

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
  
ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Thursday, July 11, 2002

8:30 a.m.

Marriott Washingtonian Center  
9751 Washingtonian Boulevard  
Gaithersburg, Maryland

## PARTICIPANTS

L. Barth Reller, M.D., Chair  
Tara P. Turner, Pharm. D., Executive Secretary

## MEMBERS

David M. Bell, M.D.  
Alan S. Cross, M.D.  
Steven Ebert, Pharm.D. (Consumer  
Representative)  
Mary P. Glode, M.D.  
James E. Leggett, Jr., M.D.  
Judith R. O'Fallon, Ph.D.  
Jan E. Patterson, M.D.  
Julio A. Ramirez, M.D.  
Ciro V. Sumaya, M.D.  
Ellen R. Wald, M.D.

## CONSULTANTS (VOTING)

P. Joan Chesney, M.D.  
G. Scott Giebink, M.D.  
Robert M. Nelson, M.D., Ph.D.

## CONSULTANT (NON-VOTING)

Vernon M. Chinchilli, Ph.D.

## GUESTS (NON-VOTING)

Ron Dagan, M.D.  
Alejandro Hoberman, M.D.  
Colin D. Marchant, M.D.  
George H. McCracken, Jr., M.D.  
Jack L. Paradise, M.D.  
Michael E. Pichichero, M.D.  
Coleman Rotstein, M.D.

## FDA

Renata Albrecht, M.D.  
Rosemary Johann-Liang, M.D.  
Mark Goldberger, M.D. M.P.H.  
John Powers, M.D.  
George Rochester, Ph.D.  
Thomas Smith, M.D.  
Janice Soreth, M.D.

## C O N T E N T S

Call to Order: L. Barth Reller, M.D.	4
Introduction of Committee	5
Conflict of Interest Statement: Tara P. Turner, Pharm.D.	8
Guidance Development: John H. Powers, M.D.	11
Development of Antibiotics for Otitis Media: Past, Present and Future: Janice M. Soreth, M.D.	22
Design Issues in Antimicrobial Treatment Trials of AOM: G. Scott Giebink, M.D.	41
Experience with Tympanocentesis: Clinical Diagnosis of AOM: Michael Pichichero, M.D.	59
Double Tympanocentesis Studies: Ron Dagan, M.D.	76
Limitations of Clinical-only Studies: Colin Marchant, M.D.	100
Study Designs for Acute Otitis Media Trials: What Can Each Design Tell Us? C. George Rochester, Ph.D.	118
Lesson Learned from Past Approvals: Thomas Smith, M.D.	134
Study Considerations: Recurrent/Treatment Failure AOM: Rosemary Johann-Liang, M.D.	148
Open Public Hearing Michael R. Jacobs, M.D., Ph.D. Jack L. Paradise, M.D.	168 187
Summary and Charge to the Committee: Renata Albrecht, M.D.	192
Committee Discussion and Vote	203

1 P R O C E E D I N G S

2 Call to Order

3 DR. RELER: Good morning. I am Barth  
4 Reller and I should like to call the Advisory  
5 Committee meeting to order.

6 We have an exciting agenda with multiple  
7 presentations, multimedia. It is very important  
8 that we adhere strictly to the schedule to enable  
9 full discussion of this important topic - Clinical  
10 Trial Design for Studies of Otitis Media.

11 This is coming to fruition of a great deal  
12 of work that has been done by many individuals over  
13 the years. To help us adhere to the schedule, Dr.  
14 Tara Turner, our executive secretary, will be  
15 having a light system that will quietly but firmly  
16 give the speakers notice when there are two to  
17 three minutes left depending on the length of the  
18 talk, two minutes for the short talks and three  
19 minutes for the 15- to 20-minute talks.

20 We will see the light, you will see the  
21 light that will go yellow, when it is time to send  
22 up red when your time is up, and a short period  
23 thereafter, the floor will open, and like the  
24 Mozart opera, there will be a display and  
25 disappearance.

1           We will begin with an introduction of the  
2 committee members and starting on my far, far  
3 right, actually, the consultants and the committee  
4 members, and to the far right, Dr. Pichichero, the  
5 name and affiliation.

6                           **Introduction of Committee**

7           DR. PICHICHERO: Michael Pichichero,  
8 professor at the University of Rochester Medical  
9 Center and practicing pediatrician, Elmwood  
10 Pediatric Group, Rochester, New York.

11           DR. MARCHANT: Colin Marchant, Pediatric  
12 Infectious Disease at Boston University and Tufts  
13 University.

14           DR. HOBERMAN: Alejandro Hoberman,  
15 Department of Pediatrics, University of Pittsburgh  
16 School of Medicine, Children's Hospital.

17           DR. DAGAN: Ron Dagan, Professor of  
18 Pediatrics and Infectious Diseases, Ben-Gurion  
19 University, head of the Pediatric Infectious  
20 Disease at Soroka Medical Center in Beer Sheva,  
21 Israel.

22           DR. GOLDBERGER: I am Mark Goldberger from  
23 the Office of Drug Evaluation IV, FDA.

24           DR. POWERS: John Powers, Office of Drug  
25 Evaluation IV, FDA.

1 DR. ALBRECHT: Renata Albrecht, Division  
2 of Special Pathogens and Immunologic Drugs, FDA.

3 DR. SORETH: Good morning. I am Janice  
4 Soreth. I am the Division Director for  
5 Anti-Infectives at FDA.

6 DR. SMITH: Tom Smith, medical officer in  
7 the Division of Anti-Infectives at the FDA.

8 DR. JOHANN-LIANG: I am Rosemary  
9 Johann-Liang. I am the medical officer at the  
10 Division of Special Passages.

11 DR. NELSON: Robert Nelson, Children's  
12 Hospital, Philadelphia.

13 DR. GLODE: Mimi Glode, Pediatric  
14 Infectious Disease, University of Colorado, Denver.

15 DR. BELL: David Bell. I am Assistant to  
16 the Director for Antimicrobial Resistance in the  
17 National Center for Infectious Diseases, Centers  
18 for Disease Control and Prevention in Atlanta.

19 DR. TURNER: Tara Turner, Executive  
20 Secretary for the committee.

21 DR. RELLER: Barth Reller, Division of  
22 Infectious Disease at Duke University Medical  
23 Center and Director of Clinical Microbiology there.

24 DR. PATTERSON: Jan Patterson, Medicine  
25 Infectious Diseases, University of Texas Health

1 Science Center, San Antonio.

2 DR. WALD: Ellen Wald, Division of  
3 Pediatric Infectious Diseases, University of  
4 Pittsburgh School of Medicine.

5 DR. SUMAYA: Ciro Sumaya, School of Rural  
6 Public Health, Texas A&M University System Health  
7 Science Center.

8 DR. GIEBINK: Scott Giebink, Professor of  
9 Pediatrics and Director of Infectious Diseases,  
10 Director of the Otitis Media Research Center,  
11 University of Minnesota Medical School.

12 DR. O'FALLON: Judith O'Fallon,  
13 statistician at the Mayo Clinic Cancer Center,  
14 Rochester, Minnesota.

15 DR. CHINCHILLI: Vern Chinchilli,  
16 biostatistician, Penn State Hershey Medical Center.

17 DR. CHESNEY: Joan Chesney, Pediatric  
18 Infectious Disease, University of Tennessee,  
19 Memphis, College of Medicine.

20 DR. RAMIREZ: Julio Ramirez, Chief,  
21 Infectious Diseases, University of Louisville,  
22 Kentucky.

23 DR. EBERT: Steve Ebert, Pharmacy and  
24 Infectious Diseases, University of Wisconsin,  
25 Madison.

1 DR. LEGGETT: Jim Leggett, Infectious  
2 Diseases, Oregon Health Sciences University.

3 DR. CROSS: Alan Cross, Infectious  
4 Diseases, University of Maryland, Baltimore.

5 DR. ROTSTEIN: Coleman Rotstein,  
6 Infectious Diseases, McMaster University, Hamilton,  
7 Ontario.

8 DR. McCracken: George McCracken,  
9 Infectious Disease, University of Texas  
10 Southwestern Medical School.

11 DR. PARADISE: Jack Paradise, Department  
12 of Pediatrics, University of Pittsburgh School of  
13 Medicine and Children's Hospital in Pittsburgh.

14 DR. RELLER: Thank you. It's an exciting  
15 day. Dr. Soreth and colleagues have assembled what  
16 is recognized, it's like a Who's Who in Otitis  
17 Media in the world, if not the universe.

18 Dr. Turner will read our Conflict of  
19 Interest statement.

20 Conflict of Interest Statement

21 DR. TURNER: The following announcement  
22 addresses the issue of conflict of interest with  
23 respect to this meeting and is made a part of the  
24 record to preclude even the appearance of such at  
25 this meeting.

1           The Food and Drug Administration has  
2 prepared general matters waivers for Drs. Joan  
3 Chesney, Jan Patterson, Julio Ramirez, James  
4 Leggett, Steven Ebert, Ciro Sumaya, and Vernon  
5 Chinchilli.

6           A copy of the waiver statements may be  
7 obtained by submitting a written request to the  
8 Agency's Freedom of Information Office, Room  
9 12A-30, of the Parklawn Building.

10           All other participants did not report any  
11 financial interests relevant to today's meeting;  
12 therefore, waivers were not necessary to permit  
13 their participation.

14           The topic of today's meeting is an issue  
15 of broad applicability. Unlike issues before a  
16 committee in which a particular product is  
17 discussed, issues of broader applicability involve  
18 many industrial sponsors and academic institutions.

19           The committee members and invited guests  
20 have been screened for their financial interests as  
21 they may apply to the general topic at hand.  
22 Because general topics impact so many institutions,  
23 it is not prudent to recite all potential conflicts  
24 of interest as they apply to each participant.

25           FDA acknowledges that there may be

1 potential conflicts of interest, but because of the  
2 general nature of the discussion before the  
3 committee, these potential conflicts are mitigated.

4 We would like to note for the record that  
5 Kenneth Brown, M.D., is participating in this  
6 meeting as an industry representative, acting on  
7 behalf of regulated industry. As such, he has not  
8 been screened for any conflicts of interest.

9 In the event that the discussions involve  
10 any other products or firms not already on the  
11 agenda for which FDA participants have a financial  
12 interest, the participants' involvement and their  
13 exclusion will be noted for the record.

14 With respect to all other participants, we  
15 ask, in the interest of fairness, that they address  
16 any current or previous financial involvement with  
17 any firm whose products they may wish to comment  
18 upon.

19 I have a brief announcement. Dr. Kenneth  
20 Brown will not be able to join us today. He is  
21 ill.

22 Thank you.

23 DR. RELER: Thank you, Tara.

24 We will begin the presentations with Dr.  
25 John Powers speaking about guidance development.

1                   Guidance Development

2                   John H. Powers, M.D.

3           DR. POWERS: Thanks, Dr. Reller. I am  
4 really privileged to be the first one to get to  
5 test drive this trap door that is underneath my  
6 feet, so in case I fall through the floor, you will  
7 know why.

8           Today, I would like to welcome the members  
9 of the committee, our guests and consultants, the  
10 members of the audience, and our colleagues at the  
11 FDA.

12           [Slide.]

13           Most of you were here for the advisory  
14 committee meeting that we held for two days back in  
15 February of this year, in which we dealt with some  
16 issues related to non-inferiority trials or deltas  
17 in antimicrobial drug development, and on the  
18 second day we talked about development of  
19 antimicrobial drugs for resistant organisms.

20           At that time, we stated that that meeting  
21 was the first in a series of meetings that we were  
22 going to talk about related to antimicrobial drug  
23 development. So, here we are today fulfilling that  
24 promise, talking about acute otitis media.

25           We really see this again as part of a

1 continuing discussion and we plan future advisory  
2 committees to talk about other guidances, as well,  
3 as well as to continue the discussion about otitis  
4 media.

5 We are also planning a workshop,  
6 cosponsoring that with the Infectious Disease  
7 Society of America and the Pharmaceutical Research  
8 and Manufacturers Association in the fall of this  
9 year.

10 [Slide.]

11 The divisions that deal with antimicrobial  
12 drug products in the FDA are the Division of  
13 Antiviral Drug Products, Anti-Infective Drug  
14 Products, and the Division of Special Pathogen and  
15 Immunological Drug Products.

16 All three of these are subsumed under the  
17 Office of Drug Evaluation IV and as part of the  
18 Public Health Action Plan dealing with  
19 antimicrobial resistance, the office has been given  
20 additional resources to deal with antimicrobial  
21 drug development and resistance issues. I am  
22 honored to be the lead medical officer to move  
23 those initiatives forward.

24 In an attempt to move this process of  
25 guidance development forward, which was started by

1 Dr. Lillian Gavrilovich [ph] when she was the  
2 acting head of Anti-Infectives, and then since  
3 moved forward by Dr. Renata Albrecht, and also in  
4 order to provide some internal consistency with the  
5 kind of guidance that we offer to drug sponsors,  
6 and also we like to promote some interactions both  
7 within and outside the FDA.

8 [Slide.]

9 Why do we have these guidances in the  
10 first place? Well, these guidances are really not  
11 regulations, they are not absolute requirements,  
12 but actually they are very helpful both for us  
13 within the FDA and also for drug sponsors.

14 In terms of the drug sponsors, they  
15 provide an outline for the scope of data that they  
16 need to show the efficacy and safety of their drug  
17 products, and we often heard from industry that  
18 they want to know the kinds of things that we are  
19 looking for.

20 These guidances are also helpful within  
21 the FDA to provide some internal consistency in the  
22 kinds of guidance that we offer to drug sponsors.  
23 Over the years, there have ben several iterations  
24 of these guidances, and Dr. Janice Soreth will talk  
25 to you this morning about how each of these

1 guidances has impacted on the development of trial  
2 design in acute otitis media.

3 All of these guidances are based on the  
4 best available science and regulatory knowledge at  
5 the time they were written, but one of the things  
6 that makes medicine both fun and challenging is  
7 that the state of our knowledge is constantly  
8 changing.

9 [Slide.]

10 So, why revise these guidances and why  
11 talk about them now at this point in time? Well,  
12 obviously, there are those changes in the knowledge  
13 of infectious diseases, and since the 1992  
14 guidance, there have been several meta-analyses  
15 published on the effect of antimicrobial therapy  
16 and the natural history of acute otitis media.

17 Also, even since the 1998 guidance, the  
18 Agency for Healthcare, Research, and Quality has  
19 published an evidence report again relating to the  
20 natural history and the impact of antimicrobial  
21 therapy on acute otitis media.

22 Also, over the years we have seen a change  
23 in the resistance patterns of the common organisms  
24 associated, not only with acute otitis media, but  
25 also with many other infectious diseases.

1           Finally, there have been advances in the  
2 science of clinical trials. Both the FDA, PhRMA,  
3 and European and Japanese regulatory agencies have  
4 participated in the International Conference on  
5 Harmonisation in an attempt to bring some global  
6 consistency to how we develop antimicrobial drugs.

7           Also, over the years, this committee has  
8 discussed several of the clinical trials related to  
9 acute otitis media, and we have learned some  
10 lessons from those which we now need to incorporate  
11 into our future guidances.

12           [Slide.]

13           Each of the guidances is arranged in a  
14 similar way and covers these important points in  
15 design, conduct, and analysis of trials. They talk  
16 about the definition of the disease and how to  
17 actually diagnose it, the study characteristics,  
18 the inclusion and exclusion criteria for that  
19 particular disease which again includes diagnostic  
20 criteria, but also defines the populations of  
21 interest for that particular disease, the drug and  
22 dosing regimens used in that particular infection,  
23 the evaluation of patients, and the timing and  
24 definitions of the outcomes, and finally,  
25 statistical considerations.

1           That is an awful lot to talk about in one  
2 single advisory committee, so what we are going to  
3 try to cover today, related to acute otitis media,  
4 is not all of these points, not to say that the  
5 ones we won't cover aren't important, but just  
6 given the time constraints that we have today, we  
7 are not really going to touch on specific drugs and  
8 dosing regimens, and although the statistical  
9 considerations are very important, we hope to touch  
10 on those at a future meeting, and not specifically  
11 to discuss statistics per se today.

12           [Slide.]

13           The first thing we are going to talk about  
14 is definitions of disease. Obviously, it is  
15 important that the terms that we use are specified,  
16 so that the results that we look at are comparable  
17 across trials.

18           In the AHRQ evidence report, they examined  
19 almost 3,500 clinical trials in acute otitis media,  
20 and their conclusion was that the basic definition  
21 of acute otitis media used in many of those trials  
22 varied considerably.

23           Also, the definition of disease is  
24 important when we talk about particular subsets of  
25 patients, for instance, children with recurrent

1 disease and treatment failure versus children who  
2 are experiencing their first episode of acute  
3 otitis media.

4           It would be appropriate to analyze these  
5 populations separately if the cure rates were  
6 radically different in children across those  
7 groups, or, as we have heard from this committee  
8 before related to the development of  
9 fluoroquinolone drugs for pediatrics, if it would  
10 be appropriate to limit the use of those drugs to  
11 appropriate patient populations.

12           [Slide.]

13           The second thing we would like to talk  
14 about are study characteristics, what do we learn  
15 from different types of trials, and Drs. Dagan,  
16 Giebink, and Marchant are going to talk about this  
17 today, as well as George Rochester from the FDA.

18           When we talk about superiority versus  
19 non-inferiority trials, one of the main things we  
20 deal with again is that issue of the  
21 non-inferiority margin. In the non-inferiority  
22 trial, we need to know the benefit of antimicrobial  
23 therapy over placebo in order to be able to set  
24 that margin.

25           That actually brings up the issue of the

1 role of placebo-controlled trials in allowing us to  
2 determine that given that there is still a  
3 significant controversy about the actual magnitude  
4 of the benefit of antimicrobial therapy in acute  
5 otitis media.

6           Placebo-controlled trials have been done  
7 in Europe, and I put this trial up here by  
8 Damosieaux in the British Medical Journal that was  
9 published in the year 2000. This trial enrolled  
10 children with a clinical diagnosis of acute otitis  
11 media and also looked at clinical outcomes, and it  
12 did enroll children who were between the ages of 3  
13 and 24 months of age. So, these have been done in  
14 places other than the United States.

15           [Slide.]

16           When we look at inclusion and exclusion  
17 criteria, again, we are defining patients who  
18 actually have the disease, and one of the issues  
19 that we will talk about today--again, some of our  
20 consultants will bring this up--is the issue of  
21 clinical trials which use only clinical diagnostic  
22 criteria versus the value of baseline  
23 tympanocentesis in defining children who actually  
24 have bacterial otitis media.

25           Also, we can use the inclusion and

1 exclusion criteria to define specific populations  
2 of children. The population of children most  
3 likely to have acute otitis media is those kids  
4 between the ages of 6 and 18 months, therefore,  
5 what is the role of data in children who are over 2  
6 years of age and how can we use that in applying it  
7 to all children with acute otitis media.

8           Also, Dr. Rosemary Johann-Liang will talk  
9 today about evaluating patients who failed prior  
10 antimicrobial therapy or prophylaxis, and mostly  
11 those kids have been excluded from prior trials,  
12 and should we be looking at them today as a  
13 separate indication.

14           [Slide.]

15           Here is the big issue when we talk about  
16 enrolling children who may not have a disease which  
17 is amenable to antimicrobial therapy. If we look  
18 at the top bar and the bottom bar, let's just say  
19 that is Drug A versus Drug B.

20           If we just say for the sake of argument  
21 that 80 percent of kids in a particular trial get  
22 better either because they have viral disease or  
23 self-resolving disease, we then look at only the  
24 population of interest only comprises about 20  
25 percent of the trial.

1           There is a difference between the two  
2 drugs, and say in the 20 percent of interest, 15  
3 percent of kids get better in one arm of the trial,  
4 but 10 percent get better in the other.

5           If we then look at the overall cure rates  
6 in that trial, for the top drug, the overall cure  
7 rate would be 95 percent. For the bottom drug, the  
8 overall cure rate would be 90 percent. Therefore,  
9 the difference between the two drugs that we would  
10 examine in this particular trial would only be 5  
11 percent, driven primarily by the large number of  
12 children with viral or self-resolving disease.

13           On the other hand, if we just do the  
14 percentages in the population of interest, the cure  
15 rate in the children for Drug A would be 75  
16 percent, and the cure rate in the children for Drug  
17 B would be 50 percent. So, the first point would  
18 be the cure rate would be much lower, but the other  
19 point is that the difference between the two drugs  
20 would be orders of magnitude larger, namely, 25  
21 percent in this particular example.

22           So, enrolling children in the trial who  
23 may get better spontaneously or who do not have  
24 bacterial disease has a huge impact on the outcome  
25 of the trial.

1 [Slide.]

2 Lastly, we look at microbiologic and  
3 clinical outcomes, how good is the correlation  
4 between bacteriologic and microbiologic outcomes,  
5 and some of our consultants will talk about that  
6 today, as well as the role of the second  
7 tympanocentesis in determining differences in  
8 microbiologic outcomes and evaluating efficacy for  
9 resistant pathogens.

10 One of the other things we would like to  
11 talk about today is the timing of assessments,  
12 should we still be looking at some fixed endpoint  
13 or should we look at something like time to  
14 resolution of symptoms.

15 The last thing is what actually defines a  
16 clinical cure and how do we measure it.

17 [Slide.]

18 Finally, even if we wanted to do the  
19 perfect trial, the issues are: What are the  
20 barriers to doing that, that are practical issues,  
21 what are the barriers to performing  
22 tympanocentesis, are placebo-controlled trials  
23 practical in the United States, how acceptable are  
24 these procedures to patients and parents, and can  
25 we perform trials more efficiently while still

1 getting useful data from those.

2 [Slide.]

3 This has been a multi-person effort from  
4 folks at the FDA. I would like to thank all the  
5 people that have contributed to this, some of whom  
6 you will see speaking today, as well as our support  
7 staff without whom this would not be possible at  
8 all.

9 Thanks very much.

10 DR. RELLER: Dr. Soreth will now talk  
11 about development antibiotics for otitis media,  
12 past, present and future.

13 Development of Antibiotics for Otitis Media:

14 Past, Present and Future

15 Janice M. Soreth, M.D.

16 DR. SORETH: Good morning. I would like  
17 to add my thanks and my welcome to committee  
18 members, invited guests who are experts in the  
19 field, members of academia and industry, and  
20 consumers who may possibly be in the audience, as  
21 well, and to my FDA colleagues.

22 Let me state at the outset that although  
23 we probably could have done a better job in having  
24 a multinational group here representing the mavens  
25 in otitis, I think we have done a fairly decent job

1 in inviting the mavens in the field.

2           There are a few others who I wish, on  
3 retrospect, I had been able to invite, but I guess  
4 at the end of the day, there is only so much time  
5 and so much money.

6           As Dr. Powers said, this won't be the last  
7 meeting we have on guidance development in general  
8 or in the furthering of the guidance document for  
9 developing an antimicrobial for otitis media as we  
10 fully expect that we will get additional written  
11 comments to a docket, whose number I will give you  
12 later, so that if your thoughts at this point are  
13 not at a point where you wish to speak them at a  
14 microphone, you still will have ample opportunity  
15 to make written comments to us here at FDA and  
16 submit them, so that we can review them and, as is  
17 fitting, incorporate them into whatever the next  
18 iteration of the guidance is.

19           I feel especially privileged to come  
20 before you today because I was an otitis-prone  
21 child, and I think it had a tremendous effect on my  
22 development as a child and as an adult, because for  
23 much of my childhood, I don't think I could hear  
24 very well, so muffled is my perception, my memory  
25 of what it was like to learn language in between

1 many, many bouts of otitis media.

2 I am convinced that at some point I had  
3 that bioactive membrane that Dr. Giebink spoke of  
4 some years ago where the middle ear cavity is not  
5 just filled with pus, but probably has a  
6 pseudocolumnar epithelium that is secreting gunk  
7 all the time, which intermittently gets infected.  
8 That is quite a challenge for any anti-infective to  
9 go after and probably different from the garden  
10 variety not often happening acute otitis media.

11 I have also given birth over a decade ago  
12 to an otitis-prone child, so I have a special  
13 vested personal interest in this field, as well as  
14 professional interest, despite the fact that I  
15 turned out to be an internist, and many of the  
16 pediatricians in this from Pitt were my mentors,  
17 for I am also a Pitt alumna.

18 With that as background, then, let me go  
19 to the next slide.

20 [Slide.]

21 We had, starting in 1977, written  
22 guidance, which I will briefly go through, followed  
23 by a period of formal silence, that is, nothing  
24 written between '77 and '92, although there was not  
25 silence in the office, there was not silence in

1 speaking with academicians in the field or with  
2 industry. A lot went on, and I will try again  
3 briefly to summarize what is now oral history,  
4 anecdote, et cetera, and I will count on my other  
5 senior colleagues in both special pathogens and  
6 anti-infectives to keep me on track and speak up if  
7 I misspeak and misremember.

8           In '92, the Anti-Infectives Division came  
9 out with a Points-to-Consider document, talking  
10 about many different indications and infections,  
11 and how to go about trying to get a claim for them  
12 in one's antimicrobial product development, and  
13 that dovetailed in '92 with a contract that we had  
14 with probably some of the folks in this room and  
15 others, with IDSA, in writing, and what you call  
16 this depends on where you are. If you are in the  
17 FDA, you call these the IDSA guidelines, and if you  
18 are in the IDSA, you call them the FDA guidelines.

19           Finally, in 1997 and '98, we took another  
20 hit at coming up with an iteration of a draft  
21 guidance on many different infections including  
22 acute otitis media, and in '97 and '98, brought the  
23 guidance document formally then before this  
24 committee, whose composition in '97 and '98 was  
25 different because members do rotate off and go back

1 to doing what they always do, or doing it in  
2 addition to this, I should say, because we  
3 appreciate that you have very, very full schedules  
4 and full professional lives, so again our thank you  
5 for your full participation in today's proceedings.

6 [Slide.]

7 I say "back to the future" because I  
8 think, as you will hear today, we started in the  
9 seventies with a paradigm under which all children  
10 underwent tympanocentesis if they entered a trial  
11 with the clinical diagnosis of acute otitis media.  
12 We are going to read this at that. Some may think  
13 that is overkill, others may think it is the only  
14 way to go if you want to understand the  
15 microbiologic etiology of this infection.

16 So, questions that will come up throughout  
17 talks and certainly in the discussion this  
18 afternoon will focus on whether or not we need to  
19 return to a paradigm in which we have  
20 tympanocentesis for all, and then if we develop  
21 that further, should it be tympanocentesis at  
22 baseline only or tympanocentesis at baseline  
23 combined with a look, a further tympanocentesis, a  
24 repeat tympanocentesis on therapy, does that make  
25 scientific sense, is it ethical, and so forth. I

1 am sure these will come up in our discussion, I  
2 hope they will, should all failures be tapped, is  
3 that practical, can you often do it, what do you do  
4 with a child at 3:00 a.m. on the eve of Christmas,  
5 Hanuka, New Year's, whatever, and it's virtually  
6 impossible to get it done.

7           One of the pivotal trials that we have  
8 held or recommended to companies to do is something  
9 we refer to as a "clinical-only" trial, a trial in  
10 which you make a clinical diagnosis of acute otitis  
11 media, and we will argue about whether or not that  
12 is an easy call, a difficult call, or something in  
13 between, are those studies serving us at this  
14 point.

15           I fully believe that any guidance document  
16 written, is written with the best of intentions in  
17 mind, and while some issues that we discuss today  
18 may appear to be Monday morning quarterbacking, I  
19 think that it is true that guidance documents and  
20 such provisions are written with, at that time, the  
21 best thinking in mind, the best of intentions, the  
22 most efficient way to get at testing a hypothesis  
23 and coming up with answers that are good for the  
24 public health, but as Dr. Powers said, our  
25 knowledge changes over time, at least we hope that

1 it does, and we hope that it improves over time and  
2 maybe that is why we call it the practice of  
3 medicine, hoping that at some point, we really will  
4 get it completely straight and right and perfect.

5           Is there a role for placebo-controlled  
6 trials? I was happy to hear a report on NPR,  
7 because that is where I get a lot of my  
8 information, that when put to scrutiny,  
9 arthroscopic surgery in adults compared to placebo  
10 is no better, at least if you believe the data that  
11 have just come to light, and may be deleterious.

12           Is it time, is it neat and right at this  
13 point to consider the "P" word, placebo-controlled  
14 trials, in the context of studying patients,  
15 primarily children, many of them under 2, who have  
16 acute otitis media or who have an otitis media even  
17 if it's somewhere between acute and chronic

18           Regardless of the paradigms that we talk  
19 about in a given clinical trial development  
20 program, are we talking one trial, multiple trials?  
21 I don't expect that all of these ideas will be  
22 developed in today's proceedings. We do have a  
23 full agenda, many, many speakers with many things  
24 to say, and just note parenthetically that this  
25 will be one of a number of discussions in a public

1 forum that we will have on this document, on  
2 guidance development for acute otitis media and  
3 going forward.

4 So, what is the bottom line, what do we  
5 know, what do we need to know to conclude that a  
6 drug works and it is safe for children with otitis  
7 media?

8 [Slide.]

9 What are some of the stats? Well, over 25  
10 million visits for otitis media yearly, and that is  
11 just in the United States, and we know that we are  
12 part of a global community, so there are millions  
13 more out there in other countries, accounts for 1  
14 out of 3 pediatric visits, and I have done my share  
15 to contribute to that number.

16 By 1 year of age, upwards of 60 percent of  
17 children have at least one episode of acute otitis,  
18 and 17 percent more than 3. By 3 years of age, 80  
19 percent have had more than one episode of otitis,  
20 one or more, and 46 percent, greater than 3  
21 episodes.

22 It is a spectrum of disease. I am a  
23 lumpner, not a splitter, and I see things along a  
24 continuum starting out with garden variety acute  
25 otitis media where there is pretty much a normal

1 middle ear cavity and pus in it versus changes in  
2 histopath--I always wanted to be a pathologist, but  
3 I didn't get there for a number of reasons--changes  
4 in the histopath that bring you over to a  
5 fundamentally different protoplasm in that patient,  
6 bioactive membrane, and do we lump all of these  
7 children together in a single study, if we do,  
8 should we be cognizant of that and come up with  
9 schemes in which we stratify to understand the  
10 effect of a drug in different subpopulations, and  
11 then do we power it to be able to look at.

12           So, anything that we say today, as much as  
13 may not have the time to get into all the  
14 nitty-gritty for the statistical plan and  
15 considerations, that is not to say that we are not  
16 cognizant that that is an incredibly important part  
17 of clinical trial design.

18           I am looking at some of our dear  
19 statisticians smiling at me, because I think that  
20 we have to recognize that anything that you might  
21 recommend to us today has definitive implications  
22 for clinical trial design sample size.

23           If you are talking about non-inferiority  
24 margins, necessarily, delta determinations, the "D"  
25 word, and we may not get to the specifics of numbers

1 today and what do you recommend and what do we  
2 think, et cetera, but at some point in the  
3 discussion, it will rear its head. It is going to  
4 grow arms and legs, and it will be in front of us  
5 to deal with.

6           Likewise, the implications of clinical  
7 trial design, non-inferiority, placebo-controlled,  
8 whatever, have implications for the whole economic  
9 side of the house, one that we don't often talk  
10 about, but is obviously a very important part of  
11 the business of drug development, for if we take a  
12 tack or accept a recommendation that at the end of  
13 the day, completely skyrockets by orders of  
14 magnitude what is costs to do a clinical trial, I  
15 am afraid we won't get it, because there is only so  
16 much money that a corporation or NIH, or anybody,  
17 has to put to the study of anything.

18           So, we have to have a balance between what  
19 is I think right in terms of science and  
20 regulation, and the good of the public health,  
21 because ultimately, we are taking care of pediatric  
22 patients, patients in general, at the same time  
23 that we are cognizant of the fact that there is, by  
24 and large, corporate development of new  
25 anti-infective compound, not individuals working in

1 their basements or in their garages, and that if it  
2 is much more profitable to develop, and practical  
3 and doable, to have a cardiac drug used forever and  
4 ever by a population or a drug for Alzheimer's that  
5 there is only so much money in the pocket that can  
6 be devoted to the study of any given entity and  
7 that common sense and practical issues also  
8 necessarily come to play.

9 [Slide.]

10 So, let's go back to 1997, to the guidance  
11 on acute otitis media. The number of trials in  
12 this guidance were not addressed, but there was a  
13 case definition that spoke to having clinical  
14 evidence of acute otitis media or evidence of  
15 inflammation of the tympanic membrane and middle  
16 ear.

17 The guidance document recommended or  
18 required that in both studies, you have a tap at  
19 baseline, and it went to say that a second tap was  
20 desirable to obtain data on middle ear fluid  
21 concentrations and the promptness of bacteriologic  
22 eradication or cure.

23 Endpoints were both then clinical and  
24 microbiologic, and while the document did not  
25 specifically address a test of cure, it did

1 recommend a four-week follow-up period.

2 I think at times, people and groups, and  
3 so forth, went back and forth on this. If you have  
4 a tap on therapy, you know it is sterilized, end of  
5 story, you don't have to worry about it anymore,  
6 you just need to see the patient at the end of the  
7 treatment course and no longer.

8 Others have argued, no, you really need to  
9 look at the patient for several weeks beyond that  
10 period of time, so that you can see whether or not  
11 the effusion resolves to make sure the child  
12 doesn't relapse, and certainly in the setting of an  
13 active control trial, that you can compare even  
14 longer term what happens even if at the end of day,  
15 you want to argue, but that is not really drug  
16 effect, you can't hold the drug's feet to the fire,  
17 so to speak, four weeks out, five weeks out, six  
18 weeks out.

19 Again, I expect this to come up in our  
20 discussions and be further developed.

21 [Slide.]

22 The 1977 guidance concluded that in the  
23 absence of culture of the middle ear fluid, no  
24 specific claim could be made regarding the  
25 effectiveness of any anti-infective drug.

1 [Slide.]

2 In the eighties, as I mentioned, there was  
3 no new formal guidance on otitis, and what I am  
4 going to give you now is what we talked about in  
5 the corridor, anecdote, the lowest level of  
6 evidence of what was going on, but in our internal  
7 discussions of acute otitis media, we really talked  
8 quite a lot about the requirement to perform or the  
9 heavy recommendation to perform tympanocentesis on  
10 every child enrolled in a trial.

11 From what I remember from those  
12 discussions a decade ago, and admittedly, my memory  
13 is not what it used to be, but what I remember from  
14 those discussions is that we often heard from  
15 colleagues in industry and others that the  
16 procedure was not that easy to do and was not well  
17 known by many, many pediatricians, many family  
18 practitioners, the very folks who were taking care  
19 of these children, and that it was much more  
20 involved than a venipuncture.

21 That may be incorrect. I am just telling  
22 you what we heard that I think caused a fundamental  
23 shift in paradigm that led to what we came out with  
24 in '92 from IDSA or from the FDA. Too few were  
25 really trained to do it or do it well. It seems to

1 be slowing down enrollment in trials, hampering  
2 enrollment in trials, and that the cost was going  
3 up in requiring that every child have a  
4 tympanocentesis.

5           So, was there a better way to design these  
6 trials, better, without costing the patient  
7 anything, better for the efficiency of doing a  
8 trial, and at the same time, in that better way,  
9 not give up the opportunity to know whether a drug  
10 works or not.

11           [Slide.]

12           The 1992 points-to-consider then said that  
13 two trials should be conducted in investigating a  
14 drug and its treatment effect on acute otitis  
15 media. One could be a clinical-only study in which  
16 no tympanocentesis was necessarily performed at  
17 baseline to establish equivalence to an approved  
18 product, and that a second trial that had both  
19 clinical and micro endpoints would be done with, at  
20 a minimum, a tympanocentesis at baseline.

21           The case definitions should be rigid.  
22 This is an important point, because I think, at  
23 least my understanding of what was going on back in  
24 the early nineties, was that we thought we really  
25 could come up with a rigid case definition, a look

1 to the TM, a set of signs and symptoms that would  
2 be virtually pathognomonic for acute otitis media  
3 mediated by bacteria.

4 I see Dr. Pichichero is smiling because I  
5 think he is going to give us information that is  
6 other than what I said, that it is at times maybe  
7 more often than not, not such a straightforward  
8 call. It is probably why I went into internal  
9 medicine. Those little structures were so little,  
10 you know, sometimes it is really hard to tell is  
11 this acute otitis media with effusion, is it otitis  
12 media with effusion with a child who is sick  
13 otherwise and has something else going on, but not  
14 a bacterially-mediated otitis media, could we have  
15 been in error that we thought this was so  
16 straightforward that we could say rigid case  
17 definition, this child has a bacterial-mediated  
18 acute otitis media, no need to do a  
19 tympanocentesis?

20 The 1992 points-to-consider strongly  
21 encouraged--oh, my gosh, is that red light going  
22 on, the yellow, I have another minute and a half,  
23 okay, I will move faster--tympanocentesis was  
24 strongly encouraged in patients who were  
25 therapeutic failures at any point in the trial, and

1 the endpoints, as I mentioned, both clinical and  
2 micro. Test of cure wasn't specifically mentioned  
3 in terms of the timing.

4 [Slide.]

5 The open micro study should establish  
6 acceptable outcomes in, you know 25 patients with  
7 H. flu, 25 patients with Strep pneumo, and 15 with  
8 M. cat.

9 [Slide.]

10 By and large, this dovetailed with what  
11 was published in the IDSA FDA guidelines.

12 One other think I want to mention about  
13 the '92 document and then to move on, the 1992  
14 points-to-consider document stated that the micro  
15 trial could be uncontrolled, could be  
16 non-comparative, and the interpretation of that  
17 almost exclusively was is non-comparative, so once  
18 we say something can be some way, it probably will  
19 be, so we have to be very careful what we ask for  
20 because we know we will probably get it.

21 [Slide.]

22 In '97 and '98, then, when we revamped the  
23 guidance document and took it before the Advisory  
24 Committee, we again spoke of two trials, a micro  
25 study, which could be non-comparative, but should

1 have more numbers in it, and a comparative clinical  
2 trial. Again, case definition, please let's  
3 tighten it because I think we were certainly  
4 beginning to appreciate at that point that it  
5 wasn't maybe so very easy to have a rigid case  
6 definition, that there was a lot of wiggle room and  
7 a repeat tap to be considered day 3 to 5 as a  
8 critical measure of treatment efficacy, perform  
9 tympanocentesis in all failures, primary efficacy  
10 endpoints being clinical at the test of cure and  
11 pathogen eradication.

12           This test of cure, we have talked about a  
13 lot in the past five years in product-specific  
14 meetings, and the consensus at the last couple of  
15 meetings, when we have talked about Augmentin ES,  
16 or talked about azithromycin, short course  
17 treatment, I think the consensus that we have is  
18 that when we are looking at test of cure from the  
19 clinical perspective, we should define that closer  
20 to the end of therapy, and that still do a look  
21 several weeks out as another measure outcome, but  
22 the test of cure be closer to that last pill that  
23 is taken for clinical.

24           [Slide.]

25           Further recommendations that came from the

1 committee were to enroll more patients under 2  
2 years of age, because as we look back at different  
3 products in development over the past 15 years,  
4 some had few or no children under the age of 2,  
5 very striking, so I am sure we will talk about that  
6 at length, and gain much more experience in this  
7 era of resistance.

8 [Slide.]

9 Increase the number of patients under 2, I  
10 have said that, and we just skip forward.

11 [Slide.]

12 Timing of assessment of clinical outcome.

13 Primary endpoint, I have mentioned, again, the  
14 recommendation to encourage that those who fail,  
15 have another tap, whether it is the second tap or  
16 the third or whatever, and that the most  
17 informative tap would be baseline to understand  
18 what was the etiology, and then a consensus that  
19 on-therapy taps could tell us a lot.

20 Whether or not that has to happen all the  
21 time, some of the time, again, I am sure we will  
22 get into.

23 [Slide.]

24 Experience has told us that this can be a  
25 difficult clinical call in some hands, and that

1 even when the inclusion criteria are tight, we have  
2 experienced in looking across many different drug  
3 development programs that some investigators bat  
4 .800, 80 percent of the time they have a positive  
5 culture, and others are batting .200, 20 percent of  
6 the time they are getting a positive culture, so  
7 something is going on.

8 [Slide.]

9 So, back to the future. We want to  
10 revisit the case definition, is it strict, is it  
11 strict enough? Trial design considerations, I have  
12 really already talked about, as well as endpoint  
13 and timing of assessments.

14 I think at some point in our discussions  
15 today, we will revisit the issue of  
16 placebo-controlled trials because what we want to  
17 understand is not only does a drug work in this  
18 disease, but the general question of what is the  
19 role of antibiotics development in acute otitis  
20 media.

21 I want to hold up for a moment as I walk  
22 off before the floor swallows up in Don Giovanian  
23 fashion--thank you for that opera reference--the  
24 management of acute otitis media and evidence  
25 report by colleagues at the Agency for Healthcare

1 Research and Quality, it was actually done on  
2 contract to a group in I believe Southern  
3 California led by Dr. Michael Marcy [ph] if you  
4 have not read this, and I think many of us have  
5 not.

6 On the FDA side, I want to thank Dr. John  
7 Powers and Dr. Erika Brittain for bringing this to  
8 my attention. It is quite a comprehensive report  
9 that is certainly I think teaching us a lot about  
10 what we thought we knew and what we do know.

11 [Slide.]

12 The key question is again what do we need  
13 to know, what constitutes substantial evidence that  
14 a novel antimicrobial drug works and is safe for  
15 children with acute otitis media or some other  
16 variety of otitis media.

17 With that, I will stop and I will turn the  
18 podium back over to Dr. Reller.

19 DR. RELLER: Thank you.

20 Dr. Scott Giebink will now speak to Design  
21 Issues in Antimicrobial Treatment Trials of Acute  
22 Otitis Media.

23 Design Issues in Antimicrobial Treatment  
24 Trials of Acute Otitis Media  
25 G. Scott Giebink, M.D.

1 DR. GIEBINK: As we are getting started,  
2 since Dr. Soreth went back in time, it is  
3 unfortunate that Medline searches only go back to  
4 1968, because what this group needs to know, and I  
5 want to put in the public record, is that we are  
6 all indebted to a physician/scientist at the Mayo  
7 Clinic, between 1958 and 1962, who conducted four  
8 separate clinical trials of acute otitis media,  
9 comparing antibiotics we wouldn't consider today,  
10 but put the whole issue of AOM design on the table,  
11 and that now retired Professor of Pediatrics is  
12 Gunnar Stickler [ph], who had maintained a  
13 life-long interest in otitis media, and really  
14 brought us out of the dark ages into the era of  
15 clinical trial design for otitis, and as we have  
16 heard already, there have been lots of innovations  
17 and we refinements to that over the years, but it  
18 really started with those publications in 1958 to  
19 1962.

20 It is worthwhile going back and looking at  
21 some of those for some of the early thoughts on  
22 design.

23 [Slide.]

24 Well, I wanted to pick up a few design  
25 issues now, to just basically put them on the table

1 for your consideration, and I thought I would start  
2 by saying the obvious, that we really have three  
3 ways we look at outcome in these otitis media  
4 trials.

5           The one that has been mentioned is a  
6 bacteriologic cure, which is basically defined as  
7 sterilization of middle ear fluid, eradication of  
8 the original pathogen, and that obviously requires  
9 an on-therapy tap, just as a second urine culture  
10 would require in urinary tract infection.

11           We have issues that Dr. Dagan is going to  
12 talk about later that relate to eradication of  
13 organisms versus growth suppression of organisms,  
14 that I think to be considered by the committee.

15           The second, of course, is clinical cure.  
16 Dr. Soreth just mentioned that. This is the  
17 resolution of clinical signs and symptoms. For  
18 reasons that should become apparent over the next  
19 couple of hours, the test of cure is really too  
20 obscured by issues of relapse and reinfection to be  
21 useful in measuring otitis media outcome, so as Dr.  
22 Soreth mentioned, moving that test down to end of  
23 treatment makes a lot more sense, and I will say a  
24 bit more about that in a moment.

25           Finally, Dr. Craig has put into the

1 literature, as have others, issues of  
2 pharmacokinetics and pharmacodynamics, and our use  
3 of the kinetic parameters to describe an expected  
4 clinical and bacteriologic outcome, and the  
5 parameter that seems to be holding up over time or  
6 at least the last half-dozen years is this  
7 parameter Time over MIC.

8           There, the issue I think that needs to be  
9 more considered is whether we can really rely on  
10 Plasma Time over MIC or should we be talking about  
11 Middle Ear Fluid Time over MIC, and this will get  
12 into some of the characteristics of chronic otitis  
13 media I will mention in just a moment.

14           [Slide.]

15           Now, the design issues, the four specific  
16 design issues I would like to comment on here in  
17 the next 15 minutes are some of the issues around  
18 the double tap design and using that in a  
19 non-comparative setting. I know that Dr. Dagan is  
20 going to amplify on this considerably.

21           I have already mentioned that the  
22 sub-issue there is the timing of the second tap and  
23 the related issue, the question of eradication  
24 versus growth suppression.

25           The second issue that I would like to show

1 you some data on is the issue of enriching subject  
2 populations in clinical trials for the infection  
3 with penicillin resistant and multidrug resistant  
4 *Streptococcus pneumoniae*, PRSP.

5           The bottom line is I will show you that  
6 the risk factors for PRSP infection are those very  
7 same risk factors for recurrent and chronic otitis  
8 media, so that by enriching, by definition, you  
9 change the subject population, and then you have  
10 questions about generalizing data results from such  
11 a trial back to the whole population at large.

12           It has become clear, certainly in studies  
13 we have done, in studies Dr. McCracken has done,  
14 and several others, that these PK parameters that  
15 we talk about are valid in a particular patient,  
16 but they are incredibly variable. There is a  
17 tremendous variation in PK parameters.

18           The otitis media pharmacokinetics probably  
19 don't relate very well to the murine models where  
20 these PK parameters have been used extensively, and  
21 one of the big issues is most of the PK studies in  
22 humans are single-dose studies, and single-dose  
23 studies don't measure drug accumulation over time.  
24 We know that that is a factor in the middle ear.

25           So, using PK and PD parameters as

1 surrogates of clinical effectiveness or  
2 bacteriologic effectiveness, I think is  
3 problematic.

4           Finally, I would like to show you evidence  
5 that otitis media severity at entry correlates, not  
6 only with clinical cure, but also with  
7 bacteriologic cure, and these issues have rather  
8 large implications for sample size determinations  
9 in clinical trials.

10           It is a fact that we have actually known  
11 for a decade, but has not been strongly considered  
12 in most trial design.

13           [Slide.]

14           I am going to show you the exact same  
15 numbers Dr. Soreth just showed you, that there are  
16 24 million visits at least as of about 1995, in the  
17 United States for AOM, a tremendous burden in very  
18 young children.

19           The reason I put in, in half of the 7 to  
20 12 million cases of pneumococcal otitis, 25 to 40  
21 percent are now resistant to penicillin, the reason  
22 I put this number up there is to emphasize that  
23 very small differences in treatment response have  
24 an impact on millions of children, so when we talk  
25 about 3, 5, 7, 10 percent differences in outcome,

1 we are talking about 2, 3, 4 million children, and  
2 we shouldn't lose sight of that fact as we make  
3 these decisions, which seem very small in terms of  
4 percentage response, but very large in terms of  
5 number of children affected.

6 [Slide.]

7 I would like to use the data from  
8 Pittsburgh, and Dr. Paradise and Drs. Wald and  
9 Hoberman can amplify on this later. This was a  
10 study led by Phil Kaleida at Pittsburgh in the late  
11 1980s, early '90s, looking at a placebo-controlled  
12 trial of AOM.

13 I remember sitting on the opposite side of  
14 the table with Ellen and Jack in the early 1980s as  
15 this was being designed, going through all the  
16 ethical questions about placebo-controlled trials,  
17 and I am delighted to hear that it will come back  
18 on the table here for discussion, because I think  
19 it is time to do that.

20 Let me just make a point about enrollment  
21 severity, the severity of otitis media at entry.  
22 These are the bacteriologic data from that study  
23 that show that there is a tendency of a difference  
24 in the bacteriology of mild versus severe AOM. You  
25 will notice that the incidence of pneumococcal

1 otitis in the severe group is almost twice that of  
2 the mild group, and the Hemophilus-infected ear is  
3 lower in the severe group than in the mild group.  
4 I believe Dr. Dagan is also going to talk about his  
5 recent fairly large experience with Hemophilus  
6 otitis when he talks.

7           So, there is a difference in the  
8 bacteriology, I believe, of mild and severe otitis  
9 media.

10           [Slide.]

11           In that study, the older children, I  
12 believe the age cutoff was 2, were given placebo  
13 treatment compared to  
14 amoxicillin, the younger children had myringotomy  
15 if they had severe otitis.

16           If we lump together the placebo and the  
17 myringotomy groups, we see that there is a 92  
18 percent spontaneous resolution rate that we have  
19 already seen in the mild group and the 76 percent  
20 spontaneous resolution rate in the severe group.  
21 Those differences were significantly different, but  
22 small compared with amoxicillin.

23           Now, what happens when you put together  
24 the bacteriology and the clinical response?

25           [Slide.]

1           That is what I have done in this rather  
2 jumbled slide, but I think you can follow me  
3 through here. In the first line of the mild and  
4 the severe group are the percentages we just saw  
5 two slides ago of those different bacteria isolated  
6 from the ears.

7           On the second line of both groups are the  
8 spontaneous cure rates that were described 30 years  
9 ago by Virgil Howie in his studies in Huntsville,  
10 Alabama, and have been large correlated by other  
11 placebo studies since then with bacteriology, that  
12 there is a spontaneous cure rate of about 20  
13 percent with pneumococcal otitis, about 50 percent  
14 with Hemophilus, about 70 percent with Moraxella  
15 catarrhalis, roughly 30 percent in the mixed  
16 groups, and, of course, 100 percent when there is  
17 no growth in the middle ear fluid.

18           So, multiplying the first and second line  
19 together, you see the bacteriologic cure rates that  
20 would be anticipated, and on the far right are the  
21 total cure rate adding up that row, 63 percent  
22 bacteriologic spontaneous resolution or cure with  
23 mild AOM and 50 percent with severe AOM. That  
24 delta of 13 percent is one of the deltas that we  
25 speak of.

1           If you remember on the previous slide, the  
2 clinical cure rates from the Kaleida study. Here  
3 is a 92 percent and a 76 percent, a delta of 16  
4 percent. So, these deltas are very similar, but  
5 the magnitudes, as the statisticians can comment  
6 later on, are quite different, and these  
7 differences have big implications for sample size  
8 and are an issue that I think need to be discussed  
9 further in the day.

10           [Slide.]

11           The group that Dr. Marchant was a member  
12 of in Cleveland a number of years ago, led by Susan  
13 Carlin, most recently summarized all of their  
14 experience with clinical and bacteriologic  
15 outcomes, and demonstrated that if you compare  
16 clinical with bacteriologic outcome, the clinical  
17 status failure or success predicts about 93 percent  
18 of the bacteriologic responses, and it misses about  
19 63 percent with a specificity of only 37 percent,  
20 15/40.

21           [Slide.]

22           The cells I think of interest really are  
23 these cells, this one and this one, and that is the  
24 discordance between the bacteriologic and clinical  
25 response, and you might ask then why is there

1 bacteriologic success in the absence of clinical  
2 success.

3           A couple of the reasons for this are the  
4 presence of persisting bacterial and host  
5 inflammatory mediators in the middle ear, which we  
6 know continue the inflammatory process after  
7 organisms have died, and concurrent viral  
8 infections that may be related to or have nothing  
9 to do with the middle ear bacterial infection, but  
10 cause what is interpreted as a clinical failure.

11           That constitutes about 6 percent of the  
12 total pie, and then we have about 9 percent  
13 bacterial failures with clinical successes. Why  
14 does this happen? Perhaps it's because we have  
15 low-grade pathogens in the middle ear or these  
16 pathogens are growing more slowly because of  
17 inhibitors in middle ear fluid. This gets to the  
18 issue of bacterial suppression in double tap  
19 studies.

20           [Slide.]

21           Other reasons for persistent symptoms  
22 during treatment, in addition to concurrent viral  
23 infection, is obviously that the organism continues  
24 to grow either because of noncompliance with  
25 treatment or resistant organism, or because the

1 drug does not distribute into the ear, and I am  
2 going to comment on that in just a minute. Dr.  
3 Soreth mentioned the continuum of otitis media, and  
4 I will show you why I think that is critically  
5 important.

6           The persistence of inflammation after  
7 organisms have cleared and then the very rare case  
8 of immune deficiency that impairs the response to  
9 clearing those organisms, those are all reasons  
10 that symptoms may go on during treatment related or  
11 unrelated to continued bacterial presence and  
12 emphasize why a clinical outcome is so problematic  
13 in this disease.

14           [Slide.]

15           The group in Finland has probably, along  
16 with Tasni Chalmatri's group in Galveston, have  
17 done a lot in the last decade to tell us about  
18 respiratory viral infection in otitis media.

19           It has been clear for a long time that  
20 respiratory virus play a major role in acute otitis  
21 media, and in addition, the studies, particularly  
22 in Finland, show us that in the absence of  
23 bacterial isolation from the middle ear,  
24 respiratory virus play a large role, as do absence  
25 of any pathogen in the middle ear causing the

1 clinical diagnosis of acute otitis media, and since  
2 all of these ears were tapped, this 16 percent had  
3 middle ear fluid.

4 I think that represents the host clearing  
5 the organism by the time the needle is put into the  
6 ear, but you will notice in each one of these bars,  
7 Pneumococcus, Hemophilus, Moraxella catarrhalis,  
8 that there are ears with both pneumo and  
9 respiratory virus and without. So, respiratory  
10 virus play a very important role in this disease.

11 [Slide.]

12 This diagram may be one of the most  
13 important summaries of otitis media pathogenesis  
14 that I could show you because it demonstrates how  
15 heterogeneous this population of otitis media  
16 really is.

17 The acute uncomplicated acute otitis  
18 media, which perhaps every child gets before they  
19 go to school, at least 80 percent get this disease  
20 documented in medical record studies, these days  
21 has very few suppurative complications although we  
22 do occasionally see mastoiditis still today. We  
23 just had a child with facial nerve palsy due to  
24 mastoiditis last week. So, these issues do  
25 continue to occur, but they are much less common

1 now than they were 50 years ago.

2           The difficulty in designing a clinical  
3 trial is that we have this conundrum of a clinical  
4 mixture of AOM and chronic otitis media with  
5 effusion, shown in the green here, most of which in  
6 young children is mucoid otitis media or "gunk," I  
7 think Dr. Soreth called this, is these glue ears,  
8 and many of these ears are becoming acutely  
9 infected and appear to be AOM, but, in fact,  
10 pathologically, are chronic OME with a  
11 superinfection, and studies are starting to  
12 demonstrate that drugs distribute more poorly into  
13 the chronic OME ear than they do the AOM ear.

14           Then, we have children that go on to those  
15 nonsuppurative sequelae that include hearing loss,  
16 as well as pathology of the middle ear.

17           So, when we enrich a subject population  
18 for recurrent otitis media or for  
19 penicillin-resistant pneumococcus, we are creating  
20 a study cohort that is not representative of  
21 uncomplicated AOM, and yet, the indications go back  
22 to that uncomplicated AOM population and one has to  
23 ask the question is this a valid extension of those  
24 studies.

25           [Slide.]

1           I have just put side by side here for you,  
2 fairly well accepted risk factors for PRSP on the  
3 left, and for AOM treatment failure and recurrence  
4 on the right, and you will notice that there is a  
5 tremendous similarity, antibiotics within the last  
6 month, in the case of treatment failure, any AOM  
7 diagnosis within the last month, recurrent or  
8 persistent AOM for PRSP, recurrent and persistent  
9 sinusitis, as well, infection during the winter or  
10 spring for PRSP, obviously is an AOM risk factor,  
11 too, young age, young age at the first otitis  
12 episode, daycare center attendance, which Dr.  
13 Wald's studies demonstrated clearly.

14           For treatment failure, not necessarily for  
15 PRSP, bilateral versus unilateral disease. So,  
16 when we select for treatment failure or PRSP, we  
17 are getting both.

18           [Slide.]

19           This is a figure that I extracted from Dr.  
20 Wald's study that demonstrate this very clear  
21 increased incidence of OM complications of common  
22 upper respiratory infections based on daycare size  
23 from the home care, group care, to the center care  
24 group in the children that are less than 1 year.

25           [Slide.]

1           In more recent studies, the day care  
2 center A, B, and C, all in the same community  
3 showed extension of a multidrug-resistant Type 14  
4 pneumococcus that spread across the community  
5 through these daycare centers.

6           It was not detected in general pediatric  
7 practices. So, daycare centers serve as a  
8 reservoir for transmission of organisms that cause  
9 AOM and these penicillin-resistant pneumococci to  
10 show you the impact of multiple risk factors.

11           [Slide.]

12           This is a study that Dr. Daly, with our  
13 group, did back in the mid-1980s, taking just three  
14 risk factors - bilaterality, daycare, and otitis  
15 for more than four weeks at entry in this AOM  
16 epidemiologic trial, looking at the percentage of  
17 children that had OME persisting six weeks later,  
18 and you will notice if they had none of these risk  
19 factors, a third of them had persisting OME.

20           If they had all three risk factors,  
21 two-thirds of them had persisting OME. So, risk  
22 factors are very important in identifying this  
23 subset that have persisting disease.

24           [Slide.]

25           Dr. Dagan is going to say a lot more about

1 carriage rates, but it is all about these very  
2 young children.

3 [Slide.]

4 The rates of pneumococcal resistance by  
5 drug are shown in the figures that you have. They  
6 are all significantly greater rates of resistance,  
7 these are susceptibility rates, are lower rates of  
8 susceptibility in ear infection compared to eye,  
9 respiratory, blood, and central nervous system.

10 [Slide.]

11 And younger children have lower rates of  
12 susceptibility or higher rates of resistance than  
13 older children.

14 [Slide.]

15 Finally, pneumococcal conjugate vaccine  
16 selects those very serotypes that are carrying the  
17 resistance genotype, at least today, and you will  
18 notice here that the seven types contained in the  
19 Wyeth-7 valent conjugate vaccine include the most  
20 frequent resistant types including two types that  
21 are closely related to serotypes in the vaccine  
22 with fairly high resistance rates not found in the  
23 non-vaccine types, indicating that routine  
24 pneumococcal conjugate vaccine, I believe is going  
25 to have a significant impact on the early childhood

1 rates of PRSP, and it is going to make the design  
2 of studies for enrichment with PRSP very difficult  
3 in the next few years if we can get enough  
4 conjugate vaccine in the pipeline to immunize all  
5 of these children.

6 [Slide.]

7 So, in conclusion, I would again  
8 emphasize, as the previous speakers did, the  
9 importance of controlling enrollment in these  
10 trials and call your attention to the fact that  
11 bacteriologic and clinical cure rates are very  
12 tightly related to these clinical definitions.

13 The importance of end of treatment cure,  
14 not test of cure, at 25 to 30 days.

15 The issues with enriching for PRSP that we  
16 have just finished talking about, and, finally, the  
17 issue of pneumococcal conjugate immunization and  
18 its anticipated impact on PRSP prevalence in young  
19 children, all issues for us to consider.

20 Thank you.

21 DR. RELER: Our next speaker is Dr.  
22 Pichichero. The presentations have been wonderful,  
23 although each drifting into the red zone. We will  
24 pick up the time one way or the other, so think  
25 about it either eating into lunch or eliminating

1 breaks.

2 Dr. Pichichero.

3 Experience with Tympanocentesis:

4 Clinical Diagnosis of AOM

5 Michael Pichichero, M.D.

6 DR. PICHICHERO: Thank you, Dr. Reller.

7 As I mentioned in my introduction, I am  
8 blessed or privileged depending on your religious  
9 viewpoint, to continue to practice primary care  
10 medicine half-time, as well as spending the other  
11 half of my time at an academic medical center. As  
12 such, tomorrow morning at 8 o'clock, I will be  
13 seeing patients once again as one pediatrician in a  
14 10-pediatrician private practice group in  
15 Rochester, New York.

16 In sitting at my desk, I calculated that  
17 as a pediatrician, I have looked at in excess of  
18 100,000 ears over my 20-year career, and that  
19 number will continue to climb. Many of my patients  
20 are the children of physicians or nurses, and many  
21 of them are on clinical trials.

22 I have participated in over 150 clinical  
23 trials, about 20 of them involving tympanocentesis,  
24 and this year, for the first time, we intend to  
25 attempt a double tympanocentesis trial at the

1 encouragement of my former student, Dr. Ron Dagan,  
2 who was a fellow in our training program, so  
3 student became teacher. I don't know how it will  
4 go in that patient population, but we are going to  
5 give it a try.

6 My presentation will have three  
7 components. As Dr. Reller implied, it is a  
8 multimedia presentation. The first part will be a  
9 12-minute video demonstrating a tympanocentesis  
10 procedure by myself on one of my patients. Then, I  
11 have a mannikin, and I am going to actually perform  
12 a tympanocentesis for the committee on an infant  
13 mannikin, live. That will take two or three  
14 minutes.

15 Then, I am going to show a video, which we  
16 produced in collaboration with the Pittsburgh  
17 group, Dr. Hoberman and Kaleida, on otitis media  
18 diagnosis.

19 These three pieces of teaching material  
20 are used in workshops which are taught around the  
21 country since 1999. Faculty of those workshops  
22 include Dr. Giebink and Dr. Marchant, and we have  
23 now trained in excess of 3,000 primary care  
24 providers in the tympanocentesis procedure through  
25 these workshops. Less than 10 percent of them went

1 on to actually do tympanocentesis as a routine in  
2 their practice, as we do in our practice in  
3 Rochester.

4 If we could roll the first video.

5 [Video.]

6 DR. PICHICHERO: Hello. I am Michael  
7 Pichichero of Rochester, New York, and I am going  
8 to be performing a tympanocentesis procedure on  
9 this young man, 4-year old Nicholas.

10 Tympanocentesis procedure, which we  
11 perform in our office every day, has a series of  
12 indications, so these are met in all of the  
13 children to one degree or another. Tympanocentesis  
14 in our office is performed when a child is toxic in  
15 their appearance in association with acute otitis  
16 media. We also will perform a tympanocentesis if  
17 the child has a very bulging eardrum to the point  
18 where we anticipate it is going to rupture  
19 spontaneously anyway.

20 We also perform a tympanocentesis in the  
21 highly febrile patient, which would be acute otitis  
22 media with fever over 102 degrees Fahrenheit orally  
23 in the teenager or young adult, or over 104 degrees  
24 Fahrenheit in the young child, such as Nicholas.

25 We also would perform a tympanocentesis on

1 the patient who has been unresponsive to previous  
2 antibiotic therapy. There is some discussion  
3 whether we would perform the procedure after a  
4 single failure of first-line therapy, such as  
5 amoxicillin or trimethoprim-sulfamethoxazole,  
6 whereas, most every physician expert in otitis  
7 media would agree that following failure with  
8 first-line therapy, such as amoxicillin, end of  
9 failure with a second-line therapy, that in this  
10 circumstance, a tympanocentesis can be very helpful  
11 to determine whether there is a pathogen present,  
12 and if so, what is the pathogen and what would be  
13 the preferred antibiotic therapy for that isolated  
14 bacterial species.

15           The benefits of tympanocentesis include  
16 immediate relief of pain in the crying child who is  
17 suffering from the pain of a bulging tympanic  
18 membrane, we can provide instant relief, as acute  
19 otitis media really is an abscess of the middle ear  
20 space.

21           We can determine whether the infection is  
22 a bacterial etiology or if it's a viral etiology,  
23 and if it is of a bacterial etiology, we can  
24 perform sensitivity testing in order to determine  
25 whether the organism will be killed with

1 traditional first-line agents or whether a  
2 second-line agent would be preferred in this  
3 circumstance.

4           Typanocentesis has the benefit of  
5 draining an abscess, which we know is therapeutic  
6 in and of itself, and last but not least, we feel  
7 that typanocentesis can improve a physician's  
8 diagnostic accuracy.

9           Nothing is more self-educating than to  
10 diagnose acute otitis media, perform a  
11 typanocentesis, and find that the ear tap is dry,  
12 the patient never had acute otitis media.

13           Also, we think that it is very beneficial  
14 if you perform a typanocentesis and no bacteria  
15 are isolated, then, no additional antibiotics are  
16 necessary, and that can be very beneficial, as  
17 well, in avoiding the unnecessary overuse of  
18 antibiotics.

19           For the typanocentesis procedure, we  
20 typically do not provide any anesthesia, we don't  
21 put the children to sleep. Some offices do give a  
22 medicine called Versed, which is taken orally, and  
23 then the child becomes very sleepy, but then they  
24 have to remain in the office for an hour or so  
25 before they are completely recovered.

1           Other times we will give a child some  
2    tylenol with codeine and a little valium mixed in  
3    to make the child relax, but in the case of  
4    Nicholas, his eardrum is so bulging with infected  
5    fluid, actually, I think he is going to feel relief  
6    rather than pain when we perform the  
7    tympanocentesis.

8           It is like opening a pimple or a boil  
9    yourself. When you open it up, it actually feels  
10   better, and you don't even feel the needle go  
11   through. So, that is what we are anticipating with  
12   Nicholas.

13           So, the first thing we will do is we will  
14   lay him down, make sure he is completely still with  
15   something we call a papoose board. My nurse will  
16   hold his head firmly, and then we will look into  
17   his ear with the Welch-Allen otoscope, not this one  
18   which you are used to seeing me examine him with,  
19   but rather we use this otoscope because it allows  
20   me to put the needle through, and I can still see  
21   through this mirror, so I am watching the whole  
22   time exactly what I am doing, so I put the needle  
23   exactly in the spot I want in the eardrum, so that  
24   there won't be any damage to his eardrum.

25           To do the procedure, we take a needle that

1 looks like this. It's a spinal needle, and I bend  
2 it and hook it to a syringe, and then, as you see  
3 in this picture, the needle will be inserted  
4 through the ear canal until it touches the eardrum,  
5 and then we will suck the fluid off of the middle  
6 ear space in order to--the needle will be inserted  
7 through the ear canal until it touches the eardrum,  
8 and then we will suck the fluid off of the middle  
9 ear space in order to culture it and in order to  
10 drain that middle ear abscess.

11           There are some potential rare or  
12 hypothetical complications from tympanocentesis.  
13 Certainly, you would expect the possibility of some  
14 bleeding because we are going to put a hole, a tiny  
15 hole through his eardrum, and some pus and fluid  
16 may come out of the eardrum puncture site which I  
17 create with the tympanocentesis needle.

18           That should stop in a day or two as the  
19 hole heals over. Usually, three days after a  
20 tympanocentesis is performed, you can't even tell  
21 where the hole was.

22           Now, if the child is not properly  
23 restrained and they move their head about in the  
24 middle of the procedure, then, there are other  
25 possible complications where the little ear bones

1 behind the eardrum could be scratched or injured,  
2 and there are blood vessels back behind the  
3 eardrum, and they could be scratched or injured, so  
4 that is why it is necessary for us to restrain your  
5 child and hold him very still during the procedure.  
6 The only real risks are when the child moves very  
7 suddenly and very unexpectedly, and they are not  
8 properly restrained.

9           A critical element to the tympanocentesis  
10 procedure is proper immobilization. Here, Mrs.  
11 Koon will put Nicholas into our papoose board, and  
12 my nurse Julie will secure him into the papoose  
13 board.

14           We usually do allow the parent to remain  
15 in the room throughout the procedure to reassure  
16 their child, and we will papoose children up to the  
17 age of about 4 or 5 years of age. After that, it  
18 may not be necessary to papoose the child, but in  
19 all cases, we require an assistant to restrain the  
20 child at the arms, and a second assistant who will  
21 restrain the child at the head.

22           We then will remove the spinal needle from  
23 its container. We use a 20-gauge. Other  
24 physicians who practice tympanocentesis recommend  
25 an 18-gauge needle. Of course, the stylet is

1 removed and then the sterile syringe is attached to  
2 the spinal needle, and then the needle must be bent  
3 at a 45- to 90-degree angle, approximately  
4 one-third from the hub.

5           So, I will bend it thusly, and this  
6 depends on your own comfort level and how you hold  
7 your hand during the procedure, but in all cases,  
8 the needle must be bent, but the precise angle  
9 according to your own comfort zone.

10           Now, we maintain sterility by keeping the  
11 sheath over the spinal needle tip until we are  
12 ready to proceed with the actual procedure.  
13 Visualize the tympanic membrane. I am proceeding  
14 now down through the canal. I am right at the  
15 tympanic membrane, everybody takes a breath, and  
16 there we are.

17           We suck back the fluid, pull out, and we  
18 are finished. It is as quick as that.

19           So, we are going to perform the  
20 tympanocentesis procedure. The speculum is  
21 inserted. We visualize, we ask the nurse assistant  
22 to pull back on the pinna. We now insert the  
23 needle through the speculum, through the ear canal,  
24 get in good position, we are ready, and, pop, we  
25 are through. We draw the fluid. We pull out and

1 we are done.

2           For needle placement, here is a normal ear  
3 for orientation. The preferred location for the  
4 tap, interior quadrant, where the light reflex is.  
5 An acceptable alternative is the  
6 posterior/inferior. It is essential to completely  
7 avoid the entire superior half of the tympanic  
8 membrane.

9           Now, here is an image of an abnormal ear  
10 bulging with infection. Again, the preferred  
11 location for the tap is the anterior-inferior  
12 quadrant. An acceptable alternative is the  
13 posterior-inferior quadrant. it is essential to  
14 completely avoid the entire superior half of the  
15 tympanic membrane.

16           Following the tympanocentesis procedure a  
17 decision is made regarding antibiotic selection.  
18 This can be guided by gram staining of the  
19 tympanocentesis material showing gram-positive or  
20 gram-negative bacteria, and then specifically  
21 directed at the pathogen and penicillin-susceptible  
22 versus resistant pneumococci, if isolated,  
23 beta-lactamase positive or negative, Moraxella or  
24 Hemophilus, as isolated. So, you can do directive  
25 therapy.

1           Of course, follow-up is necessary. We  
2 usually see the children back in three weeks,  
3 sooner if the bleeding or fluid persists beyond a  
4 day or two, or any alarm on the part of the parent.

5           [End of video.]

6           DR. PICHICHERO: Okay. That is a  
7 tympanocentesis. If we could have the lights up,  
8 please.

9           [Demonstration]

10          DR. PICHICHERO: This is a baby mannikin.  
11 We train pediatricians how to do tympanocentesis  
12 with this mannikin. The manikin is loaded with a  
13 disk. The disk looks like this. This is four  
14 tympanic membranes. You will see that in the top  
15 half of the tympanic membrane, when it is in the  
16 right position, will be a red dye. If the needle  
17 goes in through the red dye, you fail the test.

18          In the bottom half, you see a yellow pus.  
19 If the needle goes into the yellow pus, be it  
20 anterior or posterior, you have had a successful  
21 tympanocentesis. If you put the needle too far,  
22 you get a blue dye. This is to indicate that you  
23 have now hit the posterior--you have hit bone,  
24 periosteum bone at the posterior aspect of the  
25 middle ear space.

1           So, when we test our doctors, it is very  
2 easy. You have either got red dye, yellow dye, or  
3 blue dye.

4           This mannikin is engineered for the disk  
5 to go into a position, so that when it slides into  
6 the head, it is has the proper angulation and  
7 anatomical position of a real child.

8           Here is the otoscope that you saw in the  
9 video. You turn it on. I have already pre-bent my  
10 needle, and I won't maintain sterility today. So,  
11 you look into and you locate your anatomy. I can  
12 see the red dye and the yellow dye, and then go  
13 into, I progress down, I puncture, withdraw the  
14 fluid, and come out, it's that fast.

15           We can do another one. Rotate the disk  
16 one-quarter turn. In it goes. Again, put my light  
17 on. You see it. The red is the top, the yellow is  
18 at the bottom. I go in, puncture, draw the fluid,  
19 and come out. It's as quick as that.

20           I personally performed a little over 1,000  
21 tympanocentesis. I have not had any major  
22 complications. I have had a few patients with  
23 minor complications like the hole stays open for  
24 more than two or three days. I had one where I did  
25 hit the posterior wall, and the bleeding was

1 sufficient that there was blood that stayed in the  
2 middle ear space for a little over a week, which  
3 made me quite nervous, but resolved on its own  
4 thereafter.

5 I have had the privilege of polling some  
6 of the major tympanocentesis centers. Some of  
7 those people are in this room. Over 10,000  
8 tympanocentesis in primary care, no major  
9 complications reported by any of those in the  
10 survey.

11 I am now ready to show you another video.  
12 We will need the lights down.

13 [Video.]

14 There will be a lot of discussion about  
15 the causal diagnosis of otitis media. This video  
16 is shown during our workshops, and it has taught me  
17 a lot and the other faculty a lot about what we  
18 should know a lot about.

19 This video was developed in cooperation  
20 with Drs. Hoberman and Kaleida at the University of  
21 Pittsburgh, and we are very grateful for their  
22 cooperation. They actually took video with an  
23 otoendoscope. It is a lot like a laparoscope that  
24 you put in the ear, and you simply take pictures,  
25 and they have made some beautiful pictures, and

1 during our course, we show examples of sclerosis,  
2 atrophy, retraction pockets. We won't have time  
3 for all of that today. I am just going to show you  
4 four ears.

5           The first two are examples. Here is an  
6 example of a normal tympanic membrane. You will  
7 notice that all the wax has been removed, and here  
8 is an easy to-and-fro movement, which occurs with  
9 pneumatic otoscopy properly performed when there is  
10 an air-filled middle ear space.

11           Here is the light reflex. Here is the  
12 malleus. Our participants actually vote and we  
13 record their diagnosis. You will notice that this  
14 eardrum is gray in color, it's in a neutral  
15 position, that is, neither bulging nor retracted.

16           It's translucent. You can see right  
17 through it including seeing the malleus, and it has  
18 a nice normal landmark, notably light reflex in the  
19 malleus. This would be a null effusion, a normal  
20 ear diagnosis.

21           Here, in our second example, this is acute  
22 otitis media. It is a bulging tympanic membrane  
23 filled with pus, limited mobility. Only with  
24 positive pressure do you get a little bit of  
25 backward movement of the tympanic membrane; with

1 negative pressure, it is so bulging, it can't bulge  
2 further.

3           This is what you might consider a severe  
4 acute otitis media, which includes a smattering of  
5 hemorrhagic area on the surface of the tympanic  
6 membrane. You will notice that it's kind of a  
7 mixture of red and white or yellow. It's bulging,  
8 it's opaque, you cannot see through it.

9           There is some mobility, but only with  
10 positive pressure, and the diagnosis would be yes,  
11 an effusion is present this is acute otitis media.

12           Now, if you were examining a child and you  
13 saw this ear, what would you think? Now, you are  
14 getting to look at this ear for 20 to 30 seconds.  
15 All the wax is gone, the mother is not breathing  
16 over your shoulder, the child is not screaming.  
17 What is the diagnosis?

18           Well, we could argue about that amongst  
19 ourselves, but although there is yellow fluid, this  
20 eardrum is retracted. We know that from the  
21 anatomical position of the malleus. You have got  
22 some air fluid levels; 88 percent of ENT physicians  
23 say that this is otitis media with effusion, but  
24 only 40 percent of pediatricians think it is otitis  
25 media with effusion. What is it?

1           Here is ear number two. Again, all the  
2 wax is gone, all the time in the world to look at  
3 it and think about it. The average pediatrician  
4 looks at an ear for less than two seconds. You are  
5 looking at it for 30 seconds. Usually, the cerumen  
6 blocks more than 50 percent of the view. What did  
7 you think that was? Did you notice the bubbles?  
8 Eighty-two percent of ENT physicians thinks this is  
9 OME, about 60 percent of pediatricians think it's  
10 OME. What do you think?

11           Do you want to see another one or have you  
12 seen enough? One more. The chairman says one  
13 more.

14           I am going to show you the ear. This is  
15 going to be a good one, Barth, because watch the  
16 malleus. At the beginning of the video, the  
17 tympanic membrane is gray. Then, the child starts  
18 screaming, and the eardrum turns red, first, a  
19 blush down the malleus, then, the whole canal turns  
20 red. By the end of the video, everything is red,  
21 but at the beginning of the video, everything was  
22 gray.

23           So, when Dr. Giebink and Sylvan Stool and  
24 other leaders tell us that color is the  
25 worst--there it is, it's gray, folks, but watch a

1 child cry, watch the blush of the capillary bed  
2 down the malleus. Here it comes, boom, and then  
3 the whole eardrum turns red. What is that, is that  
4 otitis media? It's red. It's red.

5 No, it is not otitis media. There was not  
6 even effusion behind that tympanic membrane. That  
7 child had a retracted tympanic membrane, probably  
8 had a cold or an allergy, and there is nothing  
9 wrong with that ear.

10 That's otitis media again, by the way.  
11 Those white flecks are epithelial cells on the  
12 surface of the tympanic membrane, peeling off from  
13 the heat of the infection. The eardrum is so  
14 bulging that when you puncture it, pus explodes out  
15 of the tympanic membrane, and the child stops  
16 crying on the table from the relief of pain.

17 Thank you very much.

18 [End of video.]

19 DR. RELLER: This has been choreographed  
20 by Dr. Soreth. Dr. Ron Dagan perhaps is the only  
21 person who would be willing to follow Dr.  
22 Pichichero.

23 Ron.

24 DR. DAGAN: If you think I am going to  
25 dance, I am not.

1 [Laughter.]

2 Double Tympanocentesis Studies

3 Ron Dagan, M.D.

4 DR. DAGAN: I was asked to talk today  
5 about the bridging between double tympanocentesis  
6 and clinical outcome studies.

7 [Slide.]

8 This is, as you see, a very bulging  
9 eardrum, and just to remind all of us, a double  
10 tympanocentesis means that before treatment, we do  
11 one tympanocentesis, as you saw now, and we take it  
12 for culture, and during treatment, and usually,  
13 after 3 days to 5 days, because this is really the  
14 middle, but at 72 hours of treatment, this is day 4  
15 to 6, if this is day 1, and then you do another  
16 one, and you take for culture.

17 The double tympanocentesis means that we  
18 are going to see whether the organisms that exist  
19 here, they disappear on the second tympanocentesis,  
20 and then you can compare to drugs or compare to  
21 virus MICs or whatnot.

22 [Slide.]

23 Now, I have a series of seven questions  
24 that I have tried to see whether we get answers in  
25 terms of bridging, and the first question, of

1 course, in acute otitis media, is there any  
2 difference between drugs in regard to bacteriologic  
3 eradication of day 4 to 6.

4 [Slide.]

5 I am not going to show all the slides from  
6 all the studies, but I wanted to bring a summary  
7 from the recent studies, and this is, as you can  
8 see, cefaclor, cefuroxime-axetil, amoxicillin or  
9 amoxiclav at the regular doses, ceftriaxone, one  
10 dose, azithromycin, 3 to 5 days,  
11 trimethoprim-sulfa, ceftriaxone, 3 days, Augmentin  
12 ES-600, and the gatifloxacin. These are the recent  
13 studies that we have data for.

14 If we look at placebo, you remember that  
15 84 percent of the 3 to 4 days is still persisting,  
16 so this is percent of persistence, and you see they  
17 all times were quite nice days, whatever you gave  
18 had eradication that was significantly better than  
19 placebo. Hopefully, after the pneumococcal  
20 vaccination, we will see something more similar to  
21 this.

22 However, the situation with the resistant  
23 era, is that you can see all drugs are affected  
24 somewhat, and you can see really much differences  
25 between the drugs. You can see that for those who

1 are beta-lactams, when you have penicillin, no  
2 susceptibility for the macrolides or for the  
3 trimethoprim-sulfa, et cetera, you do see much  
4 difference between the drugs nowadays in  
5 eradication of the nonsusceptible organisms.

6           We don't have data on quinolone  
7 nonsusceptible pneumococci yet, but I think that in  
8 a year or two, when we meet, I will bring you  
9 probably already resistant quinolones because that  
10 is the way it will go if the quinolones will be  
11 given to children.

12           As you can see, there are drugs, such as  
13 cefaclor here, ceftriaxone one dose, and  
14 azithromycin as presented of the macrolides,  
15 trimethoprim-sulfa where really are not very much  
16 different than placebo in terms of eradication of  
17 the organisms. Others are sort of reasonable, and  
18 others may be good.

19           [Slide.]

20           If you look at the Hemophilus, remember 50  
21 percent eradicated around these and 50 percent  
22 persist, and you can see again excellent drugs  
23 versus not so good drugs. Cefaclor is not too far  
24 from placebo. Azithromycin is in the range of  
25 placebo in terms of eradication rate.

1           You have some sort of acceptable. With  
2 trimethoprim-sulfa, if it's resistant, it's not  
3 eradicated, but only 30 percent are resistant, so  
4 you still have some good results. Here, you can  
5 see better results, but there is a big variety.

6           Now, with Hemophilus, when you have  
7 beta-lactamase, then, you have amoxicillin, of  
8 course, because then amoxicillin is placebo when  
9 you have beta-lactamase.

10           With Hemophilus, there is much more  
11 experience that can be drawn from the past, because  
12 in the past, the differences in Hemophilus today  
13 and in the past are not as big as with  
14 pneumococcus.

15           So, I took all the studies I could find,  
16 which is about 35 or 36 studies all together with  
17 double-tap tympanocentesis, and compared to  
18 placebo, and you can see that there are two groups  
19 of drugs, one group that is ranging from excellent  
20 eradication rate to reasonable eradication rate,  
21 and this is the number of studies done, not  
22 necessarily by our group, but all groups all  
23 together, and these are what I think is not too  
24 acceptable, cefaclors are frozen of the  
25 beta-lactams and the macrolides.

1           So, you can see that really there is a big  
2 difference between drugs in terms of potential  
3 eradication exactly on the same timing.

4           [Slide.]

5           The second question is can double tap  
6 studies determine an MIC concentration cutoff,  
7 above which a given drug is not bacteriologically  
8 efficacious, because now you get for licensure  
9 sometimes application which is hooked to an MIC.

10          [Slide.]

11          This is again one of our first studies  
12 looking at cefaclor versus cefuroxime-axetil.  
13 These are the placebo eradication rates as found by  
14 Howie in the past. Remember that both drugs are  
15 good for pneumococcus that are susceptible to  
16 penicillin.

17          If you see a nonsusceptible, and this time  
18 we really didn't have resistance only to immediate  
19 you could see that both are effective, but you can  
20 see one drug that is more effective than the other,  
21 and this is sort of the gradual increase in MIC,  
22 you can find some cutoffs. Hemophilus is not  
23 relevant to this question here in this.

24          [Slide.]

25          Now, with trimethoprim-sulfa, for example,

1 since MIC of 0.5 is considered to be the cutoff, we  
2 wanted to see whether MIC of 0.5 really is  
3 associated with eradication failure. You can see  
4 that for both pneumococcus and Hemophilus here, you  
5 have 37 cases, 100 percent eradication with  
6 trimethoprim-sulfa, while if you have above MIC of  
7 0.5, basically, for pneumococcus and for  
8 Hemophilus, you have a placebo.

9 So, again, I think I mentioned last time  
10 with a question that will come whether we need  
11 placebo studies, we have some placebos here that we  
12 don't really need to give placebos, they are as  
13 good as placebos for eradication.

14 [Slide.]

15 With azithromycin, there is now a study  
16 where we did from 3 days and 5 days, and  
17 pharmacokinetic/dynamic calculation predict a 0.25  
18 or less than 0.25 actually than MIC, below which  
19 you should see a response, and above which you  
20 should not see a response.

21 These two studies actually show that for  
22 pneumococcus that is susceptible to macrolide, you  
23 do have almost 100 percent response, while if it is  
24 above that, which is usually above 2, because you  
25 don't have really intermediate values, this is

1 basically placebo rate of eradication.

2           For Hemophilus, there is no Hemophilus of  
3 less than 0.25 MIC for azithromycin. Up to 4, it  
4 is susceptible, but you can see that for both  
5 studies, 3 and 5 days, at 5 days, even one at 0.5,  
6 which are not the majority of the cases, you have  
7 basically placebo eradication rate, the same goes,  
8 of course, if the MIC is higher. They are all  
9 acting about the same.

10           So, definitely, here, in this case, and  
11 the previous slide, you could see that there is an  
12 MIC where we can really measure above which you are  
13 not going to see good results.

14           [Slide.]

15           This is the Augmentin ES study that was  
16 published. The data, you can see that again this  
17 is penicillin MIC, and this is pneumococcus, and  
18 the majority had an MIC of 1 or less, and you have  
19 100 percent eradication, but you start to see  
20 increasing failures with MIC, and as far as I know,  
21 the FDA did not approve it for MIC maybe because of  
22 this.

23           For Hemophilus again, 0.5 or less, you  
24 don't have all those failures, and then you start  
25 to see more and more failures, and we need a little

1 bit more cases to know where it is starting to be  
2 unacceptable, but definitely with a double  
3 tympanocentesis, you can go down to talk about MICs  
4 and for which MICs you start to see problems in  
5 eradication.

6 [Slide.]

7 The third question is, of course, is there  
8 a relation between bacteriologic eradication on day  
9 4 to 6 and clinical outcome? I think this is maybe  
10 the most important question.

11 [Slide.]

12 We have two studies actually, only two  
13 studies that looked at this because in order to  
14 look at this, you need to do double tympanocentesis  
15 and to be able to follow clinically, otherwise you  
16 cannot correlate those.

17 One is a study that was mentioned by  
18 Carlin, et al, and the other one is ours. This is  
19 the cases where you did eradicate the organism.  
20 You start with positive culture in cases you  
21 eradicate the organism, you see that there is  
22 about--no, I am sorry--you don't eradicate. This  
23 is culture-positive, about 40 percent would be  
24 clinical failures.

25 If you eradicate the organisms, you get

1 less than 10 percent clinical failure, so I think  
2 there is no argument that most of the clinical  
3 failures will be those for whom you did not  
4 eradicate the organisms after 3 to 5 days. This is  
5 very clear.

6           But if you really want to see how the  
7 children feel, you have to start to use some  
8 scoring. This was the scoring we use, giving from  
9 each one of those from zero to 3, and this was  
10 evaluated by an independent ENT who did not know  
11 what the children were receiving and what the  
12 organism was.

13           The maximum score is 15, the minimum is  
14 zero, and if you look on day 4 to 6, and you try to  
15 see how the kids feel by scoring, this is the  
16 culture-negative, this is the children that  
17 responded to treatment bacteriologically on that  
18 time, and you will see that 45 percent have zero or  
19 1 score, and very few have 4 or more. This would  
20 be equal or above.

21           Those who are still culture-positive, you  
22 see the difference, a highly statistically  
23 significance, very few with zero to 1, and  
24 one-third above 4. So, the children in this group  
25 definitely feel better than children in this group,

1 and this is the group where you eradicated the  
2 organism.

3 So, there is a correlation, there is no  
4 doubt about that, between bacteriological  
5 eradication and how you feel after a few days, and  
6 how you feel at the end of treatment and whether  
7 you fail or not.

8 [Slide.]

9 The fourth question is can we determine by  
10 double tap studies if an organism is not important  
11 in acute otitis media?

12 [Slide.]

13 This is very important actually, because  
14 there are some authorities and some manufacturers  
15 and some clinicians who think this *H. influenzae* is  
16 not important, and the *Hemophilus* is relative or  
17 absolutely is going to be more important after  
18 pneumococcal vaccination than it is now.

19 There was already data to show replacement  
20 of *Haemophilus influenzae* that replaced some of the  
21 vaccine type that disappear in the Finnish study,  
22 and definitely now since the vaccine types are  
23 going to be reduced, you are going to see maybe  
24 less of pneumococcal resistance, but more  
25 *Hemophilus*, so this is a very important question.

1 [Slide.]

2 One of the studies that was done by our  
3 group and presented at ICAAC a year and a half ago  
4 was looking at the regular bug that we have now in  
5 Israel, which is not very different from what you  
6 had in the States before starting with vaccination.

7 Pneumococci were mainly  
8 penicillin-nonsusceptible, Hemophilus with about a  
9 third that were beta-lactamase-positive, very few  
10 Moraxellas, 43 patients, 56 bugs receiving what is  
11 recommended in the status of first liner, 80/kilo  
12 amoxicillin, and 13 failed with 16 organisms.

13 You can see that now we have very few  
14 pneumococci that are penicillin-susceptible, the  
15 susceptible went away, and you see very clearly  
16 that you have now lots of beta-lactamase, and  
17 actually, if you look at 13 here, 8 here, so  
18 basically what you have got is again this  
19 spontaneous eradication of the beta-lactamase  
20 production, which is still placebo effect and most  
21 of the beta-lactamase not producing went away.  
22 Most of the children have beta-lactamase producing  
23 organisms.

24 So, it depends on what drug you have, but  
25 with amoxicillin, Hemophilus is definitely a very

1 prevalent one. The question is whether it causes  
2 any symptoms.

3 [Slide.]

4 We have now quite experience with reading,  
5 giving a scoring. This is more objective without  
6 ear tapping, giving a scoring by the ENT that sees  
7 the child before the first attempt, which means it  
8 is sort of a blind reading because you don't know  
9 what the organism is going to be when you tap, and  
10 you score the child.

11 We have now about 1,000 cases like that  
12 where we can start to summarize those. You can see  
13 we have 762 that are culture-positive, 240 that are  
14 culture-negative, and the mean score is here, and  
15 the culture-negative, of course, has lower score  
16 despite the fact that all are involved as acute  
17 otitis media cases.

18 [Slide.]

19 Now, if you look at the organism, this is  
20 a negative, this is mixed pneumococcus and  
21 Hemophilus, pneumococcus alone, Hemophilus alone.  
22 You see the numbers are quite big, and you see that  
23 the culture-negative has a different score than the  
24 culture-positive, and because of the big numbers  
25 here, the P is significant between Hemophilus and

1 no growth, and really not different from the  
2 others. If anything, this is a little bit higher,  
3 not significantly.

4 So, basically, you can see that Hemophilus  
5 really does not have a different score when you see  
6 the child, when you look at the tympanic membrane  
7 and the fever than pneumococcal when they come to  
8 you, and I think that these big numbers really  
9 makes it more accurate than the few small series  
10 that characterize 1 or 2 or 5 or 20 patients.

11 Even more important, if you look at  
12 eradication, what happened to the score after you  
13 give antibiotics. This is just an example of a  
14 score that was given before antibiotics. This is  
15 day 4 to 6, another score, and what is really  
16 important is the delta, and we want to see whether  
17 the delta is the same if you did not eradicate and  
18 did eradicate pneumococcus and Hemophilus.

19 What you get is first when you eradicate,  
20 the organism is gone, the second test, you see  
21 quite a nice big delta, which is no difference  
22 between Hemophilus and pneumococcus from mixed  
23 infection.

24 When the organism was not eradicated, the  
25 delta is much smaller, and again, not different

1 between those three, and definitely it means that  
2 if you did not eradicate the organism, Hemophilus  
3 is as bad as pneumococcus, but remember that within  
4 3 to 5 days, you have more eradication of  
5 Hemophilus compared to the pneumococcus, so all in  
6 all, there will be more cases that will look better  
7 with Hemophilus than pneumococcus, but the 50  
8 percent of where you do not eradicate the  
9 Hemophilus, are going to look as bad as  
10 pneumococcus, and think this is proof that  
11 Hemophilus is not negligible at all in otitis  
12 media.

13 [Slide.]

14 This is the next question. Can we bridge  
15 between double tap studies and studies with  
16 clinical outcome? This is the main question coming  
17 from the previous questions.

18 [Slide.]

19 I use here an example of the one study of  
20 the previous dose of amoxicillin or amoxiclav, or  
21 the regular dose, if you will, of 45 mg/kg compared  
22 to azithromycin, 5 days, and here you see the  
23 placebo rate again of eradication, and you remember  
24 that, or I am not sure I showed it, but basically,  
25 the results were that you have 87 percent

1 eradication rate.

2           Now, this is not persistence, this is  
3 eradication rate with Augmentin and 40 percent with  
4 azithromycin, and all together it is high  
5 statistically significant. Now, this is  
6 bacteriological eradication.

7           [Slide.]

8           If you look at this, this is what I show  
9 now, this is bacteriological eradication of  
10 pneumococcus alone. There was some difference,  
11 which was not statistically significant, and the  
12 overall bacteriological eradication rate was  
13 significant.

14          [Slide.]

15          But when you look at the clinical outcome  
16 now, you could see that here, there is no  
17 difference, significant difference in clinical  
18 outcome. Here, here is a significant difference in  
19 clinical outcome, and all in all, you have here 16  
20 percent difference, which is statistically  
21 significant clinical outcome.

22          Now, by doing the double tympanocentesis,  
23 this is the clinical outcome, but by doing the  
24 clinical tympanocentesis, you know that the main  
25 difference that accounts for this 16 percent

1 between the two drugs is coming from the Hemophilus  
2 eradication, not really much from the pneumococcus.

3 So, by doing this, and then doing clinical  
4 studies, you are going to see that the clinical  
5 studies don't say much different that we have here,  
6 but you can know that this is not because of  
7 pneumococcal problems, but because of Haemophilus  
8 influenzae issues.

9 [Slide.]

10 Now, if I take this, again, I am  
11 surprised, I am the fifth speaker or so, and nobody  
12 mentioned yet the Pollyanna phenomenon, but this is  
13 what I call--I don't call it anymore Pollyanna  
14 phenomenon--I call it the Colin Marchant drum,  
15 because this diagram was shown first by Colin  
16 Marchant.

17 Remember, this is the eradication rate  
18 after 3 to 5 days. Placebo is very low. One  
19 hundred percent is best. You heard from Scott that  
20 even if you have 100 percent eradication, you are  
21 not going to see 100 percent clinical response  
22 here. With placebo, you get up to 70 percent  
23 clinical response just because some and most of the  
24 organisms go away within 10 days.

25 The difference is that small here. I take

1 the data that I showed in the previous study, and I  
2 try to put them here. So, for pneumococcus with  
3 Augmentin, a regular dose, you have about almost 90  
4 percent clinical success rate, which is well  
5 located.

6 With azithromycin, you have 80 percent.  
7 It might be a difference or not, it is an issue of  
8 sample size, but they are located in the upper 50  
9 percent. If you look at the amoxiclav, Hemophilus,  
10 it is here, 87 percent bacteriological eradication,  
11 it is well located here.

12 If you look at the azithromycin, it is  
13 located basically in the range of placebo.

14 So, this is what we saw with clinical  
15 response. This is what we saw with bacteriological  
16 response. This is just to show you how we are--and  
17 I am trying to take this diagram, it's the bridging  
18 diagram for clinical studies--and try to see what  
19 happens if I put clinical studies on that.

20 [Slide.]

21 In order to choose that, I took the only  
22 one, the only FDA meeting I was in was the previous  
23 one, which now it says 7/11, the other one was  
24 11/7, in November, for licensure of one dose and  
25 three doses of azithromycin, and I took data from

1 clinical studies that have one tympanocentesis,  
2 that were obtained, but clinical outcome, it was  
3 obtained by the people who wanted to have the best  
4 results because this was shown, this was presented  
5 by the people from Pfizer, and you can recognize  
6 those slides from work you can download from the  
7 Internet.

8 [Slide.]

9 What you can see here is--I didn't find  
10 the slide with macrolide-resistant pneumococcus,  
11 but with penicillin-resistant pneumococcus, I could  
12 find one slide and, of course, the more penicillin  
13 resistant you are, the more it is enriched with  
14 macrolide resistance.

15 They showed, the point was that even if  
16 you are susceptible intermediate resistant,  
17 although you have a little bit lower response, you  
18 still have quite a nice response for all three.

19 [Slide.]

20 Well, if I put this again in this, what I  
21 find here is that penicillin, pen-susceptible  
22 pneumococcus has 95 percent success, which is the  
23 best you can have, you cannot have better than  
24 that, which really is concordant with what we found  
25 in our studies on azithromycin.

1           If you have penicillin, it is immediate,  
2 which is enriched with macrolide resistance, you  
3 already drop to not too nice results, and if you  
4 have penicillin resistance, which is even more  
5 enriched, you actually are within the placebo  
6 range.

7           So, with the same drug, in the same study,  
8 clinical outcome only, if you put it here, you  
9 actually find a very nice distinction although the  
10 sample size is not sufficient, but if I bridge it  
11 with a double tympanocentesis study, then, this  
12 drug should not be approved for macrolide-resistant  
13 or penicillin-resistant pneumococci in the States  
14 why it was approved.

15           [Slide.]

16           Now, if I take the Hemophilus versus  
17 pneumococcus data for 3 days, 1 day, this is  
18 post-treatment, this is EOT, this is after 28 days,  
19 and you can see that there is a difference between  
20 Strep pneumoniae and Haemophilus influenzae, the  
21 same here, the same here.

22           Again, take those here, and I show 3 days  
23 pneumococcus 94 percent, excellent; one day  
24 pneumococcus, about the same. It is not a  
25 comparative study between those two, so I am not

1 sure that you can deduce anything with the  
2 difference especially that it's a small size, but  
3 it might be that there is a difference between one  
4 day, but they are excellent, both of them are  
5 excellent.

6           This is Hemophilus 3 days, this is  
7 Hemophilus 1 day. I think again, what they showed  
8 basically is that for pneumococcus, they get an  
9 excellent drug, if it is not pneumococcus that is  
10 macrolide resistant; for Hemophilus, in my opinion,  
11 it should not be approved because it falls into the  
12 placebo range.

13           [Slide.]

14           The next to last question is how do double  
15 tap studies help in understanding the best timing  
16 for clinical outcome?

17           We heard end of treatment versus test of  
18 cure.

19           [Slide.]

20           You remember this? Basically, you have  
21 still a way to go until here, and we heard about  
22 the otitis-prone children, and many of these  
23 children are otitis prone, so what happens here?

24           The FDA elected until now to look at test  
25 of cure here, and if there is a clinical relapse,

1 to put it as a failure. What we have documented,  
2 and again, about 800 kids we have positive culture  
3 here, negative here, and we have clinical relapse,  
4 and the question that Scott was asking, do we have  
5 really eradication or it is just a suppression, and  
6 you get it back here.

7 [Slide.]

8 Of those kids, we have 108, of the over  
9 800, that came with a clinical relapse, and we were  
10 able to do a tympanocentesis, 30 tympanocentesis,  
11 and see what happens compared to the previous bugs.

12 In 20 percent of the clinical relapse,  
13 there was culture negative. In 54 percent, it was  
14 totally new infection with a different bug. That  
15 means, and I will tell you a second what it means.  
16 Only in 28 percent, it was a different organism.

17 So, the real bacteriological relapse was  
18 only 28 percent, the majority just reflected the  
19 child's otitis-prone nature.

20 Even if you had a pneumococcus that was  
21 replaced by a pneumococcus, when you do serotypes,  
22 you find that the majority are not the same  
23 pneumococcus. If Hemophilus is replaced by  
24 Hemophilus, the majority is not the same  
25 Hemophilus, so even if it's the same organism, sort

1 of, it is not the same, it's a new infection.

2 So, definitely, what I can say, that if  
3 you think about EOT versus TOC, definitely, what  
4 reflects more is EOT and not TOC, and I think this  
5 should be taken into consideration. Again, without  
6 the double tympanocentesis, you cannot determine  
7 the third one, of course.

8 [Slide.]

9 The last question. Are the patients that  
10 are studied in double tap studies different than  
11 those in purely clinical studies?

12 Because the question is how can we  
13 extrapolate from them, and my question is do we  
14 need to extrapolate from them, and I will tell you  
15 why I ask this.

16 [Slide.]

17 First of all, yes, they are different. As  
18 Scott alluded a little bit to you, in order to be  
19 able to get kids for double tympanocentesis, they  
20 usually have to be less than 2 years. Older kids  
21 are less cooperative despite the nice kid that Mike  
22 was showing. I believe this child was deaf,  
23 because you heard all those things about the  
24 tympanocentesis, and he was smiling.

25 [Laughter.]

1           Tympenic membrane bulging plus pus is not  
2 the rule for every single child with otitis, but  
3 these are the ones that we take really to  
4 tympanocentesis.

5           Positive culture, you only take the ones  
6 with positive culture, and also, as Scott said,  
7 they are enriched for more complex acute otitis  
8 media, so, of course, they are different kids than  
9 the rest, but in my opinion, these are the ones who  
10 need antibiotics.

11           You cannot extrapolate to the majority of  
12 kids that get antibiotics because those are diluted  
13 by older kids, mild disease, those who don't have  
14 otitis at all, and other things, and if I have to  
15 really say I don't want them to reflect what is  
16 usual to get patients given antibiotics, I want  
17 them to reflect the ones that need antibiotics, and  
18 I think therefore, these are the appropriate  
19 patients to study despite that they don't reflect  
20 the rest.

21           [Slide.]

22           So, in conclusion, double tap studies  
23 clearly demonstrate a considerable difference  
24 between drugs in regard to their ability to  
25 eradicate the pathogens with 3 to 5 days.

1 Double tap studies can determine an MIC  
2 concentration cutoff above which a given drug is  
3 not bacteriologically efficacious.

4 Bacteriologic eradication within 3 to 5  
5 days and clinical outcome correlate.

6 [Slide.]

7 Double tap studies demonstrate that  
8 Haemophilus influenzae is an important pathogen in  
9 otitis media.

10 We can bridge between double tap studies  
11 and studies with clinical outcome.

12 Double tap studies help in understanding  
13 that the best timing for clinical outcome  
14 determination is EOT rather than TOC.

15 The patients that are studied in double  
16 tap studies are those who need antibiotics more  
17 often than patients enrolled in purely clinical  
18 studies.

19 DR. RELER: Thank you very much, Dr.  
20 Dagan, for a succinct, focused delivery and an  
21 early arrival.

22 I should like to have our 10-minute break  
23 now. We will begin promptly at 10:50.

24 [Break.]

25 DR. RELER: Dr. Marchant.

1                   Limitations of Clinical-only Studies

2                   Colin Marchant, M.D.

3                   DR. MARCHANT: Good morning. First of  
4 all, I would like to thank Dr. Soreth and her  
5 colleagues for inviting me and for allowing me to  
6 speak.

7                   I have spoken several times before and I  
8 am not going to repeat all of that, but perhaps  
9 take it a little bit further. As you can see, I am  
10 from Boston University, and the teaching hospital  
11 affiliated with Boston University is Boston Medical  
12 Center.

13                   We have had a number of talented chief  
14 residents, but one in particular had an unusual  
15 talent. He was an amateur cartoonist, and during  
16 grand rounds, conferences, meetings, he will sit  
17 with a piece of paper and draw cartoons pertinent  
18 to what is going on.

19                   On a morning like this if he were in the  
20 audience, he would have at least six cartoons  
21 floating around the audience making cryptic  
22 comments about what had gone on.

23                   So, I am fortunate to have some of his  
24 cartoons and I am going to use them loosely as a  
25 metaphor as we talk about some of these things.

1 [Slide.]

2 Here is his first cartoon. Some people  
3 can't see the forest for the trees.

4 [Slide.]

5 The next cartoon, some people can't find  
6 either the forest or the trees. Maybe the cell  
7 phone will help.

8 [Slide.]

9 Some people get lost in the forest.

10 [Slide.]

11 And some people find a path through the  
12 forest, and it is our task to find a path through  
13 the forest here, of all this data and all these  
14 ideas, all these concepts, et cetera.

15 [Slide.]

16 This is the slide that Dr. Dagan already  
17 showed you. What is important about this earlier  
18 was raised the question what is the correlation  
19 between bacteriologic outcome and clinical outcome.

20 Well, the answer, we have facts. We have  
21 two studies, and they both came up with the same  
22 answer. It may not be the correlation you wanted  
23 to see, but this is what the data shows, and in  
24 addition to the comments and the details that Dr.  
25 Dagan mentioned, the importance of this data is

1 that it validates the bacteriologic outcome. The  
2 bacteriologic outcome would not be important if it  
3 didn't result in a better clinical outcome when you  
4 kill those bacteria, eliminate them from the site  
5 of infection compared with when you don't.

6 [Slide.]

7 This data, specifically the Carlin data,  
8 but the Dagan data could be used in the same way,  
9 leads us to the Pollyanna phenomenon where  
10 excellent drugs look worse than they are, and poor  
11 drugs look better than they really are, and then  
12 that shows us that there is a very narrow  
13 difference at the clinical efficacy level between  
14 one drug and another.

15 [Slide.]

16 That leads to the next issue, which is the  
17 sample size issue if we do the double  
18 tympanocentesis, we don't need a lot of patients.

19 Notice, this is in thousands. If we do a  
20 single tympanocentesis with a clinical outcome, we  
21 have trouble telling the difference between a 90  
22 percent effective drug and 70, we are getting near  
23 2,000 patients here, and if we do clinical-only  
24 studies, then, at this end of the graph, we can't  
25 really do a study of 15,000 or so patients or

1 particularly to see fine differences, but we even  
2 need hundreds or thousands of patients just to do  
3 that.

4 [Slide.]

5 The next issue that comes from this same  
6 data is the issue raised by Dr. Giebink, and that  
7 is, he said that because there is so many millions  
8 of children treated with otitis, we need to think  
9 about it because there is just such a large number,  
10 and this data allows you to calculate what that  
11 burden is with various levels of bacteriologic  
12 efficacy, and obviously, the perfect drug, there  
13 aren't going to be any children who have persistent  
14 symptoms on days 3 to 6 who otherwise would have  
15 been better, but even at 90 percent, there is going  
16 to be 20,000 per million, 60,000 per million,  
17 100,000 per million, 140,000 per million, and so  
18 this data allows us to put some numbers of what is  
19 the cost of not finding out whether a drug is  
20 efficacious or not efficacious.

21 [Slide.]

22 So, I am going to cover some design  
23 issues. I have put up here that they are all  
24 important, yes, they are all important. This is  
25 just my preference, order of the day, if you will,

1 but they are all important.

2           In the IDSA guidelines, they covered these  
3 general issues, that trials should be randomized,  
4 double-blind, should measure compliance, et cetera,  
5 et cetera, but the place that the guidance has  
6 fallen down, in my judgment, is where the issues  
7 are otitis media specific, which means you have to  
8 go to the data on otitis media to get properly  
9 designed studies for industry.

10           I noticed in Dr. Powers' talk that  
11 statistical issues will be talked about later, but  
12 I say you can't divorce yourself from the  
13 statistical issues, you can't divorce yourself from  
14 the sample size issues because the sample size is  
15 so affected by the outcome, because the sample  
16 size, in fact, is affected by the patient selection  
17 factor, and the sample size, if you use poor  
18 diagnostic criteria and put a lot of non-otitis, we  
19 saw Dr. Pichichero's illustrations, it is really  
20 not always easy if we don't have good diagnostic  
21 criteria, then, we will also drive up the sample  
22 size, decrease the power of our trials, so even  
23 when we spend time talking about these, they all  
24 have sample size statistical implications, and we  
25 can't get away from them.

1 [Slide.]

2 So, I am going to talk in the next few  
3 slides about four trials designs - a double tap, a  
4 tap at entry to the trial where you then do a  
5 tympanocentesis on the clinical failures, a tap at  
6 entry with clinical outcome only, and then clinical  
7 criteria at both entry and by outcome.

8 [Slide.]

9 This is just for reference because these  
10 slides are in your handout or end up on the web  
11 site or what have you. These are the statistical  
12 parameters used in the tables that I am going to  
13 show you.

14 Here, in this table, I am showing you if  
15 we compare a drug that is very good, 90 percent  
16 bacterial efficacy versus tap water or placebo at  
17 30 percent, we look at the number of patients we  
18 have got to recruit, the number of taps we are  
19 going to do, the number of patients that we  
20 analyze.

21 At this lowest level, we see that the  
22 double tap study shows us was small numbers, but  
23 also notice that amongst the three studies with the  
24 tap designs, we also do fewer tympanocenteses.  
25 Yes, they are repeated on the same children, but

1 actually is fewer tympanocenteses that are done.

2 [Slide.]

3 Now if we do these calculations for a poor  
4 drug, the numbers are going to rise in each column.  
5 We are now close to 100 with the double tap study.  
6 We are close to 300 with a tap and tap of failures,  
7 we are already over 1,000 with the clinical  
8 outcome.

9 This relationship remains the same, fewer  
10 tapes in the double tap than the tap and tap of  
11 failures and respectively the initial tap only.  
12 Then, when we get up to a 20 percent difference,  
13 and that is equivalent to 40,000 children per  
14 million remaining symptomatic at the time of this  
15 second tap, who otherwise would have been better,  
16 that difference is going to take you near 300, near  
17 1,000, and up at 4,000.

18 [Slide.]

19 So, sample size clearly depends on the  
20 outcome, the population, even diagnostic criteria,  
21 and the minimal standard should be that the trial  
22 is large enough to have shown that an antibiotic  
23 that was no better than placebo, that it, in fact,  
24 was efficacious, so the sample size should really  
25 be that large.

1           Let's think of the high jump. In the high  
2 jump, you jump over a bar. If you jiggle the bar  
3 and it shakes, it may fall off. When you do a  
4 trial, you would like to be jumping over the bar,  
5 but, in fact, most of the trials have been ducking  
6 under the bar. When you look at the result, the  
7 bar is still standing, but you didn't jump over it,  
8 you ran under it.

9           [Laughter.]

10           In the November 11th meeting, people went  
11 under the bar. So, how large should it be? I am  
12 suggesting that perhaps a 20 percent difference in  
13 bacteriologic efficacy might be the standard. So,  
14 we need to move on. We need to find a path through  
15 the woods, if you will, so we need some recommended  
16 guidance for industry, so I am going to propose  
17 some for consideration in the sample size area.

18           [Slide.]

19           One of the main, as I look back at  
20 previous guidance, at the IDSA guidelines, et  
21 cetera, one of the big problems has been that  
22 guidance was based on general principles, on expert  
23 opinion, and not by going back and saying what does  
24 that data say, what does the best data tell you  
25 about how the disease behaves.

1           Sample sizes, if you are going to  
2 calculate them, should not be based on assumptions  
3 or expert judgment, but based on data, and there is  
4 data in the literature that you can use from  
5 previous trials to make more informed projections  
6 of how you base your sample size.

7           I have already said that we need to at  
8 least exceed the tap water standard proposed the  
9 40,000 children is what we should look at, and we  
10 also need to consider the power of subgroup  
11 analyses for specific pathogens if we want to look  
12 at those.

13           Previous guidance, the 1998 one had I  
14 think arbitrary 25 pneumos, 25 Hemophilus, 15  
15 Moraxella. Where do these numbers come from, how  
16 are they powered, what is the chance of showing  
17 them, are they going to show anything by looking at  
18 those?

19           [Slide.]

20           So, now let me shift to the outcome,  
21 which, of course, is linked to sample size, but the  
22 outcome should be directly meaningful like is the  
23 child better at 72 hours or 48 hours, as used in  
24 the Pittsburgh Kaleida study. That is a meaningful  
25 outcome, and the bacteriologic outcome is only

1 meaningful because it has been validated by the  
2 data I showed you earlier, the data Ron showed you,  
3 the data that Scott showed you earlier.

4           The outcome should be objective or at  
5 least reproducible. The outcome should be  
6 sensitive, that is, it has to be an outcome that is  
7 affected by antibiotic therapy, and there is data  
8 in the literature to tell you what outcomes have  
9 been affected by antibiotic therapy, and it should  
10 be timely. You have got to measure it at the time  
11 point when it is, according to the data, affected  
12 by antibiotic therapy.

13           So, we have already pushed back the test  
14 of cure thing as being incorrect. We are now  
15 getting closer to the end of therapy, and the end  
16 of therapy guideline appears to me that it came  
17 from the general guidance in the IDSA  
18 recommendations or guidance, and not otitis  
19 specific, but just as a general principle that it  
20 is at the end of therapy that we are interested in,  
21 but many of the outcomes in otitis media, in fact,  
22 happen earlier, and if we are going to actually  
23 measure them, we need to measure them when they  
24 happen, and not at some time later. I have already  
25 been vigorous in looking at that issue.

1 [Slide.]

2 So, if we take the four designs--your  
3 handout is incorrect here, it is incorrect here, as  
4 well, and this should read increases as you go from  
5 double tap to clinical outcome, the sample size  
6 increases--but the other important point is we get  
7 more information as we climb this order.

8 Dr. Dagan has showed you that if you do  
9 double taps, you can find out what MIC it takes to  
10 or what the relationship is for a specific drug and  
11 organism and MIC. Pathogen eradication rates, you  
12 can only get those if you tap the ears, and then  
13 there is the emerging area of PK/PD data, and that  
14 has become clinically relevant because Dr. Craig  
15 correlated the double tap outcome studies with the  
16 serum concentrations and MIC's of organisms, and  
17 Dr. Jacobs, in the public session, I believe is  
18 going to amplify that.

19 So, one of the values of going up this  
20 hierarchy is that we find out more, it teaches us  
21 more, it will help us go in better directions to  
22 manage these children.

23 [Slide.]

24 So, here are the recommendations I would  
25 make. We should do double tap studies, and they

1 are preferred for the reasons that I have just  
2 mentioned, and a tap and tap of clinical failures  
3 is an alternative that if large enough, will also  
4 provide useful information.

5           If clinical outcome studies are going to  
6 be done other than symptomatic response, which, of  
7 course, will require thousands and thousands of  
8 patients, we need to use outcomes that are  
9 validated, that are against the clinical response  
10 to the clinical outcome.

11           [Slide.]

12           I didn't spend a lot of time on that, but  
13 this was mentioned. Dr. Dagan mentioned it, what  
14 should we say we should do for the recommended  
15 guidance on population selection and enrichment.

16           It is these enriched populations, the  
17 young, those that fail treatment, those with prior  
18 antibiotic therapy in daycare, that are most  
19 challenging, and we need data. Clinicians want to  
20 have data on how our drugs behave in those groups.  
21 We should include those, not exclude them.

22           [Slide.]

23           Diagnostic criteria, I am just throwing  
24 these up into the mix. Yes, they should be  
25 symptomatic otitis because that's our goal, is to

1   relieve those symptoms.  Yes, we should use some  
2   good diagnostic criteria, the kind that have been  
3   championed by Dr. Paradise and others, and the  
4   other issue that Dr. Soreth has raised, that some  
5   folks doing these studies bat 80 percent and some  
6   bat 20 percent on their bacterial isolation rate,  
7   and those batting 20 percent, we are not sure what  
8   disease they are studying most of the time, and we  
9   would want to do better.

10           [Slide.]

11           I have deliberately left the ethical  
12   issues until later because I think if we are going  
13   to stay out of the woods, we have to think through  
14   the science first and then ask the ethical  
15   questions, because the ethical questions aren't  
16   show-stoppers.

17           If the ethical questions were so large, we  
18   wouldn't even go here, but they are not that large,  
19   they are important, but they are not show-stoppers.  
20   So, think through the science first, we will get  
21   further, and then let's move on to the ethics, and  
22   there is more than one ethical question, there is  
23   broad ethical questions, as well as focused ones.

24           Of course, is it ethical to perform  
25   typanocentesis, is it ethical to perform double

1 tympanocentesis? Those are two important  
2 questions, but these other questions are important  
3 also.

4           Is it ethical to license, market and  
5 prescribe drugs without knowing that they are  
6 efficacious? Is it ethical to duck under the bar?  
7 Is it ethical to perform drug trials in humans that  
8 will not yield scientifically valid data? I  
9 suggest no, they aren't.

10           With regard to tympanocentesis, the  
11 question in part is, well, the question about the  
12 ethics of it, we haven't really heard from anybody  
13 that there is a significant permanent damage.

14           Dr. Pichichero talked to you about the  
15 case of the blood behind the eardrum for a week  
16 that made him nervous, but healed. It appears to  
17 be a fairly safe procedure, and every day in our  
18 country, otolaryngologists do a more extensive  
19 procedure. They put tympanostomy tubes in the ear,  
20 which stay there for months. They perforate the  
21 eardrum, and although there are issues of scarring,  
22 and so forth there, many eardrums heal and  
23 tympanocentesis is very much a lesser procedure  
24 than that.

25           So, it is primarily the pain of

1 tympanocentesis that is the objection here.

2 [Slide.]

3 So do the benefits outweigh the risks? I  
4 believe this to be true, and therefore, I believe  
5 that the benefits of the knowledge gained from  
6 properly done studies that are going to give us  
7 answers, do outweigh the risks.

8 That, of course, is a judgment. However,  
9 tympanocentesis is still a painful procedure, and  
10 in order to move guidance for industry forward, in  
11 order to move forward clinical trial design and to  
12 get it right, to see a path out of forest and not  
13 stay back in the woods, we need to do something  
14 else, and that is we need more efforts to find ways  
15 to make this procedure less painful and less  
16 objectionable.

17 Currently, it has been pointed out that  
18 many practitioners don't do tympanocentesis, and  
19 this is true, it is really a very small number of  
20 people that do this procedure, many more could, but  
21 when something is not familiar with people, they  
22 tend to fear it and many of the objections to  
23 tympanocentesis come from those who are really not  
24 that familiar who fear it, who aren't experienced,  
25 not solely, but in many cases. We have more work

1 to do to do that.

2           So, in summary, then, I offer up for  
3 consideration some, not a complete list, it doesn't  
4 cover all the issues, but some things that we  
5 should offer as a guidance for industry.

6           One last comment. Dr. Soreth mentioned  
7 the problem where you have to be worried about  
8 making these things too expensive for industry, and  
9 I think that's right, but the first and foremost  
10 duty we have really is the public, and in this  
11 case, the public is the children, and it's all  
12 about how many have ear pain as a result of what  
13 our decisions are.

14           That is what we need to do first.  
15 Industry, they are business people, and what they  
16 do is they negotiate. That is very much part of  
17 their culture and part of what goes on in business.  
18 So, when they tell you it's too many, it's too  
19 much, it's too expensive, that is part of their  
20 negotiating position.

21           So, you need to judge them by their  
22 behavior, and when they stop coming around  
23 proposing new drugs for otitis media, then, we will  
24 know that we have gone too far in coming to high  
25 standards, which are going to get us the data that

1 will help us make clinical decisions and  
2 license-effective drugs for this indication.

3 Thank you.

4 DR. GIEBINK: Colin, could I ask a quick  
5 question of fact here? Okay. On your first  
6 recommended guidance slide, the last bullet says,  
7 "If clinical outcomes other than symptomatic  
8 response are to be used as outcomes, they should be  
9 validated."

10 Do you mean externally validated,  
11 internally validated, validated against tympano? I  
12 just would like a definition for that word.

13 DR. MARCHANT: Let me give by example. If  
14 you were to propose acoustic reflectometry or  
15 tympanometry, or the appearance of the drug on  
16 otoscopy as important outcomes, then, those  
17 important outcomes have to relate back to what the  
18 child care is about, which is whether it hurts or  
19 not, just as the bacteriologic outcome has been  
20 shown to be important in terms of whether there are  
21 persistent symptoms or not, that is the validation  
22 that I would be speaking about there, or any other  
23 new measure that somebody came up with.

24 DR. RELLER: Dr. Soreth.

25 DR. SORETH: Very briefly, a point of

1 clarification for Dr. Marchant. I did not say that  
2 we need to be worried about the cost, but rather  
3 cognizant that any particular set of  
4 recommendations for clinical trial design has  
5 implications at the end of the day for cost, and it  
6 is just one of many, many factors that are taken  
7 together as we are all on the same page about  
8 caring for the public, in this case, caring for  
9 children who have acute otitis media, and that at  
10 times, not necessarily for otitis, but that at  
11 times, one can conclude that a set of  
12 recommendations in the ideal world are best, but  
13 that in the practical world, sometimes cross some  
14 line of practicality and doability.

15           That was really my only point, that in  
16 some measure, it is also part of the overall  
17 complex equation of what can be done, should be  
18 done in an ideal world or in the real world, and  
19 that was my only point.

20           DR. MARCHANT: I didn't mean to put any  
21 words in your mouth, and really, what I did, was I  
22 extended the issue that you raised with my own view  
23 of it is what I did.

24           DR. RELLER: Dr. Rochester will present  
25 for the FDA, Study Designs for Acute Otitis Media

1 Trials: What Can Each Design Tell us?

2 Thanks, Dr. Marchant. We will have much  
3 discussion later on all of the important issues  
4 raised and perspectives given.

5 Study Design for Acute Otitis Media Trials:

6 What Can Each Design Tell Us?

7 C. George Rochester, Ph.D.

8 DR. ROCHESTER: I am George Rochester. I  
9 am a mathematical statistician in the Division of  
10 Biometrics III, and I am co-located with Division  
11 of Anti-Infective Drug Products.

12 The purpose of my talk today is to discuss  
13 the topic briefly, study designs for acute otitis  
14 media, and what can each design tell us.

15 I would like to begin with just a couple  
16 of opening works in the sense that when we start  
17 thinking about acute otitis media, as well as any  
18 other kind of infectious disease, we must have some  
19 clarity about what exactly is the question that we  
20 want to answer with our study.

21 Until we have clearly articulated our  
22 hypotheses and ensure that we are going after the  
23 correct populations that we are studying, we tend  
24 sometimes to go amiss in terms of the value and  
25 interpretation of what we get out of each study.

1 So, I want us to bear that in mind as I move  
2 through these.

3 [Slide.]

4 The outline of my talk essentially will  
5 address three main areas. One will be the role of  
6 tympanocentesis, which I abbreviate as TAP, and  
7 will speak of as TAPS in acute otitis media trials,  
8 and then advantages and disadvantages of each  
9 design, and I will speak primarily of two types of  
10 designs, the superiority design in which we will  
11 refer to placebo-controlled, and the  
12 non-inferiority design, which has been the design  
13 that we have used mostly in the last probably  
14 decade or so.

15 [Slide.]

16 Acute otitis media represents a spectrum  
17 of illness, and I think that has been nicely  
18 described by other speakers already. In order to  
19 demonstrate the efficacy of a new drug, one needs  
20 to provide both clinical and microbiological proof  
21 of efficacy.

22 We must be cautious. We need to guard  
23 against post-hoc subset analyses as proof. We have  
24 all been confronted with a situation where at the  
25 end of a trial, when our data has been analyzed, we

1 get this kind of ah, oops, I think I should revise  
2 my protocol here in order to restate my hypothesis  
3 for what I wish I had studied now that I have found  
4 something.

5           We have seen where people do become very  
6 enthusiastic and very excited because we have seen  
7 something that looks really wonderful in a small  
8 group of patients that we didn't otherwise  
9 anticipate when we started the trial.

10           I get excited about that, accept that in  
11 the context that that generates a new hypothesis  
12 that I would like to see studied in a future trial.  
13 It may offer certain important reassuring  
14 information, but it is not enough for me to call it  
15 solid clinical or microbiologic proof.

16           Then, we want to also guard against  
17 extrapolating to populations not directly studied.  
18 In the era of evidence-based medicine, where we  
19 want to really provide a good, solid foundation  
20 upon which to make medical decisions, it is  
21 imperative that we understand that having completed  
22 a study, having generated the data, that we are  
23 very careful when we make extrapolations to  
24 populations we did not actually study.

25           Now, those extrapolations need to have

1 solid scientific pinnings and underpinnings for  
2 what we are doing. The temptation is very easy to  
3 just say, well, we have studied, you know a group  
4 of children from age 5 to 12, and that's just as  
5 good for the ones that are under 2, I don't see any  
6 reason why not, pain is pain, and so on, and so on.

7           These generalizations, really, one needs  
8 to be careful and very cautious about that.

9           [Slide.]

10           The current state of affairs, what is the  
11 evidence that we are getting now, that we are  
12 looking at in terms of a dossier for registration.  
13 We tend to get a clinical-only study, comparative  
14 in nature, non-inferiority in design, in which we  
15 are comparing a new versus a standard therapy.

16           Dr. Dagan's statement, this actually  
17 nicely concurred with our thoughts on this, back  
18 and at the November 2001 Advisory Committee, where  
19 he said, "Most of the acute otitis media trials  
20 with clinical outcome as currently conducted are  
21 virtually guaranteed to show no differences between  
22 agents, dosing, or duration of treatment."

23           I would like us to think about this within  
24 the context of Dr. Marchant's ethical framework  
25 that he just provided, that if we are going to make

1 a study in which we really do not have a real high  
2 probability of successfully answering our question,  
3 that may call into question our ethics in human  
4 trials.

5           Then, we get another study, which is a  
6 baseline bacteriology study, some baseline  
7 bacteriologic information at study entry, followed  
8 by a clinical outcome at some later time point,  
9 usually at end of therapy or at some test of cure,  
10 which we might agree on should be different.

11           That is often non-comparative although not  
12 required to be non-comparative, but we often see  
13 that people take the path of least resistance.

14           [Slide.]

15           Why do some trials fail to detect  
16 differences among treatments? Well, for one,  
17 differences among these different treatments may,  
18 in fact, truly not exist. These drugs probably are  
19 not different.

20           We also may have the issue of "noise," and  
21 noise in statistical jargon probably means kind of  
22 all these things that are confounders that you are  
23 probably not controlling very well, things you are  
24 not measuring very well, imprecision in terms of  
25 how you are carrying out your study.

1           Sources of noise in AOM studies include  
2 enrollment of subjects without bacterial infection  
3 at baseline, an example, they have got viral  
4 infection, or they probably just have some sort of  
5 situation in which, for example, effusion leads to  
6 diagnostic confusion.

7           We have got loose case definitions. We  
8 have seen a situation where you have spontaneous  
9 resolution even with a bacterial infection, and we  
10 have just heard about the tympanocentesis, for  
11 example, that it, in and of itself, has some  
12 therapeutic value.

13           So, we are not even sure, that we may go  
14 in, perform a TAP, pull out fluid. We have nicely  
15 cleansed this nice little pocket of pus, and maybe  
16 that, in and of itself, has some clinical benefit  
17 to the extent that we are now attributing that  
18 benefit to a drug, I am not sure.

19           Determination of treatment response  
20 includes both subjective components, as well as  
21 objective components, but the subjective  
22 components, in fact, may be subject to significant  
23 inter-rater variability.

24           So, strategies for handling noise would  
25 include designing placebo-controlled trials, and

1 for differences observed in the placebo-controlled  
2 trial, we know that we can say we have demonstrated  
3 a clinical benefit.

4 We may also have a non-inferiority trial  
5 in which we could have either a baseline TAP, which  
6 reduces noise in terms of at the diagnostic phase,  
7 and we may have a repeat TAP, which actually  
8 reduced some noise, as well, in terms of our  
9 outcome assessment.

10 [Slide.]

11 Should TAPS be performed? I think we have  
12 heard many other speakers address this issue.

13 Placebo-controlled trials, in general,  
14 will provide clear evidence of clinical benefit,  
15 but if you add TAPS to a placebo-controlled trial,  
16 then, it does add efficiency to the trial.

17 Baseline TAP is probably a little bit more  
18 critical if we are thinking of the non-inferiority  
19 design where "noise" sometimes may lead to a false  
20 proof of efficacy.

21 Then, a follow-up TAP in which we have  
22 bacteriologic outcome becomes more objectively  
23 determined.

24 The optimal time and number of TAPS to  
25 perform may need further research. I have heard

1 several speakers may use timing of day 3 to 5, some  
2 people say day 4 to 6. We do know that if we tap  
3 probably too early, it may not be as helpful to  
4 differentiate differences between drugs; if we tap  
5 too late, it may not be ethical, the children are  
6 actually cured, their fluid has gone away, they are  
7 fine, they are happy, and so on. People do not  
8 feel that may be a good to tap.

9           However, tapping all failures has always  
10 been encouraged, it seems, in all the guidances I  
11 have read, however, there is also a difference  
12 between clinical trial and clinical practice.

13           What I have seen in a lot of the studies  
14 that come to us for review, is that physicians  
15 sometimes forget the difference between practice  
16 and a trial. A clinical trial is an experiment in  
17 which a protocol has been designed and agreed to,  
18 and should be followed.

19           It ensures uniform documentation and it  
20 ensures that we can interpret our data with a  
21 certain rigor. In clinical practice, however, a  
22 patient appears to a health care provider for care,  
23 and that care means that physician has a wide  
24 latitude of discretion in the way the patient is  
25 ultimately managed.

1           If, in a trial, you have a protocol and  
2 the investigators are not following the protocol,  
3 it actually becomes very difficult in order to  
4 really interpret and understand the information.

5           [Slide.]

6           A single TAP at baseline. You have got  
7 bacteriological diagnosis and a clinical outcome  
8 assessment, that is the standard trial we have been  
9 talking about in a non-inferiority setting.

10          The baseline TAP ensures that patients in  
11 the primary analysis have baseline pathogens. It is  
12 better than having no TAPS, but the bacteriological  
13 outcome is presumptive if we are going on a  
14 clinical outcome assessment to determine success or  
15 failure.

16          In practice, failures do not usually get  
17 follow-up TAP regardless of what the protocol  
18 specification is. A non-inferiority with baseline  
19 TAP may allow a wider non-inferiority margin which  
20 leads to a smaller sample size, and Dr. Marchant  
21 did speak about sample size actually quite nicely,  
22 so I won't go further into that.

23          [Slide.]

24          Repeat TAPS provide objective  
25 bacteriological outcome. Blinding in this

1 situation is not as critical for the bacteriologic  
2 endpoint, but it is essential to reduce bias during  
3 study if the clinical outcome is the ultimate goal.

4 Study is successful, though, if efficacy  
5 is shown at both the microbiological and the  
6 clinical assessment time points.

7 [Slide.]

8 Fundamental question regarding the utility  
9 of a microbiological endpoint. Bacteriological  
10 endpoint is a surrogate and the correlation with  
11 clinical endpoint sometimes may be less than  
12 satisfactory given current data.

13 So, I think until we are really certain of  
14 whether or not we can truly predict the clinical  
15 course or the ultimate clinical outcome of this  
16 patient from the bacteriologic data, bacteriologic  
17 endpoint, then, it needs to be seen as probably a  
18 co-primary kind of information with the clinical  
19 outcome.

20 I am not sure if we are at the point in  
21 the literature where we can say we can substitute  
22 one for the other.

23 Much uncertainty still remains about the  
24 bacteriological endpoint.

25 [Slide.]

1           The Agency for Healthcare Research Quality  
2 Evidence document, published in 2001: Management of  
3 Acute Otitis Media, makes the following quote that  
4 I find very useful:

5           "There is still a need to adequately  
6 address the role of antibiotics in the initial  
7 treatment of acute otitis media in children  
8 compared to placebo or observational treatment  
9 especially in terms of various influencing factors  
10 such as age and otitis-prone status.

11           "Close monitoring of patients in these  
12 studies with a priori plans for appropriate  
13 intervention should allay any concerns about  
14 suppurative complications and should also be a  
15 focus of research."

16           So, when we are talking about any trial in  
17 a pediatric population, children fall within a  
18 group that we consider vulnerable populations who  
19 deserve significant additional protections.

20           So, whether you are doing a  
21 placebo-controlled trial or a non-inferiority  
22 trial, it is important that we have an ethical  
23 framework, such that children are monitored  
24 carefully and all strategies that are important to  
25 protect them from any harm is actually in place and

1 followed.

2 [Slide.]

3 The randomized, double-blind,  
4 placebo-controlled trial is kind of what I am  
5 thinking of when I say placebo-controlled trial,  
6 and that is the gold standard. It is efficient and  
7 easy to interpret, it provides direct evidence. We  
8 may consider a three-arm trial in which we have a  
9 new drug, a standard drug, and a placebo.

10 We want to have certain features of  
11 blinding, randomization, all of which ensure that  
12 we are minimizing the bias that can be present  
13 during study conduct, and, of course, the placebo  
14 helps in terms of giving us direct estimate of the  
15 treatment benefit, and the placebo-controlled  
16 information is what becomes the scientific  
17 foundation on which to plan future trials.

18 [Slide.]

19 So, advantages and disadvantages are that  
20 the placebo-controlled trial will provide clear  
21 evidence of a clinical benefit. If TAPS are added,  
22 it will improve the efficiency of the trial and  
23 provide direct bacteriological information and  
24 obviously may help with a smaller sample size than  
25 a non-inferiority design. Once we add TAP into the

1 design, it also improves upon efficiency of one  
2 that wouldn't have had a TAP.

3           A disadvantage would be that one treatment  
4 group is untreated, and that could be taken two  
5 ways. You may say one group did not get treated,  
6 they ultimately could have not reaped the benefit  
7 that it could have otherwise had if it turns out to  
8 be useful, but they also were not exposed to any of  
9 the toxic effects that they could have experienced  
10 on drug, so to some extent, that could be an  
11 advantage or a disadvantage. If no TAPS are done  
12 in the placebo-controlled trial, certainly an  
13 additional microbiological study would be necessary  
14 and preferably in a comparative study.

15           [Slide.]

16           Non-inferiority trials. You are comparing  
17 a new drug against a standard. Your estimate of  
18 the treatment benefit will depend intricately upon  
19 knowing the benefit of the standard over placebo.

20           Efficacy here is indirect and is  
21 demonstrated only if we actually knew that the  
22 control itself would have had a benefit over  
23 placebo. The choice of non-inferiority margin will  
24 depend upon microbiologic rigor, as well.

25           [Slide.]

1 Advantages of this one include  
2 acceptability, all patients get treated, so parents  
3 probably may sign up for this one more readily. It  
4 does provide some comparative clinical information.

5 But I couple of the disadvantages I want  
6 to point out are that bacteriologic infection may  
7 not clearly have been established at baseline if  
8 you have no baseline TAPS, and over time, the  
9 magnitude of the initial benefit of the control may  
10 not be maintained.

11 So, this one may not give us real good  
12 assurance that the new drug could actually beat  
13 placebo.

14 [Slide.]

15 In a non-inferiority design with a  
16 baseline TAP added, then your additional advantages  
17 would be that you have better microbiologic  
18 diagnosis, setting your non-inferiority margin  
19 becomes a little bit easier, but a clear  
20 disadvantage is that determination of efficacy is  
21 still indirect and relies upon clinical judgment,  
22 because the outcome is being measured as a clinical  
23 response.

24 [Slide.]

25 Certainly, with a repeat TAP, we now can

1 assess two endpoints. We can assess a delta for a  
2 micro, which is our overall microbiologic response,  
3 we can assess for clinical response, and certainly  
4 a combination of clinical and micro endpoints would  
5 be what we would call a successful trial.

6 [Slide.]

7 So, which design to use? If you want to  
8 demonstrate absolute efficacy, and a  
9 placebo-controlled is your design, if you want to  
10 demonstrate absolute and relative efficacy, then  
11 you can consider a three-arm trial in which you can  
12 compare new drug to placebo, new drug to the old  
13 drug. We get relative efficacy and, of course, we  
14 have a placebo arm there.

15 Now, if the magnitude of the advantage of  
16 the active control over placebo is known for the  
17 primary endpoint, then, we could consider a  
18 non-inferiority design, and the ICH E-10 gives us  
19 some advice probably on how to consider setting  
20 those non-inferiority margin.

21 The basis idea is be conservative if our  
22 historical information is poor or if it is not  
23 relevant. Do not extrapolate beyond the strength  
24 of your data.

25 [Slide.]

1           So, what does each design really tell us?

2           In a placebo-controlled setting, we know  
3 that the new drug beats the control and so it shows  
4 a clear clinical benefit among the patients  
5 studied.

6           If have a non-inferiority design and with  
7 no TAPS, then, all we are saying is a difference in  
8 clinical success rates is less than some  
9 non-inferiority margin  $\delta$  that we set.

10          If we have a baseline TAP, then that  
11 difference is within the  $\delta$ , but with patients  
12 with baseline pathogens.

13          If we have one in which we have repeat  
14 TAPS, then, we have an observable difference in  
15 both a microbiologic endpoint and a difference in  
16 the clinical endpoint.

17          [Slide.]

18          So, in summary, TAPS do improve the  
19 efficiency of AOM trials. Repeat TAPS provide  
20 objective microbiologic information in which to  
21 judge not only the subjects who are successful at  
22 the end, but it also helps us to understand why  
23 subjects are failing.

24          Placebo-controlled trials are efficient,  
25 easy to interpret, provide direct evidence, and the

1 non-inferiority design, microbiologic rigor can  
2 improve the quality of those trials if the benefit  
3 of the standard over placebo is known.

4           Then, we come to the real question, when  
5 we are setting all these studies up, what it is we  
6 really are interested in, is the microbiological or  
7 the clinical endpoint more desirable to patients,  
8 what it is that we really, truly are interested in  
9 at the end of the day? So, bear that in mind as we  
10 proceed with the discussion for today.

11           I just want to thank the other members in  
12 our Division of Biometrics III, who contributed to  
13 this presentation.

14           Thank you.

15           DR. RELLER: Thank you, Dr. Rochester.

16           Dr. Smith. Lessons Learned from Past  
17 Approvals.

18           Lessons Learned from Past Approvals

19                   Thomas Smith, M.D.

20           DR. SMITH: Thank you.

21           In this presentation, I am planning to use  
22 some examples from recent approvals to highlight  
23 specific areas of the current draft guidance where  
24 we have had problems and where we would like to get  
25 the committee's advice as we prepare to make

1 revisions.

2 [Slide.]

3 The current draft guidance speaks of two  
4 clinical trials. The first one of these is a  
5 statistically adequate and well-controlled  
6 multicenter trial that uses rigid case definitions  
7 with specific subjective and objective diagnostic  
8 and effectiveness parameters clearly defined.

9 We have heard from Dr. Pichichero's  
10 presentation and from some of the other speakers  
11 today of some of the difficulties with these rigid  
12 case definitions and the fact that the diagnosis is  
13 not always so easy to make.

14 In these studies, baseline tympanocentesis  
15 need not be performed, and as a result, in fact,  
16 most of the trials that are submitted to us are  
17 clinical-only trials. Tap of failures is strongly  
18 encouraged to document inadequately treated  
19 pathogens.

20 Again, the taps of failures are rarely  
21 performed in studies even though the guidance  
22 recommends it and, in general, the protocols that  
23 are submitted also strongly encourage the tapping  
24 of failures.

25 [Slide.]

1           The second trial is a tympanocentesis  
2 trial. The guidance actually is silent on whether  
3 this trial should be comparative or non-comparative  
4 and, as a result, most of the trials that are  
5 submitted are non-comparative in design.

6           These trials should establish acceptable  
7 outcome in at least 25 patients with Haemophilus  
8 influenzae, 25 patients with Streptococcus  
9 pneumoniae, and 15 patients with Moraxella  
10 catarrhalis.

11           Tap of failures is strongly encouraged.  
12 Again, even though baseline tympanocentesis is done  
13 in this studies, failures rarely get tapped.

14           [Slide.]

15           This is an example from our most recent  
16 approval, which was actually for a labeling change  
17 in which the applicant very closely followed the  
18 recommendations of the current draft guidance and  
19 submitted as the two major trials, a clinical-only  
20 trial and a non-comparative tympanocentesis trial.

21           The clinical-only trial was a  
22 double-blind, double-dummy, randomized trial that  
23 enrolled 350 patients from 9 United States sites.  
24 The ages of the children eligible for the trials  
25 were 6 months to 12 years, and 60 percent of the

1 children turned out to be over 2 years of age.

2 [Slide.]

3 The clinical outcomes from this study are  
4 presented here. I have shown both the end of  
5 therapy and test of cure results. Although the  
6 current guidance uses the test of cure, which is at  
7 day 28 to 32, in this study as the primary outcome,  
8 the committee recently voted unanimously that the  
9 end of therapy clinical outcome was of greater  
10 value.

11 These results are typical of most of the  
12 clinical-only studies in acute otitis media in that  
13 you have high end of therapy success rates, which  
14 are somewhat lower at the test of cure visit. The  
15 other thing to notice here is that there is no  
16 difference between the drugs. There is a  
17 satisfactory confidence interval around the  
18 treatment difference.

19 [Slide.]

20 The second trial submitted as part of this  
21 package as a tympanocentesis trial, which was an  
22 open-label, non-comparative trial with baseline  
23 tympanocentesis. 248 patients were enrolled from  
24 22 U.S. and Latin American sites.

25 The ages of the eligible children were 6

1 months to 12 years, and in this study, 65 percent  
2 of the children were over 2 years of age with a  
3 mean of 3.4 years. Fifty-one percent of the  
4 children who had tympanocentesis had positive  
5 cultures.

6 [Slide.]

7 Clinical outcomes by pathogen are  
8 presented here, and I simply presented them for the  
9 end of therapy visit. The overall success rate at  
10 the end of therapy was 89 percent, which is  
11 consistent with what was seen in the earlier study  
12 that was presented.

13 For the individual pathogens, the point  
14 estimates for successful clinical outcomes ranged  
15 from 71 percent for *Haemophilus influenzae* to 100  
16 percent for *Moraxella catarrhalis*.

17 [Slide.]

18 These data were presented before the  
19 Advisory Committee in November 2001, and there was  
20 a great deal of discussion that was generated.  
21 Much of it centered around the limitations of  
22 clinical-only trials, the fact that you are relying  
23 on a clinical diagnosis of otitis media, and that  
24 this necessarily includes a lot of patients who do  
25 not have bacterial disease.

1           There were issues raised with the  
2 microbiologic data, questions about some of the  
3 point estimates presented and about the  
4 non-comparative nature of this data. There were  
5 comments made also concerning the age distribution  
6 of the patients and the fact that the population in  
7 this study was not representative of the population  
8 where the incidence of acute otitis media is  
9 greatest.

10           Finally, there were several calls from the  
11 committee members for the revision of our draft  
12 guidance.

13           [Slide.]

14           A couple of months later, in the Pediatric  
15 Infectious Disease Journal Newsletter, there was a  
16 comment by Drs. Nelson and McCracken to the effect  
17 that, "The supporting studies for these two  
18 regimens have shortcomings, similar to studies of  
19 other therapeutic agents in acute otitis media. It  
20 is time for the FDA to establish strict criteria  
21 for conducting clinical trials in patients with  
22 acute otitis media if a new antibiotic is to be  
23 approved for therapy."

24           [Slide.]

25           "Such clinical trials should include a

1 predominance of children younger than 2 years, a  
2 tympanocentesis at diagnosis to establish etiology,  
3 a repeat tympanocentesis at 4 to 5 days in a subset  
4 of patients to establish bacteriologic cure or a  
5 repeat ear tap in patients who are considered  
6 clinical failures, and follow-up evaluation at 10  
7 to 14 days as the primary clinical endpoint."

8 [Slide.]

9 I think the example of this recent  
10 approval raises a couple of the major issues that  
11 we would like the committee to address in the first  
12 question for discussion today. These issues are  
13 the value of comparative studies with diagnostic  
14 tympanocentesis, and these studies might be single  
15 tap, double tap, or some combination, and also the  
16 issue of the future role of clinical-only studies.

17 [Slide.]

18 Now, another area of the study  
19 considerations of the current draft guidance talks  
20 about the listing of pathogens, and it states that  
21 pathogens listed in the label should have  
22 acceptable eradication rates.

23 These rates are not otherwise defined in  
24 the guidance. It does state that if a product  
25 fails to have acceptable clinical and microbiologic

1 effectiveness against all three major pathogens, it  
2 should be listed only for those it has eradicated.  
3 This would take the form of a restricted listing as  
4 not a product for first-line therapy.

5           This restriction is based on the empiric  
6 nature of treatment and the need for first-line  
7 therapies to be effective against all common  
8 pathogens.

9           [Slide.]

10           I have here a couple of examples of  
11 pathogen labeling in which products have not  
12 achieved approval for *Streptococcus pneumoniae*.

13           This first one is for otitis media caused  
14 by *Haemophilus influenzae*, *Moraxella*, and Group A  
15 *Streptococci*. The clinical study section states  
16 that the response rate of *Strep pneumoniae* to this  
17 drug is approximately 10 percent lower and that of  
18 *Haemophilus influenzae* or *Moraxella catarrhalis*  
19 approximately 7 percent higher than rates of these  
20 organisms to the active control drugs.

21           [Slide.]

22           The second label is for a product, which  
23 again is approved for acute bacterial otitis media  
24 due to *Haemophilus influenzae*, *Moraxella*  
25 *catarrhalis*, or Group A *Strep*. There is a note

1 here that although this drug used empirically was  
2 equivalent to comparators in the treatment of  
3 clinically and/or microbiologically documented  
4 acute otitis media, the efficacy against the  
5 pneumococcus was 23 percent less than control.  
6 Therefore, this drug should be given empirically  
7 only when adequate antimicrobial coverage against  
8 Strep pneumoniae has been previously administered.

9           The clinical study section of this label  
10 contains a table showing bacteriologic eradication  
11 rates for the pneumococcus for this drug of 65  
12 percent versus 88 percent for the active control.

13           This example demonstrates two important  
14 points. First, it shows some of the problems with  
15 restricted labeling in situations in which a drug  
16 is approved when it lacks acceptable efficacy  
17 versus all three major pathogens.

18           This is labeled as a second-line drug  
19 which is indicated empirically for treatment  
20 failure only when adequate coverage against the  
21 pneumococcus has been previously administered.

22           In an era of increasing pneumococcal  
23 resistance, however, many formerly adequate  
24 therapies no longer are adequate and the treatment  
25 failure population for whom this drug is prescribed

1 actually had a disproportionate share of resistant  
2 Strep pneumoniae compared to the general acute  
3 otitis media population.

4 I think the second important point from  
5 this example is that it demonstrates the importance  
6 of having comparative rather than non-comparative  
7 microbiologic data in evaluating pathogen-specific  
8 efficacy.

9 [Slide.]

10 Among the issues for discussion then  
11 related to the microbiology of acute otitis media  
12 are whether it is important for a drug to  
13 demonstrate efficacy against all the major otitis  
14 pathogens in order to obtain approval, whether  
15 per-pathogen efficacy should be demonstrated using  
16 comparative as opposed to non-comparative data, and  
17 whether it is feasible to have objective criteria  
18 for the inclusion of individual pathogens in the  
19 label.

20 [Slide.]

21 I would like to talk briefly about some  
22 issues with inclusion and exclusion criteria. The  
23 draft guidance states that among the inclusion  
24 criteria, clinical-only trials ordinarily should  
25 not enroll children less than 6 months old.

1           There is no recommendation, however, in  
2 the guidance about the actual distribution of the  
3 children in these studies. This lack of guidance  
4 has resulted in several instances of submissions  
5 that contain unrepresentative study populations.

6           I have a couple of examples here of  
7 products where one product in the 90s, although the  
8 tympanocentesis study that was submitted had 44  
9 percent of the children under age 2, the large  
10 clinical-only study had less than 20 percent of the  
11 enrolled population that was under age 2, and had a  
12 median age of 4 1/2 years.

13           We have other approvals from the 90 of  
14 products where another product, as part of the  
15 package submitted, one clinical-only and two  
16 tympanocentesis trials, all of which enrolled only  
17 children from 2 to 15 years of age.

18           Even the most recent supplement that I  
19 have described for you in the two major studies  
20 that were submitted, 60 to 65 percent of the  
21 children were over 2 years of age.

22           We have heard from the speakers today and  
23 from previous committee meetings that when you  
24 consider that the peak incidence of acute otitis  
25 media is between 6 and 18 months of age, the fact

1 that these children have lower rates of successful  
2 treatment, it seems that we should be considering  
3 whether the future guidance should include some  
4 type of recommended age distribution for future  
5 trials.

6 [Slide.]

7 Under exclusion criteria in the current  
8 guidance, children with tympanostomy tubes,  
9 children with acute otitis externa are excluded.  
10 Recent systemic anti-infective therapy for  
11 clinical-only trials, children treated within the 7  
12 days prior to enrollment are excluded, and for  
13 clinical and microbiologic studies, children  
14 receiving systemic therapy 3 days prior to  
15 enrollment are excluded.

16 The guidance also recommends exclusion of  
17 children who are receiving antimicrobial  
18 prophylaxis for recurrent otitis media. I think we  
19 have heard today and particularly for studies in  
20 which baseline tympanocentesis is going to be done,  
21 and you will have bacteriologic confirmation of the  
22 etiology of the acute otitis media, that it  
23 certainly seems reasonable to allow for the  
24 inclusion of these children in acute otitis trials.

25 [Slide.]

1           The issues for discussion then related to  
2 these inclusion/exclusion criteria issues are the  
3 age distribution of children enrolled in trials and  
4 whether there are other methods of capturing  
5 populations of greatest interest, where the  
6 exclusion criteria, as I mentioned, the issue would  
7 be to permit enrollment in clinical/micro studies  
8 of recently treated patients and patients receiving  
9 prophylaxis.

10           [Slide.]

11           The final topic regarding recurrent  
12 guidance, and this, the committee has already voted  
13 on, is the timing of outcome assessments. The  
14 current guidance recommends study evaluations at  
15 entry, on-therapy, which is 3 to 5 days into  
16 therapy, there is a visit strongly recommended.

17           The end-of-treatment visit is actually  
18 optional in the current guidance, and the  
19 recommended test-of-cure visit is 2 to 4 weeks  
20 after study entry with an optional late  
21 post-treatment visit.

22           The current guidance uses, as the primary  
23 endpoint for both clinical and microbiologic  
24 assessments, the test-of-cure visit at 2 to 4 weeks  
25 after entry.

1 [Slide.]

2 The committee recently has voted on this  
3 issue, and in regards to clinical outcomes, the  
4 committee unanimously voted that the relevant  
5 clinical test of cure is at the end of therapy,  
6 with the later follow-up visit, meaning the one  
7 that we currently use as the test of cure, being an  
8 important secondary endpoint.

9 Furthermore, in studies that contain a  
10 repeat tympanocentesis component to assess  
11 microbiologic response, the committee voted that  
12 the most informative repeat taps were on therapy,  
13 followed by those obtained at the time of clinical  
14 failure.

15 [Slide.]

16 In summary, then, regarding the general  
17 indication of acute otitis media, we would like to  
18 get the committee's comments during today's  
19 meeting, and we would also appreciate other  
20 comments in the form of written comments to the  
21 docket, regarding some of these issues here - the  
22 value of comparative studies with diagnostic  
23 tympanocentesis, the role of clinical-only studies,  
24 how best to demonstrate efficacy against all the  
25 major pathogens, and issues regarding the inclusion

1 of pathogens in the label.

2 [Slide.]

3 Changes in recommendations for the age  
4 distribution of children who are enrolled in these  
5 trials, and limiting the exclusion criteria to  
6 permit enrollment of recently treated patients, and  
7 patients who are receiving prophylaxis for children  
8 who are in tympanocentesis studies.

9 The next speaker will be Dr. Rosemary  
10 Johann-Liang, who will be talking about design  
11 issues for studies targeting acute otitis media in  
12 special populations, particularly as it relates to  
13 recurrent otitis media in kids with treatment  
14 failure.

15 Study Considerations:

16 Recurrent/Treatment Failure AOM

17 Rosemary Johann-Liang, M.D.

18 DR. JOHANN-LIANG: I am delighted to speak  
19 before the committee one more time, although  
20 today's topic is very different from yesterday, and  
21 I had the pleasure of being the last hurdle before  
22 all of us and lunch.

23 [Slide.]

24 Today's topic is on recurrent and  
25 treatment failure acute otitis media. As we

1 consider revisiting the current guidance, we have  
2 heard quite a lot this morning about clinical trial  
3 designs.

4 I would like to draw your attention now to  
5 the types of children who will populate these  
6 clinical trials. Specifically, we will be  
7 discussing the proposal for an additional  
8 indication that will study the population of  
9 children with recurrent and/or treatment failure  
10 acute otitis media.

11 I will be following this outline. The  
12 relevant sections in the current guidance will be  
13 first shown, then, the rationale and proposal for  
14 change will presented. This will be followed by  
15 the discussion of definitions and the types of  
16 trials for the indications. I will end with some  
17 issues we hope will be included in the committee's  
18 discussions this afternoon.

19 [Slide.]

20 The 1998 draft guidance taken after the  
21 1992 Points-to-Consider lays out study  
22 considerations for one all- comers indication of  
23 acute otitis media. There is no differentiation of  
24 different populations, however, there are exclusion  
25 criteria and they include the following: children

1 who have received systemic anti-infective drug  
2 product in the previous 7 days prior to enrollment  
3 in the clinical-only study, systemic anti-infective  
4 drug product in the previous 3 days prior to  
5 enrollment in the clinical micro study, and  
6 patients receiving antimicrobial prophylaxis for  
7 recurrent otitis media.

8           Various beta-lactams and macrolides have  
9 been approved thus far under one indication by  
10 studying all-comers population with these  
11 exclusions.

12           [Slide.]

13           You all have been telling us that changes  
14 need to take place to the current guidance. Of the  
15 various recommendations for change by the  
16 committee, these are a few of the advice we have  
17 heard regarding populations to study.

18           Dr. Leggett's statement from last year's  
19 November meeting - "There was a thing about not  
20 being able to use antibiotics within the last 7  
21 days of the last month. I think that would be  
22 another way to actually enrich the resistant  
23 population because isn't that who we have the  
24 trouble with, the more severe illness and the more  
25 resistant pathogens?"

1           Dr. Wald's comment - "I think that groups  
2 of children that we should be studying are children  
3 with severe disease."

4           You have also heard Dr. Giebink and the  
5 other experts this morning so wonderfully discuss  
6 population issues.

7           [Slide.]

8           So, in thinking about this in picture  
9 format--and I would like to ask for your indulgence  
10 at this point, all my PowerPoint diagrams are  
11 conceptual in design, and not proportional and not  
12 drawn to scale--we have the all-comers population  
13 for acute otitis media in the large green oval.

14           You are telling us that the recently  
15 treated population should not be excluded, in fact,  
16 they should be perhaps studied more in depth. You  
17 are also telling us that the population with severe  
18 disease should be especially studied.

19           What is the driving force behind these  
20 proposals for change? I think you will all agree  
21 with me that the underlying factor is resistant  
22 pathogens, specifically, at this point, PRSP. PRSP  
23 is a critical factor for otitis media disease in  
24 general, but a problem of greater magnitude in  
25 these subpopulations.

1 [Slide.]

2 Rising to meet the challenge of resistant  
3 pathogens in otitis media disease, drug development  
4 programs are already ongoing. I would like to  
5 spend the next several slides briefly reviewing  
6 with you the lessons we have learned and are  
7 continuing to learn from looking at these examples  
8 of drug development programs.

9 I want to share with you this morning two  
10 examples, the high-dose formulation of Augmentin  
11 and the development of fluoroquinolones in  
12 pediatrics.

13 [Slide.]

14 High-dose Augmentin, the 14 to 1  
15 formulation was presented to this committee in  
16 January of last year. As you are aware, the  
17 high-dose formulation was developed with PRSP in  
18 mind, and enrichment strategies were used in its  
19 clinical trials to maximize patients with bacterial  
20 disease especially PRSP.

21 However, the restricted subpopulation that  
22 this formulation is currently labeled for was not  
23 prospectively defined and therefore not the defined  
24 population studied during development.

25 How does this label currently read? It

1 says, "Augmentin ES-600 is indicated for the  
2 treatment of pediatric patients with recurrent or  
3 persistent acute otitis media, characterized by the  
4 following risk factors: antibiotic exposure for  
5 AOM within the preceding 3 months, and either of  
6 the following - age less than or equal to 2 years,  
7 daycare attendance."

8 This recurrent or persistent indication  
9 was inserted post-development following this  
10 committee's advice that this 14 to 1 formulation  
11 should be differentiated from the 7 to 1  
12 formulation, and should not be used for routine  
13 acute otitis media.

14 The lesson learned here was that the  
15 population that the indication will be labeled for  
16 needs to be pre-defined.

17 Next, I would like to walk you through a  
18 time line of a series of recommendations by this  
19 Anti-Infective Drugs Advisory Committee on the  
20 development of fluoroquinolones in pediatrics.

21 [Slide.]

22 The story starts in 1989 where the  
23 committee recommended that mainly due to safety  
24 concerns, fluoroquinolone development in pediatrics  
25 should be restricted to older children with severe

1 underlying diseases of cystic fibrosis and cancer  
2 needing therapy for gram-negative resistant  
3 pathogens.

4           The committee met again in 1993 regarding  
5 this matter and recommended expanding the types of  
6 diseases and age, but again unanimously voted that  
7 this class of drugs was not for investigation in  
8 routine indications.

9           By 1997, there is a change. There was  
10 again the recommendation to continue the pediatric  
11 study of these drugs for severe indications,  
12 however, the committee began to discuss the  
13 development of these drugs to treat the sick  
14 subpopulations of generally well children due to  
15 the increasing emergence of gram-positive resistant  
16 organisms.

17           [Slide.]

18           This is a statement by Dr. George  
19 McCracken from that committee meeting. "The  
20 fluoroquinolones could then be evaluated in  
21 hospitalized pediatric patients with community or  
22 hospital-acquired pneumonia and possible middle ear  
23 or sinus infections caused by resistant pathogens,  
24 PRSP, i.e., recurrent or persistent otitis media."

25           Currently, the development of

1 fluoroquinolones for use in pediatrics is ongoing,  
2 and it is not just for severe indications, but also  
3 for the sicker subpopulations in routine  
4 indications, such as acute otitis media.

5           One example is the gatifloxacin  
6 development program, parts of which were presented  
7 at the 41st ICAAC last year. That sicker  
8 subpopulation within the acute otitis media being  
9 studied with gatifloxacin is called recurrent  
10 and/or non-responsive otitis media.

11           Clearly, the committee has pointed out  
12 throughout the time line that I have just presented  
13 to you that fluoroquinolones are not for study in  
14 routine cases for routine indications due to the  
15 safety issues especially the arthrototoxicity, the  
16 fact that many other alternative drugs are  
17 available for routine use, and the worry of more  
18 resistance if this class of drugs are to be used  
19 widely in pediatrics.

20           [Slide.]

21           To summarize what we have heard from you  
22 and the lessons learned regarding populations for  
23 study in acute otitis media, you have told us to  
24 enrich the populations for study for better yield  
25 of patients with bacterial disease especially those

1 with PRSP, and that this may be accomplished in  
2 part by studying the subpopulation of children with  
3 recurrent and/or persistent disease, and not to  
4 exclude children recently exposed to antibiotics.

5           Furthermore, you have told us that the  
6 drug development programs geared towards treatment  
7 of resistant pathogens, especially PRSP, should not  
8 be pooled together for study in routine use. This  
9 is due to safety issues at the individual level and  
10 the judicious use of drugs to curb more resistance  
11 at the public health level.

12           All in all, what we have learned is that  
13 this not for routine subpopulation of acute otitis  
14 media need to be precisely defined as we move  
15 forward in developing drugs for resistant  
16 pathogens.

17           [Slide.]

18           So, bringing together all that you have  
19 told us through multiple advisory meetings, we have  
20 a possible solution to propose. The proposal is  
21 for an additional indication termed recurrent  
22 and/or treatment failure acute otitis media.

23           This is a population-driven concept. I  
24 think it is fair to say that we would all agree  
25 that the child coming into the office with an

1 occasional episode of acute otitis media is a  
2 distinct entity in comparison to the child that is  
3 constantly in the office with multiple and frequent  
4 episodes of acute otitis media requiring repeated  
5 and cycling of therapy.

6           The proposal for change then is that we go  
7 from the one all-comers indication that is  
8 currently in guidance to two indications relevant  
9 to the targeted populations, one for routine acute  
10 otitis media, and one for the recurrent treatment  
11 failure AOM.

12           This would, in turn, facilitate drug  
13 development programs by pre-defining the  
14 appropriate populations for clinical trials. For  
15 example, a regular dose beta-lactam being studied  
16 here for routine AOM, going on to be labeled for  
17 this indication at the time of approval, while  
18 high-dose formulations or fluoroquinolones being  
19 studied here, will eventually be labeled for the  
20 indication of recurrent treatment failure at the  
21 time of approval.

22           It is also possible for a drug without  
23 particular safety or resistant pattern concerns and  
24 having necessary efficacy parameters, may be able  
25 to pursue both indications concurrently with data

1 from both programs complementing and supporting  
2 that overall development program.

3 [Slide.]

4 A simple illustration of this concept may  
5 be as follows: In choosing the clinically distinct  
6 populations as the basis for separating out the  
7 indications, we will be able to clinically  
8 distinguish the population that will be studied  
9 under routine acute otitis media here in the large  
10 pretty pink color from the recurrent and/or  
11 treatment failure disease here on the smaller green  
12 oval.

13 The resistance factor will overlap both  
14 populations, but will have a greater overlap for  
15 the not-for-routine indication.

16 [Slide.]

17 With that change in general concept in  
18 mind, let's spend a few minutes on defining the  
19 elements of the additional indication, so that as  
20 we revise the guidance, we can reflect the  
21 consensus that was reached on this concept and be  
22 precise with our definitions. Defining exactly  
23 what we mean by the terminology used will provide a  
24 clear channel for communication by all interested  
25 parties and avoid confusion.

1 [Slide.]

2 First, the definition for recurrent. Are  
3 we correct in hearing from you that recurrent  
4 otitis media should be part of the not for routine  
5 population for study? The generally accepted and  
6 used definition for recurrent AOM is shown here:  
7 greater than or equal to 3 episodes of AOM over the  
8 last 6 months or greater than or equal to 4  
9 episodes of AOM over the past year.

10 This population of children includes  
11 children with various underlying and predisposing  
12 factors to acute otitis media including young  
13 children with anatomical immaturity. Clinically,  
14 this definition would encompass the children  
15 thought of as a distinct entity.

16 Microbiologically, however, when the  
17 literature is carefully scrutinized, this  
18 population defined exactly and precisely, as shown  
19 here, may not have significantly higher rates of  
20 PRSP when compared to age-controlled children with  
21 routine AOM.

22 [Slide.]

23 Next, the definition of treatment failure.  
24 Are we correct in hearing from you that children  
25 recently treated with antibiotics or early

1 treatment failure should not be excluded from  
2 clinical trials for AOM, but rather be studied  
3 vigorously since this is the population that  
4 microbiologically appears to have higher rates of  
5 resistance?

6           One definition, then, one definition that  
7 we may be able to propose here is this. During  
8 therapy: No improvement observed in signs and  
9 symptoms of acute otitis media after at least 48  
10 hours of antibiotic management, or post-therapy:  
11 Presentation with signs and symptoms of acute  
12 otitis media within 7 days of completing a course  
13 of antibiotics for acute otitis media.

14           This definition is inclusive of the  
15 accepted definition of persistent acute otitis  
16 media, signs and symptoms continuing on the third  
17 day after start of therapy, while being exclusive  
18 of the time point beyond 1 week after end of  
19 treatment, where it becomes very hard to  
20 differentiate reinfection from new infection.

21           [Slide.]

22           Now that we have proposed some definitions  
23 for what the elements of the new indication might  
24 be, I want to clarify what the new indication is  
25 not synonymous with.

1           Some terms that we have been seeing in  
2 recent protocols that are used as names for  
3 subpopulations of otitis media are:  
4 difficult-to-treat otitis media, otitis-prone  
5 children, hard-to-treat otitis media, and children  
6 "at risk."

7           For example, we have been seeing protocols  
8 wanting to study the hard-to-treat or  
9 difficult-to-treat acute otitis media with  
10 high-dose formulations or fluoroquinolones that has  
11 the listing under the inclusion criteria of less  
12 than or equal to 2 years, daycare attendance, or 3  
13 or more siblings, et cetera.

14           This would mean that even with the  
15 first-time otitis, just by being a 6-month-old  
16 infant, that infant will be exposed to drugs like  
17 fluoroquinolones, for example, which I don't think  
18 is what anybody wants at the moment.

19           [Slide.]

20           These listings are then not the elements  
21 of the proposed new indication, but rather  
22 enrichment strategies to yield patients with  
23 bacterial otitis media especially PRSP otitis media  
24 for both indications.

25           Again, the two distinct populations are

1 shown here in the pink and green ovals with the  
2 resistance factor overlapping both populations.  
3 The enrichment groups are overlaying both  
4 indications and the resistance factor.

5 Now, taking into account all the  
6 definitions that have been discussed, I would like  
7 to walk through a series of possible scenarios in  
8 the next slide.

9 [Slide.]

10 This is an illustration of a hypothetical  
11 AOM drug development schema. Having used  
12 enrichment strategies to increase the chance of  
13 having a patient with bacterial otitis media, a  
14 6-month-old infant in daycare full time is  
15 identified.

16 If this baby is in the office with his  
17 first episode of AOM or has now grown to be a  
18 9-month-old and is having a second episode of AOM,  
19 for both of these scenarios, the infant will be  
20 studied under the indication of routine AOM,  
21 enrolling in drug trials seeking first-line  
22 therapy.

23 If this baby has treatment failure OM  
24 meeting the predefined definitions or is now a  
25 12-month-old and is always in your office because

1 this is the fourth episode of acute otitis media,  
2 this infant will be studied under the indication of  
3 recurrent/treatment failure AOM, enrolling in drug  
4 trials seeking not-for-routine therapy.

5 [Slide.]

6 So, I have presented to you what you have  
7 told us about targeted populations and have laid  
8 out for you our responsive proposal of relevant  
9 indications corresponding to appropriate drug  
10 development programs that can move forward with  
11 prospectively defined populations that needs  
12 consensus on precise definitions.

13 In the next slide, I would like to  
14 highlight some particulars about the types of  
15 trials that would be part of the drug development  
16 program for this additional indication.

17 [Slide.]

18 We would be looking for well-controlled  
19 single or double tap tympanocentesis trials with  
20 non-inferiority or superiority design with  
21 pathogen-specific diagnosis by tympanocentesis at  
22 entry.

23 For single tap studies, the primary  
24 outcome assessment will be clinical at end of  
25 therapy, and for double tap studies, the primary

1 outcome assessment will be on-treatment micro and  
2 end of therapy clinical.

3 I might mention here that if the claim for  
4 PRSP is being sought for the label, it may be  
5 particularly valuable to include a double tap trial  
6 in the drug development program.

7 These two types of trials may be  
8 supplemented by empiric or actual use therapy  
9 trials to increase the safety information for the  
10 product. This type of trial is particularly  
11 encouraged for new molecular entities, drugs with  
12 specific safety issues, or drugs with limited  
13 safety data and should be inclusive of children  
14 with various underlying conditions.

15 Non-comparative double tap trials may be  
16 another supplemental study in cases where efficacy  
17 data on a specific organism, for example, needs  
18 more support. Relevant studies from "other"  
19 indications may also provide supplemental  
20 information.

21 [Slide.]

22 Finally, I would like to show a broader  
23 schema for our considerations regarding the types  
24 of trials for acute bacterial otitis media overall.

25 [Slide.]

1           As we consider revisiting the guidance on  
2 acute otitis media, this is a summary overview of  
3 our overall proposal.

4           We have heard from you that acute otitis  
5 media should be studied in a  
6 microbiologically-driven, comparative manner with  
7 populations enriched to yield the patients having  
8 bacterial disease under the indication of routine  
9 acute otitis media, drug development programs for  
10 regular beta-lactams, macrolides, et cetera, or new  
11 drugs can proceed.

12           The types of trials for study in this  
13 indication would include single tympanocentesis  
14 trials, double tympanocentesis trials,  
15 placebo-controlled trials, and other supplemental  
16 studies.

17           Under the indication of recurrent and  
18 treatment failure otitis media, drug development  
19 programs for high-dose formulations,  
20 fluoroquinolones, or other new drugs can proceed.

21           The types of trials for study in this  
22 indication include single tympanocentesis trials,  
23 double tympanocentesis trials, empiric therapy  
24 safety trials, and other supplemental studies.

25           We have arrived at this overall conceptual

1 proposal in response to your recent recommendations  
2 for change by incorporating what you have told us  
3 and the lessons that we have learned.

4 [Slide.]

5 We would like to turn this proposal back  
6 to you now for discussion and further advice. Some  
7 items for discussion are listed here for you. We  
8 would like to know if you agree with the  
9 definitions for recurrent AOM, the definitions for  
10 treatment failure AOM. Do these two groups fit the  
11 population to pre-define for "not-for-routine" drug  
12 development programs with PRSP emphasis?

13 Is it reasonable to have these two groups  
14 be placed together in the new indication?

15 Are the types of trials for this  
16 indication appropriate? Can you suggest any other  
17 types of studies?

18 Thank you so much for your attention and  
19 we look forward to listening to your discussions  
20 this afternoon.

21 DR. RELER: We have had a packed and  
22 informative morning. It is just after 12:15. This  
23 is the plan for the afternoon with a reward for  
24 promptness and punctuality.

25 At 1:15, we reconvene. There will be a

1 20-minute open public hearing. Dr. Jacobs is the  
2 only speaker. When you look at your schedule, that  
3 would bring us to 1:35. Thereafter, if you take  
4 one-half hour off all the listed times, we will  
5 finish at 3:30 p.m. Stick on schedule and we will  
6 be done at 3:30 for the people meeting the  
7 commitments for flights including international  
8 ones.

9 Thank you.

10 [Whereupon, at 12:15 p.m., the proceedings  
11 were recessed, to be resumed at 1:15 p.m.]

1 AFTERNOON PROCEEDINGS

2 [1:20 p.m.]

3 DR. RELLER: We will begin the second half  
4 with the open public hearing, actually presented by  
5 a colleague of all of ours in the field, Dr.  
6 Michael Jacobs from Case Western Reserve  
7 University.

8 Michael.

9 Open Public Hearing

10 DR. JACOBS: Mr. Chairman, committee  
11 members, advisers, guests, I am pleased to have  
12 this opportunity to give my thoughts on this  
13 complex area and while I will be giving you a lot  
14 of information, I will try and make the points that  
15 I want to make clear about the issue of what the  
16 problem is with respiratory tract infections and  
17 using antibiotics, and validity of evidence for  
18 using those.

19 One of the points I wanted to make is that  
20 otitis media is a very good example and we probably  
21 have the best data on respiratory tract infections  
22 for otitis media, but most of what I am going to  
23 say applies to other respiratory tract infections  
24 as well.

25 [Slide.]

1           Now, one of the big limitations we have  
2 with respiratory tract infections is there is a  
3 high rate of spontaneous resolution that makes it  
4 difficult to show differences between agents.

5           Bacteriologic outcome studies are not  
6 often performed due to necessity for invasive  
7 procedures, and you have heard a lot about those.  
8 Most studies are therefore designed to show  
9 equivalent clinical outcome between established and  
10 new agents, and what that means is that if there  
11 are inadequacies of agents, they are often not  
12 apparent.

13           [Slide.]

14           I found this slide that Dr. Soreth showed  
15 very interesting and very informative. In the  
16 absence of culture of middle ear fluid, no specific  
17 claim can be made regarding the effectiveness of  
18 any anti-infective drug. This statement was in  
19 force in 1977, and this was a very important year  
20 for me because that was the year I started working  
21 on the pneumococcus and found the multi-resistant  
22 pneumococcus, and I hope that we can go back to  
23 this statement.

24           [Slide.]

25           Now, some of my objectives are to define

1 pharmacokinetics and pharmacodynamics because this  
2 gives us a basis for predicting the activity of  
3 most antibiotics certainly against extracellular  
4 pathogens, and if we just look at these basic  
5 parameters, we can see where many of our problems  
6 are.

7 I want to show you how we can correlate  
8 pharmacokinetic parameters with outcome of  
9 infection, show examples in animal models and in  
10 humans, and apply these to otitis media.

11 [Slide.]

12 Now, we need to be able to accurately  
13 predict efficacy. We need newer dosing regimens,  
14 we need newer antimicrobials, we need revised  
15 susceptibility breakpoints, and we need  
16 statistically valid clinical studies, and many of  
17 these points were discussed extensively this  
18 morning.

19 [Slide.]

20 I am going to try and bring this into  
21 focus by looking at what pharmacokinetics and  
22 pharmacodynamics do for us, and basically, you are  
23 all familiar with oral ingestion of a drug. We  
24 talk about oral drugs, and the drug is absorbed  
25 through gastrointestinal tract, distributed through

1 the bloodstream, and this is where we can  
2 conveniently measure drug concentrations and  
3 kinetics, but we must not lose sight of the fact  
4 that what we are looking at is the actual effect of  
5 the drug in the extracellular compartment of  
6 tissues.

7           However, what is driving the concentration  
8 of drugs there is the concentration in serum, so  
9 that even though the serum concentration doesn't  
10 correlate with what is going on in tissues, it does  
11 drive what is going on in tissues certainly in  
12 instances where you have acute inflammation. This  
13 is why blood concentrations are so important, not  
14 only in antibiotics, but in many areas of  
15 therapeutics.

16           [Slide.]

17           Now, looking at the serum pharmacokinetic  
18 profile of a drug, we can measure this very  
19 conveniently, we can time it, whereas, measuring  
20 this at the site of infection is very difficult and  
21 very difficult particularly to do over time.

22           [Slide.]

23           As you can see here, we can look at  
24 various parameters, the concentration of the drug  
25 present for various percentages of the dosing

1 interval, we can look at the peak serum  
2 concentration, we can look at the area under the  
3 curve.

4 [Slide.]

5 For time-dependent agents, time above MIC  
6 correlates with outcome. For  
7 concentration-dependent agents, either area under  
8 the curve to MIC ratio or peak to MIC ratio.

9 [Slide.]

10 For beta-lactams, this needs to be 25 to  
11 35 percent of the dosing interval for penicillins  
12 and 35 to 40 percent for cephalosporins. The  
13 presence of neutrophils decreases this by a further  
14 5 to 10 percent, and free drug levels of these  
15 drugs therefore need to exceed the MIC for between  
16 35 and 50 percent of the dosing interval to produce  
17 maximal survival.

18 [Slide.]

19 This is showing an animal model, as you  
20 have all seen this figure of Dr. Craig, and I would  
21 like to acknowledge Dr. Craig and the other key  
22 people who work in this field for teaching me about  
23 this area.

24 You can see here it shows the value for  
25 cephalosporins, and I have tried very extensively

1 to apply these principles to respiratory tract  
2 infections and also see if I can find examples of  
3 where these principles don't work, and I can find  
4 very few.

5 [Slide.]

6 For concentration-dependent agents, it is  
7 the area under the curve to MIC ratio or the peak  
8 to MIC ratio. From the data that I have seen,  
9 either of these parameters works equally well.

10 [Slide.]

11 This again shows the animal data at 25 to  
12 30 ratio for immunocompetent animals.

13 [Slide.]

14 At dosing comparable to dosing in humans,  
15 looking at a rat pneumonia model with both  
16 pneumococcus and Hemophilus published last year,  
17 azithromycin and clarithromycin were able to reduce  
18 the inoculum for macrolide-susceptible pneumococci,  
19 but not for macrolide-resistant pneumococci with  
20 either of the common resistance mechanisms, the  
21 efflux or the ribosomal methylase, and it could not  
22 do this against Haemophilus influenzae either.

23 [Slide.]

24 This is another study showing the same  
25 thing, and I am quoting directly from the paper.

1 "This is a chinchilla otitis media model. After  
2 administration of azithromycin at 30 mg/kg as  
3 single daily doses in our chinchilla model of  
4 experimental otitis media due to non-typeable  
5 Haemophilus influenzae, we were able to achieve  
6 levels in serum and AUCs approximately twice those  
7 observed in children treated with the dosing  
8 regimen given, and concentrations in the middle ear  
9 fluid comparable to those found in children, as  
10 well.

11 "Our observations provide evidence that  
12 current doses of azithromycin administered to  
13 children are likely to have a modest antibacterial  
14 effect on otitis media, characterized by a  
15 reduction information density of infection, but not  
16 eradication of infection. Maximizing the dosing of  
17 azithromycin in children has the potential to  
18 improve the microbiologic outcome."

19 However, I also want to point out that  
20 even going to 4 times this dose, which would be  
21 equivalent to about 8 times the dose we give in  
22 humans, the high dose still did not eradicate  
23 Hemophilus from the ears in 15 percent of the  
24 animals.

25 [Slide.]

1           Looking at human data, Dr. Dagan has shown  
2 you this data in different format, and you can see  
3 here that when you get to above 40 percent of the  
4 dosing interval, you get greater than 80 percent  
5 bacteriologic eradication. Note also the cluster  
6 of *Haemophilus influenzae* around about the 40  
7 percent point here. This is not 40 percent  
8 eradication, this is spontaneous resolution of  
9 disease. These are drugs with no activity against  
10 *Haemophilus influenzae*. Similarly, this point here  
11 of 20 percent is a drug with no activity against  
12 pneumococcus.

13           [Slide.]

14           There is very much less data in sinusitis,  
15 but when this data is available, it shows exactly  
16 the same thing.

17           [Slide.]

18           This is a very interesting study that was  
19 done on community-acquired pneumonia, predominantly  
20 in patients treated with intravenous levofloxacin.  
21 In 134 patients, predominantly with pneumonia, you  
22 can see here how well the PK/PD correlated with  
23 outcome.

24           When these parameters were optimal area  
25 under the curve to MIC ratio greater than 100 or

1 peak to MIC greater than 12, then, there was almost  
2 100 percent clinical and bacteriologic success.  
3 This is based on clinical outcome in these  
4 patients. There was only one patient judged to be  
5 a clinical failure. This patient was not a  
6 bacteriologic failure.

7           When your parameters were below those  
8 which have been shown to work in animals, in other  
9 words, area under the curve to MIC ratio of less  
10 than 25, then, there was a 43 percent clinical  
11 failure, and the successes were due to spontaneous  
12 resolution.

13           When the values were between these, you  
14 got an intermediate value of 12 percent clinical  
15 failure, so you can see this is one of the best,  
16 although one of the few, pharmacodynamic studies  
17 ever conducted in humans, and it shows how well  
18 these parameters correlate.

19           [Slide.]

20           When you take these parameters and for  
21 beta-lactams and macrolides, you then  
22 determine--and Dr. Dagan discussed how to do  
23 this--the microbiological, the MIC breakpoint, this  
24 is what you come up with, values between 0.1 and 2  
25 mcg/ml depending on the mechanism of action and the

1 actual concentrations you get with these drugs.

2 [Slide.]

3 However, when you look at what the  
4 regulatory agencies have come up with, this shows  
5 the same PK/PD breakpoints, you can see for the  
6 pneumococcus, these values as of the year 2000 were  
7 changed, and are very similar to those that are  
8 predicted, whereas, those of Haemophilus influenzae  
9 with the exception of cefixime are all considerably  
10 too high and are based on four clinical studies  
11 that were not adequate to show differences.

12 [Slide.]

13 When you look at susceptibility of our  
14 pathogens, you see that these agents vary  
15 considerably in achieving pharmacodynamic  
16 breakpoints, and if you believe that these  
17 pharmacodynamic breakpoints are correct, then,  
18 would believe that this information is correct, and  
19 you can see here there are very few agents that  
20 cover the majority of all three of our major  
21 pathogens in otitis media and other respiratory  
22 infections.

23 You can see, in fact, if you go by this,  
24 our choice for empiric therapy in both primary  
25 disease, as well as recurrent disease or

1 complicated patients is really pretty limited, and  
2 we have a great need for new drugs.

3           Hopefully, the situation with the  
4 pneumococcus, we are expecting the resistance to  
5 decrease because of the vaccine, but we started to  
6 see evidence of this, but we don't know how  
7 extensive this is going to be. We don't know  
8 whether replacement is going to be by susceptible  
9 pneumococci or by Hemophilus, and we don't know  
10 whether replacement organisms are going to develop  
11 resistance.

12           Just to mention one point also which  
13 disturbed me considerably when I was hearing many  
14 of the presentations this morning, I was hearing  
15 many of the speakers refer to PRSP,  
16 penicillin-resistant Streptococcus pneumonia, as an  
17 acronym for drug-resistant organisms in these  
18 respiratory tract infections.

19           To me, that is a very bad terminology and  
20 particularly when you are discussing  
21 non-beta-lactams to try and describe a drug being  
22 active against a totally different class where you  
23 have resistance, to me, that makes absolutely no  
24 medical and scientific sense.

25           If you want to use a macrolide for

1 pneumococci, you need to use it for  
2 macrolide-susceptible pneumococci. There is  
3 cross-resistance with beta-lactams, but macrolide  
4 resistance is the reason for the macrolide working  
5 or not working in those agents, not the penicillin  
6 resistance.

7 [Slide.]

8 Now, let's look at a couple of drugs in  
9 more detail, starting off with  
10 amoxicillin-clavulanate. As you saw from the data  
11 Dr. Dagan showed, it has activity against  
12 Hemophilus, but its activity is pretty close to the  
13 breakpoint of 2 mcg/ml, and by extending the dosing  
14 regimen to the new dosing regimen, if we have such,  
15 is 90 mg/kg of the mass component, you can bring  
16 the concentration that you are going to achieve up  
17 to 4 and possibly even 8 mcg/ml.

18 The way I have colored these graphs is the  
19 green area shows you the pharmacodynamically  
20 achievable breakpoint, the yellow area that can be  
21 achieved with higher doses, and the red area are  
22 strains which you would expect to be in the  
23 resistant range.

24 When you look at the pneumococcus, when  
25 you go back to strains that we had 20 years ago,

1 they were all at 0.03 mcg/ml or less, but now 30 to  
2 40 percent or even more of our strains have higher  
3 MICs, but you can see that amoxicillin still covers  
4 the majority of our pneumococci.

5           When you look at *Moraxella catarrhalis*,  
6 almost all of these would be lactamase producers,  
7 so we need the clavulanate, but again, those are  
8 all well within pharmacodynamically achievable  
9 concentrations.

10           You can see that the breakpoints we have  
11 with *H. flu* are maybe a fraction too high, but  
12 otherwise the breakpoints are correct.

13           [Slide.]

14           Looking at cefaclor, not a very active  
15 drug against *Haemophilus influenzae*, and, in fact,  
16 as Dr. Dagan showed you, acts as you would expect a  
17 placebo to in otitis media. As far as bacterial  
18 eradication, not a very good drug even against  
19 penicillin-susceptible pneumococci, and not a very  
20 good drug against *Moraxella catarrhalis*.

21           When you look at the breakpoints that we  
22 have for cefaclor, the pneumococcal breakpoint is  
23 reasonably correct, the *H. flu* breakpoint is  
24 totally incorrect.

25           [Slide.]

1           Looking at cefuroxime, reasonable, pretty  
2 similar parameters to amoxicillin-clavulanate  
3 against *Haemophilus influenzae*, fine against  
4 penicillin-susceptible pneumococci, but doesn't  
5 cover the nonsusceptible strains because of dosing  
6 limitations, and also not a very good drug against  
7 *Moraxella catarrhalis*.

8           Again, you can see the *Haemophilus*  
9 *influenzae* breakpoint that we have is too high.

10           [Slide.]

11           Cefprozil, not a very good drug against  
12 *Haemophilus influenzae*, and if you remember, Dr.  
13 Dagan showed you bacteriologic outcome with  
14 *Haemophilus influenzae*, which was very poor, not a  
15 very good drug against penicillin nonsusceptible  
16 pneumococci, and not a very good drug against  
17 *Moraxella catarrhalis*.

18           You can see here the breakpoint for  
19 pneumococcus is reasonably correct, that for  
20 *Haemophilus* is way too high. Also, just to make the  
21 point that no one has official breakpoints for  
22 *Moraxella catarrhalis*.

23           [Slide.]

24           Looking at cefixime, very good drug for  
25 *Haemophilus influenzae*, okay for

1 penicillin-susceptible pneumococci, it doesn't  
2 cover nonsusceptible pneumococci, and is adequate  
3 for *Moraxella catarrhalis*. Breakpoint, there is no  
4 breakpoint for pneumococcus, the breakpoint for  
5 *Haemophilus* is correct.

6 [Slide.]

7 Looking at macrolides, azithromycin,  
8 pharmacodynamic breakpoint is 0.1 mg/ml, covers  
9 virtually no *Haemophilus influenzae*, and as you saw  
10 from the bacteriologic outcome studies, acts  
11 accordingly.

12 About 30 percent of our strains are  
13 macrolide resistant, and we see two resistance  
14 mechanisms, the efflux strains which have MICs in  
15 the 4 to 16 range, and you can see even these are  
16 nowhere near the MICs you need for being able to  
17 treat this organism, and obviously, the strains  
18 with ribosomal methylase are way out of any kind of  
19 reasonable range, but even these strains here, you  
20 can see it is not surprising that you don't get any  
21 response with these strains here even though the  
22 MICs are not very high, and, in fact, they are  
23 fairly similar to those in *Haemophilus influenzae*.  
24 They are way above the breakpoint.

25 Even going to 4 times the dose of

1 azithromycin, as I showed you in experimental  
2 animals, has great difficulty in covering  
3 Hemophilus. So, the breakpoint you have for  
4 pneumococcus is too high, but it doesn't make much  
5 difference because we don't get many pneumococci in  
6 that range. That for Hemophilus is way too high.

7 [Slide.]

8 Clarithromycin, very similar, very poor  
9 against Haemophilus influenzae, covers only  
10 macrolide-susceptible pneumococci, however, does  
11 cover Moraxella catarrhalis. The breakpoint again  
12 for Hemophilus, much too high.

13 [Slide.]

14 Clindamycin, a drug that is not often  
15 talked about and is difficult to administer in  
16 children because of taste, but is used in some  
17 patients, again is well known it doesn't have  
18 Hemophilus activity, but its activity against  
19 Hemophilus is no worse than macrolides, and also is  
20 only active against pneumococci, but it is active  
21 against pneumococci with the efflux resistance  
22 mechanism, so as opposed to macrolides, which cover  
23 70 percent of pneumococci, clindamycin covers 90  
24 percent of them. The breakpoint is correct.

25 An experimental drug, telithromycin, I am

1 mentioning because that is one of the next drugs on  
2 the horizon for use. It has already been approved  
3 in Europe. Its *Hemophilus* activity is very similar  
4 to that of azithromycin potency-wise, but again,  
5 the pharmacodynamic breakpoint has now been fairly  
6 well established to be 0.5 mcg/ml, and this makes  
7 *Hemophilus* pretty much resistant to this drug.  
8 Some strains will come up as intermediate if you  
9 use one as the intermediate range.

10           *Pneumococcus*, it does have an advantage  
11 over macrolides and clindamycin even though it is  
12 in the same group, it does seem to be active  
13 against all resistance mechanisms at the moment,  
14 but there is a lot of potential for resistance to  
15 emerge. With *Moraxella catarrhalis*, it is also  
16 active. The breakpoint that has been approved  
17 pharmacodynamically, is 0.5, and that was the  
18 breakpoint, in fact, that was approved in Europe.

19           [Slide.]

20           Doxycycline is not applicable to  
21 pediatrics, but in my remarks, if you remember, I  
22 said were going to be applied to all respiratory  
23 diseases. It is fairly commonly used, but not much  
24 is known about it, and it is not a very active drug  
25 against *Haemophilus influenzae* even though there is

1 no specific tetracycline resistance mechanism.

2           It has greater potency against  
3 pneumococcus, but we have about 25 percent of  
4 strains that are resistant, and it is active  
5 against *Moraxella catarrhalis*.

6           [Slide.]

7           Going on to the quinolones, as these are  
8 now starting to be used more in pediatrics and some  
9 of them are being tested, starting off with  
10 ciprofloxacin, one of the original quinolones, very  
11 active against *Haemophilus influenzae*, but  
12 inadequate activity against the pneumococcus, but I  
13 note that it is still approved for pneumococcal  
14 infections to this day in its product insert, and  
15 also very active against *Moraxella catarrhalis*.

16           With the quinolones, there is no  
17 breakpoint problem. The breakpoints are all  
18 correct.

19           [Slide.]

20           Levofloxacin, MICs against *Hemophilus*  
21 remain extremely low, better MICs against  
22 pneumococcus in relation to the breakpoint, so that  
23 all strains or pretty much all strains are  
24 susceptible. We only have a few percent of strains  
25 that are resistant, currently less than one, and

1 also highly active against *Moraxella catarrhalis*,  
2 also no problem with the breakpoints.

3 [Slide.]

4 Looking at trimethoprim-sulfa, an old  
5 drug, but one that was mentioned several times this  
6 morning, what is not well appreciated is that  
7 approximately one-quarter of the strains of  
8 *Hemophilus* are resistant to trimethoprim-sulfa, and  
9 probably slightly more than that of pneumococci are  
10 also resistant, and also *Moraxella catarrhalis* is  
11 intrinsically resistant to trimethoprim-sulfa, as  
12 well.

13 So, again trimethoprim-sulfa is not nearly  
14 as useful as it was 10 or even 20 years ago.

15 [Slide.]

16 So, my conclusions are antibacterial  
17 choice for empiric use in respiratory tract  
18 infections, most clinical studies do not show  
19 clinical differences between agents.

20 Pharmacodynamic parameters correlate with  
21 bacteriological and clinical outcomes in animal  
22 models and, where we have the data, in humans.

23 These parameters can be used to select  
24 agents with maximal potential for bacterial  
25 eradication, and currently available agents very

1 significantly in achieving these parameters.

2           Going back to the 1977 statement, I want  
3 to make the following statements. We need new FDA  
4 guidance on AOM. Do we admit there is a problem?  
5 Do we admit that we were right in 1977? What does  
6 it take to fix the problem, and hopefully, that is  
7 being addressed today.

8           Will we fix the problem? I certainly hope  
9 so. And when will this be achieved? I think that  
10 is a crucial point because some of the discussion  
11 that we are having today goes back, in fact, to  
12 1977, and a lot of it, in fact, goes back to 1998,  
13 and not much has happened between 1998 and now.

14           Thank you for your attention.

15           DR. RELLER: Thank you, Dr. Jacobs.

16           I would next like to call upon Dr. Jack  
17 Paradise for some supplementary comments to this  
18 morning's presentations.

19           Dr. Paradise.

20           DR. PARADISE: These are just a few  
21 random, not necessarily connected thoughts that I  
22 had about what was discussed this morning.

23           The evidence report on acute otitis media  
24 that was issued with the sponsorship of AHRQ, I  
25 think is based in many instances on studies that I

1 think are questionable in terms of methodology, and  
2 I think many of the studies that were included were  
3 studies in which diagnostic criteria were not  
4 satisfactory, much too loose, and allowed for the  
5 admission of children with OME or perhaps even  
6 children without otitis at all.

7           With respect to tympanocentesis, the point  
8 was made earlier today that tympanocentesis may, in  
9 itself, be therapeutic, and if that is the case,  
10 and I think we don't know with certainty whether or  
11 not it is, but if it is the case and it seems  
12 likely to be true, then, incorporating  
13 tympanocentesis may have one of two effects in a  
14 clinical trial.

15           One effect, and the likeliest one, would  
16 be to blur the distinction between efficacy of the  
17 two drugs being compared, but another possibility,  
18 a little more far-fetched, would be the possibility  
19 of enhancing apparent effectiveness through  
20 interaction, because how tympanocentesis affects an  
21 infection due to Hemophilus may differ from that of  
22 how it affects an infection due to pneumococcus.

23 The group in Denmark under Dr. Toser's [ph]  
24 direction has recently shown, and I think it has  
25 been shown in other studies, that there are

1 distinct microscopic differences between changes in  
2 the epithelium when the infection is due to  
3 pneumococcus as compared with Haemophilus  
4 influenzae.

5           The issue of double taps and ethics, I  
6 certainly would agree that no research is  
7 justifiable that doesn't stand a reasonable chance  
8 of producing new information no matter what the  
9 activities of the research consist of, but I think  
10 that it is questionable.

11           The issue of ethics was raised earlier,  
12 and I think it is questionable ethically to perform  
13 a painful procedure on a child who is doing well  
14 symptomatically and who is apparently improving in  
15 all respects from a clinical standpoint, and I  
16 believe irrespective of my opinion on the subject,  
17 that my experience with our own review board  
18 suggests that they will not tolerate that as a  
19 study procedure.

20           Colin's comments that fewer  
21 tympanocenteses would be done, I think is entirely  
22 accurate if studies were restricted to double tap  
23 studies, overall, fewer procedures would be done,  
24 but all of the procedures that were done in a tap  
25 failures-only study, which is what I would

1 personally like to see as the usual type of study,  
2 all of the children who got tympanocenteses  
3 initially at baseline and then, if failure  
4 occurred, would stand a chance of benefitting from  
5 the procedure itself, and I think that is the issue  
6 rather than the number of procedures that are done.

7           On another vein, I think that it may be  
8 artificial to try to dichotomize patients into two  
9 categories, those with ordinary garden variety AOM  
10 and those with persistent or recurrent AOM.

11           First of all, I think persistent and  
12 recurrent may be different animals in some cases,  
13 and, secondly, I think there is such a multitude of  
14 variety of presentation of children with otitis,  
15 that a child on one occasion may have a mild  
16 episode, a sporadic episode that you think is not  
17 likely to be problematic, but then, in fact, turns  
18 out to be persistent or problematic, and one is  
19 dealing with histories based often on information  
20 that is of questionable reliability. Lots of  
21 studies have shown that parental recall is not  
22 necessarily adequate for demonstrating what  
23 actually has happened with children.

24           So, I would be inclined to have studies be  
25 fairly inclusive of children with bona-fide acute

1 otitis media and to collect as much information as  
2 possible about their past histories and  
3 particularly about the degree of severity of the  
4 episode, which could be greater in a clinical  
5 rating scale similar to the one that Ron used this  
6 morning or using other parameters, as well.

7           One last point, and that is, it seems to  
8 me that the emphasis has been on bacteriology and  
9 on the organism, but in categorizing children as  
10 likely to have resistant organisms or not, it is  
11 also important to take into account the host.

12           Children vary a great deal I think in  
13 their susceptibility to the disease and in their  
14 ways of responding, and the problem may not always  
15 be a resistant organism, but rather the child who  
16 anatomically or immunologically is performing less  
17 well than his peer with the same infection.

18           Thank you.

19           DR. RELLER: Thank you.

20           The open public hearing has been closed,  
21 and we will now hear from Dr. Renata Albrecht with  
22 a Summary from the FDA and Charge to the Committee.

23           After, we will have the discussion, may or  
24 may not have a break, and vote.

25           Dr. Albrecht.

1                   Summary and Charge to Committee

2                   Renata Albrecht, M.D.

3                   DR. ALBRECHT: Thank you. I think I will  
4 address this group from the podium, so that I may  
5 advance my slides. Before I begin, let me  
6 apologize. I made these summary slides during the  
7 lunch break, and therefore, I do not have copies of  
8 them. However, I believe they will be posted on  
9 the FDA web site should anyone need to gain access  
10 to them.

11                   [Slide.]

12                   My responsibility is to provide a summary  
13 and a charge to the committee. As I do that, I  
14 stand here feeling truly privileged having been  
15 able to listen to these august group of presenters  
16 that we had today, both the distinguished external  
17 consultants and truly even our FDA colleagues.

18                   I think I am quite humbled by the  
19 expertise in this room on this topic, and I feel I  
20 have got a daunting task to try to summarize that,  
21 but I will give it a try, and cover some of the  
22 issues that we would like to have you deliberate  
23 on, and a couple of questions that we would  
24 specifically like you to vote on.

25                   [Slide.]

1           With that, and at the risk of introducing  
2 yet another term today, I have inserted the word  
3 "bacterial" into the indication of acute otitis  
4 media, and I have done that intentionally really to  
5 focus us on the fact that within the Divisions of  
6 Anti-Infective and Special Pathogen and Immunologic  
7 Drug Product Divisions, we are responsible for  
8 regulating the drugs for bacterial infections, as  
9 well as some others, and it is bacterial pathogens  
10 that are responsible for otitis media and the  
11 morbidity associated with it that have been  
12 discussed today. Parenthetically, we acknowledge  
13 that some of these bacterial etiologies do cause  
14 self-limited disease.

15           I have mentioned that the drugs that we  
16 are reviewing do involve treatment of bacterial  
17 pathogens and equally, importantly, as has been  
18 included in several presentations today, the  
19 product labeling that is written as a result of  
20 review of these drugs, does include the listing of  
21 bacterial pathogens for the indications.

22           Dr. Giebink reminded us that viruses also  
23 contribute to morbidity in otitis, however, those  
24 are generally self-limited and we certainly have  
25 not yet had any drugs to treat viral otitis.

1 [Slide.]

2 Let me go ahead and talk to some of the  
3 categories that were covered today, as Dr. Powers  
4 indicated during the opening presentation this  
5 morning.

6 The first of these, the diagnosis of acute  
7 bacterial otitis media, as we have heard, the  
8 current guidance talks about clinical signs and  
9 symptoms as the basis of diagnosis. It talks about  
10 using a strict or rigorous case definition. I  
11 think we have heard what may or may not be some of  
12 the limitations of using a clinical diagnosis.

13 We have also heard about the use of  
14 tympanocentesis at baseline to establish the  
15 diagnosis of a bacterial etiology of otitis media,  
16 and actually, I guess the third bullet, if you  
17 will, is perhaps the diagnosis can best be  
18 established by using a combination of both clinical  
19 and tympanocentesis results to make the diagnosis.

20 [Slide.]

21 Let me turn to another category that has  
22 been discussed, which is endpoints, and I have  
23 added timing as part of those endpoints, and, in  
24 fact, parenthetically say this is relating to the  
25 baseline characteristics that were documented,

1 because again I think what we recognize is that we  
2 look at the endpoints and compare them to the  
3 baseline to come to the conclusion of whether the  
4 child, in fact, did get better or did not as a  
5 result of the intervention be it treatment  
6 tympanocentesis or some other management.

7           The endpoints that we have essentially  
8 used consistently before '77, since '77, and today,  
9 are clinical, and the one that I think we have  
10 heard repeatedly recommended is probably the one  
11 that we should be focusing on, is the end of  
12 therapy assessment. I have put in parentheses that  
13 we actually don't mean the last day of therapy, we  
14 tend to be thinking in terms of 2 to 7 days after  
15 the last dose. Again, those dates could vary  
16 depending on the drug used and the half-life and  
17 perhaps other parameters.

18           I have used a softer font to just remind  
19 me to mention that an on-therapy clinical  
20 assessment has not been used rigorously. I think  
21 we recognize clinically it is used to make a  
22 decision whether a patient is responding to therapy  
23 or not, but from a regulatory perspective, it has  
24 not been a major evaluation time point.

25           However, perhaps we might consider whether

1 in the future we could use it to assess time of  
2 resolution of patients as supported by some of the  
3 information that Dr. Dagan presented to us this  
4 morning.

5 An endpoint that I think has been a topic  
6 of much discussion today, that we might consider  
7 looking at a new way of evaluating is the  
8 microbiological endpoint. What we have done in the  
9 last decade or so as far as the microbiological  
10 endpoint is in clinical-only studies, we didn't  
11 have it in studies where a tympanocentesis was  
12 performed at baseline. We would look at the  
13 clinical outcome and extrapolate that the organism  
14 was eradicated if the outcome was successful, and  
15 the organism was presumed to be persistent if the  
16 outcome was not successful.

17 I think we have heard that there may be  
18 limitations to that kind of interpretation. I  
19 think the newly proposed way of looking at  
20 microbiology that we are hearing or have heard  
21 actually in several Advisory Committees and again  
22 today, is the possibility of using a  
23 tympanocentesis on therapy, and this would be day 3  
24 to 5. Some have suggested 4 to 6 days, or 48 hours  
25 into therapy, to be able to actually compare the

1 pathology of the otitis at baseline and on therapy,  
2 again, just for sake of discussion, is perhaps one  
3 of the options to get both of these.

4 [Slide.]

5 We have heard today about populations.  
6 The studies over the past several decades have  
7 focused primarily on patients with acute otitis  
8 media, and the drugs like in the penicillin,  
9 cephalosporin, macrolide classes have been  
10 developed for that indication.

11 You have heard today the proposal that we  
12 consider recurrent acute otitis media and treatment  
13 failure, also sometimes referred to I guess as  
14 persistent or nonresponsive otitis media, as a  
15 separate category.

16 For example, I think we have seen studies  
17 looking a fluoroquinolones for these kind of  
18 indications and also high-dose beta-lactams. As  
19 was brought up earlier today, I think one of the  
20 reasons to consider this is, is this a population  
21 likely to predict patients with PRSP or otherwise  
22 resistant organisms. A corollary of that is  
23 whether this would be a way to encourage a more  
24 limited use of agents that we would feel should be  
25 reserved for treating organisms that are resistant.

1 [Slide.]

2 Then, we heard several presentations about  
3 clinical trial designs. The two that have been  
4 discussed are active control, normally, a  
5 non-inferiority design although I think the  
6 possibility could exist that one could even do a  
7 superiority design in an active controlled trial,  
8 and then placebo-controlled studies.

9 [Slide.]

10 Putting these three elements together,  
11 clinical trial design, diagnosis, and endpoints, I  
12 have tried to summarize sort of the categories of  
13 studies that could be done, and I was going to say  
14 in the interest of time, let me skip them, so that  
15 I think I will get an opportunity to go over them  
16 during the questions, as I read those.

17 [Slide.]

18 Let me just mention one thing. We have  
19 been talking clearly about the science of otitis  
20 media and treating children, but as regulators, I  
21 just did want to mention that there are certain  
22 constraints under which we operate, and the rules  
23 and regulations that are relevant in this  
24 particular context is the Code of Federal  
25 Regulations, Title 21, 314.126, which defines

1 adequate and well-controlled studies. These are  
2 relevant because our approval of drug products  
3 should be based on adequate and well-controlled  
4 studies. The different choices allowed us are  
5 placebo-controlled, dose-ranging, no treatment  
6 control, active control, or historical control.

7           There is another part in this section that  
8 I thought is also important, which is that these  
9 adequate and well-controlled studies should be  
10 conducted in patients who have the disease, and in  
11 quotations is the definition of that, which is  
12 that, "the method of selection of subjects provides  
13 adequate assurance that they have the disease or  
14 condition being studied."

15           In this case, we would assume that what we  
16 are looking for is patients with acute bacterial  
17 otitis media in contrast or just to compare them to  
18 patients who may be managed clinically as patients  
19 with otitis media.

20           [Slide.]

21           I just wanted to briefly then refer back  
22 to some of the remarks made by Dr. Powers earlier  
23 this morning, about the practical issues that face  
24 us. I think as we talk about tympanocentesis, this  
25 is not the first meeting that this topic has been

1 brought up, the question is really what are the  
2 barriers to performing tympanocentesis in clinical  
3 trials in the United States.

4 Another issue or question is that are  
5 placebo-controlled trials practical in the United  
6 States at this point in time. We have heard from  
7 Dr. Rochester and others that sample sizes could be  
8 smaller if placebo-controlled studies are  
9 undertaken.

10 How acceptable are these procedures to  
11 patients and to their parents? Can we perform  
12 trials more efficiently while still obtaining  
13 useful data?

14 With that overview, let me go ahead and  
15 turn to the questions.

16 The first question before us is:

17 Should a comparative trial incorporating  
18 tympanocentesis be required--and that word I think  
19 is used in context of what the Code of Federal  
20 Regulations requires that we do adequate and  
21 well-controlled studies--should it be required for  
22 demonstrating the effectiveness of drugs for acute  
23 otitis media?

24 As you deliberate this question, I think  
25 we would like you to keep in mind some of the

1 topics that have been discussed today including  
2 clinical-only studies, single tympanocentesis  
3 trials, double tympanocentesis trials, and  
4 placebo-controlled trials.

5 Consider also how predictive is a strict  
6 case definition of clinical otitis media to the  
7 pathogenesis of a bacterially documented acute  
8 otitis media. Consider also the relative value of  
9 comparative versus non-comparative studies and the  
10 use of tympanocentesis in these.

11 The second question we would like you to  
12 consider is whether you agree with the proposed  
13 definitions for recurrent otitis media and  
14 treatment failure in otitis media, and that this  
15 actually represents a separate population that we  
16 should study.

17 As you deliberate this question, consider  
18 whether the use of this definition is helpful in  
19 identifying patients who are more likely to have  
20 penicillin-resistant *Streptococcus pneumoniae* or  
21 perhaps other resistant pathogens, as well.

22 Consider the likelihood of differences in  
23 treatment response in this population versus the  
24 general population, and consider this as possibly a  
25 means to suggest that agents developed for this

1 population might not be used in the same wide range  
2 of patients as drugs developed for acute otitis  
3 media.

4 I am sorry, we have provided for you the  
5 definitions that Dr. Johann-Liang reviewed with you  
6 earlier.

7 The final question is: Do double  
8 tympanocentesis trials have a role in demonstrating  
9 effectiveness of drugs for general otitis media,  
10 acute otitis media, and all-comers, or for the  
11 subset of patients or the population of patients  
12 that have recurrent or treatment failure in acute  
13 otitis media.

14 In considering these questions, consider  
15 the timing of assessments, both clinical and  
16 microbiologic. Consider the importance, the  
17 relative importance of clinical and microbiological  
18 assessments.

19 Consider the ability of the on-therapy  
20 tympanocentesis results to predict clinical  
21 outcome, and whether practically, there are  
22 adequate sites within the U.S. and other parts of  
23 the world to perform the double tympanocentesis  
24 studies.

25 If we are so fortunate as to have time,

1 you could perhaps also give us some advice on  
2 alternative methods of clinical outcome assessment,  
3 such as I mentioned earlier, the time to  
4 resolution, the expected activity against the major  
5 pathogens, the role of other results, such as  
6 PK/PD, in vitro susceptibilities, age distribution  
7 within placebo and active controlled trials, and  
8 other factors, daycare attendance, prior antibiotic  
9 use, exclusion criteria, and seasonality.

10 DR. RELER: Thank you, Dr. Albrecht.

11 Committee Discussion and Vote

12 DR. RELER: In the ensuing discussion, I  
13 would like to encourage all of the persons at the  
14 table, both voting and non-voting consultants and  
15 guests, to express their viewpoint. There is much  
16 expertise here. Some individuals we have not heard  
17 from as yet. This is your opportunity, as well as  
18 responsibility, to speak up.

19 Secondly, to get a vote on these  
20 questions, I think it may work well to have a  
21 discussion of the subcomponents, then hearing that,  
22 which will be captured for the record as has been  
23 delineated earlier, some of you have seen remarks  
24 from past meeting portrayed on the slides, captured  
25 going back even decades, so don't be intimidated

1 that you will be quoted in perpetuity.

2 On the other hand, everything is not  
3 captured in the vote alone, but also the discussion  
4 is captured for the Agency's consideration in  
5 carrying forth the next steps.

6 Then, on the specific questions 1, 2, and  
7 3, we will actually have a show of hands to see how  
8 strong the consensus is on the individual questions  
9 posed.

10 Then, we will conclude with some  
11 additional discussion on the important but  
12 secondary fine points that Dr. Albrecht alluded to  
13 at the end of her discussion.

14 Dr. Dagan had a couple of points of  
15 clarification in terms of terminology, so we are  
16 all talking about the same thing.

17 DR. DAGAN: There are four points where  
18 people don't always mean the same thing, and I  
19 think we have to have it at least very clear. When  
20 you say "post-therapy," I mean some drugs are given  
21 for 3 days, some are given for 10 days, some are  
22 given for 5 days.

23 That is the point that I want to raise.  
24 My opinion is that we have to have one time for  
25 everybody because if you start to give 3 days, you

1 don't want to be in fewer than 10 days, so probably  
2 10 days would be the time when you end therapy by  
3 definition, even if you give 3 days.

4           That could be discussed or not, but this  
5 is the point where we have to at least know that it  
6 might be controversial.

7           The second point is day 4 to 6 or day 3 to  
8 5, it depends how you actually start to count. In  
9 our studies, and this is came to 4 to 6, we counted  
10 the first pretreatment day, I mean the first day of  
11 involvement is day 1. Now, we want to test the  
12 second tympanocentesis after 72 hours at least, so  
13 that is why it comes day 4 to 6, which is after 3  
14 to 5 days of treatment.

15           So, I don't think that day 3 to 5 is  
16 appropriate if day 1 is the first day. So, that is  
17 another clarification. We want to have 72 hours of  
18 treatment before we assess bacteriological outcome.

19           Then, people have used PRSP as a synonym  
20 to antibiotic resistance, Strep pneumonia, which is  
21 inappropriate. It is RSP. If you give macrolides,  
22 you really want to look at macrolide resistance,  
23 and if you quinolones, you want to look at  
24 quinolone resistance.

25           A secondary question could be penicillin

1 resistance and how you promote those. So for the  
2 summary slide, one of the summary slides uses PRSP,  
3 but should be actually resistant Strep pneumonia,  
4 not PRSP.

5           The fourth point is that when you do  
6 one-arm, say, Augmentin high dose, whatever,  
7 gatifloxacin, it could be still a comparative  
8 study, it depends what is your question.

9           If you establish a drug that is  
10 appropriate, penicillin-susceptible or whatever,  
11 pneumococcus is susceptible to that drug, you still  
12 do a comparative study, actually, it's a  
13 double-blind sort of study, because you don't know  
14 what is going to grow there, comparing the  
15 resistant organism to the established already  
16 treatment of the susceptible, so it could be still  
17 a comparative study, and then you have to site it  
18 appropriately, but it could be something that  
19 sounds like one arm, but it could be actually a  
20 very nicely non-comparative study looking at  
21 exactly cutoff of MICs and all others.

22           So, not necessarily you don't have a  
23 comparative drug, it's a non-comparative study, and  
24 that is another point that I wanted to make.

25           DR. RELLER: Thank you.

1           The first question, should a comparative  
2 trial incorporating tympanocentesis be required for  
3 demonstrating the effectiveness of drugs for acute  
4 bacterial otitis media?

5           Let's have then the discussion on the  
6 bullets below that would enable us to vote on this  
7 question, in essence, the centrality, if that is  
8 the conclusion, or complementary, what is the  
9 positioning of tympanocentesis in the regulatory  
10 requirement for rigorous, adequate clinical trials.

11           Discussions in the context of the bullets  
12 and the relevant issues.

13           Dr. Giebink.

14           DR. GIEBINK: Dr. Reller, I think that we  
15 should be aware that if the committee accepts the  
16 FDA's suggestion that the word "bacterial" is  
17 inserted into the title, then, we can skip over  
18 this bullet, because there would have to be  
19 tympanocentesis for middle ear culture, and we  
20 would be automatically then accepting the 1977  
21 guideline that absent a middle ear fluid culture,  
22 no claim could be made regarding the effectiveness  
23 of the anti-infective.

24           So, I think that point that was made by  
25 both FDA speakers slipped in, and perhaps we should

1 decide are we measuring antibiotics and developing  
2 indications for their use in clinical otitis media  
3 or in bacterial otitis media.

4           This gets to the issue of do you do  
5 scientific studies of antibiotics for the treatment  
6 of a particular infectious disease, or do you try  
7 to replicate clinical practice. I will express my  
8 bias right now for the former, and not the latter,  
9 because you can't get to clinical practice unless  
10 you have done the scientific study.

11           So, I favor doing tympanocentesis to  
12 define the bacterial nature of the infection, so  
13 that we can then measure the outcome, and we will  
14 talk about double taps later on. I have some other  
15 thoughts about that.

16           DR. RELLER: I purposely slipped that word  
17 in to get exactly what you hit on, because from the  
18 discussions presented, if other phenomenon, apart  
19 from bacterial infection, are self-limited, then,  
20 no matter what you were saying about acute otitis  
21 media, how would you know what category you were in  
22 without a microbiological confirmation of either  
23 the presence or the absence of an agent.

24           Additional discussion. Dr. O'Fallon.

25           DR. O'FALLON: I think that there are some

1 other ethical issues that haven't actually been  
2 expressed here explicitly, they are implicit, but  
3 they have been bothering me throughout this whole  
4 two or three years that we have been at this.

5           We have underneath this the fact that  
6 there is a large percentage of patients who are  
7 misdiagnosed as having --well, they don't have  
8 bacterial otitis media. Something like 25 percent  
9 is the data that we are seeing from these guys.

10           So, if there is no tap upfront, what we  
11 have is a bunch of patients who are being treated  
12 with something that isn't going to do them any  
13 good, and I think there is an ethical issue there.

14           Secondly, there is the ethical issue of we  
15 have been struggling with the creation or  
16 enhancement of the fast development of resistance,  
17 and if we are treating people with antibiotics that  
18 don't need them, I think my understanding is that  
19 that is going to increase the development of  
20 resistance.

21           So, I think that those two issues really  
22 need to be addressed when we try to argue that it  
23 is not fair to do the taps on the children.

24           Also, if we don't do a tap, there is  
25 inability to identify the subsets that would

1 benefit from that particular treatment. We have  
2 seen a lot of information that has been given here.  
3 I think that is a very important scientific and  
4 again ethical issue, because what we realize is  
5 that with so many children or in so many people,  
6 but mostly children, who have these acute otitis  
7 media, that we are looking at thousands, hundreds  
8 of thousands of people that are going to be treated  
9 based on these studies, and if we don't get the  
10 answer right, that is going to have a tremendous  
11 impact on the future of treatment of an awful lot  
12 of people.

13 I think this is a big stakes' game that we  
14 are dealing with here, and we need to get the  
15 answers right.

16 If we do a single tap versus a double tap,  
17 there is talk about it is not fair to the patients,  
18 but as they pointed out, I thought that was a very  
19 interesting thing. Because of this Pollyanna  
20 effect, if you do the double tap, you use so many  
21 fewer patients that actually, the number of taps  
22 administered is fewer. You are tapping fewer kids  
23 if you do a double tap study.

24 So, if you are going to argue on the tap  
25 business, I think that that is an important piece

1 of information to think about, again, as a critical  
2 issue.

3 I do think, again, placebo or not, the  
4 question is what are you trying to do. If you are  
5 trying to prove the effectiveness of a new drug, if  
6 you are trying to show that it has any activity,  
7 then, it really should have a placebo.

8 Again, the fact that 25 percent or better,  
9 even the ones that have pathogens there, treatable  
10 pathogens, the fact that some high percentage, 75  
11 to 80 percent of them are going to resolve without  
12 any treatment means that we are not being unfair.  
13 It is not like they have leukemia or something.

14 The ethical issue of not treating them, of  
15 giving a placebo, is not the same as it is, say, in  
16 a leukemia study. So, I think there is an ethical  
17 issue there.

18 I think that I will quit there because I  
19 have other points, but I can't read them.

20 [Laughter.]

21 DR. RELLER: Dr. Bell.

22 DR. BELL: I want to congratulate Dr.  
23 O'Fallon. She has said probably better than I  
24 could exactly what I wanted to say. I totally  
25 agree that for the clinical studies in the future,

1 clinical diagnosis at entry is not acceptable. I  
2 am in favor of tympanocentesis at entry. We have  
3 to make sure these antibiotics work, not just for  
4 the patient, but also to minimize the selective  
5 pressure that is exerted on favoring antimicrobial  
6 resistance.

7 I would be very interested in seeing  
8 placebo-controlled trials and I would also just to  
9 say we need to know which bacteria are in the ear  
10 and whether they are sensitive to the antibiotic  
11 being studied, because it could turn out in the  
12 future that those incidence rates of bacteria  
13 etiology might change, and we need to know that  
14 information for that drug.

15 So, I just want to totally agree.

16 DR. RELLER: Dr. Nelson and Dr.  
17 Pichichero.

18 DR. NELSON: What has impressed me here is  
19 the devil is very much in the details of all of  
20 this information. Personally, I found the most  
21 helpful presentation to me and sorting out from the  
22 perspective of someone who chairs an IRB is Dr.  
23 Pichichero's presentation of benefits, risks, and  
24 the like.

25 I would like to present what I see as

1 perhaps a way of getting through the forest. It  
2 would bother me if we started tapping kids, which  
3 everyone says we diagnose poorly, in order to use  
4 that as an enrichment strategy to make sure that we  
5 have the right group to go into a study.

6           The thought that occurred to me is given  
7 the 80 percent response rate and the percent viral  
8 etiology, that you could argue quite convincingly  
9 that a three-arm placebo trial is appropriate for a  
10 clinical diagnosis and a clinical endpoint, and  
11 that you actually could use that as a first phase  
12 of an enrichment strategy defining failure, which  
13 could be defined in a way similar to the  
14 indications for doing a tympanocentesis that was  
15 presented by Dr. Pichichero.

16           You could also have an arm that goes in,  
17 which could be into that second phase, which could  
18 be a severity of illness, toxic, bulging, febrile  
19 child, perhaps other things, to where they would go  
20 in immediately to the second phase, which would be  
21 a double tap comparative trial.

22           I think the whole issue of the efficacy of  
23 the tap itself, I think raises an interesting  
24 question of how you would design that, does that  
25 really mean it's an add-on trial of antibiotic on

1 top of tap, or should you have a tap alone arm.

2 So, in listening, I think I would hope  
3 ultimately that FDA would begin to list 50, 51, 52,  
4 53, and 54 as part of their regulatory constraints  
5 besides just the desire to have good science.

6 I think there is equipoise if you are in  
7 the clinical setting, and so that fits in 50-52,  
8 which is the direct benefit. If the tap is being  
9 done by someone who has done 1,000, and teaches  
10 others to do it, it looks to me like it fits in a  
11 minor increase over minimal risk, and the second  
12 tap wouldn't necessarily have to meet a constraint  
13 of providing benefit.

14 The first tap would provide benefit, but I  
15 would also be worried that those taps would be done  
16 by people without sufficient expertise unless they  
17 are privileged or certified in some way to be able  
18 to perform it.

19 I have never done one, and I work in an  
20 intensive care unit. I have never actually seen  
21 one done until today. So, you know, it is not out  
22 there being used a lot.

23 So, I guess to summarize, what I began to  
24 sort of think about is a way that the Phase I, the  
25 clinical diagnosis could be enriched by not using

1 the tap, but by using basically a three-arm,  
2 randomized phase to get into it, and then, at that  
3 point, take the non-responders, the recently  
4 treated, and the severe ones immediately that could  
5 bypass that first phase and put them into a double  
6 tap trial at that point.

7 A company that wants to do that through  
8 both phases could end up potentially with labeling  
9 either for the general indication or for the  
10 specific limited indication, because their  
11 motivation obviously is to want to have the general  
12 indication, so it might be able to kill a bunch of  
13 birds with the same stone.

14 DR. RELER: Dr. Pichichero, Dr. Chesney,  
15 and Dr. Sumaya.

16 DR. PICHICHERO: I wanted to comment on  
17 the notion of placebo-controlled trials before  
18 there gets too much of an enthusiastic endorsement  
19 of that idea by the committee or the FDA.

20 Several of you are quoting a rate of 75 or  
21 80 percent placebo response rate. As Dr. Paradise  
22 briefly alluded, if you look at the actual studies  
23 of placebo-controlled trials, there are not many.  
24 The entry definition of otitis media is so vague or  
25 nonexistent that I would question whether many of

1 those children had otitis media, and if they did,  
2 whether they had otitis media fusion rather than  
3 acute otitis media.

4           So, I think at this time we really don't  
5 know what the placebo response rate of children  
6 with otitis media might be, but my suspicion is if  
7 you use a bulging tympanic membrane as the single  
8 most important criteria, it is not going to be 75  
9 or 80 percent spontaneous cure.

10           Secondly, it was mentioned in Dr.  
11 Rochester's presentation that if we were to do  
12 placebo trials, we would need careful follow-up.  
13 Does that mean that you are going to follow the  
14 patient and see them every day, and even if you do,  
15 how many cases of meningitis or mastoiditis that  
16 you pick up early would be a tolerable level in the  
17 United States?

18           In my own practice, one would be  
19 intolerable. Therefore, as an investigator in the  
20 field, I would be very reluctant to participate in  
21 a placebo-controlled trial to ask my patients to  
22 accept a placebo in what I think is bona-fide  
23 otitis and to accept a risk in my community that I  
24 would cause one child to get meningitis or  
25 mastoiditis.

1           My last point about the tympanocentesis is  
2 that in my experience, this procedure causes no  
3 more pain than a venipuncture, which we do  
4 routinely, for example, in vaccine trials multiple  
5 times to children, and what I see in terms of the  
6 amount of pain that it induces, the amount of  
7 change in heart rate on the pulse oximeter, the  
8 amount of times it takes a child to recover, in  
9 experienced hands, it is the same as a  
10 venipuncture.

11           Those are my points for the moment.

12           DR. RELLER: We will stick with our  
13 rotation, so that everyone gets a chance. Then, we  
14 will come back to Dr. Marchant. Dr. Chesney.

15           DR. CHESNEY: Just three brief comments.  
16 Dr. Paradise's comment that we have all wondered  
17 about whether a tap is therapeutic, and if we limit  
18 our studies to those involving tympanocentesis,  
19 that is not going to apply to the real world,  
20 because most people are not going to do taps before  
21 they treat otitis media, so can we really  
22 extrapolate studies that involve tympanocentesis to  
23 the real world.

24           The second point, I think we do need  
25 tympanocentesis studies for sure, and again we have

1 all talked about this now for a number of years,  
2 particularly now that we have the pneumococcal  
3 vaccine, because we really don't know that PRSP is  
4 going to persist.

5 We don't know that other strains are going  
6 to pick up the resistance organisms, so I think we  
7 really don't know what the future of otitis media  
8 with respect of PRSP is, I don't think, or RSP.

9 The third point that I wonder about is if  
10 we really do placebo controls, and a year down the  
11 road that child turns out to have hearing deficit  
12 or developmental delay, where are we going to be at  
13 that point legally, and do we know enough about the  
14 relationship between acute otitis media, no  
15 treatment, and hearing and developmental delays  
16 following that.

17 DR. RELER: Dr. Sumaya, then, Dr.  
18 Marchant.

19 DR. SUMAYA: I am reaffirming what Dr.  
20 Pichichero has just said, because I was very  
21 worried about the discussion on the 70, 75 percent,  
22 up to 80, of spontaneous resolution, because I  
23 think it is very unclear how that relates to  
24 specific pathogens in the ear, whether they are  
25 viral or if it's a pneumococcus or whatever.

1           The other part of it was the complication  
2 rate that may be related to that, and, thirdly, is  
3 clinical manifestations that the child may have on  
4 day 1, 2, 3, 4, that may be different depending on  
5 the pathogen.

6           Secondly, on the tympanocentesis, again, I  
7 would refer to what he just said. When an RFP  
8 eventually comes out, I would assume that there is  
9 going to be some very good requesting of  
10 experienced people who do tympanocentesis, because  
11 I think in experienced hands, it is a simple  
12 procedure; in non-experienced hands, I wouldn't go  
13 for that.

14           I am in favor of the tympanocentesis on  
15 entry.

16           DR. RELLER: Dr. Marchant.

17           DR. MARCHANT: The first thing I would  
18 like to do is comment on the issue of placebo  
19 trials. I think there are some placebo trials in  
20 the literature that are instructive. None of them  
21 are completely ideal. The one that was done in  
22 Pittsburgh is an interesting case in point. There  
23 is also some European trials that were reasonably  
24 well done, although typically on selected  
25 populations.

1           In terms of what do the best placebo  
2 trials say or what do the meta-analyses of placebo  
3 trials say about the response of otitis media  
4 antibiotics, it is that children get better a  
5 little bit faster perhaps by a day, a day and a  
6 half, if you use antibiotics than if you don't.  
7 There is a benefit.

8           So, if we are going to do a  
9 placebo-controlled trial, then, we are going to  
10 withhold a therapy that might have some benefit to  
11 that child. I think that, yes, as Dr. O'Fallon  
12 pointed out, they are going to get better, most of  
13 them, fairly quickly.

14           That doesn't preclude doing a  
15 placebo-controlled trial, but I would want to see a  
16 placebo-controlled trial that was going to really  
17 teach us something new, and not just be a  
18 placebo-controlled trial for the purposes of new  
19 drug B that we are now testing for licensure, but  
20 rather that if we are going to do the placebo  
21 group, that we do it to identify a group of  
22 patients that don't need treatment because they are  
23 milder or something of that sort.

24           The other thing, I know I sound a little  
25 bit like a broken record, but it keeps coming up,

1 and that is, if you do a clinical-only trial at  
2 entry with a placebo arm, et cetera, you just drive  
3 that sample size issue back up again, and it always  
4 needs to come back into the conversation.

5 Those are my comments.

6 DR. RELLER: Dr. Dagan.

7 DR. DAGAN: Again, going for a second to  
8 the placebo issue, it is very nice to talk about  
9 placebo, but if you really read those articles, and  
10 I promise you I read them much more than once, all  
11 the placebo except the one that was done by Howie,  
12 which I use all the time as my reference point,  
13 they have limitations because they don't want to  
14 put into that study, patients that are going to be  
15 actually in danger if they get placebo.

16 So, the one that you cite, of 1 day out of  
17 14, or whatever, took away those with high fevers,  
18 took away those with real bad bulging, took away  
19 those who were looking a little bit more sick, et  
20 cetera, so eventually, you will come down to those  
21 who don't really need antibiotics, then, it is only  
22 1 day out of 14, so the real placebo study that  
23 enrolls all patients with otitis including those  
24 who need antibiotics the most is nonexistent for  
25 the moment except Howie's study.

1           So, I think this is one very important  
2 point. I don't think the Ethics Committee will  
3 approve us, or ourselves will approve ourselves, to  
4 do a study with placebo without a priori ruling out  
5 those who need antibiotics the most. So, this is a  
6 point, and I think therefore, it is not feasible to  
7 do it.

8           The other point is talking about Dr.  
9 Nelson's remark. He works at the ICU, and he  
10 rarely sees these because this is not an ICU  
11 procedure, this is a very benign procedure, you  
12 don't do it in ICU.

13           Actually, my ICU people, it is very  
14 difficult to convince them to take blood cultures,  
15 they are so busy doing the big stuff. This is the  
16 small stuff. A second blood culture in study to go  
17 to ICU to get it, which is totally benign, they  
18 always forget to do it.

19           My point is that Dr. Paradise mentioned  
20 the word "dangerous." Now, we were talking about  
21 this last time, and people have talked about this  
22 time. I don't think it is dangerous, I didn't see  
23 any real complication out of the dozens of  
24 thousands of tympanocentesis we do in our center,  
25 and it is one center for the whole region. If we

1 had this complication, we would have seen them.

2 I think that the point again and again and  
3 again, otitis media is a disease with  
4 complications, inappropriate treatment is procedure  
5 with complications. Giving drugs that act similar  
6 to placebo is much worse than placebo because they  
7 promote resistance, and therefore, knowing what you  
8 do is the most ethical thing, and therefore I don't  
9 see any danger of doing tympanocentesis.

10 I think this is a very, very important  
11 point, and I would like everybody who says it is  
12 dangerous to justify why he or she says it is  
13 dangerous.

14 The last point that I want to make is that  
15 Ethics Committee, like all of us, like the FDA,  
16 they are subject to continuous education, and what  
17 is ethical and what is not ethical, 10 years ago it  
18 would be unheard of.

19 Dr. McCracken is the editor of his  
20 journal, sent me back a case report of quinolones  
21 in children with a letter, which I keep, saying  
22 that he would never publish a study on such drug  
23 that would never be used in the United States.

24 So, what is ethical now and what is not  
25 ethical changes. If FDA thinks this is the most

1 appropriate study to do, together with the Advisory  
2 Committees, and together with experts, it is going  
3 to become ethical slowly but surely as people would  
4 never believe that we can move the FDA to do again  
5 bacteriology, and it is now moving.

6 Don't take a snapshot of what is ethical  
7 now, convince the Ethics Committees how dangerous  
8 it is to treat without knowing what you do, and  
9 therefore, it will become slowly but gradually  
10 ethical.

11 DR. RELLER: Dr. McCracken.

12 DR. MCCRACKEN: Well, one thing I have  
13 learned in medicine, never say never, so I don't  
14 think I said never in that letter I wrote.

15 The comments I want to make, obviously, my  
16 bias is well known, it has already been on the  
17 screen a couple of times, but it harkens back to  
18 the very simple principle, what is an antibiotic  
19 for. Why are we giving an antibiotic for otitis  
20 media? It is not a decongestant, it's an  
21 antibacterial, and if you are going to be  
22 evaluating a drug for otitis media, for meningitis,  
23 which happens to be my real love, you have got to  
24 know whether it works, and you don't know unless  
25 you can show bacteriologic eradication. That is the

1 only thing that drug does.

2           Now, it has secondary benefits obviously,  
3 but its primary benefit is only for the eradication  
4 of that organism either with the help of the host  
5 or not, but it is the eradication.

6           So, not only am I in favor of an initial  
7 tympanocentesis for the reasons stated, and I think  
8 Scott did a good job in doing that, but I am still  
9 in favor of a second tympanocentesis at least in a  
10 substantial subpopulation to demonstrate exactly  
11 what this drug is doing, does it eradicate it in a  
12 timely fashion.

13           This is true in many bacterial diseases -  
14 sepsis, meningitis, otitis, urinary tract, it is  
15 all the same. You just have to pick the time when  
16 you want to demonstrate that.

17           Two other points. It has been stated that  
18 tympanocentesis probably may improve outcome, and  
19 that could be true to a certain extent, but I just  
20 remind you of Ron's study that he showed already,  
21 with azithromycin versus Augmentin, the regular  
22 formulation of Augmentin where both groups got  
23 double tympanocentesis, and yet there is still a  
24 difference, both in the clinical scores and in the  
25 outcome.

1           So, if it does help improve symptoms to  
2 whatever the modest degree might be, it doesn't  
3 obscure the clinical outcome, which is very  
4 important.

5           The final point about placebo. Mike  
6 Pichichero is concerned about meningitis, and I  
7 will just say that in the British Medical Journal  
8 placebo study, published in 2000, in the placebo  
9 group was a case of meningitis, so it is not a  
10 far-flung possibility.

11           DR. RELER: Dr Wald has a comment, but  
12 just to follow up on that point. It seems to me  
13 this issue of placebo and the requirement for  
14 tympanocentesis are related. Accepting, I think all  
15 would agree that the rare, but potentially  
16 devastating complications are related to bacterial  
17 infection, the abscess in a closed space, I mean it  
18 was described earlier.

19           So, the need for placebo, it seems to me  
20 is related to showing a difference, tap water, if  
21 you have got a study population that is so diluted  
22 by people who don't have the real thing, that you  
23 might come up with not being able to show a  
24 difference, but if you have a tympanocentesis, and  
25 you know where you are to start with, as Dr.

1 McCracken has just mentioned, one can show  
2 differences in efficacy of agents that would  
3 otherwise be obscured for the reasons that Dr.  
4 Marchant has emphasized earlier.

5 Dr. Wald.

6 DR. WALD: I would comment on that, as  
7 well, the need for placebo-controlled trials, and  
8 that is, that there is tremendous enthusiasm now  
9 among physicians, as well as the lay public, to not  
10 treat acute otitis media. Now, there don't seem to  
11 be too many of those folks in this room, but there  
12 is a tremendous enthusiasm for a no-treatment  
13 policy, and I think it is essential that we show,  
14 in fact, that this is an acute bacterial infection  
15 that benefits substantially from the antimicrobial  
16 therapy, and the only way that we can do that is  
17 with a placebo-controlled trial that is very  
18 tightly monitored.

19 Although I share concerns about  
20 meningitis, I would say two things along those  
21 lines. One, there has never been very good  
22 evidence that otitis leads to meningitis. They  
23 occur in some patients together, but I think that  
24 one leads to the other is not clear, and that we  
25 were never in a better position to do this study

1 than we are now because of the availability of  
2 pneumococcal conjugate vaccine, which is really  
3 going to protect the meninges of the majority of  
4 children who we will be studying who have been  
5 immunized.

6 In fact, you could make it a requirement  
7 that anybody who entered a placebo-controlled trial  
8 had received the pneumococcal conjugate vaccine,  
9 and I think that would provide a lot of protection.

10 I think there is a general consensus in  
11 the room that tympanocentesis is appropriate for a  
12 lot of patients who are going to be studied, and it  
13 is essential, I think, in terms of establishing the  
14 microbiology, which is an ever-changing phenomenon.

15 I would like us to require that when  
16 investigators submit cases or when industry submits  
17 cases, that there be a certain minimum level that  
18 investigators achieve in order to enter patients  
19 into those studies, you know, whether that be a 75  
20 percent positive culture or an 80 percent positive  
21 culture, I think we need to insist on some minimal  
22 level, and that those very same investigators who  
23 achieve competency at that level, be the people who  
24 can do clinical-only studies where we know that  
25 they have established their expertise in the

1 diagnosis of acute otitis media.

2 Just one word about double tap studies.

3 It is true that you will tap fewer children and do  
4 fewer taps if you do double tap studies, but you  
5 will not be benefiting all the children when you do  
6 that.

7 When a child is symptom-free on the 4th or  
8 5th day of therapy, I think it is very hard to ask  
9 permission of that patient to tap that child,  
10 whereas, at least at the entry points, there is  
11 some thought that every child who undergoes  
12 tympanocentesis will benefit from that procedure.

13 DR. RELLER: I don't know who was first  
14 here, but Dr. Marchant and Dr. Soreth.

15 DR. MARCHANT: I am having a little  
16 trouble understanding here. If we withhold  
17 antibiotics from children in a placebo-controlled  
18 trial, and they have symptomatic otitis media, even  
19 the mild variety, such as the one in the Kaleida  
20 trial, I think we are using a study design which is  
21 going to result in more discomfort and more pain  
22 for those patients.

23 So, my earlier comment was motivated we  
24 need to learn something good from doing such a  
25 trial because if we are going to have a trial that

1 has more discomfort or pain, we should at least get  
2 something scientific about it.

3           On the flip side of that, when you talk  
4 about tympanocentesis, the second tympanocentesis,  
5 in my mind, is justified even in an asymptomatic  
6 patient because we are getting the data that we  
7 need to know whether the drug is going to work for  
8 all those children out there, and for that reason,  
9 it is justified.

10           Now, there are other design approach, tap  
11 and tap of failures, but it has other implications  
12 in order to get that information, but I think there  
13 needs to be some consistency about how much  
14 discomfort we are going to design into trials and  
15 for what benefit for patients, and be clear about  
16 what those are.

17           DR. RELER: There will be additional  
18 discussion about double tap. We will be voting on  
19 whether tympanocentesis is essential for any trial  
20 that would claim to show efficacy for the treatment  
21 of acute otitis media.

22           Dr. Soreth, Dr. Leggett, Dr. Ramirez, and  
23 Dr. Nelson.

24           DR. SORETH: I think a comment that  
25 pertains either to active control trials or to the

1 prospect of a placebo-controlled trial is that in  
2 the development of a novel compound for any  
3 infection and this one, acute otitis media, we  
4 can't forget that part of the equation involves  
5 safety.

6           So, whether we have an active-controlled  
7 trial with some standard agent that we feel we know  
8 a lot about or a placebo-controlled trial, we can't  
9 assume that the new drug is completely safe or safe  
10 enough, so part of what we might get out of a  
11 placebo-controlled trial is information about  
12 safety, and similar information can come in an  
13 active-controlled trial, but we can't assume that  
14 we have all the data to say absolutely the way to  
15 go in every case of acute otitis media is  
16 antibiotics because we know that a day's difference  
17 is the end-all and be-all.

18           It may be, but I don't know that we have  
19 enough data to say that definitively, it is, so we  
20 can dismiss completely placebo-controlled trials as  
21 an issue.

22           I think I had a second point, but my  
23 thought train may have been derailed.

24           DR. RELLER: We will hear from Dr. Leggett  
25 and Dr. Ramirez. It is very important for the

1 continuity, the togetherness of the session that we  
2 all here to the end, so after comments from these  
3 two, and there will be time to have throwbacks to  
4 some of these issues because they are all  
5 interconnected, we will vote after these two  
6 comments on Question 1, move on to Question 2.

7 Dr. Leggett.

8 DR. LEGGETT: I had two questions to bring  
9 up along the lines of the tympanocentesis and the  
10 single or double, in the sense as follows. If we  
11 are going to try to include folks who have  
12 recurrent otitis or who have recently received  
13 therapy, and therefore, are more likely to have the  
14 more severe disease, and we tap them, and because  
15 they have just been on antibiotics, the  
16 tympanocentesis is negative, what do we do about  
17 that?

18 The second question is presumably one of  
19 the purposes of the guidance is to improve upon  
20 some places where the FDA recognized that there  
21 were some problems as in the recent azithromycin  
22 case. Without a double tympanocentesis study, I  
23 would like to hear some comments about how we avoid  
24 doing the exact same thing again.

25 Those are two questions.

1 DR. RELLER: Dr. Ramirez.

2 DR. RAMIREZ: I just want to make a  
3 general comment regarding the first tap. It was  
4 already mentioned, it seems to me that the clinical  
5 symptom of acute otitis media involved a large  
6 number of patients that may not have the disease or  
7 less number of patients may have a viral infection,  
8 and when we design clinical trials for infectious  
9 diseases, we never say, okay, I want to see what  
10 happened with these antibiotics against meningitis,  
11 because we don't take the meningitis syndrome and  
12 try an antibiotic, because we know there are plenty  
13 of patients who have a viral meningitis.

14 We always design antibiotics for bacteria  
15 meningitis, we don't discuss antibiotic for chronic  
16 extravasation of chronic bronchitis, we discuss  
17 antibiotics for acute bacterial extravasation of  
18 chronic bronchitis.

19 I think that this is supposed to be a  
20 discussion of antibiotics for acute bacterial  
21 otitis media. Now, how do we know if the  
22 meningitis is bacterial? We put a needle, and we  
23 figure out is this a virus or is it a bacteria.

24 I think that we have the possibility to  
25 make a microbiological diagnosis, it is not just to

1 define the etiology, it is to define the disease  
2 because we don't put needles in the lung to define  
3 if the patient has a bacterial pneumonia, because  
4 then the complications are a bit high, but  
5 otherwise, if we all of a sudden find a way to put  
6 a needle in the lung without complications, we  
7 would put needles to figure out what is there.

8 I think that was already explained clearly  
9 by the experts that this is a very simple  
10 procedure, and if have the possibility to eliminate  
11 all the known bacterial cultures of otitis media,  
12 to me it is a no-brainer that if I decide on a  
13 study to study acute bacterial otitis media, I need  
14 to make the right diagnosis at least in a  
15 significant number of patients.

16 Now, where we are mixing those, we  
17 discussed yesterday in this committee, one thing is  
18 a clinical trial for the right indication, and the  
19 other thing is clinical practice. Now, we know  
20 that what we get approved here for these 20 percent  
21 of acute bacterial otitis media is going to be used  
22 in the other 80 percent that have viral disease,  
23 but this is a different discussion, because this is  
24 because the general practitioner, it seems to me,  
25 they use the clinical syndrome for diagnosis, they

1 are not going to be doing the tap.

2           The antibiotic is going to be overused in  
3 some patients with viral otitis media, but I don't  
4 think that we are going to be able to prevent this  
5 unless we have a very, very simple way to define  
6 these are bacterial or viral with a needle, and  
7 this is why we have an overuse of antibiotics, but  
8 still, it is going to be justified overuse from the  
9 clinical point of view.

10           To me, to define that antibiotic that is  
11 well expressed, it needs to kill a bacteria. This  
12 is the only thing that we ask for the antibiotics.  
13 First of all, we need to figure out is there  
14 bacteria there.

15           DR. RELLER: Thank you.

16           From the voting consultants, Drs. Chesney,  
17 Giebink, and Nelson, and the current members of the  
18 committee, a vote. We will start to my right.

19           Basically, should the FDA require a study  
20 that incorporates tympanocentesis, not necessarily  
21 as the only evidence, but as one criterion for the  
22 approval, looking forward, of a drug that would be  
23 claimed to demonstrate efficacy in the treatment of  
24 acute otitis media?

25           Dr. Nelson, yes, no?

1 DR. NELSON: I have not heard enough  
2 information for me to vote, and I had a specific  
3 question which I wanted to ask to get that  
4 information.

5 DR. RELLER: Excuse me?

6 DR. NELSON: The question I was going to  
7 ask if you said we would vote before, I wanted to  
8 ask to get the information so then we would vote,  
9 so I am happy to abstain and wait, or whatever, but  
10 I am not going to vote yes or no based on what I  
11 have heard.

12 DR. RELLER: Okay. So, that's an  
13 abstention.

14 Dr. Glode.

15 DR. GLODE: Yes, I think a comparative  
16 trial incorporating tympanocentesis should be  
17 required.

18 DR. BELL: Yes, I think that  
19 tympanocentesis should be required initially. I do  
20 not believe it should be required for follow-up. I  
21 am not sure it is ethical. I think too many  
22 parents will not consent, and it will make subjects  
23 too hard to enroll.

24 DR. RELLER: Thank you, Dr. Bell.

25 I vote yes, I think we need to know what

1 is there to be able to judge efficacy.

2 Dr. Patterson.

3 DR. PATTERSON: I think tympanocentesis  
4 studies should be the standard. I think many of  
5 those may be single tap studies, which should be  
6 accepted because they will be done over a wider  
7 geographic range, and I think we need the  
8 information about the microbiology and  
9 susceptibility over a broad geographic range.

10 The double tap studies will be useful in  
11 subsets in centers where those are the standard of  
12 care. Placebo trials, I have some concerns about.  
13 Even with the Prevna [ph], which is I think of  
14 interest, would we be selecting then for less  
15 severe disease, making pneumococcal disease less  
16 common in this group, and therefore, less sick or  
17 severe population.

18 The clinical-only studies in the setting  
19 of safety or placebo trials, which I have a little  
20 discomfort with, and I am going to throw in age  
21 distribution. I think at least 50 percent should  
22 be 6 to 24 months.

23 DR. RELER: Thank you.

24 Dr. Wald.

25 DR. WALD: Yes.

1 DR. SUMAYA: Yes.

2 DR. GIEBINK: Yes.

3 DR. O'FALLON: Yes, and I enthusiastically  
4 endorse what Dr. Patterson said.

5 DR. RELLER: Dr. Chesney.

6 DR. CHESNEY: Yes, also without  
7 qualification.

8 DR. RELLER: Dr. Ramirez.

9 DR. RAMIREZ: Yes.

10 DR. EBERT: Yes, although I think that we  
11 need to be clear on entrance criteria for patients  
12 to enter a study involving a tap.

13 DR. RELLER: Dr. Leggett.

14 DR. LEGGETT: Yes, a comparative  
15 tympanocentesis trial should be the pivotal trial.  
16 I wanted to address one of the other points we were  
17 supposed to, and I haven't heard yet, about the  
18 non-comparative versus comparative.

19 If we use non-comparative data, it should  
20 be used for gathering more safety data or for  
21 boosting the N for efficacy purposes, but I think  
22 that is where we can incorporate PK/PD things with  
23 MICs to give us more information about the  
24 breakpoint while we are doing the trial.

25 DR. RELLER: Dr. Cross.

1 DR. CROSS: My answer is yes, but since I  
2 didn't have the opportunity to make a number of  
3 comments earlier, I will take this opportunity to  
4 say that if we do encourage comparative trials of  
5 drug A and drug B, it seems that we almost have to  
6 invite either a placebo trial or ask the FDA to  
7 come up with a response if drug B is 70 percent and  
8 drug A is 90 percent, what happens in terms of  
9 judging the 70 percent of there is no placebo, will  
10 the FDA accept that for approval, that is, is that  
11 70 percent drug sufficiently effective for approval  
12 even though it is inferior to another approved  
13 antibiotic.

14 So, I think that the question is kind of  
15 in a way tied into the issue of placebo-controlled,  
16 and in terms of addressing the point of a placebo  
17 control, that Dr. Dagan made, I mean I think it is  
18 really incumbent upon us if we include  
19 placebo-controlled, that we would have to really  
20 tighten up the clinical definitions in a way that  
21 would really incorporate who are the people who  
22 were excluded out of all those other  
23 "placebo-controlled" trials.

24 Then, lastly, in terms of the issue of  
25 double tap, I would like to return to an issue

1 raised by Dr. Giebink, where he showed the cells,  
2 and there were certain people who were  
3 bacteriologically cured, but were clinical  
4 failures.

5 I think by doing a double tap in those  
6 patients, it really affords us the opportunity to  
7 say are there any inflammatory media that may have  
8 resulted from the bacteriologic cure which may  
9 account for the clinical failure, which may at  
10 least lead us into other therapeutic areas.

11 DR. RELER: Thank you.

12 Question 2. Does the committee agree with  
13 the definitions below of recurrent acute otitis  
14 media and AOM treatment failure, used to identify a  
15 separate population of patients for study?

16 There are some additional things that we  
17 are to address in the discussion, but the two  
18 definitions are listed below, and I think it would  
19 be helpful to take these individually.

20 So, first of all, does the committee--and  
21 maybe a brief discussion on this--does the  
22 committee feel comfortable with, feel it is  
23 appropriate to define recurrent acute otitis media  
24 with the numbers given, that is, 3 or more episodes  
25 of AOM over the last 6 months, and 4 or more

1 episodes of AOM over the past year?

2           Those have been used earlier in slides  
3 from the experts in the field. Are these pretty  
4 well accepted? Do they need to be modified?

5           Yes, Dr. Hoberman.

6           DR. HOBERMAN: One additional comment.  
7 There is two different groups of children that will  
8 not be included if those two definitions are used.  
9 One is children that have early infection during  
10 the first six months of life, but we can argue  
11 whether it should be nine months, may not have had  
12 enough time because they did not live through the  
13 previous winter to have declared as otitis-prone,  
14 so an early in life otitis media would probably be  
15 similar to more than 3, and children that have had  
16 an otitis media within the previous month might be  
17 at a similar risk as somebody that had 3 episodes  
18 over the past 6 months or 1 year.

19           So, those two additional groups of  
20 children may enrich the population at risk.

21           DR. RELLER: Dr. Paradise, Dr. Giebink.

22           DR. PARADISE: I would just want to add  
23 the qualifier of documented episodes, because it  
24 has been our experience, and that of many other  
25 people, that situations don't always pan out as

1 they had been forecast.

2 DR. GIEBINK: I would feel more  
3 comfortable with a definition that embraced the  
4 high risk and the low risk child, and to not try to  
5 wordsmith the definition of high risk at this kind  
6 of a setting.

7 The beauty of the schema that was proposed  
8 by Rosemary is that this is the exact scheme that  
9 came from a CDC consensus discussion about five  
10 years ago, published by Scott Dowell [ph] in  
11 George's Journal.

12 So, it is a scheme that is being used now  
13 in clinical practice, and in terms of meeting the  
14 pragmatic threshold for industry to develop trials,  
15 it has a relatively large hoop to jump through.

16 So, I think that high risk and low risk,  
17 good idea. I share Dr. Hoberman's worries about  
18 age and number of episodes, and I think that just  
19 needs a lot more discussion to define what is a  
20 high risk episode.

21 DR. RELLER: Dr. Marchant.

22 DR. MARCHANT: In terms of the reasons why  
23 in a single episode, a child will not do well, one  
24 is resistant bacteria, which is mostly related to  
25 prior antibiotic use and daycare exposure, thereby

1 prior antibiotic use by their mates in daycare.

2           The other one is young age. Dr. Paradise  
3 earlier talked about the host and the clear factor  
4 we have that predicts bacteriologic failure and  
5 clinical failure in Pittsburgh trials and double  
6 tap trials, and so on, is young age, and so the age  
7 factor, if you are going to enrich a population in  
8 terms of their risk for not doing well on  
9 antibiotics, age is an important issue, and you can  
10 cut it at 1, you can cut it at 2, or 18 months, or  
11 whatever, but that is a factor.

12           The recurrent otitis media definition per  
13 se, I believe that it is enriching the population  
14 mostly because those kids have already been on a  
15 lot of antibiotics, and maybe daycare, et cetera.  
16 On its own, I am not aware of it being a predictor  
17 for poor response inside a single episode of acute  
18 otitis media, so I am not sure it, on its own  
19 merits, is critical here, and I would be interested  
20 in the other folks that know the otitis literature,  
21 what their comment would be.

22           DR. RELLER: Dr. Wald and then Dr.  
23 Ramirez. I have asked Dr. Johann-Liang to bring up  
24 the definition that Dr. Giebink alluded to, because  
25 to the extent that there are vetted definitions

1 that might not as a necessarily definitive  
2 statement, but close to the mark, it might save us  
3 a lot of time if we have a target for trying to  
4 reach some degree of consensus.

5 Dr. Wald.

6 DR. WALD: I agree with the definitions,  
7 but I think that sort of categorizing children  
8 according to risk is more helpful, however, most  
9 children, the peak age incidence for acute otitis  
10 media is under 2, and we know that age is a risk  
11 factor.

12 So, most of the children that we will be  
13 entering into these studies, by definition, have an  
14 important risk factor. Although some of them may  
15 not attend daycare, we know that that is an  
16 increasing trend among U.S. children, and even  
17 those who don't attend daycare, go to church on  
18 Sunday morning, in the play group, or they go to  
19 mother's exercise class, and they are in a play  
20 group, or they go to McDonald's once a week, and  
21 they are in that little playground.

22 So, I think that a daycare equivalent is  
23 almost universal, as well. I think most children  
24 are in the high risk category, and maybe what we  
25 want to create is a low risk category for children

1 who are over 3 or 4, and who never had an episode  
2 of otitis media before, but the majority of  
3 children are really in a high risk category.

4 DR. RELLER: Dr. Dagan.

5 DR. DAGAN: Some risk studies looked at  
6 daycare center versus age versus previous  
7 antibiotic treatment, and they found each one to be  
8 independent risk factor, so what you say is  
9 correct, but probably if you go every day for 5  
10 hours together with kids, it is different than if  
11 you see them on Sunday morning for whatever, 3, 4  
12 hours at the play group.

13 So, I think that so far, the evidence  
14 tells us that each one is independent, and if you  
15 have all the 3, you multiply each risk by the  
16 other, and you get enormous risk. So I still think  
17 that this should be taken into account as for risk  
18 factors.

19 The other point is that when we take our  
20 1,000 cases with double tympanocentesis, and we  
21 look at those who have, first, otitis media or at  
22 least did not have otitis media in the last three  
23 months, or those who have clinical  
24 nonresponsive/recurrent otitis media, and you look  
25 at the MIC of the bug, this is the number one thing

1 that counts, and not the previous episode in terms  
2 of bacteriological eradication.

3           If you don't see lower bacteriological  
4 eradication, what you see is, in general, you have  
5 lower bacteriological eradication because you  
6 select for more resistance, but if you break them  
7 by MICs, you actually find exactly the same. Not  
8 only this, even if you have mixed infections, each  
9 of the bugs behave according to what they were  
10 supposed to behave according to the MIC.

11           So, I think that if you look at  
12 bacteriological eradication, it doesn't really  
13 matter. There are two slides that you want us to  
14 consider in this Question 2. One is in relation to  
15 whether you do to groups or one group, and I think  
16 that bacteriological eradication, what counts is  
17 the MIC and the dose of the drug.

18           For clinical responses, for the second  
19 group that has recurrent, relapsing, et cetera,  
20 they returned immediately, during treatment, to get  
21 to the next complication, then, the clinical  
22 outcome is going to be worse in one group than the  
23 other.

24           So, if eventually, this group here decided  
25 they want double tympanocentesis study, and look at

1 bacteriological outcome, it doesn't really matter  
2 which kids to take, and we have the evidence, and I  
3 can send these tabulated.

4           If you look for clinical outcome, it makes  
5 a lot of difference if you accept this--I am not  
6 sure you need two groups, but you need to analyze  
7 them separately.

8           DR. RELLER: Dr. Glode.

9           DR. GLODE: I don't see that there is two  
10 distinct populations, and I think it is very  
11 confusing to have them as two indications, so I am  
12 doing the study for group 1 indication, but not  
13 group 2, because it's a spectrum.

14           Recurrent otitis media, as an enrichment  
15 issue, is just a selection for people who have  
16 gotten antibiotic courses. So, if they got it for  
17 sinusitis, then, they are in group 1. Because they  
18 didn't have recurrent otitis, they are still going  
19 to have a higher risk of resistant pneumococci.

20           So, I think you can look at that by having  
21 the bacteriology and analyze that way, and I just  
22 think this is, I don't know, more confusing and  
23 suggests that there is two distinct populations  
24 when I don't think there really are.

25           DR. DAGAN: I think this was invented

1 because some drugs are intended not to be given to  
2 all children. Nobody mentioned that, but this is  
3 the main justification for me to put it in two  
4 groups.

5           If I don't want to give quinolones to  
6 every child, only to those that don't respond,  
7 then, I take this group and study this group as an  
8 indication for the specific study in order to limit  
9 the drug, not in order to get the better  
10 information.

11           DR. GLODE: Then, you do that as your  
12 Phase II of your bacteriologic failure, and you  
13 have no other choice, and so you must go now to  
14 this less safe antibiotic, but I think to use it as  
15 an excuse for testing those kinds of drugs is also  
16 a wrong reason to make these two groups.

17           DR. RELER: I think we are making some  
18 progress here. The last two comments, and then we  
19 are going to have a vote, and maybe, given what is  
20 heard, I mean we will see whether people think this  
21 is crucial to have this, not that it couldn't be  
22 incorporated, but crucial to have it, or is it the  
23 real issue is part (b), namely, treatment failure  
24 and what might be appropriate approaches there.

25           Dr. Bell, Dr. Ramirez, and then we must

1 take a stand on 2(a).

2 DR. BELL: Drs. Giebink and Dagan are  
3 correct in that this was developed some years ago  
4 by a group, some of which are in the room, that CDC  
5 convened to try and identify episodes where  
6 second-line treatment was not needed, at least  
7 empirically.

8 I guess the question is does this refer to  
9 clinical trial designs only, or is it what I think  
10 is the intention is the practical use by a  
11 practicing pediatrician, who is not going to do ear  
12 taps, and this is a nice, convenient category, and  
13 the clinical trials, the pharmaceutical companies  
14 might find it attractive to have this admittedly  
15 rough distinction. I am inclined to support it.

16 The final comment I want to make is that I  
17 guess I was a little surprised to see  
18 fluoroquinolones appear on the FDA slides and be  
19 kind of mentioned glibly as options. I think that  
20 requires a lengthy discussion in its own right, and  
21 I just would hate to see a message go out that that  
22 is a done deal.

23 DR. RELLER: Dr. Ramirez, do you have a  
24 comment?

25 DR. RAMIREZ: Yes. If I remember right,

1 we discussed this a lot. In this committee, we  
2 discussed the amoxicillin-clavulanate. The idea  
3 was trying to enrich the population. If you have  
4 an antibiotic that you want to get approval for  
5 penicillin resistant Streptococcal pneumonia, you  
6 don't want to get 1,000 children and get only 10  
7 penicillin resistant. The idea was just study in a  
8 specific group that we call an enriched population,  
9 that you have a very high chance that you want to  
10 get penicillin resistant Streptococcal pneumonia.

11 I would say that for a drug company that  
12 is looking for this indication, for PRSP, then,  
13 this may be a good possibility for them just to  
14 select these populations.

15 Now, this is different to say that because  
16 in this population, you have the greater chance for  
17 getting pneumococcal resistant, but as already  
18 mentioned, because all children or most children  
19 with this disease are less than 2 years of age, I  
20 would not use the same criteria to say to the  
21 clinician, now, you have a child with this.  
22 Without these risk factors, the penicillin  
23 resistance is not going to be there, because by  
24 definition, these are disease where penicillin  
25 resistance is going to be prevalent, and if one of

1 the risk factors is less than 2 years of age, it is  
2 going to be very difficult to make an algorithm for  
3 clinical practice to say you have these risk  
4 factors, use second line, you don't have these risk  
5 factors, use the first line, because you have to  
6 put less than 2 years of age as a risk factor, and  
7 he is going to read the first line only for  
8 patients that are 3, 4, 5 years of age.

9 I think the intention here is to separate  
10 populations for a study, to identify patients with  
11 higher risk for penicillin resistance, then, I  
12 would say yes for these, but not for empiric use of  
13 antibiotics, you know, first line, second line, as  
14 it seems to me that was the intention of the  
15 presentation.

16 DR. RELLER: One has heard some of the  
17 major points of discussion, so the vote is do you  
18 agree that it is important to differentiate into  
19 high risk, low risk, or are these particular  
20 categories not necessarily limited to those, in  
21 other words, to differentiate the population, and  
22 perhaps that is less necessary, although it could  
23 be part of the analysis if one has a  
24 tympanocentesis and knows whether you have got the  
25 organism in the first place, if these are tools to

1 get at the surrogate for knowing what you have,  
2 because of the likelihood of having a bacteria.

3 We are going to start over here this time.

4 Alan, do you think it is crucial to incorporate  
5 these or it is part of trial design, but not  
6 essential to separate them into two categories,  
7 whatever the definition?

8 DR. CROSS: I am not a pediatrician, but  
9 from the discussion I have heard, the frequency is  
10 not sufficient to define the population at risk,  
11 and high risk/low risk has its problems for what we  
12 have heard.

13 It seems to me the most logical is that if  
14 we truly want to focus on the resistant population,  
15 that after our tympanocentesis, of the failures,  
16 those are the folks who are the most highly  
17 enriched for failure by definition, and would be a  
18 good population to study the antibiotics, which we  
19 don't want used for initial therapy.

20 So, the answer is that I don't think we  
21 have enough information to simply use the  
22 definitions as proposed here, and I think that the  
23 best information will come from the double tap  
24 studies.

25 DR. RELLER: Thank you.

1 Dr. Leggett.

2 DR. LEGGETT: I am not sure that the use  
3 of these two definitions per se will help us  
4 delineate well enough to make it worthwhile to  
5 industry or anyone else, especially if our  
6 guidelines are now going to be tympanocentesis at  
7 the baseline and the inclusion of lots of kids  
8 under 2. So, we will have so much overlap between  
9 the kids under 2 with everything we have heard  
10 about all the other things that is going to happen,  
11 that these are no longer going to be very useful.

12 DR. RELLER: Dr. Ebert.

13 DR. EBERT: I think overall I believe that  
14 the age group under 2 should be a broad focus  
15 regardless of other risk factors, that even in  
16 simple, uncomplicated cases of otitis media,  
17 increasing the percentage of children that are  
18 under 2 would be useful.

19 Having said that, I think that using other  
20 factors, such as recurrent infections, may be of  
21 benefit because they may enrich the likelihood of  
22 having more resistant organisms, and I think they  
23 also parallel in many ways the clinical stepwise  
24 approach that many physicians take to treating  
25 recurrent cases, that you tend to up the ante, if

1 you will, as far as the types of antibiotics that  
2 you are using with recurrent cases.

3 DR. RELLER: Thanks.

4 Dr. Ramirez.

5 DR. RAMIREZ: I agree with the  
6 definitions. I think that these plus other risk  
7 factors can be used to identify patients that are  
8 more likely to have penicillin resistant  
9 Streptococcal pneumonia for clinical trials of  
10 enriched populations. We are looking for this  
11 indication.

12 DR. RELLER: Dr. Chesney.

13 DR. CHESNEY: Could you restate the  
14 question again?

15 DR. RELLER: Basically, the question is do  
16 we agree with these definitions, and we are taking  
17 them in two parts. The way I interpret it is  
18 should clinical trials, the patients necessarily be  
19 categorized as being recurrent or non-recurrent, or  
20 is the population that you really want to study,  
21 the under 2's, the ones that are at higher risk  
22 because of daycare, the children under 6 months of  
23 age, in effect, that this becomes a component, but  
24 not a critical one that really you are talking  
25 about studying the patients who really have the

1 disease, but this as a tool to get there alone is  
2 either not enough or is too restrictive, I mean  
3 however you want to look at it.

4           Basically, I know how I am going to vote.  
5 I am going to vote that it is not crucial. I was  
6 convinced by Dr. Glode's comments and Dr. Wald's  
7 comments earlier.

8           DR. RAMIREZ: More than the two  
9 definitions, I would like to see what are the risk  
10 factors for penicillin resistant Streptococcal  
11 pneumonia, and mostly because we know that having  
12 two or three risk factors is different to having  
13 one. I would like to see at least risk factors for  
14 otitis media produced for penicillin resistant  
15 Streptococcal pneumonia, and then incorporate in  
16 the trial, and then you can see these, you have a  
17 population with five risk factors or three or none  
18 of the risk factors. These may help.

19           DR. CHESNEY: I think I understand the  
20 question, and I think my answer is no, and what I  
21 think it is saying is would we break down this into  
22 a separate population, and my answer would be no to  
23 that, but I think it is a much more complex  
24 question in terms of when you rephrased the  
25 question, you complicated the issue for me even

1 more, because you brought in age.

2 I am not sure that I wouldn't use age in  
3 some way, but to be very concrete, my answer is no,  
4 I wouldn't use recurrent acute otitis as a  
5 discriminating factor.

6 DR. RELLER: We are actually in agreement.  
7 I mean you want to use age as an additional thing,  
8 Dr. Hoberman brought that up, as well, and I think  
9 that this is not sufficient to identify the  
10 patients that you want to study, or that is an  
11 adequate separator, if you want to look at it that  
12 way.

13 Dr. O'Fallon.

14 DR. O'FALLON: As a statistician, I have  
15 to answer as if I were your statistician working  
16 with you on developing a study. After listening to  
17 the discussion here, what I would say is the  
18 factors that you have identified, I think age has  
19 to start out as being the most important one.

20 So, where I am going is we are going to go  
21 for stratification. Okay. Statisticians do that.  
22 I would say we are going to have to be able to  
23 stratify the population. How that will be done is a  
24 whole discussion but the principle is we have got  
25 to stratify by age to start with.

1           But it seems to me, listening to your  
2 discussion, there ought to be something like has  
3 this patient ever had antibiotics before, and so  
4 there will be a class of patients that have never  
5 had antibiotics before. That is one group.

6           Then, there is the group that have. Now,  
7 there seems to be levels of that, and how you break  
8 that down, it sounds like that is a topic for  
9 discussion that you guys have to duke it out, but  
10 it sounds like that there ought to be some sort of  
11 a prior treatment history factor.

12           So, I think that they sound like the two  
13 things, an age factor and a prior antibiotic  
14 therapy factor that ought to be involved, and this  
15 one isn't it.

16           So, I vote against this one.

17           DR. RELLER: Dr. Giebink.

18           DR. GIEBINK: I will tell you what I  
19 believe, but I don't know, given the question,  
20 whether to say yes or no.

21           DR. RELLER: Well, we are actually more  
22 interested in the comments and what you believe  
23 than a yes or a no.

24           DR. GIEBINK: Let me tell you what I  
25 believe. As long as the trial includes entry

1 tympanocentesis, the whole business about enriching  
2 for antibiotic-resistant organisms is moot, because  
3 it will be addressed.

4           So, just leave that aside. There is a  
5 concern about heterogeneity of the subjects with  
6 regard to ear chronicity. So, I do believe you  
7 have to stratify for ear chronicity and probably  
8 the best parameters are recurrence and age.

9           So, I would stratify based on recurrence  
10 and age, and I would leave the rest of this aside,  
11 and not try to enrich for resistance.

12           DR. RELLER: Thanks.

13           Dr. Sumaya.

14           DR. SUMAYA: Again, I am not totally clear  
15 on the question, but what I was interested in is in  
16 having some identification of the patients that  
17 would be a proxy of sorts for a complicated case,  
18 and so recurrence and treatment failure fall under  
19 that category, and there could be others.

20           I would use that as my indication of why I  
21 would favor a second tympanocentesis. This would  
22 be the subgroup that I would be in favor of having  
23 that done, because I am not favorable to doing a  
24 double tympanocentesis on all who would enter a  
25 study.

1 DR. RELLER: Dr. Wald.

2 DR. WALD: Essentially, I agree with  
3 Scott. I think that it is important to collect all  
4 the information, such as age at first episode,  
5 number of occurrences, recent antibiotic use,  
6 attendance at daycare, and then either take that  
7 into account by stratification or in your ultimate  
8 analysis. I don't think we need a separate study  
9 for those children.

10 DR. PATTERSON: I agree with Dr. O'Fallon  
11 and Dr. Giebink that some stratification of high  
12 risk versus low risk would be very useful to  
13 physicians in delineating the role and hopefully  
14 conservation of broader spectrum antibiotics.

15 DR. RELLER: I agree.

16 Dr. Bell.

17 DR. BELL: I agree with Dr. Giebink that  
18 as long as ear taps are required for entry, this is  
19 moot, and so these people don't need to be  
20 targeted. I do think that we want to be sure that  
21 there is a sufficient group of penicillin  
22 non-susceptible or other drug resistant organisms  
23 in the study population to draw conclusions on  
24 them, but if the ear taps are done, this doesn't  
25 need to be required.

1           The only final comment is that these are  
2 common clinical problems, and somehow in the  
3 guidance to physicians, these concepts might be  
4 useful, because they are not going to do ear taps  
5 routinely.

6           DR. RELLER: Dr. Glode.

7           DR. GLODE: I don't think we need these  
8 separate groups and having companies go for  
9 separate indications. I do think that one could  
10 modify their exclusion criteria to eliminate the  
11 issue of not including children who have had recent  
12 antibiotics again if you want to enrich.

13           So, I favor stratification on the front  
14 end and analysis on the back end, and the  
15 microbiology.

16           DR. RELLER: Dr. Nelson.

17           DR. NELSON: In listening to this, I guess  
18 I would support if the goal is to move to riskier  
19 antibiotics that would be stronger and therefore  
20 deal with issues of resistance. It would concern  
21 me that you have narrowed your population, and a  
22 bacteriologic diagnosis, to narrow that population  
23 would be important.

24           I would like to clarify what I think was a  
25 misinterpretation of my earlier remarks. The

1 reason why I felt I could not address the tap was  
2 because I hadn't heard clear diagnostic criteria  
3 for what acute otitis media is.

4 If, indeed, it meant bulging eardrums, I  
5 would have no problem with that. The difficulty I  
6 have is the bouncing back and forth that is going  
7 between what pediatricians do in their office,  
8 which we are all admitting is haphazard, and what  
9 actually happens in a trial.

10 I think the reluctance of IRB to deal with  
11 this issue is that when someone says can you tap  
12 acute otitis media, they are thinking of what  
13 happens in the pediatrician's office, and to the  
14 extent the tap is used to compensate for faulty  
15 diagnosis, I think that is a problem.

16 To the extent the tap is used in a narrow  
17 population defined by good criteria, that is not a  
18 problem.

19 DR. RELLER: Thanks for that  
20 clarification.

21 In my positioning the microbiology, I mean  
22 there is a clinical presentation, an examination  
23 that Dr. Pichichero went over, and others, and then  
24 there is the tap, which is the only way to  
25 establish etiology in what has been a targeted for

1 clinical trial definition of who would be  
2 appropriate for tap in the first place.

3 DR. NELSON: But the key there is the  
4 skilled diagnostician who says this is an ear worth  
5 tapping, which is what I heard in his presentation  
6 as opposed to this is maybe otitis media and an ear  
7 worth treating with a drug that might not be any  
8 better than tap water or placebo, and not tapping  
9 and not going into trial.

10 DR. RELLER: I think we are actually in  
11 agreement and related to some of the remarks you  
12 made earlier about the IRBs, there are additional  
13 requirements that all of us face in terms of  
14 minimal training to participate in NIH grants and  
15 other things. It seems to me that clinical  
16 trials--and I think everybody in this room would  
17 agree--are far more complex that meets the eye, and  
18 if you do not have appropriate training and  
19 education to do whatever is necessary to  
20 participate in a clinical trial, you have no  
21 business gathering data on those patients because  
22 it is just going to end up with stuff that is  
23 devilishly difficult to interpret in the end.

24 So, it all comes together in terms of  
25 people who are appropriate candidates for entering

1 into study in the first place by the criteria that  
2 have been discussed, having them entered by people  
3 who know what they are doing in clinical trials,  
4 and know what they are doing for procedures that  
5 might be required for an objective assessment.

6 We must go on because the down side, I  
7 mean we have tried very hard to have everyone have  
8 an opportunity to speak, but we are going to start  
9 losing members unless we have at least some  
10 comments on all three questions.

11 When the turn comes around, anything that  
12 people want to say that they missed before, that  
13 will be the opportunity.

14 Dr. Nelson, to finish Question 2(b),  
15 treatment failure. There is a definition of  
16 treatment failure that has been put forth here, and  
17 I would like to ask you and around the table do you  
18 agree with this as a definition that would be  
19 acceptable, not final necessarily, but is it a  
20 reasonable definition of treatment failure, and if  
21 you would change it, how would you change it.

22 DR. NELSON: I will confess that this is  
23 probably not in my area of expertise, but I will  
24 just say that I was impressed by the correlation  
25 between bacteriology and the symptom scores that I

1 think were presented earlier from some of the  
2 clinical studies, and whether 48 hours was  
3 sufficient to see those changes or not would be an  
4 open question, but it would look to me like you  
5 could potentially use some of those symptoms, if  
6 you will, appropriately. The signs, I will defer.

7 DR. RELLER: Thanks.

8 Dr. Glode.

9 DR. GLODE: I think one has to distinguish  
10 between clinical treatment failure and  
11 bacteriologic treatment failure, so in Dr.  
12 Marchant's study of the 40 bacteriologic failures,  
13 62 percent were clinical successes.

14 So, I think it is very important, so  
15 treatment failure, you will have to ask me  
16 whether--I want bacteriologic failure or success I  
17 think is my definition.

18 DR. RELLER: We will get into this a  
19 little more with the double tap issue, but  
20 basically, if a child had persistent symptoms after  
21 48 hours or 72 hours, whatever you want to say, or  
22 had it all over again within 7 days after finishing  
23 treatment, is that a child that, in general, in the  
24 context of a trial, that you would want to know  
25 whether the organism was gone or not gone.

1 DR. GLODE: That would be a clinical  
2 failure, which then would raise the question of--

3 DR. RELLER: Trigger a microbiological  
4 confirmation.

5 DR. GLODE: Yes, which may or may not be a  
6 bacteriologic failure.

7 DR. RELLER: Exactly.

8 DR. GLODE: Right.

9 DR. RELLER: These are basically, if you  
10 want to get right down to it, that if you were a  
11 double tap believer, would these be children that,  
12 at a minimum, you would want to re-tap?

13 DR. GLODE: Except I would change 48 to  
14 72.

15 DR. RELLER: Thanks. That's exactly what  
16 we want to hear. I mean what you would do.

17 David.

18 DR. BELL: I agree. I don't have anything  
19 more to add.

20 DR. RELLER: The 72 hours has been  
21 mentioned earlier. I think that is what I would do  
22 is I would give them 72 hours, and by that time, it  
23 should have done what it is going to do or not.

24 Dr. Dagan mentioned about what to call day  
25 1, and it is sort of like tertian malaria. I mean

1 it gets very confusing. There is 40 hours between  
2 the cycle, but day 1 is day 1, day 2, day 3, it is  
3 actually only 40 hours between, so 72 hours of  
4 treatment it would be if you start at day 1, and  
5 then day 4.

6 Dr. Patterson.

7 DR. PATTERSON: I agree.

8 DR. WALD: I think there are two issues.  
9 There is no improvement by 72 hours, with which I  
10 agree, there is worse at any time, so if a child  
11 deteriorates in 24 hours, that's a failure.

12 I don't think I would call it a treatment  
13 failure, I would call it an early recurrence for  
14 what you are calling post-therapy, because that  
15 could be anything. It could be a brand-new  
16 infection. So, it's a second early infection.

17 DR. RELER: Would you like to know  
18 microbiologically what the status is?

19 DR. WALD: I would.

20 DR. RELER: Good.

21 DR. GIEBINK: I would use 72 hours after  
22 initiating treatment for the during, and 1 to 5  
23 days after the end of therapy.

24 DR. O'FALLON: This is hardly my area of  
25 expertise. What I am hearing, I agree with what

1 you have said before, and I just want to make the  
2 comment that I was not all that impressed by the  
3 correlation between the clinical and the  
4 microbiological points.

5 That is very debatable from a statistical  
6 point of view, and it needs more discussion.

7 DR. CHESNEY: I like Dr. Wald's comment of  
8 worse at any point, and I would defer the 48 to 72  
9 hours to the experts. I also would agree with Dr.  
10 Giebink that 1 to 5 days after completing the  
11 course.

12 DR. RELLER: Dr. Ramirez.

13 DR. RAMIREZ: I agree. In most  
14 respiratory infections, we use 72 hours. We need  
15 to give at least 48 to 72 hours to the antibiotics  
16 to start having some killing or bacteria decrease  
17 to see clinical response in at least 72 hours, I  
18 want to take the chance now to go back to the prior  
19 question, because I think that some members of the  
20 committee are missing or at least I consider that  
21 the enriching population, what we discussed here  
22 before, was that yes, you want to do a tap, eardrum  
23 tap.

24 Then, you say, well, I look for the  
25 resistant organisms, but you have in the

1 population, 20 percent of resistant pneumococci,  
2 and 50 percent of otitis media is caused by  
3 pneumococcus, and then you have 10 percent of all  
4 the bacterial otitis are going to be resistant  
5 pneumococci.

6           They will say to a company go ahead, do  
7 100 taps to get the 10 percent resistant  
8 pneumococci. What we are saying is that in  
9 enriched population, we are saying we have these  
10 inclusion criteria, if you don't meet this  
11 inclusion criteria, you don't get into the study.

12           Then, we are going to need probably 30, 40  
13 taps to get this. They were worth doing, we  
14 increased the population, not to enroll 100  
15 patients, again, only 10 patients for the study,  
16 just from those 40, I get 10 patients for the  
17 study. To me, the idea of enriched population in  
18 clinical trials looking for penicillin resistant is  
19 very valid.

20           DR. RELLER: Thank you.

21           Dr. Ebert.

22           DR. EBERT: I agree with the treatment  
23 failure during therapy being at 72 hours or after  
24 72 hours of therapy. As far as post-therapy, I am  
25 reading within 7 days as meaning 1 to 7 days after

1 therapy, and I will defer to the experts whether it  
2 should be 1 to 7 or 1 to 5.

3 DR. RELLER: Dr. Leggett.

4 DR. LEGGETT: Ditto.

5 DR. RELLER: Dr. Cross.

6 DR. CROSS: And the same.

7 DR. RELLER: Question No. 3. Do double  
8 tympanocentesis trials have a role in demonstrating  
9 effectiveness of drugs for general AOM, for  
10 recurrent/ treatment failure AOM?

11 Then, you can see all of the related  
12 issues about timing, relative importance of  
13 clinical and microbiology assessments, et cetera.

14 I think lest we lose some members, it is  
15 now 3:30. We can continue on as long as there is a  
16 healthy number. There has much discussion, some  
17 allusion to this before, but let's start with you,  
18 Alan.

19 Dr. Cross, what do you see as the role, if  
20 any, for double tympanocentesis trials for  
21 demonstrating effectiveness of drugs?

22 DR. CROSS: I think they are essential. I  
23 think we saw some data early on that showed a very  
24 good correlation on some limited data, on clinical  
25 outcome after doing studies with a single tap.

1 Perhaps at some point in the future, we will  
2 reinforce that data. If after an initial tap, a  
3 patient does well clinically, we might not need a  
4 second tap, but that's in the future. We still  
5 have to firm up that correlation. I think it's  
6 essential we do double taps.

7           The timing of the second tap, whether it's  
8 during therapy or at the end of therapy, I am not  
9 sure. We heard positions at both ends, that  
10 perhaps end of therapy is better than during  
11 therapy, obviously unless a patient is worsening.

12           I am not sure if there are any other  
13 issues in this last question that you would want us  
14 to address.

15           DR. RELLER: Thank you. This is great.  
16 The comments like Dr. Cross has made for or  
17 against, and then the additional discussion points  
18 we had scheduled until 4 o'clock, so let's go  
19 around on Question 3, the central issue about  
20 double tympanocentesis, and then we will fit the  
21 remainder of the discussion in the time allotted,  
22 and then that's it for this meeting.

23           I think from an optimist's standpoint,  
24 that there has been clear demonstration of the  
25 Agency's commitment to pursue and revisit these

1 issues for however many times and however many  
2 decades it takes to get it as close to right as  
3 possible, and to revisit it to keep it right.

4 Dr. Leggett.

5 DR. LEGGETT: In talking about this, I go  
6 back to the question I had before, how are we going  
7 to avoid another azithromycin problem without some  
8 sort of confirmation that it actually works. So,  
9 whether you call it a double or a single, and then  
10 with failure as long as you actually see somebody  
11 at day 4, or whatever it is, and decide at that  
12 point to do the double tap or not, I will leave to  
13 the experts and people arguing with IRBs, but we  
14 need to have some confirmation that the drug is  
15 actually working against the bacteria, against what  
16 it is supposed to be doing.

17 DR. RELLER: Dr. Ebert.

18 DR. EBERT: I think double tympanocentesis  
19 does have a role. I am very strongly in favor of  
20 second taps in patients who have clinical failure  
21 based on the data that Dr. Giebink presented, as  
22 many as 50 percent of those patients will have a  
23 positive culture.

24 I am also supportive of double taps in a  
25 smaller number of patients where you may still see

1 clinical response, but still looking for recurrence  
2 or persistence of the organism, but I am hoping that  
3 that will not need to be as large of a patient  
4 population as the primary descriptor of where you  
5 have just a single tap.

6 I am hoping that our earlier suggestions  
7 of assessing clinical response at the end of  
8 therapy as opposed to at a later time point, will  
9 help us to delineate some of the issues that Dr.  
10 Leggett mentioned.

11 DR. RAMIREZ: I think it was mentioned in  
12 the presentations that the use of an antibiotic,  
13 that you may decrease the inoculum of bacteria to  
14 the point that the patient clinically respond, but  
15 without clinical cure.

16 In these group of patients is when we may  
17 see a relapse. I think that is going to be  
18 necessary to ask, that we are asking the  
19 antibiotics to kill the bacteria, it is going to be  
20 necessary to have repeat taps in as many number of  
21 patients as the statistician requires to see if  
22 there is any difference between one antibiotic and  
23 the other.

24 I totally agree with Dr. Dagan regarding  
25 the education of the IRB, because if we are

1 convinced that a poor antibiotic that doesn't  
2 stabilize the middle ear, is going to be on  
3 schedule with relapse, and repeat the tap is going  
4 to be necessary, and repeat tap is no good even  
5 though the patient may be doing clinically better,  
6 still is going to be an indication to see if this  
7 antibiotic is really going to prevent relapse.

8           It may be even beneficial for this  
9 patient, and be beneficial for the future to see  
10 what is the best antibiotic to use for otitis  
11 media. I don't think there is an ethical issue to  
12 repeat a tap when you are really defining what is  
13 going to be the best antibiotic that you need to  
14 use in this disease.

15           DR. RELLER: Dr. Chesney.

16           DR. CHESNEY: Could I have another day or  
17 two to think about this? Let's see. Double  
18 tympanocentesis trials, I feel definitely have a  
19 role in both (a) and (b). The timing of clinical  
20 assessments and of microbiologic I think should be  
21 between that 48 to 72 hours, and I think the  
22 clinical should be obviously end of therapy and  
23 even beyond that.

24           On-therapy tympanocentesis in a child who  
25 is clinically improving, I think that is what we

1 are all having trouble with, and that is the one  
2 that I feel like I would need more time for, but I  
3 think we probably do need to do some number who are  
4 clinically improving.

5 In order to answer the third bullet, which  
6 is can we predict clinical outcome based on the  
7 on-therapy tympanocentesis, so to me you would have  
8 to do double studies in order to answer the third  
9 bullet, and the fourth issue is I don't think there  
10 would be any problem finding enough study sites in  
11 the United States.

12 DR. RELLER: Thanks.

13 Dr. O'Fallon.

14 DR. O'FALLON: Yes, obviously, I think  
15 that the double tap is essential. Now, my reason  
16 is a little different. Everybody is worrying about  
17 the ability of the tap to predict the clinical  
18 response, which is important, but I am more worried  
19 about the clinical response being used to predict  
20 the microbiological one, and I am not impressed  
21 with the--well, let's put it this way--I am  
22 impressed with the misclassification rates between  
23 the success and failure in those two endpoints. I  
24 think you had better go back and take a look at  
25 them and see if you really think that is such a

1 good idea.

2           So, yes, I think double taps are needed in  
3 both kinds of studies.

4           DR. RELLER: Dr. Sumaya.

5           DR. SUMAYA: I would favor the double taps  
6 for the treatment failures of acute otitis media.  
7 Presumably this would occur at around 72 hours  
8 after initiation of therapy.

9           I would also advocate for a tighter  
10 clinical evaluation at entry and then at 72 hours  
11 and probably at the end of therapy, as well, and  
12 very interested in the scale that is used, but more  
13 particularly in the criteria that are used within  
14 the scale of clinical assessment and if it could be  
15 made into a semi-quantitative type of an  
16 assessment, I think would be of value.

17           I am not in favor of a double tap in  
18 general acute bacterial otitis media unless there  
19 is some type of complication.

20           DR. RELLER: Dr. Wald.

21           DR. WALD: I certainly agree with doing  
22 second tympanocentesis in any treatment failure,  
23 and while I think the microbiologic data on repeat  
24 taps, even where there isn't treatment failure is  
25 of interest. I like to look at microbiologic data,

1 and I think it teaches us something.

2 I don't think it is essential for judging  
3 outcome in the majority of patients because, in  
4 fact, there is a reasonable correlation between the  
5 bacteriology and the clinical outcome.

6 Some of the differences that we may see in  
7 children who are bacteriologic failures and  
8 clinical successes may be a function of the fact  
9 that we don't stop there beyond day 4 or 5 or 6, in  
10 fact, we continue treating the majority of those  
11 patients until day 10, and by that time, they may  
12 be a bacteriologic cure.

13 I think when we look at the data that  
14 exist, we need to look at that precisely were they  
15 children tapped on day 4 or 5 or 6. I think we are  
16 going to see differences according to the duration  
17 of therapy.

18 DR. PATTERSON: I think double tap studies  
19 have a role in efficacy studies as a subset in some  
20 centers where they are routinely done. I don't  
21 think the efficacy studies should be exclusively  
22 double tap studies because I think we need probably  
23 a broader geographic range for pathogens and  
24 susceptibilities for where those might be done.

25 I think that in single tap studies, the

1 second tap is useful for therapeutic failures  
2 particularly with regard to the resistance issue  
3 and how to direct the use of broader spectrum  
4 agents.

5 DR. RELER: I think there is an important  
6 role for double taps. Perhaps the only exclusion  
7 would be a patient who at the appropriate time of  
8 follow-up, who is doing well, and on examination by  
9 an experienced investigator, is so fortunate to  
10 have no evidence of the signs and symptoms that  
11 caused them to be enrolled in the study in the  
12 first place.

13 Dr. Bell.

14 DR. BELL: I think double taps are nice,  
15 but in terms of an FDA requirement, I do not think  
16 they should be required for the patient who is  
17 clinically improving. For treatment failures, I  
18 want to see the information. Whether it should be  
19 required, I guess I would like some more input from  
20 people who have done these studies as to how  
21 feasible this is and how much information it  
22 provides, but I would very much, I would like to  
23 see it for treatment failures. I don't think it  
24 should be required for people who are improving.

25 DR. RELER: Dr. Glode.

1 DR. GLODE: I think they do have a role  
2 and I agree with what most other people have said  
3 here, that for treatment failures they have a role,  
4 and I think in a small group of children, the  
5 double tap studies are also important. If you  
6 don't do them, it looks to me from the information  
7 provided you will overestimate the efficacy of the  
8 drug if you believe in bacteriologic eradication.

9 Now, it could be as Dr. Wald said, that if  
10 we were doing quantitative cultures, we would find  
11 that when you tapped them on day 3, they are still  
12 positive, but it's a 2 log kill, and that is why  
13 they are a clinical success, but in the absence of  
14 that knowledge right now, I think in a small study  
15 that there should be smaller studies of two taps.

16 DR. RELLER: Dr. Nelson.

17 DR. NELSON: I will give an IRB answer to  
18 this. First of all, I think we all need to be  
19 better educated about the ethics of our pediatric  
20 rules in addition to IRBs as well. In a treatment  
21 failure, I would presume the tap is potentially of  
22 benefit, so that doesn't sound to me like that  
23 would be terribly controversial to do a second tap.

24 In a child who has already had the first  
25 tap, if we had that population appropriately

1 defined, what you would need is the tapping down by  
2 someone with the skill to be able to argue that it  
3 is only a minor increase over minimal risk.

4           It certainly is an experience that is  
5 reasonably commensurate--this is the language from  
6 the regulations--with that child's experience  
7 because they just had one, four or five, six, seven  
8 days ago.

9           But then the other threshold is it has to  
10 be of vital importance for understand or  
11 ameliorating the child's condition, and I have  
12 heard a mixed message on that point, some saying it  
13 is vitally important, others not so sure,  
14 particularly for the children that are improving.

15           So, from my point of view, I would remain  
16 agnostic on that vital importance, but if you want  
17 to convince your IRB, that is what they have to be  
18 convinced that it is, in fact, vitally important  
19 and that may demonstrate the variability from  
20 institution to institution depending upon what the  
21 investigators actually believe ought to be done for  
22 that population.

23           DR. RELLER: Thanks. We have 15 minutes  
24 or so for additional discussion, and I would like  
25 to pose a question related to Dr. Nelson's

1 important comments.

2           For Dr. Pichichero, Dr. Hoberman, Drs.  
3 McCracken, Paradise, others, would we more often  
4 see clinical failures, that is, the symptoms that  
5 were microbiological successes, or if you had  
6 double taps, the flip side of that, because there  
7 was perhaps if quantitatively done, it would be a  
8 decrement, but not enough, and when the treatment  
9 is completed, if it's one of the courses that is  
10 longer in treatment, that it would eventually  
11 improve, and what about the issue of the proportion  
12 of children in the population that goes to daycare,  
13 I mean the higher risk patients, of the probability  
14 of having fluid that can be tapped at 3, 4, 5 days  
15 into--let's just assume that it is an effective  
16 drug, how long does the fluid last, and is there  
17 something to tap safely.

18           Comments please.

19           DR. PICHICHERO: On a number of the items  
20 you just voted on, you didn't ask the opinion of  
21 the consultants before you voted. I just wanted to  
22 give a few sobering facts.

23           Regarding the diagnosis of otitis media,  
24 for example, to define recurrent otitis media, you  
25 rely, as Dr. Paradise alluded to, it was a correct

1 diagnosis in the past. Physicians, pediatricians  
2 who come to our CME course and see that video miss  
3 the correct diagnosis 50 percent of the time. When  
4 we have taken the course abroad, they miss the  
5 diagnosis 65 percent of the time.

6           So, Dr. Nelson's comments about a skilled  
7 operator to do the tap are well stated, and  
8 similarly, skilled people to make the diagnosis.  
9 The practicality is today that many of the centers  
10 enrolling children are not like our center, they  
11 are referral centers. They rely on diagnoses  
12 coming in to them for the background history, which  
13 may or may not be reliable, and I would submit that  
14 they are not reliable.

15           Dr. Chesney said there should be no  
16 problem getting such a number of sites. I was  
17 recently at an investigative meeting, two of them,  
18 in fact, which called for a double tympanocentesis  
19 in the protocol design.

20           There were 30 sites sitting approximately  
21 in each of those audiences. Three of those sites  
22 were in the United States, 27 sites were outside  
23 the United States. Dagan was at both of them. The  
24 other sites, which I chatted with Dr. Hoberman  
25 about, many from Latin and Central America, they

1 have never done tympanocentesis double tap, so I  
2 don't know whether they are going to do it or not.

3 I don't know about their diagnostic  
4 capability. I don't know whether they have a  
5 certificate from outcomes management or somewhere  
6 else that they are killed in tympanocentesis, and I  
7 have a lot of concerns about some of those issues  
8 the practicality of what you might be about to  
9 mandate here.

10 I think double taps definitely need to be  
11 done, but I am concerned about those issues of  
12 accurate diagnosis, and for me, the ear needs to be  
13 bulging, and we don't know so much about symptoms.  
14 We don't know whether that ear tugging really means  
15 they are in pain or not, if they are irritable.  
16 Children get irritable, but if that ear is not  
17 bulging, it is not otitis media in my opinion, and  
18 if it is bulging, it still is otitis media, and it  
19 deserves to be tapped because there will be pus  
20 there, and there are two papers to say that more  
21 than 90 percent of the time, if they have not been  
22 on an antibiotic, you will get bacteria.

23 DR. RELLER: Drs. Chesney and Hoberman.

24 DR. CHESNEY: Just to make a correction.  
25 I didn't mean to imply that there were plenty of

1 centers already set up, but I think that I am  
2 already planning to send all our house staff to  
3 your course and including all of the general  
4 ambulatory faculty, and I think that if this came  
5 out as being a requirement, then, we would become  
6 skilled at a technique probably we should all be  
7 skilled at.

8           Maybe that's your fault for making it look  
9 so easy.

10           DR. RELLER: Dr. Hoberman.

11           DR. HOBERMAN: I could not agree more with  
12 Dr. Pichichero with regards to the accuracy of  
13 diagnosis. I think we went by the definitions of  
14 otitis media, and they were not addressed today but  
15 they need to be more stringent than what you had as  
16 stringent in the last draft guidelines.

17           The repeat tympanocentesis in the case of  
18 clinical failure, I absolutely agree with it, and  
19 there has to be some limitation. It needs to  
20 happen at the end of treatment basically, but there  
21 is no need to repeat a tympanocentesis at day 25 if  
22 the child is failing because the odds of that being  
23 related to the antibiotic treatment that was used,  
24 it is nil.

25           The other key point is that after recent

1 visit of Dr. Nelson to Pittsburgh, the IRB has  
2 become very, very stringent with regards to the  
3 criteria for a repeat tympanocentesis, and I think  
4 I heard--I wasn't at your presentation, but I  
5 watched the video, and I agree with the concepts  
6 that were raised there, but one thing came up which  
7 was the 13 tympanocentesis.

8 I was asked the question based on this  
9 protocol, whether there was going to be a 13  
10 tympanocentesis. There should not be 13  
11 tympanocentesis in any child. Either they get  
12 re-tapped at day 4 to 6 and the criteria that we  
13 are debating with the IRB are bulging of the  
14 tympanic membrane of 2 or 3+, or 1+ plus ear pain.  
15 Those would be the instances in which we may be  
16 allowed to repeat a tympanocentesis, of course, in  
17 anybody that has clinical failure, but not in a  
18 child that is failing at 28 days.

19 So the point, and you raised the question  
20 today about greater than minimal risk with no  
21 prospect of benefit to the patient, which will put  
22 us in the category 3 that requires vital importance  
23 and hoops that nobody will be able to jump over.

24 We still feel like the repeating  
25 tympanocentesis is greater than minima risk, but of

1 prospect of benefit to the patient if we identify  
2 children with bulging of the tympanic membrane at  
3 day 4 to 6.

4 DR. RELLER: Dr. McCracken and then Dr.  
5 Bell.

6 DR. MCCRACKEN: The point raised by Ellen,  
7 and Dr. Nelson actually also, about the rate of  
8 kill of bacteria and whether, at 3 or 5 days, it is  
9 sterile or at least nothing grows because you can't  
10 be completely certain that it is not suppressed and  
11 would grow, or whether at 8 days, it would be okay,  
12 too.

13 Well, there are several things about that.  
14 First, the rate of bacteriologic kill is different  
15 than the rate of eradication. Time to eradication  
16 is one thing, rate of kill is yet another, and  
17 where the comes into focus, and hasn't been done  
18 yet, but I think Ron has started to do this, is to  
19 determine the concentration of bacteria, because we  
20 know in meningitis if you have 10  
21 your kill is the same as for two drugs in 10<sup>5</sup>, it  
22 is going to take longer. Time to eradication  
23 depends on those two factors.

24 However, when you look at the data and at  
25 bacteriologic eradication at 3 to 5 days from  
8 organisms, and

1 several of the studies I have already mentioned, it  
2 does correlate with clinical outcome and the  
3 argument has been with the macrolide, while they  
4 may not tell it 3 to 5 days, but they probably do  
5 at 7 to 9 days. Well, that could be because no one  
6 is going to be probably tapping at that time in the  
7 normal child, but nevertheless, the positive  
8 culture at 4 days correlates with a poorer clinical  
9 outcome, both in score and just globally.

10 This has come up with meningitis, too,  
11 they say why do you do 18 hours and not 30 hours?

12 Renata and I have talked about this. I  
13 think 30 hours is the way you do it, so that you  
14 get away from the impact of the higher  
15 concentration in some children, because by 30 to 36  
16 hours, that has dissipated, and I suspect by 3 to 5  
17 days, it has also.

18 DR. RELLER: Thank you.

19 Dr. Bell.

20 DR. BELL: I was happy to hear Dr.  
21 Pichichero's comments because underlying my  
22 hesitation has been the concern that double taps,  
23 although scientifically justifiable, practically,  
24 just may not get done, and we don't have anybody  
25 from the pharmaceutical industry commenting on that

1 here, but I am cognizant of Dr. Soreth's comments  
2 this morning about something to the extent that,  
3 you know, we have to be sure that what--I am  
4 paraphrasing it--but if we set the bar too high,  
5 then, the studies won't get done, so I think we  
6 have to keep that in mind.

7 DR. RELLER: Dr. Soreth.

8 DR. SORETH: I think an important  
9 experience that we discussed here in January of  
10 2001, was that of GlaxoSmithKline's trials with  
11 Augmentin ES, the 14 to 1 formulation in which  
12 double taps were done in children who had, on the  
13 first tap, penicillin resistant Strep pneumoniae.

14 As I recall--and Dr. Winn can correct  
15 me--there were between a dozen and 2 dozen centers  
16 all told within those trials, and I think roughly  
17 half were in the United States, perhaps, and half  
18 not. I mean there were a goodly number of centers  
19 that were U.S. based that were inexperienced hands,  
20 and the percentage of positive cultures at the  
21 baseline tympanocentesis was quite high.

22 When I look back over many different  
23 applications that we have had in the past dozen or  
24 15 years, there is a great range, low to high, of  
25 even in what I would submit to you on paper would

1 be a tight clinical case definition.

2           They checked off the box that said bulging  
3 TM, they checked off that box. I don't know what  
4 that child's eardrum looked like because that data  
5 we don't get, we don't ask for pictures as yet, but  
6 perhaps we should.

7           But the box is checked off that there is a  
8 bulging TM, the box is checked off that we did  
9 acoustic reflectometry. The boxes are checked off  
10 that there is an effusion there and that the child  
11 meets the definition of AOM, presumably ABOM, and  
12 not OME, and then when you look across centers, at  
13 the rate of positive cultures on that baseline tap,  
14 it might be as low as 20 percent or as high as 90  
15 percent even with the tight clinical case  
16 definition, so there are limits to who tight you  
17 can make it.

18           There probably are things that we could do  
19 in terms of assessment of one's level of training,  
20 expertise, competence, so that if you were batting  
21 .200, maybe you shouldn't be an investigator in  
22 these trials and that maybe you bat something at a  
23 minimum to be such a learned investigator.

24           DR. RELLER: Drs. Hoberman and Marchant.

25           DR. HOBERMAN: There are ways of getting

1 pictures of tympanic membranes. We are using those  
2 systems and Dr. Smith has copies of the computer  
3 system we are using to capture pictures every time  
4 we enroll a child in an acute otitis media trial.

5 With regards to they are batting too low  
6 or batting to high, I absolutely agree that the  
7 batting high should be the ones entered in patients  
8 in clinical trials.

9 On the other hand, with regards to  
10 encouragement of re-tap of clinical failures, when  
11 clinical trials, pharmaceutical companies, quote,  
12 end quote, "encourage" investigators to do it, it  
13 doesn't happen, so there has to be some mandated  
14 proportion of children that have a clinical failure  
15 that need to be retapped.

16 I frequently encounter our site and a few  
17 other sites being the only sites as part of  
18 clinical trials or retapping the clinical failures.  
19 So, i would suggest a 75 percent of clinical  
20 failures if we want to learn something about it,  
21 will need to be retapped as part of the design of  
22 the study.

23 DR. RELER: Dr. Marchant.

24 DR. MARCHANT: I think Dr. Nelson's  
25 concern about training is well taken. At our

1 hospital, we got our pediatric ER physicians to  
2 learn tympanocentesis, and we had each on of them  
3 do a minimum of 6 taps in the OR while the patient  
4 was under anesthesia, as the otolaryngologist put  
5 in tubes as a way that they became competent, and  
6 there are available practical ways to get people to  
7 be competent in the procedure and that can deal  
8 with the issue that you raised.

9 DR. RAMIREZ: May I ask a question?

10 DR. RELLER: Yes, Dr. Ramirez.

11 DR. RAMIREZ: I get the feeling that  
12 sometimes we are thinking that in a clinical trial,  
13 we cannot go beyond clinical practice because it is  
14 unethical, because it seems to me that the second  
15 tap is never, unless it is a failure, is never  
16 clinical practice, but this make a definition of  
17 unethical, because when we do clinical trial for  
18 sinusitis, we require a tap. I would never tap any  
19 person with sinusitis when we see the patient in  
20 the office.

21 We do always clinical type things that go  
22 beyond clinical practice, and if we want to see  
23 what is the base antibiotic to treat an infection,  
24 we may need to repeat the tap even though it may  
25 not benefit these children, but, yes, sometimes you

1 discuss with the patient, you are doing a Phase  
2 II/Phase III antibiotic study, you don't even know  
3 the antibiotics are going to work.

4           You may say to a patient, well, you know,  
5 this may not work, may work, but it may not benefit  
6 you, but in the future we are going to know what is  
7 the baseline antibiotic, and this is not just for  
8 you, it is for Dave, for future patients. I don't  
9 see why this would be such a big ethical issue.

10           DR. RELLER: Thanks.

11           Dr. Nelson.

12           DR. NELSON: I think going beyond clinical  
13 interventions can be appropriate. The issue is, is  
14 the risk of going beyond roughly similar to the  
15 risks of the kinds of procedures that child would  
16 experience otherwise.

17           The regulation specifically restrict  
18 exposing particularly a child to risk for others on  
19 that basis, but from what I have heard, it sounds  
20 to me like in experienced hands, tympanocentesis  
21 fits with something that could be done when it is  
22 not only clinical indicated for benefit, but the  
23 issue of experience and context is crucial to that  
24 decision.

25           DR. RELLER: Thank you. Dr. Soreth, in

1 the time allotted, we have tried our best to  
2 address the issues put to us. I think the points  
3 that have just been made about the standards of a  
4 clinical trial with appropriate design to  
5 demonstrate efficacy and safety within the confines  
6 of independent IRB review, adhering to the highest  
7 ethical standards that have been talked about.

8           In my view, from summarizing the  
9 discussions, if you want to look at it, the bar  
10 needs to be raised, I think there are concerns  
11 about the stability of the bar and passing under it  
12 in the past, and this is coupled with a higher  
13 caliber of criteria as well for clinical  
14 investigators who are capable of carrying out the  
15 trials and adherent to all of the requirements  
16 including a rigorous review by institutional review  
17 boards.

18           The potential end result of that is  
19 greater confidence in drugs that would be approved  
20 for specific indications by the FDA, in general use  
21 by practitioners that they would do what they are  
22 licensed to do.

23           My final query, and this is for a future  
24 meeting , is what within the regulatory process  
25 would enable the Agency to reconsider looking

1 backwards for drugs that may be approved now for  
2 indications that in our heart of hearts, we have  
3 grave questions about whether they do what they say  
4 they do.

5 DR. SORETH: I can hazard an answer.

6 DR. RELLER: Dr. Soreth, you got us--and  
7 colleagues--got us all together. You get the last  
8 word and then we will conclude the meeting.

9 DR. SORETH: Quickly, we will publish in  
10 the Federal Register the appropriate docket number  
11 to which anyone and everyone is invited to send in  
12 written comments. I don't want to give you the  
13 previous number, because that may not be the best  
14 way to address this.

15 We will publish it in the Federal Register  
16 and we will also put it on the web site together  
17 with slides and transcript from today's  
18 proceedings.

19 Secondly, to try to answer your question  
20 about what do we have within the regulatory  
21 framework to address, that which we approve, at one  
22 point in time maintaining being safe and  
23 efficacious in current times, and I think there are  
24 a couple of mechanisms that we have and a couple of  
25 databases to try to answer that.

1           We have with all of the caveats attendant  
2 to it a postmarketing spontaneous reporting system  
3 for adverse events for any and all drugs and for  
4 vaccines. That includes coding such reports for  
5 drug lack of efficacy for infections that one may  
6 get as a result of taking an antibiotic, in other  
7 words, there are codes and queries that you could  
8 do of this spontaneous reporting system and marry  
9 that information to usage data in a crude attempt  
10 to try to get a denominator to understand within a  
11 given drug, across drug class, within a given drug  
12 class or across drug classes, et cetera, whether or  
13 not something that used to work, might not still be  
14 working.

15           Perhaps more rigorous than scientific, we  
16 have theoretically surveillance data that tell us  
17 with current isolates and current antibiotics and  
18 old antibiotics what theoretically should still be  
19 covered and what ought not to be covered from  
20 isolates and from real people who have real  
21 infection.

22           I think that we are trying to be diligent  
23 in our efforts to embrace those two real big  
24 databases and get our hands around them to try to  
25 answer the simple question that you raised, which

1 on inspection, is actually rather complicated.

2 DR. RELER: Thank you. The meeting is  
3 adjourned.

4 [Whereupon, at 4:00 p.m., the hearing  
5 adjourned.]

6 - - -

