UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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OPEN SESSION

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Thursday, May 11, 2000

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The meeting took place in the Kennedy Room, Holiday Inn, 8777 Georgia Avenue, Silver Spring, Maryland, at 9:15 a.m., Dr. Harry Greenberg, Chairman, presiding.

PRESENT:

DR. HARRY GREENBERG, Chairman

NANCY CHERRY, Executive Secretary

DR. ROBERT S. DAUM, Member

DR. ALICE S. HUANG, Member

DR. STEVE KOHL, Member

DR. KWANG SIK KIM, Member

PRESENT (Continued):

DR. DIANE E. GRIFFIN, Member

BARBARA LOE FISHER, Member

DR. WALTER L. FAGGETT, Member

DR. DIXIE E. SNIDER, JR., Member

DR. DAVID S. STEPHENS, Member

DR. BARUCH BRODY, Temp. Voting Member

DR. THOMAS FLEMING, Temp. Voting Member

DR. NORMAN FOST, Temp. Voting Member

DR. JOEL VERTER, Temp. Voting Member

DR. WILLIAM EGAN, FDA Representative

DR. KATHRYN CARBONE, FDA Representative

DR. C.D. ATREYA, FDA Representative

DR. WILLIAM SHIELS, Invited Participant

DR. MELINDA WHARTON, Invited Participant

DR. RODNEY WILLOUGHBY, Invited Participant

PUBLIC COMMENT:

SALLIE BERNARD

TERESA BINSTOCK

ALBERT ENAYATI

DR. BRUCE INNES

DR. A.C. KAPIKIAN

DR. DAVID MORENS

C-O-N-T-E-N-T-S

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

(9:14 a.m.)

CHAIRMAN GREENBERG: Good morning. I'd like to welcome all of you to the May 11th and 12th meeting of the VRBPAC Committee.

We have an interesting agenda today, and I'd like to in a relatively new venue -- I hope all of you had less trouble getting here than I did, and as I said earlier for those, I arrived at two in the morning, and so if I fall asleep during a presentation, it's not the presenter's fault. It's just sleep deprivation.

Dixie, you look like you would say the same thing.

Okay. Nancy, do we have any housekeeping?

MS. CHERRY: I do. I have the standard statement to read in a moment.

CHAIRMAN GREENBERG: Do I have your statement?

MS. CHERRY: No, I don't think so. It was lying here a moment ago though.

But while I'm finding the conflict of interest statement, I do want to make a couple of announcements.

First of all, if you look at your

schedule, you will see that we did not plan a morning coffee break, and that's because we're trying to get as much actual working time in as possible. So we'll just ask that when you feel like you can't go on another moment without a cup of coffee, that you just go out and get your cup of coffee. There won't be a formal break unless Dr. Greenberg thinks the meeting is going on so well that we can afford to take that time.

CHAIRMAN GREENBERG: No, I like --

(Laughter.)

CHAIRMAN GREENBERG: I like the idea of just gritting it out.

MS. CHERRY: Okay, and also we do have a late lunch. So let me call that to your attention. When you're getting the coffee, you might want to get something to tide you over until one o'clock.

The second announcement is if you would please turn your cell phones off and put your pagers in silent mode so that we do not have a little symphony of buzzers and beepers going off.

And I think then I'll just go ahead and read the meeting statement.

The following announcement addresses conflict of interest issues associated with the

meeting of the Vaccines and Related Biological Products Advisory Committee on May 11th and 12th, the year 2000, for the discussion of the update of vaccines for the prevention of rotavirus and the development of a policy regarding use of types of neoplastic cells, the substrates for vaccine manufacture.

Of our standing committee members, Dr. Mary Estes could not be with us today, and I would like to comment that since earlier this morning I am pleased to see that our other two members were able to get here, Dr. Snider and Dr. Huang. And welcome especially to you. We didn't get to say that earlier.

The Director of the Center for Biologics Evaluation and Research has appointed Dr. Baruch Brody, Thomas Fleming, Norman -- by the way, it looks like maybe Dr. Fleming is having difficulty -- Norman Fost and Joel Verter as temporary voting members for today's discussion on rotavirus vaccines and associated intussusception.

In addition, we are joined by Drs. William Shiels, Rodney Willoughby, and Melinda Wharton, who were invited to join us today as consultants.

For tomorrow's discussion on use of neoplastic cells as substrates for vaccine

manufacture, the Director has appointed Drs. Donald Blair, Philip Minor, and Sidney Wolfe as temporary voting members.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all financial interests reported by meeting participants. As a result of this review, the following disclosures are being made.

In accordance with 18 USC 208, Drs. Griffin, Fleming and Kohl have been granted waivers, which permit them to participate in the committee discussions on rotavirus.

Dr. Norman Fost disclosed a potential conflict of interest which was deemed by FDA as not requiring a waiver, but does suggest an appearance of a conflict of interest.

A written appearance determination under 2635.502 of the Standards of Ethical Conduct has been granted to permit him to participate fully in this discussion.

Dr. Harry Greenberg has recused himself from the rotavirus discussion.

For the discussions related to cell substrates for vaccine manufacture, Drs. Greenberg, Griffin, Huang, Kohl and Blair have been granted

waivers, which permit them to participate fully in the discussion.

Dr. Stephens disclosed a potential conflict of interest which was deemed by FDA as not requiring a waiver. A written appearance determination was granted to permit him to participate fully in that session.

Dr. Robert Daum has recused himself from the cell substrate discussions.

In the event that the discussions involve specific products or firms that are not on this agenda and for which FDA's participants have a financial interest, participants are reminded of the need to exclude themselves from the discussions. Their recusal will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you state your name and affiliation and any current or previous financial involvement with any firm whose products you wish to comment on.

Copies of all waivers and appearance determinations addressed in this announcement that I'm reading are available by written request under the Freedom of Information Act.

And that's my part of the meeting.

CHAIRMAN GREENBERG: As usually, brilliantly done, Nancy.

I would like to now move on to start the meeting, and we did this in the closed session, but I'd like to repeat it. Could the members of the committee, starting with you, Dr. Daum, just introduce themselves to the public and for the record?

DR. DAUM: I'm Robert Daum from the University of Chicago.

DR. STEPHENS: I'm David Stephens from Emory University in Atlanta.

DR. KOHL: Steve Kohl, Oregon Health Science University.

DR. SNIDER: Dixie Snider, Centers for Disease Control and Prevention.

DR. HUANG: Alice Huang, California Institute of Technology.

DR. FAGGETT: Walter Faggett, Washington, D.C.

DR. GRIFFIN: Diane Griffin, Johns Hopkins.

DR. KIM: Kwang Sik Kim from Children's Hospital, Los Angeles.

MS. FISHER: Barbara Loe Fisher, National Vaccine Information Center.

CHAIRMAN GREENBERG: Harry Greenberg, Stanford University and the Palo Alto VA Hospital.

DR. BRODY: Baruch Brody, Baylor College of Medicine.

DR. FOST: Norm Fost, University of Wisconsin.

DR. VERTER: Joel Verter, George Washington University.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention.

DR. WILLOUGHBY: Rodney Willoughby, Johns Hopkins University.

CHAIRMAN GREENBERG: There's a little button there that if you push -- there you go.

DR. SHIELS: Bill Shiels, Children's Hospital, Columbus, Ohio.

CHAIRMAN GREENBERG: And I would suggest that most of you realize this. After you've talked if you turn off your microphone, things will work better.

So I'd now like to proceed with a bunch of updates of FDA activities that Dr. Bill Egan is going to tell us about.

DR. EGAN: Good morning. I would just like to take a few minutes this morning to update the committees and others here on several areas of current

interest and concern to FDA and to the vaccines community. The areas that I'm going to talk about are just listed on the first overhead, and I'd just like to say a few words about the ongoing saga of SV-40 and oral polio vaccine, a few words about thimerosal and vaccines, aluminum and vaccines, congressional hearings on autism, and bioterrorism and counter-bioterrorism activities within the Office of Vaccines.

These issues are primarily related to vaccine safety. This has been an ongoing theme over the past year, safety concerns related to vaccines.

Let me first talk about SV-40. There continue to be a number of reports on the isolation of SV-40 in a variety of human tumors, particularly mesotheliomas, osteosarcomas and others, and I think that there's little doubt at this time that SV-40 is actually being isolated from these tumors. These are not laboratory contaminants.

The key question, however, is whether or not this association is causal for these tumors or is a co-factor in these tumors or whether it's coincidental.

And there is additionally the over arching question: how did SV-40 get into the human population? Did it get into the population from the

oral polio vaccines or the polio vaccines, primarily IPV in this country, or did its presence in the population predate the vaccine?

Also, how prevalent is SV-40 in the population, and how is it maintained, transmitted in the population? There are all questions that need to be addressed, and that we within the Office of Vaccines have been discussing and addressing to a limited extent.

I'd like to concentrate now on two specific articles that address this issue of OPV and SV-40, and I'll come to my reasons in that in a moment. The first article is from or was from the February issue of the Atlantic Monthly, and it was an article that was written by Debbie Bookchin and Jim Schumacher. It's actually a very well written overview of the SV-40 tumor issue.

And I mention the article for two reasons: one, that it's in the popular press and, you know, has been widely read, but also because it raises the possibility that SV-40 could have been the oral polio vaccine that was used during the '60s, '70s, '80s, and even the '90s.

And more specifically, the basis for raising the question in this article relates or

derives from an article that was published by Michele Carbone and his associates in cancer research in December of '99, and at issue or one of the issues is the ability of the test that are done for screening polio vaccines for SV-40 to detect all variants of SV-40.

And the variant strains that I'm referring to and that are mentioned in the article are strains that differ in the number of copies of a 72 base promoter sequence that's in the SV-40 genome.

By way of nomenclature, these two variants are referred to archetypal strains, which have a single 72 base enhancer region and non-archetypal strains, which have partial or complete duplication of this 72 base enhancer, and the strains with the single enhancer at least in certain cell cultures are slower growing, and that's the point, that the two variants differ in their rate of growth in cells.

And what Dr. Carbone found, reported in this paper, with the presence of archetypal strains, that is, strains having the single base enhancer in isolates of IPV from -- he got old samples of IPV from the 1950s, a Parke Davis sample, and found these strains -- found evidence for SV-40 with the single enhancer, and this would have been a slower growing

variant.

And in additional studies he looked at the growth rate of an SV-40 strain with a single base per enhancer relative to one with two copies of the enhancer using TC-7 cells.

And basically noted at low doses that he was not able to see vacuolization in these cells or lysis of the cells, you know, on day 14, but rather needed to wait until day 19 to see these.

If I could have the next slide.

And what he reported in his paper was that, I quote, "Our finding of archetypal SV-40 in these lots raised questions regarding the safety of the current polio vaccines," and referring specifically to the OPV vaccines.

And one of the questions that I had raised right in the beginning was how is SV-40 maintained in the population, and this would raise the question that one way is that there were very low amounts of SV-40 in the OPV vaccine that was undetected by the current methods because there were cycles of 14 days.

Now, unfortunately Dr. Carbone did not test using the current OPV protocols. For example, with current OPV vaccine testing is done using African green monkey cells, rhesus monkey kidney cells, rabbit

cells, and BSC 1 cells. It's an African green monkey derived cell line.

There are four different cell lines. There is multiple testing of these vaccines, and the control tests are done. The control tests, the control cells are tested on two 14-day cycles following 13 days of growth. So it's a very different protocol than was reported in his paper using a different set of cells.

Now, as growth characteristics of these variants are not absolute, but rather depend on the cell substrate, and I think this is an important consideration and what will need to be done is to go back and test these strains side by side on this TC-7 cell line or to take the current cell lines that are used for testing and test the two variants concurrently in this.

But also there were additional studies that were done that are not reported in this paper, and one of the things that was asked for in the paper is that more modern techniques be used to look at these vaccines.

And I'd like to mention two. One, and this was reported several years ago, but Phil Minor and his colleagues at the National Institute for

Biological Standardization and Controls in the U.K. did examine some 190 batches of oral polio vaccine spanning the years 1971 to 1996 by PCR techniques, and all samples were negative by PCR, these 190 samples.

And OPV, samples of OPV were also examined; archived samples of OPV were examined in our own laboratory, and specifically both bulk monovalent lots -- and here there were 30 bulks -- and final containers, another 30 lots of trivalents were studied, and these vaccine span the time frame from 1972 to 1996, and no SV-40 sequences were found by PCR in any of these samples. All of the bulks and monovalents were negative.

Do you have the next slide?

And the first study that I mentioned by Phil Minor is the developments in biological standardization referenced from 1998, and the one on the monovalent bulks and trivalent final fills were done by Drs. Honigman and Krause in our laboratories and have just recently been published in biologicals.

There are two advantages to using the bulks, the monovalent bulks. One, the test becomes more sensitive, the PCR methods, more sensitive using the bulks, and the bulks go into many fills. So the bulks go between ten and 75 bills, different final

fills. So testing one bulk is the equivalent to testing a very large number of final fills.

And again, I'd like to stress that all samples that were tested were negative. So I don't believe that oral polio vaccine at least in this country could account for the continued appearance of the virus.

Nancy, next.

Okay. Just a very brief update on these other topics. To come back to the thimerosal, I'm happy to say that quite recently, at the end of April, FDA approved the licensing of SmithKline Beecham Biologicals Enterix B vaccine. This is the hepatitis vaccine, and then this is a reduced thimerosal vaccine. The amount of residual, there's only trace amounts of thimerosal in the vaccine, less than one microgram of thimerosal per dose.

And as the committee is aware, a thimerosal free presentation, Merck's Recomboivax HB, was approved by FDA last summer. So both Hepatitis B vaccines for the childhood immunization are now available in thimerosal free or reduced versions.

At the moment, I think the emphasis needs to be placed on having additional DTaP vaccines that are thimerosal free, having these presentations

available.

At the moment, the only DTaP vaccine that is thimerosal free is the SmithKline Beecham biologicals Infanrix.

Let me just turn to aluminum. There has been a lot of concern in the past year about mercury and thimerosal levels in vaccines, and there are similar concerns that people have raised about aluminum. Aluminum ions are neurotoxic.

And at the moment, today and tomorrow, a workshop is being held in San Juan, Puerto Rico, to discuss aluminum and vaccines, and this is a workshop that's similar in agenda content to the workshop that we held last summer on thimerosal.

It's unfortunate that the aluminum meeting is being held concurrent with this Advisory Committee meeting, particularly as I was invited to go down to talk at the meeting, and although I like Silver Spring, a trip to San Juan would have been nicer.

CHAIRMAN GREENBERG: Why are we here?

(Laughter.)

DR. EGAN: Because we are dedicated servants of the public health.

And so at this meeting there will be a lot of discussion on the pharmacology and toxicology of

aluminum, and I think one of the things that aluminum, like thimerosal, we have to consider is dose. Everything is relative to amounts, and we will update the committee on the outcome of this meeting at the next opportunity.

Now, let me turn to autism and congressional hearings. A month or so ago Representative Dan Burton of Indiana held hearings on autism that focused primarily on links or potential links between autism and vaccines. The emphasis of that meeting was primarily on the MMR vaccine and its potential link to autism, and this was, in essence, a follow-up to many of the studies that had been published, were begun by Andrew Wakefield in the U.K. and others.

The committee at the end requested that there be an evaluation of the existing data on vaccines and autism to be conducted jointly by the Public Health Service agencies, CDC, NIH, FDA. So that's where that issue is at the moment..

And finally, just to come back to bioterrorism, counter-bioterrorism, the Center for Biologics received recently from the department $7 million to initiate programs in small pox and anthrax research designed to facilitate the development of new

and improved vaccines for these agents. A good portion of that money went to the Office of Vaccines.

The programs are now beginning to be developed, and we'll have more to say about them in the future, and we'll come back to the committee with what is being done and what is being accomplished with regard to those important vaccines.

That's the end of my update.

CHAIRMAN GREENBERG: Thank you, Bill. I'm sure there are a few questions that you maybe you can answer.

Can I just start off and ask you just for my information? While I keep hearing about new vaccines for smallpox for bioterrorism, I just wonder what the status is of the old vaccine, which at least worked, and is there some sort of feeling about do we have enough old vaccine before we get the new vaccine?

DR. EGAN: Yeah, the old vaccine did work. There was no question about that. Smallpox has been eradicated in the world. The question there is the limited number of doses. You know, it's in the tens of millions rather than the hundreds of millions that might be needed, and there are a number of issues that are related to the vaccine or new vaccines, but certainly one that I think we all can appreciate is

that even if the vaccine strain were the same that was used or that is stockpiled, nobody is going to be producing the vaccine the way it had been produced, which was, you know, scraping lymph off the hides of calves.

So I think any new vaccines would be tissue culture derived. Maybe Dr. Snider would like to say a few more words. He's been much more involved in this area.

DR. SNIDER: Well, I was just going to suggest, Bill, rather than take up time at this meeting that we do a joint presentation because CDC got a substantial amount of money both to work with the current vaccines around safety and efficacy issues, as well as working on new vaccines, and I think you would find it interesting to get that kind of an update. And perhaps we could do a joint presentation.

DR. EGAN: No, I think that would be a very interesting presentation. I just wanted to mention at this point that the center did receive some funding to start some programs.

CHAIRMAN GREENBERG: Thank you, Dixie. I actually think it is an important area, and maybe you can get that on the agenda.

And I think there is still room for thought about how to go forward on it, and this committee hasn't really done that.

Any other questions? Walter.

DR. FAGGETT: Thank you, Dr. Egan, for a very clear update.

The question relative to PCR screening for SV-40, the question is the level of sensitivity. You seem to imply that you're very comfortable that even very small particles would have been picked up.

And the second part of that question: are there other tests other than PCR that would be available if there's any concern about smaller particles?

DR. EGAN: Well, it was the number of particles that could be picked up, and from Dr. Krause's study, he was estimating that he was able to detect between one and ten copies per does.

CHAIRMAN GREENBERG: Dr. Huang.

DR. HUANG: Relative to SV-40, again, do you know what the immune status is in the population of the United States to SV-40?

DR. EGAN: No, I don't know what it is now, and I don't know what it was in 1950. One of the things that we have been doing in our lab is trying

to, with others from NCI and the U.K., see if we could develop serum, antiserum that was specific for SV-40 as opposed to JC and BK virus, and if we could do some surveys of current and past archive serum samples.

When people have done it, they've found prevalences on the order of five percent or so.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: These may be naive questions, but humor me.

SV-40 is not inactivated by the procedure that inactivates polio?

DR. EGAN: Okay. Let me go back to two vaccines, IPV, the original Salk vaccine in the 1950s. Yes, SV-40 is inactivated by formalin, but under the conditions under which the polio vaccine was produced, not all of the SV-40 was inactivated. There was approximately 0.1 percent that was not inactivated, and this is the original study by Hilleman and Sweat and repeated by other.

Now, whether that fraction of material that was inactivated was due to small aggregates that may have been present and just formalin wasn't getting to, you know, which was then taken care of by an additional filtration process, or some other reasons, you know, we don't know. Dr. Hilleman thought that

there were two populations, two confirmations of DNA within SV-40, that there was some kind of an equilibrium, and with there being a small population that was not susceptible to inactivation with formalin.

But whether that was the answer or simply the aggregates, we don't know. So there definitely was SV-40 present in the IPV.

Before OPV was licensed and put on the market, the SV-40 had been detected, and so it was required to remove that. So the seeds were -- the IVP, the polio virus was propagated with antisera against SV-40, and then those used for production.

So the OPV had no detectable SV-40 by the CPV testing that was done,a nd it was this testimony, however, that was called into question by Dr. Carbone, whether it was sensitive enough, and we feel that it is.

DR. KOHL: So Carbone's paper finding SV-40 and old IPV lots is basically a confirmation of Hilleman's work; is that right?

DR. EGAN: Well, I mean everybody --

DR. KOHL: Right. Knows that.

DR. EGAN: -- knew that SV-40 was present in the IPV.

DR. KOHL: Okay.

DR. EGAN: It may not have been in all lots of vaccines, and the concentration would have been varying, but --

DR. KOHL: And I presume it's not present in current lots of IPV.

DR. EGAN: That's correct, yes, and I'm one of those recipients of this Salk polio vaccine from the '50s. So I guess I could titer my own serum for SV-40.

DR. KOHL: I was in the double blind placebo controlled trial in 1954.

DR. EGAN: Okay.

CHAIRMAN GREENBERG: Other questions? Ms. Fisher.

MS. FISHER: But it is conceivable that the current tests used may not be sensitive enough to screen for all adventitious agents or their derivatives, right? I mean, isn't that conceivable?

DR. EGAN: I mean, well, first of all, that's a very difficult question. Let me try and address it.

I mean, first of all, OPV is not being used anymore. It's all IPV.

Secondly is you want to ask is it

conceivable that the tissue culture screening test which looks for, you know, CPE in vacuolization is not sensitive enough. I think what we have to talk about a little bit is what does sensitive enough mean. There's going to be limitations on every test that we do.

I mean, we could never get to the point where we could have, you know, a gallon of OPV and look for one viral particle in it without testing the entire gallon. In this case you would have no vaccine.

MS. FISHER: Unless you used another production method.

DR. EGAN: Well, I mean, I think we would still have the same questions. What needs to be done following Dr. Carbone's paper is to take those two variants and go side by side through the two testing procedures. We have gone back and looked at many bulk and final fill lots by PCR, which you know we have demonstrated is sensitive to in the range of, you know, one to ten viral particles per does, and every single one of them have been free.

So, I mean, you start off, you know, when this was done with the monkeys that are in closed colonies, are SV-40 free, you know, serologically.

They're tested for antibodies. They've got to be negative, and then there's multiple testing, you know, on those production cells, but you know, we can always argue about that final viral particle. So what is sensitive enough?

But what remains to be done from Dr. Carbone's paper is to look at the two side by side. Now, these sequences with the single enhance, that is what is normally in the monkey cells, and this is, you know, the virus that the original tests were developed to detect.

CHAIRMAN GREENBERG: Are there any --

DR. EGAN: Not a laboratory adapted strain.

CHAIRMAN GREENBERG: Are there any other questions?

(No response.)

CHAIRMAN GREENBERG: If not, Bill, I'd like to thank you for that update, and now I would like to move on to session number three, which is open public hearing.

Excuse me. I'm moving on to the open public hearing, and we have three speakers on autism. Are the speakers in the audience? The first speaker I have here is Sallie Bernard.

MS. BERNARD: Yes, I am.

CHAIRMAN GREENBERG: Could you -- I guess there's a microphone, Ms. Bernard --

MS. CHERRY: There's one there.

CHAIRMAN GREENBERG: -- to your left now.

MS. CHERRY: Or the lectern.

CHAIRMAN GREENBERG: Or would you rather come up to the front? Whichever is more convenient.

MS. BERNARD: That's fine, as long as it works.

Okay. Good morning. My name is Sallie Bernard, and I live in New Jersey. I run a market research company and am a board member of the Cure Autism Now Foundation. I'm also the parent of a 12 year old son with autism and am here to speak to you today as a parent.

Autism is a severe neural developmental disorder which, according to the latest CDC figures, may now be affecting as many as one in 150 children. The incidence of autism appears to be rising and, as such, represents a significant public health issue.

Due to the high likelihood that many, if not most cases of autism are caused by the mercury in childhood vaccines containing thimerosal, and due to the fact that every child today can be fully

vaccinated using a thimerosal free product, I am asking you to join me in urging the FDA to call for an immediate ban on thimerosal containing childhood vaccines.

In July of 1999, when the FDA first released preliminary statements that the amount of mercury injected to infants and toddlers through childhood immunizations exceeded government safety levels, a few parents, including myself, began to investigate whether mercury toxicity might be a contributing factor in our children's autism.

Our review of the available medical literature summarized in a report, "Autism and a Unique Type of Mercury Poisoning," found that the symptoms and abnormalities that characterize autism are identical to those found in past cases of mercury poisoning. These similarities include the defining characteristics of autism: social withdrawal, OCD behaviors, and loss of or impairment in language, and they include traits strongly associated with autism and found in nearly all cases of the disorder: sensory disturbances, motor disorders like toe walking, hand flapping, clumsiness, and choreiform movements and cognitive impairments in specific domains like short term verbal and auditory memory and

an understanding of abstract ideas.

The biochemical abnormalities in autism and mercury poisoning are similar as well. These include damage to the same brain areas as the Purkinje cells, granule layer, amygdala, and hippocampus; autonomic system disturbances like abnormal sweating, increased heart rate, and poor circulation; immune system dysfunction; altered neurochemistry in the areas of serotonin, dopamine, norepinephrine, and others; and EEG abnormalities of the same patterns.

These are just a fraction of the similarities which we have identified from the medical literature.

The population characteristics are consistent in both orders. First, the prevalence rate of autism closely matches the introduction and spread of thimerosal containing vaccines. Autism was first discovered in the early 1940s among children born in the 1930s. Thimerosal was first introduced into vaccines in the 1930s.

Prior to 1970, autism was estimated to be occurring in one in 2,000 children. After 1970, studies showed a higher prevalence of one in 1,000. This was also a period of increased immunization of American children.

In 1996, the NIH estimated the rate of autism to be one in 500, and just recently as I said before, the CDC has found it to be one in 150 children. This dramatic increase coincided with the introduction and spread of two thimerosal containing vaccines, the Hib and Hepatitis B.

Second, mercury is more toxic to males. Autism is more prevalent among boys, with a ratio estimated at four to one.

Third, low doses of mercury adversely affects only genetically susceptible individuals, which are defined in terms of high responders and those prone to auto immune disease. Autism has been recognized as one of the most heritable of all neurological disorders and is strongly associated with familial autoimmune disorders.

Fourth, exposure to mercury in vaccines occurs at the same time as autistic symptoms emerge, given the latent period common in mercury poisoning. Symptom emergence is similar in both diseases, starting with abnormal movement in sensation and moving on to abnormalities in speech and hearing, and in the full blown array of symptoms and signs.

Our group has also documented a number of cases of autistic children with toxic levels of

mercury in hair, urine, and blood. The breadth and specificity of these similarities from defining and associated traits to biological abnormalities and population characteristics, as well as the timing of onset with exposure and the case studies of autistic children with toxic mercury levels strongly suggests a causal relationship rather than one arising from mere chance.

Despite the fact that there have been no published studies on the effect of bolus doses of injected ethylmercury on susceptible infants and toddlers, some individuals have nevertheless concluded that the amount of mercury in vaccines is too low to cause any real impairment.

On the contrary, we have outlined four rationales describing how the mercury levels in vaccines would lead to significant harm in a small number of children.

First, the cumulative amount of mercury which a six month old infant can receive exceeds the acceptable dose levels set by government agencies, including the EPA. Some have countered that since the EPA added a safety factor of ten, the risk of harm is insignificant.

However, if you actually read the EPA

report, it clearly states that the safety factor was added, one, to account for uncertainties of possible inaccuracies in the calculation and (b) to protect sensitive groups.

By exceeding the guidelines, these sensitive groups are at real risk and arbitrarily ignoring the safety guidelines merely because it is inconvenient to follow them violates sound medical practice.

Second, the EPA equation, which uses data of fetal toxicity from 81 mother/infant pairs poisoned by methylmercury in seed grain, is based on factors which would result in a lower relative risk than those involved in an infant vaccine exposure scenario. Higher risk factors include bolus doses versus chronic daily doses, injected versus ingested delivery, ethylmercury toxicity versus methylmercury toxicity, direct exposure to the infant versus indirect to the fetus through the mother, lack of adequate excretion by infants resulting in high brain mercury accumulation versus adequate maternal excretion and relatively lower brain accumulations in mother and fetus, more rapid metabolism in infants resulting in greater conversion of ethylmercury to its toxic inorganic form versus slower metabolism in the

mothers, and the involvement of mercury sensitive individuals rather than the average person.

Third, the population distribution for mercury sensitivity, like that for all toxins or most toxins, is log normal following a normal distribution. Thus, statistically a small percentage of the exposed population if large enough will be impaired at the lowest doses. The fact that some groups will be impaired at a very lose dose is not just theoretical. It has been found true for certain strains of mice and rats, and it is also true for the form of mercury poisoning called acrodynia, or pink disease, which impaired approximately one in 500 children earlier in this century even at low doses and has been described as being independent of dose and arising more from age and individual sensitivity.

And finally, the risk assessment for vaccines does not take into consideration that infants may receive mercury from maternal sources, including maternal dental fillings and Rhogam shots each of which contain 30 micrograms of ethylmercury themselves.

Thimerosal is not a necessary component of vaccines, and every child can be fully immunized today with a non-thimerosal alternative. Immense harm has

been caused by thimerosal in childhood vaccines.

Do not risk neurological damage to another child by allowing the continued use of thimerosal containing vaccines. Official policy should err on the side of safety. Rather than waiting for formal studies to determine whether thimerosal should be taken out, the FDA should require that thimerosal be banned entirely from childhood vaccines immediately.

Thank you.

CHAIRMAN GREENBERG: Thank you, Ms. Bernard.

I will now move on to the second speaker, who is Teresa Binstock. Is Ms. Binstock in the audience? Fine.

MS. BINSTOCK: Is it on?

CHAIRMAN GREENBERG: I think it's on.

MS. BINSTOCK: Okay. I'll bend over a little.

My name is Teresa Binstock. I am diagnosed with Asperger's Syndrome, rather a diagnostic cousin to high functioning autism.

From 1990 to 1998 I conducted independent research while affiliated with the University of Colorado Health Sciences Center and have published in molecular genetics, neuroanatomy, virology and

immunology, and autism.

Since 1996, my focus has been autism, and, Mr. Chairman, I express thanks and appreciation to you and the committee for giving me this opportunity to speak.

I'd also like to thank Diane Griffin for her wonderful series of studies on measles virus, both wild type and vaccine strains.

Since mid-1997, I have perused immune panels and other medical data from autism spectrum children. I have been integrating their data with information derived form medical articles and then writing analyses for physicians, researchers, and parents.

Since late '99, I have been participating with Sallie and Albert and several others in writing of the mercury autism paper initiated by Albert and Sallie, as well as reading far more mercury neurotoxicity articles than I had ever expected.

And this morning I would like to outline several points I think are worthy of continued concern even as thimerosal vaccines are going to be used less often.

First, the temporal association we hear about between vaccinations and autism. Numerous

anecdotes describe the temporal association between a specific vaccination episode and the onset of regression into autism. Many commenters would have us presume that this association is merely temporal.

However, immune panels and other medical data, such as CBCs, along with medical histories, when interpreted through medical literature suggest that in many cases the association is causal, and that the risks from injected ethylmercury are increased if the child is sick or has been recently sick.

Furthermore, the possibility of mercury related causation in autism is increased by a wide body of literature describing the known mechanisms of neurotoxicity. This addresses things like microtubules, astrocytes, synaptic development, et cetera.

Is there a link between mercury vaccinations, in particular, and autism? Well, medical literature documents organic mercury's effects, again, on microtubules, neuronal functions, synaptogenesis. The timing of infant and toddler thimerosal injections corresponds to major neuronal development in synaptogenesis that occurs postnatally in the human. This synaptogenesis occurs in regard to eye contact, smiling. We're talking holding an

infant. You see it happening. Early language, the little babbling we do with a baby, other traits that become central to the diagnostic criteria for autism.

In many cases, the temporal associations among vaccination timings injected ethylmercury and autistic regressions are more likely to have been causal because mercury's mechanisms of neurotoxicity are well documented and provide basis for a precautionary hypothesis. Thimerosal injections during critical periods of postnatal central nervous system development are likely to induce neurologic sequelae in some children, and this leads to an important question.

Why are only some kids affected? Well, Sallie listed some of the reasons known to be genetic. I'll mention a few others.

Numerous studies have documented a range of mercury responses from not affected to severely affected in all species thus far studied. This range of reactions derives from genetic predispositions, as well as from altered detoxification capabilities, which themselves can involved liver function and a small substance known as glutathione, and many factors can affect liver function and glutathione availability in infants and toddlers.

For instance, a recent or chronic active infection can deplete glutathione. In the attachment I have citations for many of these notions. The factors which predispose towards mercury neurotoxicity and their primary citations are also reviewed in the paper Sallie and Albert and I and several others are working on, a copy of which has been made available to the committee.

Similarly, thalidomide and Pink Disease provide examples whereby only some individuals within the exposed populations developed adverse effects.

Well, I would like to discuss one more point, and that is the EPA's current safe limit is too high. At least that's said in a Smith Beecham and Merck presentation that we think of as the hepatitis control report, Volume 4, Number 21.

First of all, because vaccinations induce immune reactions that include extended cytokine's pulses, and a marvelous study was done, and this was the MMR, but in human infants, Pabst (phonetic), et al., 1997. But the vaccinal mercury is more dangerous than injected mercury, studies suggest, because interferon gamma pulses increase permeability of tissues, such as the blood-brain barrier and the gastrointestinal tract.

Thus, when ethylmercury participates in a vaccination response, more mercury is likely to enter the CNS.

Secondly, the hepatitis control report, Volume 4, Number 21, 1999, I believe, offers a flawed estimation for the maximum safe levels of mercury as set forth by the EPA. That report mentions higher guidelines by the FDA and the CDC, and suggests that the EPA level, which was lower than the other two, is unnecessarily low.

In other words, the rhetoric in the hepatitis control report suggests that a higher level of mercury exposure ought to be acceptable for infants and toddlers. I disagree. The EPA' determination was based on the amount of ingested mercury needed to inverse adverse neurologic sequelae in ten percent of exposed fetuses, but vaccinal ethylmercury is not first filtered by the maternal liver or placenta, as was the mercury poisoning incident used in the EPA calculations.

When ethylmercury is injected as part of a vaccination, the infant brain is a far likelier target. Furthermore, the Smith Beecham discussion mentions that since a ten percent rate of neurologic sequelae is clearly not acceptable, we might dwell

upon ourselves what level of mercury would it take to induce a one percent rate of neurologic sequelae, and what is still a ludicrous question: is that an acceptable rate?

In fact, the necessary level of mercury would be lower for these lower rates than the EPA's current estimate. To achieve a .25 percent rate of neurologic sequelae which approximates the rate of autism during the 1990s, an even lower rate than the EPA's level would be required.

For these reasons, I believe that even the EPA's guidelines for mercury toxicity are artificially high and ought to be lowered. My recommendation to this committee is as follows.

For the reasons outlined in this letter and in a letter to Congressman Burton, which is attached here, no additional children ought to be injected with ethylmercury.

Thank you.

CHAIRMAN GREENBERG: Thank you, Ms. Binstock.

The final speaker that I know about is Mr. Albert Enayati. Did I say that right? Thank you.

MR. ENAYATI: Good morning. I'm Albert Enayati, father of a child with autism, and I am

President of New Jersey Cure Autism Now Foundation, which is now the world's largest nonprofit organization funding medical research in autism.

I hold a Bachelor's degree in chemical engineering, Master of Science in mechanical engineering. For a number of years, my wife, Sima, who is a chemist, and I have worked in pharmaceutical firms in research and development.

Mr. Chairman, I would like to express my thanks and appreciation to you and your committee for giving me this opportunity to speak regard the issue of thimerosal in vaccine and autism.

I would especially like to thank Dr. William Egan, the Acting Director of Center for Biological Evaluation and Research, Office of Vaccines Research Review, for his leadership on this issue.

I would like to commend Dr. Egan especially for his recent presentation at a Third World conference on vaccine research in Washington, D.C., regarding the U.S. Food and Drug Administration proposal to move in the direction of single dose presentation of vaccine without preservatives.

Mr. Chairman, 18 years ago as described in the Federal Register, Volume 47, Number 2, Tuesday, January 5th, 1982, a meeting much like today's a panel

from the U.S. Food and Drug Administration met to review mercury containing drug products for topical antimicrobial over-the-counter for human use. In the FDA summary for advanced notice for proposed rulemaking, the panel addressed drugs containing mercury, as well as thimerosal, in particular, and stated:

"At the cellular level, thimerosal has been found to be more toxic for . . . epithelial cells in vitro than [was] mercuric chloride, phenylmercuric nitrate, and merbromin . . . and was found to be 35.3 times more toxic for embryonic chick heart tissue than for Staphylococcus aureus."

Furthermore, and again I'm quoting the original document:

"The Panel concludes that thimerosal is not safe for OTC topical use because of its potential for cell damage if applied to broken skin and [also because of] its allergy potential. [Furthermore,] it is not effective as a topical antimicrobial because of its bacteriostatic action can be reversed."

Thus, in 1982 the FDA panel recognized that thimerosal causes cell damage, has potential for allergy, and is not effective as bacteriostatic.

The Hepatitis Control Report, Volume 4,

Number 21, summer of 1999, details how FDA via its own Center for Biologics Evaluation and Research had failed for 17 years, since the 1982 report, to follow its own organizational directives, which specify insuring product safety. Due to its known toxicity, thimerosal in vaccines should have been tested for safety.

Fortunately, the FDA was forced to look at thimerosal in vaccines because of the FDA Modernization Act of 1997. As specified in this act, New Jersey Congressman Frank Pallone gave the FDA two years to compile a list of drugs and foods that contain intentionally introduced mercury compounds and to provide a quantitative and qualitative analysis of the mercury compounds in the list."

Despite this mandate, one year went by before this important issue got any attention from FDA.

Finally, on December 14, 1998, just 11 months before the congressional deadline, the agency published a notice in the Federal Register requiring manufacturers to provide data on mercury content. At long last, the FDA's Center for Biologics Evaluation and Research was going to analyze vaccinal mercury.

Mr. Chairman, despite the warning in 1982

and the known neurotoxicity of thimerosal, the FDA has allowed the continued injecting of cell damaging neurotoxic product to the children in the United States and other countries around the world.

Although recommendations to inject infants with thimerosal were recently changed, for years the FDA and CDC hand in hand exacerbated the potential neurological damage by allowing thimerosal to inject into day old and two month old infants.

I am here because of my son Payam. When Payam was born, he was the joy of my life. In persian, his name means "Good News." For more than a year, he passed his developmental milestones, but after his DPT booster shot, Payam began not responding to his name, no longer ran to greet me when I returned from work. His spoken language disappeared, and he no longer responded to his parents' words.

Within a few months, he had begun biting himself, hitting his head against the wall, flapping hands, toe walking, and was running aimlessly around the house. Even sleep patterns had deteriorated. Every symptom of my son's autism mirrors images of mercury poisoning, and after years of intensive and expensive therapies, my son still remains autistic.

Today, eight years after my son's

deterioration into autism, many experts would have us believe that my son's regression was a mere coincidence with his DPT booster. Yet my reading of mercury literature indicates that every trait that defines autism can be induced by mercury.

Mr. Chairman, I'm here today to plead to you and this committee that no one -- and, Mr. Chairman, I mean no one -- ought to be allowed to inject a toxic heavy metal in a child's body, no one.

As documented in the thousands of research articles and books, mercury is one of the deadliest elements on earth for children's developing brains. How can anybody with their right mind justify injecting one of the most toxic elements and call it safe without having ever tested it?

And to have done so for years without even having calculated the total dosage being injected, a total that includes all the thimerosal vaccinations, not just those that are given in the infant's first six months?

Mr. Chairman, medical research makes clear the mercury compounds are toxic to the developing brain and to the other organs. Vaccines containing thimerosal are not safe, and as we are speaking, there has not been a serious attempt to stop injecting

vaccinal mercury.

Furthermore, a thorough review of medical literature indicates that the percentage of infants and toddlers receiving vaccinal ethylmercury are likely to have experienced neurological deficits, and for many children and their families and communities, the diagnosis is autism.

I repeat, published scientific research about mercury neurotoxicity has caused us to believe that vaccinal injections with thimerosal have been a cause or a contributing factor in many and perhaps most cases of autism and related neurological disorders.

Finally, in the White House ceremony several months ago, vaccine manufacturers volunteered to donate a vast amount of vaccine for administration to the children in Third World countries. Most, but not all of these donated vaccines contain thimerosal.

I appeal to you to recall these vaccines which contain mercury immediately.

Furthermore, a recall of all vaccines containing thimerosal should occur in the United States and elsewhere. This recall would not disturb the current vaccination schedule because vaccines without thimerosal are available.

Injecting mercury into infants and toddlers ought to be discontinued immediately.

Thank you.

CHAIRMAN GREENBERG: Thank you, Mr. Enayati.

And thank you, the three speakers, for sharing with us your views, and I'm sure the FDA staff and the members of the panel have listened to it carefully and will think about it through the days and when we move on.

I'd like to now ask whether there are any other people in the audience who -- Walter, before, I'd like to make sure there's anybody out there.

Is there anybody sitting in the audience that wishes to make some sort of statement?

(No response.)

CHAIRMAN GREENBERG: If not, okay, Walter.

DR. FAGGETT: Faggett.

Will we in the committee be able to get copies of testimony that was given?

CHAIRMAN GREENBERG: I have copies of one. I would ask the other two speakers if they could provide us with copies. We will take care of distributing it to members of the committee.

Ms. Fisher?

MS. FISHER: Yes. I thought those were excellent presentations, and of course, as a consumer representative, I totally support the FDA's move to direct the manufacturers to take thimerosal out of the vaccines. I think it's important, however, to not assume that simply by taking the thimerosal out of the vaccines that brain inflammation that's been associated with pertussis toxin, with MMR vaccine, et cetera, is not going to continue to occur and that that brain inflammation and the subsequent encephalopathy can cause brain damage which could take the form of autism.

I just wanted to make that statement, and I have another. Seeing as how we did have three members of the public come forward here today, I have received several letters from parents who were upset that there was not appropriate notice put in ahead of time. They were not notified ahead of time, and it was not in the Federal Register to notify people that there was a shortened time period for public notification.

I'm not making any judgment as to, you know, why that occurred or the reasons or whatever. Just to point out that it is the perception on the part of the public when this occurs is not a good one,

and so I just hope, you know, that for whatever reasons that it doesn't happen again because I do get letters from people upset about it who had planned to attend or wanted to attend.

CHAIRMAN GREENBERG: Thank you, Ms. Fisher.

As you are all aware, I think the FDA makes an exemplary effort to have public participation in these meetings, and that open public sessions will continue in this meeting and in the future meetings, and I am not aware of the specifics of the notification, but I think these public sessions are basically available to the public at all times to state their conscience.

And so I would advise you to tell people if they couldn't make it here today they can make it here the next time.

Are there any other comments?

MS. CHERRY: Let me respond to that. Probably in the packet that was out there at the door that has the agenda there should be a location for a Web site, and you can go on, and there usually would be at least four weeks' notice, maybe six, maybe eight weeks' notice of a meeting coming up, and also on our telephone line.

MS. FISHER: So that would have been on there?

MS. CHERRY: It should have been on there.

MS. FISHER: Okay. I'll let people know.

MS. CHERRY: Not the fact that we were having any speakers on autism, but the fact that there would be open public hearings and the times.

MS. FISHER: I'll spread the word on that.

MS. CHERRY: Okay.

CHAIRMAN GREENBERG: Okay. If there is no further comments, I'd like to shift gears now and move on to Session 3, which is an open public session entitled "Rotavirus Vaccines and Associated Intussusception," and we're going to just change horses here.

Dr. Daum, can you come up to the front?

And Dr. Daum will chair this session.

MS. CHERRY: While Dr. Daum is settling in, let me say that I'll have the copies of these statements made and given to the committee tomorrow rather than paying commercial prices to get the copies made.

DR. DAUM: It's a paradox that people often with the greatest expertise have to recuse themselves from important parts of these hearings, but

nevertheless, these are the procedures by which we operate, and we must go forward.

Session 3 is an open session on rotavirus vaccine and associated intussusception to review an experience that we've had with our first licensed rotavirus vaccine in the United States, and we will begin by calling on Dr. Carbone of the FDA to give us an overview.

The session is packed. The time is tight, and I would ask the speakers to re-review their notes and presentations, to try their very best to keep on target time-wise.

Dr. Carbone.

DR. CARBONE: Thank you.

I have some good news. Between a typo that I'm sure is my fault and not Nancy's and between some last minute streamlining of the FDA talks, we will probably have little additional time for the first few speakers, but if they don't need the time, that would leave us with additional time for discussion at the end.

I would like to begin very briefly by reviewing information much of which was already been presented at this and other forums, but I wanted to, since we have new voting members and members of the

audience, I wanted to get everybody on the same page as quickly as possible before we introduce the first speaker.

Just as an introduction, rotavirus is a double stranded RNA virus which has 11 different segments. It has the unique feature that these segments permit the formation of hybrid viruses which we call reassortants, and you'll hear that term frequently associated with vaccines so that two different viruses may infect the same cell, and the resulting progeny may have viruses, segments from two different or more viruses.

It's also important to note in rotavirus multiple strains can infect multiple species that can cross species lines, and that there are multiple serotypes. Therefore, the approach typically of a polyvalent; the fact that the various replicates in the gastrointestinal tract has also stimulated an oral vaccine strategy.

As far as the rotavirus of the disease, the magnitude of the health problem. As a quick introduction, it is the single most important etiologic agent of severe diarrhea in infants and young children worldwide. Virtually all children are infected and exposed to the virus.

Severe diarrhea tends to be caused in younger children three to 35 months of age and in the U.S. is a seasonal disease between November and May that spreads across the country in a pretty well established pattern.

Next slide, please.

Rotavirus disease in children under five years of age causes significant morbidity in the United States. Half a million physician visits per year, one out of every seven children at that age, 50,000 hospitalizations, and the deaths in the United States are estimated to be approximately 20.

Internationally the disease becomes somewhat more significant from a mortality point of view, where upwards of 600 to 800,000 children die per year in the world of rotavirus diarrhea.

Next slide, please.

Just to review the license product experience, RotaShield vaccine was produced by Wyeth-Lederle Vaccines in Pediatrics. It was a live, attenuated reassortant of a rhesus rotavirus strain designated RRV with a human strain.

Four serotypes were contained within the vaccine. Serotypes one, two, and three are, indeed, a hybrid of the chimeroviruses, the reassortants, and

serotype three was covered in the rhesus rotavirus strain.

Next slide, please.

The vaccine was administered orally at two, four, and six months. As you can see, the numbers of studied subjects were quite large, over 12,000. Any dose, any formulation of the vaccine during its development licensed dose and formulation over 8,000.

The adverse reactions that were statistically significantly associated with vaccination were in the moderate and high fever, and the vaccine was approved for licensure in August of '98.

Next slide.

Since approval for licensure, there were approximately 1.5 million doses administered between August of '98 and June of '99. Intussusception, which is a bowel obstruction, and I won't dwell further on it -- Dr. Shiels will present a very nice talk about me on that subject -- was observed in 15 vaccinees that were reported between September of '98 and July of '99.

This report of intussusceptions stimulated a CDC analysis of RotaShield vaccination with

intussusception. They initially recommended ceasing vaccination to further study the vaccine, and they found in the studies -- and I won't dwell on this again; Dr. Wharton is here to discuss this -- that there appeared to be a highest risk of intussusception following the first two weeks after vaccination, and the vaccination was associated with one to two GI, gastrointestinal, related deaths.

With government agency recommendation, therefore, the manufacturer voluntarily withdrew the product from use in October of '99.

Next slide, please.

So just briefly to review the agenda, Dr. Shiels will speak to us about the clinical presentation and diagnosis of intussusception. CDC analysis of rotashield and intussusception will be presented by Dr. Wharton. Dr. C.D. Atreya of the FDA will discuss the pathogenesis of rotavirus vaccine current research knowledge and research gaps, and I will end the session with the discussion of the safety assessment of vaccines specifically pertaining to rotavirus vaccines.

DR. DAUM: Thank you very much, Dr. Carbone.

I think we'll move right on to hear from

Dr. Shiels, who will give us Intussusception 101.

DR. FOST: Dr. Daum, could I ask you a question?

DR. DAUM: A review. Yes.

DR. FOST: Are you holding questions until all FDA --

DR. DAUM: I would like to have the entire presentation come, and then we will have, if people are good about keeping on track with time, adequate time for discussion.

DR. SHIELS: We'll stay close to the microphone here, and we should be able to keep nicely on time, and I'll begin.

The handout is available in the back for anyone who does not have it at their chair or desk. In the next 30 minutes what we will discuss is a hopefully inclusive gamut of topics on intussusceptions. We'll talk about the types and etiologies, the pathologic features, the clinical features of intussusception imaging and accuracy of various imaging options, therapeutic options and techniques and expectations that we have of ourselves as far as outcomes when we treat intussusception.

The Intussusception 101, intussusception by definition is telescoping of one part of the

intestine into another part of the intestine. That gives a subsequent bowel obstruction. The outer intussuscipiens then encases the inner intussusceptum.

The types of intussusceptions are defined by their anatomic location. Very simply, if the normal intestine, the junction between the small intestine and the large intestine -- the ileocecal valve is defined here -- then we define intussusception based on the small or large bowel components that are part of that intussusception.

The most common types of intussusception are the ileocolic, where the ileum or the distal small bowel invaginates or telescopes into the cecum in the colon, which the cecum is part of the colon, and the ileocolic, where you have two portions of ileum then folding as a group into the colon.

And those are the two most common that we see in children, and those are the most common that we see with rotavirus. The pathophysiology of intussusception as a disease simply stated, when you take one part of intestine, stuff it into another part of intestine, the intestine has arteries, veins, and lymphatic channels that drain fluid. Those get plugged up. You then get back pressure. You get obstruction of the venous flow, the arterial flow, and

everything gets swollen.

Essentially then you lead yourself into a position where you can have gangrene. Gangrene of the intestine is death of the intestine. Death of the intestine can result in death of the patient. We try to avoid that at all cost. We want to attack this disease, diagnose it early, treat it, and hopefully avoid surgery.

So we have vascular congestion. We have edema, which is swelling of the tissues, intestinal hemorrhage bleeding into the intestine, intestinal ischemia, which is that gangrene and loss when we have this gangrene. Then the strength of the tissue, the tensile strength decreases, and then we have the potential for loss of bowel integrity. We have compromised bowel, and the barriers to anything that's inside of that intestine break down, and the risk of perforation and, again, there are multiple causes for this ischemia, one of which is just pressure of the two parts of that intussusception, that telescoping and rubbing against each other.

This is what intussusception looks like grossly. We have colon. This is the appendix dangling off -- this turns out to be very important. We're going to address this a little bit later as a

potentially key marker for some of this lymphoid activity.

But the bottom line is we have the colon receiving the swollen small bowel, and you can see if this gets swollen enough, it will eventually die. The simple analogy is taking a rubber band and winding it around your fingertip as we all have done at some point. Your fingertip gets blue, eventually it starts to hurt, and then you take off the rubber band before your fingertip dies. And that's what we want to do with intussusception.

This is what the surgeon sees with intussusception. This is the telescope part invaginated into the outer receiving part of the intestine. This is the collapsed part that's downstream. This is the blocked, swollen part of intestines that's upstream trying to send material forward, meeting this blockage so we have an obstruction, a small bowel or large bowel obstruction.

And the multiple causes for this disease are listed here in this summary slide. We refer to the most common cause as idiopathic. There's no definite known cause or the better way to say that is there is no definite abnormal resectable or surgically removable mass. That disease is caused by most

commonly inflammation of the intestines similar to the lymph nodes in the neck, the lymph nodes where the lymphoid patches in the intestines are felt by the intestines, grabbed forward and everything telescopes forward. So that is the idiopathic type, greater than 90 percent.

When we have a tumor that's abnormal and definable and resectable attached to the small bowel or the colon and that is felt and moved forward, that is then referred to as a pathologic lead point, a much lower percentage of the cause of intussusception, and post operative is a very rare type.

The rotavirus associated in intussusception would fall into this idiopathic category. The clinical presentation, the incidence in your handout you can see is roughly one in 2,000 infant years. The ages you can see it breaks down anywhere from newborn to 18 years. For relevance of today's purposes, the most common risk group or the highest risk group that we need to look at are the children three to nine months of age. That constitutes roughly 40 percent of all the cases of intussusception.

And we see a male predominance. We see a seasonable incidence in North America, usually

midsummer, and there is a second peak midwinter.

There is also association with GI and respiratory viral infection, specifically adenoviral infections and enterovirus is the two most common.

The rotavirus vaccine, the wild type is not associated with intussusception. The rhesus type was associated with intussusception.

We notice that the children are well nourished that get intussusception as a general rule. The importance there is children need to be well nourished to have a lymphoid response to any inflammatory agent. Malnourished children don't get this sort of response, and therefore, in our circles when there is an associated infection, well nourished children will then be set up for intussusception.

Interestingly we do see a geographic distribution of risk in the United States that seems to predominate in the mid-continental region. If you follow a jet stream, there's not the same degree of intussusception in the south and the high north as you see in the mid-continental portion.

As to the signs and symptoms of the children, abdominal pain due to this obstruction is important and a very high incidence of that. Because of the obstruction, vomiting then precipitates. When

the gangrene and the bleeding is present, then we see blood per rectum, and the abdominal mass is felt in a smaller percentage of cases than we would like to think, but indeed, roughly 60 percent with a good surgeon usually under general anesthesia can feel the mass externally.

And the mass may present all the way downstream in the colon as a rectal mass. The symptoms can be present anywhere from hours to weeks, and children can reduce their own intussusception. So we can see how we can account for a week's worth of symptoms, and sometimes diarrhea. A very sleepy child, a lethargic child or an obtunded child may be the only presenting symptoms.

Mortality, something that we don't tend to talk about much in the United States before this whole issue of the rotavirus came up, but it is a very key issue worldwide. We don't see much mortality in the United States, certainly less than one percent. We should we shocked if we had a death from intussusception in our city. In other countries though death from intussusception is not uncommon, and there is a very clear clinical correlation between the delay in diagnosis that results in a high percentage of patients requiring surgery, and again, the surgical

rates for some countries are as high as 100 percent.

Surgical percentages in our institution are roughly ten percent.

This is the gangrene , the frank gangrene that we want to avoid, and we want to approach a very early diagnosis so that we can approach early nonsurgical therapy. The intussusception that we see most commonly, the idiopathic type, again, we have talked about the locations. We talk about the causae. Again, these hypertrophied or overgrown lymphoid follicles, those clumps of lymphoid white cells in the wall of usually the ileum and in that first part of that colon; the mucosal and submucosal edema that then is a secondary finding due to the obstruction, and the virus particles can then result in an intracellular inclusion, which we'll show you a photomicrograph of.

And we have a variable degree of obstruction which is a relevant issue for us in radiology as we treat these. We need to understand how the obstruction occurs.

So again, this is small bowel, then folding into large bowel. This is the hemorrhagic and early gangrenous state. The outer portion is less involved. This is the lower power photomicrograph. This is the outer casing which is not as involved with

the hemorrhage and congestion and frank gangrene.

This is that hemorrhagic gangrenous portion of the inner portion of the intestine. This is that valve junction of the small intestine and large intestine, and notice how red, beefy red and swollen this is. This gives you an idea of the inflammatory change that occurs before the intussusception is then presented.

These are some of these blue lymphoid follicles that occur in the wall of the intestine. If these get large enough, they are felt as a lump, move forward in telescoping, then occurs as a secondary problem.

This is the inner lining of the intestine, the small intestine. These are these blue lymphoid follicles in the wall of the intestine.

Again, these are reactive changes to inflammatory or external causes. We carry these lymphoid follicles around, but give us a reason to react and these will get swollen, and this slide demonstrates nicely viral inclusions in the cells of the intestine.

What about pathologic lead points? Very briefly, this is a list of some of the most common lead masses that will occur causing intussusception.

This, again, this whole category constitutes less than ten percent of all the cases that we see, and lymphoma is the concern of the surgeons. That is why they will operate if there is a recurrent intussusception more frequently than the reducible and nonrecurrent type of intussusception.

The X-ray findings that we have, and this gets into our surveillance issues as we look at these vaccine issues worldwide. How are we going to find these cases of intussusception? What are the most sensitive tests and what should we approach first?

The X-ray findings are most commonly soft tissue mass, and that's usually up underneath the liver in the right upper abdomen. We see a coiled spring sign as a sign with air around this telescoped mass. The air around the edge of the mass gives us a cap sign, and paucity or a small amount of bowel gas is seen because the child is both vomiting and having cramping abdominal pain with colonic evacuation of gas. So there may often be very little bowel gas present in these children, and a small percent of the children will present with a frank high grade small bowel obstruction.

Plain X-rays have a sensitivity certainly under 50 percent accuracy. This is why we cannot rely

on plain X-rays to make a diagnosis. This is a child with intussusception.

For anybody in the room, I would challenge you to find the intussusception. Having done studies on these, I know where to look, and can tell you that this is a subtle finding of the mass, but the mass blends in with everything next to it.

So the plain X-rays in and of themselves are not terribly diagnostic and have a very, very high false negative rate, 40 percent false negative rate, and again we see some early evidence of bowel obstruction with gas distention of the intestine.

This is the small bowel obstruction that we will see as the intussusception stays long enough to cause gas collection to form in the small intestine and give us that small bowel obstruction.

Ultrasound or sonography has turned out to be quite a sensitive, noninvasive diagnostic test. We can use sound waves to look through toe see the mass. Since the mass is full of water and blood and solid tissue, if we use ultrasound and put it right over the abdomen where the issue is addressing the child, we can see this mass, and. I will show you these ultrasounds.

We see two common signs, the pseudokidney

sign and the doughnut ring sign, and the central portion of the intestine reflects echoes very well because of the nature of the lining of the intestine, and that is dead center in this target lesion, and we see that reflecting from the lining, the mucosa and the next layer, the submucosa.

And, again, because of the nature of this telescoping, we see multiple layers on our ultrasound.

These are schematic diagrams of what we would expect to see with ultrasound. This is looking down the barrel or the long axis of the intussusception, and we can see a variable appearance of either layering or a very swollen pseudo kidney sign, if you will. The kidney bean has very much this sign or this appearance, and this is what we would see with that elongated mask of telescoped, swollen bowel.

This, again, is that same portion of intussusception with the outer layer. The inner swollen portion, and if we cut this in cross-section, then we get either a target sign with multiple layers or the doughnut with a much more swollen inner part.

These are the ultrasound images that we expect to see. The sensitivity of ultrasound approaches 100 percent. It's very much operator dependent. It requires a careful examination, but if

it's done well, we should be able to hit nearly 100 percent as a diagnostic accuracy without any invasive tests.

This is that swollen intussusceptum, and you can see the multiple layers of the intestines stuffed into themselves. That is in the long plane. This is cutting across in the cross-sectional or transverse plane. You can see the circular, multiple rings of the intestines and the hemorrhage and edema congestion of the intussusception.

What about X-ray contrast studies? this is a little bit more of an intrusive test where we have to place a catheter into the rectum of a child under X-ray and define the mass from a reverse approach or a retrograde approach from the rectum.

The enema is used either as a liquid enema or air enema. What we see is that soft tissue mass. Again, we see the air defining the outer edge of that mass, the coiled spring appearance, and once the mass is encountered, we can see it anywhere from the rectum to the ileocecal valve, and again, we can have an opening of the lumen, which is more important for us treating this.

What about the options that we have before the child is forced to go to surgery? X-ray options

are essentially two: water and air.

Water, liquid contrast agents or saline used in some countries and in some centers in the United States, much less frequently here than liquid contrast agents, but the bottom line is they all have a common mechanism. They have a pressure head of water that is incompressible. When stool mixes with that, it carries it, and the stool is dispensable in the liquid.

Barium has a unique ability to be a potentially legal agent. When stool mixes with talcum powder if there's a perforation, then the child can be at risk for death if there is perforation with barium. That's why we highly encourage all of us to stay way from barium as an agent, but liquid contrast agents, anything with liquid in it has a similar perforation risk of larger holes when there is a perforation, unlike air which has a unique safety margin and a higher efficacy rate.

Where air provides a compressible medium as opposed to incompressible liquid there is very little mass component. So when there is a perforation, air can sneak through layers of bowel and give us partial thickness holes where tiny pinhole perforations that surgeons may never find when they

operate on the child, and stool is not suspended in there. So there is no stool in the working field.

And we just lost our advancing. If somebody could help me advance these slides, our remote is no longer working. Here we go.

Now, what about fluid? A lot of centers around the world will still use fluid, and again, our guidelines patients will go to surgery if they have frank inflammation of the entire abdominal cavity or bowel perforation. We only do the enema therapy if the child is stable and fluid resuscitated.

The guidelines for hydrostatic enema were given to us in 1948 by a brilliant surgeon at Johns Hopkins, Dr. Ravitch, and those guidelines are generally used today. The guidelines give us about a 50 percent, 60 percent success rate, but the bottom line is they are very safe.

In barium or water soluble contrast, agents are used, and you can see the rules that we use. The column of fluid is held at three feet above the patient for three minutes and a maximum of three attempts, three minutes for each attempt, and this is what the intussusception looks like with the barium. Here is the mass in the right abdomen. This is the right. Here is the left. We're looking at though the

patient were looking at us. This is all of the barium outlining the mass, and then as it outlines it further, this pressure head of barium will then push this down into the right colon and hopefully reverse that telescoping and push it back.

So the key principles for therapy both for water and for air,b ut specifically for air is we require this to be engaged in as a team sport if you will, a team approach with surgeons. Intussusception is a surgical disease, and we need to keep the surgeons in a loop. Even though we can treat close to 90 percent of these, still if anything goes wrong, it's still important to keep a surgeon wired ahead of time.

So the contraindications again, bowel perforation or shock and peritonitis, the inflammation of the abdominal cavity. Enema therapy, again, is engaged in if the patient is stable. We do teach the patient's families about the different options and the reason why we're not doing surgical work and the potential for a perforation. The parents are in the room with us when we do these procedures.

We then will immobilize the child for a controlled, accurate procedure, and we use a controlled mechanism that we'll show you in just a

moment.

Simply stated, air versus fluid, if you look at the world literature over the past 40 years, there is a consistent theme that air is much more effective than any sort of water medium, and air is safer, faster, easier, cheaper, more easily controlled, and less messy for everyone concerned, including the surgeons, if there's a problem.

The guidelines, we do have a guideline, a very controlled guideline, a maximum pressure that we put into the patient, the most that we will insufflate. The child can then strain or bear down and give us what's known as a valsalva maneuver. That protects the patient, protects the colon with an external sleeve of pressure from perforation or extension of any hole that may occur, and it actually assists the patient in reduction.

We know that 17 percent of children can reduce their own intussusceptions. So this whole mechanism plays out very well in the radiology suite, and again, we maintain moment to moment control with this hand operated pump, similar guidelines to fluid with three to five minutes for each attempted and three to five attempted maximum, and if the intussusception is not reduced, we may wait anywhere

from 30 minutes to two hours and then try again.

This is the air system that we use. We use a hand pump. You can see that that is controlled with fingertip decompression, which is instantaneous if pressure ever does get to a point where it's undesirable, and the operator will monitor both the pressure gauge and the X-ray monitor while the child is being controlled by the operator and the technologist in the room.

This is what the images looked like during an air enema. We have the colon coming in from the rectum. We see the left colon being insufflated and distended with air, meets the mass in the right abdomen most commonly up in the upper quadrant.

The air then pushes this mass down to the junction with the small bowel of the ileocecal valve, and with roughly 100 millimeters of mercury of pressure on average, this then pops through and telescopes and reverses the obstruction.

Again, what can we expect of ourselves as far as outcomes? We get to the bottom line with air. We should be able to see roughly 85 to 90 percent success. These were our numbers with a very focused series controlling as many technical variables as we could.

And we sent to surgery cases that required resection or required a surgeon to do something other than easily unfold this telescoped bowel. We pushed the limits to the point where surgeons essentially had no easily reducible cases. So we reduced everything possible in X-ray and sent only to surgery only those patients that required a surgeon's instrumentation.

This is what the surgeons will do when they have to reduce it. It looks like squeezing a tube of toothpaste. It's known as the Taxis maneuver, and they generate pressure that then reverses this obstruction as well.

These slides get into something that is new to this audience. This was brought up as a question at the NIH meeting. The question about lymphoid follicular hyperplasia rose many questions when we brought this forward. The point that children under the age of three months don't have lymphoid follicular tissue to respond to things like vaccines or viral infections, and that's why we see intussusception so infrequently in one month old children.

I was challenged to produce some data that confirmed what we knew. We have just finished our pilot study confirming, indeed, for the first time, it

looks like, that the appendix, number one, is a great marker. So that if we're doing surveillance and children go to surgery, the surgeons will usually take out the appendix.

If we have appendices available, we can look at these for the potential reaction of the child to a vaccine. This is the appendix, and this is a newborn child. There is no lymphoid follicular tissue. You don't see those blue lumps that I showed you earlier in the wall of the intestine. That is something we refer to as grade zero.

This is grade one. The child begins to form these little clusters of lymphoid tissue. The trading from one to four extends over the first 12 weeks of life.

Then we get into stage two and three, where we begin to see these germinal centers. These are the centers that produce the hormones or the humeral factors, rather, the antibodies. Here are the lymphoid tissues. These are the germinal centers, and this, again, is the wall of the appendix.

The appendix turns out to be a fabulous marker to define the lymphoid reaction of the child. This is stage four or grade four where we see wall to wall lymphoid tissue in a relatively significant mass

of this lymphoid tissue in and around the entire circumference of the appendix.

So, again, data and clear images about the role of the appendix as the potential surveillance marker for lymphoid activity.

The complications we will go through very, very briefly. The bottom line is that water has a much more potentially adverse outcome with complications than air. Air can be decompressed if there is a perforation in X-ray. Water cannot be, and we'll save you these details. We'll show you these graphically. This is what an abdomen looks like when there's a barrier perforation mixed with stool and barium. Surgeons never want to see this, and they will curve the name of my colleagues if they ever see this again. It happens all too often.

This is what an abdomen looks like with air. It's extremely clean, and there's no stool that leaks out with the air.

This is a small perforation with barium contaminated and may often require a colostomy. You can see centimeter rule markings. This is a one centimeter as the smallest perforation that we had in an experimental study that we performed looking at fluid versus air agents.

This is one of our small perforations with air. It never made it through the back wall of the intestine. It then tracked through this layer of bowel and ended up somewhere downstream. This was never seen on the outside, and you can see these small holes are one-tenth of the size.

So essentially we can diagnose intussusception very eloquently with ultrasound. We can treat it well if we get the child early enough, if our surveillance is aggressive and we educate patients. We can make a significant impact.

Children shouldn't die from intussusception if we can get them to centers that can treat them well, and hopefully this review has been helpful for you in going over clinical pathologic features, treatment features and outcomes expectations.

Thank you for your attention.

DR. DAUM: Thank you, Dr. Shiels.

I think we will continue the policy of trying to get all of the information downloaded and then have questions and comments after. So we will then go on to Dr. Wharton's presentation.

DR. WHARTON: On August 31st, 1998, RotaShield, a rhesus rotavirus, a tetravalent rhesus

based rotavirus vaccine, or RRV-TV, was licensed by the FDA for use in infants to prevent severe gastroenteritis due to rotavirus.

As Dr. Carbone or as I think will be mentioned later on, there had been several cases of -- there had been a few cases of intussusception noticed in prelicensure studies, and for this reason post licensure surveillance for intussusception was conducted, and an early assessment of VAERS data was undertaken by CDC and FDA.

By May 21st, 1999, ten cases of intussusception in recipients of rotavirus and other vaccines had been reported to the vaccine adverse event reporting system of VAERS, a passive surveillance system jointly operated by FDA and CDC.

The interval after vaccination was known for nine of the ten cases. Six of these cases had onset of intussusception three to six days after receipt of rotavirus vaccine.

In response to these cases, as has already been mentioned, CDC did suspend use of the vaccine in mid-July, and following that suspension and the publicity accompanying it, we received a very large number of reports of previous cases of intussusception that had occurred prior to the cessation of use of the

vaccine.

Ultimately there were 60 confirmed cases of intussusception reported among infants who had receive rotavirus vaccine within the week preceding onset of intussusception. This is about a fourfold increase over that expected based on the observed baseline rate of about one in 2,000 infants.

At the same time this was going on, CDC undertook a large multi-state investigation of the association between intussusception and rotavirus vaccine and the remainder of the slides I'm going to present are from that study.

This study was led by the national immunization program. Dr. Trudy Murphy, who couldn't be here today, was the principal investigator on that study which involved 19 state health departments and a very large number of state and local health department personnel, and without their cooperation, this activity never could have been undertaken.

The objective of the study was to estimate the relative risk of intussusception among infants vaccinated with rotavirus vaccine and for unvaccinated infants for prespecified risk periods. The study was a matched case control study with four controls selected per case.

Cases were ascertained in hospitals which, based on historical data, were those likely to take care of patients to young infants with intussusception. These were largely hospitals with large pediatric services.

The cases were then identified by systematic review of hospital discharge and radiological records. Controls were selected from the hospital of birth of the case and matched closely on age, plus or minus seven days.

All vaccination records were provider verified.

The study was performed in areas where rotavirus vaccine had been distributed. The manufacturer shared with us information on distribution of vaccine during the previous period, and we focused on those areas where there was the opportunity for exposure.

The age of the patients were one to 11 months, that is, the ages at which rotavirus vaccine was approved for use, and the study period was November 1, 1998, through June 30th, 1999. Note that the case ascertainment did end before the announcement of the association in mid-July.

What I'm going to present are interim

analyses that have previously been presented for the Advisory Committee on Immunization Practices and also the Infectious Disease Society of America last fall. While these are not final data and, indeed, there are not yet final data available, I believe that the final results will not substantively differ from what I'm going to present to you today.

At the time of the interim analysis, data were available for 2,046 subjects, 427 cases, and 1,619 controls. Ninety-three of the cases had four matched controls.

This slide shows the vaccination status of case and control infants for the first dose of rotavirus vaccine, oral polio vaccine, and inactivated polio vaccine. Of the cases, 75, or 18 percent, had received rotavirus vaccine, and of the controls, 192, or 12 percent, had received rotavirus vaccine.

In contrast, for oral polio vaccine 18 percent of cases and 21 percent of controls had received that vaccine, and similar percentages, 68 and 71 percent, of cases and controls had received inactivated polio vaccine.

The odds ratio for intussusception determined on the entire data set by conditional logistic regression are shown here for infants who

were ever vaccinated with rotavirus vaccine compared with infants who were never vaccinated with rotavirus vaccine. The odds ratio for intussusception among vaccinated infants was 1.8, with a 95 percent confidence interval of 1.3 to 2.6.

This represents an 80 percent increase in the risk of intussusception after vaccination compared with the risk of intussusception without vaccination.

Shown here are the number of cases of intussusception among rotavirus vaccinees for the first 21 days after vaccination with doses one, two, and three. There were no cases of intussusception observed on day zero, one or two after any dose of rotavirus vaccine.

For dose one, there was a large cluster of cases between days three and seven after vaccine. A smaller cluster of cases occurred during the second week of vaccination, days eight through 14. There was no clustering of cases after day 14 following dose one.

For dose two there does appear to be a small clustering of cases between days three and seven after vaccination, but no subsequent clustering.

And for dose three, no clustering was observed, and the results that follow will be for

doses one and two.

This slide is actually remarkably similar to the VAERS cases as well, which was somewhat of a surprise, given the potential for bias in a passive reporting system.

This slide shows the odds ratios for intussusception by prespecified risk windows following dose one. There were 412 case control sets considered in this analysis. There were no cases of intussusception in the day one to two window after vaccination. Therefore, there was no odds ratio estimated for that period.

For the three to seven day window, the odds ratio was 24.8, with a 95 percent confidence interval of 9.5 to 65.1, indicating an approximately 25-fold increase in the risk of intussusception during days three to seven after receipt of rotavirus vaccine.

For the eight to 14 day window, the odds ratio was 7.1 with a 95 percent confidence interval of 2.3 to 21.9, indicating a sevenfold increase in the risk of intussusception in the second week following dose one.

There was no increase seen in the risk of intussusception 15 days or longer after receipt of the

first dose of vaccine.

Similarly, this slide shows data for intussusception following dose two. There were no cases of intussusception occurring during the period one to two days after vaccination with the second dose. The odds ratio for intussusception three to seven days after the second dose was 13.4, with a 95 percent confidence interval of 2.6 to 69, with a point estimate indicating a 13-fold increase in risk.

There was no significant increase in the risk of intussusception eight days or more after vaccination in the eight to 14 day and 15 to 21 day windows after receipt of vaccine.

To estimate the number of vaccine attributable cases of intussusception we used the odds ratios from the case control study and baseline incidence rates of intussusception from the New York State Hospital discharge database covering the period 1991 through 1997, and we assumed that 80 percent of children would receive dose one at age two months and 20 percent at age three months. Sixty percent would receive dose two at four months, 40 percent at age five months, and for dose three a third of children would receive it each at six, seven, and eight months of age, which are reasonable assumptions given the

timeliness at which children in the United States receive vaccines.

Without vaccine, we would expect approximately 2,000 cases of intussusception in the typical annual cohort of four million infants. With full implementation of a rotavirus vaccine program, we estimated that there would be about 888 excess cases of intussusception primarily in infants receiving a first or second dose of vaccine.

Based on these interim results, we estimated that there would be one vaccine attributable case of intussusception for about each 5,000 children vaccinated with rotavirus vaccine. With universal use of the tetravalent rhesus based rotavirus vaccine, there would be about a 40 percent increase in the baseline number of cases of intussusception expected in the United States.

Based on these data, as well as data from other studies, the Advisory Committee on Immunization Practices withdrew its recommendation for use of rotavirus vaccine in the United States in October of 1999.

Thank you.

DR. DAUM: Thank you, Dr. Wharton.

And we've gained a few minutes from your

concise presentation. So we'll move on to hear from Dr. Atreya from FDA regarding updates on rotavirus vaccine, intussusception pathogenesis/research issues. Quite a title.

DR. ATREYA: Okay. So far we already know what intussusception is, and there are some links between wild infections and intussusception. So intussusception is associated with adenoviral infections as well as lymphoid hyperplasia, and it is not known to be associated with wild type rotavirus infections.

However, we just now know that intussusception is associated with RV vaccinations.

It is also known that not all of the vaccinees get intussusception. Therefore, the etiological factors of intussusception associated with live attenuated RV vaccine are unknown at this time, and also the underlaying mechanisms of this RV associated intussusception is not known.

Therefore, research is needed to characterize mechanisms of RV vaccine associated with intussusception. The research approaches could be something like, for example, you should have clinical epidemiological studies and then the basic research.

The basic research probably should involve

molecular biological studies at the state-of-the-art technology using these things, and then the tissue culture and then animal models.

And all of these research approaches should have a goal towards improving the vaccine safety, and for example, I didn't find the host, virus or environmental factors that are associated with the risk of intussusception after RV vaccination, and also applied these techniques and data that is available after we do these experiments to incorporate to develop a new and improved vaccine in future.

Rotavirus vaccine, as I said, possible factors are host, environmental or virus. So let's see what the host and environmental factors that we need to address as part of the research.

We need to see that the cellular immune responses to virus infection. For example, the induction of cytokines, and what kind do cytokines play on the gut physiology relation to intussusception, and then we also have to look into the gender differences, probably then the developmental, that is, age related differences, and also then we have to look at another critically important issue, that is, the alteration of virus application in certain heterologous host-virus

combinations.

What I mean by heterologous host-virus combinations is that most of the vaccines now we are thinking of are non-human rotaviruses, and so if those viruses are given to humans, what will be the consequences?

In fact, we do not know, and the other one is the environmental factors, such as in dietary or even concurrent infections, something like bacterial or other vital infections, along with the time of giving the RV vaccine, what kind of play they have.

And then the next one. What are the possible viral or virus factors? It could be that the strain of zero type specific replication could be one of the reasons. As we know, the RV vaccine that was causing intussusception is multivalent different zero type vaccines. So they may have a role to play.

And then also the effects of the viral proteins themselves on the host. For example, data from animal studies suggest that the diarrhea which is the diagnostic factor of this rotavirus infection is probably caused by enterotoxin, which is called NSP4 protein.

And also, the fluid loss accompanied by this diarrhea is stimulated by the enteric nervous

system. So what are the links between these kind of studies that probably have a role to play in intussusception has to be looked into.

Then the next one, please.

Given all these factors, it is good if we have already an animal study in intussusception. However, we do not have one. So what all we know right now are that there are some established animal mouse models for RV pathogenesis. The elegant work of Dr. Estes has, years of work, showed how the pathogenesis of RV can occur and what are the other factors associated with that.

The other animal study mouse model is recently known to public, that is, the LPS induced intussusception, and comparing these two studies and learning from these two studies, the question to us now is based on this knowledge is there a chance to develop a suitable animal model, and it is likely that we can develop. Of course, it is not an easy task to do.

So moving on to that, the animal model research, if we believe that we can establish one animal model, then the study should be focused to understand the mechanisms of intussusception associated with RV vaccine to assist rational design

of future vaccines which are much more improved, and for example, by collecting the specific virus genome sequences that are associated with intussusception, and then you can develop and validate some new diagnostic techniques or methods, for example, early detection, like ultrasound, as we heard now.

Our new treatment strategies, such as noninvasive, example, pharmacological. So with this in mind, we at FDA initiated a small research program to study RV associated intussusception at the front level. At this point we are carrying some studies to see the effect of individual virology and products on host cells, what kind of cytokines and other facts that it can induce, and also the other protein, which is an enterotoxin of the virus, which is NSV4, and we are currently looking into the cytotoxicity versus attenuation of this particular protein.

And a small result is that where we identify the domain of heterogeneity near the NSV4 cytotoxic domain, and in different RV strains, and currently what role does this variable domain play has to be seen.

Thank you.

DR. DAUM: Thank you, Dr. Atreya.

We'll now hear the final presentation in

this series, which will be from Dr. Carbone of FDA on rotavirus vaccine, clinical studies, design and safety issues.

And then we'll have committee questions on this series of presentations.

DR. CARBONE: Today I'd like to give an overview of some of the considerations that all people involved in clinical study design and vaccine safety issues deal with both from industry and from the review community.

Next slide, please.

So part of this will be a general discussion and part will refer specifically to considerations evaluating rotavirus vaccines in clinical studies.

The question comes with the experience with the licensed vaccine. What is the current status of rotavirus vaccine development? This information comes from published and public information and serves merely to give examples and demonstration that rotavirus vaccine development activity is still quite active in the United States.

These include live attenuated vaccines from other sources, bovine human, attenuated human strains, even a lamb derived strain in China,

inactivated virus-like particles that don't replicate, and even some recombinant salmonella and vaccinia is expressing rotavirus proteins.

Next slide.

The safety assessment is, of course, a critical part of the vaccine developmental process, and one thing to be established up front is all vaccines carry some risks. What we aim to do is keep the risks as a minimum and the efficacy at a maximum.

There are, of course, some minor risks that we're all aware of, the sore arms following vaccinations, but there are some major risks which we aim to keep rare, and an example would be progressive vaccinia when an immunocompromised person received smallpox vaccine.

There are a very small number of cases, five cases per million doses it's estimated, but the fatality rate was fairly high. Two of those cases would be expected to succumb to the infection, and therefore, vaccines are approved for use and actually use clinically based upon the efficacy and analysis of benefit.

And the safety analysis always includes a study of the risk and benefit of the vaccine.

Next slide.

Vaccine safety is classically derived from what we call attenuation. This would be live viral vaccine, and by attenuation, we can define that as the disease with the wild type infection is significantly worse than the risks of the vaccine.

And I've listed some examples in smallpox. Wild type was estimated to kill approximately 20 percent of people infected, whereas the vaccine caused five serious adverse events per million doses.

In polio, and this would be live oral polio vaccine, the wild type vaccine was associated with up to 5,000 cases of paralytic polio per million infections, whereas the vaccine produced two cases of paralytic polio per million. That would be the first dose, significantly less risk than the second dose.

Rotavirus vaccine, we've basically presented the risk for the disease in the United States, and of course, the risk of vaccine use has to be determined for each vaccine, but just to note in a recent international meeting with the WHO in February of this year, the conclusion was arrived that significant health risks of wild type vaccine -- sorry -- rotavirus disease supports the continued rotavirus vaccine development study.

Next slide, please.

One thing to note -- this is very important in assessing vaccines -- is that the risk-benefit assessment is always a moving target. Vaccine safety profiles can change for a variety of reasons. When natural history of the disease changes, for example, the eradication of small pox, even a low risk of death following vaccination may become unacceptable. When the risk of natural disease varies by geographical area, what may be a serious risk-benefit in one area might be a risk-benefit worth using the vaccine in another.

One of the ways we deal with this in the United States, for example, is we don't recommend universal vaccination for Japanese B encephalitis, but for a traveler traveling to an endemic or high risk area, the benefits may then outweigh the risks.

When safer vaccines are developed, the risk of the old vaccine, the risk profile of the old vaccine may change, and a recent example would be the preferred use of acellular pertussis based on reactogenicity data.

With evidence of exposure to natural infection, those exposed to rabies are obviously at higher risk, and therefore, the benefits of the vaccines increase.

And finally, the risks and benefits associated with viruses can change with post marketing studies following licensure, and RotaShield in intussusception would be an example of that.

Next slide.

How can vaccine safety be assessed? As Dr. Atreya has discussed, basic research and a better understanding of the mechanisms of natural disease pathogenesis, vaccine adverse event pathogenesis, and vaccine attenuation can only help in our ability to design rational and safer vaccines.

Preclinical evaluation is an important part. Either testing in animals or adventitious agent testing in tissue culture or molecular biological testing are good examples of steps that can be taken before clinical testing to improve safety profiles of vaccines.

Obviously the vaccine then moves into clinical trials for safety testing, but we don't stop there and continue with post marketing surveillance and post marketing studies following licensure.

Next slide.

So how can we determine the vaccine safety profile for use in humans? We can't determine the safety profile of the vaccine definitively until it is

actually studied in a clinical trial.

What kind of adverse events do we look for? Well, traditionally one looked for adverse events that could be predicted based on what we knew about wild type disease. An example in rotavirus would be obviously disease and fever -- pardon me -- diarrhea and fever.

And as we've learned perhaps from this rotavirus experience, that there may be unexpected adverse events as well in intussusception and, of course, question mark. Those may not become obvious until the vaccine is studied.

So how do we design a clinical trial to assess future vaccines, rotavirus, for safety? Well, of course, we start by reviewing the available safety information on the new candidates to identify potential adverse events. At that point the decision is made whether the vaccine has a reasonable safety profile to proceed to clinical use.

And since we're not addressing efficacy, of course, the vaccine would have to have a reasonable efficacy profile to make it valuable for future study in addition.

Then the task is to design a clinical trial adequate to safely in the study subjects detect

a significant increase in an adverse event in vaccinees versus placebo recipients.

Next slide.

Again, we have what might be called a moving target in that the ability of a clinical trial to identify adverse events can be affected by the frequency of the event. Low frequency events, such as intussusception, may require large studies in order to accurately detect a change in placebo versus vaccinee recipients. Our ability to diagnose or define the adverse event also affects our ability to pick it up in a clinical trial. A qualitative event, such as intussusception, which is initially a disease syndrome, may be more difficult to define and diagnose than a syndrome which might be a change in blood counts, for example, which would be a simple lab test and a quantitative number.

The studies have to be performed in an area where there is adequate medical and technical resources to identify rapidly the adverse events, particularly those that are serious. Parents and guardians require good education in order to identify serious consequences that need to be brought to medical attention.

Safety monitoring design of a study is

critical. The frequency of monitoring, taking into account information such as the timing of intussusception following vaccine administration is essential.

In addition, passive monitoring is important, and patient-parent education are helpful, but active monitoring is believed to be also an essential event.

Next slide, please.

In clinical trials, it is very careful, a safety assessment, to carefully select the subjects and carefully define exclusion and inclusion criteria for subjects in the study.

Informed consent is a paramount concern, and informed consent for rotavirus vaccine use may contain the previous rotavirus vaccine experience so that the parent and/or guardian is fully educated, and that includes to presence of intussusception risk, therapies that include surgery, and other therapies which may have their own risks, and the very rare but reported risk of death.

Monitoring of adverse events rates in ongoing studies have to be considered during the study. It is simply not appropriate to perform a study and look at the end. Monitoring of the adverse

events during the study is an important feature.

Again, frequency has to be considered, how often it's monitored. Monitoring carries the risks of losing the double blind nature of the study, which is critical, and that needs to be considered, and there need to be carefully defined, reasonable stopping rules predetermined so that when an adverse event is detected at an unacceptable frequency, the study can be stopped quickly.

Next slide.

And finally to consider, there are many things to consider, but finally here clinical trial design for vaccine safety assessment requires careful statistical considerations, again, including the number of subjects, because statistical power to detect a difference in adverse events in vaccinees versus placebo recipients if key, and also the process of data analysis, the statistical process, has to be predefined and carefully determined.

Thank you.

DR. DAUM: Thank you, Dr. Carbone.

And to all of the individuals who helped orchestrate that concise sharing of information with committee.

What I would like to have now is questions