm only addressing that part. Whereas in Figure 3 you see a differential effect of mortality and differential effect of rescue therapy -- rescue rate in both the test drug as well as the control.

So in a noninferiority trial all these will be classified as clinical failure, although there is a differential effect in the treatment arms based on the mortality as well as the rescue rate. So this is going to be a problem in noninferiority trials.

Future trial design and considerations. Dr. Gitterman is going to talk about all these issues tomorrow. However, I would like to discuss a few issues.

Primary endpoint: all-cause mortality is probably the ideal endpoint; the practicality is different, but it has the

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backing of the historical studies.

Clinical failure, including mortality could be another option for whatever we can strongly, we can justify that extrapolation of the clinical -- the noninferiority margin based on mortality rates.

PRO Instrument is another option. However it lacks historical data to link, and therefore at this time can only be used in superiority trials to establish the effect.

One example could be the time to resolution of clinical signs and symptoms.

Now how about the primary hypothesis, are we talking about superiority or noninferiority type hypothesis? If it is a noninferiority type process, then we need to discuss about the choice of margin. So that raises the following issues.

What is the magnitude of antibacterial treatment effect based on historical studies? Did we control for the

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variability in historical data, and discount for the uncertainties? If so, in what patient population and for which endpoint?

Did we preserve some fraction of the control effect?

So we have to answer all these questions before we move into a noninferiority discussion.

How about the patient population? Identify patient populations that are comparable to those in historical studies to precisely estimate the treatment benefit.

Now the question is, who should be enrolled? Should it be based on PORT scores or some other clinical criteria?

Dr. Alexander has gone through the details this morning, discussing about the PORT scores and the mortality rates.

Now the second question is, should we enroll only patients with a confirmed bacteriological etiology? Again these issues are going to be discussed today and tomorrow.

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So with that I'd like to conclude the talk.

ACTING CHAIR TOWNSEND: Thank you, Dr. Valappil. Time for a couple of questions? Dr. Dowell?

DR. DOWELL: I want to follow up on that last point you raised, which has been alluded to a number of times, and that's enrollment criteria.

The presentation before he went through nicely the enrollment criteria for the modern studies, including a new chest X-ray infiltrate I think, and two or more of a list of six or so other features.

What we haven't heard about is the enrollment criteria for the historical trials that we're comparing all these to. I imagine for the bacteremic patients that's relatively straightforward because they had pneumococcal bacteremia, but the -- what about all those patients without pneumococcal bacteremia? It seems if we are going to be comparing patients

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in the modern trials to patients in the historical trials, we need to know whether the enrollment criteria were similar, and in particular, for the historical trials, what about those nonbacteremic patients? Can you or anybody else tell us some more details about the type of chest X-ray that was required? What other clinical features were they, like the modern trials that we just heard about?

Mostly it sounded like, they didn't have fevers, they mostly had cough, sputum production, not much else.

DR. VALAPPIL: You are absolutely right. I wish I could shed some light on that, but historical studies, other than the bacteremic patients, you really couldn't ascertain any clear direction as to what the signs and symptoms or inclusion criteria.

ACTING CHAIR TOWNSEND: Dr. Musher.

DR. MUSHER: Interestingly I was going to comment on the same point, sir. You

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mentioned in your talk that those earlier studies were, I think you used the phrase, limited to patients who had moderate to severe pneumonia. So I'd like to comment that I was an intern at Bellevue already 20 years into the antibiotic era. You met so many of you -- just about everybody in this room is younger than I am -- if you had an infiltrate and a fever and you came to the ER at Bellevue, even if you were otherwise perfectly stable and perfectly fine, you got hospitalized.

In the pre-antibiotic era, I assure you that if you came to a hospital or to a physician and you had a pneumonia, you were put in the hospital.

So they put in everybody. Now that has two implications. They didn't start out with moderate or severe pneumonia, so I think that should inform any discussion by anybody on the subject of placebo. They all began with some range of disease, but if you don't treat them, guys, guess what happens?

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They get more severe, and some proportion of them die. So they didn't begin with what we might call moderate to severe pneumonia. They just began with pneumococcal pneumonia.

Now with regard to getting into the studies, I think that is also terribly important. Because we do have -- we had patients then who all -- they all had pneumonia, and really the vast majority were pneumococcal, and it was because they -- look, some of them died at home. If you had a bad pneumonia, and you didn't come to the hospital, you die at home. So you can't say, well, only the severe ones came into the hospital. If they were sick enough, or they felt bad, and they were able to get to a hospital, they would come. So I do think that that is very important, and it is quite different from our scoring system.

ACTING CHAIR TOWNSEND: Thank you very much.

All right, we'll move on to the

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next discussion before the break. Dr. Tornoe exposure response analysis for community-acquired pneumonia.

EXPOSURE-RESPONSE ANALYSIS FOR CAP

DR. TORNOE: Thank you, Dr. Townsend.

So we're gathered here for this two-day meeting to discuss choices of noninferiority margins.

And the question I was tasked with was to figure out whether exposure response analysis can contribute to this discussion of our NI margin for studies of CAP.

So just to explain exactly what we mean by exposure response analysis, we tried to link the probability of clinical cure with some measure of exposure. In this case area under the concentration curve divided by the minimum inhibitory concentration for the particular pathogen identified for a subject.

So this is an example for grepafloxacin was given against AECB.

So the intercepts on the Y axis here shown at 70 percent can be used as untreated or placebo response rate.

And the difference between the upper part of the curve, where you get adequate AUC/MIC ratio, the difference between this level and the untreated placebo response rate can be used as a measure of the treatment effect.

So this will be a conservative estimate since these are not truly untreated patients; they do get some drug, but just not enough.

So before I walk you through the analysis, I want to give you my conclusions to keep you out of suspense. So what is the exposure response derived treatment effect against streptococcus pneumonia in patients with mild to moderate CAP?

We identified a treatment effect of 37 percent, but the confidence intervals are pretty wide, ranging from minus six to 80

percent.

So can exposure response analysis support the choice of NI margin for studies of CAP? It's very likely, but with the current amount of data we have, we cannot adequately or precisely quantify the treatment effect, and thus not come up with a NI margin for CAP trials unless minus six percent sounds doable.

Okay, so the background. We first looked through the database at the FDA to look for, what data do we have available. And fluoroquinolone antibiotics came up as a pretty decent attempt to try to quantify the effects, because they've been widely studied in the treatment of CAP.

They reported -- they've been reported that they exhibit concentration dependent killing of pathogens responsible for CAP, and the free AUC over MIC ratio is the PK/PD parameter that correlates with therapeutic effectiveness.

So we have vast information also

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from preclinical information. So this is not just some hypothesis exploratory. It's more of a confirmatory hypothesis.

Since studies done in mice with six different fluoroquinolones have shown that if you plot the survival against the free AUC/MIC you see that the lower left part of the free AUC/MIC range you have zero percent survival, but as soon as you hit about 30 you see a difference. You increase the survival rate, and then above a certain, 50, you get 100 percent survival rate.

And similarly for the bacterial activity, you see as you increase the free AUC/MIC ratio you kill more of the pathogens.

So the devil is in the details to drill down on how to pool data across drugs, and make sure that you got the right -- the similar patients so you can draw conclusions from pooling data across trials.

So we picked the fluoroquinolone antibiotics. The rolling criteria in the

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studies we looked at were clinical signs and symptoms of CAP, and the presence of new or progressive infiltrate on chest X-ray.

The patient population was mild to moderate, and a few severe patients were also in these studies without any specific details of classification.

There were in and out patients based on their clinical status. And most patients were between 40 and 65 years of age.

The treatment at administration was from seven to 14 days. Oral therapy was given to mild to moderate diseased patients, and IV with a switch to PO for the moderate or severe patients.

So I've listed here the three studies with four different drugs that we identified with PK information in them.

And as you can see the studies were done both in U.S. and multinational. They were all conducted around the year 2000.

The subset, unfortunately the

subset of patients with PK was not that big, ranging from 10 to 50 percent of the patients had actually PK samples drawn, and even fewer of them had the clinical outcome were associated with streptococcus pneumonia.

We have both IV and IV to oral administration, and they were given for seven to 14 days. And the test of cure visit was seven to 14, 21 days after treatment.

So in this table I've listed the top five pathogens we saw in these CAP studies where we have both PK and clinical response data.

So on the right-hand I've listed the free AUC/MICs, and I've highlighted those for streptococcus pneumonia. And that shows that only in -- with the strep pneumo that is possible to start looking for a treatment effect, since these drugs have been dosed in such amounts that very few patients show low ranges of free AUC/MIC ratios.

So you see the levofloxacin in

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treated patients, they have a mean free AUC/MIC of about 100, and the lowest observed value is 26, while if you go to some of the other pathogens it's up in the 100s, so it's going to be hard to estimate that Y intercept on the exposure response analysis.

So in order to get a measure of the drug exposure, we need three measures. First, the area under the concentration curve, we need a measure of the protein binding, and we need the MIC value associated with the pathogen for each individual, so that together we can then calculate the free AUC/MIC.

Then we also need a clinical response, which is clinical success is defined as resolution of signs and symptoms of pneumonia at the test-of-cure visit, seven to 21 days after the treatment.

When we have these two components we can then perform our exposure response analysis where we first use our CART analysis to separate these untreated or subtherapeutic

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treated patients from those were well treated, and then perform a logistic regression.

So if we start with the whole clinical database of these data pooled, they all have a dose associated with it. We can use that as a measure of drug exposure, or the dose divided by their body weight.

If you want to get a more accurate measure of their drug exposure, we could impute their PK by using a demographic covariate such as serum creatinine since most of the drugs are read-only cleared.

And then finally we can take only those subjects who have actually observed PK, and we can derive the AUC from that.

That was the approach we took for our analysis to get the most accurate estimate of drug exposure.

Second of all, we need to know the protein binding of these drugs in order to pool -- you don't need it if you just do analysis on a single drug, but in order to

pool drugs we need to know what fraction of the drug is actually free and not protein bound, and then can have its activity.

And here you see big differences for gemi and garenoxacin from the total 24-hour AUC/MIC ratio, and their free AUC/MIC ratio.

Another subset we do is, we first look at all the patients who have pathogens isolated at their screening. A subset of that is those who have pathogen with an MIC value associated.

A subset of that is for streptococcus pneumonia with an MIC, and then where the streptococcus pneumonia is the pathogen with the highest MIC, which then is most likely to be associated with the clinical response.

So again we take the tip of the iceberg of all the data available for the exposure response analysis where patients with streptococcus pneumonia identified, and being

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the most resistant pathogen was then used for the exposure response analysis.

So in the next few slides I'll try and visualize what data we're dealing with.

So on the left-hand side we have on the Y-axis the free AUC measurements from the four different drugs, and then on the X axis we have the percentiles. So we take each drug, we rank the free AUC, we sort and rank the free AUC values, and then plot them from the zeroth percentile to the 100th percentile.

The symbols show the clinical failures. So as you can see there are only four clinical failures in this database of 74 subjects.

What you also can see is the variation in free AUC is about two to threefold, except for the gemifloxacin, where it's an eightfold difference from the lowest to the highest free AUC.

But for the MIC values shown here on the right-hand side, the ranges are much

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greater, up to a 50-fold difference.

So when we combine these two measures, and we take the free AUC and divide it by the MIC, the biggest -- the thing that causes the variation or the separation is mainly the MIC values.

You can also notice with the levofloxacin treated patients the two failures occur at the lower 50 percentile, while the garenoxacin treated are at the very top of the exposure and in the middle.

And these two levofloxacin patients also had isolated pathogens at the test of cure visits, so the pathogens were persistent, while the two pathogens for the garenoxacin treated patients could not be -- no sputum could be produced, so they were perceived assisted.

So then we have now our drug exposure for the exposure response analysis, the drug exposure for a particular pathogen.

So on the X-axis again we have the

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free AUC/MIC ration on a log scale for the four treated -- for the four drugs tested. And if you look at the lower range, lowest 20th percentile for each of the drugs, it's only the levofloxacin treated patients that are actually down below 30, which is this level here.

So only levofloxacin treated patients show a very low free AUC/MIC ratio, which is you look at the preclinical information where it's related to less survival.

So now we are ready to perform our exposure response analysis. So now we link the probability of clinical response with free AUC/MIC ratio.

I've listed the clinical failures down by the zero, on the Y axis, where you have the levofloxacin treated patients down here at the very lowest end, and you have the garenoxacin failures up here.

And then you have the 70 clinical

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successes up by one.

So the CART analysis tries to use -- to select the optimal breakpoint for the predicter variable, which is the free AUC/MIC, that maximally distinguishes the response, the clinical response.

So it takes into account both the free AUC/MIC and the clinical response.

When we perform this analysis, we get a breakpoint of 37, which matches what we saw for the preclinical and other reported values in literature.

Unfortunately there are only five subjects in this subtherapeutic treated ratio. And they all treated with levofloxacin, while 69 subjects were of two -- failures are -- have free AUC/MIC values above 37.

So if you do the math for the two failures out of five, you get a 60 percent response rate for the subtherapeutic treated patients with free AUC/MICs below 37, while the patients above 37 have a treatment

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response of 97 percent.

So these are the mean values. So just focus on that. There is a 37 percent treatment difference.

When I then put on the confidence intervals, which we might say are pretty wide, we see that they overlap, and the treatment effects, confidence intervals, go from minus six to 80 percent, mainly because we only have five subjects here in the low range.

So to summarize we did establish a relationship between the free AUC/MIC and clinical response, but there are some limitations to this analysis.

There were only five subjects out of the 74 who has a subtherapeutic AUC/MIC ratio, and the reason for this is that most quinolones are dosed in a manner that result in significantly higher exposures than those associated with failure in animal infection models.

Only levofloxacin treated patients

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had subtherapeutic exposures, and we only had four out of the 74 patients with clinical failures.

So more exposure response data with low AUC/MIC ratios are needed to adequately quantify this treatment effect.

If we had PK samples strong for all subjects in all these studies we might be in another position to -- and be able to quantify the treatment effect.

So to recap to the questions, what is the exposure response derived treatment effect against strep pneumo in patients with mild to moderate CAP? We saw 37 percent treatment effect but with a wide confidence interval, and we conclude that we cannot, with the current set of data, propose a choice of a noninferiority margin for future CAP trials. But it's very likely with more data that we can come up with a treatment effect, and use data to support this choice.

Thank you.

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ACTING CHAIR TOWNSEND: Thanks very much, Dr. Tornoe.

Any questions from the panel? Dr. Venitz.

DR. VENITZ: Yes, what limits your sample size, Chris, if we had only 74 in your final analysis? Was it the lack of MIC or the lack of AUC information?

DR. TORNOE: Mostly the lack of MIC values. Sorry, of PK, of AUC values. So we had plenty more of patients with MIC.

DR. VENITZ: Did you try to use proprietary information to predict AUC?

DR. TORNOE: Well, many of these studies have various bars so some of them are predicted by pop PK. But we don't try to -- if they don't have a single sample we did not try to calculate a typical patient's AUC.

DR. VENITZ: And what covariance did you include in your various proprietary models?

DR. TORNOE: Well, serum creatinine

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was one of the covariates used. Body weight was also --

DR. VENITZ: Okay, thank you.

ACTING CHAIR TOWNSEND: Dr. Kauffman.

DR. KAUFFMAN: A single question. Is this applicable at all to non-quinolone antibiotics? It seems like I mostly see it talked about with quinolones.

DR. TORNOE: I think it would be adequate also for other treatment effects. But the breakpoints might be different.

We did try to look for other drug classes and pool it, but we saw different breakpoints, so we couldn't adequately pool and do a combined analysis.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: To follow up on Carol Kauffman's question, why is it that the numerical breakpoint for, let's say, quinolones versus some macrolide is the relevant observation? It would actually be

relatively striking, I think, to line up qualitatively similar curves that had similar Y intercepts. It's absolutely going to be a different breakpoint, a different numerical cutoff for macrolide X versus quinolone Y; no good question about it. But it's the biological plausibility that underwrites all this that makes this such a powerful observation.

As you said yourself, the clinical data here are actually not exploratory; they are confirmatory, because the prior probability of this being a true result is actually very high.

DR. TORNOE: That's true. So performing or pooling data for other drugs would be -- and showing somewhat similar treatment effects would add to the plausibility of these findings.

ACTING CHAIR TOWNSEND: Dr. Temple.

DR. TEMPLE: It sounds like this is most promising where the drug's toxicity is

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dose limiting, so you have to be a little closer to the MIC, and where you have a lot of variability for one reason or another.

So that sounds true, I guess. And that's where this is going to be most promising. I mean if you can give an infinite amount of something, you are never going to have anybody too low.

DR. TORNOE: That's exactly what we're seeing right here. We also tried to perform the analysis just using MIC as the predictor variable, and that could also separate. And we would beef up the numbers in the highest group with -- the group with the highest MICs, but still the confidence intervals are overlapping.

DR. TEMPLE: So if you used just MIC then you are saying, well, you are much more likely to be a little on the low side if it was a very high MIC no matter what. But even there it depends on the drug class problem?

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DR. TORNOE: Yes, so we only saw a two to threefold difference in the PK, which was much less than the MIC, so the MIC seems to be driving the patients to the lower end.

ACTING CHAIR TOWNSEND: Dr. Fleming.

DR. FLEMING: So when I look at your Figure 3, how do I know whether or not I'm simply putting a label on those people who were inherently more vigorous and would have had a better response? I.e. it's not randomizing to one strategy that yields a low AUC/MIC to another that yields a high AUC/MIC and then seeing the later as a high response rate that also had a high AUC/MIC. How do I know that causality is not in the other direction, and essentially what I've done is, I've put a label on the vigorous people who would have inherently done better?

DR. TORNOE: Well, we did explore confounding, whether it was the obese patients who would get the lowest AUCs, but we did not

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find these. These things have already been taken care of in the dose finding, in the previous phases of the drug development, where they give the dose in a manner so all get adequate treatment.

But we did not identify age or weight or any of these confounding variables to be those who then had the lowest AUCs.

DR. FLEMING: So you looked at some of the factors that could explain that confounding, but I would say what makes you different from me, that's based on known or recorded covariates, is the tip of the iceberg. So there is a whole lot that we couldn't adjust for.

DR. TORNOE: True. And if we had more subjects that five in the subtherapeutic treated regimen, we would look for covariates that could explain differences. But we didn't have the numbers to investigate these relationships.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: Dr. Fleming raises a really good point. How do we know that you got a different AUC, that there is not some link between the AUC that you got when you took 500 milligrams of drug X, and the likelihood that you are going to respond. So a very good question.

And were this the only piece of data we had, then that question would take on a great deal of force. But it's actually not. I mean I don't want to be overly repetitious, but the fundamental underpinning of this is that in a laboratory setting, where we can take genetically homogeneous animal species, a constant organism, and where we can control the exposure very precisely, deliberately, experimentally, we find that the same thing is true.

So if it weren't a single observation, if it stood alone, and I guess I'd argue for any one of the patients in the data that we look at you don't know for sure.

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It's not about an individual observation; it's about a grand aggregate.

And there are other data. I have seen data with telythromycin that actually had a reasonably good size number of observations to the low AUC/MIC pool. And there is publicly available data.

So you can find other things and bring them together that cause the story to take on a great deal more weight than just the limited pool of macrolides.

Now your observation that if the AUCs don't vary much then you can just look at the MICs I think is an important one, and should not be -- you may want to show that analysis as well, because those MICs are -- they are telling.

DR. TORNOE: I think we have it here. So then we have a bigger end, but not substantially bigger. And then now it's not divided by MIC. This is the MIC, so the breakpoint of 0.75, then you have a 6 or 7

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percent treatment effect instead of a 98 percent -- still the confidence levels are overlapping. But it's showing the same trend, and you might be able to get larger numbers for this.

And it doesn't depend on -- these MICs are not drug dependent. Or you would just pick the -- against a particular drug, and then get the MIC for that drug, and you can get much bigger numbers.

DR. MUSHER: And this is a much simpler concept for people to deal with.

(Laughter)

DR. FOLLMANN: I hadn't seen this kind of analysis before, but it's pretty interesting. But four failures is really not enough to do anything with it.

So what are the prospects of getting more data for this. I guess that's my question. But even if you have more data, I think there are questions about the use of this method, some of which Tom raised. And

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the other is that really you are trying to estimate what is the effect at zero AUC, and you don't have anyone there, or hardly anyone there, so even if you get a lot of data you will necessarily be doing an extrapolation on what the shape of the curve looks here at 10 or five and so on, and then pushing it on to zero.

So it's intriguing, I'm skeptical, and I wonder how much data can you realistically get.

DR. TORNOE: I absolutely agree. This is going to be a conservative estimate of the treatment effect, because there are no untreated. They do have substantial amounts above the MIC values.

The possibility of getting more data, we looked at our database, but most of it was only around -- and back to the year 2000, where we had electronic versions of the databases.

So there might be plenty of

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studies we haven't seen, or phase II dose-ranging studies, which would be also very helpful and you might have more subjects with PK information.

So if one could pool all that information, that would greatly beef up the numbers, I would suspect.

DR. TEMPLE: These problems arise all the time whenever you try to do modeling on concentration response, and we always have these discussions with our modelers.

Another factor is that you have usually very little data at the part that is most interesting. So almost all the concentrations are nice and high, and this curve that looks sort of nice is driven by one or two people who are down low, and we have that all the time.

But there is really little impediment to, in all the trials, all the active control trials in review, there is very little impediment to getting some blood

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levels, and getting more data to look at.

And maybe it just sort of adds to the idea that the active control trial is plausible if you start to see these relationships.

There is an ICH guidance on this that raises all those various issues. What it likes is to randomize to a concentration; ha ha, we don't see that very often. But in the absence of that, you always, as Tom says, you have to wonder whether there is some factor that both makes you fail and gives you a low concentration. That's just inherent in it.

I have to say on this one, that doesn't seem totally plausible, unless they are so sick they are not absorbing anything because their gut is falling out or something. It's got more plausibility than most things do, it seems to me.

ACTING CHAIR TOWNSEND: Thanks very much.

I think we'll take a break. We

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are running a little bit late, though, so if we can come back here at 10 minutes to 4:00 we'll make up a little bit of time. See you then.

(Whereupon at 3:38 p.m. the proceeding in the above-entitled matter went off the record to return on the record at 3:54 p.m.)

ACTING CHAIR TOWNSEND: I think we'll go ahead and get started. Welcome back, everybody.

So we're in the end run here on today's session. Just a brief housekeeping thing, for those of you who are staying here tonight, tomorrow morning you are checking out, you can bring your bags down here and we will store them somewhere or other.

So the final presentation this afternoon will be Dr. George Talbot, critical considerations in CAP trial design from a consultant's perspective.

CRITICAL CONSIDERATIONS IN CAP TRIAL DESIGN:

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A CONSULTANT'S PERSPECTIVE

DR. TALBOT: It looks like a lethal weapon I was just given.

Dr. Townsend, ladies and gentlemen of the committee, thank you for coming back from the break at the end of a long day.

Dr. Cox, members of the FDA, thank you for asking me to present. It's an honor and a privilege to do so.

Now you see on this first slide actually my title: critical considerations in CAP trial design, a consultant's perspective, which begs the question of, well, what kind of perspective is that?

You've heard from a number of academics from various societies. You've heard from the agency itself. Tomorrow I think during the public session you'll hear from industry, so that sort of leaves me.

So I'm calling this, instead of the consultant's perspective, sort of neither fish nor fowl, and hopefully what that means

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is, a blend of some of the perspectives that you will hear from other people.

Now this actually is my first slide. And the reason I put this in here is to remind myself to tell you a little bit about my process for beginning to construct this presentation.

I've been working in this area for quite a few years, and because of that I have quite a few preconceptions, maybe I should call them learnings, about the approach to some of these issues.

But in preparing for this talk, I did try to set aside some of those preconceptions and look at the data as objectively as I could; and I also tried to think about what would be useful to the committee in terms of understanding or appreciating some of the issues not only in trial design but issues that companies have to deal with as they think about undertaking a CAP clinical trial.

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I should say the previous slide also was my first thought when asked to give this thought, which was, whoa. But fortunately the FDA did give me some guidance, which I appreciate. And I was asked to provide a reality check concerning what is feasible vis-a-vis trials conducted by industry, based on my experience, and thank you for acknowledging that I might actually have some connection with reality; and also my vision of what might be a reasonable path forward for future trials for CAP products.

Now being at the end of the day is usually a disadvantage, especially since you have to put your slides together a couple of weeks before, or maybe not quite that long ahead. But I've also had the opportunity to hear all the observations presented today, and I'd like to perhaps highlight some of those as I go through my talk.

So the discussion points today will be why do we need new antibiotics for

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CAP? I think we know that, but there are a couple of key points I'd like to make; the decisions that go into undertaking a CAP clinical trial program, and then some major trial design issues, and the conclusions I've drawn about them.

You've heard my disclosures. I think so far I'm the only one to put my disclosures back up, but because I am neither fish nor fowl I did want to put them up, so you could see what I've done, what my involvement is. It ranges from having been CMO, chief medical officer, of a private company, to having various consultancies.

I'd point out that for Cerexa, Cerexa has a CAP program, and I still consult to Cerexa on CAP, so that is a potential conflict of interest.

I'd also mention that I am a member of IDSA's AATF and participated in a drafting of the position paper.

So why do we need new antibiotics

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for CAP? The point about emerging resistance has been made. We've talked about strep pneumo in particular, and mentioned macrolide resistance and fluoroquinolone resistance.

I'd like to emphasize also that there are some emerging data that suggest that resistance to ceftriaxone is beginning to occur, high level resistance to ceftriaxone. Some isolates have been seen, and therefore I think we have another concern in that area.

Another example of emerging resistance in CAP could be the appearance of really new pathogens in CAP. Staph aureus has been a relatively infrequent cause of CAP, as mentioned previously, but we now know that there are still isolated reports of MRSA as a pathogen.

Hopefully that trend will not continue, but in drug development the trends have to be anticipated, and investments have to be taken based on anticipation of those epidemiologic trends, and therefore this is

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one of the things that is of concern.

I think another reason we need new antibiotics for CAP is that despite the changing landscape for sinusitis, AECB, and acute otitis media, there clearly are some patients who need therapy with antibiotics for their conditions: chronic sinusitis; sinusitis in immunocompromised hosts; recalcitrant culture positive otitis media; et cetera. And since they are the same bugs, the best place we have to understand the efficacy of new antibiotics is in CAP.

If new antibiotics can't be studied easily in CAP -- pardon me, in these indications that I've listed here, CAP becomes the last bastion for respiratory tract infection development. And that's one of the reasons why we need clear and timely direction from the advisory committee about how to move forward, because there will be patients who will need these same antibiotics.

You've heard IDSA probably ad

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nauseam mention the antibiotic pipeline being at risk. I do have some perspective on that.

The first four bullets or sub-bullets here I think you've heard. I believe them to be true. This one in particular is that companies large and small are considering that there are more predictable as well as more profitable options elsewhere.

The two points I'd like to emphasize in particular is that because of some of these parameters, many of our newer molecules that you are seeing reach market are coming from Japanese innovators. One I'd mention in particular is Doripenem.

The other point is that when a compound is launched, the new descriptor can be falsely reassuring as to the -- whether the pipeline is a cornucopia of new products or not. And this is because many quote unquote new compounds have been, as I would put it, recycled from older innovators. This is not to say that these are not useful compounds.

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I mentioned daptomycin, for example. And there are others.

But they do not represent the fruits of recent research efforts.

The CAP pipeline has had problems. I should have added garenoxacin here, but I put these up here to highlight compounds that have had difficulties, and in some cases have been withdrawn or not filed.

I emphasize the fact that many of these are oral, and we need options for oral therapy, not just IV products but oral products, partly for the reason I mentioned about other RTIs, but also because of the hostile admission and discharge pressures that you're all familiar with; the fact that there is quite a bit of outpatient CAP as mentioned; and also because there are many hurdles for oral compounds in terms of the safety profile that must be demonstrated for them to be approved for marketing.

And certainly as noted earlier,

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new classes and mechanisms of action are highly desirable.

Personally speaking, another reason is that one day some of us, or one of our family members, may need an antibiotic for CAP.

So I'd leave you in this section with a couple of thoughts. The decisions made in 2008 about moving forward with CAP programs are going to affect what antibiotics are available or not available in 2010, 2012, 2015, and as John Bartlett, the chair of the AATF has said, the lesson of history is that we need a pipeline.

We went back to Dr. Cox's first slides, he had a list of -- I think it was your slides, Ed, excuse me, it's been a long day -- showing how the drugs evolved from pathogen-directed to different steps.

What's interesting about that slide is that you can't use for treatment most of the compounds in those first few categories

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