DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV)

June 10, 2010

Parklawn Building
5600 Fishers Lane
Rockville, Maryland

Proceedings by:
CASET Associates, Ltd.
Fairfax, Virginia 22030
703-266-8402

Table of Contents

P R O C E E D I N G S

Agenda Item: Welcome and Chair Report, Charlene Gallagher, Chair

MS. GALLAGHER: Good afternoon, ladies and gentlemen. As he told you this is the 76th meeting of the ACCV, and I'm am privileged to begin my term as chair of this commission. I would like to start the meeting by having all of the commissioners and the ex-officios introduce themselves, any who are here, so that the people on the phone know who is in the room. Unfortunately Magdalena Castro-Lewis will not be able to join us today.

MS. DREW: Good afternoon, I'm Sherry Drew.

MS. TEMPFER: Tammy Tempfer.

MR. SCONYERS: Hi, I'm Jeff Sconyers.

DR. MULACH: Barbara Mulach.

DR. FISHER: Meg Fisher.

MS. HOIBERG: Sarah Hoiberg.

DR. HERR: Tom Herr.

MS. BUCK: Tawny Buck.

MS SAINDON: Elizabeth Saindon.

DR. EVANS: Geoffrey Evans.

MS. GALLAGHER: Thank you all very much. We are aware of the difficulties that people on the phone have encountered in hearing parts of the meeting previously. So we are endeavoring to speak into the microphones and to

keep our voices up throughout the meeting. If there are any further difficulties, if, Tawny, you would be kind enough to let us know we will try very hard to correct them on the spot.

Okay. We would like to start out - our agenda is going to deviate very slightly from what was posted on the website. And I want to start out by first thanking the staff and the members of the agenda committee for helping out, setting up the agenda, getting the agenda posted so that everybody could have advanced notice of the topics that we anticipated, and for all of the work on the website and the postings on the website. I am very pleased at how well that went, and we hope to continue that and to continue to give people advanced notice of topics and of the presentations whenever that's possible.

I would like to ask Gary Golkiewicz to come up to the microphone now and he is going to introduce us to the new Chief Special Master. Gary, could you please come here; and this is only because we're having these audio problems. So, if everyone who is speaking would please come up to the front, we understand that the volume is better here.

Agenda Item: Introduction of Chief special Master Sandra Lord, U.S. Court of Federal Claims, Gary Golkiewicz, J.D., U.S. Court of Federal Claims.

MR. GOLKIEWICZ: Thank you, first of all, for accommodating us on such short notice. As you're aware, on April 8, 2010 the Court announced the appointment of Special Master Dee Lord as the new Chief Special Master. It's a change in leadership that has been discussed between the Court and myself for several years.

In a minute I will introduce my colleague. However, before doing so I would like to use this forum to express to everyone connected with this program what an honor and privilege it has been serving as the Court's Chief Special Master for over the past 21 years. To say the least, there have been very few dull moments.

From my perspective, the most enjoyable part of being Chief, and the part I will miss the most, is interacting with policy groups such as the commission, the leadership of our bar past groups and parents. I simply want to say to all of you thank you for the opportunity to discuss the immensely important issues that impact the compensation program.

I note that I'm well into my transition of serving as a Special Master with no administrative responsibilities. I've already noticed that I sleep better, I get to the gym each day at lunch, I don't work at home in the evenings or on the weekends, and since my boss is here today, I've actually begun preparing for conference

calls and after this month will be caught up on my decisions. I look forward to serving out my current term, and, if the Court deems it appropriate, at least one thereafter.

That said, I'd like to introduce our new Chief Special Master, Dee Lord. I won't go over Dee's biography - it's available online - except to note that Dee has a very impressive and distinguished legal career as an attorney and as a judge. I knew quite a bit about Dee before she started as a Special Master. I was on the hiring committee that selected her. The qualities that we saw during the interview have borne out in practice.

Dee is an exceptional legal talent, but more importantly to her colleagues, and very importantly to Dee in her new role, is her calm demeanor, sense of humor, and pragmatism. Dee is quick to zero in on what is important, seeks out the relevant information and acts accordingly. She has all the attributes of an excellent leader, and exhibits no hesitation in leading.

The federal courts changes chiefs regularly. In fact, except for our court and the Supreme Court, it is by law every seven years based on seniority. Only in the Supreme Court is it Chief for life. Changes can be difficult in any organization, but not at the Office of Special Masters. The transition has been seamless due to

Dee's personality and abilities.

In fact, in the first days after the announcement I was frequently asked why did the Court make the change. Now, as Dee has become active as Chief Special Master, I'm asked what took the Court so long to act. It is my pleasure to introduce my friend, colleague, and the Court's new Chief Special Master, Dee Lord.

MS. LORD: Thank you, Gary. I want first to thank the commission for the opportunity to be here today to say hello to everyone and to be introduced. Then I want to thank Gary for his kind comments, which I wasn't expecting.

On these occasions it's become a familiar feeling for me when I get applause because of being the Chief Special Master that I have done absolutely nothing to merit any accolades. I hope that I will be able to serve the Office of Special Masters in a way that continues the tradition that Gary Golkiewicz established and has carried through for more than 20 years.

It's a program that he contributed to at the beginning and at every step along the way has worked enormously hard to make into a credible, honorable, and accomplished program that I think, based on my observation, serves very well the constituency, the participants, and the public. So I can't say enough good things, and I can't

thank Gary enough for having created the environment in which I am privileged to work at this time.

I look forward to working with all of you. I hope to reach out, and already have reached out to some of the members of the petitioner's bar and to the Department of Justice, and I'm encouraged by the willingness of the participants who work with us in the Office of Special Masters as we move forward to achieve more and better results for everyone who's interested.

I'd like to take this opportunity, as well, to invite you to the Judicial Conference of the Court of Claims, which will include again a vaccine component. The conference will be held in Washington. It will take place on October 26th and 27th. On the 26th we will have a program by the Special Masters who have been assigned to the autism cases and they will provide an update on those cases at that time and be available for questions and answers. And then on the 27th there will be a panel discussion about the Vaccine Injury Compensation Program and some of the issues that face us today. So I will be sending out more information about that, but I hope that as many of you can attend as possible and can participate.

Thank you again for putting us on the agenda on very short notice. And, again, I look forward to working with you and I appreciate the opportunity to serve in this

capacity.

MS. GALLAGHER: Thank you very much, and we welcome you. And I also want to take this opportunity to give heartfelt thanks to Gary who has been so gracious and so accommodating to this commission whenever we reached out to him for his assistance and for his expertise. So, I really will miss him. He has been wonderful to us in accommodating our schedules. And thank you very much, and I hope you continue to get lots of sleep.

Agenda Item: Chair Report

MS. GALLAGHER: Traditionally this is the time for the Chair to give a report. I would say that I have little to report other than the Communications and Outreach Working Group has been making great progress on many fronts. And we had another meeting of that group this morning. And I'm going to defer discussion of that until Sarah gives her report later on in the program.

At this point I think we should turn our attention to the minutes of the meeting. And I was wondering if anybody would like to make a motion.

Agenda Item: Approval of March 2010 Minutes

MR. SCONYERS: Move approval -

MS. GALLAGHER: Are there any additions, comments, deletions for the minutes that need to be discussed?

DR. FISHER: Excuse me. I just have one correction. It's Meg Fisher. On page 2 in the second paragraph, I think it's a typo. The vaccine that's listed is ETaP.

DR. EVANS: Oh, it should be DTaP.

DR. FISHER: Right, but DTaP is the next one. So I'm not sure exactly whether it's Tdap or which vaccine it's supposed to be, but it - ETaP is not a vaccine. So it's page 2 of the minutes, the first full paragraph, the fourth line. Well, it could be Tdap.

MS. GALLAGHER: Dr. Evans, maybe you can help us out here.

DR. EVANS: Td is probably what it should be. Td or Tdap. Td/Tdap. I'll check that.

DR. FISHER: So that was the only thing I noticed.

MS. GALLAGHER: Okay. Is there anybody else who has any comments on the minutes? Okay, with that amendment, all in favor of approving the minutes say, "I".

(Commission members respond affirmatively.)

Any opposed?

(No response.)

All right. The minutes are approved. Thank you.

Now, Dr. Evans, would you please proceed to your report from the Division of Vaccine Injury Compensation?

Agenda Item: Report from the Division of Vaccine Injury Compensation, Geoffrey Evans, M.D., Director, DVIC

DR. EVANS: I'd be very pleased to. Thank you, Charlene.

So I'll be the third person to welcome everyone to what is now the 76th quarterly meeting of the Advisory Commission on Childhood Vaccines. The meeting highlights today will include my update, the Division of Vaccine Injury Compensation, then an update from Mark Rogers from the Department of Justice Vaccine Litigation Office.

Following that will be an update on the omnibus autism proceeding by Kevin Conway, a review of several vaccine information statements by Skip Wolfe from the Center for Disease Control and Prevention, then updates from various ACCV ex-officio members, from the National Vaccine Program Office, CDC, FDA, and NIH. We will then end the meeting today with a review of PCV and rotavirus vaccines by Dr. Philip Krause, and a follow-up discussion with postmarketing safety of U.S. licensed rotavirus vaccines by Dr. David Martin, both from FDA.

For tomorrow's session we'll have a clinical case review presentation by Dr. Rosemary Johann-Liang who is our chief medical officer. Several of you have expressed interest in finding more about the kinds of cases that we have going through the program. Following that we'll have

Dr. Kathleen Stratton from the Institute of Medicine provide an update on a project that's been going now for some time and I know a lot of you have expressed interest in that. And we will end with Sarah Hoiberg giving an update on the Communications and Outreach Workgroup.

In your blue folders you will find today's presentations on the right side and tomorrow's presentations on the left side. That's pretty simple. In terms of the program statistics that are in your folders, you can see that it's been a fairly busy fiscal year for the non-autism program. If my calculations are correct, we are on track for about 390 or 400 claims at this pace. Again, the program is predominantly now receiving a majority of adult claims alleging injuries in adults, and influenza vaccine is nearly half the claims filed.

So the program is now twenty-one and a half years old, so the adult age group that we're now finding in terms of our claims. And so it, because the influenza vaccine is of course given in more than a hundred million doses per year, so that's a very active vaccine that we cover for this program. And the other noteworthy thing is that the autism claims have continued to trend downward. There have been 12 claims filed so far this fiscal year.

In terms of adjudications, again, it's a very brisk pace. We're on for equal if not exceeding what we

had this past fiscal year. So we're at now 117 adjudications so far, and in terms of the breakdown that we always report, the trend is staying pretty close to what it's been the past couple of years. There's been a slight decrease in the percentage of settlements. It's gone from 83 percent the past couple of years now down to 78 percent, and perhaps there's been a slight increase in - whether it's a real trend or not - in concessions in court decision are now at 11 percent, up from 8 and 9 percent. But the compensation numbers and pattern really hasn't changed remarkably over the past couple of years.

MR. SCONYERS: Can I ask a question? Jeff Sconyers. This chart that you're putting up talks about concessions, decisions, and settlements, and as you know Mark Rogers provides us with statistics from the Department of Justice, breaking cases down into concessions settlements, proffers and decisions. So I'm just wondering how the two sets of numbers fit together?

DR. EVANS: There's always going to be this difference, Jeff. And, Mark, when he gets up he'll report how he has a different cut-off for the, he goes from --

MR. SCONYERS: It's not about date; it's about characterization.

DR. EVANS: Well, when Mark presents, he'll describe how their breakdown is a little bit more

discerning than our breakdown.

MR. SCONYERS: You can't correlate your cases to his category of proffer? That's the thing that's missing.

DR. EVANS: Right. That's something that Mark will comment on and we'll try in the future to make that more clear.

In terms of awards, we're on track also for the highest amount of compensation outlays, projecting now to possibly as high as $100 to $125 million this year. This is because we've had several cases recently that have resulted in awards of greater than $10 million dollars, the highest being $16 million dollars. And, again, just to remind folks that an award is usually a lump sum payment and also the purchase of an annuity that will pay a lifetime strewing the benefits out. So a $16 million dollar award over the lifetime of a child or an adult will pay out much more than that. So you can see that the trend has been for the awards to be going up on an annual basis, as have the attorney's fees and costs. They now average $6 million dollars. And the bump up that you see in fiscal year 2009 was because of the interim fee payment in the autism proceeding.

The trust fund balance is currently over $3.3 billion dollars as of the end of March - 3.2 I should say, but probably now even closer to 3.3 now that there's been a

couple more months since then. And the net income if you project out for this year will be somewhere in the order of $240 million dollars, which would easily cover the outlays that I was just talking about.

In terms of significant activities this year, I'm pleased to report that medical staff attended three conferences as part of the DVIC outreach efforts. From April 15 to 17 Carol Marks and Jean Jackson-Southard staffed the VICP exhibit booth at the National Association of Pediatric Nurse Practitioners, otherwise known as NAPNAP, at their 31st annual conference in Chicago. Nearly 1,200 pediatric nurse practitioners who provide comprehensive health care to children attended and Ms. Marks and Ms. Southard handed out about a hundred information packages. Most who came by the booth were interested in the H1N1 vaccine; at that point that was much more in the news.

From May 17 to May 19 Annie Herzog and Kay Cook from our office staffed the booth for the 50th Annual Clinical Meeting of the American Congress of Obstetricians and Gynecologists, and that was in San Francisco. And they had over 3,600 attendees and both Annie and Kay handed out about 90 information packages. And most were interested in the HPV vaccine and also expressed interest in autism.

And finally from May 31 to June 2nd, Carol Marks

attended the American Academy of Physician Assistants Annual Conference in Atlanta. And there were over 3,000 PAs and students that were in attendance. And Carol handed out about a hundred information packets. And, again, H1N1 vaccine, there was a lot of interest over that, and also the idea that adults are covered by the program. I continue to have people still express to me surprise over learning that adults can follow the program, because it is the National Childhood Vaccine Injury Act that created the program, and we do cover vaccines that are routinely recommended for children by CDC. But anyone that receives a covered vaccine, no matter what age, can file a claim or have a claim filed on their behalf.

And finally, Magdalena Castro-Lewis and I attended the National Vaccine Advisory Meeting that was in Washington last week. And we presented an update on the program as well as the ACCV activities. And I would also mention, and I've said this to some others, that our own Tawny Buck, who now has dual roles on the ACCV, as well as the National Vaccine Advisory Committee, did a stellar job as one of the co-chairs presenting an update to NVAC on the recent activities of the Vaccine Safety Workgroup. So they have taken on tremendous responsibilities in the past year or two; a lot of work.

I thought I would throw in a couple slides on

communication. I know you've expressed some interest in the kinds of inquiries we get. By vaccine, you can see that both emails as well as phone calls, DTP, DTaP -- more the DTaP, of course, now DT childhood vaccines are a frequent source of inquiry, as well as MMR vaccines. But the second most common is the influenza vaccine. So you have a mix both I think of parents as well as adults that are contacting the program and asking for information. And you can see after that there's a significant drop off of the remaining vaccines that are covered under the program.

And in terms of the nature of the requests, the most frequent is information on how to file a claim, which would make sense. But then after that are questions about the statute of limitations, about the autism proceeding, and then after that there's a drop off to things such as seeking medical advice, questions about pair of last resort, and vaccine mandates. So that gives you an idea of the kinds of work that we do in our communications branch.

For the telephone audience I'm going to read slowly the points of contact for those that are interested in contacting the program. And you should write, if you wish to, to The National Vaccine Injury Compensation Program, 5600 Fishers Lane, that's in the Parklawn Building, Room 11C-26, Rockville, Maryland 20857. And the telephone number, toll-free, is 1-800-338-3382. And the

website address for our program is www.hrsa.gov/vaccinecompensation. And those wishing to submit public comments, or participate in commission meetings should write to Andrea Herzog at the address that I just provided. Her direct phone number is 301-443-6634 and her email address is aherzog@hrsa.gov.

And with that I will end my update. I'll take any questions that people have.

MR. SCONYERS: I just want to go back to my earlier question and now convert it to a comment, which is your data sets don't match up. And so it makes it very difficult for members of the commission to understand what you're talking about when we get pretty detailed information from the Department of Justice and from Mr. Rogers, and can't correlate that to what you guys have. It doesn't seem like it would be that big of stretch to use corresponding definitions, because presumably the same definitions apply to all of the cases. So, speaking just for myself, I would make that request, if possible.

DR. EVANS: You know, and I did not mean to underwhelm you with my answer, but this has been a challenge, let's say, over the past years. And there are also some differences in data that the court will send to us or send to the Department of Justice. The numbers don't always agree. But you're talking about something that's

more qualitative, and that's just the understanding of the various terminology and how the numbers intersect. And that's something that we will work on and see if we can make that more transparent.

MR. SCONYERS: Thanks.

MS. GALLAGHER: All right. Thank you very much, Geoff, and thank you for your report. I would like to move on and ask Mark Rogers to please come up and give the report from the Department of Justice. Thanks, Mark.

Agenda Item: Report from the Department of Justice, Mark Rogers, J.D., Deputy Director.

MR. ROGERS: Thank you. Chairman and members, I'm happy to be here. I'm Mark Rogers and I represent the Justice Department.

The statistics are very similar to the statistics last time. Again, our statistics are from ACCV meeting to the next, so it's a short-term snapshot of what's happening in the program. These are the filings echoing Jeff's comments. We are down tracking on the number of autism cases filed. The non-autism cases are slightly up ticking. There are more adult than child cases, and that's been true for some time.

Okay, the totals cases adjudicated, 54; compensable cases, 22. We had two conceded by HHS, twenty not conceded, 15 settled, one decision, and four proffer.

And responding to the question, a proffer is a hybrid situation. The decision is a decision by the special master resolving a controversy between the two parties. DOJ, Secretary takes one position, and petitioners another, and the special master has to resolve it. That's a classic decision. A proffer has a lot of the features of a settlement. And that is, what a proffer is when both sides agree as to what the evidence shows, but they put it before the special master to decide the case.

And it's different from a settlement because a settlement is a handshake between the parties as to what the award should be. And it sounds like, well, that's a distinction without a difference. It's one that I would say is engendered by a very important nuance within the Department of Justice, and that is: a settlement has to be approved through a somewhat difficult process, bureaucratic process, if you will. But it has to be approved depending upon the amount.

A proffer is an agreement as to what the evidence shows, but it's up to the special master. The special master can award more than what the evidence shows -- it's hard to imagine that the special master would do that -- or less, conceivably. But it's a decision by the special master from which either side could appeal; and neither is going to appeal if it's consistent with that proffer.

We separate it out because we think it gives perspective on a substantial number of the decisions -- here four out of five -- that when the special master was deciding the case, the parties were in agreement. It wasn't a disputed case. And so it's representative, we think, of a good resolution where the parties have worked together and resolved their difference, albeit necessitating a decision by the special master.

I looked at HHS's numbers. I'm almost positive -- I haven't asked the question; we will, and we'll have a positive answer -- they are counting proffers as decisions. So we think we need at least an asterisk beside the decision category that some of those are made up of proffers where the parties really didn't duke it out. I hope that's helpful and I apologize for these nuances. And I have proffer defined in the glossary of terms. Are there any questions on that? Have I totally muddied it up?

MR. SCONYERS: That's very helpful. I would have guessed that proffers were actually in the settlements. But it's a guess, so it would be helpful to use common terminology.

MS. BUCK: Mark, when you talk about a proffer, you say it needs to be approved. Can you explain, you know, when you're trying to understand the hierarchy of who does what, can you explain to me who approves the proffers?

MR. ROGERS: The special master. And it's something frankly more important within the Department of Justice than to anyone else, and that is whether or not we need to move this agreement, if you will, through the settlement process of approval. And for differing amounts it's more processing. And we're very careful with it internally, because we do not want to circumvent that approval process. We don't want anything that looks like a wink by us as DOJ attorneys that circumvents our superior's authority to approve settlement.

And so here's the key touchstone, and that is that the parties genuinely agree as to what the evidence demonstrates. There is no material difference between the parties on what the evidence shows. That's different from a settlement where DOJ thinks the evidence shows this award should be given and petitioners believe a higher award should be given, and we agree to split the difference. That is a settlement.

A proffer is where -- a classic case is where we've agreed to use a joint life care planner, there is only one life care planner reviewing the case. Neither party, after agreeing to that life care planner, can -- well, you can, but it just wouldn't go over very well -- disagree with that life care planner's recommendations. I mean, everything happens in life. But normally that life

care planner's plan becomes the evidence in the case, the only evidence in the case, the undisputed evidence in the case. So rather than go through the rather long, laborious process of getting a settlement approved, they say, "Special Master, we've got one life care plan. We both agree that's the only evidence in the case. Do what you will." And then the special master approves it. Does that help?

MS. DREW: I just wanted to further confuse or clarify by saying that you can have a proffer in a case where entitlement has been conceded. And after entitlement is conceded, then you have a joint life care planner. So, the parties are in agreement on everything, but it's still not technically a settlement.

MR. ROGERS: That's a good clarification. And, again, we have them up here because we're proud of them. We think they show that we're working hard to resolve these cases quickly and fairly with everybody satisfied with the result. So, decision makes it sound like, you know, we had to go to the special master and we had duked it out. So, I'm belaboring it.

MS. BUCK: If the proffer process is faster, I mean if the parties all genuinely agree, then is it faster to do a proffer than to just have them present all of that for a decision? Is that, is there some element, because

I'm still a little confused on that piece?

MR. ROGERS: That's a good question. It is faster than a settlement at that point.

MS. BUCK: What about a decision? How does it differ from a decision? I mean, if everybody agrees, then -- or maybe I'm just very confused about the process -- but then wouldn't they just go before the special master and wait for a decision?

MR. ROGERS: It really is, that is what the proffer does. It tees it up for the special master to decide it. And when both parties are telling the special master, usually at a status conference, this is it, we both agree, the special master turns to their clerk and says write it up. So it makes the decision very quick.

If both sides come to the special master and say, you know, we've got a problem. Our life care planner says this; their life care planner says that. You've got to decide it. Then we're waiting for as long as it takes the special master to get to that case. You know, they line them up and prioritize them. So the proffer is very fast.

MS. DREW: I just wanted to add one more thing. Every case has a decision, whether there's a proffer, whether there is the special master actually deciding a disputed case, it all ends with the special master's decision, and then following that a judgment on the

decision.

MR. ROGERS: Right, yes. I think that one confuses -- it certainly confuses our statistics. You are correct. The settlement has to be approved by the special master. So, in the end, there is a decision, something going to judgment. What we're trying to clarify here is how we get to that ultimate decision. Was it a resolution by the special master of a contested matter? Was it an agreement by the parties as to what that award should be? Or was it an agreement by the parties as to what the evidence shows, which drives a very quick decision? Does that help

MS. GALLAGHER: I thought that was very helpful in explaining the difference. Tom?

DR. HERR: Both questions about the proffer deal with settlement as opposed to the actual compensability or non-compensability of the case?

MR. ROGERS: Yes. The proffers deal with the level of compensation. They generally -- never say never -- I can't recall a case where we've proffered the evidence on whether entitlement is appropriate.

DR. HERR: For me that is an important issue.

MR. ROGERS: Yes. We're not talking about that here. There are times when we agree the evidence is what the evidence is; special master decide on entitlement. But

that’s different.

MS. BUCK: Does it make any difference on what information can be shared publicly after the case is all done, whether it’s settled, a decision, or a proffer?

MR. ROGERS: I’d have to look at the -- what I know can be shared publicly is the published decision of the special master. I know what that looks like for a settlement and for a decision. I’d have to look at an accepted proffer to answer that question. My best guess is that it makes no difference, that the proffer is published as part of the decision. So, I don’t think it makes a difference.

MS. BUCK: Thanks.

MR. ROGERS: And if that’s not true, I will say so and clarify at the next meeting.

MS. BUCK: Okay.

MR. ROGERS: Then non-compensable cases, 32, of which 21 are autisms. So, yes, that would -- we’ve been tracking the autism cases separately because we think they mask the background performance of the program. The numbers were so great, and they are episodic. So, you can compete the numbers either way. If you include the autism cases, we’re at about a 40 percent compensation rate. If you exclude them and consider non-autism cases, Geoff’s numbers track with ours, and those presented here, they’re

at about 66 percent.

MR. SCONYERS: Procedurally what's happening with the autism cases? Why are they being decided now? I've lost track of where the individual cases are against the background of the test cases.

MR. ROGERS: They are being activated in an organized fashion by the special masters, basically asking the parties to take a look at these and start categorizing them as to jurisdictional problems, documentation, and working them towards resolution, not all at once, but a certain number per month.

MR. SCONYERS: Thank you.

MR. ROGERS: There are terms in here we have a negotiated settlement signed by the parties. The special master has to approve them, but generally -- almost always -- the special master is leaving it to the parties to resolve when he approves that settlement. Whereas a proffer we're agreeing to what the evidence shows.

The cases have been moving through our decision chart here in much the same way as you saw in the numbers a couple more went down the conceded side. A settlement could be a case that went down the non-conceded side and then moved over for a decision through a proffer or a settlement.

And the autism cases we've briefly discussed,

theory one, what's new for this meeting is we have the oral argument -- that was earlier today. And Hazelhurst was affirmed on May 13th. The other case wasn't appealed.

MR. SCONYERS: Could you say what the issues are on appeal in Cedillo?

MR. ROGERS: The issues in Cedillo, I sat in the argument this morning. What was discussed in the argument were the process issues, the submission of the Buxton evidence, and there was an argument about -- there was a Dalbert argument that was made by petitioners. The focus was on the process.

MR. SCONYERS: So similar to the issues in Hazelhurst?

MR. ROGERS: Yes. Theory two, the trials have been -- (audible dial tone)

MS. GALLAGHER: Thank you very much. There was an inadvertent disconnection of the line. So we will proceed again with Mark Rogers' presentation. And can I just at this point remind people who are on the phone that although the draft agenda said that public comment would be at approximately 5:15 P.M. today, we plan to have public comment immediately following the meeting. And right now we're maybe five or ten minutes ahead of time. And so if we finish a little early or a little late, public comment will be a little before or a little after, the published

time. We just gave the best approximation we could. Thank you. Mark?

MR. ROGERS: Thank you. On the appeals at the federal circuit level we have three new ones. And the takeaway here is this continues a trend, if you will, that by and large the appellate practice has been based on petitioner appeals, not respondents' appeals.

And the recently decided cases; Hazelhurst was affirmed. Cloer was decided, that's a statute of limitations case that was reversed. Doe 11 was decided; that was affirmed. And Moberly -- we had some discussion at the last meeting about that case -- it had been decided earlier a Request for Rehearing En Banc had been filed as of the last meeting. And I believe I explained that it's very unusual for the federal circuit to grant such a petition, and indeed here they have denied it.

Now, the Moberly case is not final, because now were within the period for a Request for Certiorari, should that be filed. That's an appeal to the Supreme Court.

MS. BUCK: Mark, is there anything that you can tell us about Cloer. You know, there's been a lot of interest in that ruling and how it affects the statute of limitations.

MR. ROGERS: Well, I really can't. And the reason is we are within our period for seeking rehearing.

And so that is very much under review. So, I think we'll have some clarity on where that's going to go by the next meeting, but right now that is in the decisional stage within HHS, and the Department of Justice, and the Office of the Solicitor General. So, that's a work in progress.

MS. BUCK: In terms of whether or not it will be appealed?

MR. ROGERS: Yes.

MS. BUCK: So, until that time it's not having an effect on any other cases until it's decided what you'll do and whether or not it will be appealed?

MR. ROGERS: Well, it's a panel decision of the federal circuit; it's the law of the circuit right now. It has to be honored by other panels of the circuit, and the courts below, right down to the special masters. So it will affect those cases until --

MS. BUCK: Can it have any potential effect on any of the cases in the Omnibus proceedings then?

MR. ROGERS: I don't know. We'd have to look at the case individually. It would affect a case that is untimely looking strictly at the date of the alleged first symptom of onset, because the Cloer court found that the statute of limitations does not run until one of two events. One is the medical community recognizes a causal connection between the vaccine and the injury. Or, two,

the petitioner is given notice by a medical practitioner of a causal relationship. That's a very short, simple statement of Cloer. So, it would affect those cases that were untimely based on the governing interpretation of the act before Cloer.

MS. BUCK: Mark, does this basically stop the clock at this point on anything that is in process that hasn't been decided on or any decision has been made, if it meets the criteria that you're talking about?

MR. ROGERS: That would be up to the, whoever the sitting judicial authority is. In a case before the special master, the special master would have to decide am I going to proceed with this case because I have a Cloer issue, or am I going to wait to see how the dust settles on Cloer, you know, wait for the periods for appeal to run. So, it would be up to the special master or the Court of Federal Claims judge handling the case. They could not proceed as if Cloer is not the law. But they could stay the proceeding until they're sure that it is the law.

MS. BUCK: Right.

MR. ROGERS: I can put it that way.

MS. BUCK: Thanks. I appreciate the insight into that.

DR. HERR: Is it possible with Cloer that -- maybe I'm still misunderstanding it, but let's say there's

someone who's had a change in their medical condition. And they're, because of maybe just general acceptance not pursuing the change in their medical condition. And it isn't until later that someone says, "You've got this condition." And tracing back the history that it started at a particular time and saying okay, this certainly could be vaccine related. Ten years later, ten years after the fact, could they still, with Cloer, bring a successful petition?

MR. ROGERS: I'd have to say I don't know.

DR. HERR: Because they weren't aware of it.

MR. ROGERS: Yes. I think Cloer deals with that issue, and how Cloer would be applied in an individual case, given the hypothetical one, I think is very much an issue under review. And, you know, I hate to speculate. If Cloer were not appealed, we'd be working through those issues case-by-case, giving full fidelity to the language of Cloer. I mean, if it's not appealed, it's a panel decision, it would have to -- we'd have to work it into our legal analysis. It sounds like a dodge, but a long way of saying I don't know.

DR. HERR: (Indiscernible)

MR. ROGERS: Yes, Cloer does treat that issue, is the most I can say with certainty.

Pending cases at the Court of Federal Claims,

these are appeals of special master decisions. We have five new ones. Again, just a quick takeaway, this is largely litigation by petitioner's bar. None of the appeals were taken by the Secretary.

Recently decided by the Court of Federal Claims there were five different cases. And we've parenthetically indicated what they were about: fees and costs, statute of limitations, entitlement, entitlement, fees and costs. And, again, petitioners have taken all of those appeals. Cedillo, we've already talked about. That argument was completed this morning.

Now, this is a little different from last time, per your request. Running through the stipulations we have a paralegal who pulls the stipulation as it comes through our office as it's signed, and on it's way to filing. So some of these aren't available on the court's website yet, but will be.

We've listed the vaccine, the alleged injury, and that's the injury listed normally in the petition. And what we have new here are the time it took to get from the petition filing to the filing of the stipulation, kind of the beginning and end of the process. It's not completely the end of the process, because we still have to go to judgment, we still have to either elect to accept or reject that judgment, and perhaps to go to HHS for funding. But

from my neck of the woods, the litigation, this is what we had control over.

DR. FISHER: Can I stop you for one second?

MR. ROGERS: Yes, Doctor.

DR. FISHER: Stipulations, I realize I should know what that means, but --

MR. ROGERS: Oh, I'm sorry. The stipulation is the agreement between -- that's the settlement. It's the stipulation of settlement. The agreement by the parties is finally signed by everybody that needs to sign it. I sign it, Geoff signs it, the petitioner signs it, the trial counsel both sign it, and then it's sent to the special master. The special master says this is great and files it under a decision saying I've seen it, I've read it, I approve it. And then we move into a 30-day period where one or the other party can appeal; but they never do. And usually we can get a waiver of that appeal period and get judgment to enter even sooner. Then it goes to HHS for payment.

DR. EVANS: Mark, just to be clear, getting back to categories, would a conceded case or a court decided cases, as well as a settlement ever be in the form of a proffer?

MR. ROGERS: No. A case -- well, if the case is conceded and then settled on damages, yes. If the case is

-- if it’s a death case it would go right -- there wouldn’t be a stipulation because the statute provides what the compensation amount would be.

DR. EVANS: No, think you’re doing sometimes -- that case there should be a stipulation.

MR. ROGERS: Okay. Are there any questions on that?

MR. SCONYERS: Just to make sure, these are stipulations that resolve essentially all aspects of the case; not just entitlement, but also the question of compensation?

MR. ROGERS: Yes.

MR. SCONYERS: Okay. When I first saw this, I thought they were just stipulations as to entitlement. But they’re complete resolutions of the case, as between the parties, waiting entry by the special master.

MR. ROGERS: Yes. I’m glad to clarify that. This is the end of a case for which compensation is being awarded, where the parties have shaken hands on the amount of that compensation. That is the stipulation of settlement that’s being filed. That’s the end point on these time periods. The beginning point is the filing of the petition.

Now, the important takeaway is, this is how long it takes in a settled case to get to that final act by the

parties that tees it up to be paid. And you'll see that generally -- and again I'd qualify this as one snapshot of just a couple of months -- you're looking at about a year and a half as your median.

MS. HOIBERG: Mark, this is Sarah Hoiberg. What went on with that detective that took computers --

MR. ROGERS: Well, I anticipated the question. I knew that -- and unfortunately I can't say. And here's the reason why: what you see before you is information that can be gleaned from the stipulation itself that's public information. How the case got to that point, you'd have to look at the docket sheet. It's there and in painful detail will explain exactly what happened in that case, who was asking for more time, who was doing what, who was on the dime for what order by the special master to do what, and had the whole procedural history of that case on the docket. The docket is not publicly available. And here's my concern: if you look at this number, you can go to those stipulations and figure out what case this is. And so anything I say about that case beyond what you have before you is privileged.

Now, anyone who wanted to find that stipulation and go to the petitioners, and say would you mind waiving confidentiality on that docket, by and large we would waive it too. And we would go through that case. I would

caution that when you go through an outlier case that might be informational on the outlier case. It wouldn't be very helpful in looking at the typical case. But beyond that it's something that you could do.

I can speak generally. If a case, if we went back down to our decision tree, if a case is not conceded, not settled, and developed for a decision by the special master, it's going to take a lot longer. And if a case goes that route and is appealed, it's going to take even longer.

MS. HOIBERG: So this could have been when it had appeals and all that?

MR. ROGERS: It very well could be.

DR. HERR: Any of these of record?

MR. ROGERS: You know I was looking at some of those. Yes, there are some very quick ones here. And what I'd say on that is that if you have all the planets aligned, that is you get a petition that's fully documented, and that's somewhat unusual. That, I dare say, is the biggest problem, if you will, the biggest impediment to quickly resolving a case is that the petition comes in with little more than an allegation. And it's a process driven by petitioner usually asking for more time, generally not objected to by respondent, to develop that documentation. That is the longest pole in the tent, if

you will.

And so if a case comes in and it's fully documented, and this is a stipulation, meaning that there wasn't a confession. Now, it's conceivable -- I don't actually know on this case -- it's conceivable it could have been conceded and then stipulated on damages within that five months. But it would take a fully documented case. It would have to be very clear issues between the parties. It would have both sides leaning into moving this to an agreement. I mean five months is an extraordinarily short period.

And I would say probably an uncomplicated case, because another requirement that makes these cases take a long time is you'll have petitioners with a very complicated life care situation, and they need time to develop what the life care needs are. That is another area that is time consuming.

Bruesewitz, last but not least, this is a case that Certiorari has been granted. That is very unusual; I think the running ratio is 1 in 100. It was granted just a few days after our last meeting. What I've provided to you is a brief filed by the solicitor general that contains the government arguments in the case. Now, it wasn't filed in Bruesewitz; it was filed in Ferrari. And the gist of the recommendation was that Cert be granted in Bruesewitz. I

have the issue before you. The issue is very straightforward. The language of the statute, I won't say is straightforward; I will say that is the subject of the litigation. And there are two different views of what that statute means, and that is what the Supreme Court has agreed to look at. Are there any questions on that?

MR. SCONYERS: I noted that Ms. Saindon is on that brief, and I congratulate her for that.

MR. ROGERS: And I guess I could add that a Petitioner's brief in Bruesewitz has been filed just recently, and six amicus briefs have been filed -- amicus to Petitioner's. And we looked for a link that you could go and see those, but we haven't successfully come up with one. We can give you one to the Petitioner's brief, but the amicus brief, we have them, but we haven't found a link to them. And that concludes my remarks.

MR. SCONYERS: I'd just like to say again thank you for getting your materials to us ahead of time. Thank you for your responsiveness to our requests, your last several slides looking at the time to resolve the cases is really incredibly helpful I think and provides a lot of insight into the way the programs are actually working. And I think that by and large cases are getting resolved pretty quickly -- always with some outliers. And I'm sure in each of those outlier cases the people involved feel

that acutely. But, on average, it looks like within the limits of litigation things are moving reasonably quickly through the system. So, I appreciate you bringing that information back to us. I know we've asked you for it and you've been very responsive to all of our requests.

MR. ROGERS: Well, thanks for your comments.

MS GALLAGHER: And I would like to second that and say, yes, I've found the information that you bring us extremely enlightening and well put together, and we really do appreciate it, particularly getting it in advance of the meeting so we can study it. So thank you very much for that.

MR. ROGERS: You're quite welcome.

MS. BUCK: I have a question and I'm not sure if it's for Mark or Geoff. But the one thing that we haven't gotten information on here or even last week at NVIC was about the Countermeasure Injury Compensation Program. And the reason that I ask about the status of that and the claims filed in there is because H1N1 strain is going to be included in this year's seasonal flu vaccine, which then would lead most people to believe will be then covered under this program any claims filed. So, it would be interesting to know what types of claims are being filed and even settled in the countermeasure program, but we just don't seem to be getting any information about that. Is

there anything you guys can share with us about what's happening with H1 counterclaims?

DR. EVANS: Tawny, this is Geoff. As you may know, last week's NVIC actually for a while Dr. Vito Caserta was on the agenda to provide a CICP update. And because the program is still in the developing phase it does not publish its regulations in terms of its operational framework and so on. That has to be done first. In the meantime the program has received more than 200 notices to file and is collecting them and making efforts. I think there will be something in an MMWR coming out shortly to let people know about the deadlines to the program and so on.

Many questions exist now. I think that over the next four to six months when the regs are finally published and the program really begins to process theses claims we'll be able to give much more information about where things stand. But for right now that's where things are at the moment and your point about the H1N1 being in this year's seasonal flu vaccine is a very good one, one that we're all aware of, and therefore the program for the 2010-2011 flu season will be covering the H1N1 vaccine, because it will be part of the trivalent.

So I guess what I'm saying in conclusion is that I think the September meetings of both NVIC and ACCV,

particularly the ACCV, will have much more information about where things stand with both programs.

MS. BUCK: It sounds just like the countermeasure program will be processing claims about the same time that you all might be processing the same types of claims, if the timeline is what you say it is. So, is there some system in place for you guys to do these in cooperation? You're going to be looking at a lot of the same kinds of things then, and about the same time, although H1N1 program will be looking at from when it occurred. But if the timeline is what you say it is, then you guys will be sort of processing things together.

DR. EVANS: There will certainly be some overlap, but in terms of the ability for the two programs in terms of proximity, we share the same office space pretty much and we're around them and meet with them quite frequently. So we're quite aware of what's going on with their program, as well as the opposite. So I think that they will be -- there's a six-month, at least a six-month delay between claims being filed with our program, if not longer. So I would think that they will be, hopefully with the regs published later this year, they will be significantly into their processing by the time we start seeing claims for our seasonal flu vaccine for this next year.

MS. BUCK: Just a statement on the record that

there was very little at all in terms of outreach to the public on the H1N1 campaign on the countermeasure program, and there's been very little even to those of us who spend our daily lives working on this topic. And I also understand that the statute of limitations for filing in the countermeasure program is extremely short, like one year. So, you know, I find that to be pretty disappointing for the kinds of issues that people may face in the aftermath of the H1N1 vaccine. But I certainly hope that there's cooperation between the two programs as you guys start to wade through claims that come in this year.

Thanks, Geoff, for the update.

MS. GALLAGHER: Thank you very much, Mark. Now, I was advised that our next speaker is on his way right now, so we'll just wait for a couple of minutes because he's in the building and coming down.

Agenda Item: Omnibus Autism Proceeding Update, Kevin Conway, J.D.

MS. GALLAGHER: I want to thank Kevin Conway for agreeing to come here and present to us. If you would be kind enough to come to the front, we're having some problems with people hearing on the phone, so we're making a concerted effort to have everybody come to the front so that we can -- if we could pull that mic over? Thank you very much.

For those of you that don't know Kevin, he is with the firm of Conway, Homer, and Chin-Caplan, and he has been involved with issues of vaccine compensation since the inception of the program. And I am told that he is a wealth of information and knowledge, and we're just so grateful to him for coming here to address us today. Thank you very much.

MR. CONWAY: I'm happy to be here. It's my understanding that I'm here to give some information as to what my perspective is on the future of the autism cases in the vaccine program. And I would ask anybody that has any questions to feel free to ask questions. My partner, Warren Homer, is here with me in the audience, and he's also a wealth of information, especially probably even more qualified than I am to talk about what's going to happen to these cases in the future.

But let me just tell you from our perspective, from my firm's perspective, we represent several hundred autistic children. And we actually represented Michelle Cedillo, who was the first test case in the autism proceeding, and she proceeded on a theory of whether the thimerosol-containing vaccines and MMR vaccines together can cause autism. She lost her case before a special master. We've made a motion for review to the Court of Federal Claims, and they upheld the decision of the special

master. And her case was argued this morning at the Federal Circuit Court of Appeals, and we're expecting a decision within the next few months on her case.

There were actually three test cases on that theory. One case, the Snyder case, also lost at the special master level, appealed to the Court of Federal Claims, lost again, and decided not to take it to the Circuit. The third case was the Hazelhurst case. That case also lost at the special master level, lost at the Claims Court level, and a couple of months ago also lost at the Federal Circuit level.

So on that theory, so far every case has lost at every stage of the way. And Michelle Cedillo's case is the only one of the test cases that's still outstanding and we're waiting for a decision from the Federal Circuit.

There were also a group of cases called the mercury only cases that alleged that the mercury in the vaccines by themselves caused autism. There have been decisions by the special masters on those cases dismissing the petitions again, and counsel on those cases decided not to move for review, so those cases are in essence over.

So the question is, where do we go from here? It's not a simple answer. First of all, every case in the vaccine program is a different case. Each one rests on its own merits. Each one has a different back situation. The

idea behind the test cases was to give some guidance as to what theories had merit, what theories didn't have merit, whether there was any merit to any theories at all.

And my sense is -- and I'm sorry I didn't hear Mark Rogers talk; I would have enjoyed that, because it lets us know what the respondent's perspective is -- but our perspective is that it will give a lot of guidance in a lot of cases. My sense is that mercury only cases, you know, probably will leave the program for not having a theory, not being able to get expert witnesses.

Now, the autistic children who have this theory, again, they're individual cases, and each one has to be looked at individually. And by and large most of the cases in the autism proceeding have not been looked at individually. We have collected records in some cases where it looked like there might be statute of limitations problems, but there's still a lot of work to be done from our standpoint. So what do we do? We will look at cases, we will make a decision as to whether we have a reasonable basis to continue with the case, whether we can get an expert.

And for cases that we don't believe we can, we probably will just try and assist the client in exiting the program, and then they will go into the civil arena, and they will hopefully wait until the science develops or

doesn’t develop and make some choices in the future as to what their rights are. But they do have the right to file a civil action, at least as of right now. That may change in the future. But as a right now they’ve got a right to file a civil action against the pharmaceuticals.

We need to hear a decision on the Cedillo case on the MMR theory. That case will give a lot of information as to how we’re going to act with our other cases. But we will look at every one of our cases individually. There are some issues involved. There is, first of all, the Hannah Poling case where it was our understanding a petitioner of the vaccine program was compensated for, she had an underlying mitochondrial disorder, and then developed autistic-like features and she is going to be compensated.

Science now shows that there are many autistic children who have mitochondrial disorders. We will probably be looking, to some extent, at whether our clients could proceed forward on that type of a theory. It involves medical testing. You diagnose it with a muscle biopsy. We haven’t examined our cases closely enough to see how many muscle biopsies have been done, whether people do it, whether it’s an accurate theory, whether we can get expert testimony. But from our standpoint we have to evaluate it. We have a duty to, if our client has a

reasonable basis to continue, we have a duty to bring those cases forward.

So my sense is that the test cases will certainly result in probably a large majority of the cases in the vaccine program leaving the vaccine program and going into the civil arena. My sense is that a fair number of cases will probably remain.

If you're a family with an autistic child, you're fighting a daily battle to try and help your child. And whether it's medicine, or education, or legal, you know, they try to do everything they can to fight for their child. And these are fighters that are in the vaccine program. And they provide us lawyers with a lot of information. And we listen to that information, and our hope is to give them every chance that they have.

So that's where we are right now. Since the Cedillo case in June of 2007 there's been a lot of new science that's developed. There is new science that we expect to see again this summer coming out. All of those may have influence; all of those may have some bearing on where we're going from here.

There was a Cloer decision just out of Federal Circuit. Our firm actually had a case called the Wilkerson case where we asked the Federal Circuit when does the statute of limitations run in the vaccine program? Is it

from the time that the medical community would first be aware that it was a vaccine related injury? Is that when it begins to run? Or is at the time of the very first symptom? And in our case, the Wilkerson case, the courts have just this year, just a couple of months ago, said, hey, it's when the first symptom is. You know if the symptom -- in this case it was a speech problem -- that's the first symptom, that's when the three years begins to run.

And a couple of months later the Cloer case came out and the Cloer case says, well, you know, it's really when the medical community decides it's a vaccine injury, or the parents are given medical information. So that case has thrown it wide open, and I read some of the information going around from vaccine organizations and families, and actually the sense in the Cloer case says that there is no longer a statute of limitations in vaccine, in autism cases, because the medical community at large does not recognize autism as a vaccine injury.

So there are all of these complicating issues out there. But from our standpoint we intend to, once the Cedillo decision comes down, we intend to analyze every one of our cases, make decisions as to whether we have reasonable basis to continue, and act upon those decisions.

So that's basically what I have to say, but I'd

be happy to answer any questions.

MS. GALLAGHER: Giving everybody a moment to absorb. Is there anybody who has a question or a comment?

MS. BUCK: Kevin, this is Tawny Buck. I appreciate you being there. Do you think that Cloer basically just does away with the statute of limitations?

MR. CONWAY: Well, that's certainly what the dissent thought. I don't know. You know, you have to really read these Federal Circuit decisions this year to try and make some sense out of them. But certainly an argument can be made that the Circuit has held that the statute of limitations begins to run when the medical community recognizes that there's a vaccine injury. So, certainly that argument can be made. The government will certainly say, well, Wilkerson says the first symptom is the first symptom, which is, you know, in Wilkerson it was speech, or whatever the first symptom when that begins to run.

So in a sense it may even turn on which Federal Circuit you get that has the case. So, I can't answer that, Tawny. It's a great question, you know, but maybe Congress could take a look at it.

MS. HOIBERG: This is Sarah Hoiberg. So it would have to go up to the Federal Circuit in order for Cloer to take effect, or is that decision going to affect the entire

vaccine program?

MR. CONWAY: There are two decisions. They appear to me to be in conflict. Certainly, from my clients' standpoint, I would argue that the statute of limitations has not yet begun to run, and I would cite the Cloer decision. Mark Rogers, on the other hand, would say no, I have a Federal Circuit decision that says it begins with the first symptom, and this was the first symptom, everybody agrees it was the first symptom, so your statute of limitations is gone. So we need clarity on that point.

A third panel may try and reconcile these two cases and come up with even a third ruling. But from my standpoint the answer would be to go to Congress. This advisory commission has recommended extending the statute of limitations in the past unanimously. Maybe it's worth another attempt, and I think the Federal Circuit, these two conflicting decisions, is a perfect impetus to do that. And I would recommend that. And I'll call my Congressman.

MS. TEMPFER: Kevin, just making a point of clarification, did you say you felt some of the cases may actually leave the program and go into civil cases?

MR. CONWAY: Well, when you exit the program -- as a matter of practice in our firm, there are two things you can do once you finish with the vaccine program. If you win, and you're awarded compensation, you can either

accept the judgment -- in that case your case is over -- or you can reject the compensation and say, no, I'm going to go civilly; I think I can do better civilly. If you lose a case, you can either accept the judgment, or you can reject the judgment and opt to file a civil action. And all of our autism cases that leave the vaccine program will be filing an election to file a civil action. Now, that doesn't mean that civil actions will be filed; that just preserves their right to file them.

So they will go out into the civil arena. And today they may or may not be able to find attorneys to represent them or experts to testify for them, but as the science evolves -- and from our standpoint, my standpoint, every year it seems to be more supportive of a relationships between vaccines and autism. They have the luxury of waiting, and when the science does become clear enough, of bringing a civil action at that point.

The vaccine program, it's a very harsh statute of limitations; it's three years. In most of the 50 states it's a different statute of limitations. The statute of limitations is not until your adulthood, it doesn't begin to run until you're 18 years old, or if you're mentally handicapped, and it never runs until that mental handicap is removed. So they don't have the statute of limitations problems in the civil arena that the children have in the

vaccine program.

MS. BUCK: Kevin, this may be something beyond your ability to answer, but how long do you think it's going to take for all of this statute of limitations stuff to be sorted out with Cloer?

MR. CONWAY: That's a great question, one that I cannot answer.

MS. BUCK: Yes. It just seems to me like a decision like that is going to, you know, create a whole bunch of questions for people in terms of whether they continue with their cases, whether they wait, is there a statute of limitations, isn't there? I mean, it's so huge that resolution on it would be great, but I can see that this is not going to happen quickly.

MR. CONWAY: Yes. And I'm not sure. I think a lot depends upon how the special masters react. And they certainly have a lot to say how these cases go down. Once the Cedillo decision comes in, I'm sure the special masters will be looking at ways to try and get some sense out of what cases should leave the program and what cases should stay in the program. There have been many cases where there have been statute of limitations hearings, where there are actual hearings to try to determine when the statute of limitations began to run. And Cloer is going to make those hearings even more complicated, no question

about it.

However, it's a science-driven program. And if the special masters decide that they want an expert report, if they want to make an order to show cause for an expert report in supporting the case, then they can have control over whether statute of limitations is even relevant. You know, if the science isn't there and the special masters want to require them to go with hearing with expert testimony, and there are no expert testimony, then that will, that will resolve the case. So my sense is that they're not going to hang around indefinitely. And the science is going to be more important than what the statute of limitations is.

MS. TEMPFER: I just wanted to clarify, if it goes into the civil arena, then they're actually, you're suing the pharmaceutical companies?

MR. CONWAY: Yes, in the end -- actually the whole basis of the vaccine program is to protect the pharmaceuticals from lawsuits. The law is that you're not allowed to sue a pharmaceutical for a vaccine injury unless you first go through vaccine program. However, the law is -- at least today's law is -- that if you are unhappy with what happens in the program you have a right to file a civil action, and that would be against the pharmaceutical or the administrator of a vaccine in a medical medicines

case. And those are potential cases. But the law is you have to go through the vaccine program first. And then we opt to file civil actions just to protect their rights so if the science develops in the future 20 years down the line, they will still have rights to sue the pharmaceuticals 20 years down the line if they can prove it.

But outside the program you have to show not only causation, you also have to show negligence. You have to show that they did something wrong, the pharmaceuticals did something wrong. That's not a requirement on the program, and that's the reason why there have been so few lawsuits since the program began, is because there haven't been any legal theories, any legal theories of negligence or wrongdoing on the part of the pharmaceuticals.

So, the thimerosol cases, just anecdotally, that was the -- in my experience, and I've been involved with the program since its inception -- that was the first time that there was a theory, at least a proposed theory. And the theory was that mercury, which is a very toxic substance was put in these vaccines as a preservative, and then the pharmaceuticals agreed to take them out. You know, they didn't think there was anything wrong with them, but they said we'll take them out just in abundance of caution.

But there were lawyers around the country who said, hey, this is like a product recall. You know, mercury in these vaccines, taking them out, and they advertised the cases. And that's really -- and they weren't aware of the existence of the vaccine program. And when they found out about the existence of the program they came to attorneys like me and said, well, what's this vaccine program. And we said, well, this is what you have to do.

And so I think that is a large reason why these 5,000 cases were steered into the vaccine program. They came from attorneys who wanted to file a civil action outside -- and they still want to outside. But that's not their -- that's tomorrow's issue. They will be making those judgments at a later date depending upon the science, depending upon the facts of each case. But they do have rights. To my knowledge right now I'm not aware of any intended class action lawsuits against pharmaceuticals because these cases are coming out. That was originally the intention, certainly, when the furor hit back ten years ago. But right now they will go into the civil arena and they'll wait. And if a science gets to a certain point, then they probably will sue the pharmaceuticals.

MS. TEMPFER: Thank you for the clarification.

DR. EVANS: Kevin, I don't know if you have a

sense of this, but we've been told a couple years ago by industry legal consultant that there were hundreds of claims that were pending around the country -- maybe not all states -- but that they were arguing, alleging third-party damages, derivative claims, those kinds of things. Do you have any sense of how many are existing now, how that's changed? Or are they just all stayed, or what?

MR. CONWAY: Yes, there were a lot of suits back in the early days. And, again, most attorneys were unaware of the existence of the vaccine program. So they would bring a lawsuit in state court or in federal court. And in state court, unlike in the vaccine program, you can also sue on behalf of the parents or other family members for loss of consortium, for loss of -- all sorts of emotional losses.

In many of these cases they were directed into the vaccine program. In many of the cases, they were just stayed. But my sense is, I have not heard of one successful lawsuit outside of the vaccine program for vaccines causing autism. So my sense is that these cases probably have gone nowhere.

MS. GALLAGHER: Kevin, thank you very much for coming and spending this time with us. It was great to get your perspective, particularly because of your level of expertise in this area. I think clearly it looks like

ahead of us is going to be a period of some uncertainty for a while, and perhaps at a later time you could join us again and update us on how the dust settles. So, if that would ever fit into your schedule, perhaps we could have you join us again.

MR. CONWAY: Yes, and I think that's an accurate description of the landscape right now. When Sherry first asked me to come and talk, my first thought was it's just too premature, and we're going to know a lot more in three months. But I guess, you know, sharing information is important at every step along the way, and so I think this is probably appropriate that we are here today.

MS. GALLAGHER: Thank you very much.

(Brief recess)

Agenda Item: Update from the National Vaccine Program Office, Dan Salmon, Ph.D., M.P.H, NVPO.

MS. GALLAGHER: Thank you everybody. I hope everyone has had an opportunity to get refreshed and to take a break. And we now would like to move right into the review of the vaccine information statements. And Charles Wolfe from the CDC is --

DR. SALMON: Actually if you don't mind, we're going to switch. Is that okay?

MS. GALLAGHER: Oh, yes. Absolutely. I'm sorry. We are not going to go right into VIS, we are going to

instead do an update from National Vaccine Program Office, and Dr. Salmon is going to help us with that. Would you mind coming up here and talking very articulately and loudly into the microphone so everyone can hear you? Thank you. And I hope that we're doing better, those of you who are on the phone.

DR. SALMON: So thank you for your flexibility. I need to chair a call at 4:00, so I appreciate the Commission and Skip Wolfe allowing me to go first. I want to update you folks on two areas, which we've spoken briefly about before. I'll spend a little bit of time talking about the vaccine safety working group of the NVAC, and then I went to spend a bit more time talking about the H1N1 vaccine safety risk assessment working group of the NVAC.

So let me start with the shorter one. And you've received updates on this before. And I think we still have Tawny on the phone, do we?

MS. BUCK: Yes, I'm here.

DR. SALMON: Okay. Tawny, so I'll give a brief update, but then I'll stop and allow you to add any additional insights that you'd like. So this is a group that's set up as a working group to the NVAC. And their first charge was to look at the CDC Immunization Safety Office research agenda and provide comments in terms of

content and prioritization. And they completed that task about a year ago.

Their current charge is to look at the safety system more broadly and to develop a white paper telling us how we can take advantage of new opportunities in information technology and evolving science and enhance our safety system with the goals of preventing adverse events when possible, determining the safety profile of vaccines in a timely manner, and improving public confidence in vaccine safety.

So the group has about 20 members. Tawny is one of the co-chairs. The other co-chairs are Andy Pavia and Marie McCormick. They held their first meeting in July of 2009, and this was a series of panels where they heard from a very broad range of people on a variety of topics, and it was really kind of a kick-off meeting and it was informational gathering.

From there they broke into subgroups, and they have five subgroups, three of which are content focused, and two are process focused. So the first content focus subgroup is structure and governance, the next is epidemiology surveillance, and the third is biological mechanisms. So those are the three content subgroups.

There are two process subgroups. One is stakeholder engagement, and the second is implementation.

And I'll just talk a minute about the implementation one, because it sounds a bit odd maybe to have an implementation subgroup prior to a report being completed. But this is really based on the recommendations of a recent Rand report. And Rand looked at the national vaccine advisory committee and what became of its recommendations. And one of the recommendations Rand made was that as you're developing a report and working on a topic, start thinking about implementation early on, not only after you issue a report. And that's the point of this subgroup, is to start thinking about how it can be implemented. Because at the end of the day I don't think we're looking for a lot of white paper, but we're actually looking for recommendations that are going to make us, HHS, make the most of our safety system.

So that's the basic structure of the group. They had a small stakeholder meeting in Salt Lake City a few months ago where a broad range of stakeholders were brought together, and a lot of what they focused on was structure and governance. There are also draft functions of the safety system and key attributes for achieving those functions, and those were discussed in the Salt Lake City meeting.

So functions are things like surveillance and communication and this sort of thing. And key attributes

are things like efficiency, effectiveness, transparency, and equity. So the group is pretty heavy in its work. They had a meeting June 1st, the day before the full NVAC meeting where the working group started to really review the reports from the subgroups and trying to begin to pull it together as a cohesive report.

We were initially setting a September deadline to complete this, and the reason we were doing so was because that's when we planned on having the national vaccine plan complete, and we would be working on the implementation plan. And I think you folks are familiar with this, but one of the goals of the National Vaccine Plan is vaccine safety. And our effort is to make sure these two efforts really come together and can benefit each other. We found that the safety working group really wanted more time. And at the same time the National Vaccine Plan is probably going to take a little bit longer than we had initially planned. So, with the desire to give the safety working group a bit more time, and knowing that we can do so without compromising, bringing these two efforts together, the deadline has been moved back to the February NVAC meeting. So let me stop there and turn this over to Tawny for a minute and see as a co-chairing member of the group if she has anything she wants to add.

MS. BUCK: That was a nice, quick review. I

don’t really have anything to add, but would be happy to answer any questions. But mostly, I guess, what we’ve done at this point is, you know, we’re trying to develop the tool with which we’re going to evaluate our options once we come up with the different designs for a vaccine safety system.

So, we’re kind of doing work on two pieces. One is we’re starting to get drafts from our subgroups together to come up with options for what the ultimate system would look like. But then in order to actually assess what is the ultimate system, we have to build a tool that has all the criteria, so that we know we’re all in agreement on what it is we want at the end. So that’s sort of the two pieces of this that we’re doing at the same time. And Dan did a good job of explaining how we’ve been given a little breathing room on our timeline, which we definitely needed.

DR. SALMON: Maybe before I go on to the VSRAWG we’ll stop and take any questions the Commission might have on this activity and then we can move on to the next topic. Is that okay?

MS. HOIBERG: Dan, Sarah Hoiberg. I actually got to listen in on the conference call that you guys had about the H1N1 and the different signals that were sent out and whatnot. Is that -- when you receive those signals, from those signals do you guys then go to the vaccine

manufacturers and say, listen, this is what we found, is there a way to make it safer? You are on the vaccine safety board, is that correct?

DR. SALMON: Let me get to the VSRAWG next, because I'd like to discuss this more, and then I'm happy to answer your question. Is that okay? Okay. Were there any questions on the Vaccine Safety Working Group?

MS. BUCK: I think just to add, one of the pieces that we haven't built into this process that we're working on right now is the public engagement and stakeholder engagement. So for those of you -- if any of you have actually been following this process, that would be the logical question at this point is at what point do I as a stakeholder or as the public have the opportunity to weigh in on where we're at. And we're aware of that, and what we're working on right now is the design for capturing that.

DR. SALMON: So let me move on to the NVAC H1N1 Vaccine Safety Risk Assessment Working Group. And maybe I'll take a step back and talk a little bit about how this got put together. So, when H1N1 first came out and we were realizing that we were going to have a very large vaccine program, there was a look at the entire vaccine enterprise and how well it could support such an endeavor, because we really haven't tried to vaccinate so many people so quickly

with the vaccine before.

And there was a lot of uncertainty. At that point we didn't know what the vaccine was going to look like, whether it was going to be adjuvant or not. We didn't know if we needed one dose or two doses, and we didn't know how the vaccine was going to be delivered. Was it going to be delivered through the normal mechanisms of vaccine delivery, or were there going to be mass vaccination clinics?

And all of these things have enormous implications for how one does safety monitoring. So we worked quickly to put together our plans, reviewing what our safety systems would look like and making additions to those systems for H1N1 and trying to have as much flexibility as possible so that the safety monitoring could follow how the vaccine was used and delivered. And we developed a draft plan. This was developed by a group that Secretary Leavitt put together a couple of years ago, the Federal Immunization Safety Task Force. So this is a group of feds, including the HHS agencies that have assets in vaccine safety, as well as DOD and VA.

So we developed this draft plan of what our intentions were, and then we formed a subgroup of the NVAC to look at these and provide us guidance. And they looked at our plans, they heard from us what we were thinking. It

was a great group that included people like Harvey Fineberg, who's the President of the Institute of Medicine -- who actually reviewed the '76 swine flu affair, so he knew the topic very well -- as well as others with expertise in safety surveillance, state and local health departments, and a broad range of expertise.

They made a number of recommendations to us in terms of how we could enhance our efforts for H1N1. They included things like looking at background rates of disease. So, if we saw a certain rate of outcome after the vaccine, we would get a sense of whether that's what should be anticipated versus more than what would be anticipated, because most diseases already happen in a population anyway. So the question is, is this more than you would expect?

They recommended that we enhance our active surveillance, so we would have more people under active surveillance, and the ability to look at outcomes faster, and look at subpopulations. They recommended that we cast and develop messages for communications and ways of working with the media, realizing that vaccine safety is often not an easy area to communicate.

And they also recommended that we develop an independent group to provide ongoing and transparent review of the safety data. And that recommendation is what led to

the H1N1 Vaccine Safety Risk Assessment Working Group. And what you're looking at here in your folder I think everyone received is their most recent report, which is literally just hot off the press. It was voted favorably at the June 2nd meeting and signed and approved by the Assistant Secretary for Health June 7th.

So this is the background of why this group was established. The idea was to have them look at data on an ongoing basis, and then provide advice to the department as well as share that publicly in terms of what we know about the safety profile of the vaccine.

So maybe I can first just draw your attention to, I guess it's the back of page 1 and the beginning of page 3, which is the membership of the group. And what we did was we took members from the five federal advisory committees that had a role in H1N1 vaccine. So that included VPAC, ACIP, NVAC, the NVSD, which is the advisory committee, and the Department of Defense Health Board. So there's a member from each of those committees. It is also chaired by Marie McCormick, who's an NVAC member. It includes a couple of other consultants that bring in very specific expertise, and then Vicky Debold, who is the public representative to the VRPAC.

And, in fact, the people that were put on this committee, we had established in advance very high levels

of conflicts of interest. So probably each of you being on the Commission have gone through the typical SGE requirements to be on the federal advisory committee, which can be onerous at times. And in fact, for this advisory committee we set the bar much higher. And we did so because we realized that they could be operating in a situation where there was a lot of public controversy, and we just wanted to make sure that any potential conflicts or perceived conflicts of interest were really minimized.

So the way this group worked was, we started by briefing them on all the systems. They saw presentations of all the clinical trials data. And we briefed them on all the different systems that would be providing data to them as the program continued.

And if you look at Table 1 on here, this goes through each of the safety programs that were used for H1N1. The table gives you the name of the program, what outcomes were monitored, the size of the population monitored, how many doses were captured in that system, and then how current the data was, what the analysis were, and how the results were. So we had a lot of systems looking at data a lot of different ways. I hate to say the most, because sometimes you'll be proven wrong when you say this. But I think this vaccine program probably had the most surveillance in the history of the U.S. vaccine program in

terms of looking at safety. I mean, really a tremendous amount of effort was made around this.

So we started by giving them a complete briefing on what we knew from clinical trial, what each of the systems were, how they operated, what their strengths were, what their limitations were. And then we started bringing them data every two weeks. And the way we would do it is on a Thursday we would have the Immunization Safety Task Force meet, which is all the different feds, and we would share the data from all the different programs. And that was an opportunity for us to all make sure we're on the same page, and for us to ask each other questions.

And then on the following Monday, the data would be presented to the VSRAWG. I know that's a horrible name we gave them. I think in content and quality they make up for the poor name we gave them. But they would look at all of the data.

Now, they weren't actually doing the analysis themselves. We weren't given them enormous sized data sets and saying please analyze it. We were giving them formal presentations, which in fact is how the different agencies were reviewing the data as well. They could then ask any questions they'd like.

And typically the way we structured the calls were that we would present the data to them, they had an

opportunity to ask any feds any questions, and then there was kind of a closed session where just the VSRAWG and NVPO staff would be on the call where they could discuss it amongst themselves.

And then according to FACA we have to have a fed on the call, so that would be me. But it gave the opportunity for the VSRAWG to kind of discuss it amongst themselves. And if they had questions, if I could answer them I would. And often I would instead go back to the agency who was running the system and say, hey, they had a question about X, can you provide this answer.

So the VSRAWG was looking at the data every two weeks. And then once a month they would bring a report to the NVAC, and when the report was brought to the NVAC, that's a public meeting. So it was discussed in public, deliberated upon by the NVAC, and often they would ask additional questions and discuss the issue. And then once they voted on it, it would then be given to the Assistant Secretary for Health. And once he accepted it we would post it online and share it with the WHO and other health authorities internationally.

So our goal was to do this as quickly as we could. I think we initially said we wanted to have it go from the committee to public within 72 hours, that was our goal. And you can see on this date that it was voted on

the 2nd and signed by the ASH on the 7th, which is really fast for us. It just takes time. Part of it is that the Secretary for Health travels, so he has to be in Washington to sign it.

But our goal was to have an ongoing process, one that had a fair amount of independence, and one that had a fair amount of transparency, so that the public would be getting reports on a regular basis that would really summarize everything we knew.

So with that background, I can walk you through this report, and then maybe answer your question, Sarah. And I think it's almost self-explanatory. So they talk about what the goal of it is in the background.

As of this report about 105 million doses of the inactivated vaccine, and about 21 million doses of the live vaccine have been distributed. So that's really pretty much through the whole program. And one needs to be a little bit careful, because doses distributed isn't necessarily the same thing as doses administered. Some of that may get lost, some of that may get sent back, some may be sitting on shelves.

We'll move on to talk about the last report. And on that last report there were three, well there were two weak signals, and one preliminary weak signal that was discussed.

DR. HERR: Now, a signal again is when something occurs more often than you anticipate it?

DR. SALMON: Yes, so there's actually a definition for a signal here. And one needs to be really careful with this because there are a lot of different definitions for a signal, and I think it can very easily be misinterpreted. So give me one second, I want to just find on this report where their language is.

So if you look at on the back of page 1 or page 2 in the middle of the third paragraph, it says "as designated in Table 1, a weak signal implies a low level of risk and/or association of vaccine exposure and adverse event as possible."

DR. HERR: You skipped a line.

DR. SALMON: I'm sorry. I skipped a line. Thank you. "A weak signal implies a low level of risk and/or substantial methodological limitations in data or study design." So the way that I would describe a signal for these purposes is it's something that warrants further investigation. A signal does not mean there's a real association.

In fact, maybe I should describe this more. The VSRAWG developed three criteria they would use, the first being a signal, the second being an association, and the third being a causal relationship. And their first seven

reports -- two reports before this said there's enough data to assess whether or not the signal is a signal, and so far there's been no signal. In this report and the one before it they identified what they called weak signals, or potential weak signals.

So what this basically means is, there's something that warrants further investigation. They don't think that it's -- they don't have enough information to say this is real. It's not being categorized as an association. And they also say in the end report --

DR. HERR: Would it be -- it's a report of an untoward event. And then it's like, okay, what does that mean? Let's talk about the frequency of the event.

DR. SALMON: Yes. So we can talk about this more. There's a lot of ways that signals could be generated. They could be that a report was made that just looks really unusual. It could be that there's a cluster of reports that look unusual. A lot of the analysis that was done for this is what's called rapid cycle analysis. And let me try to explain this in a way that's useful to both those that have a lot of technical experience in epidemiology and those that don't.

But basically these are large surveillance systems, such as the Vaccine Safety Data Link, or PRISM, or Department of Defense. And what they do is they look at

the number of expected events. So we started with a list of 18 prespecified events. And we said here are events that we're interested in looking at. Maybe they've been associated with other vaccines in the past.

One -- let's use Guillain–Barré syndrome as an example. So the '76 vaccine was associated with, I think most people would accept the IOM said caused Guillain–Barré syndrome rarely. But it did cause Guillain–Barré syndrome. So we said for H1N1 let's look careful at Guillain–Barré syndrome. So in these systems they started by looking at how many cases of Guillain–Barré syndrome would you expect to see based on the number of doses distributed.

And the way that they did that was they looked at people that historically got the seasonal flu vaccine and the rate of Guillain–Barré syndrome in the 42 days after the vaccine. And the 42-day window was determined based on what happened in '76.

And then as people started to get the H1N1 vaccine, they started counting cases of Guillain–Barré syndrome. So the question was, are we seeing more than we would expect? Let me stop there. Does that make sense to people, because I know I'm getting into a lot of epidemiology here.

DR. HERR: But again, it's an incidence of event greater than your expectation?

DR. SALMON: Right, something that looks like more. Now, one has to be careful with that, because the rapid cycle analysis is a fairly new method. What's nice about it is that it's quick, and it's very sensitive, so it's likely to pick up something if there's a real problem. The problem with it is a lot of times it picks up things that turn out not to be real problems.

So the Vaccine Safety Data Link has been doing this for a number of years, and they looked at different signals that came out of rapid cycle analysis. And nine out of ten times when they investigated it further, it turned out not to be real. Maybe there was a coding problem, because these are based on ICD9 codes, maybe the risk window wasn't right, maybe the comparison group wasn't right. So it's a very sensitive approach, but it has the propensity for false positives.

MR. SCONYERS: This is Jeff Sconyers. A couple of questions for you. So, looking at the charts that you've got here, I see that there's a weak signal for TP/ITP from the Defense Medical Surveillance System, and also apparently from the Indian Health Service. Are these independent signals coming from these different sources?

DR. SALMON: The answer is yes and no. The actual data systems are independent. But the manner in which they're doing the calculations, the epidemiology of

their statistics, the math, is almost identical.

MR. SCONYERS: I'm asking the data source.

DR. SALMON: The data sources are independent.

MR. SCONYERS: These are separate populations, separate data sources reporting the same weak signal?

DR. SALMON: Yes.

MR. SCONYERS: Okay. The other thing that I just can't tell from this is, what do you expect in terms of signal from a vaccine? I'm looking here and I see Bell's palsy a couple of times, TP/ITP a couple of times, GBS -- that seems like a fair number to me. Does it seem like a fair number to you? Do you have any baseline to compare these data against say, whether this is expected or unexpected?

DR. SALMON: Yes, so the answer is yes and no. No, it's not surprising to me that there are a few signals. We looked at 18 different outcomes in a half a dozen different systems. So for an individual outcome in an individual system, there are statistical adjustments that are made for looking at the data multiple times. But when you're looking at 18 outcomes in six systems, by chance alone you would expect a few things to pop up. In fact, a month an a half ago I was saying, God, I can't believe nothing has popped up. You know, 18 different outcomes, six systems, I would expect something to look funny. And I

guess I shouldn't have said that, because the next week we had a few things pop up.

So, no, this doesn't look unusual to me. What I think it warrants is further investigation, which is really what the definition of a signal is. And that's exactly what's happening. In fact, I need to get off at 4:00 for the task force call for us to discuss this.

But this is worthy of further explanation, but it's not by any means alarming. And in fact if you look at the VSRAWG report, they say in the end "the working group does not view these results as necessitating any immediate response by the NVAC, but wishes to make the NVAC be aware of the progress to date."

So, the way this was discussed and how I interpreted it was keep doing what you're doing, keep looking at this further, but this is not an alarming issues. And the VSRAWG certainly wasn't alarmed by it. I mean, any signals we get are and should be taken seriously. But, you know, this is par for the course. One wants the system, it looks at a lot of different things, and they're sensitive. And then if something a little bit peculiar pops up, you investigate it carefully using the best possible methods. And that's exactly what's happening.

Your second question was is there something to compare it to? And the answer is not really. I mean, I

used the 90 percent rule from rapid cycle analysis. So, that's historically when you do rapid cycle analysis and you have initial signals, nine out of ten go away. So that's the best comparison we can make. But those are different vaccines and different systems, and it's not a perfect comparison.

MR. SCONYERS: I'm asking a different question, and probably not asking it very articulately, which is for any other vaccine, what's your expected rate of signal generation? Or is that just not an answerable question?

DR. SALMON: Yes, I think it's really hard because we haven't had such an elaborate process, a number of systems, a number of looks at data. So I don't have a comparable experience to base that on.

DR. FISHER: This is Meg Fisher. The 42 days to me seems like a very long time to look for something that might have been related to the vaccine, when we're talking about things like Guillain–Barré or cranial nerve palsies. And that's based on just -- I mean, is the only, the 42 days, which is also an odd number, comes out of just the 1976 influenza?

DR. SALMON: Yes, it does. There's a couple of papers that were published on this that show the curves very nicely. But basically 42 days was the risk window where an elevated risk was found for Guillain–Barré

syndrome in 1976. The biggest risk was in seven to 21 days. So, in fact, one of the systems, CMS, does two analyses. They do one to 42 days, and then a second analysis, which is seven to 21.

I mentioned that the comparison that's being made is to people that got seasonal flu vaccine last year. At the end of the season -- which is what we're working on now is the final analysis -- we compare the risk in the first 42 days to days 43 to 84. And that's actually a much better analysis, because it's among people who got the H1N1 vaccine. So the problem with comparing it to people that got flu vaccine last year is the populations might be different. So that's a methodological weakness. A better analysis is to compare it among the same group, but you have to wait, it takes longer for those days to elapse.

DR. FISHER: And then just the other thing to point out is there are seasonal changes in things like Guillain–Barré syndrome. So with the meningococcal vaccine, where it looked like there was a signal, that may have been more related to the fact that you gave the vaccine before people went to college, which is the time when campylobacter happens to be the most common because it's August.

So I think that the same thing's going to happen with this. It's not what -- there may be some cases of

autoimmune diseases that are seasonal based on other things that can cause the same problem, so other infections or other things going on. And I think that -- while it sounds like it's good to compare it to people who got the seasonal vaccine, the seasonal vaccine is traditionally given in October, November, whereas the H1N1 vaccine was given more spread out into a later part of winter, which may or may not mean that they're comparable groups.

It's just there's a lot of interesting --

DR. SALMON: Yes. It's very complicated. If, in fact, there is a seasonality effect, or seasonality is the issue for Guillain–Barré syndrome, it's actually a problem for both of the analyses that I've describe, although it can be adjusted for analytically.

My reading of the science is that's an unanswered question whether or not there's seasonality to GBS. There are some studies that suggest there might be, and there are some studies that suggest there probably isn't. At the end of the day when we do the final analysis, we'll look at the distribution of GBS cases both among people that were and were not vaccinated and see in our own study populations was there a seasonality effect. If there was it can be adjusted for analytically.

But, you know, these analyses are quite complicated. And with GBS you're talking about a very rare

event. And there's one point I really want to make, which you also received this MMWR. And this is the VSRAWG report, and it's in the MMWR, and I think I would be remiss if not saying this now, which is: you're talking about a very small excess risk here.

So, if you look at the MMWR, which provides the data from the EIP study, you're talking about roughly one case of GBS per million doses of vaccines administered. So that's if in fact this turns out to be real -- which at this point we don't know that. I mean it's a signal that warrants further investigation. It is being investigated, and if it does turn out to be real, this magnitude of risk is about one in a million, which is consistent with some data with seasonal flu vaccine.

So I think, you know, it's important that we're doing a very diligent job. We're making a lot of efforts to be open and transparent about this. But at the end of the day, one needs to consider both the risks and the benefits of a vaccine.

There was a study that was done in Ontario that's estimated an increased excess risk of about one case of GBS per million doses distributed. This was for seasonal flu vaccine many years ago. And there was a paragraph in their discussion section where they articulated this very well. And they said it's important to understand this risk. It's

important to communicate this risk. But at the end of the day one needs to consider this risk in the context of the benefit of the vaccine. And it's hard to imagine a vaccine with benefit that wouldn't outweigh that risk.

So, you know, we're being very diligent in what we're doing. At the end of the day I think what matters to me is apparent, and I think for most people, is both the risks and the benefits of why you do something. This focus is really just on the safety profile of the vaccine.

DR. HERR: There are certainly a lot of educated medical and scientific people who read this information as well as read the MMWR. On the other hand there are also a lot of people who aren't so terribly sophisticated in looking at that. And as you were talking about the relative risks, and the risk of one in a million in taking a vaccine or whatever, sometimes it's also important in these situations to put relative risks and other things that people do every day.

You can get that stuff from insurance information. You know, what's you chance of being hit by a car? What's your chance of having a heart attack today or dying in an airplane accident? And you put those statistics in the same comparison when you're looking at getting a vaccine injury or having something like GBS one in a million. It makes it a little bit easier sometimes

for people to understand.

DR. SALMON: Yes, I think your point is that one needs to put risk into context, and there's lots of ways to do that. I think where people have a hard time or get criticized is when they compare it to things that are different in the analogy. But, you know, a clear comparison here is what is your risk from the vaccine?

And there was actually a study done, because influenza can cause Guillain–Barré syndrome. And there was a study done comparing the risk of Guillain–Barré syndrome from the vaccine versus the disease, and in fact, even if there was a small increased risk from the vaccine, at the end of the day your risk of Guillain–Barré syndrome was lower by getting the vaccine.

So all risks need to be put into context. I think, quite frankly, a lot of that is up to the healthcare provider. When the doctor sits down with the parent or the patient and discusses, you know, that's where a lot of the broader issues can come in.

So, are there any questions for me? I think I've generally gone through the report. We've had questions about the language in the report as well as the table. Are there any other questions that this group has for me?

Let me just finish by saying what are the next steps. And what each of these systems are really working

on now are what we're calling end-of-season analysis. So now that we have almost all the data, a lot of these systems have what's called delay in claims, because they're healthcare systems data. So, if somebody shows up to an ER today, it may not get in the system tomorrow. So there are lags for these windows to expire, and there are delay in claims lags. Some of these outcomes are pregnancy outcomes, so sometimes you have to wait for the baby to be born, and then the baby to live to whatever age for that outcome to develop.

So at this point all these different systems are putting the data together. We're expecting this end-of-season analysis to be complete by the end of the summer. There will probably be one or two more reports that come out through the VSRAWG to the NVAC, and then after NVAC deliberation, to the Assistant Secretary for Health, which will be this end-of-season analysis.

For Guillain–Barré syndrome, because we're talking about such a rare outcome -- I mean it's exceedingly difficult for epidemiology to study things at the level of risk of one in a million. So we're working on a protocol that would combine data across these different systems so that we can get the best possible answer to this question in a timely manner.

So that's kind of where we're going with this.

And I think I'll stop there, and if anybody has any additional questions, please let me know.

MS. GALLAGHER: Thank you very much. As usual, it was a very enlightening presentation by you, and we look forward to more in the future. And we really are interested in following up on the working of your group, because it is really sounding as though you're making great strides. And we'll continue to follow your progress.

DR. SALMON: Thank you. It's always a pleasure to present to the Commission.

MS. GALLAGHER: Now I think we will turn our attention to reviewing the Vaccine Information Statements. So, Chip Wolfe will come up and help us with that. Thank you very much.

Agenda Item: Review of Vaccine Information Statements, Charles Wolfe, CDC.

MR. WOLFE: Thank you for reviewing these. As you know, ACCV is one of several groups that review new VISs and VISs on which we've made substantive changes. And the ones that you've had for today are four that were just released within the last few months: the new VIS for MMRV, two for HPV, one for cervarix and one for Gardasil, and an update of the pneumococcal conjugate to incorporate PCV13.

And I guess you've all got these in your packets and have had a chance to review them, so I'll just listen

to what you say. And there are several items that I'd like to get the Commission's opinion on, and I'll interject those at the appropriate time. Is there a certain order we want to go through these in?

MS. GALLAGHER: Yes, I would very much like Dr. Meg Fisher to start out. I asked her to do her usual careful review of it from a medical scientific standpoint, and I warned her that I would call upon her first.

DR. FISHER: This is Meg. On all of every single sheet under what you need to know it says, "Many Vaccine Information Statements are available in Spanish and other languages." I believe every one is available in Spanish, so I would get rid of the "many," because if it's not, it certainly should be. And that is something that this Commission has been very, very loud about. There are a significant number of people who speak Spanish in this country, and these have to be available in Spanish, period.

MR. WOLFE: Yes, I'm pretty sure they're all available in Spanish.

DR. FISHER: Yes, I'm pretty sure, too, so just take out the many.

MR. WOLFE: Okay. We'll have to word it to make it clear that not all VISs are available in all languages, though, other than Spanish.

DR. HERR: How many other languages?

MR. WOLFE: We've got 30-some languages.

DR. FISHER: I mean, I would look at it as a major failure if they are not available in Spanish. And since Magda is not here, I will -- that's why I want to start with that as the very first --

MR. WOLFE: Sure. She's the one who started this conversation in the first place.

DR. FISHER: Exactly. So we want it to be every one.

MR. WOLFE: Okay. So, we do have -- as far as I know we have them all in Spanish. And we'll make that clear on here.

DR. FISHER: Okay. Then, my next question was just kind of a "what were you thinking" kind of question, and that is having a separate Vaccine Information Statement for the two different HPV vaccines. So, to me that's a huge change in the way that these are going. And it made me shudder to think that is somebody planning to then make a separate vaccine for every different DTaP vaccine, for all the combination vaccines, which I think would be extraordinarily difficult for physicians.

MR. WOLFE: Well, it depends on the physician you listen to. Some of them say they would like to have individual VISs for all of them. And actually that's a difficult decision to make.

And the reason we did it for HPV and not with DTaP is that when there are differences in adverse events, when there are differences in the schedule, when there are differences that would make it hard to negotiate, I mean, navigate through a VIS because you have to say, well, for this vaccine this applies, for this other vaccine this applies. And to do that in one sheet, sometimes it's easier to just have separate sheets for each one so that the patient only gets the one for the vaccine they're getting. And that was why we have two for HPV. That's why we now have two for Typhoid, too -- or for Japanese Encephalitis we also have two now.

DR. FISHER: Okay. So I think this commission, we're only, we really are mainly charged with the ones that are in the programs.

MR. WOLFE: Right.

DR. FISHER: And clearly the only ones that are in the program are the ones that -- I mean, Japanese Encephalitis is never going to be in the program.

MR. WOLFE: Right. Yes, but I just mentioned that because that's another one where we had to do -- and that's the reason. If there are too many differences between the multiple vaccines that it would be too confusing to the patient to have to figure out which one we're talking about, that's where we go for separate ones.

It was a difficult decision. We had advocates for both.

MS. HOIBERG: This is Sarah Hoiberg. The cervarix is not, that one's not approved for males; is that correct? It's just the Gardasil that's approved for males?

MR. WOLFE: Right. And that's one of the differences, too, so yes. When we can we'll try to keep them all on one VIS. But it's the same thing with influenza, for LAIV and TIV having two separate VISs, because they're so different that it would be difficult to include all the information on one page.

DR. FISHER: Okay.

MR. WOLFE: That's the reason; it may not satisfy your annoyance.

DR. FISHER: No, and I didn't mean to sound annoyed. I just am envisioning being in an office and having -- you know, how many different products are there? There's about 50 different products, so are you really going to have 50 different VIS forms in both Spanish an English that you can be able to put your hand on. It just, you know, I think it -- Tom can probably speak to this a lot better than I can, or Tammy, because these are the things people are going to be doing every day.

But if there's -- I do realize there's a different side to it in that you want to have the most information about whatever. But it just looked like a

slippery slope that I figured you must have thought about.

MR. WOLFE: It is. And it would be easier for us if we only had to do one for each type of vaccine. So I would prefer to do that. But, in a sense, it is easier for the patients sometimes to have a separate one.

DR. FISHER: Yes. And then the -- so actually on the HPV vaccine, so I actually didn't have any other specific comments other than the all one. And on the pneumococcal vaccine -- and I don't know Charlene whether you want to do this one vaccine at a time, or just let me kind of go through my --

MS. GALLAGHER: However you're comfortable.

DR. FISHER: Okay. So, I actually like -- I want to start by saying I do think they're very good and very well done. So my little annoyances should be looked at as in the context of it being a very well done item.

In the pneumococcal one, it seemed as though the reading level or the level of English was maybe revved up a couple notches for these versus some of the ones we've looked at before. So, the term in the second column, "PCV13 may also prevent some cases of pneumonia and some ear infections," and then the next line, "but pneumonia and ear infections have many causes and PCV13 works only against the types of pneumococcal bacteria targeted by the vaccine." I thought that would be maybe clearer if you

just said in the vaccine.

MR. WOLFE: I agree. Part of the way the language winds up depends to an extent on who the subject matter expert review is. Sometimes we make concessions --

DR. FISHER: So that's just my recommendation on that. I just thought targeted was kind of a hard, kind of confused the issues.

MS. GALLAGHER: Can I just offer another thought? Sometimes when you say the bacteria in the vaccine, parents or other lay people get the impression that you have live bacteria in the vaccine that's infecting children, so you have to be careful about the phrasing.

MR. WOLFE: Yes, we have to be careful about how it's going to be perceived by the patients.

DR. FISHER: Yes. And that's a good point.

MR. WOLFE: But the simpler we can make it the better.

DR. FISHER: Yes, I was trying to simplify it, but I may have gone too far. Yes, I think that's a good point. And that was my only one on the pneumococcal, so now I have none on the pneumococcal.

And then on the very last one on -- you know, I realize as you just said, some of the language is by whoever happens to be the subject matter expert.

MR. WOLFE: Sometimes they insist on certain

wording.

DR. FISHER: But sometimes when we say the same thing in just about every single statement, it would be nice if we said it the same way each time. And in this one, right above 4, the paragraph that -- not “ask your provider,” but the one before that: “Children who are moderately or severely ill at the time the shot is scheduled should usually wait until they recover before getting MMRV.” And then the next sentence, “Children who are only mildly ill may usually get the vaccine,” is really convoluted English.

So, you know, we said exactly that same line for all of the other three vaccine statements, and I think you said it better the other way. So, for instance in, for the pneumococcal the way you said it was: “Children with mild illnesses, but children who are moderately or severely ill should usually wait.” You know, we have it, you’ve done it multiple times. I was just surprised to see you end up with such awkward English.

MR. WOLFE: And just leave that last sentence off?

DR. FISHER: No, make it the same way as it was before.

MS. GALLAGHER: Children with minor illnesses such as colds may be vaccinated, but children who are

moderately or severely ill should usually wait until they recover before getting the vaccine.

MR. WOLFE: Yes, okay.

DR. FISHER: May usually I have trouble with.

MR. WOLFE: Okay. Well, if we like it better that way, then we'll change them all to --

DR. FISHER: Yes. And then my final concern, I think the most important VIS statement that I would have liked to see was the rotavirus one.

MR. WOLFE: That's coming.

DR. FISHER: No, it's out.

MR. WOLFE: It's out, but --

DR. FISHER: I mean, it's on the -- so why isn't it here I guess is my question?

MR. WOLFE: Well, we only had time to review a certain number of them. We'll bring that to the next meeting.

DR. FISHER: I guess I'd like you to bring them here, you know, like almost before they're released, not three months, four months after they're released, because we feel like this is a place where we can review them and maybe make the language better or more readable or whatever. So, to me, I'd like to see them before they're released, not after.

MS. HOIBERG: Yes, what's the point of us

reviewing it if it's already --

DR. FISHER: I mean, it's fine; you can change them, but --

MR. WOLFE: Yes, this is why we came out with what we call the interim versions because sometimes a vaccine will come out or a vaccine will change, and ACCV is not the only reviewer. There's a multi -- they have to be published in the Federal Register, they have to be reviewed by a number of other groups. And so the problem is if a vaccine comes out, there's a several month gap where there would not be a VIS unless we came up with something before it was reviewed. So what we're doing now is taking the interim --

DR. FISHER: I'm not letting you get out of this one.

MR. WOLFE: Well, no.

DR. FISHER: There's no way that they can't come to us in a more timely fashion toward when they're ready to go out -- and especially the rotavirus. I mean, as soon as you put the porcine circovirus in there, you know, just note that it has to come to use so we can look at it.

MR. WOLFE: Well, yes. That's true. But at the same time when the nanosecond the rotavirus vaccine was licensed we were getting calls saying why don't we have a VIS yet. So.

DR. FISHER: Well, now, let's be real. We all know the ACIP knows months, years before a vaccine is going to be -- and you know when the biologic licensure goes in. So I can't believe that we couldn't see them before they are -- And again, I'm sorry for sounding as if I'm annoyed, but I am annoyed about the rotavirus.

DR. EVANS: I'm glad you admitted that Dr. Fisher.

DR. FISHER: I am very annoyed.

DR. EVANS: Maybe it would help -- I know you don't play a lawyer in real life, but maybe it would help just to take a minute or two and review for the Commission again, the '93 specified that the Commission review Vaccine Information Statements that are new and that are being revised. Now, that's worked out fairly well, but that is a process, as I have understood it, of being proposed, meaning put in draft, you come and you have them reviewed by us, then you take the comments from us and other people, and then they are published as final, and that's when the DVIC, the VICP information is put on them. That's what has happened repeatedly.

Now, in real life when you have situations like rotavirus and so on, do you have any thoughts about how we can help Dr. Fisher's concerns and still the Federal Register requirements, and the review of ACCV, is there a

way that we could get some interim documents together sooner, maybe even have a telephonic consultation or something? I just wanted to throw these things out.

MR. WOLFE: If it wouldn't be dependent on actually bringing them to a scheduled meeting -- I mean if we could get the commission to review them --

DR. FISHER: So, here's my point. The rotavirus VIS statement is out. It's been out for three weeks, right?

MR. WOLFE: Right.

DR. FISHER: So, that's three weeks before our meeting. I actually emailed both Annie and Geoff asking that we have that VIS for us to review at this meeting. So I don't get it why it couldn't be here.

MR. WOLFE: Oh, I don't -- I picked the ones that we were going to review today and nobody mentioned that I remember that you wanted to review the rotavirus, so I just picked these four because that's what we had time for. If I'd have known you wanted me to bring the rotavirus, I would have brought that one.

MS. GALLAGHER: Can I make a suggestion? Could we possibly get them today and if you can't come in person tomorrow do it via phone and we could complete the review of that one tomorrow before the meeting is over?

MR. WOLFE: Sure.

MS. GALLAGHER: Would that be fine with everyone? It would require us to do a little reading tonight, but I don't have any problem with that.

MR. WOLFE: Okay. That would be fine.

DR. SALMON: Can I make a comment? And, Skip, correct me if I'm wrong, but you really can't develop some of this language until ACIP --

MR. WOLFE: That's -- yes, and I wanted to explain that ACIP, we normally can't publish even an interim VIS until there's at least a very, almost final draft, until there actually is a published ACIP statement.

DR. FISHER: But we could review it before it's published?

MR. WOLFE: You could, yes.

DR. FISHER: That's actually in our charge to this group.

MR. WOLFE: Yes, and that's what we're doing today. If you don't mind getting them between meetings, then it's -- I thought we were restricted that they would have to be only reviewed during meetings. If you would like to get them, I can send them whenever we have a completed draft.

MS. GALLAGHER: That would be great, and if you could also indicate to Geoff what the timeframe is, then we would know whether we had to call a special telephone

conference in order to accommodate any that are on a fast track.

MR. WOLFE: Okay.

DR. EVANS: I have a question for counsel, though. Is it not true that we would need, if we were going to have an official review of a new or revised Vaccine Information Statement, would that not need to have Federal Register notice and a public meeting by telephone?

MS. SAINDON: I would need to think about it a little bit further, but to the extent that we're relying predominantly on one commenter, you know, some of the dialogue that happens within the ACCV can happen over email where you could submit written comments so long as those were made available to the public or posted on the website sometime in real time. I think that it's important to understand that not only do we have to comply with the Federal Advisory Committee Act, we also have to comply with the charter of the ACCV, which really indicates that the ACCV is to review this prior to publication. And so that needs to get folded into the review process before they are finalized. And so we can work with your office to ensure that happens in an appropriate way.

MR. WOLFE: Okay. Let me just mention again that we have what we call the interim Vaccine Information Statements. And the reason for those is that the full

process, which includes ACCV review, before what you're calling publication, what we call final publication, is a way to get VISs into people's hands during the multi-month process it takes to finalize them. So it's not as easy as ACCV reviews it and we're going to have a final product the next day. And it happens with most vaccines now, that a vaccine will be licensed and people will want a VIS and it's going to be four or five months until we can get through the entire process to get a final VIS out.

MS. HOIBERG: Who is asking for the VIS, because --

MR. WOLFE: Providers.

MS. HOIBERG: A lot of providers don't hand out the VISs. They're supposed to, but they don't. And it's public knowledge that they don't hand them out. So, I mean, I don't -- I guess if you're handing out an interim one, I mean you could be handing out something -- I remember in a couple of things we found things to be not true or not accurate, not medically accurate. So you're handing out this piece of paper --

MR. WOLFE: Do you have an example of some that were not accurate?

DR. FISHER: It was among the ones we talked about last time. It was just some of the wording came off really not being exactly right. But I actually did not

find -- I don't have really any medical complaints with any of these. I think they are accurate; I think they're very well done. And it was just the awkward wording. And then my major thing was the language.

MR. WOLFE: Okay. So, yes, I'll try to get them -- when a new vaccine is licensed or a change is made, other than getting them out and having them correct, our main impetus is to get them out as quickly as possible so people will have the benefit of what VISs are mandated to do, and that tell them about the risks and benefits of the vaccine so they'll have something to use.

MS. GALLAGHER: Okay. Well, then perhaps you can work with Elizabeth before our next meeting to agree a process that will be speedy, and yet will bring them to the attention of ACCV as quickly as possible. So I would appreciate that very much.

MR. WOLFE: Okay.

MS. GALLAGHER: Thank you, Elizabeth.

MR. SCONYERS: So a couple of other comments. One is to Dr. Fisher's point. I understand you're responding to your primarily responsible person in terms of how you draft this, but I would encourage you to settle on a form of language that's repeated when the same concept is repeated. So, when parents receive a couple of different VISs at any particular visit, and the language is even

subtlety different I think it confuses them. So we don't know, are you saying something different about MMR versus pneumococcal -- if you should happen to have those at the same time? It's the same idea; it's just confusing to use different language.

So let me offer a couple of more comments. One is on the pneumococcal conjugate vaccine. I thought the schedule information in Item 3 for older children and adolescents, for kids with comorbid conditions was very confusing.

MR. WOLFE: I agree.

MR. SCONYERS: And so I might suggest starting out that whole bullet by saying certain children with existing serious health conditions -- or however you want to say it -- should follow a different schedule. Something like that, because you have to track all the way down through these bullets to find the verb, and actually the verb I think was on the other page.

MR. WOLFE: I agree, and I appreciate the comment, because that will give us ammunition when we go back to subject matter experts and say, look people, even the ACCV finds this confusing and would like us to simplify it.

MR. SCONYERS: I'm just a dumb lawyer, so don't cite me. But, no, I found it very confusing, that

particular one.

MR. WOLFE: No, I agree with you, and the more people who say that, the more we can get it changed.

MR. SCONYERS: All right. On the MMRV statement, I was talking to Dr. Herr about this at the start. So in section 1, you talk about the diseases and why it's a good idea to get vaccinated for them. And under mumps I'm curious about the omission of sterility of a potential consequence of mumps, especially in adults. So, you mention painful swelling, but you don't mention what it can lead to. And because this vaccine is now available for use with adults, and we are --

MR. WOLFE: MMRV is not.

MR. SCONYERS: MMR, though.

MR. WOLFE: Yes.

MR. SCONYERS: But it also, isn't that also a consequence of mumps?

MR. WOLFE: It is, yes.

MR. SCONYERS: I'm just -- we need to mention that. It's one of the things I think that people need to know about it.

MR. WOLFE: Okay.

MR. SCONYERS: And then, I may be confused about this, but finally also on the MMRV, you have this box here on the second column going through the one shot or two.

And if I'm reading the CDC update we have coming up from Dr. Gidudu, it looks like there's now an ACIP recommendation about separating the two -- am I misreading that? -- to do MMR and varicella as separate vaccinations for the first dose?

MR. WOLFE: That was one of the questions that I was going to put to the Commission. That just came out after this was written. CDC is now stating a preference for separate MMR and varicella for the first dose. And the question was should we mention that on here. I think we probably should, but I wanted to get the Commission's opinion on that here.

MR. SCONYERS: And I assume that this represented the thinking at the time it was drafted, and it did seem like the recommendations now are subsequent to that, but it's fairly clear.

MR. WOLFE: Yes. Yes, this gives all the data.

DR. FISHER: Is it really a preference for separating them? I thought it was an either/or.

MR. WOLFE: For the first dose only, yes.

MR. SCONYERS: That's what Jane indicates in her report.

MS. HOIBERG: In reference to MMRV, CDC recommends that MMR vaccine and Varicella should be administered for the first dose, so they are recommending,

CDC is recommending that they are separated at the first dose.

MR. WOLFE: And I think it would be a good idea to have that on here, too.

MS. GALLAGHER: So that would be, bullet point number 3 needs to be modified there.

DR. FISHER: But the catch is, if you look at the MMWR that actually -- this one from May 7th -- in the box it says for the first does of measles, mumps, rubella, and varicella at age 12 to 47 months, either MMRV and varicella vaccine, or MMRV vaccine may be used. It doesn't give the preference. Then the next line is "providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers, unless the parent or caregiver expresses a preference from MMRV, the CDC recommends..." -- okay, there it is -- "...should be administered for the first dose." Okay. So you've got to read all the way down to that last line. Sorry. So, yes, then it should be on there.

MR. SCONYERS: There was a preference voiced by ACIP when you have a situation when there's a shortage of MMRV vaccines when the workgroup was working on this issue. Now the statement, as Meg points out, gives either way -- there is not preference one way or the other.

MS. HOIBERG: No it recommends, it says that they recommend. It doesn't say --

MR. SCONYERS: In the absence of a parental preference, give them separately.

DR. FISHER: Yes, it's in the absence of a parental preference. And then they also say if there's a language barrier and you can't explain it, you give them separately.

MS. HOIBERG: Is it still true that the varicella dose is like three times stronger than in the -- by itself?

DR. FISHER: There's more in -- in the combo vaccine there's more varicella. I don't know that it's three times, but yes there is more.

MR. SCONYERS: So I think the fundamental point is to bring the language in the VIS in line with the apparently fairly complicated recommendation that's come out of the CDC.

MR. WOLFE: We'll make it as simple as we can.

MR. SCONYERS: Next time you do MMR update, make sure that's in there too.

DR. HERR: I may have made a statement about this, and maybe I'm asking too much, but people are getting vaccines all sorts of places, whether it be Kmart, Walmart, the health department, or certain sort of walk-in clinics, or an employer because it's available. With the MMRV and

other such live vaccines is it important to list somewhere for the parent or person that's getting this to know that they should notify someone that they've gotten another live vaccine, living samples, within a 30-day period?

MR. WOLFE: It's not a bad idea. So that would apply to any live vaccine? I was trying to see if there was language in there that would --

DR. HERR: I didn't see anything, and you'd probably have to give examples of what a live vaccine is.

MR. WOLFE: Yes, there's really not anything that would cover people getting vaccines at multiple providers, so it would be a good idea to include something like that.

MS. GALLAGHER: Would that go under number 3?

MR. WOLFE: It would be -- yes. Well, it would depend on, because the number is different for the -- it would be the one where we say some people shouldn't get the vaccine. Whatever number that is on a specific VIS.

DR. HERR: Again, I would carry that through the other vaccines as well --

MS. HOIBERG: Yes, put them on all of them and then name the ones that are live.

MR. WOLFE: And assuming that they might not, the patient might not know what's live and what's not. Maybe just a statement --

MS. HOIBERG: You would need to list, you would

need to say what they are.

MR. WOLFE: Or just tell your provider if you've gotten any other vaccines within the last four weeks. And let them figure out, yes.

MS. GALLAGHER: And if they ask why, because they might have to wait, depending on the vaccine. Just so they know what you're asking them to do.

MS. DREW: Sherry Drew. I just have a couple of tiny comments. One is sort of editorial on the Gardasil. Male should probably be followed by a bullet point since you've got both female issues followed by bullet points, just to make it look nice and even.

And then on the compensation program portion of each of them it says, "persons who believe they may have been injured by a vaccine may file a claim with the VICP by calling this phone number." Actually, they can obtain information on filing a claim, but they're not going to be able to file a claim either by calling the number or by visiting the website.

And if you want to get really picky, when we go to how can I learn more and it says "ask your provider," and then says, "they can give you the vaccine package insert." Probably it should be "ask your provider, comma, who can give you..." --

MR. WOLFE: That would be okay. On your comment

about males, could you elaborate on that a little bit, what you wanted?

DR. FISHER: Just the dot.

MS. DREW: Just the dot.

MR. WOLFE: Well, when there's only one, you know?

MS. DREW: The other one just has one.

MR. WOLFE: Yes, that's true. You're right. Why is that?

DR. FISHER: Yes, just take all the dots out.

MR. WOLFE: All right.

DR. HERR: I think Sherry's comment about the compensation program, I think that's true on all of these.

MS. GALLAGHER: It is. And I'm sorry I've never noticed it before.

MR. WOLFE: Well, this is relatively new. And, Geoff, I think I got that wording from you. I don't want to pass the buck.

DR. EVANS: I don't feel the least bit defensive. These VISs have gone through so many reviews, changes, thinking, back-and-forth. So this is actually -- if anything time has proven that you have additional wisdom. So, this is good.

DR. FISHER: Yes, and I totally missed that. Thank you for bringing it up. I think it's really -- it's

obviously very important that people don't think they can just call a 1-800 number and file a claim.

MR. WOLFE: This came at a time when there were probably a dozen people all giving their opinion on how we should word that section, and it was getting so out of hand, and finally I was delighted when Geoff said let's do it this way. So I may have either misunderstood what you said, or -- anyway, we'll fix it.

MS. GALLAGHER: Anybody else? Tawny did you have any comments on the VISs?

MS. BUCK: None.

MR. WOLFE: I've got a couple of questions. On MMRV, in section 2 we say "anyone 13 or older who needs protection from these diseases should get MMR and Varicella vaccines as separate shots." Does that -- and the reason is that MMRV isn't licensed for people over 13, but do you think that's misleading? Do we need to say that that's the reason so that it doesn't imply that it might be a safety issue?

DR. FISHER: Yes. It's a great point.

MR. WOLFE: HPV, both of them, we say, "it's important for girls to get HPV vaccine before their first sexual contact because they won't have been exposed to human papillomavirus." When I looked at that again, I

realized that somebody doesn't know what we're talking about probably won't know any more after they read that. Can anybody suggest a clearer way to give the rationale for getting the vaccine before the first sexual contact?

DR. FISHER: I think again, when you start out, you talk about genital human papillomaviruses, and that is actually more correct, because we're all exposed to -- children are exposed to papillomaviruses all the time that are the regular skin wart viruses. So, it is clear they're different. So I probably would put back the genital one, and I think people would then get it.

DR. HERR: Leave it out.

MR. WOLFE: And not say why?

DR. HERR: Let them make the wrong interpretation of what that means, because there are various levels that you can still become infected.

MR. WOLFE: Okay. No, I like that, if we can make it simpler and they don't think they're going to require our rationale.

PCV. One of the questions I have is one we already went over, and that was that one section that was so confusing. Another one has to do with the risk figures. And we did something with the risk figures -- this is in section 5 -- that we haven't done in any other VIS. We said that -- we simplified them by saying that we're

averaging figures instead of giving the actual numbers.

And the reason for that is that ACIP hasn't published a final statement on PCV13 yet. We got the risk figures from the package insert, and they were in tables with multiple parameters, including severity, age, and dose. So if we had, if we had put all the figures from the tables in there we would have like 18 numbers for each adverse event. So, the question is do you think it's okay to say, to tell people that we've averaged these and so we just have one figure for each one instead of a bunch?

MS. GALLAGHER: Sure. I think simplicity on the forms is important. If you look at that comment on the dosage and how that goes on as a run-on sentence; simplifying it would help tremendously. And so keeping it simple I think helps as well.

MR. WOLFE: The one that was very complicated, that was one where I couldn't come to agreement with the subject matter expert and finally just wound up going with what he said so we could get it published.

MS. GALLAGHER: I think it's compounded by the fact that it starts on one page and finishes on the next page. So it's even harder to follow.

MR. WOLFE: Okay.

MS. GALLAGHER: Any other comments?

MR. WOLFE: Should I call in a certain time

tomorrow to talk about the rotavirus? First of all, can everybody download the rotavirus and review it tonight or review it before a certain time tomorrow.

MS. GALLAGHER: Well, look at this.

(Rotavirus VIS distributed.)

MR. WOLFE: Tawny, can you look at it online?

MS. BUCK: Yes, could somebody send me a copy of it to download?

MS. GALLAGHER: All right. We're going to do the rotavirus vaccine VIS tomorrow at 9:00 A.M. as unfinished business from today. So everybody has tonight to take a careful look at it and come back with comments. Thank you very much.

MR. WOLFE: Thank you.

MS. GALLAGHER: Now we'll turn our attention to the Immunization Safety Office, Centers for Disease Control and Prevention Vaccine Activities, and Jane Gidudu will be presenting. If you could please now go to your presentation, Jane, we would be very grateful. And I believe that Geoff is driving the slides here, so if you'll just say next slide, he'll know when to go to the next slide. Thank you very much. Hello, Jane, are you there?

(No response)

MS. GALLAGHER: Okay. Well there is a little technical issue, so we will move on to the Center for

Biologics, Evaluation and Research and Food and Drug Administration Vaccine Activities and an Overview of PCV in Rotavirus Vaccines. As our speaker, Dr. Krause, is available and I believe ready to go.

DR. KRAUSE: I'm ready, but it turns out that somebody took my slides away and made copies for you all, so they're not actually in the room for my talk.

MS. GALLAGHER: Yet another technical problem.

Agenda Item: Update on the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) Vaccine Activities, Barbara Mulach, Ph.D., NIAID, NIH.

DR. MULACH: Yes, I have just a very brief update, so that might give you a little bit of a reprieve.

MS. GALLAGHER: Okay. We're going to turn to Barbara Mulach, who is going to give us an update on the National Institute of Allergy and Infectious Diseases, National Institutes of Health Vaccine Activities.

DR. MULACH: Do you want me to come up?

MS. GALLAGHER: Could you please, because we've had complaints about the volume of speakers and we're trying to correct that by having everyone come up front and speak right into the microphone.

DR. MULACH: No problem. So I just had a couple of things that I wanted to draw your attention to, several

recent advances that NIH has played a role in supporting. And the first is -- actually they're both related to sort of the idea of personalized medicine and how we eventually might get there.

And the first was a study that was funded by the Human Genome Research Institute, where basically they sequenced the entire genome of a 40-year-old man where they knew some of the history of that person and what some of his medical family members, what diseases they had. And then basically they took that genome and were able to look at specific genes and databases and find certain heart disease genes and other genes and were able to do some correlations between what they see in actually his medical history and what his outcomes might be.

And one of the other databases they looked at was the database for different effects of different drugs. So, what they're starting to be able to do is try to correlate some of what we know in our databases with the actual genome sequencing that they can do of human genomes.

So, again, this is early stage, this is one person. But ultimately it opens the door for what we might be able to do to correlate. And it would give a person an idea, an indication of maybe things that you could do behaviorally or others to try to limit the effects of what those genes might do.

And of course there are ethical and policy implications of this. I'm sure you've heard those discussions about the ethics of knowing whether you have the breast cancer gene or other things like that. So this is just going to open the door wide open for a lot of discussions that have to happen as we gather this information. And also, another component of this is of course environmental, so hopefully there are some things we can do to limit that.

And so on a related topic one of the other things I just wanted to introduce is a project that started in 2008 and we're going to be working on for many years is the human microbiome project. So what we talk about here are microbes that cause disease and that we're trying to get rid of. But if you really look in humans we have a lot of microbes that are involved in our health, help us digest our food and other things, and they're an everyday component of our lives. And what we're trying to better understand is what are these microbes doing, what makes them good, when sometimes the imbalance can make you sick? And so to better understand what flora we normally have, and what those perturbations might do in order to make us sick, and then that way can also better understand environmentally what we can do to reinstitute that balance.

Again, you guys have heard of this in some ways

when you talk about taking certain kinds of yogurts to balance out your digestive system. So, we're really talking about trying to identify what are some of those healthy microbes and what they might do, and where they're located, and what causes those imbalances. So, again, it's better understanding what a healthy human is, better understanding what that imbalance is that makes you sick, and so that we could try to make that effect.

So, just a couple of days ago there was a publication that talked about they were able to identify 178 different microbe gene sequences, and 30,000 new identified proteins. So, this is to be able to understand what all of this means in terms of your digestive tract and other parts of your body. So it's the beginning of a whole new world.

There are actually write-ups on the NIH website, and I can send you guys the links if you're interested in some of these advances. But it's a new frontier, so very exciting. So stay tuned for more as we continue our research.

DR. FISHER: This is Meg Fisher. And I think this is by far one of the most exciting things that's come along lately. There's more DNA in our microbiome by logs than in our human genes. So we have way more bacterial DNA than we have human DNA in our bodies. So the thought that

it might affect everything else, clearly it probably does, and we probably truly are what we eat. So, it's very cool.

DR. MULACH: Makes you think, doesn't it.

MS. GALLAGHER: Yes, and then I remember going over to Greece to study for a summer and all the nice healthy Greek people were eating the same thing as me and feeling fine, and I wasn't.

DR. MULACH: Absolutely, absolutely. So, I just wanted to bring your attention to those and I'm happy to answer questions or if there are other items that you are interested in learning more about, I'm glad to bring those to ACCV.

MS. GALLAGHER: Thank you very much. Very interesting.

Okay. Now, is Dr. Gidudu on the line yet?

DR. GIDUDU: I am. Do you hear me?

MS. GALLAGHER: Oh, great. Okay. So we're now ready for your presentation and Geoff has volunteered to drive the slides for you, so whenever you wish to have the next slide, just tell Geoff and he'll go on to the next slide.

Agenda Item: Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities, Jane Gidudu, M.D., M.P.H., ISO, CDC, and Karen Broder, M.D., CDC.

DR. GIDUDU: All right. So I will be providing update with my colleague, Dr. Karen Broder. She's a team lead for the Surveillance and Public Health Response Team here at the Immunization Safety Office. So I will mention a few recent publications, and Dr. Broder will provide an update on the H1N1 vaccine data. And this vaccine, by the way, will be added.

All right. So let's go to the next slide. So on the next slide here, it was published on May 7th, and it's on measles, mumps and rubella combination vaccines. So in June 2009, after consideration of the post-licensure date and other evidence, ACIP adopted new recommendations regarding the use of MMRV vaccine for the first and second doses.

And this is the recommendation: that the recommended ages for measles, mumps, rubella, and varicella vaccination continue to be age 12 to 15 months for the first dose, and age 4 to 6 years for the second dose. For the first dose of measles, mumps, rubella, and varicella vaccine at ages 12 to 47 months, either measles, mumps, and rubella, MMR, vaccine and varicella vaccine, or MMRV vaccine may be use.

Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both

vaccination options with a parent or caregiver. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose in this age group.

For the second dose of measles, mumps, rubella, and varicella vaccines at any age 15 months through 12 years. And for the first does at age 48 months and above, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines. Consideration should include provider assessment, patient preference, and the potential for adverse events. If the personal or family history of seizures of any etiology this is a precaution for MMRV vaccination. Children with a personal or family history of seizures of any etiology generally should be vaccinated with MMR vaccine and varicella vaccine.

Let’s move on to the next slide please. The next two slides were published on May 8th, and they’re all on HPV vaccines.

On October 16, 2009, the Food and Drug Administration licensed bivalent human papillomavirus vaccine, HPV2, or Cervarix, for use in vaccines ages 10 through 25 years. Cervarix is the second human papillomavirus vaccine licensed for use in females in the

United States. Quadrivalent HPV vaccine, HPV4 or Gardasil, was licensed in 2006 for use in females ages 9 through 26 years. And ACIP recommended routine HPV4 vaccination of females aged 11 or 12 years, and catch-up vaccination for females ages 13 through 26 years. This report provides updated recommendations for routine and catch-up vaccination of females.

The next slide, which is in the same MMWR, is about the other HPV vaccine, Gardasil. On October 16, 2009, the FDA licensed quadrivalent human papillomavirus vaccine for use in males ages 9 through 26 years. HPV4 had been licensed previously for use in females aged 9 through 26 years. ACIP recommends routine vaccination of females at ages 11 or 12 years and catch-up vaccinations for females ages 13 through 26 years.

On October 21, 2009, ACIP provided guidance that HPV4 may be given to males ages 9 through 26 years to reduce their likelihood of acquiring genital warts. HPV associated cancers in males include anal, penile, oropharyngeal, and oral cavity cancers caused by HPV-16. ACIP does not recommend HPV4 for routine use among males.

Let’s move on to the next slide. This is the last MMWR on GBS that was published last week. In October 2009, CDC performed surveillance of Guillain-Barré, or GBS, syndrome using active test findings through the Emerging

Infections Program, or EIP. This is a population network of CDC and academic centers in ten states. These centers were designed to provide rapid case identification and assessment of risk of GBS following 2009 H1N1 vaccination campaign.

Preliminary results from an analysis in EIP comparing GBS patients hospitalized through March 31, 2010, who did and did not receive the 2009 H1N1 vaccination showed an estimated age-adjusted rate ratio of 1.77. This is GBS incidence of 1.92 per 100,000 person-years among vaccinated persons and 1.21 per 100,000 person-years among unvaccinated persons. To remind you, normally about one person per 100,000 people per year develop GBS.

In the 1976 vaccination with swine flu, one study showed an association with GBS. The study suggested that one person out of one million vaccinated persons may be at risk of GBS associated with a vaccine. If end-of-surveillance analysis confirms this finding, this would correspond to 0.8 excess cases of GBS per 1 million vaccinations. This would be similar to that found in some formulations of seasonal influenza vaccines. No other federal system to date has detected a statistically significant association between GBS and the 2009 H1N1 vaccination. Surveillance and further analyses are ongoing.

Our will now let my colleague, Dr. Broder, to provide the H1N1 using advanced data. Let's move on to the next slide please.

DR. BRODER: Hi, this is Karen Broder. I spoke with you all last year, I think, about the MMRV. I'll be presenting a very, very brief update about data from the vaccine adverse event reporting system, about the 2009 H1N1 vaccine.

I'll just start by saying that I understand you guys have heard many updates on VAERS data, and I have also provided a more comprehensive talk to Dr. Evans for anybody who would like to see a little more detail. So as a reminder theirs is a frontline national surveillance system to look for potential vaccine safety concerns that would need to be followed up in other systems if they were identified. And it's co-managed between CDC and FDA.

If you look at the first slide in my talk, we just want to remind you what the definition of a serious report is, which is a report that comes in about an adverse event that resulted in one of the conditions listed on this slide, death, life threatening illness, or hospitalization.

I was asked to provide a snapshot of some of the clinical experience that we've seen in VAERS. There are two ways to look at this. One is through the -- every time a report comes in, the VAERS nursing staff codes terms of

symptoms from the report into a database. And also for certain reports, the serious ones and special reports we have doctors and scientists reviewing detailed information from medical records as well as the report.

If you look at the slide that says most frequent adverse event after an activated vaccine for 6,165 non-serious VAERS reports, you can see the most common symptoms that are reported on the form. Now, some people may have had more than one symptom, and those are reported, they may be counted more than once.

And so you see in this list here of events that happened with more than five percent of the time being in the report, you see things like hives and rash, nausea, vomiting, dizziness, headache, fever, and pain. There really isn't anything too surprising on this list for the inactivated vaccine.

The next slide shows a similar profile done for the non-serious reports after the live nasal vaccine. And as might not surprise you, you see fever, cough, and runny nose up there towards the top of this list, as well as symptoms of nausea, vomiting, and throat pain. And you can see some inappropriate schedule administration.

The next slide shows our results when we did it a different way with the serious reports. And here we had clinicians look through the reports and assign them to one

of several diagnostic categories, based on the most common diagnosis, or the main diagnosis in the patient. And you'll see after the 466 inactivated H1N1 vaccine serious reports that we looked at, the most common adverse event category was neurologic. And this was consistent with an earlier review of VAERS data over many years that also showed the most common adverse event category in serious reports was neurologic. Of these, 53 of these reports were Guillain-Barré syndrome.

And then you'll see that the next most common categories in the range of about ten to eleven percent of the report were of different kinds of conditions, allergic events, other non-infectious events, which would include things like diabetes and other types of conditions, and respiratory events.

There's a slide that didn't make it that I just wanted to provide for completeness, which is when we do a similar analysis for the live vaccine, we've actually found that the most common category was a respiratory category, with 31 percent of the reports being respiratory.

We did many other analyses of the VAERS data that are reflected in the bigger talk, but in the interest of time I'm just going to sum up what we found, which is that VAERS received more than 9,000 reports after H1N1 vaccine for persons vaccinated during the first four months of the

vaccination program. And this is after about 82 million doses of the H1N1 vaccine were administered.

The proportion of the serious VAERS reports after the H1N1 vaccines was not higher and was actually quite similar than after the seasonal influenza vaccines during 2009-10, and four past seasons. The H1N1 reported adverse event pattern was consistent with what we expected based on what's known about seasonal influenza vaccines.

And as you saw the most common serious report category for non-fatal cases was neurologic after the inactivated vaccine and respiratory after live. I do want to remind you that the VAERS system is not designed to assess whether the vaccine caused the adverse event, but just sort of shows the kinds of things that happen after vaccines that lead clinicians or other people to report them.

And then the Guillain-Barré syndrome and anaphylaxis reporting rate after H1N1 vaccines show that these events were rare. The reporting rate was not higher than 2 per million doses administered for each of these conditions. So this just provides a little small bit of information about our data from the VAERS system, and I'm going to turn the talk back over to Jane.

DR. FISHER: Before you go away, Karen, can I ask you a question? This is Meg Fisher. Can you hear me?

DR. BRODER: I'm here. Can you hear me?

DR. FISHER: Yes. Can you hear me? So my question is it would be really nice to have a table of -- I know you compared this to seasonal vaccine. It would be very nice to have a table of a group of people who didn't get any vaccine, and what was the incidence of these symptoms in that groups, because it strikes me that only six percent of people having fatigue is a very low number.

DR. BRODER: As you probably know, one of the limitations -- and this is in the complete talk of VAERS -- but there is no unvaccinated comparison group. This system is really set up to just look at what happens in people that are vaccinated, and generate hypotheses for further assessment.

So the kinds of systems that are going to look more clearly at addressing the question of whether or not adverse events occur more commonly after vaccination compared with either a group that received a different vaccine or a time window when a person wasn't exposed to vaccine are through other systems like the Vaccine Safety Data Link. So that's why -- alternatively, of course, for some of the more common adverse events you will sometimes see information in placebo-controlled trials before licensure. But for VAERS we really try to look at the patterns that we're seeing in the numerator data, which is

just people who were vaccinated and had an adverse event reported.

MS. BUCK: Karen, this is Tawny. Before you go I have a couple of questions also. Can you -- I see on your non-serious VAERS report you have inappropriate schedule of drug administration. Did you have other errors in administration that were reported?

DR. BRODER: The best way to look at this is actually in my complete slide set, which is -- we were actually asked about this inappropriate administration question. And there were adverse events that were inappropriately -- I mean, I'm sorry. We know that it happens, that people at least reported that they gave the incorrect dosage.

And one of the ways that we look at the -- this is going to take a minute to explain -- but one of the ways our FDA colleagues look at the bare data, is they look to see if certain adverse events are happening out of proportion after the H1N1 vaccines compared with out of other vaccines. And what they actually found for the inactivated vaccine is that there was one kind of "adverse event" -- I say that in quotes -- category that did come up more commonly in children aged less than one, and that was called incorrect dose administered. But when they actually looked at the reports there weren't adverse events

described with these reports.

For the live vaccine, when they did this analysis looking for disproportional reporting, they did find that something called contraindication to vaccines -- which is a kind of administration error -- was reported more often or a more higher proportion of them were happening after the H1N1 vaccine than other live vaccines. So they looked more closely at these reports and found that only one of them was noted to have -- one pregnant woman had a near fainting spell, and five had asthma flare ups. So, I'm sorry, it was six individuals in this 88 that actually had adverse events. And the rest of them just had the contraindications the vaccination reported without an adverse event.

And the inappropriate schedule of administration was also noted in another age group with live vaccine of 0 to 1 year olds and adults aged 46 to 64, and here there were no adverse events reported. So we know that there was some administration errors that were occurring. Very, very few of them seemed to result in adverse events, at least based on these reports.

MS. BUCK: The other question I have is, can you give us some sense of how many reports were filed in VAERS that were deemed incomplete, or? I mean, how many were thrown out? You're showing us the ones that were reviewed

and analyzed, but what number of reports were looked at and -- I guess, filed incorrectly or incomplete?

DR. BRODER: I don't know how to quite answer that. In terms of complete we have the standard VAERS form, which is a one-page form that gets filled out. And I guess we don't look to see how many of these were completely fully filled out or how many were missing one field. I haven't done that analysis.

Regarding the medical records, those are only requested routinely for certain reports. So all the serious reports, automatically we request medical records. And for the H1N1 vaccines, we requested medical records for a variety of other conditions regardless of whether they were serious.

I actually reviewed all of the serious reports. So, I was able to see all of the serious -- or all of the serious reports through January 31st. And I was able to see all of the reports that were coded as serious and look and see how many had medical records. And although I don't have the exact number in front of me, I'm pretty confident in saying it was more than 85 percent that had at least some medical records available. So it was a pretty good capture on the medical records.

Completeness of a report is a little tough to decide, because a report could be missing one minor little

trivial piece of information, or it could be missing a lot of different fields. And I don't have a quantitative answer, but I can say in looking at them I would suspect that they were possibly more complete than in the past. They were -- a lot of them were in very good shape.

MS. BUCK: Thank you.

DR. BRODER: Any other questions?

DR. HERR: Did I misunderstand, or did I understand you to say that in the 49 to 64 age range that inadvertently got the wrong dose, was that the live vaccine and that they didn't show anything significant?

DR. BRODER: Yes, and I can -- let me repaint that. Maybe it might be helpful -- I don't know if you do have in your book, but the slides that I'm referring to when you do get the final, full dataset is the data mining slides that were provided by the FDA, Dr. Martin and his colleagues. And so in their analysis they have prespecified age groups. They look at the analysis by different age groups. And what they found is that in the 46 to 64 year old age group in the live vaccine that had inappropriate schedule of administration -- keep in mind that the live vaccine actually is okay up through 49. So anybody who was 50 or older would have been technically off licensure.

DR. HERR: And nothing terrible happened to these

people?

DR. BRODER: Correct. So there were no adverse events reported in that review. So after they identify a signal, they look at the information and they found that although it was coded as inappropriate schedule, they didn't have adverse events noted on the VAERS form, suggesting that providers just wanted to let us know they made a mistake, or somebody made a mistake.

MS. TEMPFER: This is Tammy Tempfer. I just have a comment about the Gardasil with the males. I believe the ACIP --

DR. BRODER: Excuse me. I'm going to hand the phone back over to Dr. Gidudu.

MS. TEMPFER: With the Gardasil, in relationship to males, I believe the ACIP came out with saying it was permissible to give it to males, instead of coming up with the straight up recommendation -- well, they did recommend, because I think there's a cost-risk benefit involved with it. They went on to say that that is confusing. They say things like may, or can, or could in a number for recommendations, which leaves the practitioner kind of out there in limbo I think in a lot of different ways.

The VFC program is covering Gardasil for males. In our area we are using it, private insurances are coming on board to use it, and so I think it is being definitely

given to males. And I think eventually I would hope they would move to giving a recommendation for it.

MS. GALLAGHER: Okay. I think that's all of the questions. I think we're ready to move on to the next presentation. So I believe we're now up to Dr. Krause, and his slides have been distributed, and they're available to him on the laptop. So I think we have all of our ducks in a row this time. Thank you very much.

Agenda Item: Update on the Center for Biologics, Evaluation, Research (CBER), Food and Drug Administration (FDA) Vaccine Activities and an Overview of PCV in Rotavirus Vaccines, Philip R. Krause, M.D., CBER, FDA.

DR. KRAUSE: Dr. David Martin is also supposed to be here from the FDA and he's going to review the safety data on the rotavirus vaccines hopefully after I've finished talking. So that's sort of as a component of thinking about this. So I hope he will be here. But to the degree that I can answer questions about what he would have said if he's not here, then perhaps we can deal with that after that talk.

So just by way of an update from the Center for Biologics at FDA, there haven't been any new vaccine approvals since the last ACCV meeting March 2010, or the last update. There was however a meeting of the Vaccine Related Biological Products Advisory Committee, or VRBPAC,

on May 7th.

And there were two main topics that were discussed on that day. One of the discussions of porcine circovirus vaccines, and the other is the use of advanced analytical detection methods for the characteristics of cell substrates, viral seeds, and other biological materials used in the production of viral vaccines for human use. And so I'm going to spend my time now going through mostly the PCV, but I'll tell you a little bit about the new methods for detecting potentially viruses or other things in vaccines.

So the background on the PCV issue, in February 2010 GSK, GlaxoSmithKline, Biologicals was informed by an investigator at the University of California in San Francisco the DNA sequences originating from porcine circovirus, or PCV1, were detected in two batches of Rotarix, which is GSK's live attenuated rotavirus vaccine.

GSK initiated experiments to confirm those results and to conduct further investigations, and their test confirmed the presence of PCV1 DNA in Rotarix at all stages of the production process. And subsequently their studies found that it had been in the product from the beginning, including through the clinical trials, which were done prior to licensure of Rotarix.

GSK then informed FDA of the detection of PCV1

DNA fragments in Rotarix, and also in harvest, although not a final product, of an activated poliovirus containing vaccines that were produced in a related cell bank. FDA began its own internal examination and confirmed the presence of DNA from PCV1 in Rotarix vaccine, and on March 22nd, then, the FDA recommended that clinicians temporarily suspend the use of Rotarix while the agency gathered additional information as a precautionary measure.

The testing that was done by the academic investigator did not find PCV1 DNA sequences in Merck's rotavirus vaccine, but FDA did embark on testing RotaTeq, which is Merck's vaccine, and recommended that Merck do the same. And then right before the Advisory Committee, FDA received information from Merck that preliminary studies identified fragments of DNA from porcine circovirus type 1 and type 2 in the RotaTeq vaccine.

So as a response to this, CBER initiated a lot of laboratory investigations. And those investigations revealed the presence or confirmed the presence of PCV1 DNA in Rotarix, including complete virus genomes. Those studies at CBER showed the PCV1 DNA in Rotarix is particle associated, which makes it more likely to be associated with an intact virus.

MS. HOIBERG: Can I ask a question? This is Sarah Hoiberg. For those of us who are not medical, could

you please explain to me what PCV1 and PVC2 are and what they do, and what it means that they found those in the vaccine?

DR. KRAUSE: That will come up. So they're viruses -- and obviously they're not rotavirus. The vaccine is supposed to contain live rotavirus. But these are very small viruses that were found in -- well, PCV1 virus was found in Rotarix vaccine. Actually, no virus had been found to date in RotaTeq vaccine. But I'll tell you a little bit more about the viruses, and if when I'm done you have more questions, I'll answer them too.

Okay. And so then we showed that the PCV1 virus in Rotarix cell culture, which again showed that it was intact virus. And we confirmed the presence of the PCV1 and PCV2 DNA fragments in RotaTeq, which is the Merck vaccine. To date -- and that's up until today -- we haven't detected full-length virus genomes. And to date no infections virus based on our tests and cell culture has been found. The studies are ongoing and Merck is continuing to do studies on RotaTeq as well.

DR. FISHER: Can I stop you again. This is Meg Fisher. When you say "particle associated" that means it's an actual virus, like it's got an envelope or it's got something? It's not a term -- and you know, I'm an infectious disease subspecialist and I don't know what it

means.

DR. KRAUSE: Right. So that's more of a virology term. When we think about viruses, of course a virus particle is what we call a virion, and that has the DNA in it. In the case of a virus like PCV1 or 2 it has a capsid around it. This is not an enveloped virus.

When we do experiments in the laboratory, though, to study the DNA, we don't have a way -- depending on the amount of viruses present or how we look at it -- of saying just by looking at it or by doing specific studies this is a full virus particle, this is a full virus. But what we can say is we find DNA in association with particles. So we do things to the vaccine, which purify particles out of it, and leave things that are soluble behind. Then we ask, does the virus DNA co-purify with the particles?

DR. FISHER: The particle being the shell?

DR. KRAUSE: Well, so we're doing a preparation that will purify all potential particles that are in the vaccine. And then we're asking the question whether those particles contain the DNA from the porcine circovirus. And so because we ultimately showed that the virus or the material in the vaccine can infect swine cells, it's a bit of a moot point, because it shows that there's infectious virus present.

And so perhaps I'm being a little bit technical

here in refusing to say that we know for sure that the particles were all virus particles. But there are particles of the virus DNA in those particles, which means that they're likely to be virus particles, but perhaps it doesn't completely prove it. But when we can show that they're infectious in cell culture, then that proves that there's infectious virus there.

MS. HOIBERG: Could that then turn around and harm the children that it's being injected into?

DR. KRAUSE: Well, first off this is an oral vaccine. But our conclusion was, and the conclusion of our advisory committee that it was very, very unlikely that it would harm any children. And I'll go through why in a second.

So what about porcine circovirus? These are very small viruses, in fact the smallest known mammalian viruses, and they contain a single strand of circular DNA. Porcine circovirus is a very common virus among pigs, and it's found in pork products, including pork products that are sold in grocery stores and that are eaten in restaurants. And so it's very commonly -- humans are very commonly exposed to this.

In spite of a fair amount of study, PCV is not known to cause disease in humans, and so there's no evidence at this time that the porcine circovirus, or the

porcine circovirus DNA in U.S. licensed vaccines poses a safety risk.

To date no serious or unexpected safety concerns have been identified in postmarket surveillance of Rotarix or RotaTeq -- and that's what Dr. Martin will cover -- and that includes going all the way through the studies of the vaccine for licensure, including the very large studies that were done for the potential of intussusception with both of these vaccines. And the Rotarix, at least, we know through those studies contained the porcine circovirus even at that time. And no unexpected safety concerns were identified in those studies.

GSK has also done some preliminary serological studies, which means that they took children who've received the vaccine and looked at their blood before and after immunization and asked whether they developed an immune response to porcine circovirus. And if they had developed an immune response to porcine circovirus, that would have been evidence that porcine circovirus could have infected them. But if they didn't develop an immune response, then that would imply that there probably wasn't any infection.

And so these studies are preliminary and they are limited so far. But there is no evidence of any antibody response among recipients of Rotarix suggesting that the

PCV1 did not infect vaccine recipients. And then GSK, Merck, and FDA continue to investigate the findings of porcine circovirus, and/or PCV DNA in these vaccines.

MS. BUCK: I have a quick question before you go on. Were these supposed to be in the vaccine?

DR. KRAUSE: Supposed to be? No. The intent when you make a rotavirus vaccine is just to include the rotavirus.

MS. BUCK: So how did they get in there?

DR. KRAUSE: Well, the likely sources is through porcine trypsin. Trypsin is an enzyme that is used in cell culture. It's used to move cells from one flask to another because the cells adhere to the flask or to the bottle, depending on how the vaccine is made, and the trypsin needs to be used in order to release the cells from those flasks.

For rotavirus vaccines there's an additional use of Trypsin, which is that rotavirus, in order to cause infections in cell culture actually needs to be activated by treatment with enzymes like trypsin because it doesn't infect cell culture well unless you treat it. And so humans make their own trypsin also. If you imagine the virus infecting a human, it actually goes through the stomach an into the small intestine, and it's exposed to the human enzymes, and it's actually only after it's activated by the human enzymes that it get's more

infectious for humans, and a natural infection as well.

So in the cell culture, when the vaccine is manufactured, because those enzymes aren't naturally present in cell culture, the virus seeds need to be activated by exposure to trypsin, and the cells themselves, which are used to grow the vaccine use trypsin in order to passage them from flask to flask.

So those are the most likely sources of the porcine circovirus. Since the cell banks and the seeds for these vaccines were established a long time ago, the trypsin that was used back then is not available. And so we can't say for sure that that was the source, but that is the most likely source.

MS. BUCK: My other question to that, then, is are we looking at all vaccines in this way to see if indeed they also contain adventitious agents? And although it appears that perhaps this time we've dodged a bullet in terms of safety, how are we assured that the next time it wouldn't be a bigger issue, or that perhaps this type of thing is happening in other vaccines?

DR. KRAUSE: So that's a very good question. One of the difficulties is the specific techniques that were used by the investigator at the University of California in San Francisco to look at the vaccines and identify the virus in the GSK vaccine can be used, but they're actually

not so easy to standardize. And they're not so easy to apply in a regulatory setting.

If a manufacturer wants to use these techniques and get a negative result and provide us with confidence that the vaccine is okay, that's a little bit more complicated than taking a vaccine and doing a study and if you get a positive result, then publishing it. And so we are working on how that can be done and how those kinds of techniques can be implemented, but they require some standardization, and they require plans for follow up of the different results. And that in fact is one of the two main topics that was discussed at the advisory committee meeting. That's actually on a later slide, but you guys are anticipating what I had laid out here quite well.

MS. BUCK: I think one of the points would be I think in terms of the public perspective is that it would have been nice to have had the FDA do the catch on this.

DR. KRAUSE: I'm sorry. It would have been nice to what?

MS. BUCK: Have the FDA do the initial catch on this.

DR. KRAUSE: Okay. I can't argue with that.

MS. BUCK: Okay. But I'm hoping that maybe the next time because of this has occurred, that it would be nice if it did.

MR. SCONYERS: This is Jeff Sconyers. Just to follow up on that. One of the reasons that I wanted to see this item on our agenda was to understand the FDA's ongoing methods for assuring the safety of the vaccine supply and that you're continuing to monitor what -- I think everybody is surprised by this PCV being in this vaccine. But we've been surprised by other elements in other vaccines in the past that unfortunately have had significant harm. The SIV that inadvertently got incorporated into I think the polio vaccine.

DR. FISHER: SP40, not SIV.

DR. KRAUSE: That was SP40.

MR. SCONYERS: All right. Thank you. So, I think what Tawny's asking and what I'm wondering is how does the FDA monitor the safety of the vaccine supply and assure that it stays ahead of and not behind the safety of that supply. It's unfortunate that an academic researcher generated this data instead of what I think we all think of as our surveillance entity for the safety of the vaccine supply.

DR. HERR: Did they test other vaccines, and do we know why? Did they only look for PCV?

DR. KRAUSE: No.

DR. HERR: Did they only look in these particular vaccines?

DR. KRAUSE: No. So the investigator in San Francisco looked at almost all of the live vaccines that are available, and wanted to apply this new technique, which involves high throughput sequencing, which means getting a lot of sequencing data, to understand what's in vaccines better. So he viewed that as something that would be interesting to do.

It's not altogether fair that in talking with him that he was interested in looking for -- he was definitely interested in looking for potential contaminants. But he was also interested in studying the vaccine strains themselves, and asking the question how much variability is there? And one of his major findings, in fact, was -- because he was able to get a lot of sequences on polio virus strains, or polio vaccine, which isn't used in this country, but to get a deeper look at the potential for dangerous variants and things like that, and to get a sense of how variable the sequences of the various viruses are in the different live vaccines.

So in those studies, which covered almost all of the live vaccines we have -- it didn't cover the smallpox vaccine, that's a notable exception, but it covered most of the others -- this was the only finding that he had of a potential adventitious agent.

So the FDA, of course, asks the manufacturers to

do testing of their product, and they have required manufacturers to do that. And that testing then is what forms the basis for a safety assessment of each of the products.

We did actually earlier this year publish recommendations for a guidance document on testing for cell substrates and for viral seeds that are used for the production of viral vaccines. And that guidance document actually suggested for vaccines that are exposed to porcine products to test for circoviruses as well as a number of other agents. But that's a recommendation at that stage, that's not a requirement. So these things are all on our radar screen.

It's very, very difficult to keep up with all of the viruses that are being discovered these days, though. There are very, very powerful new techniques, and if you look in the virology literature, new viruses are discovered every month. So if you try to come up with a list of viruses that need to be tested for, it's likely to be out of date almost as soon as you publish it.

MS. BUCK: Can I go back to a point you just said? I want to clarify that. Did you say that the FDA asks the manufacturers to do the testing and that's the data that you use for licensing? Or maybe I misheard that.

DR. KRAUSE: So we provide guidance to the

manufacturers on how to test their vaccines. And the manufacturers provide all of the data that they have available at the time of licensure, and we evaluate that data based on our knowledge of the science at the time, and based on our understanding of the benefit and the risk of the vaccine.

And so if there are critical viruses that are not tested for at a time a vaccine is submitted to the FDA for licensure, then we don't approve it. Then we go back to them and we say, no, we want you to do these additional tests.

Complications arise when understanding of the virology changes since the time the product was licensed, since the time that the product started being studied. Or complications we can expect will arise in the future as more new viruses end up being discovered, because at the time of licensure one may not even have known that those viruses existed.

MR. SCONYERS: I think we can exactly anticipate that. And so my question is, what do you do about that? What's the FDA doing as science continues to advance in our understanding of viruses, virology, how are you assuring that you are staying with our approved vaccines in a position where you can assure the public that they're safe?

MS. HOIBERG: The FDA isn't actually personally

testing them. You're trusting a manufacturer who wants to get it out the door and on the shelves to make money. They're not -- that's like having your children check their own tests and grade themselves and say, yes, I got an A. But I'm just saying if it's FDA approved, I mean I put a lot of stock into something that says FDA approved. But I think if it's FDA approved, that means FDA has actually looked at it and tested it and made sure that it's safe. And the fact that you trust the manufacturers to do it is scary.

MR. SCONYERS: Well, but I just want to be clear, that's true about everything that happens. I mean, FDA doesn't test every drug or every biological themselves. It relies on manufacturers to do that. I mean that's just the way the system works.

DR. FISHER: And they couldn't.

MR. SCONYERS: It may or may not be the way it ought to work, but it just is how it is.

DR. FISHER: It would be billions of dollars.

MS. BUCK: I think I -- Jeff Sconyer's question is the same concern I have, which is what is the ongoing follow-up from the FDA on things that have, once they've been approved then are on the market, particularly vaccines that have been used for a very long time, in terms of ongoing safety profiles and things like that.

MR. SCONYERS: Right, exactly.

DR. KRAUSE: Well, so of course, one of the things that's done and one of the very important pieces of this is what Dr. Martin will tell you about, is the ongoing safety surveillance. And if the vaccines are safe in practice, then the likelihood that there is something in the vaccine that is dangerous to people is very, very low.

And so if the vaccine has been approved based on a substantial safety base, and it's been used for a long time and continues to be safe, then we have that information. So in this case, one of the things that strongly supported the continued use of these vaccines was in fact the overwhelming benefit relative to the theoretical risk associated with having this virus particle in the vaccine.

And so for each of these vaccines, many, many millions of individuals around the world and many millions in this country have received these vaccines and there have not been any evidence of any safety problems in the vaccine. So a huge element of what we do for safety is based on actually looking at people.

There is the additional question of as new tests become available that have the potential to test things that could be of concern, how does one implement those? And that's something that FDA has done in the past, and

that we're moving to do in this context. But it's a little bit more complicated than saying starting tomorrow we want you to do this test. And I'll explain why in a second.

So an example of this, in fact, was -- and I'm not remembering the year, but it was in the late to mid-90s -- was the finding that egg produced vaccines had reverse transcriptase. And so better assays for identifying the enzyme reverse transcriptase were made available. And people started testing vaccines and other things for the reverse transcriptase's enzyme. And the reverse transcriptase's enzyme, usually when it's present is part of a retrovirus, which is a kind of virus. And ideally of course you wouldn't want to have a virus present, but it turns out the vaccines that were produced in eggs were positive using this new assay, while they were negative using the old assay, because the new assay was much more sensitive than the previously used assay.

And so the worldwide vaccine community had to ask the question of, well, is this concerning for vaccines that are produced in eggs? And so two things happened. One of them was a lot of work was done to see whether this reverse transcriptate's enzyme activity represented anything that was potentially infectious in humans, that could potentially or theoretically cause any harm in humans. And there was, after a lot of work, there was no evidence that

it represented a virus that could infect people.

And, in fact, it was found to represent what's called an endogenous retrovirus present in chickens and in eggs. And this gets a little bit deeper into the science of this, but all species have a large amount of endogenous retrovirus sequences in them, including us, probably ten percent of our DNA. I've learned today that we have more bacterial DNA than human DNA. But a good portion of our DNA is retroviral DNA even. And so these are things that are actually potentially expected to be in different kinds of cells. And in any event were shown not to be infectious for humans.

But nonetheless, because that new test became available that was more sensitive than the old test, the FDA did go back and requested that the manufacturer start doing the new test on products under R&D as well as go back and study products that were licensed to see whether, to provide additional assurance using these new tests.

So that's sort of a case study of how this has been done in the past. And that's how I predict it will be done in this case also.

But the presence of a new test is not something that can immediately be employed for the reason that I mentioned earlier, and is on a slide a couple slides from here, which is that standardization of these tests is not

easy. These high throughput sequencing tests involve taking a product, extracting all of the DNA or RNA from it, and then randomly amplifying all of that and getting lots and lots of sequences, and then sending them to, usually to a contractor unless you're very wealthy and have your own machine, and then you get back potentially millions of sequences that represent fairly short fragments of DNA or RNA that was present in the samples you started with.

Now, many of those sequences that you get back are going to be completely meaningless. You can take those millions of sequences and compare them with the GenBank, the databases, and ask is there anything in here that looks like a virus. And if there's anything that looks a lot like a virus, then you have a hit.

But the problem that we have if you want to use these kinds of tests to screen vaccines is you need to know what you call a negative. And so you have a problem that there are going to be some things that are going to hit GenBank, which is sort of an unvalidated database. Tomorrow anyone in this room could submit a sequence to GenBank and claim that it was a new virus, and GenBank would publish it. And so there are many things in GenBank that are simply mislabeled. There are many things in GenBank that are called viruses that aren't viruses.

And so we're going to have to start off with a

better-curated database in order to evaluate these kinds of results. So if I'm an academic researcher and I get a hit, I don't need that. But if I'm going to use this as a manufacturer to assure that a vaccine is free of viruses, I do need that.

The other thing that I need if I'm a manufacturer that wants to do this, is I need very good standards for this. If I do the test, what if I run it against everything and I get a negative. Well, unless I'm simultaneously doing that test on something that everybody agrees I should get a positive on, I don't know that my test actually worked, because these tests are complicated and difficult to do.

And so if we asked all of the manufacturers to go out and do the testing tomorrow, I predict we'll get a lot of negatives, and we won't know that in fact we've really made anything any safer. So figuring out how to standardize these kinds of tests is an important part of this also. And I suspect over some period of time -- and I'm not giving you a timeline here -- there may well be standards that manufacturers and the FDA are going to share among one another in order to make sure that when a test is done, we know that if it's negative, it's a true negative rather than just the test didn't work.

And then there's an additional problem with these

particular kinds of tests, which is particularly vexing, but which can be dealt with, which is that when you send these sequences off and you get a million sequences back, some percentage of them will not match anything in GenBank at all. And probably they match -- probably they come back because the reagents that you use to do your study might have, the water might have had some algae in it or something, but nobody knows the sequence of the algae, so that's not in GenBank. Or the reagents may have had other things in them, too.

And so, Ian Lipkin, for instance, at Columbia University -- does a lot of these kinds of experiments on clinical samples to try to find viruses that are causing unusual infections. He told me a year ago, and I don't think it's gotten any better, that more than ten percent of the sequences he gets he can't identify at all. They don't match anything in GenBank.

So if you're a manufacturer and you do these kinds of experiments, and ten percent of the sequences come back and you don't know what they are, the question is, well, what does that mean? What if next week somebody submitted a virus to GenBank and it matched one of the ten percent that didn't match anything? So you need to build in a way of constantly rechecking the sequences that you got.

So all of these things, I think, are technically feasible. But they do require a lot of thought, they require figuring out what are the right standards, what are exactly the right ways to do these kinds of assays, making sure that standards that everybody can agree upon will indicate that an assay is good are going to be available. And they require -- the first thing I said, which I don't remember what it is.

So introducing these kinds of assays is a complicated regulatory and scientific problem. And it's one that we're working on very actively. But it's not one that I can tell you we've solved.

DR. HERR: What's a reasonable time frame that you can think of that will give us an idea of what progress FDA is making on looking at this issue?

DR. KRAUSE: That's a good question. And I can't commit to a time frame. So that should force the large issue of using these new tests to study vaccines. Then, of course, there's the smaller issue, but getting large also, of making sure that the vaccines are tested, at least for the porcine circovirus, and perhaps tested for other viruses that we do know about, and make sure that there isn't anything else that's being missed.

And so what we're focusing on. We're doing both at the same time, but we're more likely to come up with

answers on the PCV testing before we come up with answers on the generic virus detection scheme, simply because the generic virus detection scheme is a larger problem.

MR. SCONYERS: So, I sort of understand what you're saying. I'm following you at a safe distance. What I don't understand is what your current requirements are to assure the safety of the vaccine supply. So that's what I do not understand. I understand a bit about where you think the science needs to go, where the testing needs to go, why it's complicated, the relationship of known to unknown sequences, and whether that's data or just white noise. What I don't understand is what's the FDA doing today to assure the safety of the vaccine supply.

DR. KRAUSE: Okay. So what the FDA is doing today is what it has always done, and that is to assure the safety of the vaccine supply, because we license vaccines based on benefit. And we look at risks and we do that based on clinical trials and clinical studies. And we do that based on real data with the vaccine. We also do that based on our best understanding when we license the product of the manufacturing process and of the testing scheme that the manufacturer has come up with. And so --

MR. SCONYERS: In terms of postmarket, post-approval surveillance what's the FDA doing? I understand how you get to the point of approving. What's the, what's

in place post-approval to assure the ongoing safety of approved vaccines.

DR. KRAUSE: Okay. So that's something that Dr. Martin will cover in his talk, and he's really our expert on that. But that' an area in which the entire government enterprise has really done a huge amount. And a lot of this has been accelerated actually by the H1N1 vaccine, which has put additional resources, and figuring out how to do this kind of surveillance, post-licensing surveillance for rare adverse events.

And that includes things that -- I'm sure you've heard about -- it includes the VAERS system, it includes the Vaccine Safety Data Link, it includes new and fairly -- very cleverly put together systems that scan insurance records for hospitalizations --

DR. HERR: I think we understand some of those methods of surveillance. I guess the question -- maybe if I'm wrong in rewording it, Jeff -- is that given this information of this viral contamination of the Rotarix --

MS. GALLAGHER: Can I just, before you go further -- maybe I misunderstood -- I thought they found particles that are thought to be parts of the vaccine, but they didn't find --

DR. KRAUSE: One actually infects --

MS. GALLAGHER: -- live vaccine, or did they?

DR. KRAUSE: One actually is porcine material.

DR. HERR: There's live virus in the Rotarix, yes.

DR. KRAUSE: There is live virus in the one material, because it is affected porcine cells.

MS. GALLAGHER: Oh, okay.

MR. SCONYERS: Yes, he's right. There is live virus in there.

MS. GALLAGHER: I'm sorry. I missed that.

DR. HERR: But given this information that we know that these particular vaccines have been contaminated in that since, whether it's from the beginning or whether it's from later on, what is being done to start to look at other vaccines as well as other -- well let's say look at other vaccines to see that this doesn't happen with them, it isn't the condition with them, and how are we going to continue to watch vaccines that are being produced today, or tomorrow that haven't become contaminated by looking at this testing process? Is that sort of what you're talking about?

MR. SCONYERS: Yes, that's fine. I guess it's not very satisfying to say we look for adverse events and that's our measure of whether the vaccine's safe or not. I mean, yes, that would be one indication, but how do we assure that unsafe vaccines, things that are not

manufactured properly that have had contaminants introduced to them, or that don't have the immunogenicity that you want them to have, how do we assure that those products that aren't safe for the public don't reach the public in the first place? Not how do we measure once they have. How do we assure they don't reach the public?

DR. KRAUSE: Well, but that's of course what the pre-licensure process is about, right? It's about looking at the data and seeing whether they reached the point where the benefit of the vaccine substantially exceeds any potential risks. So that is the pre-licensure process.

MR. SCONYERS: I understand. And there was a description of a manufacturing process that was part of the pre-licensure process, pre-licensure application that you all approved.

DR. KRAUSE: That's correct.

MR. SCONYERS: So how do you know they're following it? Every vaccine has to be manufactured in accordance with GNP, right? So then how do you assure that manufacturers are actually manufacturing vaccines in accordance with the approved formulations, and that they're being transported in accordance with approved methods, and that they're being stored and preserved? The whole part of it up to the point of introducing it to humans; how does the public know that the vaccine supply is safe to the best

of FDA's knowledge in accordance with the science that produced the approval?

DR. KRAUSE: So this is a question -- you're asking a more general question about the regulatory process. And so the regulatory process has multiple different forms to it. There's the evaluation of the data, there's the clinical trials, there's the review of the manufacturing process as the manufacturer submits that to us, and it's full of the data that the manufacturer submits to us in support of that.

Prior to licensure there are inspections of the manufacturer, and data that they submit to us is verified. And their facilities are inspected to make sure that the facilities are capable of and are doing what it is that they say that they're doing. Clinical trial sites are inspected to make sure that the records of the clinical trial sites actually comport with what the manufacturers have provided us in support of the clinical data that they've given us.

And so there's -- and the manufacturers provide us with a large amount of written material, and all of that written material is then subject to inspection and verification. And so that's maybe part of the question you're asking. How does the compliance arm work?

In addition to that the manufacturers do submit

samples to us and some testing is done on those samples, although it's not the type of comprehensive testing that would allow one to test every vaccine for every potential ill agent. Very often the testing that's done at FDA is related to potency. Sometimes it's related to sterility for bacteria, and things like that. So these kinds of tests are normally not done at FDA.

But the protocol for doing a review by the FDA, the inspectors go in and they ask were these protocols followed, and were they signed off on properly by the people who did them according to the standard operating procedures? And so the actual raw data are inspected to make sure that the manufacturer is in fact doing everything the way that the license says that it should be done. And that's done both pre-licensure, and then we also follow up inspections post-licensure.

DR. FISHER: And there definitely have been plants shut down. There has been licensure held up. I mean that's happened multiple times in the last four or five years, so. So it is a pretty robust system. I think how do we keep up with the evolving things I think is problematic and probably is key. But it's hard to require something that you didn't know about.

MR. SCONYERS: You only see what you look at.

DR. FISHER: Well, right. Sure.

DR. KRAUSE: So the reason I'm here is for -- well, several reasons I assume -- but my message though is that this is complicated, and my message to you is we are on it. We are looking at this and we're figuring out how to do it. And so I'm laying out to you what the obstacles are, and I'm not laying out the obstacles because I'm saying we're not going to do it. I'm laying out the obstacles to show you that we've thought about what needs to be done so that we can surmount them.

DR. HERR: Is it something that may be six -- I'm sorry. Is it something that in six months to a year from now when we have you come back and say this is what we're doing in light of this particular problem we had today, last week, last month? Or is it something that, it's not an issue because it's something that's being looked at all of the time?

DR. KRAUSE: We're always looking at how we can improve these things. And so, I would hope -- although I can't make the commitment on behalf of CBER right now that in six months to a year we will have made as much progress as I would like us to make -- that we'd all like to make. But I'm sure we'll be farther along in six months to a year. But this is a continuous process in thinking about what testing needs to be done, to what level of sensitivity it needs to be done, and how one can make sure that the

testing is being done right.

So just to summarize, so the VRBPAC discussion on the 7th of May, the members really overwhelmingly considered the benefit of these vaccines to outweigh the theoretical risks from the presence, in the case of the Rotarix, or the potential presence at that time in the RotaTeq, of porcine circovirus. And that includes the substantial safety record of vaccine, including that known to contain PCV. They discussed the importance of transparency in providing information to the public, as well as recommended of course taking steps to remove PCV from the product.

And that's a complicated and difficult thing to do. But in response to that, what we did then was we recommended -- we reverse the recommendation to suspend the Rotarix use. We still are continuing testing at CBER to better understand these issues. And discussions with the manufacturers have taken place and are continuing on further testing, as well as how best to label the products and inform the public, as well as remove the PCV from the product.

MS. BUCK: I just have a quick question. It seems interesting to me that Rotarix was recalled for a while, and yet RotaTeq never was. And yet RotaTeq is the one that seems to have more trouble.

DR. KRAUSE: No, I don't thinks so. So, what

happened was we got the information about Rotarix first. And the information that we got about Rotarix suggested to us fairly early on that there might be live virus in there. And we wanted to have time to figure out what that meant. So we didn't actually recall it. What we did was something a little bit unusual for FDA, we recommended that people not use it while we figure this out.

And so it was still in the doctor's office, but the doctors were in general not prescribing it. I think it's very unlikely that anybody got it at that period of time. Although we didn't, at that time, have doubts about its safety based on all of the clinical data, we still wanted to figure that out. So it was sort of the precautionary principle in practice.

We then subsequently heard from Merck that they were finding actually much lower amounts of fragments of PCV in their products. And so the evaluation of the Merck products has actually lagged behind a little bit. But the levels that they had were lower, and actually in our testing of the Merck product, initially we didn't detect it at all because the levels were so low. And then we started using assays where we used a larger amount of vaccines, because when you test a larger amount of vaccines, then you have a better chance of finding it. And we were able to detect it as well.

But in our assays we did not detect longer fragments in the Merck vaccine, and in the preliminary studies that we've done -- and we're continuing these because you can do a study, and if you get a negative -- it's very difficult to prove a negative. And although we think that our assays are very good, I think one of the ways to show a negative is to continue to evaluate the assays, do additional controls, and repeat them.

But at least in the studies we've done so far of the Merck vaccine we've not gotten any evidence that it grows in the pig cells, whereas for the Rotarix vaccine, there's clearly a virus present. What you might be remembering is that the DNA fragments that were found in the Merck vaccine were both of PCV1 and of PCV2, whereas the DNA fragments and the virus that was found in the GSK vaccine was just PCV1.

And so PCV1, when it infects pigs, actually disseminates through the pig. It's found in the lung tissue of the pig, and it's found in other tissues of the pig as well. So if it infects an animal, it does get into the animal.

PCV2 if it infects a pig, does the same thing. But when PCV2 -- when a pig is infected both with PCV2 and another virus, other co-factors, the pigs get quite ill, whereas nobody has found any illness associated with PCV1

in pigs. And so there's some people who thing that because the pigs get sick with the PCV2 infection with a co-factor, that makes PCV2 potentially more dangerous in humans.

That's actually a conclusion that I reject, because I think if one is going to worry about it, one should worry equally about both. But there isn't any evidence that either of these viruses infect humans. And in fact some studies were done in the context -- so there are two other interesting things about the potential to infect humans.

One of them is that there was a study done in cell culture, because these viruses have been of interest in the xenotransplantation community for quite a while, because pig organs were being given to people in xenotransplantation. And the question is: could porcine circovirus in those pig organs be problematic? And so studies were done in cell culture to see whether, at least whether PCV1 infected human cells. The conclusions were that it could get into the cells, the virus could, but that it didn't cause infection.

The other thing that is potentially relevant is, as I mentioned, people eat a lot of pork products anyway. But there also are medicinal products that contain a lot of porcine enzymes, pig enzymes, that are given to people with cystic fibrosis or to people have ripple surgery in which

their pancreas has been removed. And they need those enzymes in order to digest their food. And people with cystic fibrosis, they need it to survive.

And so they get actually fairly large amounts of these pig enzyme preparations. These pig enzyme preparations are not purified in a way where they would remove these pig viruses. And so that's a situation where on a daily basis people are exposed to large amounts of the same kind of material. And in those people there are no clear adverse effects either.

When the FDA was faced with that, the conclusion was -- obviously because it was a life saving treatment, to go ahead and approve that. But the label for that, the package insert does inform the doctors and the people who receive those products that there's the potential for them to have pig viruses in them as well.

I think that for pig viruses -- of course, humans have lived on farms for many, many years and have been around pigs and cows for a long, long time. So it's actually very unlikely that viruses that routinely infect these kinds of livestock would cause substantial disease in humans, just because of that co-evolution. But that, of course, is not the same as -- so that's additional supporting information, but that's of course not the basis for the whole conclusion.

MS. BUCK: I just think it's interesting that, you know, as soon as a problem was detected in Rotarix -- and, again, I'm not sure what the timeline was, and I realize that that was caught early -- that you wouldn't just immediately test all the manufacturers vaccines and temporarily suspend use until you got the answers that you have now.

But it appears at least to the less sophisticated eye, is that you caught, you had a catch with the Glaxo vaccine, and some time ran where that one was sort of held off use, and the Merck one was continued to be used and looked at as well. And then you had a process with VRBPAC and so forth so they could assess about the safety. So I think just to the less sophisticated public eye, it was a little confusing as to why Merck was sort of allowed to continue to produce and use their products when Glaxo's was held for a while.

When it seems to me you could have probably made a determination on at least the adventitious agent being in both vaccines very quickly, and then waited to sort of determine whether or not that was a safety issue or not before refusing or introducing both vaccines.

DR. KRAUSE: Your point is well taken. I think that the situation with the two vaccines was a little bit different because the levels of DNA in the Merck vaccine

were lower. And there was, at the time we suspended the use of the GSK -- or recommended suspension of the use of the GSK vaccine, there was actually a lot more information about the level of virus and the fact that -- and based on the data that we had it seemed more likely to represent infectious virus -- or seemed likely that it would ultimately represent infectious virus, whereas for the Merck vaccine it seemed less likely.

Part of this also is that as we were thinking about this, we wanted to understand how we were going to deal with this problem. And it did take us some time for our thinking to evolve and to conclude that, for instance, -- and this was ultimately supported by the advisory committee -- that for Rotarix, that even though the virus is knowingly present, and even though it is infectious virus, the benefit of the vaccine greatly exceeds any potential risk from that virus.

And so I think that does provide a model for thinking about other vaccines also, where we have clear benefit. And so, while it is our goal to ultimately characterize all of these things as well as they can be characterized, and to understand what's going on with all of these vaccines, it does take some of the urgency away from addressing the specific virus for all of these vaccines because -- first off, because the live vaccines

have, in general, been looked at by the investigator in San Francisco, and this is the only one that was found to be positive.

But also because other vaccines are manufactured and other cells that don't appear to support the growth of porcine circovirus, other vaccines are inactivated, which provides an additional layer of protection. So there are reasons why the concern for other vaccines is lower.

DR. FISHER: And, Tawny, this is Meg. They did, at the time that they said suspend the use of Rotarix, both the investigators from University of California at San Francisco and the company couldn't find any PCV in the Merck product. It wasn't until they used the more sensitive tests and the higher amounts of vaccine that they found it.

So it wasn't that they weren't looking at it. They had looked at it. It wasn't there, and it was only with a different technique and a more careful technique that they -- and I don't even know more careful, just more sensitive technique that they actually found it.

So while I think you could make it into a conspiracy theory that Merck paid off someone at the FDA. But I think that if you actually do look at the timeline, it does make since, particularly with what you've shown us here with the slides and the other stuff.

MS. GALLAGHER: And I was wondering if this would be a good time to segue into the post-marketing safety of the U.S. licensed rotavirus vaccines by Dr. Martin.

DR. KRAUSE: I'd be happy to come back and answer more questions at another time. I'll bring more slides.

Agenda Item: Postmarketing Safety of U.S. Licensed Rotavirus Vaccines, David Martin, M.D., M.P.H., CBER, FDA.

MS. GALLAGHER: Is Dr. Martin on the phone? Hello? Well, thank you very much, Dr. Krause. And I guess Dr. Martin -- oh, he's here? Hello, Dr. Martin?

DR. MARTIN: Can you hear me?

MS. GALLAGHER: Now we can. Yes, thank you. You have the unenviable position of last speaker of the day. And also I think Dr. Krause has warmed up the crowd for you, so to speak. So please, if you're comfortable now proceeding, go ahead and proceed with your presentation. The slides are on and Geoff is running them for you.

DR. MARTIN: Okay. And as came out obviously in Dr. Krause's question, I'd like to emphasize that even though this is entitled –

(Telephone connection interruption)

MS. GALLAGHER: Hello, Dr. Martin?

DR. MARTIN: I'm sorry. Excuse me. Can you hear me better?

So I was just saying that obviously, as came out in Phil's discussion, really monitoring lifecycle safety is much more than postmarketing surveillance. It involves Office of Vaccines and Office of Compliance and Biologics Quality in kind of each aspect, and then finally postmarketing surveillance. And it's kind of like trying to catch a little tiny minnow with multiple nets that are a little too large, and you put one net after another and maybe you finally catch the minnow. So, I mean these are complicated problems. There are a lot of different people trying to contribute.

As far as moving to our first slide, and obviously presenting our framework for postmarketing surveillance, you can go ahead and flip to slide number 2, the framework for vaccine safety monitoring. And obviously I'm speaking about things as applied to Rotarix and RotaTeq. But broadly these are things we do for every vaccine.

And so our framework has three goals. We want to generate safety signals, we want to strengthen them, and then we want to confirm valid associations. And our sources of signals include clinical trials, which are typically undertaken in the pre-licensure phase, as well as the Vaccine Adverse Event Reporting System, which we examine both through manual review where medical officers

look at serious reports -- and there's sort of a regulatory definition of a serious report. And then all reports are examined by those medical officers through automated means, and we actually use empirical basing and data mining methods to look at all of the reports.

So you sort of have the combination of clinical intuition, or clinical epidemiologic intuition on the one hand, combined with algorithms, which are in a sense as objective as possible. And that's sort of how we look at those two major sources of information. Obviously we're also looking at the published literature on an ongoing basis, and looking to any experience with products overseas from our sister regulatory agencies.

Strengthening signals and ultimately confirming associations can be done in multiple ways. If you have a prespecified safety outcome and appropriately powered clinical trial, you can do that and you'll see later that that was done for intussusception with both of these products in question.

We also have the CDC and FDA Vaccine Safety Data Link, which is a network of eight managed care organizations, and encompasses approximately three percent of the United States population. And then obviously there are controlled observational studies being sponsored by academia, government, and industry.

So if you can go to the next slide please. I'd like to state that overall the primary strength of the Vaccine Safety Monitoring System is its multifaceted nature. There are weaknesses with each modality, but the combination is what we rely on.

And clinical trials obviously are truly experimental because they have a random allocation of treatment in comparative groups. And VAERS gives us the most heterogeneous population we can look at, and this allows us to find rare adverse events, because it truly is a national system.

Another advantage I'd like to point out that came out during H1N1 is that when you have a new product -- and obviously you've already had clinical trials, but in terms of your postmarketing information, VAERS is kind of like your sentinel system. I mean, before anything is prepared from any other method, whether it's some kind of observational study, or rapid cycle analysis, which I'll address in a minute, you're getting VAERS reports from day one.

Now, the next portion, as far as a strength, is that VSD, which again was the network of the managed care organizations, it allows us to do weekly monitoring for multiple prespecified adverse events across a range of products and outcomes.

And then finally, controlled observational studies are what we rely on because they give us large populations with real world product use. And then we can make inferences about vaccine adverse events associations.

So if you can go to the next slide, I'd like to point out a few of the limitations. The, you know, and again this list of limitations is not all inclusive, but it highlights some important issues. So first of all obviously clinical trials, you know, we hear all the time that they're the gold standard for whatever it is that you're trying to demonstrate, whether it's efficacy or safety. But the reality is that they're typically not powered for rare adverse events. And indeed, the intussusception trials for both of these vaccines in question are among the largest safety clinical trials that have been undertaken ever.

So, in most cases we are not going to detect rare adverse events in a clinical trial. Now, VAERS again is a means to in a sense generate hypotheses about rare adverse events, but these associations remain hypotheses because we don't have denominator data, and we don't have a control group, and there's issues with data quality, underreporting, and stimulated reporting, which I'm sure the committee is familiar with. So, it's a great sentinel system, but again those associations remain hypothetical

initially.

VSD rapid cycle analysis, again, it's hypothesis generating with the network of eight managed care organizations. But it at least sort of has a controlled population and a little bit better data quality. But obviously it's not as comprehensive in terms of covering the whole populations.

In controlled observational studies, their extent obviously varies based on who's sponsored them and how or why they were designed. But like in clinical trial, they are used to confirm associations. An issue that arises here is that obviously because it's not an experimental study you can have systematic error from the way a study was designed -- an observational study. And so if you have small increased risks from a rare adverse event, that might be sort of washed out by systematic error, or might be attributed to systematic error. And so it might not be something that you can clearly state that you believe it's a true causal association.

Now the one thing, the one limitation that's common to all of the modalities that we use is that long-latency effects are difficult to detect. If you think about it, a typical VAERS reporter is usually reporting false outcomes that happened within days to weeks after they received their vaccine. And then if you look at the

follow up period for clinical trials, that's usually measured in weeks, sometimes up to a year. And controlled observational studies may be a few years at most. So that's just a, again, a caveat for the entire system, the way it's designed.

If you could please flip to the next slide, I'll speak first about RotaTeq. And as you're aware, RotaTeq was licensed in the U.S. in February 2006. The contraindications are hypersensitivity, as well as a history of severe combined immunodeficiency, which I'll discuss in a moment. And I also have the labeled adverse events from passive surveillance that are on the label that are listed there.

So you can flip to the next slide. I have a recap here of the clinical trials. Now actually the clinical trials are typically overseen by the product office rather than by my office, which deals with postmarketing. But the clinical trials for RotaTeq included over 70,000 infants.

Overall rates of serious adverse events were similar between RotaTeq and placebo groups. There was a sort of numerical imbalance with Kawasaki disease, which was then folded into some postmarketing studies. And then notably, again, as I mentioned before, an extremely large trial enrolling 69,625 infants was undertaken to assess

intussusception. And as you can see, there were no statistically significant association within 42 days of any dose, or within one year of does number one.

If you could flip to the next slide I'll outline some of our postmarketing safety activities. First of all, globally 37 million doses of RotaTeq have been distributed through March 2010. And Merck completed a controlled observational study of 85,000 RotaTeq recipients, and this was indeed reviewed by a medical officer in my office, and there were no statistically significant associations with confirmed intussusception or Kawasaki disease.

The Vaccine Safety Data Link has registered 207,000 doses over a two-year period, May 2006 to May 2008, and there was no elevation in risk for intussusception, seizures, meningitis, encephalitis, myocarditis, grand negative sepsis, bleeding, or Kawasaki disease.

In VAERS we have found one report of secondary transmission, which we have been examining in cooperation with OVRR, the product office, to consider a possible addition to the label. Originally when these vaccines were licensed there were warnings about administering these products to infants with some type of immunodeficiency. And what we found through VAERS surveillance was that there were several infants who had prolonged gastroenteritis after they were given RotaTeq. And in the end ultimately

they were found to have a preexisting condition known as Severe Combined Immunodeficiency. And so this has now been added as a contraindication. And, you know, unfortunately these vaccines are given before this diagnosis is made. Although in sort of an unrelated development it turns out that a HRSA advisory committee has recently recommended the addition of SCID to neonatal screening. So, it would be hoped that in the future clinicians would actually be able to act on the guidance in the label, that this is indeed considered a contraindication.

Through VAERS surveillance, the data mining of VAERS surveillance, through literature review, and all of these other activities, we've had no other new safety signals that have emerged since licensure for RotaTeq.

Next slide please. So, as you're aware, Rotarix was licensed in the United States in April 2008. And the contraindications include hypersensitivity, history of Severe Combined Immunodeficiency, and any malformation of the GI tract that would predispose the infant to intussusception. I've also included the labeled adverse events on the slide there.

So we can again flip to the analogous slide, covering the clinical trials, which is the next slide. And for Rotarix, again, over 70,000 infants participated in clinical trials that were used to support product safety.

And, again, overall rates of serious adverse events were similar percentages for events; rates were similar. There was again a statistically not significant, but sort of a numerical imbalance with Kawasaki disease. And obviously with the prior experience with RotaTeq, again this was folded into postmarketing studies that were planned.

And then again a very large trial was undertaken to address risks of intussusception in Rotarix, and there was not statistically significant elevation of risk at 31 days after any dose, or at 100 days after dose number 1.

So you can please go to the next slide, which covers our postmarketing safety activities. And obviously this vaccine was approved; it's the more recently approved vaccine. Global exposure, there have been 68 million doses distributed. Although United States exposure is lower, only 2.5 million doses through March 2010 in the United States.

GlaxoSmithKline currently has two controlled observational studies, which are looking at intussusception, Kawasaki disease, convulsions, lower respiratory tract infections, and death. But we do not have any date from those yet.

VSD has -- basically there's just a low uptake in VSD thus far. There's only been approximately 5,000 doses administered. But as you can see there's an extensive list

of outcomes listed there, which was informed by experience in the clinical trials. And there is also an analysis of all cause hospitalization or ED visits that's I believe actually being run by the CDC -- it's not being run by my office -- to compare Rotarix and RotaTeq within the VSD.

Within VAERS surveillance we also had a case where an infant -- and this was actually a manufacturer providing a report from overseas of a manufacturer -- excuse me, of an infant, who was later found to have SCID, who had a clinical picture similar to those with RotaTeq. And so a contraindication was added to the label for Rotarix February of 2010. We've had no other new safety signals that have emerged since licensure for Rotarix.

So, in summary, on the last side, I guess overall I would say that components of the vaccine safety monitoring are complementary. There are issues, but we attempt to leverage the strengths of modality. And we are currently evaluating every safety signal from the pre-licensure phase in controlled observational studies during the post-licensure phase. And we have the two post-licensure safety signals that were not apparent from the clinical trials. And that is obviously the increase risk posed by the vaccine to infants with SCID, as well as this case report of secondary transmission with RotaTeq.

So we have no other new safety signals, and their

multifaceted postmarketing monitoring continues. And as I said, in our office we don't just kind of flip from, you know, one topic du jour to the other. This is an effort that encompasses all 72 licensed vaccines in the United States. They're divided and the medical officers follow the same sort of -- they look at the same aspects of surveillance, and if deal with the VAERS database, with medical literature, and with these other modalities.

And so it's kind of a -- I hate to use a sports analogy, but it's a bit of a zone defense. So we, when these things come up, we definitely shunt resources in that direction, but we do the very best we can never to ignore our other products so that everybody kind of knows that this sort of final aspect -- we obviously can't guarantee product quality in my office, but we kind of see ourselves with that last line of defense.

And so that was really all that I had. I know most of the action was on Phil's side.

MS. GALLAGHER: Okay. Thank you very much. Are there any questions for Dr. Martin?

DR. HERR: Dr. Martin, this is Tom Herr. So the children how had SCID and got the rotavirus -- or got the vaccine, they only had prolonged diarrhea?

DR. MARTIN: Right. But I mean in this case some of these individuals were admitted and were quite ill, and

it was obviously one of the medical officers in my office who review each case individually. I did not review each one, but these were -- this was not an unimportant finding. And most of them ultimately ended up having the transplantation. So you can ultimately have definitive treatment for the SCID.

MS. GALLAGHER: Okay. I have no further questions here. Tawny? All right. Then I think we can move on to the time for public comment. Operator, are you there? Can you please tell people we now have time for public comment and let us know if there's anyone who signals that they wish to comment?

Agenda Item: Public Comment

OPERATOR: If you'd like to submit a comment, please press *1 and record your name. Again, to submit a comment, please press *1 and record your name. One moment while we wait for the first call. Our first comment comes from Jim Moody. Your line is open.

MR. MOODY: Okay. Thank you very much, and thank you for the opportunity to make comment. I have three comments on the different parts of the day.

Regarding H1N1 safety studies, summaries are great, but much more important were Dan Salmon's commitment to total transparency. The point of any safety inquiry must be what are the rate of adverse events, and that can

only be determined by comparison to placebo immunovaccines and not just other vaccines.

And two, what steps can and are being taken to reduce or eliminate those risks. Several features of the reported data raised some concerns about the true nature of the adverse events risk. One is disease definition, two is -- in other words Guillain–Barré has a specific definition, but when something is close to Guillain–Barré, it doesn't exactly fit, but yet it is an adverse event.

Over aggregation by sex and age groups, that could hide safety signals. Another concern would be selection of adverse events for studies, as opposed to looking at all possible adverse events and administrative versus research data and differences in quality of those data across the safety systems. One suggestion would be for this committee to endorse full transparency of all of the raw data so that various academic and independent experts could conduct their own studies and let the experts sort out what the true nature of the safety risks is.

Regarding the Vaccine Information Statements, I think that it would be very helpful if they more clearly identified inclusion and exclusion criteria for efficacy and safety studies. And either a statement that the candidate vaccine is recommended for use in children whose health profile is the same as the studied population. Or

that it's being recommended for use in children whose health profile is different. So the parents could make an informed choice as to there kids like them, for example, the use of the word -- I can't remember the language, but it was fairly ambiguous, and one of those statements was mild disease. That can vary across different parents. That can certainly vary across inclusion and exclusion criteria.

Two, they must clearly state there have been no safety studies in either humans or animals in which the recommended schedule is compared to placebo, against actually the population. The vaccines have not been studied in the context of multiple simultaneous administrations. Or to the extent they have been so studied, clearly the full indication is important. Accordingly under ethical principles, applicable to patient-centered decision-making, the schedule must be regarded as an experiment until further safety studies have been completed. The lack of this safety data should be clearly disclosed.

My third point is that there's much more disclosure about the availability of the procedures of VAERS reporting, as well as the Vaccine Injury Compensation program. And the fact that there would be no additional state product liability remedies, and he thinks there's a

very short, at least for now, statute of limitations.

The third point would be related to the report on the Omnibus Autism Proceeding. And one of the things that comes through from these oral arguments, one of which was today in Cedillo, is that the science is still evolving and we know so little about how vaccines affect the individual cell, the immune response, the safety response, and the body as a whole. And particularly, in light of the absence of baseline data on unvaccinated humans and animals, so much more needs to be learned. And as this is being learned, we'll have to learn a lot more about what the true safety risks are of vaccines.

And it's very, very important that this committee take a stand similar to what the National Vaccine Advisory Committee did, and identify the safety gap, and make an immediate recommendation for conducting such ongoing research in an independent accountable way in both humans and animals. Only then can we get to ground the true nature of the risks faced by the increasing vaccine schedule. Comments I think like from Dr. Krause, such that the vaccines are safe; millions of doses have been administered and the benefits so far outweigh the risks, as some sort of a reason, possibly if not taking steps immediately to reduce the risks, they're very worrisome. But these are based on faith and guesses, and not sound

science.

It’s very, very important that the ACCV take a strong stance in favor of closing this safety gap so that we’ll have the science to make improvements in the schedule if safety signals are indicated. Thank you very much.

MS. GALLAGHER: Thank you for your comment. Is there anyone else on the line who wishes to make a comment?

OPERATOR: There are no further comments in queue

MS. GALLAGHER: Thank you. Then I will adjourn this meeting, to be continued tomorrow morning at 9:00 A.M. Thank you very much for your participation, and I want to thank the staff for helping us with all the technical difficulties that arose; job well done. Thanks.

(Whereupon, at 5:55 P.M., the meeting was adjourned.)