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INSTITUTE OF MEDICINE

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IMMUNIZATION SAFETY

REVIEW COMMITTEE

CLOSED SESSION

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P R O C E E D I N G S (9:05 a.m.)

DR. BEHNEY: One of the interesting aspects of this process is report review. It is blinded, it is run out of my office.

You will find that the report will change. It is not necessarily that your recommendations, should you choose to make them, or your bottom lines will change, but it will be looked at by a number of people unknown to you, although you can suggest the names, and you do have to respond.

You don't have to agree with the comments, but you do have to respond and say why you did or didn't change, and what those changes are you made in response.

Count on it taking some time. The one minute version of the steps of the process is that you all, along with staff, suggest reviewers.

We try to make sure those reviewers are balanced just like the committee is. You can go a little bit further out on the tails, because they don't have to reach consensus like you do.

So, it is good to get reviewers a little bit farther out on the extremes, because then you can anticipate, by having confidentially someone say what the reaction is going to be to your report.

We send them the draft. When you all sign off on it, then it is ready for review. We send the reports out to

the reviewers. They send their comments in.

We give them to you via the staff, but the identity of the reviewers is blinded.

A coordinator is appointed, who is another outside person, often an IOM member, who looks at the totality of reviews and gives guidance to you on which things are the most important points and, even more important, plays the role of making sure that your response to the reviewers is responsive, that you have adequately taken into account what the reviewers said and whether the way you changed the report is appropriate or, if you didn't change it, your logic for not changing it, that that is acceptable.

Then the whole academy complex has somebody on the report review committee who also kind of monitors that process with a particular person.

When the coordinator and the monitor agree that the response is adequate, they sign off and you are free to go public.

Now typically I would say count on it taking two to three months. If you are lucky, it will be less. In this, we will have to work out some kind of an abbreviated schedule, and I think we can make one.

DR. MC CORMICK: From what I understand from Ken, there is going to be a sort of -- I don't know whose arm he is going to break, but there is going to be a sort of

standing review committee with additions as needed for individual topics.

They are going to be prepared to review so that we are not going to have, each time we send a report, someone new questioning our argument for causality or something like that.

There is going to be some poor soul for three years, or some poor souls, that are going to handle this, so that we can go through a more expedited process.

DR. JOHNSTON: The product is much, much shorter and therefore should be much more easily reviewed than the usual book.

DR. MC CORMICK: Right, but he has promised a standing group that will do this, so that we are not always confronting a new group of reviewers. We haven't sat down and done a specific schedule. Thank you. Good luck.

[Brief recess.]

DR. MC CORMICK: I think I will start by sort of having anybody who wants to comment on issues that they think are relevant, raised in either yesterday's open or closed session, that we should discuss as part of the process of coming to grips with what we are going to do.

That certainly can have something to do with the causality argument, but also I know the issues, the composition of the committee, also will come up.

Before that, however, Kathleen, who is waving her hand here in my left field of vision, wants two minutes of housekeeping.

DR. STRATTON: In your folders had been a copyright assignment form. You need to sign that and give them to Anne St. Clair. You are signing over the copyrights of all these reports and this is one form that will cover all of them.

The academy gives permission to reproduce, you know, and that sort of thing, everything that we do to anybody who asks.

So, it will never prevent you from using this, but we do officially hold the copyright. So, you need to sign that and give that to Anne.

If you have any questions about your travel expense report that is in your folder, you can call Anne or Kysa, who are experts at trying to resolve all this.

The sooner you get them in, the better. If you really can't cope with figuring out the forms, staple everything together, do your best to write a little memo or e mail, and send it to Kysa and Anne, and they will fill it out for you. We really want it to be as easy as possible.

We are taping on a new tape, not the tape that we did for the bias discussion, these discussions. This is a professional transcription service. They will do a verbatim

transcript.

This meeting, which is a closed meeting, the transcript is only for staff's use in trying to remember what it is that you said, and those pearls that come out of your mouth that I don't have time to write down because I am a lousy note taker, and closed session transcripts will never be shared with anybody outside the committee and the staff.

Yesterday's transcript is another story, and that will be made available to the public, against the happiness of our legal counsel, who has to review every transcript to make sure there was no slander involved in what was said, before we release the transcript.

The final bit of housekeeping is that you recognize from yesterday's very interesting discussion on HIV in the blood supply and the swine flu, Mike Stoto.

If you remember, Mike Stoto was a staff person at the IOM for many, many years and he worked on the original pertussis and rubella project.

He was smart enough to me to do the adverse events project and was a division director. He did a couple of studies after that.

He was the study director for the last project that Marie chaired on perinatal transmission of HIV.

He is no longer with the institution. He is at

George Washington University.

He is, however, frequently a consultant, paid or unpaid, depending on the nature of the work, to IOM studies, because he really is an extremely experienced IOM person and a good thinker.

Mike is a consultant to this project. As such, he is allowed to be in closed sessions with us. He has an awful lot of wisdom and thoughts about some of the ways that we think about this project and other aspects, and he is here for help for us, hopefully in an ongoing manner throughout the course of it but, at least for now, in helping us think through this.

DR. STOTO: Stop making me sound so old.

DR. STRATTON: He is not. So, welcome Mike. I think you do know some of the people here and you heard a lot about them. Mike knows a little bit about this project.

It was actually helpful to me, as we started thinking through how we might create something like this. Please use Mike as you see fit. Now I am done with housekeeping and we can go back to the real committee.

DR. MC CORMICK: What I would like to do is sort of get some issues out on the table for at least perhaps maybe a half hour or so, longer if we need, and then begin to try to think how we might organize ourselves to accomplish some of the tasks we are going to have to do, at

least to come out with some draft concepts about how we might go about this task.

I would also like to hear, if people really feel that this is an undo-able task and you are ready to bolt out the door, because I think we need to confront that as well.

I would like to begin with anyone who has some comments or some issues that were raised yesterday by the presentations or by our discussions.

DR. SHAYWITZ: There were a couple of issues that I thought were really critical. It seems to me that one of the driving forces to the whole question is the advocates who have an ally in their congressman, who has a very personal interest in it.

There is a very important question about the relationship between autism and vaccination that it seems to me that we have to address.

The woman, Mrs. Fisher, is of the belief that there is a new paper that somehow documents this. It seems to me we have to acknowledge address what they believe is evidence in a peer review way.

So, it seems to me that we have to have some kind of peer review of that. Somebody else mentioned O'Leary. Somehow there is pathology or virology. We should look at the pathology.

We need people either as consultants to us, or who

can address that. Then we need a whole group of people to talk about autism.

It is their belief that there is this dramatic increase and I just have no idea whether that is the case or not, and everything is lumped into it, autism, attention disorder.

It seems we have to address those issues head on, whoever else is a member of the committee. That is the way you would do it if you are trying to do the science of this.

DR. MC CORMICK: One of the issues that came up in the discussion afterwards with Mrs. Fisher was her enthusiasm for Dick Johnston's discussion that some of their conclusions were actually based on case stories, and not really understanding that the particular case that was involved was a re-challenge case that kept getting the disease with each re-challenge.

She is all prepared to cull through her files to get specific cases. I think if there are any conditions we might place on that as part of the evidence that comes in here, what we might think about, if she is really energetic about this, to be careful that she is not being led astray, that individual case stories are going to sway our conclusions, unless they are very particular kinds of cases that might illustrate a causal principle.

DR. STRATTON: Can I just say that absolutely,

when we take on MMR and autism, we will invite the appropriate people to in depth be able to review Wakefield and O'Leary's data, including Wakefield and O'Leary probably themselves, you know, and outside people.

That is sort of a separate issue of when we get into specifics of reviewing those data. We will bring in whomever within reason you all believe is important to get at the root of the story.

I will depend on you to help me identify who those people are and what an appropriate level of expertise is, as those ad hoc experts. Rest assured that that will happen.

DR. WILSON: One of the other things that is, I guess, true about that issue is that others at that same institution, Royal Free, using other methods -- real time PCR and so forth -- have been unable, apparently, to identify the virus that O'Leary claims to have identified, I believe by culture, in these intestinal specimens.

Again, that in no way proves that it caused the disease, but it is viewed as a link.

If you are going to invite those two individuals, it seems to me it would be useful to have one of the individuals who were unable to replicate the presence of measles virus from the same institution. Presumably there is some tension between those groups.

On the other hand, that is the kind of pro and con

we would like to hear, I think.

DR. SHAYWITZ: I think we also need lots of external peer review, too. I mean, like someone who is a great expert in looking at valid performance, and some of the people who know a lot about inflammatory bowel disease.

For all we know, these are just sort of the things you are going to find in many young people. I don't know. It is not my area.

DR. WILSON: There is another interesting association, another thing that varied. If you look at that original paper, the other thing that was found in all those kids -- almost all -- were high urinary levels of mevalonic acid.

The fascinating thing about that is that mevalonic aciduria produces a syndrome with very striking immunologic features, including periodic fever that occurs on about a monthly basis.

So, there is a periodic fever syndrome. They may have mental retardation, they have adenopathy.

They look like a patient with lymphoma, Caspell's disease. It is one of the periodic fever syndromes like Mediterranean fever, and so forth. That is the only reason they have been recognized.

Now, it may be that the mevalonic aciduria is secondary in those patients. It makes one wonder, if you

identified a group of patients who might have a genetic predisposition.

All they did was look at the urine. They didn't go back and see the kinase.

DR. KABACK: That is like the story of Reyes syndrome and medium chain ACLD hydrogenase deficiency. Many of these kids were diagnosed as Reyes syndrome, aspirin related, and it turns out that they had inborn errors of fatty acid metabolism. They would be exactly right.

DR. WILSON: I was astounded.

DR. BERG: I think this discussion illustrates that I need some reassurance on, and that is that just an issue like this could take us days or months or years to get through.

I would like some reassurance on a match between our scope of activities, the resources that we have, the time table.

I am especially intimidated that we are going to do autism and MMR at the next meeting. I find it hard to imagine, given the level of scientific care that I think members of this panel have, that we are actually going to be able to feel good about working through all the issues related to that one issue within the time table that we have.

You said, are we ready to bolt. Well, I need some

reassurance through a very intimidating challenge, especially yesterday, with everyone piling on more things that they would like us to do and more expectations. I am concerned.

DR. MC CORMICK: I think there are some things that we are not going to do. I think that the issues of policy that kept coming up on a routine basis is not part of our charge to look at, at all.

Kathleen and I were discussing this earlier, about to what extent people are going to feel ready to do the end of this meeting. My answer is, I am not sure at all.

I think two things. I think we are either going to feel reasonably confident that we can at least make a crack at it.

I also think that, until we get our grips around one problem to see what we are dealing with, such as the MMR autism, we may not understand either the full scope of what is being asked.

Then I think we put on the brakes and say, if we are going to do this right, we do it right. That is my reaction, and we have some feeling that CDC may feel that way as well.

I think personally that, as I look at the list, this is the toughest one.

DR. JOHNSTON: There is also a tremendous amount

of heat on this one. It is just accelerating. The usage of the MMR is dropping away. This is really a key issue.

DR. BERG: This really endorses the necessity of doing it right.

DR. MC CORMICK: I agree.

DR. KABACK: Just a point of information, yesterday, when NIH and CDC spoke, they alluded to grants and contracts that were apparently ongoing and applications for grants and contracts relating to vaccine-safety-related issues.

I think we charged them -- I asked the question, that is not quite the same as a charge -- that they provide this panel with a list of all their applications and abstracts of grants funded from both CDC and NIH that relate to vaccine safety.

Then the other issue on the same vein is, can we find out -- this may help us -- that either Canada, Great Britain, the Scandinavian countries, Finland -- I put Finland separate because they don't consider themselves Scandinavians. Well, they are quasi-Scandinavians.

Anyway, have they looked at any of the issues, because of the nature of their health care systems, that would be relevant to these questions.

It turns out, I spoke with Marty Myers after one of the breaks. Apparently, CDC has now a project going with

Denmark related to autism.

DR. MC CORMICK: There is also a huge NICHD research program in autism that we need to hear from as well.

DR. KABACK: Right. Again, maybe what you facilitate in our next two or three-day get together, would be to have this information.

Maybe there is some stuff out there that will weigh heavily on our deliberations and make things scientifically perhaps a bit cleaner.

It is also possible to make it scientifically less clean, and that will make our jobs a little more difficult. We need to follow up on those.

DR. STRATTON: They spoke to me afterwards and said that they would indeed work with us to get us a list.

DR. KABACK: Again, if we will receive that material well in advance of the next meeting so we can look at it and review it, that would be helpful.

DR. BERG: It would seem to me that both NICHD and NIMH have been working with autism.

MS. DAVIS: I am going to step back a minute. I may be the only one who is not clear from this. Representative Weldon said that our primary issue is safety, not public policy implications of the findings.

Looking at the charge, it talks about recommending

the appropriate action of the Federal Government for each hypothesis.

I need a little clarification of exactly what it is that we are doing or not doing in terms of public policy with these recommendations. It is just not clear, based on what people have said.

DR. MC CORMICK: I think, at least if I am understanding the extremes, we could potentially come up with, there isn't evidence for this one way or another, keep going full court press, or there is so much evidence to support this adverse reaction, pull the vaccine.

I think those are the two and I don't think we are going to come anywhere close to either with those extremes.

I think in between the recommendations for -- and CDC keeps backing away from the word recommendations, but at least the suggestions we would be making would be either the kinds of studies, the kinds of information, the kinds of directions that you would need to move forward to either establish or not establish the relationship or the safety factors, would be my understanding of what we would be coming up with.

We would not be talking about immunization programs. For example, Mrs. Fisher was very concerned about the article on exemptions.

I don't think we would be talking about whether

there should be an exemption policy or not. What we would be talking about would be the risks to those who are vaccinated and the risks to those who are not vaccinated, whatever that lack of vaccination means.

MS. DAVIS: So, our recommendations can then influence public policy, but we will not be specifically recommending that they follow them.

DR. STRATTON: Right. When CDC and I talked about sort of how far we would go, and the president of the IOM and I spoke about this project, it is clear that it is not the purview of this committee.

It is competent in terms of who we proposed, or what the IOM does, to say that a vaccine should be pulled, to say that a schedule should be changed, to say that certain people should or should not get a vaccine.

We could say, we could go probably as far as saying the evidence is so compelling that the appropriate advisory committees need to address this and consider their immunization policies in light of this evidence.

What that means is that CDC would feel the need to bring together ACIP and the FDA committee might want to reassess it.

We would never say something should be covered, something should be pulled, some schedule should be changed, but just suggest the evidence is sufficient that they

themselves take a look at it.

To say more research is influencing, to some degree, public policy, to say you need to change how you communicate about this issue is, in a sense, policy, but it with a small p and not the big P, which is vaccinate or not vaccinate.

DR. STOTO: In Walt's notes yesterday, he talked about comments on -- the third product was comments on potential future activities and one of them was policy review.

DR. STRATTON: That is what I mean by policy review.

DR. CASEY: So, we would probably not venture into this discussion about mandatory laws, state laws, for vaccination, just as a corollary to that.

DR. MC CORMICK: That is my understanding.

DR. GATSONIS: It would help me understand a bit of the time frame for what is considered evidence for the committee.

Is evidence everything that has been published up to today, or by the time the report is issued. You mentioned first the peer review of these articles that are in the process right now and they will come out some other time.

When you are in an area where there is a lot of

ongoing research and attention, you always have this difficult task of identifying what is the basis of evidence on which you are basing a particular recommendation at this point.

What is the practice here? Are we going to go ask for preference from a number of sources?

DR. MC CORMICK: Actually, the paper they are talking about is in your briefing book.

DR. GATSONIS: I understand. I am saying, I am sure these people are still doing more work.

DR. SHAYWITZ: I was using the term peer reviewed, not so much that it was published, but the fact that people who are knowledgeable about this area actually debated with the people who published it. That would be helpful. I don't know how logical it is.

Everything is based on that article, it seems to me, a lot of the beliefs of the advocacy groups and the congressmen are based on that article, and we need to see sort of how secure it is.

DR. GATSONIS: There was also mention of a lot of autism research at NICHD.

DR. MC CORMICK: I think a lot of that would be sorting through whether there is anything relevant to the committee and safety decisions. I would probably guess 98 percent of it is not relevant.

I think if you are talking about future directions where you might go, it would certainly be helpful to know what is in the pipeline so that you are not duplicating what people are already doing.

I would guess that most of the research that we are going to hear about would have very little to do with safety.

It may have something to do with competing hypotheses and biologic plausibility, which are some of the other assessments that we might want to make.

DR. STRATTON: I think the committee needs to decide how far they are willing to go in reviewing unpublished early data.

There is no hard and fast rule that the only thing you consider is something that has been published in a certain type of journal or the peer reviewed literature.

I mean, you can make decisions based on unpublished data that is presented to you, that you feel you understand well enough, it has been vetted and discussed enough.

Clearly, a report needs to make clear, you know, what kind of research and in what category.

Some committees have decided that they won't review any un-peer reviewed literature. I believe that is probably the stance we took in vaccine safety, other than

the case reports in the federal system, which is another situation.

I mean, the committee just decides. What are you comfortable considering evidence, and just make clear what that is.

DR. BERG: Again, this isn't the time to really go through this, but I completely agree. One of the things this committee needs to do quickly is to settle on its methods.

I would have to say as not a regular participant in the IOM process that one of the criticisms of the IOM products is that there is a lack of consistency from panel to panel about how they approach issues and about the explicitness and transparency of their methods.

It was illustrated somewhat yesterday in the variety of different vocabularies and causation association that one finds across IOM reports.

I think the core of credibility of this panel is going to depend on the transparency and the explicitness of our methods, whatever they are.

A decision like Kathleen is raising needs to be clear. We should probably have a paragraph or sentence that says, this is how we deal with the published material. These are the criteria we use for including it or not including it.

Again, it gets to an issue of reassurance. It is a complicated business, coming up with a complete methodology in the time frame that we are being presented and concerned about, where that methodology is going to come from, and whether we are going to have an opportunity to really examine it before we plunge in.

MS. HORAK: It is especially important for someone like me to understand clearly the use of materials from peer reviewed journals, writings, as opposed to things that are in the pipeline.

I don't have the same science background as some of you do. I wouldn't be able, on my own cognizance, to pick up the subtleties of what should be important in the outcome of any particular research.

I would have to rely on the rest of the panel in order to direct my thinking in that way.

If I had something that was peer reviewed, I would at least have the assurance that other scientists had looked at it and that the methodology was probably more consistent with rules than if I were attempting to do it myself.

DR. MEDOFF: I have a little bit of discomfort in getting into what Bennett was suggesting, having people come opposed to one paper and one point of view and sort of engaging in that.

DR. SHAYWITZ: I didn't want to do that.

DR. MEDOFF: What I see us doing is looking at the available literature, but not specifically picking out one paper saying that it is crap and that is good, but after looking at the literature, coming up with a paradigm of what we would consider to be very persuasive proof of an association with something, and showing where the existing literature, in a general way, either meets the mark or doesn't meet the mark.

Then if there was some suggestion about how studies could be conducted, that could be more definitive.

So, we deal with things in a more -- what is the best word --

DR. KABACK: Editorial.

DR. MEDOFF: In a more editorial way and not a personal way or attacking this guy from England. I think one of the things we really want to do is to try to be very neutral and not judgmental, so much, on the literature, but at least to try and establish some kind of framework, some architecture, whereby studies could be done in the future to maybe shed more light on the question.

So, you can come up with a conclusion by the criteria you used in the 1994 thing where there is an association, a strong one, but go one step further and say, you know, how could we shed more light on this problem.

That perhaps is what the CDC is looking for in

terms of direction and that goes along with what Dr. Orenstein was saying about future research.

I mean I think that deals with things on a less personal level.

DR. KABACK: I would worry about that. We do have to make a decision. We don't have the luxury of sitting back and saying, yes, well, let's see what happens in a few years.

There is a real risk that there will be lots of unvaccinated children. If it turns out that everything has been just a worry that shouldn't be a worry, then there will be two years that go by where you will have lots of unvaccinated people.

DR. MEDOFF: I think that being truthful with the public is really the best. I think if you could get people to understand what the problems are if you are truthful with them and you give them access to information.

Saying that there may be this problem but we don't have enough information yet to really know but, as somebody said yesterday -- I think it was David Weiss -- who said, you can define it in sort of general terms.

If it is a problem, it probably doesn't occur more than one time in a thousand, one time in 10,000 or something like that.

So, people have a framework for being able to say,

yes, I can understand that, and make a decision, the right decision to have their kids vaccinated, but also to give them the information that some of the people who were talked about yesterday lacked.

What is a vaccine reaction. How do you identify it and what do you do when you think it is occurring in your kid right after the vaccination.

DR. SHAYWITZ: I think we actually have to address the issue with the data that we have. I think that if this is a major -- if this evidence is being purported to be the major evidence that is driving a lot of people who want to vaccinate children, that we should address it.

We have that information and it shouldn't be a personal attack, I agree with you. It shouldn't be in any way a personal attack.

Suppose this is a very idiosyncratic view that happened to get published in Lancet. It has never happened before, I know, but it could happen.

So, people ought to know that this is idiosyncratic or other people don't believe in it. If you have two publications from the same institution that disagree, well, we as scientists need to know, does it make sense.

What is inflammatory bowel disease. Would everybody have the same thing, or 95 percent of kids? We

have to actually address that issue with the data that we have. We can't sort of sit back and ruminate.

DR. MEDOFF: I am not saying we should ruminate. I think as one of the speakers said yesterday, we have different layers in terms of how you convey the information.

If we just take the general public and say there are two papers that disagree, that is one way of, I think, getting people very worried and troubled.

On the other hand, if you say this is an unsettled issue that requires more study and then give some estimate of what you think the complication rate might be, if it does occur, I think people understand that.

That is giving them some numbers. It gives them a basis for making a decision.

DR. JOHNSTON: It sounds to me like, Gerry, you are focusing on an extension. Ben is focusing on an earlier step process that comes to grip with what you then transfer or try to communicate. I think you are talking about a little bit different things.

DR. MC CORMICK: I would see, if this is a seminal paper, regardless of its validity, that one would have to carefully use that as a framework for both looking at the association of the vaccine, but also what are the other issues, the competing hypotheses that might be raised by that paper, in terms of looking at it.

I think that if they do have something seminal like that, that people are really hanging their coats on, it really has to be critiqued.

Whether you need to have someone duking it out in front of you, whether we can commission knowledgeable people in the field, either inflammatory bowel disease or whatever, to comment from a variety of perspectives on this paper to bring it to the committee, I think, is another story, about how we go about it.

DR. CASEY: The only thing that I was thinking about in providing to the committee, I do not know this literature.

I am trying hard to understand the biological plausibility of the MMR and the leaky cut syndrome and absorption of these toxins, not just the one that Chris mentioned.

There are laboratories, one of which I know is Oklahoma, and I can find it after we leave today, where families send specimens out there and they get a complete sort of chronograph result of all the toxins that are in a child's gut, telling them other things, and when it is related.

It is related to the MMR discussion, but that means there are neurotoxins that have been circulating and these are highly atopic kids.

You know, they have high IGEs. Some of them have anti-immune antibodies. So, it is a very GI discussion. But there is another set of literature there that we need to add, should this Wakefield and O'Leary discussion cover that stuff.

I will get that for us, and I am sure there are many labs throughout the country who are doing that. That is what these parents are looking for.

The MMR is related, somehow, they think to also the gut is abnormal. They relate stuff in here to the known antibodies to the brain.

I will try to find that today before we go. I am just not finding it here.

MS. ANTHONY: Gerry, I was just concerned about, when you start to get statistical odds for people, that is why I was looking at this.

It goes back to the anxiety and some of what was discussed yesterday. It is still very, very hard, how people would receive any vague interpretation on our part.

I was taking your line, Rich, just today, that I saw MMR rates just driving down. That may not be true. I am concerned that if we convey a significant amount of doubt, maybe if it is category three or something, that would have really a major significant impact on people's rates of declines in vaccines.

DR. MEDOFF: I think you have to give people something.

DR. KABACK: I have spent a fair number of years involved in the counseling area about risks and probabilities, as it relates to genetic disease.

It is a little bit different, but it has to do with a literature that concerns the layman's -- you know, we are sitting in a room filled with people who think probablistically in terms of statistics and numbers.

The general public does not, and there is lots of evidence to support that notion.

There is a paper, it is a very famous paper done by Claire Leonard and Barton Childs some years ago called Genetic Counseling, the Consumer's View.

What Claire did, she went to a group of people who had to make, and who had made decisions based on information received in counseling.

They were families who had children with cystic fibrosis which was, at the time at least, a disease of high recurrence risk and high burden, families who had kids with Down's syndrome, which was low recurrence risk, high burden, and kids with PKU, which was high recurrence risk, low burden.

Then, as a group of controls, there were families with kids with rheumatoid arthritis, which was thought to be

non-genetic.

Claire asked these people a series of questions. I am taking just a few minutes, because it is very important for everybody to hear what I am going to tell you about.

She would sit down with a person -- these are parents of children -- and say, there are 10 marbles in this box. One is red and nine are white.

I reach in the box and I pull out four white marbles. What is the chance, on the next pull, that I pull out a red one. Forget it.

Next question. There was a series of these. I flip a coin. It comes down heads nine times in a row. I pick up the coin again and flip it again. What are the chances that it will come down heads again. Incredible, the answers that she gets from families.

These are families who had to use risk and probability in making reproductive decisions. Yet, their ability to determine simple probabilistic statistical information was devastatingly bad. They weren't mentally deficient people.

The weatherman says there is a 25 percent chance of rain tomorrow. What does that mean to you. Open-ended question.

People looked at Claire and said, well, it means that it will rain for one fourth of the day and it won't

rain for three fourths of the day.

Some people looked and said, well, that means it can't rain because it is less than 50 percent.

Some people looked at her and looked at her and looked at her and said, well, I never listen to those damned weathermen anyway, because they don't know what they are talking about.

They could not explain what a 25 percent risk statement meant. We kid ourselves in the biomedical field when we talk to people about risks and odds, and assume that they understand and can interpret and integrate that information into the decisions that they make.

Now, I don't disagree totally with what Gerry said about at least giving people ball park ideas of what risks a given problem may be.

What do you say when you are a practicing physician and they bring in the baby and you are about to apply the vaccine and the mother says, I have been reading that there are some really bad reactions to this. Is that true.

What does the physician say? Does the physician say, don't worry? Forget about it? I think that is one of our problems.

DR. JOHNSTON: It is one of the problems.

DR. KABACK: The physician might say yes, and then

the mother says, what are the chances of having a bad reaction.

I think you can say, well, it is so small that it is not even worth --

DR. SHAYWITZ: You say quite small and some people are very happy with quite small and other people say, what does quite small mean.

DR. MEDOFF: There are layers of communication. I think that one of the charges of this committee might be to instruct the CDC about that, or the agencies.

DR. KABACK: I agree with you. I think that is what is badly needed in this field, is some communication mechanisms for health care professionals who are dealing with vaccinations.

Now, the suggestion has been made that anything you say about risk is going to decrease adoption of the procedure.

That, of course, is the worry. Then you deal with lowering immunization rates and increasing disease, deaths and problems associated with it.

Yesterday, throughout the discussion, and even here there is a sense of how do we ensure safety associated with vaccinations.

I don't think that notion is the right notion. We are not trying to ensure safety. We are trying to maximize

safety.

We recognize that there may be some risk. This gets back to the probability issue. There are small risks associated with anything.

The question is how small are they and how do you phrase that, how do you communicate that in the context of a health care system that gives doctors how long, did you say, two minutes or six minutes for the total visit, 1.7 minutes for the vaccination discussion?

That is the other big hang up we have here. We are talking about human communication to people with various levels, various ethnic and cultural groups, various abilities to understand statistics probability and scientific information.

It all has to be done in 1.6 minutes in a way that they can make a -- I will come back another time and give you a nice anecdote about informed decision making.

That, of course, is threaded through all of our vocabularies, this great notion of informed choices that patients make.

We need to think a lot about that. We have got a dragon by the tail here. At the end of the line, what we know is -- and I agree -- that the more negative that presentation is, the less likely people are to use vaccination, immunization, and we know what the results of

that will be.

We are kind of caught in a trap. How we work our way out of the trap, I think, is the charge. It does have a kinetic component.

That is why I think we can't sit two years to do it. I think there is this growing -- I have heard it multiple times already about the issue of autism with MMR. It is building.

Of course, we live in a 24-hour-a-day, seven-day-a-week media blitz on our public. They are always looking for things to fill up the time and the newspapers with. This makes a great story. So, we have a big job.

DR. MC CORMICK: Apropos of this comment, I took away actually an issue that we may have to confront, and that is actually the definition of what we mean by safety.

It is safety on a population basis, but it is also safety for the individual child.

I am wondering, if we take this dual perspective, we may address more of the parent concerns, perhaps developing a better message if we think about what comes down the stream as opposed to CDC, which wants us to declare, well, these things are pretty safe on a population basis.

I offer that as one strategy as we take this dual track. We may come up with more useful kinds of

conversations to have in terms of thinking about that. That was one thing that I took away.

DR. GATSONIS: Two small items. One is to communicate notions about risk to people. I mean, there is a lot of literature that is out there about how to do those things.

You can describe a particular risk as comparable to something else that people understand, and people make decisions about that in their daily lives, like crossing the street or putting your kid on a bus to go to school in the morning, et cetera, et cetera.

There are ways of explaining risk. It seems to me, at least, from the little that I managed to glean from all of this, is that the first and major task of this community is to define what is the level of the risk in scientific ways. Then be concerned about how this will be communicated.

It is that decision that has to be done based on the -- now you are back to the question I raised in the beginning, based on the literature that is available today. From there on, you know, things could be revised.

DR. KABACK: I believe yesterday someone commented correctly that there is a continuum of scientific information. That picks up on your point.

DR. GATSONIS: As you know, medicine, like other

parts of life is not immune at all to the hottest thing since sliced bread syndrome.

There was always a sliced bread that came along and then there is something that comes along every week. I see this in the area I work, in the diagnostic area, every week there is a new thing.

Ditto. There will be a new paper coming out next week and the week after. You have to draw a line someplace and say, this is what I am based on, and this is what I am basing my interests on, and something new comes and it takes a while to be incorporated in the literature.

DR. KABACK: The second part, I think, becomes a little bit of the charge of this committee, to identify what kinds of new information might be developed, which is the research component, that would influence the position we are taking now, based on the available data.

What else might be done to get additional data that might change this current position. That, I think, is part of what our charge is as well.

MS. ANTHONY: I am not a researcher, like most of you in the room, but I would think from a layman's perspective that if we were to reference a couple of documents that might be suspect, that we individually know about.

I am inclined to say that we might want to draw

the line of not using unpublished data, unless we refer to, oh, by the way, some of this new data is being worked on.

DR. MC CORMICK: That is exactly how we used it in past reports. I mean, you get the published reports that are available.

If you know there is a study that directly addresses something you are doing and that study may change your opinion, you clearly want to recognize that it is coming down the pike.

DR. JOHNSTON: I think so, too.

DR. MC CORMICK: I think that is absolutely the case.

DR. MEDOFF: We can develop a paradigm based on each of these entities. So, you would have the first question, the correlation between X and Y. You find that there is a weak association possibly.

Then it becomes the different levels of communication. Up until the scientific one where you tell the right kinds of study, whether it is a randomized controlled trial or whatever, that would be the most convincing, or lower layers, the lower cuts in terms of what you tell the people, that this is possible but, if it does occur, it occurs very rarely.

There is a conclusion in terms of communication between communication being for the CDC about what they

should do in terms of scientific studies to solidify or nullify the hypothesis, but a communication to the public, to society, mothers and fathers, about what the state of the literature is, so they are not dissuaded by a neighbor or looking on the internet.

I think that is what people were saying yesterday and I agree with that. I think the information that we derive from our communication has to be on several different levels.

DR. MC CORMICK: That is part of my dividing it between population and personal safety.

DR. MEDOFF: Is a paradigm part of it? Do we make a conclusion about what would be the most appropriate study or whether it should be studied or not studied.

DR. MC CORMICK: Yes, I think that is absolutely a part of the conclusions.

DR. COHEN: I have been spending a fair amount of mental energy trying to come to grips with exactly what the charge of this committee is.

I mean, you know, it is written down on paper but in the final analysis what is it really going to mean to people.

I think ultimately -- not being a scientist, of course -- but we are not going to be able to look at the literature and come up with, okay, this is the answer, there

is an association, there isn't an association.

Clearly, something of great value that I think will come out of this committee is, gee, what should be done next, and we have been talking a bit about that.

I think that in terms of coming up with that prescription, we need to make sure that it is complete enough so that if X,Y,Z studies were conducted, that it would actually get people to the point where they could be more confident in the decisions that they have to make, be it CDC or whoever is going to make policy about this, parents making decisions about this.

In other words, if we, for example, recommend that -- just to pick on the Wakefield study, the issue of whether the measles virus is really present or not, suppose that we could actually resolve that question.

Would CDC, tomorrow, be in a better position to make policy on this. Would parents be in a better position to make decisions about whether they think their children should or shouldn't get this vaccine.

In other words, we need to come up with enough of a recommendation that if, in fact, we were running the world and all the studies that we said were actually conducted, that at the end of the day, people would feel more confident that they knew what to do.

DR. STRATTON: Josh may have just said what I was

going to say, but I am going to try together something Al started with and which Constantine carried forward.

I think that CDC has an immediate need. That is why they came to us and asked for something somewhat different, which is the daunting task of trying to get all of this together in a reasonable time frame, instead of a two-year or three-year process. So, there is a need.

We just have to know that what we are saying is the best decision for the evidence at the moment, and that things will change.

Because of that, we have to do exactly what you urged us to do, Al, which is to make it very transparent and very clear, how we thought about this, how we evaluated data, and how we came up with putting them together somehow to end up with a conclusion.

If, in a year, a new study comes out, someone else, not us -- they are not going to come back every time -- I hope. They are not going to come back to us every time a new study comes out to say, well, what do you think now. This new piece of data, does it change your mind.

They need help so that they can figure out what it means, because we have been transparent enough.

Some IOM groups are good at that and some haven't been. You know, hopefully we will be, and certainly by the end we will be real good at it, I hope.

I think an important question, and I think somebody just said it is, CDC doesn't only want to know -- they don't -- in addition to being told what to do next, they need to be told whether it is worth doing something next, or has the available evidence just put together not been compelling enough for them to continue pursuing a hypothesis.

That is really what they want from us. What they really and truly want is, should they be pursuing this and how vigorously or not.

Is there ever a case for which the scientific evidence, the biologic plausibility, the competing hypotheses and other factors day, don't go whole hog on this.

Right now they are being told by different constituencies at every turn, go after this, no, no, no, go after this, no, no, no, go after this. They need some help at figuring out when and how vigorously.

That is what I see. I think that is what Walt was trying to say -- Walt Orenstein yesterday -- when he said, it is not enough to just say more research is needed. Give me a feel for how much and what sort.

It may be that more research is needed is just better research in your passive surveillance systems to try to get a handle on whether you really have a signal, and we

are not ready to do virology and scoping autistic kids in this country yet.

I mean, you may decide otherwise. You may decide that the whole Wakefield hypothesis is compelling enough on a number of levels that we should scope kids and do virology.

They want some sort of guidance about when to pursue. Right now they are being told to pursue everything with equal vigor, and it is a squeaky wheel phenomenon.

We are supposed to step back from the squeaky wheel and use your scientific judgement and your public health judgement and your community level judgement about when to move forward.

DR. COHEN: In other words, this is what it would be helpful for you to know about now. So, pay attention to this, get more information on this.

DR. WILSON: Well, be explicit why.

DR. COHEN: Yes, and be explicit why.

DR. WILSON: If the following data was obtained, it would or would not refute the hypothesis. It would or would not make a likelihood reference.

DR. STOTO: That will help with the transparency in the first point. It will say, we can't say definitively because we don't have this particular information.

I think if you say the kind of information that

would help you make the case, that would help you make clear how well you know things in the first place.

DR. MC CORMICK: I think also sorting through squeaky wheels. I think if a particular problem, even if the level of evidence isn't particularly strong but it is emerging from a whole number of sectors and really is driving the debate, that that is something they should pay attention to, even if the evidence isn't particularly strong, as opposed to a relatively rare condition, there is only one squeaky wheel and we can't find any evidence supporting it whatsoever.

DR. MEDOFF: What if there is an association between MMR and autism, and we assume there is. So, then it becomes really a question of the frequency of occurrence.

Then, what is acceptable to society. That is the normal path.

DR. MC CORMICK: I think I would also -- let's take the hypothesis you are given. You have got measles virus in the gut and there is some association.

What would be the risk to the individual child of wild type measles versus getting the vaccine and running the risk of autism.

I suspect you might come up that the risk of wild type measles, if they were not immunized, might be quite substantially higher. I don't know that.

DR. CASEY: Or of having neuroencephalitis.

DR. KABACK: Isn't it the MMR -- I know it is the measles virus component, but Wakefield is now giving measles individually.

It isn't the measles immunization per se that they are claiming autism. It is the measles when it is given with mumps and rubella.

DR. MC CORMICK: I understand that and I don't understand that logic at all.

DR. WILSON: What is the feasible mechanism by which you could argue that the immune response might be different with the triple than with one.

DR. KABACK: That is what I always assumed by that.

DR. WILSON: The probability of that is truly small, but is it possible? Is it feasible? Do we have proven biological plausibility in the case of these viruses? I don't know.

Yes, you could construct a mechanism whereby that might be the case.

DR. KABACK: In fact, people have used the alternative recommendation, that you give these individual immunizations not combined, for this very reason.

DR. CASEY: We are getting pushed to do that more, but I am not at all clear on whether that is any safer.

DR. MC CORMICK: Then couldn't you recommend a large randomized trial between the triple dose and the single?

DR. WILSON: Only if the incidence of the disorder is sufficient that the randomized trial would give you statistical power adequate to address that hypothesis, and that is unproved.

DR. MC CORMICK: There are two things you would demonstrate. One is the questions about whether you would have decreased compliance and decreased immunization because of three shots versus one. There are two trials that you could think of.

DR. WILSON: In a trial setting, of course, you drive the system to accept the vaccines, because people are compelled, in essence, to take one or the other.

That is not a field trial of acceptance under the conditions that would prevail if you had this as a normal part of routine health care. That is very different.

There are published studies -- I guess it didn't get in here, but there is the Finn study where they have looked at all the adverse effects.

They published a recent one in Pedes, and they had the previous one that did not support an association between MMR and autism in Finland. They recapitulated that finding in a more recent report.

Then you would say, okay, here is a huge study of the whole Finnish population that did not show an association.

In order to do the study you want to do, it is not easily done. This gets back to Josh's question.

DR. BERG: We need to back up to methods. One of the comments that was made about how great the IOM was is process.

Yet, this last discussion is way ahead and we need to focus. I don't know how long it will take us to figure out what the question is.

I am a veteran of one panel that took six days for a group about this large to figure out what the question was that the panel was going to address on otitis media. So, it can be a formidable issue.

I don't know what the question is, whether it is MMR or whether it is measles.

DR. MC CORMICK: The question is MMR.

DR. WILSON: Is it only MMR? We are also supposed to look at thimerosal.

DR. MC CORMICK: Not this round.

DR. WILSON: Wait a second, not this round. But if we are going to look at autism and we have three candidates, can we really fundamentally look at them in isolation.

In fact, in the real world, they don't occur in isolation. Individuals that got MMR vaccine also received vaccines with thimerosal.

DR. BEG: What I am trying to get at -- excuse me -- is I think if this panel is going to meet for three years, presumably we are going to have to have a method for how we focus the question many times.

This is one of the questions we need to focus on, but there are lots of other opportunities ahead of us. How are we going to frame the question. What kind of process are we going to go through on the question. Then there are just a lot of other methods that follow that.

I feel it necessary to figure out, in general terms, what process we are going to use to focus the question. How are we going to discuss it.

I would like some reassurances about the general processes before we get to the specifics of autism and MMR.

DR. MC CORMICK: That is actually what I would like to spend the whole day on. I am still in the process of trying to elicit whether there are topics that we need to bring up.

I also still have on my list the composition of the committee. I am still at the information gathering stage. The rest of the time is really supposed to be devoted to coming to grips with that process.

DR. CASEY: We can come back to that, because I was trying to ask about natural measles, biological plausibility type things. So, we can do that when we are really working on that.

DR. MEDOFF: So, you are interested in basic questions that can be used over and over again for whatever association?

DR. BERG: How we attack the science of developing these kinds of reviews is rather far advanced. The issue of specifying the question is an important step. I would like to know how this panel is going to specify the question.

DR. WILSON: Why don't you make a proposal.

DR. BERG: It is an issue. Do we look at just burden of suffering? Do we look at squeaky wheels? What information will this panel collect in order to decide what is the question that we are going to address. There are lots of competing ways of doing that.

DR. KABACK: I am not sure what you just said. Which information do you collect in order to determine what question you address, or is it the other way around?

DR. BERG: Yes.

DR. KABACK: You determine the question and then that determines the information you collect.

DR. STRATTON: I just need a clarification now, on the question. Do you mean which safety hypothesis or which

question in terms of how are you going to assess causality and how are you going to assess biologic plausibility.

DR. BERG: I don't want to dominate the discussion here. Even with what the CDC has suggested, within the question that they have given us, there are many ways we could approach it.

DR. STRATTON: You mean the general question, the general charge.

DR. BERG: Yes, determining where we are going to put our effort, where we are going to focus, I think, is an issue that we have to deal with.

It can be at quite a specific level or it can be at a higher level, but I think that we need some way as a group of saying how we are going to approach the topic.

There have been many things suggested in this discussion. I don't have a sense yet of how we are going to collect those and make those decisions.

DR. GATSONIS: Would it help if it was just the specific issue of MMR and try to approach it and then see at the end of it.

I mean, what would be a typology of approaches. I mean, what exactly is the typology of approaches and where do we find out about them.

DR. BERG: I am not an expert in immunizations but we could decide, for example, that we are going to address

an issue if there are adverse events that have been suggested that are really serious.

We could decide that we are going to address an issue because there are squeaky wheels out there who are worried for whatever reason.

We could decide that we are going to address an issue because there are empirical data that we are aware of that lead us to concerns.

We could address an issue just because a vaccine is out there and it is being used in millions of doses.

What are the criteria that we might use in order to focus the questions.

DR. GATSONIS: So, from an empirical point of view, it is not like there is something else out there that describes --

DR. BERG: There are thousands of questions that this panel could address.

DR. JOHNSTON: Al, why not any or all of those reasons, used together, to come up with where the most heat is.

I mean, the heat is part of the issue, the interest. I think we know -- I think there are a lot of very logical relationships with vaccine adverse events that will take us well into next year, if not further.

DR. MC CORMICK: I think, if I am hearing you

correctly -- and I am also confused -- I would see what you are talking about as something for selecting the next topic.

I don't see any of the criteria you just mentioned not reinforcing looking at MMR and autism.

DR. BERG: I absolutely agree. I was intimidated by the list. We have nine more meetings and even in the list that was presented to us there were 25 topics.

The potential adverse effects, clearly, MMR and autism is going to be one of the issues. Even there, we need to be clear about exactly how we are going to address that.

I am interested in the general methodology that this panel is going to use. This may be our only chance, I understand, to talk about methodology.

What general methods are we going to use to prune the tree. How are we going to decide that issue X is more worthy of our time than issue Y.

DR. STRATTON: Actually, you don't have to make that decision. We don't have to make that decision. CDC will tell us which topic we will address when.

DR. JOHNSTON: That is news to me.

DR. STRATTON: The list of 30 topics -- see, because it could take a committee three years to come up with a way to decide how to prioritize within the 30, which ones to be dealt with when -- they don't know yet, by the

way, which ones they are going to ask us to do out of that 30 list, other than that they know that they have asked us to do MMR, to look at MMR and autism first.

Then they have asked us to do thimerosal and autism second. We can get to the issue of how they are related, that is a separate issue, in a sense.

Then will then decide what the third topic is, based on whatever this interagency group on vaccines is, who will decide what is bugging them, what are they being attacked on.

So, they will decide and they will say, in six months, you know, your next topic will be X. How we then deal with X is your purview, absolutely.

They will tell you -- the reason for that is, besides the fact that it could take a committee three years to decide just how to prioritize them, is that something new might come up that all of a sudden has erupted from a trial or from a surveillance or from just a squeaky wheel or from a 60 Minutes.

All of a sudden, Jeff Copeland and Walt Orenstein and the Surgeon General and everybody is being beat over the heads and they need to try to resolve something.

We don't have to make that decision. Whether we like it or not -- and there are pros and cons of letting them determine the topic -- to be expedient, it is better

that they determine it.

DR. MEDOFF: They are paying for it.

DR. STRATTON: A lot of times we don't actually care about that, within reason. This is a case where it was decided that their need for what to be addressed next was primary.

We probably could object if we thought something was totally ridiculous, and we can shape it a little. We have -- you know, what are the boundaries. Does that make you feel any better?

DR. BERG: Now I am curious what other parts of the methods the CDC has figured out for us.

DR. STRATTON: None.

DR. BERG: Thank you.

DR. STRATTON: They just say, this is the topic we need help on this quarter, this six months. This is the topic.

They gave us some suggestions yesterday. You certainly heard from Walt Orenstein. They no longer -- the only thing they get approval over or power over is which topic do we take next, in general. The rest is up to you.

MS. HORAK: The issue that is driving CDC is their perception and probably knowledge of utilization of immunizations; is that correct?

DR. STRATTON: In general, of course they have a

worry that if there is a big safety concern that people won't get immunized when they should.

They say -- and I believe them -- that people are getting immunized when they really shouldn't. What if there really is a terrible hidden truth about one of these things.

Of course, they are worried about immunization coverage rates and whether they are going to go up or down.

I think it is more the squeaky wheel phenomenon. They have 100 squeaky wheels beating them over the head every day and they can't respond to all of them and they want your advice whether something is worth responding to.

DR. JOHNSTON: Some of those, Abby, there is more to it, that there is a fundamental concern about red flags being raised.

Thimerosal is one that I happen to know about. They have had ongoing studies.and they have asked the question, what is the relationship between thimerosal and attention deficit activity, other central nervous system problems.

There was some data that worried them. I think it comes from different directions but it comes from sometimes they are genuinely concerned that there is an issue.

DR. MC CORMICK: I think there may be a third phenomenon going here that also reflects the anthrax story and it reflects the Gulf War and agent orange experience

that we listened to.

You know, they go for 10 years hearing these stories and they sort of shuffle them under the carpet and don't react to them.

Then all of a sudden people really develop a fairly strong constituency plus perhaps some congressional support.

If they had set up prospectively a mechanism for looking at some of these adverse events in a much more systematic way, it would have been more reassuring and at least acknowledging that they occurred, as opposed to now sitting there with this organization with 20 years worth of case report saying, you have been doing harm to our kids and you have been shuffling on us and ignoring us.

I think, as I listened to yesterday, one of the things that we may want to come up with is some advice about how to use these examination centers to really develop some realistic evidence about what is going on.

This is exactly what was kind of forced on the Veterans Administration, because the Gulf War veterans and the agent orange people kept beating on them, beating on them, beating on them. They finally had to set up a realistic mechanism, or at least a mechanism. I don't know how realistic it was.

At least, adverting to what was going on and

trying to document it in a reasonable fashion.

MS. HORAK: This is establishing process which may be an ongoing process in order to continually address issues of safety.

DR. MEDOFF: I think that is a very nice formulation. Again, I get back to this idea of a paradox. What is the appropriate process to deal with when we have vaccines and all these complaints are coming in.

I think they haven't done a very good job of communication and I think there is a real question of credibility.

I mean, we could work with one of these questions. I think it is very important that the method be set up which then transfers and is usable for whatever other questions.

We give them the guidance. This is how you should do this stuff. This is how you should react. Give them a road map, you know, just in terms of how they collect data, what they do with the data in terms of process, how quickly it is acted upon, and how it is communicated. I think communication is very important.

I think that we need to first develop a process in general. For the specific question, we could use the MMR and autism.

DR. MC CORMICK: What I would like to do now is

sort of bring this portion of the meeting to a close. I would like to reflect on the discussion we had yesterday about having members of the lay community who are interested in this issue.

I took fairly seriously Amy Fine's concern that we should have both someone from the parents' vaccine community and someone from the sort of chronic disease community, child chronic disease, be it autism or diabetes or something of that sort, the kind of parent who is looking for answers as opposed to concerns directly about immunizations.

I guess I would like to propose, sort of as a solution to that, that we ask staff to try to identify such people as the vaccine parent's community, to nominate someone who will meet the same criteria as the other members of this committee, see if we can find someone who would be helpful and supportive and not disruptive, and that we talk to some of the child chronic disease organizations, like Family Voices, and see if perhaps we can find one or more folks who might be useful, unless people object to that.

DR. KABACK: You mentioned juvenile diabetes.

DR. MC CORMICK: What I am talking about is a parent who is involved with either developmental disability or one of these chronic diseases like diabetes or asthma.

DR. KABACK: When you go to the organization to request, obviously the step before that is important in

terms of the person that would come forth.

If you went to the Juvenile Diabetes Association you would get hopefully a recommendation of a parent of a juvenile diabetic. If you go to the Epilepsy Foundation --

DR. MC CORMICK: I was thinking more of Family Voices, sort of more broad based.

DR. KABACK: I see, okay.

DR. STRATTON: Do you want a parent or do you want somebody who is sort of a congressional staff advocate. Does it have to be a parent of a child with a problem, or can it be someone who represents that -- who is clearly devoted to the issue and understands the concerns.

DR. KABACK: Most of them are parents in those organizations, but not all of them.

DR. STRATTON: Sometimes the executive director or the scientific advisor or the policy advisor of those organizations might represent a larger view, because they have a whole constituency as opposed to one parent.

DR. KABACK: It is a trade off.

DR. STRATTON: I just want you to think about what is your advice to me and Alicia about who to go after.

DR. STOTO: That kind of person might also feel more constrained to represent the organization, which is not what you want.

DR. STRATTON: Then that is a problem as well.

DR. KABACK: I would lean toward the parent, personally.

DR. JOHNSTON: I think the passion is going to be more likely to be with the parent. That would sensitize how they view potential conclusions and how we articulate them.

MS. HORAK: I like the idea of making it clear who that person is supposed to represent. When you sent material to this committee, you made it clear that the persons on this committee would not be speaking for a constituency, in that representatives of the Academy of Pediatrics or the American Nurses Association had nothing to do with this, that they were supposed to bring their talents and their discretion to the subject at hand.

I think that that is important to make clear to the nominees.

DR. MEDOFF: I would agree with that, but I think that it excludes someone who is working with one of those organizations.

I mean, we had people from Act Up on our committee. They weren't speaking for Act Up. They were speaking for everyone who was infected with HIV.

Again, we got good people who were concerned. If you can find a parent who is not associated with any of these groups who has also kept up with the literature and so on, that would be fine, but I think you are going to have a

very hard time doing that.

DR. GATSONIS: I would have a similar concern about having a hard time. In the case of Act Up, these were people who had read enormously and they were very much experts in a very specific area.

Here, we are talking about a very broad area. I mean, there are several kinds of vaccines, several kinds of chronic diseases. It is a very broad kind of community.

So, one issue, I guess, in my mind is, what can we do to avoid tokenism. I mean, from the point of view of the workings of this committee, especially if this committee does not get into making policy recommendations, which it will not.

Then you don't need to get into tokenism, unless you think that there will be something very specific that can be contributed to the workings of the committee by somebody or somebodies out there.

It could be that it is more than one person we are talking about. Maybe there are more than one.

DR. MC CORMICK: I think the conversation that went on yesterday was the concern was we would not have someone bringing parental concerns to us nor reacting as the recipient of our information and critiquing it one way or another as to its understandability and utility. Is that my understanding of what --

DR. GATSONIS: Yes, but if parental concerns are the issue, several of you are parents. I mean, seriously, I don't want to belittle this, but several of you are parents. I don't see why this parental concern --

DR. KABACK: I don't know whether you knew this, because it was discussed yesterday -- I didn't know until yesterday -- that one of the charges of the group is that, in the position statement that is written by each of these issues, it will be accompanied by a two-page for-the-lay-person version, which is going to be distributed to pediatricians and doctors offices all over the place.

That is the reason for having the input, I think, of the consumer. They are going to get that two-page version.

They may have important input into the design and structure of that topic.

DR. STRATTON: Those weren't the only reasons.

DR. KABACK: That is not the only reason but it is certainly important.

DR. STRATTON: That can be handled through other mechanisms than having a committee on it. I am still not exactly clear myself.

DR. WILSON: It is more than that.

DR. STRATTON: I need to be clear about how you see their input so that we can explain it to people.

DR. STOTO: I think that the second product that they have asked for, local and public health concerns, gives some sense of how important this thing is. I think you need more than scientific input.

MS. HORAK: I would like to follow up on something Constantine said, and that is the term that you used, a token representative. I think that that builds resentment, if we just have somebody who is a token. It has to be somebody who is bright enough and involved enough to participate fully, or the fears of the parent groups will be borne out.

DR. MC CORMICK: I think a way it might be articulated is someone who is also going to be reflecting the sort of density of concern of these groups of affected parents.

MS. DAVIS: I would be open to having someone who is not a parent, who is a professional who is trusted by that group and works with that group frequently.

Coming from Michigan, some of those parent advocate groups have people who are a part of them that they love, and some of those parents are actual parents of children who have problems, too.

One of our staff persons, who was the staff person who was the parent advocate for the children developmentally disabled, was also the parent of a developmentally disabled

child.

She would be more effective in a group like this because she could make that linkage between the professional side and the parent side.

I think from a staff perspective, we could look at that. I wouldn't exclude that, although there may be some parents, and maybe between the two, maybe one would not --

DR. MEDOFF: I think the group is overwhelmingly rich in science.

MS. DAVIS: If you can find some good people who have the trust and respect of those groups who is not one of the parents only, I think we could at least look at that.

DR. CASEY: And part of their nomination, instead of just their credentials, just to ask the organization to make a statement about why they think the person would meet our criteria.

DR. MC CORMICK: I was thinking another source of nomination may be some of the state agencies that deal with crippled children child disabilities that know the parent groups as well.

DR. KABACK: We have a relatively short time frame to identify this person or persons. We are not necessarily limited to one.

DR. STRATTON: I was saying last night, we have been looking at a conference on transitions of disabled

youth to adulthood. Boy, the circle comes down real small real fast, in the number of people who really are active in this area.

I don't think there is a large pool out there of people. It obviously will be one of our first priorities, to get those people on board.

DR. KABACK: In the same category, I just was thinking last evening, after listening to yesterday's talks, again, it will depend to some degree on what we choose to be our target and our purview in these efforts.

If we are going to be directed at issues like communication, which Gerry has alluded to a number of times and I agree with, as one of the most fundamental products of the effort, that is, what kinds of information will need to be communicated, we heard yesterday about the issues of informed decision making and communication and risk communication issues and informed consent.

I wondered last night about whether it would not be helpful to have, as a member of this committee, someone in the -- for want of a better term -- bioethics community with particular interest in informed consent and communication-related issues.

This is a field and it is a field with considerable expertise. There is a lot of relevant input that such an individual could provide for us in our

They had never talked about our giving something as sort of simple as a one through four, you know, how concerned should you be.

It was my impression that you could infer what that is by the nature of the actual recommendations we make for next steps.

I mean, if we say there are no next steps, then I think that means that we probably don't think that it is a big issue, and it is a non-issue.

DR. STOTO: I think there is something separate in two that is separate from one. You might say this is a vaccine that is only given to a couple thousand kids a year and it only affects kids who have red hair and has a very mild reaction. That is probably not something you have to worry about.

DR. MEDOFF: That is separate from the evidence is strong that the vaccine causes -- is this supposed to say if the concern is appropriate or inappropriate?

DR. GOODMAN: I think the word concern is unfortunate here. I don't think we can assess more than likely public health impact, something like that.

This issue of mixing up the reaction to our recommendations or judging what is appropriate is, I think, what makes it a little bit problematic

What he is really saying there, when you read it,

I think, is likely impact. Then we can spin that separate in terms of saying, therefore we think these actions could be taken.

I don't think we have that much control, at some level, over how much concern there is going to be beyond saying, this is unlikely to affect more than one in every million children vaccinated. At least, that is my view.

I think that may not be the best way. That does make it look like we are being judgmental of possible responses, that if we find some connection and there is a group that gets hysterical about the connection, that we are saying that is inappropriate concern.

DR. STRATTON: I don't think that is what he meant.

DR. GOODMAN: If we use the language and they are using the language, we are going to hit head on.

DR. STRATTON: We can come up with better language.

DR. MC CORMICK: I think if we are going to get down to nuts and bolts, let's get down to nuts and bolts. Seriously, is it appropriate level of public health reaction?

DR. GATSONIS: I don't think they are asking here what is the public's impression of this and how concerned they are.

I think it is probably scientific and whatever else is the perspective of the committee. How important is this issue.

What concerns me is that, if I read this, then I read in the next page where it says the committee has not -- in capital letters -- been asked to make public health policy and blah, blah, blah.

Obviously there is a very fine line there, that this committee should say that autism and MMR is very important and the public policy implications are very --

DR. STOTO: How about public health impact?

DR. GOODMAN: That is what I said, impact. Then you can separate policy from what we have said. If we say likely impact, then it becomes clear that policy then becomes separable and we can draw the line just one hair short.

DR. GATSONIS: But there is a policy right now to vaccine people. If you say there is a major concern, then you are changing policy perhaps. In any case, I am just saying that it is a fine line.

DR. BERG: May I ask a question of Marie and Kathleen? It relates to my question earlier. The CDC has specified the questions. Have they specified the products?

DR. MC CORMICK: That is what we are discussing now.

DR. BERG: The question is, can we talk about whether we need three products or four products or five products, or are we talking about what do we call product two?

DR. MC CORMICK: Oh, yes. We are talking about, if this is what we are going to try to produce, is this a reasonable formulation. Do we need to reformulate it. We are talking now about reformulating just even the title of one of these.

I think this is a useful tee-off point, and if there is another product or, let's say, area that needs to be addressed in whatever communication we have, I think the word product is also kind of important.

These areas are not inconsistent with other areas that have been mentioned in other descriptions of the charge. At least we have to address these areas in any communication or conclusion.

DR. STOTO: Can I raise a different question about the second item there? I think that this is framed in terms of how big are the consequences of possible adverse effects.

I wonder if it also makes sense to think about the disease you are trying to prevent. I mean, is this a very big disease or is this like the varicella vaccine, where the vaccine really doesn't prevent that much morbidity.

DR. KABACK: This is where we say the number of

persons affected and the seriousness of the effect.

DR. MC CORMICK: Yes, but it is affected by what.

DR. STOTO: Is it the disease or the vaccine.

DR. KABACK: The adverse effects.

DR. MC CORMICK: I think the other trade off is the seriousness of the disease that is being prevented.

DR. GOODMAN: We can also define this.

DR. MC CORMICK: Correct.

DR. GOODMAN: We can put that there. We can say -- I think we have to have both sides of the equation. So, you have public health impact.

You could have public health impact of X percent reduction in vaccination.

DR. MEDOFF: Does everyone accept number one?

DR. MC CORMICK: No, we haven't done number one yet.

MS. HORAK: The statement of task seems to refer primarily to the urgency and the issues related to the adverse events, not to the disease.

DR. MC CORMICK: I don't think you can separate them.

DR. KABACK: Disease is the other side of the coin, the other side of the equation.

DR. STRATTON: Let me say something about statement of task. This is just a little bit of

bureaucratic arcania that most of you probably don't care about.

The statements of task is an NRC bureaucratic document that, in fact, gets written before the contract is even in place, based on our understanding of what the government wants.

It is fundamentally very similar to what I think they still want. There are some differences. We will now decide what it is that we think we are going to do and we will change that to be identical to our understanding.

The contract that we signed with the CDC is very similar to that, but there is always the leeway for committee discretion.

I tell you, when they first thought this through, their definition of what they are now calling significance assessments in this product two, their significance assessment at the time, in the contract that they wrong -- not me, but they wrote to me -- said, for example, you might consider seriousness of the adverse effect, number of people potentially affected, cost and feasibility of collecting more information -- meaning resolving the issue -- perceived urgency of the product.

They listed a lot of, for example, the committee might consider. Then they started getting nervous about those things.

Now they have limited it down to suggest that the committee only consider two things, the seriousness of the adverse event and the number of people.

It doesn't matter what they are now suggesting. I think they need our best judgement on what those factors are and we will define them, for example, the seriousness of the disease and however you think that is.

So, Abby is right to worry about that statement of task, mostly because we need to make sure, when we are done, that we know how to fix that to adequately represent what it is that we believe that we are doing, but it was a good point. It was a slightly discrepancy.

I think there are two things that we absolutely have to do and there is no doubt about it. We have to give them your best judgement of the causality assessment.

Exactly how you define that -- are you going to do vaccine safety standards, are you going to come up with your own, are you going to do preventive services standards, are you going to do agent orange standards, you can decide.

This committee has to make a causality assessment. That is clear, and they have to recommend action, inaction, you know, how much action in some sense.

How you get from one to the other is your judgement. They have made suggestions for the things that you might want to consider. But we must give them a

causality assessment.

DR. GOODMAN: Just to go back to the point that we are not being asked to make public health policy, when you say action, how are you defining action? How far down the line are you defining actions?

DR. MC CORMICK: Product three.

DR. STRATTON: We said this before you got here, and I think we said this yesterday. The point of no return, the line we will not cross in public policy is pull the vaccine, change the schedule.

We could say it is time to revisit this, but we would never recommend that level. Even recommending research is recommendations for policy.

We wouldn't say compensate, we wouldn't say pull the vaccine, we wouldn't say stop the program.

DR. MC CORMICK: The other example was the paper on exemptions, philosophical and religious exemptions. We wouldn't talk about the policy of exemptions, but we could certainly talk about the implications of not immunizing, for whatever reason.

DR. BERG: If I can comment on product one, I am comfortable with the overall approach here. It seems to me that with the first bullet our task, then, is to develop methods for what is adequate evidence, and it could be based on the previous vaccine safety panels or others, but there

is a method there.

I am not sure that I have seen methods for how we would evaluate biologic plausibility, what would our rules of evidence be, how would we code the strength of evidence for continuing causes.

It seems to me that methodologically there is more work to be done on, if the evidence is limited, than on the first part.

For each of those, I think that as long as we come up with a method and it is explicit and transparent and people understand it, then that is fine. I am sort of eager to get to work on what those numbers are going to look like, but the scope looks okay to me.

DR. MC CORMICK: Since we started on product or area two, I am going to push one nuts and bolts push. When we are talking about the seriousness of the problem, I know that the preventive services task force uses a burden of illness kind of methodology. Are people comfortable? Do you want to talk about other methods?

DR. BERG: I am not an expert at all. I could talk about how the process looks at burden of illness, how many people are there out there with the condition and how bad is the disease, and is there anything that anybody has proposed to be able to do about it.

So, there are like two or three criteria and I

presume we would want to come up with some like that.

DR. MC CORMICK: So, here would be seriousness and treatability? I mean, we have got number affected as a separate category.

DR. COHEN: Certainly also there is the issue of rating the seriousness of various conditions, is something that the medical decision sciences literature looks at all the time.

There is no real good way to do this because it inherently involves subjective judgements.

The advantage of the approaches that are used in the medical decision sciences literature, such as quality adjusted life years, is that, at least in theory, somebody can use that information to evaluate trade offs.

It is not a one to seven scale. You know, well, how do you rate a five versus a seven. I mean, there is some theoretical basis.

I don't know if we want to consider either recommending that the various health effects trade offs, side effects and the target disease be evaluated, in some cases, in a way that could be used in a decision analytic framework or not.

DR. GOODMAN: I actually think that is something that we would defer. I think the use of decision analysis, in and of itself, is very useful but is a sort of normative

tool.

To sort of add utilities up is very problematic. We saw it in some of the presentations yesterday, when you have a very, very powerful expression of the problem or sort of averaging over populations which is the sort of utilitarian calculus that decision analysis represents.

I think we have to be very, very careful. I think that decision analysis would be enormously useful even for many of the things that we might do.

For quantifying the impact of the side effects, I just think that we are going to have to be very careful. The very use of it will be seen by some -- partially legitimately and I think partially illegitimately -- as sort of an ideologic bias of the committee.

DR. MC CORMICK: I guess what I would try to think about is, I am not talking about using a decision analysis to make trade offs at this point.

If there are some standard descriptions of ranking conditions by severity, that that may help us not have to reinvent the wheel, and I am thinking something like DALYs which are sort of less ideologically driven, disability adjusted life years.

If that system includes some of these conditions where we could rank off some of this stuff, at least we can use that as an existing paradigm, rather than coming up with

our own ranking of severity.

DR. STOTO: DALYs, those are all loaded.

DR. MC CORMICK: I know they are all loaded.

DR. GOODMAN: It is really order of magnitude, I think. That I think we can do.

DR. MC CORMICK: The trade off of autism versus chicken pox, for example. Clearly, they are different orders of magnitude.

DR. MEDOFF: I just want to understand. The second part of it is to establish some causality or lack of causality or some unknown.

Then the next point is what you are saying with the categorization is that that is the one in a thousand or some estimate of the seriousness in terms of one in a thousand or one of a hundred thousand? Is that what you are talking about?

DR. MC CORMICK: No, it was simply trying to get at the definition, if we could avoid developing our own definition of seriousness of condition.

DR. SHAYWITZ: Do you think you have to develop a seriousness of condition? Each of the adverse effects that we are going to look at is essentially a condition.

DR. MC CORMICK: Right.

DR. SHAYWITZ: Why do we have to then say what the seriousness of that condition is. By definition, people

will have their own views of how serious autism is or how serious chicken pox is.

DR. MEDOFF: Also, seriousness could be something which is not a death but that occurs one in a hundred times. Is that more serious than death which occurs once in a million times? So, frequency, in some ways -- I mean, it is hard.

DR. MC CORMICK: We have got frequency built in. I believe this is a further debate. It is a question still to be resolved.

DR. KABACK: Don't you also, if you are going to balance the impact of adverse effect versus impact of disease, you have to then look at the frequency of variations of the disease.

So, you have to take nepotizing faciaitis(?) and take varicella pneumonia and its seriousness, not just chicken pox seriousness.

A number of those kids who get chicken pox who are unimmunized are going to get nepotizing faciaitis, or they are going to get varicella encephalitis or they are going to get varicella pneumonia and be very, very seriously ill.

So, that equation is not a simple one. It becomes more complex because you have to take in the variety of relatively rare, but we are talking about relatively rare against relatively rare.

Then you get back to Gerry's balancing of numbers issue, which gets complicated.

DR. STOTO: Kathleen doesn't like to think about this, but the IOM actually worked on a report where they tried to do some of this for vaccines. Maybe it would help to look at that.

DR. STRATTON: It is a dicey road to go down and I regret that I ever did it. I regret that I personally ever did it, not to mention the IOM.

DR. CASEY: What do you mean, Kathleen?

DR. STRATTON: Well, if you want to decide the health impact of a particular condition -- it was a project to help put some logic behind which vaccines should be developed in the future.

So, we calculated quality adjusted life years to be gained by a vaccine strategy and comparing, in the United States alone, how many million cases of rotavirus versus many fewer cases of insulin-dependent diabetes.

So, then you have to do what Mike was just talking about. You need to say, well, there is a health impact of just having the condition.

There is a health impact of blindness and how many people are going to go blind. There is a health impact of how many people are going to lose their kidneys. There is a health impact of how many people are going to have

neuropathy.

You try to figure it all out and then you use health utility indices to decide how people rate. Is it worse to be blind or is it worse to have to go to dialysis. Well, that sort of depends. It is a nightmare and I am not doing it.

DR. WILSON: In essence, it seems to me that the question is posed and the way that I would see addressing it is, they simply want us to tell them how often the adverse event occurs and the seriousness of the adverse events. That is pretty much what it reads like to me.

That doesn't require us to make a comparative assessment of the frequency of other or similar adverse events from the disease itself.

They know that information full well at the CDC. They know what the rates of varicella pneumonia are in primary varicella.

Unless we are going to weigh this value of discontinuing vaccination versus continuing vaccination, which is their decision to make, and I don't believe they have asked us to tell them that, then do we really need to make that comparison?

DR. KABACK: What about the consumer perception?

DR. WILSON: That is the question. What are we trying to do. Are we trying to put all the information out

there for the consumer to compare it for themselves or simply state what the risk of the event is.

DR. KABACK: What minimal information would you want the consumers to decide on, in varicella vaccination. To say the kid could get chicken pox versus what adverse events?

DR. WILSON: You are talking about in our lay --

DR. KABACK: That is what I meant by the consumer. There, I think it is important to be able to state that chicken pox is not always a mild self-limited condition but may have very serious complications which occur at certain frequencies.

Then you have to balance that against the adverse effect that you maybe identify.

DR. GATSONIS: For the consumer information, getting into QALYs, that is really off the scale.

DR. GOODMAN: All you have to do is list the frequency.

DR. STRATTON: We are not going to know the frequency, by the way. We are not going to know the frequency of the adverse event.

DR. MC CORMICK: I think what we are talking about here is the frequency of the complications of the disease that is being prevented.

DR. GATSONIS: This kind of discussion is generic,

in the sense that every time you want to move the synthetic results, like overall degree of something, you have to find some way of putting everything on a common basis. That is what QALYs does. That is what all the decision analysis type of methodologies do.

They give you a way of finding a relative scale to judge a whole bunch of things.

It is kind of ironic that, in a sense, we are saying, you know, all you guys and all the statisticians and everybody else are working to make this available to policy makers at the clinical or at the overall level, and here is a policy, something that could be impacting policy, and we are stepping back from it.

I think I agree, though, that we should step back from it in the sense that there is no well understood and sort of well appreciated set of utilities and evaluations that we could use to judge all of these things, as far as I can tell.

So, anything that you do, you are going to be attacked from a whole variety of different points of being ideological or what have you, in the sense of any kind of utilities to make these comparisons.

DR. SHAYWITZ: I wonder if we are just over-complicating the question that CDC is asking us. They really want to know -- it is a complicated enough question

for us scientifically.

They really want to know the causality of -- they want to know about adverse effects. Obviously, in this time, right at this time, the adverse effect they are most interested in is what the congressman talked about yesterday.

That, I assume, is what drove their interest, and next year it may be something else and we will be asked a different question.

I think we should just try to be as focused as possible, because it is a complicated enough thing.

I remember sitting there reading case reports from all sorts of things for this pertussis. We are going to have this same thing for MMR. It is very time consuming and complicated.

DR. MC CORMICK: I would like to propose the minimal stance that at least there be one description of what we know about the complications of live disease, to remind people and ourselves what those numbers are.

DR. KABACK: I had a structural thought as Ben was talking, and this may not be appropriate, but let me just throw it out so people think about it.

As a format, if we think about the real goal of this thing is to provide the public -- not the CDC and not the congress, but the public -- with a reasonable basis upon

which to make decisions about immunization.

If we think of that as the really ultimate goal of the product, of our work -- that is why that lay document, to me, is the most concerning, because it drives my thinking -- if we work from that back and say to ourselves, what information do we need to have, or to put on that piece of paper to give to the average consumer, that will drive what information we need to develop in the process of the committee about each of these adverse effects.

It seems to me, just staying with the one topic that we were just on, that we would need to not only say the risk of eschewal meningitis, but what that can mean in terms of some of the serious complications -- death, blindness, et cetera -- that can occur with some frequency, whether or not you want to include those or not, but you at least have to allude to that. The same is true with chicken pox or the same with whatever.

If you start with what information you need to provide to the consumer and then what information you need to have to put that information on the document, it seems to give you some structure as to how we have to get to where we need to get to.

So, we need to define the kinds of things they are after, but in a way, for the purpose ultimately of providing the consumer with that information.

Yes, by the way, we are going to provide CDC and the Congress with that information, but the ultimate goal is the consumer. That is just a thought.

It does change the way you think about how you develop -- what information you want to develop and how you want to get there, and what you want to include and not include.

DR. MEDOFF: As I read this for product two, they say the plausibility assessment. So, we probably would have dealt with that in number one.

DR. MC CORMICK: That is number one, right.

DR. MEDOFF: Then the significance assessment, which would include whether, based on that, there is a high, intermediate or low necessary concern.

That concern would be based on the safety factors for the vaccine, the number of complications that result from the vaccine, versus the importance of the vaccine in terms of preventing disease.

That is the balance in terms of the description of what would happen if you eliminated MMR.

I am just going through this, just to make sure it makes any sense. That is the number of persons eventually affected.

The seriousness of the health concern would be the safety plus the effectiveness of the vaccine.

DR. MC CORMICK: I think the number of persons affected is two-fold. There is both the wild disease and the adverse event.

DR. CASEY: Basically the significance assessment is two-fold. It is going to be disease and vaccine effects.

DR. MC CORMICK: I would see the effects of the wild disease as pretty stereotypic from whatever the literature is. We are not going to have to decide that. That is just to remind everybody that this is a bad problem.

DR. CASEY: The last one, the categorization, that is where we will need some consensus, to look at both prongs of that, and try to --

DR. MEDOFF: We can say that this is really a very important health problem but not enough is known about it and that it requires more study. Again, that is sort of the paradigm, or their process of dealing with this is faulty or not faulty.

DR. GOODMAN: Again, I don't think we should use the words appropriate or concern. I think we should try to stay away from that language.

Almost everything you said was loaded, only because you used those words. I think if we talk about public health impact public health consequences, we will be on completely safe grounds.

DR. KABACK: Again, I am thinking about that lay

document. When you come in with your three month old, you are not concerned about so much the public health concern, but about your three month old. That document has got to communicate.

DR. GOODMAN: We do have the seriousness of the health concern information.

DR. MC CORMICK: Part of this was a discussion earlier this morning. One of the messages I took home from both the parent representatives and Amy Fine is that we are talking about two levels of safety.

One is, is it safe to throw out in the community, at some level of training, and as the parent coming in, is it safe for my child. So, I think we need to keep that dual thinking in our head.

DR. GOODMAN: That is why, again, the word concern is so difficult.

DR. GATSONIS: Putting the word impact is important, I think, in framing the question. By the time you have to quantify whether it is high impact or low impact, this becomes immediately a matter of concern. So, you can't get away from that really.

DR. GOODMAN: There is going to be concern in reaction to whatever we say.

DR. GATSONIS: The impact, we would say, this is going to have high impact, aka, this is a matter of high

concern. They are not the same.

DR. MC CORMICK: I actually think there is a step before that. What is the mechanism by which we -- are we going to try to develop an approach, and a transparent approach or explicit approach to this categorization.

DR. GATSONIS: That was the discussion before. To be explicit, you have to go through a structured methodology. To go implicit, you would be attacked. I mean, you will be attacked each way.

I don't know that there is time and energy enough and even, you know, knowledge enough to go explicit.

DR. KABACK: Walter suggested this opinion scale, a one to six rating, in his talk, an opinion scale one to six, and the example he gave was thimerosal.

DR. STRATTON: That is the document I passed out at the break. You just got it.

DR. KABACK: So, there would be some consensus, numerical value, given to the level of concern.

DR. GOODMAN: Is that in the plausibility assessment?

DR. KABACK: It was in the likelihood rating of giving a probability judgement.

DR. GOODMAN: Right, but that was in the plausibility assessment. It was not the bottom line categorization of global --

DR. KABACK: Right, it was in the plausibility assessment.

DR. JOHNSTON: If the evidence was limited.

DR. KABACK: Yes, if there was limited evidence.

DR. JOHNSTON: That is when you go to that.

DR. KABACK: That is correct.

DR. MC CORMICK: I will throw out some things we may want to think about. I am trying to think of whether we can break down this level of public health impact into some smaller subscales that we may be able to rate.

One might be level of congressional pressure. We may not want to consider it. We may.

Those are some of these other thoughts about where this fits that might break out our decisions and our thinking about this into finer detail, that would give us more confidence that the overall assessment of public health impact is a reasonable one.

DR. BERG: One of the terms that Amy used yesterday that I thought was helpful is not so much the issue of appropriateness, but sort of the alignment between public health concerns and the evidence base.

I thought that the vocabulary she used was a little bit less value laden.

In coming up with our final categorization of this, I thought some of the things she suggested were

provocative.

We don't have time to work through them all here, but I thought she was had some valid points.

DR. GATSONIS: Frankly, I think if you talk about impact, you can stay away from this very low, high low, whatever if you put out on the table this is what you may expect to happen if you go in a particular direction.

Then this committee will have done that part of its work on whether this is a matter of high concern or low concern.

DR. BERG: That actually gets to the bulk of your comments, the level of major public concerns that include professional concerns or other things, risks and benefits for the individual vaccinee is exactly what you are suggesting, and risk benefits to the population as a whole, and then you sort of look at the alignment of those three things.

This is page 15 of the handout that Kathleen just handed out at the break. I was just paging through. I remember being struck at the time --

DR. MC CORMICK: May we will try to lay out some of these dimensions and see.

DR. GOODMAN: I think what this says also is that some of our assessments of the concern issue are going to be implicit in what we say in terms of our recommendations.

If we say, as a result of product two, step two, that this is the public health impact, however our sense is that, say, theoretically, that we sense either formally or informally, that the level of concern is way out of proportion to what we think is the actual danger, we don't have to say that explicitly, but that can be addressed in what we choose to do.

DR. MC CORMICK: What I am trying to push you is to say exactly that. What would be the dimensions upon which you might identify public health impact, not just your sort of gut, but it is a fairly frequent problem, or boy, it really is resonating out there in all sorts of groups. Concern is out there, even if the level of evidence is small.

I jokingly said congressional pressure, but that might be one. Pending legislation or something, that is what I am pushing on. Can we break out level of public health impact to some more dimensions in which we can say, this is how we thought about it.

MS. HORAK: When you first said congressional interest I winced, thinking we shouldn't respond to what bee they get in their bonnet. There is a larger issue here.

Yet, to think explicitly about that will help to sort out what drives the public concern. I think that it would be wise to respond to what evidence is being produced,

that there might be an association between a health problem and a vaccine, but to also fully recognize that we work in a political system and that our recommendations have to reflect or at least be cognizant of the kind of pressures that might come from another direction.

DR. STOTO: The level of concern by congress and the public is important, because that drives whether people get the vaccines or not.

DR. MC CORMICK: Yes, it is all part of a political process.

DR. MEDOFF: One possibility might be to say, what do we know about the frequency and severity of the adverse event and what do we know about the frequency and severity of the natural disease.

How does this align, to use Amy's word, with the discussion.

DR. WILSON: Not to try to put it into a category, but just to lay it all out.

DR. MC CORMICK: Maybe we ought to break out, not categorization of public health impact, but then say, other factors driving public health impact.

DR. KABACK: I think the level of concern drives the question that we are dealing with. We are dealing with questions that congress is pushing, that the CDC is getting.

DR. GOODMAN: I think there is some value in

separating out the factual material.

DR. WILSON: There is concern and there is actual severity of outcome. Those are not the same.

DR. KABACK: That is one that you suggested for each one. It would be an interesting one, the severity and the frequency and the level of concern for each one of them, and they may not be in concert. They may not be aligned.

DR. MC CORMICK: I am trying to break this out more explicitly. One factor that might be driving the public health impact is the availability of a new vaccine or a new formulation of a vaccine that would reduce some of the side effects.

I don't know. What I am trying to get at is -- let me back up and say my experience on this, which I am pushing on -- is that we were required, as part of our evaluation of the national Healthy Start program, to rank the adequacy of implementation of the program in each site, and these were 15 sites.

They all had about 10 different things that they were implementing, 10 to 15. It was very helpful for the site visitors to go through and explicitly break out, for each of these, the actual number of patients seen, actual services delivered, these dimensions that you then could rank back up and say, this has a high public impact or not.

At least you knew on what dimensions you were

making those decisions. That is why I am trying to push you to say, rather than this just gut high low, are there more explicit things that we can pull out, ala Al's comments, that this should be as transparent as possible, about what we are considering.

DR. MEDOFF: If we start at the beginning and say, we are dealing with this question because there is a high level of concern, a high level of congressional pressure, or a new vaccine is being developed.

So, whatever the issue is, the justification for dealing with that question, is stated up front.

DR. MC CORMICK: I think the issue is that we are going to be told by CDC which issues they want us to address. We may have to sort out.

DR. KABACK: On this graph, the number of new challenges against the years 1997, 1998, 1999, I had this thought that it is actually a reflection of public concern, in a sense, responses to what, CDC calls, challenges? I was not quite sure what that meant.

He has mercury and vaccines, autism and so forth, up at the high end of the scale in the year 2000. Is that an accurate reflection?

DR. GOODMAN: I think it is cumulative over time.

DR. KABACK: Each is one.

DR. GOODMAN: It is not saying that is the

highest. He is just saying it is the latest.

DR. KABACK: He is just indicating that there is an ever-increasing number of challenges to vaccine related injury.

DR. GOODMAN: Just cumulatively over time it is going up.

DR. KABACK: Over two years' time it has gone from zero to 24?

DR. GOODMAN: He is just saying that -- it is cumulative.

DR. STOTO: Some of these challenges have gone away.

DR. KABACK: I understand and I looked at them all. It was a reflection of the issue of challenges, public challenges to vaccine related concerns, the reasons for dealing with these issues, whatever those reasons are.

The main thing is to have a justification for doing autism and MMR first. So, whatever that is, public opinion, congressional pressure or --

DR. WILSON: Well, short of death, autism could certainly fall into most people's severe and untoward outcome category.

Asthma, obviously, is going to vary. Occasionally it is fatal, but oftentimes it is more of a modest disability for which other therapies exist.

Since no truly effective therapy for autism exists -- that is, one can make the individuals functional -- they remain disabled and often they are unable to function adequately in terms of self sufficiency as adults.

It doesn't take me very long to figure out that autism is a severe outcome. So, I am not going to spend more than a nanosecond thinking about whether to call this a severe outcome.

DR. MC CORMICK: I am not disagreeing with that, believe me. What I am trying to get at is, do we want to simply, on our gut, say looking at the significance of the wild disease that you are protecting, and the seriousness and potential association with the vaccine -- because we are not ever going to come down that it is a true side effect -- is that going to be sufficient for you to judge public health impact?

DR. WILSON: Okay, natural disease has rare severe outcomes, and we can rank -- encephalitis with long-term disability would rank up there with autism, and the frequency of that.

Then there are outcomes such as pneumonia, which has a certain mortality, and that could be figured out. Then there is illness which keeps you out of school and so on and so forth, mild outcome.

You can rank those. You can figure out the

frequency of those if you wish.

Then you can take autism. When it occurs in your child, you have got a devastating outcome and then you can rank that. That, to me, is pretty straightforward.

DR. MC CORMICK: The margin on autism is, is the marginal increase in autism due to the vaccine.

DR. WILSON: That is causation. That we will have determined under product one.

DR. MC CORMICK: But on product two we are trying to say --

DR. WILSON: Tell me where I am wrong here.

DR. STRATTON: If the committee determined that the evidence supports a causal -- that doesn't mean, of course, that all autism is caused by vaccines.

DR. WILSON: No, of course not.

DR. STRATTON: I don't know that we would ever get to that sort of attributable kind of interpretation.

DR. WILSON: I think product one is, you tell me the likelihood that this vaccine causes autism.

DR. GOODMAN: In anybody.

DR. WILSON: Yes, just given. Product two doesn't ask that question in my mind. It simply says, okay -- well, there are two ways it asks.

Is autism severe? The answer is yes. What is the total public health impact of attributable autism. Well, we

may not figure that out for most of these things. That would be where that would come in.

We all know that all these things are going to be gray. The only thing we can do is, if autism were caused by this vaccine, the outcome is in the severe category.

What is the frequency of autism and what are the boundaries on the estimate, if any, of what fraction of autism might be related to this disease. That will give you sense of that.

Without any conclusion on one, there is nothing to say about two. Assuming we make some finding on one -- that is, in one of the categories -- it almost certainly will not be hard core proof because we all know that we don't have that right now.

DR. STOTO: I think that the difficult in my mind with number two is the suggestion that you can put things into categories. I am not sure that is necessary.

I think that if you just said, what do we know about the likelihood of the incidence, and the severity of both AE and the disease and sort of describe that, I mean, I think that would be useful, both for parents making decisions about immunizing their kids and for the public.

DR. GOODMAN: I think Amy's language is really perfect, assessment the alignment between concerns and the evidence base.

So, we can put out the evidence which is sort of the impact. We can talk about the concerns as we understand them.

DR. MC CORMICK: What is the metric by which you talk about concerns?

DR. GOODMAN: As we understand them.

DR. WILSON: It is not one dimensional.

DR. MC CORMICK: No, I understand that.

DR. GOODMAN: I guess this would be something that, in prose, we would discuss what our understanding is of the concern and what our sources of evidence are for that concern and then explain.

I mean, everything here would be transparent. So, if somebody challenged it, they could say, well, we disagree with this point.

I do agree that every time we compress some of these very complicated things into a number without the expression of the richness of both the judgements and the source of information, we invite trouble.

So, this is exactly where we can say why we think it goes here or it doesn't go here.

By not putting a number, it is also -- we don't have a number that is challenged. We have an argument that is challenged, and they can debate premises of the argument, which is fine.

I mean, the debate doesn't have to end here. We just have to show why a group of people came up with this sense.

DR. GATSONIS: Where is there that you show the data base for the concerns of what you hear in the hearings?

In other words, nobody has done a survey of the public to see if they are even concerned about this. What is the data base for that?

DR. GOODMAN: Maybe other people can address it better. There are certainly some things that we know about ourselves and we have heard.

First of all, we know the potential impact on immunization rates in Ireland and the United Kingdom of simply dissemination of this information in particular forms.

There is the potential, you know, impact of heightened concern that we know, at least in those countries, that can have an effect.

I am pretty sure there is evidence in this country of lowered immunization rates in certain areas or whatever as a result of publicity about things. So, those would go into it.

DR. BERG: Amy suggested, on page 14 -- again, not to propose her particular approach -- but she actually gave us a methodology for assessing public concern.

She said, you ought to look at VAERS, you ought to look at web sites, look at media. I guess media would pick up congressional testimony. Do some focus groups. Work with those most vocally concerned.

I don't want to get into the merits of that methodology, but it gets to your point. I think if we are going to say something about public concern, we can't do it quantitatively, but we can at least say these are the four or five sources of information that we looked at.

DR. GATSONIS: See, what I was thinking, trying to understand how this alignment between concerns and evidence base would work would be, concern number one, this vaccine concerns such and such a bad effect in a lot of people, or this concern, here is the evidence base for that, concern number two, concern number three and so on.

That is why I want to find out sort of how prevalent -- what is the list of these concerns out there.

If we start looking at the web bases, you are going to find everything from the most extreme to the most extreme.

So, we need to have some kind of listing of what are the prevalent concerns.

DR. STOTO: That is what CDC is going to do. They are going to say what the topic is.

DR. MC CORMICK: I think in judging her content

between alignment, and I think autism is one of these -- there is going to be very slim, if any, association but people panic about the disease.

DR. SHAYWITZ: It seems to me that you should assume that Congress represents the American people. That is the presumption and if this congressman didn't have a grandson who had the problem and we didn't know anything about that, we would still respond to several congressmen who were concerned, because we presume that they are reflecting public concern. That seems to be a reasonable assumption.

DR. MC CORMICK: Let's not prolong this discussion because this is my hobby horse. Let me see if I can use some of this stuff that Amy has done and some of these other concerns and say, if we are going to talk about level of concern, what are some of the things we might consider in this text paragraph so that at least we have a checklist of things we might have gone down.

DR. GOODMAN: I just want to say one other thing. We don't necessarily have to deal with -- I mean, clearly we are all sitting around this room and that represents social expression of concern, and it has come from many sources.

We influence the concern as well prospectively. So, we don't have to deal just with the forces that brought

us here and say, well, were they appropriate.

What we choose to say and the potential impact, the potential concern, is also of relevance. That is why I was talking about some of the evidence about the impact of publicity.

So, we can also have an eye toward what we would hope the impact of our statements would be.

DR. MC CORMICK: I think this may actually differ because if something became hot next year and CDC said, look at this, that would be the public health impact of why it is popular and none of these other things might pertain.

You know, it may be different at different times. Let me try and see if I can list out some stuff we might consider, using some of Amy's stuff. Do we want to start on product one? We have been dodging it for about an hour and a half.

DR. GATSONIS: I have a suggestion that will take us all off the hook. Do we have a biologist, a basic scientist, on this committee, in addition to the MD virologist, or do we need to have one if we don't have one?

I couldn't see from the list of people who are on the committee whether that branch of basic science is represented. Do we need to have that?

DR. KABACK: Which branch of basic science?

DR. GATSONIS: Biology at the level, and virology,

from the PhD point of view?

DR. SHAYWITZ: Are you talking about to evaluate the biologic plausibility?

DR. GATSONIS: Yes. In other words, I can just see getting into some of these discussions about this particular assay and that particular assay and so on and so forth.

I mean, there may be people around the table who know all this, in which case my suggestion is off base, but it could be that we could be informed more by some of the people who are bench scientists day in and day out.

DR. WILSON: That is what I do day in and day out.

DR. GATSONIS: A bench scientist.

DR. WILSON: Although I am an MD, my time is spent entirely in this area, minus about two weeks out of the year when I do clinical rotation. So, I work on viral host community and I work on development of immune response.

DR. MC CORMICK: I think the other approach to this is that the biologic plausibility arguments are going to differ from condition to condition, and that we are going to need to identify that expertise for each condition for the presentations.

I think that is what we would be working with for that biologic plausibility.

DR. JOHNSTON: Constantine, I also have a

background similar to Chris' but biologic plausibility will depend on our getting data in some cases, just as we will need to do for a lot of the questions that are raised.

Interpreting those data, I think, can be accomplished by this group very easily.

DR. MC CORMICK: I guess the first decision to be made, in terms of the evidence of causality, are people comfortable with the previous IOM vaccine committee's approaches to that?

Dick, would you recommend vax AE-2?

DR. JOHNSON: Vaccine 2?

DR. WILSON: You have some modifications of that.

DR. JOHNSTON: We have had questions recently from Jeff Evans from the American Academy of Pediatrics that deal with the vagueness that so many of the vaccine adverse events relationships fall into and the need, on the part of the masters who determine the compensation or not, is one place that it is coming from.

The CDC is asking us to do the same kind of thing. I think we are going to have to have -- I think we will fall away -- my guess is that we would start with some structure that we agree upon, and then we would fall away by looking specifically at biologic plausibility and the other hypotheses and those kinds of things, and then maybe come up with some kind of scale or weighing.

When we took what we did with vaccine 2, which I think I felt was an improvement over what we had with vaccine 1, and it was based on feedback that gee, this is great language but we don't understand it, then we took it and we looked at another kind of background disease, and that was asthma and all the constituents that might be included.

We used the word there, association. Well, it is a different use from that in agent orange. They defined it in a certain way and we defined it in a different way in the asthma study.

Now, in thinking about, as I have been over the last couple of months, about coming back to vaccines, it seems to me that what we were doing with some of the language in the vaccine studies, and vaccine 2, we were not as specific about what we thought the relationship was as we might have been.

Partly what we were doing, we were dealing with an association now, in the epidemiologic sense, that there is a more precise way of defining a relationship than just that the evidence is sufficient or insufficient or the evidence suggests.

In other words, it described a relationship and whether or not it was sufficient for causality.

Let me take a step back and say, too, my own

personal view is, causality should be the focus of what we are thinking about, what we are trying to do, which would be the word up there that we are thinking about.

Sometimes you fall short of being able to really say this is causal or this is not causal.

DR. KABACK: Can I interrupt. Are you making a distinction between causal and associated with?

DR. JOHNSTON: Yes.

DR. KABACK: That is a very important distinction to make.

DR. JOHNSTON: I am trying to say, Mike, that we know this. You can have an association but you cannot be comfortable with causality.

There is a common one that is going on now in public health, and that is elevated homocysteine, there is absolutely no question it is associated with cardiovascular disease and stroke.

I mean, there are suggestive evidence that it is associated with dementia, Alzheimer's, colon cancer, cervical cancer.

The associations with cardiovascular disease are unquestionable. The American Heart Association won't do anything. They won't say take folic acid.

All you have to do is lower homocysteine is take a simple multivitamin containing the recommended daily intake

of 400 micrograms and it just plummets right down, right down into normal.

Fortification is lowering homocysteine. Fortification of grain products is lowering homocysteine.

The American Heart Association will not make that pronouncement until there is a randomized controlled trial.

That is now what we expect. Now, on causality, I think, no longer we will make pronouncements, because we have been wrong.

For example, the American Heart Association recommended focusing on cholesterol without there being any interventional data showing that if you lower cholesterol, you reduce cardiovascular disease.

Long before that, when the statins came along and you could lower cholesterol, we got those kind of data. Prior to that time, it was made on the basis of an association.

The association had to be rigorously defined by standard epidemiologic approaches. So, there is that level.

Now, when you have a firm association, as you do with homocysteine and cardiovascular disease, it points toward -- it raises the possibility that there is causality.

It is in a category that is higher. It is lower than causality but it is higher than having data that are on one side or the other or you really can't rule out bias,

confounding error, and that is a sort of suggestive category that corresponds to one of those that we had in the vaccine -- it actually splits out.

Defining that there is an association that you believe has been demonstrated separates out that category, that level, and defines it from something that is less well defined, which is another category which is, evidence suggests an association.

DR. GOODMAN: I would like to argue against that. I think it is a very important point.

DR. JOHNSTON: Let me say, Steve, I don't have anything invested in this. I am not an expert. I have come around to thinking about this, but please, my expectation was that this would be a starting point.

DR. GOODMAN: I think it is an extremely important discussion and if we don't have it now, we will have it 10 times in different guises.

I understand -- and I am looking at the categorization where you have, after vax 2, establishes an association and favors a causal relationship. So, you are making a distinction between association and a causal relationship.

DR. JOHNSTON: I am sorry, this is?

DR. STOTO: In the short version of your handout, it is on the top of page three.

DR. GOODMAN: Which is what you are sort of arguing about now, making a distinction between things for which there is shown to be strong association and yet the causal -- I will say a few things.

First, I think the only metric of relevance that this committee has to decide on is the causal relationship issue.

In a sense, you know, there may be these other ways that we think about how we conceptualize how we approach causality.

In the end, the bottom line is, the only verdict that is of importance is whether we say a causal relationship is likely, suggested, unlikely, inadequate. That is the only metric.

As soon as we start introducing other words that do not represent that sort of side step to causality that we say represents intermediate levels of causality, but we are not going to say causality, I think we introduce confusion.

The second thing is, I would submit, that this thing that you are calling an association but are unwilling to call causal is exactly that category of limited suggestive, or suggestive evidence for a causal relationship.

What you are saying is -- you said you can rule out bias. It is above the level where you can't rule out

bias.

That is exactly what the randomized controlled trial does, that you are not confident is done in the observational studies.

What you are trying to do here is make a very, very fine distinction in associations from observational studies that seem, in a sense, more highly likely to be causal, but not quite establish it, versus lower likely to be causal.

It is still a judgement about, on the basis of observational evidence, how likely it is to be causal.

We can decide to subdivide the suggestive category into high suggestive and low suggestive -- I don't think we should -- but I don't think we should start using words like association which, first of all, in the way you are using it, is a highly technical term, guaranteed to be misunderstood, if you are using it as a non-technical term for non-causality.

It actually hides the fact that we are making a judgement that it is not causal.

So, if we are making a judgement that it is not causal or that there is insufficient evidence for causality, then we need to say that directly and have a category -- I do think the agent orange categories work well, and we can decide how we work them.

Have a category that simply says causality is suggested but it is not sufficient.

Now, that said, that intermediate category is a very uncomfortable category and everybody here knows that. It is a very uncomfortable category. Some people will only want to use it if it is 50.01 and other people will be operating at the 94.99, whatever informal thresholds, and we can parse it any way we want.

I don't think we should subdivide it any more than having one category. I don't think we should put an association category and then a suggestive category. You know, you have suggests an association and establishes an association and favors a causal relationship.

That is really a subdivision of the suggestive causality category.

DR. JOHNSTON: Yes, it is.

DR. GOODMAN: If we want to subdivide it, then we should decide on that. I think we have to use causal association in every category.

I think we have to use that language and not use words like association. In the text we can say all the things you said, there seems to be a strong association which we can't explain, we don't have any other explanation for it, however we don't want to make a causal claim because we know in many observational studies, blah, blah, blah,

blah, blah, and explain why we are not going to put it in the sufficient category, in spite of all the observational evidence.

There is observational evidence like tobacco and lung cancer that we do, over time, actually accept as sufficient for establishing a causal relationship, combined with the biology.

It isn't true that we always don't accept observational evidence. There are clearly some class of observational evidence that we do.

DR. JOHNSTON: In the past, we commonly accepted observational evidence, very commonly. The public health standard now is higher.

DR. GOODMAN: Well, we can decide on whatever standard we are going to use. I will throw it out for discussion. I think we should use causal relationships.

DR. JOHNSTON: Let me respond by saying that I like the idea of not moving from the words that involve causality. I agree with that. I really like that idea.

There is a need to break down that data are insufficient to say whether or not there is a causal relationships.

That category needs to be broken down. The CDC is asking us to do that. The compensation program is asking us to do that.

DR. GOODMAN: Insufficient is different than limited suggestive. I wasn't saying that everything below sufficient is in its own category.

The agent orange standards were insufficient evidence -- that is, inadequate to make a claim either way -- limited/suggestive evidence; that is the sort of 50.001 whatever to the higher standard, and then the highest.

What I see this doing is trying to split the suggestive evidence into high suggestive and low suggestive.

I am not suggesting that we don't have an insufficient. I agree that there is a distinction between insufficient to make any conclusion and suggestive.

I think that I would submit that we should discuss -- although other people may not -- is whether within the suggestive category it is of value to distinguish between those we think fall between 75 and 95 and those that fall between 50 and 75, or however we want to do it.

DR. MC CORMICK: I would like to just react into this conversation a bit because I think when I am looking at these various descriptors I hear types of evidence versus causality arguments.

I would like to sort of split out types of evidence and then how we may integrate that into arguments of causality.

I don't like the statistical association but one

can talk about human epidemiologic studies, one can talk about animal studies, one can talk about biological mechanisms.

Although those are three different types of evidence that would come into this assessment of causality, I would like to break those out a little bit, because I think that might be important.

DR. WILSON: We need first to decide on the descriptors we are going to put into the categories, don't we?

DR. GOODMAN: Yes, I mean, in the end, no matter what evidence we use, we have to put it into some sort of --

DR. MC CORMICK: I agree with you, but for purposes of my argument, I would like to separate them a little because they are sort of getting contaminated.

DR. STOTO: In the agent orange, the word association really means weak evidence of causality.

DR. WILSON: Why not just say that.

DR. STOTO: Because of the congressional mandate and so on.

DR. MC CORMICK: For them, but for us we could say it.

DR. WILSON: I agree. I think we should just say it, and use the word causality. In many lay people's minds association means causation.

DR. MC CORMICK: That is why I want to separate out evidence and talk about different types of studies, not use the word association, and then saying, integrating this evidence, the arguments of causality.

DR. WILSON: In terms of the terms, let's just settle on what we are going to call it first and then we are going to talk about how we are going to put it in those categories.

DR. MC CORMICK: That is fine, but I don't want the word association.

DR. STOTO: I think the second-from-the-top category from the vaccine studies is, if you use the same words, the thresholds are different for the agent orange.

The things that have weak evidence sort of made it into the second category in agent orange that would not have made it into the second category in the vaccine studies.

I think what Dick's proposal does is to say, you know, really take the top category from vaccines, the second category from agent orange and then in between is the top from agent orange and the second from vaccines.

DR. KABACK: Could somebody write this down?

DR. MC CORMICK: I wanted to push this about the evidence. For example, we are not going to have human randomized trials.

If you had, let's say, a strong quasi-experimental

design study, plus a strong biologic model, and maybe some suggestive evidence, it might move it far up the chain of causality.

DR. BERG: I agree with you and I think I disagree with you, Chris. What Maria is suggesting is really sort of taking Bradford Hill's criteria and adding or subtracting or whatever, but coming up with what, for us, is evidence.

I think, depending on how that comes out, we might come up with different definitions of causality in our final three or four or five categories.

If what we mean by causality is that we have to have a dose response relationship, we might end up with a different four or five categories of causality than if we had all of these criteria plus a few others. I think I agree that her question is priority.

DR. WILSON: I think if that is the issue, then you are going to find that you will have to change that equation with each of the questions we address.

Some of the adverse events we are looking at are going to be a direct cause and effect. Mercury can cause brain injury.

Others are going to be predicated on a genetic predisposition in the individual. For example, if autism were actually due to an immune response, meaning an injury, that is going to only occur in a subset of individuals that

have the peculiarity that allows their immune response to make that difference.

In that case, the infections or vaccination will be a contributing factor, only evident in certain populations.

The kinds of evidence you are going to have that would allow you to make those conclusions are going to be different, because you may not find that in animal models because traditionally those are going to use inbred animals that have a very limited heterogeneity in terms of their adaptor immune system, their MHC antigens, for example.

The kind of evidence that you will be able to accumulate to provide that is going to differ, depending on the pathogenesis of the adverse event.

Another thing that we haven't even talked about, I assume, by causation, someone means it is a contributing factor for sure, even if it is not the only necessary factor, which is semantically a difference.

I think the public might see it differently. For example, if you get measles, you will almost certainly become ill with a disease that we could call measles, that we would all agree is measles, or chicken pox, the same thing.

Conversely, if someone gets immunized with this and it is only manifest in individuals who have an unusual

HLA type, the probability that that disease will occur is going to differ.

Furthermore, there are another six chains that modify the phenotype of that adverse effect, even if you have a susceptible HLA allele.

The nature of the disease actually may look quite different. In fact, we even know of single gene defects that produce quite a range of phenotypes that depend on the background genetic status of the individual and, even in completely genetically identical individuals, are not always identical in their phenotypic manifestations.

I think if we are going to insist on that, we are going to have to -- we will have to redefine it for each of the plausible mechanisms of disease that we think may occur.

I don't think they are homogeneous for the things on the list that I see.

DR. JOHNSTON: The same thing is true of measles, of course, as an adverse event from the measles vaccine is concerned, the variety and the spectrum. It has got to be simplified.

The Bradford Hill -- I mean, one approach is to take the Bradford Hill criteria, which is the way we have done it.

Whenever you are dealing with a relationship, you look down the Bradford Hill criteria and you weigh those

different components.

Lots of times the dose response is pretty hard to come up with examples where that is helpful, but sometimes you can. You look for it and biologic plausibility always, and so forth. So, use the Bradford Hill as a mechanism.

What you were trying to say is it has got to be simplified, I think, and I agree with that.

DR. WILSON: I think otherwise -- I mean, I think I know what Al is saying. The problem is what we say establishes the causal relationship, in fact, is rarely going to be -- it is probably not 100 percent. We may cut it at 99 or 98, the probability more likely --

DR. GOODMAN: Actually, I don't think we should use the word establishes either. I think it is too --

DR. WILSON: We need a strong category. You know, if certainty was there, we wouldn't exist. This panel would not be convened.

DR. SHAYWITZ: You are going to split hairs if you don't use a strong term. Make it a very high bar. You give DT and somebody gets anaphylaxis within minutes, you know.

DR. GOODMAN: Say sufficient. Establishes that this is -- that raises the bar very, very high.

DR. WILSON: I actually agree with that. That should be a high bar.

DR. GOODMAN: I think the tricky part is at this

end of the scale rather than at that end of the scale.

DR. MC CORMICK: I agree with you there.

DR. STOTO: What I have tried to do here is lay out the categories used in agent orange and the vaccine safety studies and the key words, establishes and favors causality.

I think that sufficient in the agent orange study was more parallel to the favors, maybe including that, but limited suggestive had kind of a lower threshold than favors.

DR. GOODMAN: It included it. It sort of went from 50.01 to just below what we were going to call a relation. So, it sort of included the favors, but it was also in the range that some people might call inadequate or insufficient. It covers a broad range.

DR. STOTO: I think Dick's proposal essentially was to add a new category in between this and that in the vaccine safety studies.

My question is, if we had a new category, would it draw primarily from this one, the things that would have been insufficient, inadequate, go into it, or would it include things that might have been here, if we had it, or both.

DR. GOODMAN: I think we should expand insufficient. I think it is very uncomfortable, the things

that are 55 percent certain and put it in any sort of suggestive category.

I think that is a category where people are very happy saying things are insufficient. I think there should only be three.

DR. STRATTON: What Walt said to us, and I know they are worried about, I mean, he said to us, saying something is category two, which means what Mike is calling category four, vaccine safety called category two inadequate to accept or reject a causal relation.

What he said is, telling me that it is still a category two isn't enough to tell me what to do. I want you to give me some indication somehow, within category two -- I am sorry, category four, insufficient -- within this category, what Walt -- currently, every one of these hypotheses in CDC's mind is in here.

They want us to do this assessment. Maybe you could always be -- we were surprised a few times. It may actually move up.

Chances are, when all is said and done, we are still going to be in this category. It is just a general feeling that we probably still are not going to be able to make a statement.

What Walt has said is, just telling me it is here isn't enough. That is where he started to call what he

wants, what everybody wants in the vaccine safety field is, break this one out for me. I am just telling you that is what they say.

DR. GOODMAN: I disagree with your take on what he was saying. I think he was distinguishing between calling everything short of a causal claim -- that is, the highest category -- inadequate to make a claim. I think he was saying that is not useful.

DR. STRATTON: That is not what he meant.

DR. STOTO: They have been at this for a year or two, trying to get more out of this category.

Also, the conversation that Dick and Kathleen and I have had with Jeff Evans and the guys who run the compensation program, they are clearly trying to break out that bottom category.

DR. BERG: Could I comment on this? I think this is absolutely the critical question. This panel needs to decide whether it is an honorable conclusion to end there, or whether we need to say more.

I will say that the CDC in general always wants to say more, and I will give you an anecdote.

I was at a meeting in San Diego about a month ago about prostate cancer. The conclusion of the scientists is, we don't know what causes it, we don't know how to prevent it, we don't know whether screening works, we don't know if

treatment works.

The CDC says, yes, but that is not helpful. What should we actually tell people to do. The scientists say, the answer is we don't know. The CDC says, yes, I know, but now what do you really think.

I think it is a tension and I would like to get a sense of the panel of where we are on that. I personally end up feeling like it is okay to conclude that we don't know and end there.

I would sort of like to get a sense. I will go with the group but I think it is an absolutely critical issue, and CDC is, in my view, one of the malefactors on this issue, because they are always pushing to go beyond the data and say yes, but.

DR. GATSONIS: In order to go the next step, you still need to give your sort of conceptual clarity and keeping the focus on what causality is important without mixing it up with other things.

If you have to explain -- if you have to differentiate within causality categories, you may do so, but still, you need to keep the intellectual focus, the clarity of what is causal or not or what could be. These are the three categories, basically, that are here.

It is more like a table. On one side is causality and you want to know where you are on that category or the

other.

There are various other descriptors that could be used to sort of further differentiate some levels of causality, some level of where this thing stands on causal link.

The CDC may use some of those, but I don't think -- whether the scientific process will be kept intact and we don't misinform people is if those things do not get used to sort of blur the causality question.

DR. STOTO: Could I propose a sort of different way of categorizing what is four on that list? That is to say, there may be certain kinds of individuals or certain kinds of cases where we are more likely to believe that the adverse event was due to the vaccine than others.

For instance, if it is the kind of situation where you culture the virus from the vaccine in the person, or if it happens in a way that is somehow more biologically plausible or exactly the right time window.

DR. WILSON: Isn't the other thing that they want out of category four, then, for us to provide some notion as to what type of research or additional data would allow one to draw a more meaningful or definitive conclusion? Isn't that implicit in what they want?

DR. STRATTON: Should we decide it is worthy of resolving. It is possible that we could say it is in

category two but this is not worthy of resolving because of other reasons, but yes, they would want some direction on how to resolve it.

DR. JOHNSTON: Could I make a specific proposal? You played well to my concerns about the word association and I like the idea of getting it out of there.

I don't like the idea of reducing the categories, personally.

DR. GOODMAN: Reducing from what to what? Be clear.

DR. JOHNSTON: From either four or five to clear. I don't think the way agent orange did it is the right way to go with vaccines.

I would suggest that we go back and look at how we did it for the vaccine safety committee, vaccine AE-2.

Then take the inadequate to accept or reject. That is a statement. That is our statement about causality. We don't have good data that allows us to clearly say whether it is causal or not.

Then take that one and dissect it and use the Bradford Hill criteria and say, yes, this is a four class for biologic plausibility or it is two class.

I don't mean to be that quantitative, but describe then, and force ourselves, describe why we are a little more worried about it or a little less worried about it.

Basically, that is what they want us to do. I think we have got to do that in some way. If we can do it in a way that is dependent upon something that, if it is not data, it is some kind of argument, some kind of information that bears on how we might distribute our concern -- here I am talking about an emotional concern along some axis -- and then you don't avoid -- dealing with anything other than causality in the official statement.

I can tell you right now, if our conclusion on autism and MMR is what is in cat number two, we can say that right now and go home.

If that is all we are going to do, that is where it is going to be.

DR. STOTO: We will be adding the second dimension of public health impact and --

DR. MC CORMICK: He knows. He is saying if it is only causality, we can go home.

DR. JOHNSTON: No, I don't think it should be. The CDC doesn't want that. That is not their idea of why they established this committee.

In addition, the compensation program wants something else, too, that falls short of --

DR. SHAYWITZ: It seems to me that you have that in AE-2. You have yes, there is a cause, no, there is not, then maybe there is a cause and maybe there is not a cause,

or more likely not a cause than a cause, or more likely a cause.

So, you have those intermediaries. Then you have right in the middle, it is inadequate. Then we will have to argue and name all the evidence to put it into -- obviously it is going to be hard to say the top or bottom, the extremes, but at least we have a maybe, more likely a cause than less likely a cause, and more likely not a cause, or vice versa.

Then hopefully that will take care of the CDC's worry that we are not having a gradation. It looks like in AE-2 you did have a gradation.

DR. JOHNSTON: You got it but it still wasn't there and it still wasn't enough.

DR. GOODMAN: Personally, I agree with this. I was taking issue with the second. I agree with this one. I think this is the right number of categories.

Whether we want to use these exact words we can debate. There is always some value in using the same language as before.

I also agree that, within the inadequate category, the way they handled it was not to make new categories, but to make it clear in the prose.

I want to make clear that this sort of rough -- I call this a three category system. That is, high,

intermediate and inadequate, with the other two categories being no evidence at all, or favors acceptance.

Whether we want to use favors -- if we are going to use favors, I actually think we have to use the phrase favors but does not establish within that category.

Just the phrase favors is, again, open to misinterpretation the same way that association is. Then we have to discuss do we want to use the word establish, which is a very high bar.

DR. STRATTON: We will never have it here. I think that actually you don't have to agonize over it. Not to prejudge your decisions over the next three years, but I will bet you a hundred bucks you will never come up with a category five. It won't even cross your mind.

DR. KABACK: Polio myelitis in the OPV.

DR. STRATTON: For the things in front of us, for the things that I think are in front of us the next three years.

DR. MEDOFF: If we use the Bradford Hill, do we establish that there are six and can we say that one level is below three? Do you fulfill some number?

DR. GOODMAN: I think the Bradford Hill criteria are not useful as a checklist. I think they are sort of a heuristic.

DR. MEDOFF: Objectively, how do you grade

something within that sort of nebulous category of very likely, unlikely.

DR. GOODMAN: You can do it "objectively." You can explicitly describe how you came up with your judgement.

I think the nature of the evidence will be so profoundly different, particularly some of them will be heavily lab based and mechanistically based. Others might be very epidemiologically based, which is really what the Bradford Hill criteria are more focused on.

I think the laboratory kinds of evidence are not really describable in the Bradford Hill framework. It is how things cohere and coalesce and relate.

I think our job is to be explicit about the argument. I think any attempt to come up with a checklist besides saying these kinds of considerations can come into play, will fail.

DR. JOHNSTON: We use it just as a kind of a reminder. Look at this. Was there any dose -- I thin it is a guide.

DR. MEDOFF: So, are we having four categories?

DR. GATSONIS: The fact that these five categories are not ordered in some way --

DR. KABACK: Two and three ought to be flipped.

DR. GATSONIS: Does that give anybody pause? I don't know if this is ordinal categorical. I don't know what

is the gradient, because of this category that says the evidence favors rejection of a causal relation.

That, you know, we are voting against causal relation. That comes before somehow the evidence is inadequate.

DR. STOTO: That is why agent orange didn't put numbers.

DR. KABACK: Two and three ought to be flipped.

DR. STRATTON: It is a historic -- the very first committee that Dick and Bennett and Mike were all associated with, for some reason -- I get to blame them -- they came up with these five categories, which all of a sudden became known as numbers, which nobody ever intended.

It is now just in stone. People talk about a category two and everybody in the vaccine safety field know what it means.

You can argue whether rationally --

DR. JOHNSTON: Kathleen uses it. Now I actually have to remember which direction we are in.

DR. STRATTON: That is because you have done other things in your life and I am stuck here. I don't know why you put category three there. It doesn't really matter. We didn't mean an ordering of it. I think we just won't use numbers, maybe.

DR. GOODMAN: What about putting the phrase, does

not establish, within the second-from-the-bottom, whatever the number is.

DR. MC CORMICK: No, that is fine.

DR. STRATTON: I kind of like that. I don't think that changes anything. It is a slight modification. Favors acceptance of, but does not establish.

DR. GATSONIS: So, you should do the same thing in the mid one, then, say favors rejection but does not completely throw out the window.

DR. STRATTON: That is important, because the point we always made about category -- about favors rejection and favors acceptance is that they are equal and symmetrical around the mean, but the establishes goes further, because you can never establish a negative, but you can think you established a positive.

DR. MC CORMICK: Favors rejection but does not eliminate.

DR. JOHNSTON: You are talking about still number four there?

DR. MC CORMICK: No, four is does not establish acceptance for causal relation.

DR. KABACK: And number three is, the evidence favors --

DR. MC CORMICK: Rejection but does not eliminate.

DR. GATSONIS: Does not eliminate.

DR. JOHNSTON: You can do that, but in number three, you know you can never establish it.

DR. STRATTON: Favors but does not establish rejection of.

DR. STOTO: That should be number two, then.

DR. STRATTON: If you want to reorder them to make some sense of them.

DR. KABACK: That gives them a continuum from there is no evidence to there is evidence.

DR. COHEN: There really are two dimensions. One is the strength of the evidence and the other one is direction.

DR. STOTO: I see what you are saying, no evidence, inadequate evidence, in favor of rejection, evidence in favor of acceptance, and then evidence establishing.

DR. STRATTON: I just think for communication purposes, even though we don't like it, believe me, people talk about these in those orders and they are going to continue calling them numbers whether we stop or not.

DR. MEDOFF: So, you will send out an amended version of this so we don't have to write this down?

DR. STRATTON: Yes.

DR. JOHNSTON: Rosemary is very concerned about the use of the word relation instead of relationship.

DR. STRATTON: I know where that comes from. I was told -- and I wasn't there, but I was told it was put there because the chair of pertussis and rubella, the Honorable Harvey Feinberg -- is he your provost or your president --

DR. CASEY: Provost.

DR. STRATTON: Your provost said, only people have relationships, things have relations.

DR. JOHNSTON: People have relations all the time.

DR. STRATTON: I am just telling you that is where it came from. We can call them relationships if you would like. I am happy to change it. It was Harvey Feinberg's edict.

DR. MC CORMICK: I think it is time for lunch.

[Whereupon, at 12:42 p.m., the meeting was adjourned, to reconvene at 1:30 p.m., that same day.]

A F T E R N O O N S E S S I O N (1:25 p.m.)

DR. MC CORMICK: Looking at the agenda that was suggested that we sent out, I think that in terms of the issues that should be considered we have gone a long way in terms of the causality assessment and societal concern. We have not addressed issues of biologic plausibility and alternative hypotheses.

I guess the other issue besides the types of evidence or conclusions or are going to draw is for people to start thinking in the next week about what they want to hear about MMR and autism, either singly, together or whatever, and what kind of speakers we will need to bring in.

Kathleen is working on getting Wakefield to come to the next meeting to present his data and to take questions.

That will be there, but I think other individuals and other issues that need to be addressed we really need to hear about.

DR. KABACK: When are you thinking of the next meeting?

DR. STRATTON: The tentative date for that next meeting, based on the calendars that have come in -- and I know some of you can't make it and there is nothing we can do about it unfortunately -- I think is the 7th and 8th of

March? 8th and 9th, I am sorry. It is a Thursday and a Friday, of March.

I need to confirm that Wakefield can make those dates. He had merely replied, yes, I will come. I will try to help and I prefer the February dates.

Then, of course, I woke up and there was no way that was going to happen, that I was actually going to be able to pull this off with the rest of the staff by then.

The next set of dates where most of you were available were those dates in March. We did send out an e mail about that last week.

DR. SHAYWITZ: What are you thinking about as to when you will know for sure.

DR. STRATTON: Next week. I will call Wakefield. I actually didn't have a chance to check my e mail, but I did try to again to sort of get him to confirm that.

DR. SHAYWITZ: I have to know that.

DR. JOHNSTON: Some of your speakers for autism may have difficulty, too.

DR. STRATTON: We have also sent out some people to some other people for autism about those dates, to see if they were available.

Now we need to find out some other -- for example, if we want a good pediatric gastroenterologist, just to help evaluate these data, I think, not to elevate Wakefield to a

certain status, but the primary data is his hypothesis. He is the first person we have to have.

There are probably four good pediatric gastroenterologists, pathologists, that we can choose from. So, first we need to nail down the match between him and all of you and then I will find the appropriate other autism people. I know there are some key people and we are looking into them.

DR. SHAYWITZ: Suppose Wakefield doesn't come. Suppose he just passes aggressively.

DR. STRATTON: Then we will have to do it without him. I mean, he said he will come. He told me that. He promised he would.

I think he knows he was criticized for not showing up at the American Academy of Pediatrics meeting on this.

I don't know what we do. If he says just, no, I ain't coming --

DR. SHAYWITZ: No, he won't say that. He will say he is busy or something.

DR. STRATTON: Then we will have to deal with that. I have still some faith in him.

DR. JOHNSTON: We had him in October of 1998.

DR. STRATTON: We did. I promise that I will do everything I can, short of going over to the Royal Free and tracking him down in the hall to get a commitment for that

firm date, and let you know next week for sure.

DR. WILSON: Is there any possibility we could get either one of the other groups at the Royal Free who failed to confirm the identification of measles virus in the bowel, and potentially get this -- I think the two categories of data that seem to me to be germane, the one on plausibility, is this and the second one is the epidemiological data.

DR. STRATTON: Right, that is the Brent Taylor and the CDC data.

DR. WILSON: Maybe also we could get this Finnish group. I could call COA who recently published their -- that is the biggest series I am aware of.

DR. BERG: What is this on?

DR. WILSON: On the linkage. They have gone back and looked at all their data over, I don't know, 15 years or something.

DR. BERG: Could I ask, so these individuals would be presenting in a public session?

DR. STRATTON: Yes.

DR. BERG: Might they have a concern about presenting preliminary unpublished data in a public forum? I am struggling a little with whether they are going to be able to tell us anything other than what is in their papers.

DR. STRATTON: They may not be able to tell us anything. They may choose not to tell us things. I think

the papers are sufficiently sort of -- at least, my interpretation of some of the debate -- is unclear and incomplete.

Even if they restricted themselves to the nature of their published data, there is a value in trying to dissect it and really understand it.

I don't think it is any different than any other scientific meeting. Some people are willing to talk about preliminary data and go into it and other people aren't. We just have to do the best we can.

DR. MEDOFF: Just to follow up on that, I am just trying to consider the value of having even Wakefield come and present data or information which we know is in press, and what he is going to say anyway.

I am sure he will be very supportive and have all sorts of reasons for -- that is in contrast to reviewing the papers.

We have a lot of work to do. If we can spend a fair amount of time listening to people, it detracts from the amount of time we need --

DR. STRATTON: So, you would suggest we don't need any public session and we just need to read literature.

DR. MEDOFF: I would suggest a discussion about that, what these presentations really bring and how worthwhile they are.

DR. JOHNSTON: I think that is a valid question to ask and I am not sure of the answer. What happened, when we had the vaccine safety forum, we dedicated a day to this relationship.

We had there people who were experts on autism and they described the different diagnoses and some of the newer ones and the spectrum of the disorder.

What happened with Wakefield was, there was a lot of exchange with people in the audience, go that you got a very definite sense, beyond what was in the paper, of what he had done and not done and how he had handled the samples and what material he had, and could he exchange that material, in his own view, of those data.

It was that this was purely a possibility, at that time. The conclusion that we had at the end of the day -- because he got really grilled by the CDC people.

They had asked for exchanging samples earlier and he didn't do it for that reason. So, it went back and forth and he agreed to exchange samples. The exchange was, I thought, very revealing.

DR. GOODMAN: Is there a transcript of that session?

DR. STRATTON: I actually think that I do have a verbatim transcript for that session. I certainly have some summary minutes.

The purpose of that was not to come to a conclusion about causality or anything. It was a different activity with different purposes. I could let the committee see the transcript of that session, if that would be helpful.

DR. KABACK: Did that exchange of samples take place?

DR. STRATTON: No.

DR. KABACK: It did not, even though he apparently agreed?

DR. JOHNSTON: I think what we did instead was look at O'Leary. I don't know very much about it but that is my understanding. He got a pathologist.

DR. KABACK: That is how O'Leary got into it and not primarily.

DR. JOHNSTON: That is right.

DR. STRATTON: There is currently discussion, separate from our activity, about whether or not CDC will try to enter into a collaboration of replication, duplication and verification of those virologic findings. That is beyond us.

DR. BERG: I share Gerry's concern. I have been on panels where we have had lots of testimony like this and those that haven't.

My personal experience is that the personal

testimony can take a lot of time and doesn't necessarily add new material to the debate and actually, in some senses, confuses things because you are left with information that you don't know what to do with.

DR. STRATTON: What do you mean by personal testimony?

DR. BERG: People coming in and making their point on some issue. For example, exactly the way you are proposing with Wakefield, to have him come and present his material and be subject to asking questions and so forth.

I think that with as much as this panel has to do, I think it wouldn't be a high priority. I think it is fine if he can make it, but I wouldn't want to devote a lot of energy to that.

DR. SHAYWITZ: The one virtue that it would have, Al, is that it would -- I think it would allow people to say -- what he is really going to have to depend is people saying that, however, you didn't listen to the other side of the story. You said you read it, but you really didn't. This way, you would have an advocate.

DR. BERG: You need to make sure that the other side is there, too.

DR. STRATTON: That is what we are talking about with the pediatric pathologist. You remember, Bennett, weren't you on the little DPT study?

DR. SHAYWITZ: I was on the one where we brought the people from Finland.

DR. STRATTON: That is exactly what I am talking about. You know, we brought them in and we talked at great length about the data and everything that we didn't quite understand about what they did. It isn't any different than any other sort of scientific discourse.

Once you bring in one person, then you have to have some other people to help you think through and to hear their interpretation of those data.

My suggestion about this, actually, if you don't mind is that any of you are welcome to send me suggestions for who it is that you think we need to hear, and in the most efficient way.

A small group of obvious people here be deputized to really be the point people for me, in terms of, you know, then let me make sure that I am getting the proper child neurologist to think about autism or the proper immunologist to try to fetter out whether there is an immunologic component to this that we don't understand.

Some of you are going to have to find me a pediatric gastroenterologist. I don't think we are going to do it today.

DR. SHAYWITZ: Kathleen, I would actually try to focus people on autism for different -- not so much -- I

mean, our group doesn't have to know about the theory of the mind and lots of things that people do in studies on autism.

What we really need to know is, what is the data on the prevalence and are there two points that are relevant to indicate whether it is going up or down.

If it is, what are the vagaries of a diagnosis. If we can direct people to just answer that question --

DR. STRATTON: That is what I am saying, is that you all are going to have to define those questions for me to be able to pose to the speakers to make the most efficient use of your valuable time.

That is what I am saying, is what are the ideas of causes of autism.

We will get you whatever other papers there are on this specific hypothesis of measles and autism. We didn't -- if we didn't make it clear, that is my fault.

We didn't intend what there is in this last tab to be all there is. It was really for you to start thinking about it, so you would have some vocabulary.

We will quickly get you the rest of that material to help shape your suggestions to me about who to bring in and exactly what questions to ask each speaker to address.

DR. BERG: I guess implicit also in this discussion, and I think it came up earlier that Al mentioned as well, again, if we begin to wade into a whole lot of

unpublished data that we are unable to review critically, one example would be this linked data base from northern California and Washington, et cetera.

It doesn't seem to me that we should be interrogating that because that, in fact, requires a great deal of in-depth analysis to know what you are getting out of it.

You had this panel on thimerosal and that was sort of the take home, I guess, was that without a lot more work, you can't really use that data at the present time.

That should be a rich source for future studies that we might suggest as one thing, an outcome that we would like to suggest.

At this point in time, it is not a resource that we can really utilize.

DR. JOHNSTON: Maybe we will get that out of the papers, the summary of it, because the data were really thoroughly reviewed in all aspects and criticized thoroughly by a lot of outside people.

The bottom line, it then went to the ACIP and there was no action taken, basically, except the statement to push getting the thimerosal-containing vaccines off the shelf because there could be a risk.

DR. KABACK: Because the evidence was insufficient to substantiate that.

DR. MEDOFF: Will there be a time limit for the speakers' presentations?

DR. STRATTON: Whatever we decide is appropriate, absolutely.

DR. MEDOFF: We are going to have to come out with some sort of idea of a position paper at the end of the next meeting.

DR. STRATTON: Certainly no more than a day because we don't have that kind of time and if we could have a half day, that would be great.

DR. MEDOFF: A half day might be more reasonable.

DR. STRATTON: You need to be very -- I am sure you will be very thoughtful when you suggest to me who it is you would like to hear from, or in what form you want information.

Some information can be, you know, a commissioned review on gastrointestinal pathology in kids. Some of it you want to hear in person and some of it you want to read just in the commissioned literature and some, we have money to pay background people to summarize this information.

DR. WILSON: It seems to me, though, that if we are going to have Wakefield speak, the areas of contention will be the intestinal pathology and how unique it is, whether the virus is really isolated in those patients, and how does that differ from an otherwise comparable group of

patients with inflammatory bowel disease lacking autism.

That data probably does not exist unless he has got it, and the credibility of the correct diagnosis of autism in those patients, maybe that is established. I don't know.

DR. MC CORMICK: I would say that that is a question, because it is a tough diagnosis.

DR. WILSON: The quality of the virologic analyses, because I understand that that has not been replicated by another group in the Royal Free, but I haven't seen the data.

DR. STRATTON: I believe there is a Japanese group that claims to have, that has published a paper on that.

DR. KABACK: Those were not supportive data.

DR. STRATTON: I believe there was some data that showed measles virus in the Japanese group.

DR. KABACK: In the bowel in autistic kids?

DR. JOHNSTON: And not in normal MMR non-autistic?

DR. STRATTON: I bet it was a case series and not a case control. I shouldn't be saying -- I have heard that there is another paper.

DR. KABACK: Measles virus goes in lymphatic tissue. I mean, that is the normal physiologic place you would expect to find the virus.

DR. JOHNSTON: Especially fairly recently, there

is exact administration.

DR. STRATTON: These are the kind of very, very focused areas that you are going to need to give me guidance, and as best you can come up with suggestions for who is best to help assess that to be brought in.

DR. JOHNSTON: Kathleen, you have always been good at bringing in a parent to really frame the parental and public concern.

In terms of trust in the committee, that would probably be a good idea. There was a lady there who got up and made a comment.

DR. STRATTON: She is a thimerosal specific.

DR. JOHNSTON: She wasn't in autism.

DR. STRATTON: No, thimerosal and autism, not MMR and autism. It is a niche group.

DR. MC CORMICK: That is the next meeting.

DR. STRATTON: I swear, that is what she told me. We will find --

DR. JOHNSTON: Barbara Loe Fisher could give you names. Mrs. Fisher said she had cases. I think she came up to see if you needed any cases to demonstrate the points, you could have them.

DR. MC CORMICK: She was demonstrating causality. She was taken by your case series that you did the Guillaume Barre and whatever, the tetanus. She was all

ready to get you cases to prove causality.

DR. WILSON: Well, let's see them.

DR. MC CORMICK: Let's not do that. Do you have a free weekend that you want to plod through them?

DR. STRATTON: I read all 546 of those death reports, case reports, in the system in 1993 and it is not an easy thing to make sense of.

If there is anything to be learned about the relation between MMR and autism that one could find in a case report, then let me know and I willI ask her to find me one if she has it.

I suspect there is not a sort of classic, eureka -- you know, is there a case report that could be conceived of that would be incredibly influential in this decision making. We can see if there is one out there.

Otherwise, we are going to get a list of hundreds and hundreds and hundreds of kids who were developing normally but they got their MMR and then they started to regress.

I don't think that is helpful to you all, a case report like that, not to prejudge how you are going to think about it.

DR. KABACK: Do you know, Kathleen, if any of them were just measles by itself?

DR. STRATTON: Now that would be interesting.

DR. KABACK: We need to go back to this story about MMR versus measles itself.

DR. STRATTON: That is the story. That is the whole story.

DR. KABACK: That is why it is important, if you have it in that case series, any kids with measles alone. I don't know if the time frame of the triple vaccine -- I mean, they were never separated in time, were they?

Which came first?

DR. WILSON: Rubeola.

DR. KABACK: Rubeola came first and then mumps and rubella subsequently?

DR. STRATTON: Yes.

DR. KABACK: So, there was a period of time where there was only measles vaccination by itself. It would be interesting to know, during that period of time, whether any of these cases were linked to those times versus MMR, for obvious reasons. I would be interested to know that.

DR. MC CORMICK: There is also -- and I don't know if CDC ever followed up on this. There was an old report which was measles -- I don't know whether it was measles of MMR vaccine.

It was from Texarkana, which straddles two states. One state had the immunization policy for, let's say, measles and the other didn't.

So, there was a measles epidemic in one part of the town and not in the other. I don't know if anyone has gone back and looked at what their autism rate is.

DR. JOHNSTON: You know, what we are doing here, by the way is --

DR. MC CORMICK: Designing the study.

DR. JOHNSTON: Figuring out what information we would like to have that could then shed light on this.

DR. KABACK: Since 1994, Dick, when you guys did all the work that you did do on the subject, other than this Finnish study, has there been any significant new literature to look at, other than what you guys looked at for the 1994 study?

DR. STRATTON: We didn't look at this in 1994.

DR. KABACK: Not autism, I know, but you did look at MMR. Wasn't MMR -- sure it was. You did find some associations -- I don't want to use that word any more -- suggested causality, or possible causality --

DR. JOHNSTON: Relationships.

DR. KABACK: Relationships, right. Since the 1994 data set, there has been -- will we have that literature provided to us in the next couple of weeks?

DR. STRATTON: Of every safety concern with MMR?

DR. KABACK: No, we are only going to look at autism, correct?

DR. STRATTON: We will do a literature search for it.

DR. JOHNSTON: It would be kind of interesting to see if there are other vaccine adverse events being reported that might fundamentally pathophysiologically relate to autism.

DR. MEDOFF: Mrs. Fisher said autism and attention disorder and learning disability.

DR. KABACK: She went through the list of symptoms. At one point she ran through a list of symptoms. You could take a textbook of pediatrics and find almost every disorder in there was in some way related to one or other of those symptoms, in which case they were all due to MMR vaccine or DPT, whatever she was claiming, MMR.

There was at one point in her talk a whole array of symptoms and signs that were so non-specific, and if you really ascribed those to an adverse event, you were looking at a textbook of pediatrics.

DR JOHNSTON: What she did, she constructed a list that has already gone to the CDC to raise their concern. So, some of those are going to come back.

She listed like diabetes, asthma, all these things that some parent has come and said, my child developed asthma within weeks after he got the shot.

DR. STRATTON: What you were starting to move

toward, that might be helpful is, are there other adverse events that have been reported associated with MMR, that might shed light on the autism. Is that what somebody was saying?

DR. KABACK: Yes.

DR. STRATTON: Then you need to tell me what kinds of adverse events those would be. Do you just want general neurologic?

I can ask for a search of those in the VAERS and we can do the literature search, but you need to tell me what they might be.

DR. KABACK: Learning disabilities, developmental defects of whatever kinds, neurologic deficits of whatever kind, perhaps motor.

DR. MC CORMICK: Delayed speech is the hallmark of autism, delayed expressed language. Delayed speech is one of the hallmarks of autism.

DR. MEDOFF: I am sorry, I was just out of the room. What do we say now that we want, additional neurologic complications of vaccines?

DR. STRATTON: This is a literature search that might help shed light to see if there are other reported related --

DR. MEDOFF: Besides autism?

DR. STRATTON: Yes.

DR. KABACK: Only in the sense that they may, from a mechanistic point of view, give us some information.

DR. MEDOFF: I would use them with some caution. I think we really need to be careful to stick to the specifics.

DR. STRATTON: We are supposed to look at strength of competing hypotheses, alternative hypotheses, and biologic plausibility.

If it turns out that maybe there is a lot -- I don't know what you were talking about with other things in the leaky bowel syndrome and yes, there are things that we might looked at.

There might be other things to be looked at that would say, hey, that has been found. They haven't labeled it as the inflammatory bowel autistic syndrome but there is something there about measles and whatever.

DR. CASEY: Well, seizures, febrile seizures, are well known to be, and are embedded in this study. That was looked at in 1994.

We just get into whether they are hypoxic during the seizure it tends to be developmental delay when you are talking about competing hypotheses, do you know what I mean, if a child subsequently develops.

DR. MEDOFF: I would really urge caution in trying to make this thing too diffuse. It is just going to get

into a mess.

As soon as you have one, there are five others. I think if the CDC comes up with fairly specific questions that we have to deal with, I think autism and MMR is enough.

DR. KABACK: The problem, Gerry, is that autism is very poorly defined.

DR. MEDOFF: That is what our experts can tell us about a definition of it.

DR. KABACK: You are going to hear a spectrum.

DR. MEDOFF: Then we have trouble right off the bat.

DR. STRATTON: Oh, we have trouble right off the bat.

DR. KABACK: You are talking about a spectrum, a complex syndrome with multiple plus or minus presence of various symptomatology.

What people call autism is not always autism. It can be Angelman's syndrome. It can be medical adipodal(?) dystrophy, at least in my own experience, and a variety of other things not autism.

DR. MEDOFF: That is my question. In pursuit of these other things, are we limiting it to what many people call autism rather than other neurologic manifestations like a seizure.

DR. MC CORMICK: Let me make a compromise

suggestion, that we look at two specific associations. One is, one of the early hallmarks of autism is really delayed language. That would be one. The second would be mental retardation.

The reason I say that is that most kids with autism do have some degree of mental retardation and, two, many kids with mental retardation have abnormal behaviors that might fit into the autistic spectrum of abnormal behaviors, or people got labeled and people weren't looking at their abnormal behaviors and socialism.

Those two, I am not sure I would go with -- those would be two where autism might lurk under the diagnosis.

DR. MEDOFF: I just don't want to get really too diffuse.

DR. SHAYWITZ: When you do your search, you have got to use developmental delay. Hardly anybody uses mental retardation any more.

DR. MC CORMICK: I think it is, though, in the index medicus list.

DR. SHAYWITZ: Hardly anybody is categorized that way any more.

DR. MC CORMICK: Actually, at least clinically, people talk about retardation and they talk about severe, moderate and mild. What they call mild retardation, boy, I consider quickly down --

DR. MEDOFF: In contemporary literature, it may not say that.

DR. MC CORMICK: I am just saying search both, include both. That would be my rationale for those two things. Deprivation developmental disorder --

DR. KABACK: That is sort of a larger category for autism.

DR. CASEY: I was thinking about literature search.

DR. MC CORMICK: I don't know whether the MESH title is, whether it is PPD.

DR. CASEY: It gets buried in there.

DR. MC CORMICK: I am talking about if you do a Medline search, whether it comes up under autism or it comes up under PPD.

DR. GOODMAN: You would still have to do a multiple search because the MESH headings almost certainly have changed over the years and they don't go back and re-code.

So, you pick up some MESH headings from 1992 on and some others from 1985 on.

DR. SHAYWITZ: Chris reminded me that you should look for Asburger syndrome.

DR. WILSON: That is contained with this, within autism. That seems to be the diagnosis of the late 1990s

and the year 2000. That one is going up faster than all the others.

DR. CASEY: I think it is a recognition of different --

DR. WILSON: I didn't make a value judgement as to why it is going up. I am just telling you the diagnosis is being more commonly mentioned.

DR. STRATTON: It may be putting the cart before the horse, but I think you should help us think through, help me think through -- I think it is easy to identify the very precise literature that bears on MMR and autism, and there are a few people who have done it, and I know I can get those papers. I can identify them.

What information would you need to assess biologic plausibility of this hypothesis, and what information do you need to assess the strength of competing hypotheses.

You may not be able to answer that now, in part because you haven't thought enough about it maybe, but also because I don't think we have defined yet what it is that we are going to consider as biologic plausibility and strength of competing -- that is the cart before the horse.

I am not convinced I know how you want to think through assessing biologic plausibility and strength of competing hypotheses. You need to help focus me in terms of the information that the staff and I get you, so that you

are prepared to weigh in on those topics.

DR. WILSON: The issue that comes there that is the difficult one is that we know that each of these three viruses is, in fact, neurotropic.

The syndromes that they have produced in the wild form, which is the sort of gold standard for biologic plausibility, assuming that it would be recapitulated in some individuals by the vaccine, is from acute encephalitis to, in fact, later onset, more deteriorating sorts of things like we saw in SFT or progressive rubella pan-encephalitis, you saw in children with congenital rubella.

Mumps, again, you can get into a morass there. The difficulty there is forming a link between those disorders that have a much more clear cut progressive thing than these more chronic conditions that we are talking about here.

They do have this element of deterioration. The difference is that this one stops. You know, you have this chunk downward and then it seems to have been sort of a step function rather than straight down into the tank.

DR. MC CORMICK: It is not progressive, but some of the literature does suggest that there is a further deterioration in adolescence in autism.

DR. WILSON: The difficult thing there is that, of course, is what has been described in progressive rubella

pan-encephalitis in a handful of patients and so forth. We have similar syndromes with other viruses.

DR. STRATTON: It seems to me that that is the evidence that would give you a general assessment that this is sort of theoretically possible.

DR. JOHNSTON: If you have also the classic pathology, whatever that is, and somebody could give us four Asburgers in a classic typical presentation.

DR. MC CORMICK: That is Margaret Bauman. She has been slicing brains looking at autistic.

DR. JOHNSTON: I would like to hear that.

DR. STRATTON: We have e mailed her, inviting her to come to talk on those dates, actually. We have jumped the gun. We are waiting.

DR. MC CORMICK: I guess we are talking here about the comparability of the known neurotropic syndromes with whatever looks like autism.

DR. JOHNSTON: Whatever what?

DR. MC CORMICK: Whatever the known neurologic syndromes are associated with these viruses against something, both the symptoms and pathology of autism.

DR. STRATTON: Then I think there is this issue -- correct me if I am wrong -- again, I don't totally understand this hypothesis and I think you two probably do better, but I am not quite there yet -- the three viruses

and why one would be --

DR. WILSON: Ben and I talked about that. I have at least three explanations. Do you want me to voice those now?

DR. KABACK: So, we can think about them, sure.

DR. WILSON: This, again, remember is feasibility, not plausibility. This just paints a picture. There are really two and potentially three ways. Ben pointed out a third one -- well, four ways to think about how this pathology might occur.

Wakefield has proposed that toxins get absorbed through the gut. I am not going to discuss that because we can come back to that.

The other three, the two that I would have proposed would be, okay, the virus itself injures the CNS in a process somewhat analogous to the wild type viral infection.

The second is that it is an autoimmune process. In fact, there is some notion, if you will, that some of the encephalitides that occur in these viral infections is, in fact, that, that there are a whole variety of encephalitides and encephalopathies that are thought to be perhaps partly immune mediated.

If you look at viral entry, one possibility is the following. This is, again, totally just throwing out an

idea that is possible.

If you look at the immune response to a viral infection, in particular, let's say, looking at T cell response, in many viral infections, the response will be dominated -- this has certainly been shown to be the case in some individuals with HIV -- there will be a few epitopes, that is, T cell C small peptides.

CD8 T cells see peptides with about eight to ten amino acid. CD4 T cells see somewhat larger, but still, less than 20 amino acids.

So, a very small piece of protein is seen by the T cell in the context of your HLA molecules.

The peptide literally sits in a groove formed by the HLA molecule and the T cell sits down sort of in a canted angle on top of this and sees the composite of those two things.

So, genetic predisposition that can be conveyed in one way, by the fact that each of us has a different mix and match of HLA molecules, which both shape the T cells that emerge from our thymus where they are educated by those molecules, and then also determine which pieces of those proteins are actually able to bind -- because the ability to bind in that groove is determined by the HLA haplotype -- confers different electrostatic and hydrophobic properties to this group, to then determine which peptides can bind to

the groove.

What you see in an immune response, then, is different individuals will see different peptides from the same or even different proteins.

There are some antigens that have what are often called universal epitopes. Tetanus toxoid is an example.

Many HLA types will bind tetanus toxoid presented to your CD4 T cells. Hence, it is a great vaccine. It is enormously immunogenic. Virtually everybody will see tetanus peptides really well. Other ones are going to be seen to a varying extent.

Now, if you have got a virus -- let's say a measles virus -- in fact, this is a live virus we are giving. It will replicate in the host and it makes a number of different protein antigens.

Within each of those proteins are contained a number of potential peptides that might bind to the MHC molecules which will, in some combination, do that, and that combination will vary from individual to individual, depending on their HLA type.

Now, then the immune response will see some of those better than others, and that is determined by things that we don't completely understand, but part of it is determined by the affinity with which the peptide binds to the groove, the affinity with which the T cells that exist

in this individual bind to the composite of the peptide in the MHC, and so forth.

So, if you look at immune response and you are able to follow, as we now can in very good detail, which T cells are seeing which peptides, you will see that a varying number of peptides will be recognized with a varying hierarchy between them in how well they are recognized.

That hierarchy will evolve, to some extent, over the context of infection, but typically you will see a range.

Some of them will be hugely more prevalent than the others, so-called immunodominant peptides.

For example, you may see, in a patient with HIV, in some individuals their CD8 T cells may be 20, 30 percent are seeing a single peptide. Now, in other individuals it may be more diverse and it may evolve.

Now, if you come in and throw in at the same time a whole range of different other potential antigens, you will get a stacking up of hierarchies of these things.

Now, you might imagine, let's say you have got measles virus and you are forming, let's say, your C3 peptides from the virus, that your T cells are going after.

Now you throw in a rubella virus. Let's say the rubella virus in individual X actually generates a response that is hugely immunodominant that, in fact, drives the

production of a vast number of CD8 T cells, which then, to some extent, override the response to the other antigens in the other virus.

How this plays out in each person is going to vary, depending on their HLA types and other things that happen.

Now, normally when you experience a measles virus infection, you don't get rubella and mumps at the same time. That is the honest truth.

Whatever happens in that individual with the measles virus is going to be driven by the relative hierarchy of the peptides from that virus.

You throw in rubella, you throw in mumps, you may change those hierarchies such that you could influence the nature of that response.

Let's say one possibility -- this is all fiction, now, mind you. You give somebody a rubella virus at the same time you give them measles.

Ordinarily they mounted a response to peptides A, B and C. They shut down the infection, the infection goes away and the patient does pretty well.

You throw in rubella virus. Let's say there is a hugely immunodominant antigen in rubella virus. Now the response to the measles virus antigens is less robust because there is this huge response going on to the rubella

virus.

The measles virus replicates X amounts more because the immune response is less efficient and more damage occurs.

That is one hypothesis where, using several different antigens, you might change the relative immunodominance of those and change how well the immune response responds to virus A.

DR. KABACK: When you say more damage, do you mean neurotropic effects?

DR. WILSON: Neurotropic effects of the virus. That is number one. Then you flip it around and say, okay, let's say the injury is meted, not by the virus, but by the immune response to the virus, an entirely plausible thing that we know occurs.

You can play the same scenario out there. You say, okay, let's say you infect an individual with the measles virus.

So, the measles virus generates the responses of peptides A, B and C. In this individual, peptide C looks a lot like the peptide from myeloinvasive protein, because there is a polymorphism in the myeloinvasive protein from this individual.

It then creates a peptide that is very similar, if not identical, to the peptide from this virus.

Now, if you give that virus along, then that may be a dominant response and that could be modified, then, by the presence of other antigens being seen at the same time.

So, you can see how you can change the magnitude of the response directed against this specific peptide, depending on what other peptides might be competing for response at the same time.

It is not a flat-out competition and the rules are not completely understood, but there are some effects of having different things going on at the same time.

So, you could either increase or decrease the immune response to the given peptide which, depending on the peptides from the virus or whether it is a peptide from the virus that mimics one from the host, you could modify the magnitude of the response. So, that is one.

The third one that Ben suggested is sort of, I guess, driven by this latest, surprising-to-me, results with immunization for Alzheimer's disease in the mouse, these Nature papers that just came out.

So, you take mice and you give them an amyloid precursor protein that leads to the development of an Alzheimer-like disease.

Now they immunize them with a protein to protect them from the disease. Now, you go figure how that works. You never figured that this was an immune disease in the

never would have been counted before.

My third is that we also have, with 1972, was the legislation for mainstreaming developmentally disabled kids and starting that, and we were now focusing much more on much more differentiated diagnoses in order to improve functional status, not necessarily to improve diagnosis.

I think there need to be some ecological competing hypotheses. I would offer those. I don't know if anybody else can think of any others.

DR. JOHNSTON: One stream of evidence that would pertain to that, of course, would be not just the diagnosis of autism but diagnosis of competing -- also competing diagnoses, which you would expect to go down as they were re-diagnosed as autistic.

If there is any incidence data on the -- you could outline the disorders that these kids might have been classified in preceding the change in diagnoses. It would be very interesting to see if there was a step down, if that data exists.

DR. KABACK: Except that there was a whole technology revolution going on during the 1970s with the university-affiliated facilities for disabled kids.

More and more kids were pouring into university centers with mental disability and physical disability and were being evaluated much more comprehensively than they

were in the 1960s.

In fact, the Kennedy Institute was one of the first, at Hopkins. As a result of that, I think various diagnoses increased, because of increased attention.

Plus, I think the shutting down of the institutions for mentally retarded had another big kind of surge of cases into the system that would not otherwise have been looked at.

DR. MC CORMICK: I think it would be very hard to do that. Under the impetus of 94-142, which was the mainstreaming act, there was an impetus to identify these kids in the school.

Basically, the act said, you should have between 12 and 15 percent of your population in this category.

People got diagnosed in the educational diagnoses, to some extent reflecting their disability, but to some extent reflecting what services the school could provide.

Seriously, Nick Hobbs used to tell the story about this poor parent whose kid with Down's syndrome was in a program for mentally retarded during the school year and for developmentally delayed in the summer. They said they had to pick out what the kid was so they could have constant diagnosis.

Some of these are overlapping and bizarre categories. So, I think it would be very difficult to find

first place.

I can construct a scenario for that as well, where you can imagine that an antibody in a semi-catalytic sense, could preclude the formation of the fold when the protein is amyloid precursor protein, and essentially catalyzes the creation of this tropiolar network that produces the plaques that cause the disease and so forth. There are probably other hypotheses.

You can see how, in this case, if the immune system -- this is already in the immune system. The immune system dampens a proclivity to develop such a disease and that, by perturbing that, you could get this.

By changing the numbers of antigens being seen and competed for you can change the relative hierarchy of the response. You can go on and on with these confabulations.

DR. KABACK: So, the single dose measles versus MMR should be very informative, not completely informative, but highly informative, if kids with just measles don't get autism.

DR. WILSON: Or are less likely to.

DR. KABACK: And kids with MMR do get it, then that supports a very interesting notion.

DR. WILSON: You have to remember that, at least from what I could read, the proposal from Wakefield is completely a priori.

that kind of information over that period.

DR. JOHNSTON: It has got to come from a big pool, even if you could do it, a big pool of developmental retardation.

It is so big, with all this flux and everything, I think it would be hard to see a decrement.

DR. GOODMAN: I don't know if there is any survey data. I just think looking at other diseases, whether they went up or they went down or they stayed the same, in the same period, would help us.

DR. MC CORMICK: The other problem that occurred during that period was also more access to primary care in the Great Society programs.

A number of diagnoses went up, not because the prevalence of the disease changed, but because people were coming into services.

DR. GOODMAN: That could help to support a whole bunch of alternative hypotheses. If everything is going up and they are picking out autism, you know, you have a rich -- again, I don't know if this data was even gathered.

DR. MC CORMICK: There are some general trends that suggest there might be some reasons why this diagnosis may be apparently increasing or whether it is really increasing.

There are a number of clinicians who think it is

really increasing. That, to me, is a phenomenon of the last 10 years, not the last 20.

DR. GATSONIS: Are we saying that there is no epidemiologic study with the trends, showing all the time trends?

DR. MC CORMICK: I looked at this --

DR. WILSON: I thought it was in one of the papers that you sent us that showed these curves. That is where this came from.

DR. MC CORMICK: That was autism in the year of birth in a single cohort or something. I mean, in terms of using the same diagnostic criteria, two points in time, I remember vaguely one Scottish study of a school population but I don't know how much else.

DR. KABACK: Doesn't March of Dimes have data like that, the developmental disabilities as a function of diagnosing the categories of chromosomal abnormalities, single gene disorders, birth defects?

DR. JOHNSTON: Those are CDC or National Health Statistics.

DR. KABACK: They would probably have those kinds of numbers.

DR. JOHNSTON: They would have some of them.

DR. KABACK: It is not a question I perceive, but I think Steve's point is a good one. If you look at -- of

course, you could use fragile X and you could use specific diagnoses associated with mental deficiency and show they are increasing very much like autism, because of increased awareness, increased technology.

DR. MC CORMICK: Increased survival percentages.

DR. KABACK: Survival and, as you point out, the attention because of the changes in laws vis-a-vis the school systems.

So, that categorization was required. Plus, these UAFs, I think, have had a big impact as well. There are a lot of reasons for it.

It is true, I think, you could probably find six disorders that showed curves, if those curves for autism are as Wakefield is suggesting. I don't know that they are. They would follow similar trends.

DR. STOTO: I think we have to look whether the National Health Interview Survey has data on this. That goes back to the 1950s.

DR. MC CORMICK: Those analyses looking at chronic conditions have. Peter Budetti did those in the 1970s, in the mid-1970s.

There was a concern from the 1960s to mid-1970s that there had been a doubling of the number of children reporting chronic conditions.

His conclusion really was it was a diagnosis

phenomenon, it was not --

DR. STOTO: So, maybe look at his data and then update it.

DR. SHAYWITZ: There are the epidemiologic catchment surveys. They are survey samples of several surveys. I know they have been done in children. I don't know if they have been done on all patients.

There is also a very famous study that was done in Ontario. The primary author's name is Offerd. Those are also surveys of psychiatric disorders in children.

DR. MC CORMICK: It is a classic chronic disease survey.

DR. SHAYWITZ: I think that those might be helpful and there might be updates of those.

DR. GOODMAN: There are epidemiologists, there was a group at Washington and a group at Hopkins.

DR. MEDOFF: The relatives of those in the baseline has changed. There is a new definition.

DR. GOODMAN: They are aware of those things.

DR. MEDOFF: I mean, you can get a general inference, but the question is, how do you deal with that. Does that mean that autism is part of that general increase or is there something special involved with autistic children.

DR. GOODMAN: I agree, but I would like to see the

data.

DR. MC CORMICK: Yes, I think we are at the alternative hypothesis. What else could contribute. If this is part of Wakefield's argument and others' argument that date back to this particular period, there are some alternative hypotheses.

DR. GATSONIS: If they all go up but the percentage of autism, the relative percent, goes up fantastically, that might give you some chance to think about what maybe happened. That is another way of looking at it.

DR. BERG: I feel a bit like a consumer in this discussion. I am looking to when our reports start coming out.

I have to say that what I am missing in the discussion is sort of an overall analytic framework that maps out this committee's view of how it all might fit together.

From that analytic framework, the key questions that are going to be examined. Then, for the key questions, what are search strategies are going to be for trying to find out if there are any answers.

It is an interesting discussion and there have been a lot of interesting comments, but I have no way, as a consumer, of assessing whether this is a comprehensive view

of the problem or if this is just based on this group.

I am looking for some kind of transparent methodology that we can go back to our audiences and say, this is how we did our work and this is why we think it is comprehensive.

DR. KABACK: Aren't we try to develop the kind of evidence and data that we would like to have to look at, to evaluate it? That is the first step in the plausibility issue, is the evidence.

We are trying to tell the guys here what kind of evidence do we think might be helpful to look at, to deal with the plausibility question.

DR. BERG: I am sure you are correct. I am a physician and I had trouble following all that Chris was saying, and Kathleen is not a physician and may have equal trouble.

I don't know whether, from that discussion, you have a sense about all the competing biological hypotheses or not.

DR. KABACK: I don't know that every single consumer or every single person on this panel is going to be at the level of Chris in terms of understanding the mechanisms of immunochemistry, nor should that be the goal.

There needs to be some cross fertilization within the group as to whether things are relevant that make sense

or not.

Why don't you tell us what you think we should do in terms of assessing evidence, what we are trying to do here.

We are all searching for a way to move ahead here. We agree with you, we need a good format, a good design and process. My job is to figure out how to do it.

DR. STOTO: Another way to think about this is to think about what is the best way to attack this first problem. What kind of data do we need, how are we going to look at it and so on.

Then, when we come to the point of writing it up, try to say, you know, how can we do this so that we can repeat it, but not try to work it out right now, but try to work it out in the context of doing the analysis of the first one, and bear in mind you are going to have to apply it to different situations.

DR. MC CORMICK: I think, Al, to address your question, we talked about one biological plausibility, which was a direct neurotoxicity or some altered immune response.

I suspect the others are genetic and morphologic, and I don't know enough about what is known about the genetic characteristics of autism or the morphologic brain changes that people are saying to suggest whether there are alternative hypotheses.

I think that we bring people in who can tell us those things.

DR. BERG: That is what I am looking for, whether you have enough advice on who to ask or whether there is some other process, over the next week or so, that people who are expert in this could help you decide what all those should be.

DR. STRATTON: I am actually not worried about that part of it. I think I know enough and I know who everybody is here to nag to get those specific suggestions.

I am actually still a little worried about something that you all are alluding to and are trying to suppress, which is the bigger picture of how, when push comes to shove, we haven't thought a priori how they are going to feed in.

Mike is saying perhaps we don't need to and we are going to do it and then the rules will emerge in some reasonable consistent fashion.

I had envisioned we would be able to come up with possibly that first, and then feed it into, and now I don't know how you all are going to do that synthesis.

I have always felt that each individual piece of what is in front of you is relatively discrete and technically complex, but I think we can grapple with it. I am still worried about how you are going to put it together.

DR. MEDOFF: I thought you were going to put it together.

DR. STRATTON: I will facilitate the getting out of the report, but intellectually, you know, you all have to put it together and come up with some form of synthesis.

What I think you have been trying to urge us and what I am still agonizing over is, I don't know what the rules are for how you are going to end up putting it together.

DR. KABACK: Can I just ask a question that maybe I don't understand? I thought that what we talked about all of today or most of today, one was some way of grading evidence.

We all started with the premise that it is the evidence, we are only going to use published evidence, or essentially that is what we are going to use to evaluate. That was an important decision.

It is the evidence that exists which will, within the framework of these five categories, enable us to make some judgement as to which one of those five categories a given question would fall into.

If I understood this last discussion, we were trying to determine or decide which five categories a given issue falls into. We have to have evidence.

Now, we ask, you know, what kind of evidence do we

need. What kinds of questions do we have to wrestle with. What can you guys help us get our hands on so that we can evaluate the evidence.

My judgement is that right now we are talking about what evidence do we need to evaluate.

DR. MC CORMICK: What she wants you to say is, we will give 10 points to a randomized trial, we will give three points to a strong animal model, we will give two points to biological --

DR. KABACK: That is after we have got all that evidence in our hands.

DR. MC CORMICK: I think that is what she is looking for, is how we are going to --

DR. MEDOFF: If you had that evidence in your hands, would you have wanted it.

DR. KABACK: But part of it probably doesn't exist. I mean, we know that going in, that it doesn't exist.

We are going to get as much of whatever kind of evidence exists in the areas we are talking about, before we can proceed with making any kind of quantitative judgements and assessments.

DR. STRATTON: I know. I think what I am saying is that -- well, it doesn't matter what my struggle is at the moment. I know how to get you the immediate information

and put together the next meeting and I know who to go to for that help.

My point was, I don't know if we are prepared -- I don't know what is going to happen when, at the end of a day and a half next time we meet, you say the clinical data and the epidemiologic data, as it were, lead you to this level of causality and the biologic plausibility is X and the competing hypotheses are Y.

I know how to get you to each of those points and you know how to get yourselves to those points.

What I don't know how you are going to get to -- not what the answer is, at this point, because you haven't heard the data -- but what I don't know is how you are going to get to, so, now what do we recommend CDC do about it, in some --

DR. KABACK: There was another step into it, and that is the concern issue.

DR. STRATTON: There is the concern issue. I think we have some idea. You have given me some ideas on how you are going to do it.

Then at some point, after thinking about all those four issues, you need to say, now what do we recommend that CDC -- now how do we recommend that CDC respond to this.

I think there needs to be some sort of thought process about, what do you do if the clinical data is really

weak but the biologic plausibility is extremely high and that societal impact issue is extremely high. How does that influence what you recommend CDC do. That is just my worry.

DR. JOHNSTON: Kathleen, don't you think there is an infinite variety of answers to that?

What do you do? You end up with something that is subjective at the end and it is based on common sense or something like that, and you cannot proscribe ahead of time, very systematic way, any kind of way, I don't think.

DR. SHAYWITZ: I agree with that, but I do think what we are doing here -- there is a structure here which sometimes it is explicit and sometimes it is implicit.

What you have are empirical findings that support a certain claim. We, just informally and some of us formally, know what some of those empirical findings are.

I have heard about Wakefield. I have heard about the claim about epidemiology. I haven't really heard about any other empirical findings supporting this claim, and this is aside from all the speculations.

For each empirical finding, with its associated claim, you have a series of alternative explanations for that finding.

The pairing of the finding with the claim on one side and the alternative explanations on the other side, each pair suggests a set of evidence that you have to go out

and get.

So, every mechanism that Chris mentioned might -- now, that would only be relevant to explore, I actually think, if we had empirical evidence supportive of the association on the one hand.

I don't know that we necessarily just want to explore potential hypotheses if there is no empirical data to refute.

Then we are in a real fishing expedition. If we have an empirical finding that suggests that multiple antigens, you know, presentation might actually lead to more clinical syndromes, and that data is relevant to this hypothesis, then it suggests a set of data that we need to go out and get to refute that.

What I think we were going through here was, we were sort of informally tossing out the information we thought was there, the empirical data.

Then, for each counter-argument, each alternative explanation, if that alternative explanation immediately suggests a body of information that we need to go out and get, I think in a sense that is the way we are informally structuring it.

We have empirical data, we have the claim, and then we have a series of questions, alternative explanations.

Could this be due to X, and the evidence related to that is this. Could this be due to Y, and then the evidence related to that is, nonexistent. Then we go down the list.

I think that is the way the structure of the argument goes. What we don't have in our hands right now, which makes it difficult to outline specifically is, we don't have all the positive empirical information. I mean, I just know these two pieces.

Because of that, we can't come up with the exhaustive list of all the competing explanations for that. We just began to hear the beginning of that list.

I think that is the structure we are ultimately going to end up with. I think that is something that we can sort of at least conceptualize in the abstract that we will be able to write down on paper.

We will be able to write down each alternative explanation for the data and say whether there is data or not related to that, and we will also be able to talk about the strength of the primary empirical data. I don't know if that addresses the question or not.

DR. MC CORMICK: I think Kathleen's concern is that we haven't articulated a way to weight that there are pieces of data in importance to come up with a conclusion. I am not sure that is not going to be case specific.

DR. SHAYWITZ: I think that is right.

DR. MC CORMICK: If it came up high societal concern, lots of sort of observational data that supported a multiple antigen insult, one recommendation would be a trial with single vaccines.

DR. SHAYWITZ: Perhaps if we can get the data, if it does exist, that Mike was referring to, if there is this interval of time when we only had measles vaccine -- I don't now if utilization was reasonable -- but if we had that data and some reasonable diagnosis that it was semi-reliable during that period of time --

DR. BERG: I do have to comment that, in the business of developing clinical recommendations, the process that you have suggested makes us vulnerable to claims of post hoc reasoning, where we examine the data on a case-by-case basis to figure out how to put it together.

In the business of evidence-based assessments and interventions, some sense at the outset for the process that we are going to use to reach conclusions is important to avoid that claim of post-hoc reasoning.

It is the basis of the Cochran collaboration. It is the basis for the AHCPR, now AHRQ, evidence centers.

DR. MC CORMICK: I think that is when you have enough evidence to argue the point.

DR. GOODMAN: What is implicit there, in all those

settings, is do you have enough information to even start posing the competing hypotheses. The problem is that now we don't even know --

DR. BERG: I disagree. The cochran collaboration examines all kinds of issues that are of a similar nature to what we are talking about.

DR. GOODMAN: They have RTCs already done in those fields.

DR. GATSONIS: I am in the Cochran collaboration. It is a very streamlined operation, at least when it comes to RCTs. Even there, it becomes pedantic. Here we are spanning a variety of types of evidence and so on.

I do agree, however, that some sense of what might weigh more or what might weigh less, generally speaking, would be important.

Somehow, I have heard that around here when it comes to the specific questions, the biologic plausibility, the societal impact.

I mean, for every one of these things, one could enunciate what would drive the inferences.

If you are talking about how to put it together, that is a different story, but we are not talking about putting it together in one number at the end of the day.

DR. STOTO: I think that is the key thing. I think that we have moved away from categories. Almost everything

we think is probably going to be in category four and we are just going to talk about the nature of the evidence.

The public health impact is not categorical and what they do about it is not categorical either.

DR. KABACK: So, instead of picking the questions, they are going to pick all category four or whatever number you give it as the question they start to answer.

So, that question is really already resolved, unless there is new data in the interim since 1994 or 1996, or the last time they came out. It doesn't sound like there is.

DR. JOHNSTON: The other thing just to remember, although we already think we know the answer, that hasn't been done in any way by a body like this.

DR. KABACK: In part, that is kind of what we may wind up doing.

DR. CASEY: We can look at it more specifically. We have here the idea of looking at the epidemiologic prevalence for years for autism rate, 1987 to 1994.

We were giving single measles antigen certainly into the late 1980s. Is that in the 1994 book?

I think that we were giving single measles antigen and we would have to go back and look at vaccine rates. We definitely were into the 1980s, so we will have some data here.

I think my point is that we were doing that, Marie, when those DSM-IV criteria changed. We were still giving the single measles. So, it will help maybe to sort out those variables.

DR. MC CORMICK: If there are studies that talk about prevalence at that time.

DR. SHAYWITZ: I think the key thing is going to be can you find any data that will tell you that prevalence. My suspicion is that it won't.

DR. MC CORMICK: It may be possible to suggest a number of these comparisons where studies could be done that might not be that difficult to do.

DR. WILSON: Just to come back to Steve's point, it seems to me that the epidemiologic data has to be given the highest weight amongst our things.

I think I can assure you that the biological plausibility data is not going to be strong. It is just not going to be.

We are going to have to concoct scenarios and there are two questions. One is, is MMR causally related to autism.

If it is, is that distinct from what measles did alone. We will have even weaker evidence for that as we find out.

If we didn't have that evidence, we wouldn't be

dealing with the other questions very well. Obviously we have Wakefield's case series to deal with which, fundamentally, he has to concoct a biologically plausible thing that is not, a priori, the one that would come first to the minds of many of us.

I do think there is some value to giving some hierarchy as to how we would weight the things in our decision-making process.

If we don't have an epidemiologic link, it doesn't seem to me that we would possibly argue as strongly, based on biological plausibility data, to elevate the rank to its highest.

If I were having to set a list of priorities, now, to respond to Al's question, I would clearly agree that we would define the epidemiologic data as being our most robust data sets.

I think we should be very thorough in trying to get that information as good as we possibly can. At least there we sort of have a case control kind of method and there we certainly have a temporal linkage method.

We have some additional data to provide, I think, a firmer foundation for whatever hazy recommendation we make. That would be my plea, to put that as category one.

DR. GATSONIS: I wanted to make the point. We talked about bringing Wakefield in and basic scientists and

kid got a shot. Within six hours, they were staring into space.

That is a very compelling story and we have to be able to figure out how to deal with stories like that, or whether they are actually, you know, prima facie evidence of something.

DR. WILSON: That would help us with trying to come up with biological plausibility. If, in fact, you said MMR, six hours later you got disease, that is almost certainly not due to a viral injury, because there is no replication of virus of substance within the first six hours.

It would be very fast. It would almost certainly have to be mediated, in fact, by antibody to give you a response six hours later.

Even if it was immunologically medicated, mediated by T cells, it is going to take more than six hours. So, if you narrow it down to six hours, boy, the mechanisms just shrink down real quick.

In fact, most of Wakefields were what, a week, two weeks, sometimes longer. Yes, we would like to know what the time window is of those cases. That would be very useful, if we had that. That would probably be the single-most valuable piece of data.

DR. MC CORMICK: From VAERS.

DR. GOODMAN: Also, just the distribution through early childhood.

DR. MC CORMICK: Age at the time of MMR, 18, 24 and 36 months.

DR. WILSON: And did they get DPT at the same time.

DR. GOODMAN: Even within that time period, if you had some kind of time series data you would see this almost discontinuity at that moment as opposed to a sort of smooth curve where you could predict that five percent of all diagnosed cases would be within a week. I don't know.

DR. WILSON: Recognition can be dramatically delayed for most of these. Some of these, clearly, there is this quick time frame in the Wakefield study.

DR. JOHNSTON: There is another element of time which still might be used. It is now appreciated that autism begins in the first year of life in some babies.

You can get a sense of whether that diagnosis is going up.

DR. GOODMAN: Prior to MMR.

DR. JOHNSTON: Right, before or after.

DR. WILSON: If it is going up in direct proportion to that, though, that would be a useful piece of information.

DR. MC CORMICK: It probably is not. I think that

recognition is probably within the last two years. It really involves taking known autistic children and the capacity now of videotaping and you can go back and see that there are very subtle signs of disengagement before the diagnosis is made.

I mean, it is a piece of evidence that this is a preexisting condition prior to the MMR.

DR. KABACK: How about sibship data. I haven't seen that. Is there data on sibs?

DR. SHAYWITZ: It is very rare.

DR. KABACK: I know it is very rare, but I would be interested in knowing if anybody has ever looked systematically at sibship data and extended family, both for autism or anything like it, and anything that might relate to things like inflammatory bowel disease, if you have seen it since universal MMR in the last 10 years or whatever.

DR. MC CORMICK: I have no idea about inflammatory bowel disease. There are sibship studies. I know that, because both my brother's kids are affected, Barbara Bauman is very interested in it. I know there are people who are looking at it.

I know there is at least one study that has used sort of a questionnaire about social connectedness that has shown that apparently normal siblings and parents of kids with autism, their close relatives, have fewer social

connections.

So, there appears to be a spectrum of social connectedness that may be genetically driven. I don't know any more of the data than that.

DR. JOHNSTON: There it polymorphisms, just within the last month reported. Those were families, obviously.

DR. KABACK: A sib pair analysis is what I was kind of thinking toward there. That can be a fairly powerful way for establishing linkages, genetic linkages now with the probes that are available. I have never seen that in the literature.

DR. SHAYWITZ: I think there is a study in progress. Who is the group at Duke?

DR. MC CORMICK: I think this is something we can ask NIH because they have a $30 million data bank of what is being done. That could include some of the alternative hypotheses and alternative arguments that they are pursuing.

DR. KABACK: That would really be good information to have.

DR. GOODMAN: Related to that, it would be interesting to know if there -- there was this claim that there is this genetic relationship of susceptibility to reactions, and that the susceptibility to reactions correlated with the outcomes.

We would like to see if there is any evidence of

familial clustering of vaccine reactions and then, similarly, clustering of autism. I guess we know that there is not a clustering of autism.

DR. MC CORMICK: We know there is a clustering of vaccine reactivity. The intersection set is so rare that I think you are going to have trouble with it.

DR. GOODMAN: Still, that is data that bears on that hypothesis. That was a very powerful part of her argument, that there are susceptible subpopulations of vaccine reactions. So, I would like to see the data on that point.

DR. JOHNSTON: That would be good to have just across the board.

DR. GOODMAN: Yes.

DR. JOHNSTON: If there are such data.

DR. KABACK: See, that is the kind of data that you would get from the Finnish and Scandinavian data bases, who have been using universal MMR.

You can, in their computer tomorrow, track reactions to vaccines and sibling reactions to vaccines. That is why I keep coming back to the Scandinavians.

The Danes and the Norwegians have been used many times in genetics for really clearing up a question of genetic predisposition issues.

Then you can track with DNA genotyping and try to

zero in on what are the susceptibility genes or the predisposing genes for those kinds of problems. Ultimately, that would be the way to go with these kinds of stories.

DR. CASEY: I was really susceptible of this. We will all look at it the next time where we can make copies. This is what Chris found at lunch time.

They claim that they went through and obtained detailed case histories, vaccines, clinical charts were reviewed.

In this abstract, they are just talking about neurologic events and it has febrile and dah, dah, dah, dah.

If they went chart by chart, you would think they really would have picked up autism. I mean, the are not reporting anything on that.

DR. WILSON: They specifically say that they did not find an association with autism in this study. That is a firm conclusion of their study.

DR. CASEY: This is for 1.8 million individuals.

DR. KABACK: It is a very homogeneous genetic population.

DR. WILSON: This is from Finland.

DR. CASEY: If they really went chart by chart, that is impressive. At first I thought, oh, you know, people just under-reported autism.

DR. WILSON: Contained in it, they said the

previous reference actually looked only at the autism question because this Wakefield paper had just come out, and they refer to that.

DR. STOTO: Going back to the familial thing, Bob Chen described this large linked data base, based on HMO data, because people enrolled, families. It may be possible to look at those data.

DR. SHAYWITZ: Except Chris pointed out that it is very hard for us to look at the data base.

DR. WILSON: It is raw right now.

DR. STOTO: I am not saying that this committee look at it, but it is a suggestion for research.

DR. WILSON: They know. They know that.

DR. GATSONIS: My understanding is that they have looked at some of that.

DR. WILSON: The CDC people have?

DR. GATSONIS: The VSD. My understanding is that they have looked at that.

DR. MEDOFF: They have looked at it. They have looked at more subtle neurologic outcomes than that.

DR. GATSONIS: It is based on claims data, so you have to be careful about that.

DR. WILSON: It is not based on claims data.

DR. GATSONIS: The HMO data is. It is automatic data, basically.

DR. MC CORMICK: It is a visit by visit. They do have problem lists. They can link it into pharmacy lists and things of that sort. It is still a medical claims data base.

DR. GOODMAN: Right, it is not prospective. They are just collecting data that comes in from whoever walks into their doctors' offices.

DR. MC CORMICK: In a claims format, which means it is limited data.

DR. GOODMAN: What might be helpful is to go through like Fisher's presentation and analyze it for each implicit claim that a hypothesis is being proposed there.

Some of them might not want to be considered but there are lots of hypotheses about linked reactions. You are shaking your head.

DR. CASEY: There are some very real concerns clinically with her presentation of just her one child, seriously. You know that.

DR. GOODMAN: There are things that are implicit in these kinds of presentations which we may not take seriously but others which we might address. It is all sort of embedded in there.

As we bring out each sort of claim or each observation, we find ourselves thinking of different bodies of evidence and different ways to address it.

I focus on hers only partially because of who she

is but also she presents it in a very compelling way. You can rebut it in a very compelling way by taking it piece by piece, sort of teasing out susceptible vaccine reactions, genetic sensitivity, et cetera, et cetera.

There is an argument in there that is embedded inside the rhetoric that might be of some value to parse out and take pieces of and make sure that we address it in its pieces, because it has power.

DR. STRATTON: That will be important, I think, in terms of whether or not -- to think about that, whether or not, when we put forward the report, is it in any way responsive to quelling some of her issues, not for scientific value so much as whether what we do is communicable and helpful in addressing some of these issues.

DR. SHAYWITZ: Even if we are very clear and address each of these concerns, will they take them. I mean, all of us have gone to school have heard every kind of cockamamie --

DR. MC CORMICK: They make the flu virus look stable.

DR. STRATTON: We will, as quickly as possible, meaning in the next couple of days, do a few things. One is, nail down a date.

Right now you should hold, for those of you who had it open, the 8th and 9th of March.

We will try to summarize what we believe the decisions made today were, and get it out to you all for comment.

Simultaneously, we will start dissecting every single one of these ideas, specifically for the autism workshop.

DR. MC CORMICK: I think we are adjourned.

[Whereupon, at 2:55 p.m., the meeting was adjourned.]