

Department of Health and Human Services
Health Resource Services Administration

Advisory Commission on
Childhood Vaccines (ACCV)

March 8, 2012

Conference Room 10-65
Parklawn Building
5600 Fishes Lane
Rockville, Maryland

Proceedings by:

CASET Associates, Ltd.
Fairfax, Virginia 22030

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P R O C E E D I N G S (8:15 a.m.)**Agenda Item: Welcoming Remarks/Chair Report**

OPERATOR: Welcome to the quarterly meeting of the Advisory Commission on Childhood Vaccines. All lines will be in a listen-only mode for today's conference. Today's conference is being recorded. If you have any objections, you may disconnect at this time. I would now like to turn the meeting over to the ACCV Chair, Mr. David King.

MR. KING: Thank you, Kelly. I appreciate that. First off, welcome, everybody, for coming to the meeting that is being conducted today and tomorrow. We have a published agenda. I will tell you that the times that are listed on that agenda are not cast in concrete, and so we have a little bit of fluidness to them so that we can accomplish what it is that we are hoping to accomplish. There is no listed break time except for lunch in the morning session. We will take a break at some point somewhere in the mid morning when it seems that we should. I guess we'll figure that out as we get to it.

What I'd like to do is I'd like the Commission members -- and we have several on the phone, so I'm going to ask that the two on the phone initiate and announce who you are and if you come from a special interest or

whatever, and then we're going to go around the room here and introduce the members. We have a new member who is seated for the first time as well, and I'll let that individual announce themselves as we move around also.

DR. FEEMSTER: This is Kristen Feemster. I'm a pediatric infectious diseases physician and a health services researcher from Philadelphia, one of the commissioner members.

MS. LINGUITI PRON: This is Ann Linguiti Pron. I'm a pediatric nurse practitioner, and I also work in primary pediatric care in the Philadelphia area.

MS. WILLIAMS: My name's Michelle Williams. I'm an attorney from Alston & Bird in Atlanta, Georgia, and I am an unaffiliated attorney.

MR. KRAUS: My name is Ed Kraus. I'm from Chicago, and I'm an attorney who represents vaccine-injured individuals.

LT. MARSHALL: My name is Lieutenant Valerie Marshall. I'm from the Office of Vaccines Research and Review at the Center for Biologics Evaluation and Research at the Food and Drug Administration.

DR. SHIMABUKURO: I'm Tom Shimabukuro. I'm with the Immunization Safety Office at CDC.

MR. SMITH: This is Jason Smith. I'm in-house counsel for Pfizer vaccines and a commission member.

MS. DELA ROSA: I'm Luisita dela Rosa, a commission member and a parent of a vaccine-injured child.

DR. VILLAREAL: I'm Sylvia Villareal. I'm from Taos, New Mexico. I'm a pediatrician. Previously I've been on the National Vaccine Advisory Committee in the '90s. I think that's all you need to know. If you have other questions, please do ask me.

MS. SAINDON: I'm Elizabeth Saindon with the Office of the General Counsel for the Department of Health and Human Services.

DR. EVANS: I'm Geoffrey Evans, Director of the Division of Vaccine Injury Compensation and also Executive Secretary to the ACCV.

MR. KING: I am David King. I am the new chair. This is my first time chairing. Hopefully we'll have it down smooth. I do want to make one quick announcement that Charlene Douglas is on her way. She is stuck in traffic, and when she enters the room and takes her seat, we will pause the meeting just to announce that she is physically present and is part of the meeting.

Having said that, let's move along on the agenda. We need approval of the December 2011 minutes, so I ask the

commission members if anyone has any additions, deletions, corrections, or comments as it relates to the minutes from last meeting in December.

MS. LINGUITI PRON: I already had emailed Andrea Herzog, but my credentials are incorrect.

MR. KING: That is being corrected, correct? Terrific. Any other comments? Before we move on, in the approval letter component we want to make an adjustment on page 11, which would be day two, where an approval letter to the secretary in the form of recommendations -- Geoff, maybe you can enlighten us on that.

DR. EVANS: In the instance where the program is consulting the Advisory Commission on Childhood Vaccines, that is not usually thought of in a letter. The record speaks for itself, and the department uses the record of the discussion and the outcome for its deliberations process as the rulemaking process goes forward. There's not an actual letter that goes to the secretary.

MR. KING: Just as a point of clarification, since a formal letter does not go the secretary and we just had the conversation, dialogue, discussion, that occurred in the meeting, is there a transcript of that that goes, or is it a summary transcript that goes?

DR. EVANS: It is reflected in the documents that are created as part of the rulemaking process. There's not something that is paper form that goes up separately. It's all part of the singular process as the department at its various levels considers the policy proposals.

MS. SAINDON: The fact that the consultation occurred is included in the preamble.

MR. KING: Perfect. Then we look for a motion here to approve the minutes.

(Whereupon, on motion duly made and seconded, the minutes were unanimously approved.)

MR. KING: We have a report from the Division of Vaccine Injury Compensation. Dr. Geoffrey Evans will be providing that.

Agenda Item: Report from the DVIC

DR. EVANS: In your blue folders you'll have on the left side my presentation, presentation by Mr. Rogers from the Department of Justice. On the right side of the blue folders you'll have the various presentations for the proposed changes to the Vaccine Injury Table. At the front of those presentations is a colorized version of the Table and the aids to interpretation.

At the back of that stack of papers is a 2001 notice of proposed rulemaking. This was the last major

rulemaking activity where the commissions consulted, major in the sense that there were multiple things that were proposed. That was back in December of 1999. The NPRM, as we call it, was published 18 months later. That'll show you what an NPRM looks like. You'll hear that acronym frequently today.

I want to welcome everyone to the 82nd quarterly meeting of the ACCV, and I want to thank those who brought this wonderful weather for us. Unfortunately, the workload today will not give us as much of an opportunity as we usually have to go outside.

Today is a very special day because one of the most important, if not the most important, functions of the Advisory Commission on Childhood Vaccines is to advise the secretary on changes to the Vaccine Injury Table and Aids to Interpretation. This has taken place a handful of times in the 24 years of the program. Policymaking through a deliberative process such as this advances the mission of the VICP, and we look forward to engaging the Commission and initiating this rulemaking process.

Starting with the presentation itself, these are the highlights for today and tomorrow. We have the presentations of the two main offices. My presentation will

be followed by Mr. Mark Rogers from the Department of Justice Vaccine Litigation Office.

Then we'll start the series of Institute of Medicine Report-generated task force recommendations led off by Dr. Rosemary Johann-Liang and the DVIC medical staff. That will actually comprise most of the day. When we actually leave this room this afternoon remains to be seen. We have quite a bit of work ahead.

Tomorrow we'll have a review of vaccine information statements by Jennifer Hamborsky from the CDC and updates from various ex officio members of the Commission from FDA, CDC, NIH, and the National Vaccine Program Office.

Next, let's turn to the monthly stats. In terms of the filing of petitions, the non-autism filings continue to be very brisk. We're still on pace, as I count it, with a little bit over four months gone so far, because these stats are as of February 10th. I have us on track for about 380 claims.

Just as a reminder, nearly half involve flu vaccines. It's given in such large numbers. This past year I believe there were 150-160 million doses distributed, so it's more than a third of all vaccines that were distributed. We are still continuing to have lots of

filings, lots of work for medical staff and the Department of Justice.

Turning to adjudications, you'll see that what's changed over the past couple years, not surprisingly, is that the Department of Justice working with petitioners' counsel have been dealing with attorney fees and costs with the omnibus autism proceedings. Mr. Rogers will get into that a little bit more during his talk. That's something that's been going up the last couple of meetings.

Going on to adjudication categories, this is something we've been presenting for the past couple years. My goal in doing so has always been to give you an insight into how the process is working internally. We have compensable claims, not compensable claims, and under compensable we've broken it down for concessions, court decisions, and settlements. As you can see, settlements have been the predominant way of doing business for the program, litigated with settlements or cost within settlements, over the past couple years.

The concessions are an indication of when we review a case at HHS, what case will fit the Table or where they're causation in facts shown by the evidence in the record. Relatively few cases are conceded on the basis of

causation effect. Almost all are on the basis of a table injury.

As you look for the stats for 2012, you see that there are zero cases that have been conceded. You say, gee, there's a zero there. I think that's there for a couple reasons, although as you look at our database, we've actually conceded a case at the end of January, so had it been entered in the system soon enough, there'd be a one there instead of a zero. We've actually had a second concession since then.

But if 60-65 percent of claims that are filed are for flu vaccine and HPV and they don't have Vaccine Table injuries, it makes sense that the concessions would certainly begin to decrease over time because the program has, over time, turned from a table to an off-Table program. This is just a continuation of that trend. It's not that there is different strategy that's going on internally.

Under the court decision, to me, that is we've tried to have that portrayed the times that we defend a case, but as has probably been brought up at several meetings in the past -- Mr. Rogers or Mr. Matanovski -- has gone into great detail, the court decision number also

involves proffers. Mark will explain that a little bit again. It's defined in his materials.

What that means is that these are not necessarily claims that were defended. These were claims that were proffered, meaning that they could have been a court decision or could have been a case that just ended up as a proffer, and it was not a special master looking at the evidence and deciding that compensation was deserved. That's on the back end. Concession is on the front end when we first look at it, but the court decision and settlement numbers are what happens at the back end when there's a final resolution of the case.

As much as you have voiced the desire that we make our stats as consistent as possible, we're operating with what we do over here, and these numbers try to reflect that. The Department of Justice, of course, is giving you quarterly snapshots of what they're doing. I hope I didn't confuse everybody with that explanation, but I know it's something that we seem to get to every time when we try to make sense of the stats.

In terms of amounts paid, according to my figures we're in a slower process of petitioners' awards than we were of this past year, which is the most we've ever given out in petition awards altogether. I think our outlays for

last year for attorney fees and costs and petitioners' awards, was \$234 million. Now we're on pace for something in the \$170 million range, but attorney fees and costs are still staying up at about the same range.

Turning to the trust fund, we crossed over the \$3.4 billion. This is in spite of the fact that the outlays were the greatest in the program history. We still managed to bring in around \$130-\$140 million from trust fund, again due to influence of flu vaccine, which is distributed in such large numbers. The program is still in a position where it's bringing in more money than it's paying out for ensuring that there's a future fund.

In terms of significant activities, Dr. Charlene Douglas and I attended the National Vaccine Advisory Committee at the beginning of February. We both gave updates. Charlene reviewed the rotavirus activity of the Commission at the December meeting. I also attended the Advisory Committee on Immunization Practices in Atlanta February 22nd and 23rd.

In terms of points of contact, if you wish to contact the program, you should write the National Vaccine Injury Compensation Program, 5600 Fishers Lane, Parklawn Building, Room 11c-26, Rockville, Maryland, 20857. The telephone number, toll-free, is 1-800-338-2382. That's for

you to obtain information about the programs, questions, or an information packet. You can also access information about the program on our Internet website, which is www.hrsa.gov/vaccinecompensation.

For those that wish to provide public comment at the Commission meetings, write Andrea Herzog at the Parklawn Building, Room 11c-26, 5600 Fishers Lane, Rockville, Maryland, 20857. The phone number is 301-443-6634. Andrea's email address is aherzog@hrsa.gov. With that, I will end my presentation and happy to answer any questions.

PARTICIPANT: Could you go into a little more detail on how it has migrated from a table to an off-Table to give a little bit more understanding for folks?

DR. EVANS: The short explanation is that a series of events took place in the 1990s. The program opened its doors October 1st, 1988 with a two-year deadline for the filing of claims for vaccines given prior to the program beginning. 4,200 claims came in. Three-quarters of them were DTP. Many of them had table injuries. There were vaccine injuries listed on the Table for DTP vaccine. That was the way that the program existed in the first six or seven years, predominantly a table program. That's what Congress had in mind and so on.

Over time, as we added nine more vaccines, they were added with relatively few, if any, table injuries. At the same time, we transitioned from using DTP vaccine to DTAP. We went from using oral polio vaccine to the inactivated polio vaccine. Those two vaccines were responsible for a number of table claims.

With those three things, the transition of the two vaccines as well as the addition of new vaccines to the program with no table injuries, I believe the court at the Judicial Conference likened it to 1995 and 1996. That's really the 1995 table changes where two conditions were taken off the pertussis vaccines began to really begin the change, but it was also even more importantly the transition away from DTP vaccine. Now we have an off-Table program starting from about the mid '90s.

MR. KING: Charlene Douglas has joined the room.

Shifting to an off-Table, has any thought been given to creating table injuries based on them so that there is some level of consistency or at least some standardization of measuring what we have? How is this decided case by case if we don't have table injuries? Could it vary across the board?

DR. EVANS: We have a causation in fact program now. The standard of causation is, according to the way the

program is conducted, based mainly on the decision from 2005, which you've heard before. That's how we approach cases. That's the standard according to the Federal Circuit that was articulated in that decision. That's why there are increasing amounts of litigation settlements because there's increased litigation risk with the standard that is a little bit less based on science and more based on policy.

MR. KING: Thank you, Geoff. Next on the agenda is Mr. Mark Rogers from the Department of Justice.

Agenda Item: Report from the Department of Justice

MR. ROGERS: Good morning. Following Geoff, just as an overview, the compensation moves through a litigation system. The Department of Justice handles that, and so that explains some of the terms we use, some of the jargon, and some of the challenges in processing the petitions. It's had an effect on the statistics. I'll mention more about those later.

What I give you is a three-month snapshot of what's been going on with the litigation. No autism claims have been filed and 57 non-autism claims. This is a little less than usual, perhaps the holiday period. Usually we're

seeing about 100 a quarter, a little over 100 a quarter. The ratio of adults to minors has been about the same.

These ratios are also about the same. I'll get into these in a little greater detail. We compensated 55 cases. Remember, we're picking these numbers up from judgments, the very end of the case. That's when the court has stamped it with "case over." That's where we draw our numbers.

Cases conceded by HHS. Of the cases that went to judgment, three of them were conceded. We were talking with HHS about this, and we determined that they were counting concessions at the time they conceded them, which makes a lot of sense. That is what they do. That is their role in the process, is to concede them when they first review the case.

We're counting them when the case is over, when they go to judgment. That's just one example of why our numbers are not exactly right. They're both right, but not consistent. But remember, the purpose here is to give you an idea of how just a snapshot of the cases to look at the ratios, to look at the trends, to get an idea of what's going on. In that spirit, we offer you these numbers.

With a conceded case, we had three that were resolved by adopting a proffer. The proffer was on the

damages. Proffer is the fastest, easiest path to compensation because what that means is, with a conceded case especially, that the attorneys agreed as to what the evidence showed. It's faster than a settlement. There was no disagreement for anybody to resolve, either the special master deciding the matter or the parties agreeing to some compromise. This is an agreement as to what the evidence shows. It's extremely fast.

With the cases that weren't conceded, there were 52, with 47 being resolved by settlement. There are two issues in a case that's not conceded by HHS. One is whether compensation should be paid at all. The second is if so, how much?

A settlement can encompass both of those issues. We call those litigated risk settlements. The vast majority of those fall into that category. That is HHS has not conceded the case, but the parties discuss an amicable settlement that incorporates the issue of whether entitlement is appropriate at all and how much. Some of these cases are decided by the special master, and then they're settled on the issue of damages. There are two categories of settlements.

With the proffers, all of those would have been cases in which the special master resolved the entitlement

issue by decision, and then the parties sit down and agree as to what the evidence shows on damages. That's the fastest path to compensation once the issue of entitlement is resolved.

Of those cases that weren't compensated, in the non-autism there were 50. You see just roughly there were a few more compensated than not compensated. That's one raw bit of data that you might find interesting. With the autism cases, we have this mega-number of 745.

Where those are coming from are the cases that were piled up, if you will, during the autism trial of the test cases. What we're doing now, since the test cases were decided, is sorting through and resolving each of those cases. There are two issues in those cases, primarily. One is, if your case is just like the test case, and therefore ought also to be dismissed? The second issue, which exists in all of them, is what are the appropriate attorneys' fees?

I can say that the only way that we've gotten through that enormous number is a systems-based approach. We have categorized cases according to amount of effort that was put into them by the attorneys. I can also say that that systems-based approach absolutely wouldn't work without everybody's cooperation. That includes petitioners'

counsel, the Office of Special Masters, and our office. It's an enormous number to be processing with existing staff, both at the Office of Special Masters and in our office.

DR. DOUGLAS: My understanding from lawyers' fees is that in these large cases the lawyer gets a certain amount of money. If I get \$1 million, the lawyers always get this amount, a third or whatever, and the plaintiff gets the other. You're saying for the vaccine cases you make the decision of who gets paid what.

MR. ROGERS: What you are referring to is a contingency-based fee, which is a percentage. We don't have that in this program. This program, the standard is statutory, and that is it's reasonable fees. That has been determined by the special masters by case law to require that the attorneys keep track of their time and their costs, and that a reasonable hourly rate be applied to that time and award calculated based on it's tailored to that case, the amount of effort expended. It's not contingency, and it's paid whether you win or lose on entitlement as long as there was a reasonable basis for the claim.

MR. KING: Just to follow through on that, the dollar amount, the compensation being reasonable, has that been created in terms that this is what the rate will be? I

don't know whether it's a specific dollar amount or whether it's arranged depending upon where one is in the country or things like that because of different expenses. Then the question that begs from that is does this go under periodic review for changing things based upon that cost change, or does it stay stagnant?

MR. ROGERS: Great question. Congress used the word "reasonable." The great thing about reasonable is it's very flexible and adaptable. The bad thing about reasonable is that it can spawn litigation because people can disagree about what reasonable is.

On the issue of what is an appropriate hourly rate, the word is "reasonable." It's not a specified amount. There has been a lot of litigation about what is reasonable for a particular attorney in a particular place. Some of that litigation has gone to the Federal Circuit. The issue of how much should it go up each year is a source of litigation, a potential source that's been realized in a lot of cases. How many hours are appropriate for a particular kind of work? Reasonable is the statutory standard. Minds can differ over what's reasonable.

It has created quite a bit of certainly potential for litigation. On the transactional cost side of the equation here it has challenged the system. All of that

being said, there's been a lot of success in special masters, petitioners' counsel, and respondents' counsel, talking it over and shaking hands and resolving it. By far, the vast majority of these issues are resolved in exactly that way. That was a long-winded answer, but the short answer says no more than that they should be reasonable fees.

MR. KING: Fair enough. Does the litigation -- and since it certainly ties up resources -- impact the effectiveness of the Vaccine Injury Compensation Program?

MR. ROGERS: This primarily impacts the Department of Justice because it is involved in the litigation of these issues. We have a budget. We have a fixed staff. The amount of time that we spend on these issues is time that's taken away from other issues. It's a zero-sum game. That's a long way of saying, yes, it's going to have an impact because we have a fixed number of employees, trial attorneys, with a fixed amount of time to manage.

MR. KRAUS: The only thing I would add to Mark's comment is that probably even more troubling than the resources that the Department of Justice has to devote to deciding attorneys' fees issue is the Office of Special Masters who, when they are deciding the issues over

attorney fees, are not able to get to the issues that we're all sort of here about, which is making determinations about individual cases of vaccine injury. In other words, it doesn't just affect the Department of Justice, but it also affects the ability of the Office of the Special Masters to timely and efficiently, decide cases, in my opinion.

MR. ROGERS: One simple analogy would be if your standard in your home for when your children ought to be home is a reasonable hour, you're going to have an awful lot of discussion each evening over when that was. If it's 11 o'clock, 11 o'clock it is. Maybe that's an oversimplification, but a fixed clear standard is going to engender less discussion. In our context discussion can quickly lead to litigation.

MR. KING: Let's talk about that for a moment. I would agree with you on that and that we're not going to resolve that here, but are there any solutions that are being proposed by anyone to resolve this issue if we find that it takes the time of special masters and it takes the time of the Department of Justice, which means in a zero-sum game that it may, in fact, affect the effectiveness of the program?

MR. ROGERS: The question kind of morphs us from what is to what ought to be. I can't participate in what ought to be. We are focused on the what is, and reporting to you on how that's going.

MR. KING: That's an issue that we'll put on a parking lot and something that we'll come back to at another time.

MR. ROGERS: We have this category -- and each time I'm sitting here in front of you I'm wondering whether we ought to drop it off. I guess it's important to let you know that there is a path out of the program of just voluntarily withdrawing the petition. The statute speaks to it and says you have a right to withdraw after a certain amount of time if you're case is not resolved. Those kinds of withdrawals are actually quite rare. The usual withdrawal is a petitioner that recognizes there isn't any real hope in the claim and it's just not worth going forward. That's usually what's happened here. It doesn't happen a lot.

Here are some of the terms we use. Remember, the cases kind of go through a litigation funnel to either compensation or dismissal. I've already been through settlement. It can encompass the entitlement issue, whether or not compensation should be paid at all, and damages, all

wrapped into one. Or it can just refer to just resolve the damages.

Special master's decision. Special master is there to resolve any issue that the parties can't resolve themselves.

These terms are important on appeal. Affirmed means whoever brought the appeal lost. The decision below remains intact. Reverse means whoever brought the appeal has won. The case has been reversed. It goes the other way. Remanded means whoever brought the appeal has kind of maybe won. That is, they've convinced the appellate court this needs to go back for some more work. Vacated means that the court has thrown out the decision altogether, and sometimes they'll remand, sometimes they'll issue their own decision, the appellate court.

Here's our tried and true wire diagram. By far, the vast majority of the cases move down the left side of this chart. The petition is filed. HHS reviews it. It's not conceded. Then it's either settled by the parties or the special master decides it. Most of the cases that go to compensation are settled, down to that mauve or pink color. The decided cases go either way, but most of the cases that are not compensated go through the special master and are resolved by decision.

The cases that are not conceded and decided by the special master -- and the special master says the case should be compensated, it's going down the right side of the left track -- by far most of those cases then move over to damages, where they are settled or resolved by proffer.

MR. SMITH: I know we are getting this at every meeting. On the not conceded side under your statistics there is a possibility of a proffer. I think five cases during the period were decided by proffer. Quickly, how?

MR. ROGERS: They were not conceded. They were decided by the special master who found the case compensable. It went over to damages. That's going to happen a lot because where the real issue is, whether entitlement's appropriate at all, damage is not the issue. So once the special master decides that entitlement issue, the case is quickly resolved by a proffer. That wasn't the issue. That wasn't the problem, if you will, with the case.

MR. SMITH: So the proffer is on the damages component question, too, not on causation.

MR. ROGERS: Yes. There will never be a proffer -- never say never, but I think I can say pretty authoritatively there will never be a proffer on a case that was not conceded because there's an issue there that

has to be resolved one way or the other, and it can't be resolved by a proffer.

MS. LINGUITI PRON: I just wanted to thank you. This is a nice diagram.

MR. ROGERS: You need to thank our paralegals who are far better at the PowerPoint and all of that.

MR. KRAUS: What is typically included in a proffer in a case that goes to the proffer, the five that Jason just referred to, in terms of a published or unpublished opinion? What facts become available to the public?

MR. ROGERS: That's a good question. Sometimes they are made available, sometimes they are not. There is not a set procedure on that. The petitioner has an avenue for requesting that it not be published, and there's been a little bit of litigation on that, but I can't sit here and say it's always one way or another.

Turning to our appeal practice, this is at the Court of Appeals for the Federal Circuit. We had two cases recently decided. These were appeals brought by the petitioner. Affirmed means that the appeal did not succeed.

The Kennedy case was an unusual case. It was a case that had been dismissed before, long ago, and petitioner tried to gain relief under a rule of court that

allows a judgment to be set aside under unusual circumstances. The petitioner in that case thought that the case had not been well handled the first time.

In any event, the bottom line was that the Court of Appeals for the Federal Circuit agreed with the Court of Federal Claims that there had not been a showing sufficient to disturb that judgment. A judgment in a litigation context has a lot of protections. It's intended to be final and it's protected against reopening.

These are the pending cases. This is a bit more than we usually have at the Federal Circuit. This gives you a flavor of who brought the appeals and, in just a word or two or three, what the issue is. They are all pending. Several of these were just argued just a few days ago. Hammitt and Stone were just argued. Simanski, I believe, has just been decided. That case was remanded to the special master.

This is the Court of Federal Claims. We're down one notch. These are appeals brought by the petitioner that were just decided. Affirmed means that the decision below remained intact, that the appeal wasn't successful.

MS. WILLIAMS: Maybe your paralegals could do another flow chart for us of how things get from HHS and DOJ over to the courts.

MR. ROGERS: One of them is sitting right back there furiously taking notes. She knows what the after-action here is. Can you say that again?

MS. WILLIAMS: How cases get over to the courts, appeals court.

DR. SHIMABUKURO: Can you just briefly explain what jurisdiction is?

MR. ROGERS: Jurisdiction literally means the law to say. It means whether the court had the authority to speak to the issue, whether that case was properly before that court. Lately there's been a preference towards using the word "authority," especially in a statutory scheme like this, but that's the gist of it.

DR. VILLAREAL: Is this pediatric data or adult data for these cases?

MR. ROGERS: Both.

DR. VILLAREAL: Is there a percentage? Like right now we're looking at appeals. Is that predominantly pediatric or adult?

MR. ROGERS: I don't know. We haven't tracked that. I think they're looking at them roughly about the same as the filing ratio, which is about half and half or a few more on the adult side.

These are the pending cases. The highlighted ones at the top are all new. Hammitt and Stone were just argued.

This is a list. A past commission asked us to do this to track the settlements, how long it took to take the case from petition filing to filing that settlement, the shaking of the hands, if you will, on an award. We have them listed by the vaccine.

The injuries are the injuries that were in the initial petition. Sometimes that changes as the case progresses, but that just gives you an idea of the kinds of cases that are being filed and settled and how long it takes to get to that settlement. Between a year and two years is probably the median.

As we mentioned before, some of those that are outliers in the three or four years, there are a lot of reasons for that. I would say the primary one is that the case had not been developed to the point that it could be processed for several years. Normally it's petitioner looking for medical records or looking for an expert. Or if the case is tried, that will normally add at least a year to the processing. Those outlier cases are either case record development issues or trial procedure. When you see a case that's under a year or right around a year, that's with everything working as well as it possibly can.

That includes the special masters egging it along, facilitating where that's appropriate, or getting out of the way where that's appropriate. They have a good sense of when to do each. That's all I have. Are there any questions?

MR. KING: On the settlements, are there some special masters that are more likely to be settlements with than others?

MR. ROGERS: We don't track that. I don't know. I have no reason to believe that any do more than any others.

MR. KING: But that data would be available, since we would have the decision, and we would then be able to cross-reference to it.

MR. ROGERS: It could be tracked. I would caution discretion.

MR. KING: I don't know whether we're going to request you to do that or not. I don't think we should be wasting anyone's time either.

MR. ROGERS: I would caution discretion in that there are so many reasons. One special master, for instance, may be drawing the types of cases that can't be settled. I can say that we haven't seen enough of a disparity to prompt any tracking on our part.

MR. KING: Thank you, Mark. Moving along on the agenda, we have the Institute of Medicine Task Force on Updating the Vaccine Injury Table. That would be Dr. Rosemary Johann-Liang.

**Institute of Medicine Report Task Force on
Updating the Vaccine Injury Table**

DR. JOHANN-LIANG: We have a long day ahead of us. I'm glad to be spending the day with you and the medical staff. We have worked on this really hard for many months with our colleagues at CDC, and I'm hoping that the way we organize this will allow all of us to make sense of it throughout the day.

The objective of today is to seek your advice and your concurrence on the proposed changes to the Vaccine Injury Table. What I'm going to be doing to start off is to give you some background, because many of you are new to the Commission, about why we did the IOM contract, what went into that contract, what we wanted from IOM Committee, and then once they gave us that report, what we did after that to deliver the product you have today from HHS as promised.

I want to also acknowledge all the members who worked. I'll show you a slide on that later. I'm going to be followed by Elizabeth, who will be talking about the

legal and policy implications. When we update the Table, what are the parameters legal and policy-wise that we abide by?

There are a lot of additions that we want to do to the Table, so we are going to go through presentations of translating the IOM's causality conclusions to what we want to do with the Table. We really are focused on the IOM's of what we're doing about that as far as translating to the Table. For each of these steps we'll get your input and your comments and ask for your concurrence. We will organize it in that manner.

In your packet is the Table and the Qualification and Aids to Interpretation. I call it the color-coded version. I'm going to touch up on this a little bit more later because it would be handy for you to have this, especially when we start with the medical part. Just to be clear, the blue parts are all the wordings that we're proposing to add. The green parts are delete. Then we do have for organizational purposes some moving around of the sections in the Qualification and Aids to Interpretation. That's noted by the purple color, just so that you're aware. Have that handy as we go through.

Let's start with the Institute of Medicine's review of vaccines that we requested for review and the

various adverse events. The purpose of this was really that we wanted to use their independent expertise in medicine and science to give us that background for us to be able to update the Vaccine Injury Table. We wanted the scientific basis also so that the Table will help us adjudicate future claims.

As you've heard, Congress created the Table in 1986 really to give the presumption of causation as a compromise mechanism for certain vaccines and conditions. But over time, as you've heard, for various reasons that were discussed earlier, we've really moved away from a table program to an off-Table program. It's really time that we tackle this endeavor.

Since the last revision to the Injury Table in 1997 following an IOM report, there have been nine vaccines added to the program, but no real independent scientific review. This will be the first time since then that we have been able to do this.

The IOM report contract was initiated back in September of 2008. Once the contract went out to the National Academy of Sciences, they really worked on convening the committee of appropriate medical and scientific expertise. Finally, 15 members were convened.

I, as a project officer, gave the charge to the committee in April of 2009. The charge really was that they should do an independent review of the current science, the epidemiology, the clinical. We also were very interested in biologic literature as well because for a lot of the adverse events, safety events, risk events, it's hard to study them in a randomized control or epidemiological type of setting. We really wanted to understand more of the mechanistic evidence that's available that we can use when adjudicating cases.

We also wanted them to come up with some way of frameworking how we consistently -- as Dave talked about before, we're all about trying to be very consistent within the confines of the current available medicine and how we can put that into a framework of causality. That was their charge as well.

Initially when the charge was given, we really only had enough funding to do four vaccines, but we were fortunate that with supplemental funding from other parts of HHS, from the National Vaccine Program Office as well as from the Immunization Safety Office of the CDC, in September of 2009 we were able to add four more vaccines to review, for a total of eight vaccines.

This is really fortunate because in order to seat the committee, that's a lot of funding, so if you can actually add on additional vaccines, that's really a savings for us. That worked out well, and we were able to ask the committee to review 8 vaccines, which really constituted 12 of the 16 vaccine antigen combinations constituting 92 percent of the VICP claims.

We couldn't do all of them, but I think that we were able to come up with a list that covered most of the VICP claims. These were hep A, hep B, HPV, influenza, meningococcal, MMR, tetanus-containing, and varicella. Those were the eight vaccines.

Recall that the last revision was 1997 based upon IOM review, and at that time really the left column were diphtheria, tetanus-, pertussis-containing vaccines, MMR, and polio, both OPV and IPV, were the only vaccines really listed on the Table. Since then, nine vaccines are now listed on the Table as being covered by the program. It was high time for review.

The underlined vaccines are the ones that we asked the IOM for review. That is really we felt that some of the newer vaccines we really needed to review, like hepatitis B, varicella, hep A, influenza, because that's such a huge number of claims for the program,

meningococcal, HPV, but also that we really thought that we needed some updates from MMR and tetanus-containing vaccines.

We did not request the Hib vaccine or the rotavirus or pneumococcal because they constituted such a small number of claims to the program. At that time when we were given the charge, there really weren't any major safety issues going on. That was really the rationale behind why these eight vaccines were chosen for review.

Through a number of years, we come to the actual published report. It's all on the IOM website. There were a number of public meetings that IOM held regarding this project. They convened many times, culled through all the published literature on these subjects, and finally arrived at this report, which the ACCV actually was already briefed by the committee chair, Dr. Clayton, back in September of '11. She also went on to brief the National Vaccine Advisory Committee later that month.

People have heard all of this before, but for the sake of trying to bring us to where we are today, I am going to go over what they found in a very summarized way. Also, just to reiterate, the committee went through the literature and expressed their findings. They're not the

ones that make any recommendations. We, together, are going to make our recommendations and our updates to the Table.

The other thing that I want to briefly touch upon is we've talked about which vaccines and why, the rationale behind why those eight vaccines. What about that long list of the adverse events that the committee ended up reviewing? They weren't haphazardly pulled out; there was a rationale and a lot of thought and reasoning that went on beyond it.

The way we tackled that was first we generated what are the adverse event claims that are coming in, not necessarily what the scientists think are vaccine- and adverse-event-related, but really we went from the perspective of the program. What are the adverse events that are being filed to the program? That's how we started with each of the vaccines.

Then we added to that some of the scientific adverse events and the issues that are currently at hand. Then we also opened it up to our sister agencies throughout HHS for folks at the FDA, folks at CDC, and asked our fellow medical officers to all chime in to that working list of adverse events so that we had a very broad and a complete list for each of the vaccines.

Then after coming up with that working list, we went before the IOM, and they actually sought public input to the working list. The working list was actually posted on their website in December of 2009, because remember, that's when we had the funding for eight vaccines and we had the charge and the working lists and all the input from everybody.

This is not for the purposes of you looking at each of the adverse events, because it's sort of a history, but I just wanted to show you that there were four pages to the working list that was posted publicly all this time. This is page two. The first one is a cover page. Page two, if you look at this, it's got the tetanus-containing vaccines, hep A, meningococcal, MMR.

There has been a public comment in previous ACCV meeting regarding did HHS not ask for autism as an adverse event as part of the IOM review. I just wanted to point out autism was treated like all the other adverse events into that sequence of logic that I just discussed with you. It falls under the tetanus-containing vaccines and MMR because that's where the claims were coming in. You can see that autism is listed there.

In fact, in the footnote we asked IOM -- particularly we were interested in not just what we

consider the primary autism, that we really don't know why autism happens, but if there was some sort of an underlying diagnosis such as chronic encephalopathy or mitochondrial disorder. How does that relationship for autism and the vaccine relate? We did ask IOM about this from our perspective.

Since IOM had just done a full comprehensive review on autism and vaccines in 2004 and this is just four years later, we asked them, for the sake of all the other things that were going on, to just update us on any current literature past their last review in 2004 regarding autism.

We did not ask them to focus on this theory or that theory. This is an independent review, and we asked them in a broad sense to go back and update us on issues related to autism and vaccines that the committee felt was important. This is page two, just for completeness sake.

There is a page four, which is just a little listing that says general considerations, because when we gave the charge, we had the eight vaccines and adverse events that go under each of the vaccines, but there was also a general category, such things as anaphylaxis and what Dr. Ryan will be talking about, the injection-related, for all injectable vaccines. Things like that were really

under general consideration, not under just specific categories.

Really, based upon the claims information and the change in sort of the landscape of what's coming into the program, we were particularly interested in really a lot of these demyelinating issues and neurological issues related to vaccines.

Because it's hard to see on the slides, I've expanded that footnote for you. This is exactly what was on the public website all that time since December of 2009. Just to focus in on these general conditions, we especially asked them to look at vaccine administration issues, which has never really been touched upon, for the purposes of the program and the Vaccine Injury Table and also asked them to look at anaphylaxis and autoimmune diseases. In the IOM report in the first sections before they get into specific vaccines, they do discuss these general concepts, immunology, underlying disorders, et cetera.

Just to finish off on the adverse events side, when you do the factorial permutation of all the vaccines and adverse events that were requested, it turns out to be 148 vaccine/adverse event combinations that we charged them with. We really did get our money's worth of review.

We told them please don't take anything away, but you're free to add whatever other adverse events that you want to take a look at based upon once they start to cull the literature. They decided to add ten more adverse events to that list, ending up in 158 different vaccine/adverse event combinations, which really was 8 vaccines, 76 different adverse events, and all of its permutations. It also included the three adverse events in the general category of injection-related events, which is separate from the eight vaccines.

DR. DOUGLAS: Given the number of vaccines that are administered, this number of adverse events, and the permutations, do any of these reach statistical significance? I'm just saying it's such large numbers of vaccine given, and 158 discrete events is a lot of different events.

DR. JOHANN-LIANG: I think what you're kind of saying is that if you're looking at all of the denominator and then you look at all of the adverse events and you're saying that's a lot of events you're going to have multiplicity -- but that's not what this is about. They take each of the vaccine adverse events and look at them separately. It's a review. Statistics are really not involved in this yet.

MS. WILLIAMS: So it was just whatever was written in the foldout of the literature.

DR. JOHANN-LIANG: Right. They look at vaccine and adverse event and look at the published literature. They really didn't get into all the other stuff that's pending, but they looked at that and focused in on it and saw what's available for that pair. We're not doing any statistics. I'm just trying to point out that they did do a lot of work. This has been a lot of work. Very little was left out, so from the point of the claim, what's coming is claims.

MS. WILLIAMS: What you're saying is that this 158 does match up with what's coming in as your claims.

DR. JOHANN-LIANG: At the point of when the charge was given, yes. I'll tell you in a little bit, because there's a little bit of time lag, what we're doing now, what the task force did to try to catch us up.

Moving on to the IOM's work a little bit, just so you can have a background. I'm not going to spend too much time on this, but the charge to the committee was to really figure out some sort of a causality framework that we can use when we adjudicate cases. Based upon each of these vaccine/adverse pairs, give us your assessment of causation and the evidence that backs it up. Each of those has to

have a whole bunch of publications that they use to deliberate.

For each vaccine/adverse event relationship, IOM made three assessments. They took the weight of the epidemiologic evidence. We really like the way they did this, the framework. They also looked at the weight of mechanistic evidence, as I said, for many of these events, because there such small rare numbers, but any medical intervention has the potential to have an adverse effect.

They then looked at are there other types of mechanistic evidence aside from epidemiologic evidence alone. They took those two, and then they sort of looked at those two levels of evidence. First they ranked them into high, moderate, limited, and insufficient, and then they took them and did an overall causality assessment.

The overall causality assessment ends up being whether there is convincingly supportive evidence for a causal relationship. That's category one. Or if it's not quite there, they will say it favors acceptance, it kind of goes towards a causal relationship, but we don't have definitive evidence. Or they'll say we just don't have enough evidence, whether it's epidemiologic or mechanistic, to say anything about it. That would be the inadequate to accept or reject. It's nothing more than they're just

saying that the evidence is just inadequate at the current time. Lastly, the last category is that the evidence that currently exists really favors rejection of the causal relationship between that vaccine and that adverse event. This is for each adverse event pair. They do have a causality conclusion for those 158 pairs.

Starting with the convincingly supports, out of the 158 pairs, they gave us 14 vaccine/adverse event relationships where they felt that the current literature convincingly supports that relationship. The first is varicella vaccine with four adverse events. Those are four adverse event pairs. Dr. Shaer is going to be the one to discuss this relationship, MMR and two adverse event pairs that were listed on the working list. That would be six.

Then you have MMR, varicella, influenza, hepatitis B, tetanus-containing, and meningococcal vaccines. There are six that they said there was a convincingly supports relationship for the adverse event of anaphylaxis. That brings us up to 12. Then finally, the injection-related, which is syncope and deltoid bursitis. They thought that these 14 adverse effects from relationship convincingly were supported by the current science.

The next category of causality conclusion was the favors acceptance. These were the four adverse event vaccine relationships: HPV, human papillomavirus, and anaphylaxis; MMR, both a transient arthralgia for female adults and for children; and then lastly the oculorespiratory syndrome that was with specific type of strains, antigens, that were used in Canada some time ago. We kind of put that in because it was sort of our positive control to see how this panned out. That ended up in favors acceptance. But that vaccine is not given anywhere.

The causality conclusion for inadequate to accept or reject -- we were really interested in where all the demyelinating conditions that we're struggling with were. For the most part, they all end up in this inadequate to accept or reject at the current time.

An independent body of the most expert sat around, looked through all the current evidence, and thought that we just can't make a determination. It's inadequate to accept or reject. That was 85 percent of the relationships or 135. IOM stated inadequate to accept or reject means just that. It's just inadequate. That's where we are. Science at times moves forward, but at the current time we're not quite there yet, which way it's going to go.

Lastly, the last category favors rejection. There were five adverse event vaccine relationships, and it's listed on here for you to see. Since none of these are really listed currently in our Vaccine Injury Table, it's not something we really need to do anything about.

Then let's turn over to once the report came in and the report contained these causality conclusions of the four different categories, what did HHS do with that? That's where we are now, the preparation sequence. I'm going to go through with you what we did. If you have your color-coded ready, that would be helpful.

What we did once we received this report in September was that we established the task force to start to work on how we could update the Table. The members consisted of the Immunization Safety Office of CDC and, from Division of Vaccine Injury Compensation, medical staff here at HRSA, as well as our colleagues in the Office of General Counsel who counsel us. Since ours is a medical legal program, we felt that we really needed good counseling right from the start, so we all worked together in this task force.

We did this in a very systematic way. We used the data retrieval phase one form where the nine working groups within this task force worked and reviewed their sections

and generated these phase one worksheets so that we could all review what thought processes were involved.

It was also important because remember that the IOM really swept the literature some time in 2009 and then 2010, but they really finally did the re-sweep at the end of 2010. Although the report came in later in 2011, 2011 literature was not included, and for the purposes of influenza vaccine they were only really able to make a determination up to the 2008-2009 seasonal vaccine and nothing beyond that. H1N1 information was not included. We had some catch-up to do.

The charge to the working groups and the task force was to take the IOM report and really dissect it, digest it, and catch us up to the current time. That was part of their charge. After intensive work in the nine working groups -- and it's nine because it's the eight vaccines, plus injection-related.

At the end of November when phase one was completed -- and I really heard a lot about the taskmaster that I was doing, but we really wanted to get this done and come to you in March, so we got this done by November. The nine working groups came up with 21 vaccine/adverse event combinations that they wanted to move to phase II.

Phase two is really not just what the literature or what IOM said, but phase two would be now what do we need to discuss with the policy overlay as to what should really be added or updated in the Table.

MR. KRAUS: After the working groups did the literature re-sweep, they presented 21 adverse events to move forward to phase two?

DR. JOHANN-LIANG: Yes.

MR. KRAUS: What, if anything, was sort of not included? I'm having trouble with the math. There were 14, but it's more than 14 adverse events if you do it per vaccine.

DR. JOHANN-LIANG: It's coming up.

MS. WILLIAMS: I was at 158.

DR. JOHANN-LIANG: There were 158, and then 14 was the convincingly supports.

MR. KRAUS: I'm in the convincingly supports.

DR. JOHANN-LIANG: It's all of 14, the convincingly supports, we really needed to go to phase two, plus some others that I'll discuss on the next slide.

These were the 21 that the working groups, the task force, wanted to have further discussions into phase two, that it wasn't there's nothing here or there's inadequate evidence for us to do anything at this time, we

don't have the science backup to say we want to move this forward. These 21 were the ones that they felt we really need to discuss these issues further or IOM has said it conclusively supports a relationship or favor acceptance. Those were the other categories that were added to this.

If you look, MMR and transient arthralgia, those were the two favors acceptance. We had measles inclusion as a convincingly supports. Because of the transient arthralgia issue, the task force also wanted to take a look at the current chronic arthritis/arthropathy that was on the Table. The IOM's category was inadequate, but that was also something that they wanted to move on to phase two and have a little further discussion about. Febrile seizures and MMR, which was a CS, convincingly supports, category.

All of those varicella convincingly supports. Because the disseminated Oka and the vaccine-strain viral reactivation, the disseminated disease and the vaccine viral reactivation, IOM broke them out as four different categories. We end up collapsing them just for the sake of simplicity later, but those were four and five. Anaphylaxis was the fifth one.

Flu is in purple on the slides. For flu, the IOM committee really only had one that was convincingly supportive. That was anaphylaxis. But the task force wanted

to also move to phase two, the asthma exacerbation, Guillain-Barré for flu, and febrile seizures, Guillain-Barré because that's really of an interest with the H1N1 data that was coming to light.

Really the criteria that they added for taking out some of the inadequate category to more discussions was because more updated literature. We got some more information of febrile seizures and flu. We got some more information on the asthma exacerbation and the GBS, newer data that was coming out on the H1N1 that was not covered by the IOM. It really had to do with what I explained before, that we wanted to do a little bit of catch-up with the task force.

MR. KRAUS: In other words, the only thing that the task force did was to take things that were in the inadequate category and say maybe based on new evidence or new literature, it should be discussed.

DR. JOHANN-LIANG: Yes, and that's exactly right. That's why we end up with 21 vaccine adverse events going into phase two. Coming out of phase two after all our discussions based upon science with the policy overlay, we end up actually with 10 phase two worksheets. What we end up with at the end of phase two are that pink.

We're going to include -- and you'll see all of this later broken out in an organized format -- measles inclusion, encephalitis, and MMR. There is nothing currently for varicella, so all of the varicella stuff we're proposing to add on to the Table. For flu, the anaphylaxis. The anaphylaxis for HPV -- although the committee only said favors acceptance, we felt that we had further information and also program experience to say that we wanted to propose adding that to the Table. The meningococcal anaphylaxis, and then deltoid bursitis and syncope.

The encephalitis and encephalopathy was the 10th worksheet. The committee actually said for acellular pertussis the current evidence is inadequate to say anything about a causality relationship to encephalitis or encephalopathy, however we're not proposing to remove any of that stuff.

But what we wanted to do was to primarily add a definition for encephalitis, which has never been there. It's been in the Table as listed as encephalopathy slash encephalitis or parens encephalitis, but they're not the same, so we're stuck with what is encephalitis? We wanted to define that for the purposes of the QAI, the qualifications aids to interpretation.

The pink cells are the ones that after all of these considerations, that the working groups and the task force recommended that we should move to proposing to do something about changes to the Table now. As Tom from CDC will talk to you later about, there is more work to be done in the future.

This is just our first sort of proposal based upon the IOM review and what we've done to say we've got a lot of things we want to add to the Table. But we have further work down the line based upon all the information that we have looked at. Phase two was completed in January 2012, and we're leaving phase two with those pink cells.

MR. KING: Can you just identify them, in case the people on the website are having --

DR. DOUGLAS: We have them online, so the color does show up.

DR. JOHANN-LIANG: Let me correct that. It is salmon, like your shirt.

DR. VILLAREAL: Let me ask a very naïve question. If I took evidence-based medicine and I ran this through Watson and I said Watson, give me these parameters that IOM gave me, the meta-analysis, and then you're looking at the mathematical, because that's what Dr. Douglas is asking you, fall out. Really that's what we're looking at. We're

looking at a very small subset of 158 that really had some question in your mind. Is that correct? Is that where I'm going?

DR. JOHANN-LIANG: I'm not sure if it's really math. I'm just trying to work through the process. There are no statistics involved here. We're talking about vaccine and adverse event pairs. They really should be looked at in a discrete way, each of those pairs. They don't really relate to each other, per se.

The IOM looked at vaccine and adverse event pairs one by one in a discrete way and gave us a causality assessment one by one. Remember, many of these adverse events were actually generated starting with what claims are coming in. Many of the claims of adverse events are really not what scientists or the medical people will say have anything to do with vaccine. However, we wanted to make sure that we were overreaching and just as broad sweep as possible to leave no stones unturned.

At the end of that what IOM comes back with is we found 14 adverse event vaccine pairs. They're discrete. There are no statistics involved. They're discrete pairs that we think there's a convincingly supported evidence in the medical literature to say that we have a causality relationship. They also said we have a few more that favor

acceptance, but we're not quite at convincingly. Then there are a whole bunch of inadequates. Does that make sense?

DR. VILLAREAL: It does, but I'm asking you the back question to it. If, as a pediatrician, I look at evidence-based medicine and I have a parent who comes in and says this is what happened with the shot, very basic. That's why I asked you about Watson. If I took that computer sort of analysis, that's really what you're looking at, is the pairs that perhaps, by either lay definition or physician's definition, caused a problem. That's really what you're looking at. Then you do meta-analysis behind it to see whether there's any causality to a clinical decision.

DR. JOHANN-LIANG: But meta analysis is probably not really an appropriate way to think about this because the way the committee reviewed the data was not in a meta-analytical way. They didn't look at, for example, let's look at all of the case reports and combine them and then assess them based upon a pre-specified providence that we want to look at to arrive at a meta-analytic conclusion.

What they did was they took a look at this case report, and then they said does this contribute to our convincingly supports relationship? It's a different way of looking at it. I know what you're saying and what you're

saying about if I'm in front of a patient and I'm giving a certain vaccine, can I say that those 14, we were able to go back to the literature and find evidence to support a relationship? The answer would be yes, but we may not be in a meta-analysis type of format.

DR. DOUGLAS: In a previous briefing someone spoke to a web of causation kind of approach because they said ensuring that the timeline was right, ensuring that if it was either bursitis or something else that I saw up here, that the injection was given too high. There was some pairing in one of your previous briefings that talked about some of those web of causation things, and yes, it was given up here. No, this doesn't fit because there was a preexisting something, they got the shot, and then they made the claim. You've done that work before.

DR. JOHANN-LIANG: But that would be more of trying to establish what type of criteria would go into a case definition. It's not really a meta-analysis. That would be a case definition.

That little spreadsheet with the salmon color, what I'm doing now is to actually show you something that you can read that's expanded. These are the 14. I have two slides to show you the 14 that IOM said were convincingly

supports. What do we do with those 14? That's what we wanted after phase two. What are we proposing?

For the varicella, those four things, the disseminated varicella infection, and then the vaccine-strain viral reactivation, those four categories, we're going to add all of them.

For MMR, the measles inclusion body encephalitis, we're going to add that, too, but we already have vaccine-strain measles disease on the Table. You'll see later in Dr. Rubin's presentation how we're going to fold the measles inclusion body encephalitis in and hopefully make things make much more sense and give under the Guiding Principles that Elizabeth will talk about, give a broader inclusion.

Then the MMR febrile seizures. This was convincingly supported by the IOM review, and it's not new. We all know that vaccinations can result in fever going up, and the fevers going up can cause febrile seizures. This is not being added to the Table because, as Elizabeth will talk about, in order to really be a presumption of causation on the Table, not only do you have to show that relationship or have enough of an evidence for it to go on the Table, but that there is a residual effect, that it has to meet the residual effect requirement. Since febrile

seizures, by definition, you have it and then it's over and there's no long-term sequelae, that's not being proposed to go on the Table. Dr. Rubin will go through this more in depth. This is just to give you an overview.

MMR anaphylaxis, that was also found to be convincingly supports, but it's already there on the Table, so we don't really need to do anything about that. All the other anaphylaxis for these vaccines where nothing is currently listed -- varicella, influenza, hep B, tetanus, and meningococcal, those are all going to be added. Sorry, hepatitis B and tetanus toxoid is not being proposed to be added because it's already there.

Lastly, those two injection-related. IOM came back and said yes, there is enough mechanistic evidence for us to say convincingly supports a relationship to deltoid bursitis. We are proposing to add that to the Table, but as you'll hear from Dr. Ryan, under the Guiding Principles we're going to be actually proposing what we at the program wrote about, which was disturbed by shoulder, injury related to vaccine, and menstruation. It'll be a little bit broader than just the deltoid bursitis.

Lastly, the fainting, which IOM found to be convincingly supported. We will be proposing to add that as well to all the injected categories.

The next set is the blown up version of the favors acceptance. There are four of them. We're proposing to add anaphylaxis for HPV. Even though it was favors acceptance, we're going to be adding that.

For the MMR transient arthralgia in women and children, they said favors acceptance, but we're not adding that. Again, this is very similar to the febrile seizures and MMR previously. There's really no long-term sequelae. By definition, this medical entity is transient, it's done. Lastly, the oculorespiratory syndrome. We're not adding this because this vaccine is no longer manufactured.

The third category was favors rejection. None of these are actually on the Table, so we don't really need to remove any of these. Nothing is going to be proposed about these.

Finally, that large category constituting 85 percent of inadequate, to accept or reject. As I discussed before -- and there were good questions about which of these did we discuss. The reason why we discussed these in addition to the convincingly supports and the favors acceptance categories was because there was some updated literature since IOM finished, and we really felt that these were something we need to talk about.

For asthma and febrile seizures, we did agree that there was a relationship from the newer literature that IOM did not cover, but we're not proposing to add to the Table for the same reasons as previous. There's really no long-term sequelae to support that.

The influenza and GBS. The reason why this is deferred -- and Dr. Tom from CDC will talk more about this later -- is that we have new data from the H1N1 active surveillance information from 2009, which IOM did not cover that we think is important. We need to defer this to ACCV meetings done later.

Anaphylaxis hepatitis A, no matter how much we looked for the evidence, the evidence is still not there for us to add this to the Table yet. But remember that anything that's not on the Table, if we really felt that there was an anaphylaxis reaction to a hep A vaccine, we would concede that under causation in fact.

Then the tetanus-containing, we did talk a lot about even though the committee said for acellular and pertussis, the evidence just isn't there and it's inadequate for encephalopathy/encephalitis. We did talk about it, and we especially wanted to clarify the definitions for encephalitis.

Lastly, complex regional pain syndrome. This is something that we have really been monitoring in our program. This is such a rare event, but we really feel that this is something that we need to keep an eye on. But we just don't have enough evidence right now for us to put this on the Table. This may be something else in the future that may come before the committee as a proposal. The way we've got to get there is that we have some work still to do to publish some of the case series that we've been working on from our program as well.

MR. KRAUS: You sort of have a different category for deferred and not enough evidence yet. I'm just trying to figure out the distinction that you were making between those.

DR. JOHANN-LIANG: Deferred is because we know that there is some evidence, but it's not published yet, and it's hard for us to do anything with something that's not published. No means there's nothing really published that we know of coming up. The evidence is just not there.

But we think that the reason why we discussed these things, because it is anaphylaxis and hep A, we thought that that should be part of our phase two discussions. Complex region of pain syndromes, in how we came up with the SIRVA this is something we've been

tracking for a while, but it's really not in the literature at all. That's why there's a little bit of a difference there. For the sake of the future, those are some of the flags that we may want to be bring before you again.

MS. WILLIAMS: I got stuck, when I was doing the math, that phase two you said ten, and then we cut you off and you didn't finish. Ten what?

DR. JOHANN-LIANG: Ten, the salmon boxes because they count up to ten.

MS. WILLIAMS: No, it counts up to four.

DR. JOHANN-LIANG: Do you see those salmon-colored cells that have CS? What CSI and FA denotes is what I just went through, the convincingly supports, favors acceptance, inadequate to accept. These are 21 if you count all of the cells. Out of those, that went to phase two review. Coming out of phase two, everyone concluded that we should propose those 10 worksheets, which are really what we're proposing to revise the Table.

MS. WILLIAMS: On the right-hand side, what everybody is calling salmon, that is now reflected in your color-coded sheet as to change.

DR. JOHANN-LIANG: Yes, and all the presentations are coming to really go through the evidence. I really tried to come up with a way pictorially, because there are

so many points to this, to walk you through in a short amount of time so everybody comes to where we are to be able to discuss the events that are going to come down later in the day. I'm hoping that everybody's with me here.

Now we're on the acknowledgements slide. I really want to acknowledge everyone and their efforts. This was a colossal effort. Everyone is trying to do their job too. This is over and above what we do day to day. We had nine working groups going. Each of our stellar medical officers from Division of Vaccine Injury Compensation led each of these work groups. We were supported by Scott. He was our administrative support. Thank you for setting up all of these calls, trying to find call numbers that are working.

Some of the folks here just worked on phase two, some just worked on phase two, and they're all included. But the majority of people worked on both phases, which was a lot of work. I really want to thank our Office of General Counsel colleagues as well, because we really wanted to do this right and do it very systematically and, as I said, leave no stones unturned.

I was going to do this at the very end, but Dave King, your chair, had a very good point. It may be helpful for people to kind of have what lies ahead in your minds as you listen through the presentations that are coming up

today. Basically the purples are the ones that we've already gone through. We've gone through organizing the task force. We've done the kickoff meeting with all the different task force meetings and work group meetings.

Then what we come up with now is in February once phase two ended in January, I gave the presentation with Tom to the Immunization Safety Task Force we consulted. Actually, the Assistant Secretary of Health chaired that meeting with all the different scientists, heads of the different departments in HHS. We vetted this through them already, and they were very supportive. Now it's coming before you at the ACCV. That's March. We're in March now.

Going forward, it's a little bit hard to project exact timelines because so much is not in our control. It has to do with internal review process, and it has to be cleared through multiple levels of the department all the way to the secretary.

What will be happening next is that if today everyone sort of concurs -- let's say that we get through all the agenda and concur with all our proposals and we're done, we have your support and your comments today -- then we'll take those comments and your concurrence back to the Table and actually start writing the notice of proposed rulemaking.

There will be a long preamble. We'll really discuss all the evidence that goes to all the things. We have plenty of information to add. Once that whole proposal comes together, that will go through all the clearance processes.

Then once it gets all cleared and actually gets published in the Federal Register, there has to be a six-month public comment. All of you guys could public comment again at that time or anyone else in the public could make comments. After that public comment period closes, in addressing all those comments we may want to seek another ACCV consultation at that time. Or if there are no comments or things are very straightforward, we may be able to just close it out and start writing the publication of the final rule.

The final rule, again, will have to go through all of the internal clearance process because it is rulemaking. It will need to be briefed, et cetera, and then it will get published in the Federal Register. That would be all of our work together, which would be the Vaccine Injury Table and the qualifications aids to interpretation revamped.

MS. WILLIAMS: Does the preamble come to us?

DR. JOHANN-LIANG: The preamble is basically what you'll be hearing today, all the stuff that went into us coming to the conclusion that we should do something.

MS. WILLIAMS: I'm not suggesting that it should. I'm just asking from process.

MS. SAINDON: We have provided you with the changes to the Table and the qualifications aids in draft form for your consultation purposes, but the rest of that document will be in the internal document.

MS. WILLIAMS: Anticipating this, I asked Geoff -
- I'm holding up one of the packets. This is an old proposed rule that contains the preamble, just for illustration for people who haven't been through this before about what rulemaking is. It has this preamble that we're talking about, which really is the explanation that we're all going to hear today that will be condensed into a preamble. Then the actual color-coded changes that Rosemary has put together for us really will take up just a little bit of space at the end of the proposed rule.

DR. JOHANN-LIANG: Although, it is quite lengthy. It's not like a little table anywhere. It's pretty long.

DR. EVANS: Once we go through the public comment process, which also includes a public hearing, the final rule will document the comments that came up and address

the comments that were made and whether any changes or not were made to the original proposals based on input from ACCV as well as the other comments.

MS. WILLIAMS: Will the public hearing be during an ACCV meeting or separate?

DR. JOHANN-LIANG: Usually during an ACCV meeting.

DR. EVANS: Since you meet quarterly and we have a 180-day public comment period, it's rather easy to schedule a public hearing. What we've done is adjourn the ACCV meeting, and then convene right afterwards the public hearing. That way you have the benefit to sit there and listen and to take in anybody that comes to present orally. I will just tell you that the past public hearings no one offered public comment. We should know leading up to this whether anyone's registered.

DR. JOHANN-LIANG: This is my last slide for now. I think in your packets there is a handout of the choices that you have. The way we tried to organize this so that it just makes more sense is that as each presenter goes over how we arrived at proposing a certain vaccine adverse event to the Table, we will pause and ask you to have a choice.

The choice number one is that ACCV concurs with the proposed changes to the Vaccine Injury Table and you

would like us to move forward. You can give with or without comments. Secondly would be that you do not concur and you don't want to move forward with what we're proposing. Or thirdly, you would like to defer recommendation either to at the end of later today and not just do it with each segment or to another meeting later. It would be in June of this year.

Those are some of the choices that you have before you. You have it in front of you. The reason I'm giving this to you know so everyone can see is so later when we present each section, we want to actually have up on the slide what we're proposing so you can take a look at that.

MR. KING: Thank you very much. We should take a break.

(Brief recess)

MR. KING: We are coming back into session. Next up on the agenda is the updating of the Vaccine Injury Table: legal and policy considerations. Elizabeth Saindon will be providing that information.

**Agenda Item: Updating the Vaccine Injury Table:
Legal and Policy Considerations**

MS. SAINDON: It is a pleasure to be with you this morning. I know you've already seen a lot of

information. I'm going to try to mirror the things that Dr. Johann-Liang has already said to you without being overly repetitive. This is the last of the previews of coming attractions. Then we'll actually get into the meat of what we're going to be doing here today, which is exciting.

As you know, in order to be compensated under the program, you need to be able to demonstrate either a proof of a Vaccine Injury Table condition, a proof of causation by the preponderance of the evidence of an injury, or the proof of a significant aggravation of a table or off-Table injury.

As Dr. Evans said earlier, it had been a predominantly table-injury-based program and has moved predominantly to a causation in fact-based program. The idea here and what we've been working towards is to update the Vaccine Injury Table so that, with any luck at all, we can try to shift some of the cases back to a table compensation.

In addition, by law, you need to be able to show residual effects of that injury. By law, that's defined as either a death or inpatient hospitalization and surgery. The third one -- I listed them in reverse order, and I did that for a reason -- is that you need to suffer residual

effects or complications for more than six months after the vaccine administration.

I'm highlighting this because, as Rosemary indicated earlier, there are some vaccine effects that the IOM looked at and that we have looked at in the phase two forms that are causally related, but may not have that six-month residual effect. I'm reminding you of this because this is a statutory precondition to payment.

On the Vaccine Injury Table to qualify as a table injury, you have to show that you received a vaccine, that you sustained or had significantly aggregated that injury, and that the first symptom or manifestation of the onset occurred within the Table time period. In addition to the Table, which is the actual table and has those injuries in and the timeframes that are listed, we also have the Qualification and Aids to Interpretation. They apply to the Vaccine Injury Table.

We are permitted by statute to modify the Table by promulgating regulations. The things that the Secretary has the authority to do is add to or delete from the list of injuries and the time periods. You have a copy of that table. Also important to remember that anything that we do has only prospective effect. It doesn't retrospectively apply.

We have, by statute, some rules imposed on us in terms of how we go about making these regulatory changes to the Table. We must provide a copy of the proposed regulation. As we discussed earlier, we term that to mean the actual regulation text as opposed to the preamble.

We request recommendations and comments from the ACCV and we afford the ACCV at least 90 days to make any such recommendations. We have been discussing about what "at least" means. The secretary is flexible in that time period. To the extent that there's significant discussion that needs to happen or a level of comfort, because we are throwing a lot of information at you, if you want to move it to the next ACCV meeting, I think we can stretch the statute all the way out to that.

There's very specific language as to what the secretary must do when adding vaccines to the Table. That occurs when CDC recommends a vaccine for routine administration to children. We have to amend the Table within two years to include that vaccine on the Table.

Unfortunately, there is no standard provided to us on the adding or changing of the injuries. The vaccines, yes, we know when and how we have to do that, but the actual definitions of the injuries and the time periods, we don't have any statutory standard for that.

As a result of that, one of your previous commissions developed what they called the ACCV's Guiding Principles for making recommended revisions to the Table. We've provided that to you. I think you have it in your blue folders. This is not the first time that you've heard about it.

I just want to clarify that this was one of your prior commission's best thinking on how they felt that the ACCV should make these recommendations. It is not binding on you. If you read it and you decide that it's completely wrong and you don't like it at all, you're not bound by it. You could change your Guiding Principles.

However, I just wanted to let you know that in our thinking through this process, even in working with the IOM and working through the phase two worksheets, all of us working on this task force had a copy of these Guiding Principles, and we did use it because we found it to be a valuable document in thinking through the policy and implications of what we're doing. I just wanted to be clear about that.

Some of the Guiding Principles is the Table should be scientifically and medically credible. When there is credible scientific and medical evidence both to support and reject a proposed change to the Table, the change

should, whenever possible, be made to the benefit of petitioners.

DR. DOUGLAS: When there is credible medical and scientific evidence to reject a proposed change, the change should, whenever possible, be made to the benefit of a petitioner. So if you're rejecting the change, that's never going to be to the benefit of a petitioner.

MS. SAINDON: It could be. For example, encephalopathy, the IOM indicated that there is inadequate evidence to accept or reject, whether or not there is a causal relationship between the that DTAP vaccine and encephalopathy. They're saying we don't really know if is evidence, but that injury is included on the Table currently. We can reject that finding and say we believe, for the benefit of the petitioners, that we should retain that injury on the Table.

MS. LINGUITI PRON: Do we have a copy of these, or all these all-inclusive what you have on the slides of the Guiding Principles?

MS. HERZOG: They got a copy of the Guiding Principles at the last meeting.

MS. SAINDON: The Guiding Principles were given to you last time, but they were not included, but we could probably get a copy to you.

MS. LINGUITI PRON: I can look through those.
That's fine. Thank you.

MS. SAINDON: The Guiding Principles then go through a very long process of describing what is scientifically and medical credible and discuss if there is an IOM study, that it should be deemed credible, but it should not limit the deliberations. Then for other data sources besides an IOM report, they listed out a hierarchy of data sources from strongest to weakest in terms of what those data sources are.

For this presentation we are working with an IOM report which has been supplemented and updated with additional data. All of those data sources will be provided to you, but you don't have to read them if you don't want to.

MS. WILLIAMS: In the supplements to the IOM report that the task forces did they used these hierarchy of data sources in evaluating the information that was not available to the IOM.

MS. SAINDON: That is correct. Then the Guiding Principles also discuss additional factors that could affect the relative strength of the evidence, including methodological limitations and bias, core confounding factors, and that the final principle is that the ACCV

should request assistance from DVIC in assessing the relative strength. Again, that is really what the purpose of this meeting is today.

There is an importance that we remain aware of the policy considerations underlying the Table, which is that the policy considerations are that the awards to vaccine-injured persons are to be made quickly, easily, and with certainty and generosity, and that Congress intended to compensate serious injuries. That gets to the six-month sequelae issues. If there's a split in credible scientific evidence, ACCV members should tend towards adding or retaining the proposed injury.

I meant to do this on an earlier slide, but I did notice in terms of what we need to do in terms of promulgating regulations, I did also want to reiterate that there is a statutory requirement for the public hearing.

MR. KING: Terrific.

MS. WILLIAMS: I find the Guiding Principles very useful and commend our prior commission and the work that everyone has done in using them and making them a living document. The one principle that I don't see in here would be consistency. I would submit that maybe when the Commission is considering the recommended changes today, that consistency of claims, so the results of claims, be

consistent, that there be able to be consistency. I think you've accomplished that by adding the fainting and the shoulder injury to all the vaccines.

I think that is something that was already inherently involved in the recommendations, but I would just add consistency of claims so that we're not compensating different amounts for different things, just as a criteria, just as an element to consider, furthering consistency in response to claims.

DR. DOUGLAS: I guess he was speaking most clearly to the lawyer compensation, so this is a general question. Does it exist now that for an injury from a given vaccine, everybody gets the same? Is that the policy?

MS. SAINDON: That's not really an issue for HHS to consider. That's really within the realm of the special masters.

MR. KRAUS: I think Michelle slightly misspoke at the end of her comments when she said amounts, because there's no intention to have consistency in amounts, damages, or based on the individual facts in the case. I think Michelle was appropriately referring to consistency in finding causation and including injuries on the Table from vaccine to vaccine.

MS. WILLIAMS: I misspoke, but accurately understood. I'm not talking about amounts; I'm talking about consistency in application of the program.

MS. SAINDON: I impromptu want to add one other comment that I wasn't asked to, and it speaks very much to your consistency point, because one of the things that we tried to do in the editing and the redrafting of the Table was to make it a much more consistent and easy-to-read document.

Over the years, it's been added on to and changed and now looks a little bit like a patchwork. I think that there was a real thought that because this would be the first time in so long that we were making changes, it also gave us the opportunity to make the language more consistent from definition to definition and even within the document itself in terms of how it's organized and how it's laid out.

I believe that whether or not it was one of the Guiding Principles, it's certainly a guiding principle of the own way my brain is organized. I think that hopefully you will see that in the document as you go through. Some of the reasons for moving things from one place to another is for precisely that purpose, so that it has that element of consistency so that the words mean the same thing across

the document. I think that's actually one of the benefits of going through it.

MR. SMITH: I was going to express the same sentiment.

DR. VILLAREAL: I don't want to worsen it, but quickly, easily, and then when I was reviewing some of your minutes last time, is there a potential for ethically -- okay, I won't go there.

MS. LINGUITI PRON: When is the time that we will decide whether we're going to decide each time they give the presentation on vaccines, whether we're going to wait until the end or whether we're not going to make any decisions? Because it seems like they're missing on the agenda. It's starting with the presentations of the Table changes.

MR. KING: Excellent question. What we have opted to do is that we're going to go through each one and we're either going to make a decision -- actually, it was on the last slide that was utilized in the prior presentation where we had our choices. We're going to go through each one of them, and then we're going to either determine that we can concur with it and we'd like to move forward with or without comments; we're going to not concur to the proposed changes and/or the aids to interpretation, and then we

would not like to move forward; or we would like to defer recommendation, meaning that we're going to wait until later in this meeting, which goes on until tomorrow; or we push it off to the June meeting. Those are really our options. Are you with me on that?

MS. LINGUITI PRON: Yes. We'll decide it with each vaccine? Is that what I heard?

MR. KING: That is correct, but before we do that, unless there are any other questions before I make any other comments, I think that what was highlighted here is that we are not bound by the Guiding Principles, but that the Guiding Principles have been put together and seem sound. I'm wondering whether the floor might want to entertain that we in our deliberations use those Guiding Principles so that we stick to them ourselves and don't go off on too many different tangents.

Does anyone want to put a motion that we go with the Guiding Principles on the Table? Jason has put a motion on the Table that we adopt the Guiding Principles for the purposes of our discussion on these changes. It has been seconded, and now we need a discussion on it. The floor is now open to discuss the pros and cons around this.

MS. WILLIAMS: I think it's a good idea. I think the principles are appropriate with the addition of the criteria enabling consistency.

MR. KING: Is everyone comfortable with the enabling consistency to be added to this?

MS. WILLIAMS: On Elizabeth's slide it would be awards to vaccine-injured persons are to be made quickly, easily, and with certainty and generosity and with a goal of consistency. That is slide number 14.

MR. SMITH: I think for purposes of what we're doing over the course of the next several hours, we're going to be making recommendations with respect to findings of causation. This particular bullet, I think, refers to the awards, which really won't be part of our discussion over the course of the next hours. I think what this policy was trying to get behind the compensation program is that we should do it quickly, with certainty, with generosity. I think Ed pointed out it's not necessarily consistent in terms of the awards.

MS. WILLIAMS: It has nothing to do with the awards. Forget I misspoke. Let's not perpetuate that. I'm not talking about awards.

MR. KING: You are talking about causation findings.

MS. WILLIAMS: I'm talking about that different petitioners are not treated differently throughout the program.

MR. SMITH: Maybe I misunderstood. You wanted to change the bullet.

MS. WILLIAMS: I don't want to change anything.

DR. EVANS: You are talking more entitlement, more deciding cases. Maybe it should go as a third bullet in the second full paragraph on page one. The Table should be scientifically and medically credible, and where there's credible scientific and medical evidence to support the change this should be in the Table and it should benefit petitioners. That's for consistency.

MS. LINGUITI PRON: Actually, I have a copy in front of me. On the second page, the second to the last bullet, there is a sentence that says consistency across multiple sources of evidence generally should be considered an indication of laws for credibility, I guess.

MR. KRAUS: I think we all appreciate the sentiment of Michelle's point, but I think what we're talking about here are guiding principles in making changes to the Vaccine Injury Table. The whole purpose of the Vaccine Injury Table is to provide consistency, at least in those cases where there's enough scientific evidence to add

it to the Table or take it off the Table. It might be that we don't need specifically to address consistency because it's somewhat inherent in the whole function of the Table.

MS. WILLIAMS: I think we've discussed it enough.

MR. KING: You have no amendment, so it was Jason originally put on the Table, which was that we, for the purposes of this conversation or review for the Vaccine Injury Table and what we're going to be uncovering over the next day and possibly spill into tomorrow or into the next session in the month of June, utilize and adopt the Guiding Principles that were adopted by a prior commission during their term.

(On motion duly made and seconded, the Commission unanimously agreed to adopt the Guiding Principles during the ensuing discussions.)

MR. KING: Let's go back to our agenda.

Elizabeth, by the way, thank you very much. We now have Catherine Shaer who is the Medical Officer for DVIC. We are going to be going over proposed table changes for the varicella vaccine. Just as a note, it is on page three, if I'm not mistaken, of the color-coded table. We have a slide presentation, as well, that actually has Dr. Shaer's name as being the presenter on it.

Agenda Item: Proposed Table Changes - Varicella**Vaccine**

DR. SHAER: As we said, I will be presenting on behalf of the Varicella Work Group, the information that we want to add to the Table for varicella vaccine. I will present two of the injuries proposed to be added to the Table for varicella. The others will be presented under the general consideration presentations that will come in later today.

The first one that we're proposing is to add disseminated vaccine-strain virus disease, which as Dr. Johann-Liang said earlier, was a collapse of two of the IOM findings of convincingly supports of disseminated disease with and without other organ involvement. Disseminated disease-strain virus disease for our purposes today will be a widespread chickenpox rash which appears shortly after vaccination, which can occur alone or can go on to involve an infection resulting in disease in another organ.

The second one is vaccine-strain virus reactivation. Again, we combined the with and without other organ involvement. This would be the appearance of a chickenpox rash months to years after vaccination, something most people think about as herpes or shingles.

This also can go on to involve an infection resulting in another organ.

This slide shows a summary of the justification for our proposal to add changes to the Vaccine Injury Table for varicella vaccine causing disseminated vaccine-strain virus disease. The 2011 IOM committee found that the evidence convincingly supports a causal relationship between varicella vaccine and disseminated vaccine-strain virus disease with involvement limited to the skin.

They also found that the evidence convincingly supports a causal relationship between varicella vaccine and disseminated vaccine-strain virus disease resulting in involvement of the lungs, the meninges, which is the saran-wrap-like membrane that covers the brain and the spinal cord, and the liver. But they only found this in individuals with demonstrated immunodeficiencies.

The IOM limited their finding to immunocompromised individuals because they only found one case where the affected individual was immunocompetent, and that individual had Down syndrome, a condition which is known to be associated with immunodeficiencies in some individuals. However, that individual had not been shown to have an immune abnormality, and we feel that by limiting

the Table in that way, it would not be justified, given the Guiding Principles.

In addition, our proposal does not limit the involvement of other organs to the lungs, meninges, or liver, because if they were to demonstrate the disease in an organ that the IOM did not find a case report or information for, we wouldn't want to limit it in that way because of the Guiding Principles.

The IOM found a significant amount of literature on this topic. Virtually all of it was mechanistic in nature. The next five slides do contain a listing of the medical literature the IOM considered in their deliberations. They found even more literature, but all of it did not rise to the level of being good enough literature for them to consider in their deliberations as they looked at this. I want to just talk about a couple of these references.

In the Wise article the authors identified 3,640 reports of rash submitted to VAERS from March 1995 through July 1998. The varicella virus was demonstrated in 70 of the rash specimens. Of these, the strain was not identified in 5, 43 were the wild-type varicella, and 22 were the vaccine strain of the virus.

The next one down under that, Goulleret, looked at 259 reports of a rash developing within 42 days after vaccination. The specimens were collected from 44 of the cases. In 3 of them it was inadequate to test, 4 were negative for varicella virus, and 32 were wild-type virus, with 5 the vaccine strain of the virus. I just wanted to point this one out because this timeframe of 42 days is something we use in our discussions as we developed the entire protocol for what we wanted to add for varicella.

This is the rest of the literature that you can look at at your leisure if you choose to.

This slide shows the proposed Vaccine Injury Table for varicella. Currently there is a row for varicella vaccines, but there are no injuries on the current table. For disseminated vaccine-strain virus disease, we're proposing that it be added, that injury, and we are requiring that if the vaccine strain of the virus is identified in the injured party, there will be no applicable time period.

If strain determination is not done or if laboratory testing is inconclusive, the time interval will be 7-42 days. A second injury under this disseminated varicella vaccine-strain disease would be any acute

complication or sequelae, including death, of the above event. There would be no applicable time period for that.

On this slide you see the rationale for what the QAI is going to be to support the Table injury. Disseminated varicella vaccine-strain virus disease we propose be defined as a varicella illness that involves the skin beyond the dermatome in which the vaccination was given and/or there is disease caused by the vaccine strain of the varicella virus in another organ.

For organs other than the skin, disease, not just mildly elevated abnormal laboratory values, must be demonstrated in the involved organ. If there is involvement of an organ beyond the skin and no virus was identified in that organ, the involvement of all organs must occur as part of the same discrete illness.

If strain determination reveals a wild-type varicella virus or another non-vaccine-strain virus, the viral disease shall not be considered to be a condition set for in the Table. If strain determination is not done or if strain determination is not successful, onset of the illness in any organ must occur 7-42 days after administration of the vaccine.

The justification for these QAI are that if the wild-type strain is identified, the cause of the injury

will have been found, and there will be no basis for the presumption of the vaccine causing the injury. Although in the majority of cases reviewed by the IOM the wild-type strain of the varicella was identified, the program is meant to be generous. Thus, if testing to determine the strain of the virus was not performed or was unsuccessful, the presumption of causation will be given if the injury onsets between 7-42 days after the vaccination.

This time interval was determined by considering the incubation period for the natural disease and careful review of the time intervals reported in the cases considered by the Institute of Medicine. Since it is common for individuals with no actual disease to have mildly abnormal laboratory values, that alone is not sufficient to establish that there is actual disease in an organ other than the skin.

I want to move on to our second proposed injury other than the general considerations, varicella vaccine-strain reactivation disease. The 2011 IOM committee found that the evidence convincingly supports a causal relationship between varicella vaccine and vaccine-strain viral reactivation with involvement limited to the skin.

Similarly to the previous injury, they also found that the evidence convincingly supports a causal

relationship between varicella vaccine and vaccine strain reactivation with subsequent involvement of the brain and the surrounding membranes, the meninges. Although the IOM limited their causal conclusion to the brain and meninges, there is no justification for the Table injury to be limited in that way as demonstration of the vaccine strain of the virus will be required to establish the Table injury for this particular injury.

Again, there was a wealth of literature. The next three slides contain the literature for reactivation disease. I do want to mention for both the disseminated and the reactivation, almost all the literature was mechanistic. There was very little epidemiologic evidence, but it was all very convincing. They have multiple cases where they actually found the vaccine strain of the virus in someone with injury, with a disease.

For this one, I just want to point out couple. The Chaves article looked at 981 reports of herpes zoster or shingles after vaccination, which was submitted to VAERS from May 1995 to December 2005. Of the 981 reports, 1 was due to herpes simplex, 1 was due to an allergic reaction, 11 were due to the varicella virus, but they could not identify the strain, 10 were due to the wild-type virus, and 8 were due to the vaccine strain of the virus.

I would like to point out that that's a very small percentage of the 981 cases reported to VAERS where they actually identified varicella virus at all, actually. At least in one of them it was an allergic reaction; it wasn't varicella at all. So we can't really say that anytime someone reports something like herpes zoster following vaccination that it even actually is that condition.

The latency in this paper between vaccination and presentation of herpes zoster where vaccine strain was demonstrated ranged from 1-11 years. Shingles is the disease that can show up years to decades after the person has their initial infection with the virus, be it natural or the vaccine.

On this slide the Iyer article, which is the last one there, this is a case of meningitis reported in a nine-year-old boy who developed the rash of zoster and four days later developed symptoms consistent with meningitis. He had received the varicella vaccine eight years before the development of symptoms. They did demonstrate the vaccine strain of the virus in this individual, and he was screened for an immunodeficiency and was found to be normal.

MR. SMITH: I have one question on that point, and it goes to your QAI and later slides. So it is possible

to get reactivation years later, and then still detect the varicella vaccine in a lab?

DR. SHAER: Absolutely. I'm just highlighting. There were many cases in the literature. Some of these were these large studies where they looked at VAERS or other major reporting systems. I am assuming they sent this stuff to CDC or somewhere and found that vaccine strain in the virus. But many of them were just individual case reports that people had of a specific patient, such as the Iyer one and one other one that I want to talk about. A lot of them are individual cases.

On this slide the 2008 Levin article, they report an eight-year-old boy who developed pruritic vesicles in the left shoulder in the distribution of a zoster-type reaction. He was diagnosed with herpes zoster and meningitis. He had received the varicella vaccine seven years prior to presentation. He also was screened for immunodeficiency, not as thoroughly as the patient in the previous slide, but what they did look for was entirely normal.

MS. WILLIAMS: Why did they say "in an immunosuppressed child?"

DR. SHAER: I don't know. I cut and pasted that. This is also the abstract from that article, actually. I

didn't actually look back at the title when I did this. I just cut and pasted everything that came out of the IOM report, to be honest with you, but there are many other examples in these articles of individuals who developed this many years after vaccination, and is demonstrated. Of interest, actually, we've had two this year or late last year that were found with the program, where they actually recovered the vaccine strain of the virus in two separate cases.

DR. JOHANN-LIANG: I think the proposal here is that even though IOM limited to the immunocompromise, our proposal for the second part is that it will just be reactivation. We figure if you actually isolate the vaccine strain, what does it matter what the patient have or not? The patient may actually not have identified immunodeficiency at that time, but may go on to have something that we haven't been able to find.

It's under the Guiding Principles, once again, and you'll see that theme throughout. We take the science, but then we overlay the policy to make it more generous. I think that was a point.

DR. SHAER: But also, I figured out the answer to your question. I've got the wrong Levin article. I'm talking about the first one on that slide, the one at the

top, where that child was not demonstrated to be immunodeficient. I chose that because as pediatricians or physicians we often think of the immunocompromised as the people who this is really going to happen to, and it doesn't turn out that that is the case.

For varicella vaccine-strain reactivation, there are no current injuries on the table. We propose to add the injury of varicella vaccine-strain viral reactivation disease without an applicable time period. The second injury is the same for lots of the vaccines, any acute complication or sequelae, including death, of the above event. There would be no applicable time period. I'm going to explain why there's no applicable time period for the vaccine-strain reactivation.

The proposed QAI would be varicella vaccine-strain viral reactivation disease will be defined as the presence of the rash of herpes zoster with or without concurrent disease in an organ other than the skin. For organs other than the skin, disease, not just mildly abnormal laboratory values, must be demonstrated in the involved organ.

There must be laboratory confirmation that the vaccine strain of the varicella virus is present in the skin or in any other involved organ. If strain

determination reveals wild-type varicella virus or another non-vaccine-strain virus, the viral disease shall not be considered to be a condition set forth in the Table.

The justification here is that if the wild-type strain is identified, that would be the cause of the injury, and there will be no basis for presuming that the vaccine actually caused an injury. As the majority of cases of varicella virus reactivation disease are caused by the wild-type virus and reactivation can occur decades after the initial viral exposure, if testing to identify the viral strain is not done or is unsuccessful, no presumption of vaccine causation would be appropriate.

Vaccine-strain reactivation can occur months to decades after the initial viral exposure, making it really impossible to define a relevant time interval between vaccine administration and the onset of injury. Since it is common for individuals with no actual disease to have mildly abnormal laboratory values, that alone is not sufficient to establish that there is actual disease in an organ other than the skin.

I'll also add that what we saw in some of these larger-scale studies and studies to VAERS and so forth is what people think is zoster is not always even that condition. Given that and the long lags that are possible,

we did not find that it would be really possible to have a relevant time interval.

This is the proposed Table as it will appear for varicella vaccines. What you have in color -- A, D, and E -- will be discussed in future presentations later today. We're only talking right now about disseminated varicella vaccine-strain disease and varicella vaccine-strain viral reactivation, adding to the Table with these time intervals and the QAI that I presented during this talk.

MS. WILLIAMS: On our chart in color.

DR. SHAER: That's what's going to be changed to the Table. That's Rosemary's master thing. This is just the slide I made up of the things that you will be asked to vote on one way or the other, B and C. Whatever color A, D, and E are, I haven't obviously presented any information. Dr. Atanasoff will talk about anaphylaxis, and Dr. Ryan about D and E, the shoulder injury and vasovagal syncope.

DR. JOHANN-LIANG: In your color-coded master Dr. Shaer's edition is shown on page three as additions under varicella vaccine on the Table and on page eight of the document subsection (c) (11) and (12).

MR. KING: If we're about to go into a discussion to determine whether to approve this or not, if we approve it, for argument's sake, are we just approving B and C, and

the others we would then come back -- that's on the agenda somewhere else specifically.

DR. SHAER: I just put the whole thing for varicella up here out of interest's sake, but really all I've talked about is B and C, and that's all that is before the Committee.

MR. KING: Just for clarification, what we're saying is that later on we might put in anaphylaxis, we might put in the shoulder injury and the syncope. We might not, but if we do, it'll automatically get added to the varicella vaccines, even though we did not vote to put it on the varicella vaccines. Is that correct? Or will we be putting it on that when we come to discuss them, what we're really talking about is an overall general category. Is that correct?

DR. JOHANN-LIANG: That's exactly right. Right now under varicella vaccines you're going to be concurring on just the B and C. Later in the day anaphylaxis will be handled together because it's the same principle across multiple vaccines. Then another talk would be handling the injection-related, which is not antigen-specific, but has to do with administration, which is the D and E. That will be voted separately. Then once you concur, it will go into

every that contains an injectable vaccine, including varicella vaccine, which is an injectable vaccine.

MR. KING: Could we choose to say on one we don't go forward with it on that vaccine?

DR. SHAER: You can do whatever you want.

MR. KING: When we come time to vote on anaphylaxis, let's say, will we be specifically then having multiple votes across each vaccine?

DR. JOHANN-LIANG: If you like, or since it's the same concept, you can say all together or you can say I don't want to do this one.

MR. KING: I understand.

DR. SHAER: Then it won't look like this if you decide not to go forward with some of them.

DR. JOHANN-LIANG: You're the chair. You do what you want under the Guiding Principles.

MR. KING: Catherine, thank you very much.

MR. SMITH: On the 7-42-day time interval, I know that you mentioned that is was consistent with what IOM looked at, the case reports. I would assume that's a fairly generous definition, or am I correct in assuming it's a fairly generous definition?

DR. SHAER: I went through all the IOM things and made tables for all four, the with and without for

dissemination, and tried to pick what was reasonable. We had the whole work group. It wasn't just me, obviously. The 42, I'm sure, is just within. That's probably got a buffer. We struggled a little bit with the seven because you start to get into biologic plausibility. If it's seven, then you make it five, and then people start making it four. All of this is up for discussion, but that's the proposal that we came up with. You can see on that chart all the cases they reported and what the time intervals were. We did the best we could with that information.

MR. SMITH: If I may just follow up and maybe just more for other colleagues around the table, if, for example, it was six days, it wouldn't necessarily be a presumption of causation, but it wouldn't preclude a finding of causation in fact.

DR. SHAER: Absolutely not.

MS. LINGUITI PRON: As I read it, that's only if the strain is not done or the testing is inconclusive. If the strain appears to be the same as the vaccine, there's no time limit.

DR. JOHANN-LIANG: Our logic with this is that if you identify the strain, that's presumption. But there are so many case reports where the strain is not identified. The disease is there, but you don't have the strain. In

those case series where large groups of folks actually have strains identified, actually it was more wild-type than vaccine-strain.

We are saying that here on the Table we're proposing that even if you had nothing identified, if you have the disease, we're going to give you the presumption that if that disease occurs within 7-42 days, that you would actually get presumption of causation, which is over and beyond generous, considering the literature. We're really applying the Guiding Principles here.

MR. KRAUS: As someone who represents people who are potentially injured by vaccines, I do appreciate the sort of generous approach that you've taken in this Table injury. I think Jason's point is a good one, and you acknowledged it. If you do seven, if it is five days, obviously this is a litigation context. The Department of Justice can look at five days and say it's not a Table injury, but we could concede causation here because it's really darn close to a Table injury.

But the possibility, of course, is also that the Department of Justice looks at this and says this it's not sort of not biologically plausible, even, for onset in five days. In my experience, it has the effect of sending a message to the Department of Justice that perhaps you don't

want to concede causation and you want to prove it. I haven't read all the studies, and I'm trying to review this. For example, I know there's some literature about how if somebody's immunocompromised, the incubation period might be shorter. Can you explain to me, summarize sort of the earliest cases that you found?

DR. SHAER: One thing I want to clarify is it's not the Department of Justice that decides it's too soon or it's too late; it's actually the secretary with the input from medical officers. We review every case and look up recent literature and so forth. We really do look at each case in depth.

We would take into account immunocompromised, but it is tough because a lot of this stuff was separated out, and it got kind of messy. We tried to keep it each one immunocompromised, not, with other organ involvement, without, and then it got huge just for varicella. There are some things that were compressed.

That may be something that you want to look at and say, of all the things we present, do we want to look separately at that one time interval. You may want to look at more of it, but that's the one thing that was more of a judgment call than anything else on here because it is so

obvious that this vaccine causes these conditions. That wasn't really ever a question.

MR. KRAUS: For example, is it biologically plausible for the condition to occur within five days, or can you say that it's not biologically plausible?

DR. JOHANN-LIANG: It's extremely unlikely.

MR. KRAUS: Because of the incubation, even in immunocompromised.

DR. JOHANN-LIANG: It's not just what we think, but based upon the data that we have.

DR. SHAER: For the naturally occurring illness, which is different than looking at the immunocompromised individual, we know when someone's exposed to varicella, the illness usually onsets most commonly 14-16 days. The Red Book says occasionally it can be as short as 10 days and as long as 28 days.

MR. KRAUS: That's why you went down to seven, to try to capture any outliers.

DR. JOHANN-LIANG: I think that the way the Table is written is to be as generous as we can be. To say that we want to go outside of those boundaries so that we can do causation in fact would be very highly unlikely. The whole point of the Table is to be as generous as possible right off so you know what's in and what's out. There are

occasions where there is an unusual case. As Dr. Shaer said, it's reviewed in extreme detail, and if we feel that this should be compensated and conceded, we do as much as possible.

MS. WILLIAMS: Another way to say that is you have not found any cases in the literature that were below the date.

DR. SHAER: No, none.

MR. SMITH: Or even less than 10, is what you're saying.

DR. SHAER: There were two. There was an eight days.

MS. WILLIAMS: So you went to the lower bound and then went farther.

DR. JOHANN-LIANG: We thought a lot about it. The work group, and Catherine in particular, spent a lot of time. That's why she brought this with you, because this is really important. This is the thinking that went in, to actually go literature-by-literature and go through exactly what the interval was.

DR. SHAER: If you look at this, it was very interesting. The eight-day one, that child didn't even get the vaccine. The vaccine was not identified in the child,

but two siblings developed a rash, and the vaccine strain was identified in them.

DR. JOHANN-LIANG: But that would be good enough evidence.

DR. SHAER: It'd be interesting to look over time and see what happens with the attempts to identify the strain, because when you have disseminated disease, just herpes zoster -- now it would mostly be children, down the road it's going to be adults who got the vaccine -- it can be a serious illness, but it doesn't usually maybe last six months. In some people it does, depending on if they're immunocompromised or are having treatments for cancer or whatever.

But if you have an involvement of another organ, meningitis or something serious like that, I think it's going to be come more likely that they'll look for the vaccine because in the two cases that we got the vaccine strain they did look at them both. As far as I'm aware, in recent memory we haven't gotten any with that sort of claim where they didn't have the vaccines looked at. I think it's going to be a more common thing in the severely ill. With other organ involvement and the disseminated, those people are severely ill.

DR. JOHANN-LIANG: We conceded that case.

MR. SMITH: I was moving to recommend approval of adding these two to the Injury Table, with the comment that we have just had.

MR. KING: That were already on there. Do we have a second to that?

MS. WILLIAMS: Second.

MR. KING: Even though we've had a whole big discussion, let me just offer it up for one last moment. Is there any further discussion on this motion?

DR. VILLAREAL: The question you're asking is it behooves the physician, whether it's a pediatrician, family practice or whatever, to get evidence-based medicine if we have a disseminated varicella. So really what we're pushing is for the future when this comes out, then you say to people get a PCR, or whatever you guys are using, to document what the strain is. That's really important if we're talking about EMRs or anything as far as documentation and data.

MR. KING: Any other comments?

(Whereupon, on motion duly made and seconded, the Commission approved the recommendation of proposed Table changes related to varicella vaccine.)

MR. KING: We're in favor of pressing on. We'll bring Dr. Mary Rubin to the table to discuss changes around the MMR vaccine. Dr. Shaer, thank you.

DR. JOHANN-LIANG: Take out your color-coded VIT QAI. Let's just walk through this so that we can orient ourselves. I was going to do this later, but it makes more sense now. We talked about what the coloring is, but there are sections in this. Section (a) is the actual Vaccine Injury Table. We just looked at the roman numeral X, which is varicella vaccines. Now Dr. Rubin is going to discuss roman numeral V, which is on page two. She's going to discuss under V. Then she'll show you B, the measles viral disease.

Then moving on, there is a section (b) that comes right under the Table, provision that applies to all vaccines listed. Then there is a section (c) that follows, which is the actual body of the Qualifications and Aids to Interpretation. After Section A, which is the Table, comes a little section (b), which applies to everything that's on the Table, and then comes section (c), which is the body of the QAI. Now I'm on page four.

Then the rest of this QAI, there are sections. There are 13 sections that we're proposing. It used to be nine. We're expanding to 13. I'm going to walk through all

of this with you this afternoon, but just for the purpose of orienting you right now, there are 13 sections. At the very end are 13 subsections. At the very end is the glossary that we're proposing to add, which are definitions. That's the section (d).

Dr. Rubin is going to be working on page two, roman numeral V-B right now, which corresponds to under the QAI, which is section (c), page seven, subsection 8. She's going to show everything on the slides, but just so that you guys know where this is. Don't worry. All this stuff we're going to go through step by step later, because I really learned my subsections. You can quiz me on subsections. I had no idea before.

Agenda Item: Proposed Table Changes - MMR

Vaccine

DR. RUBIN: Thank you for bearing with us. I will be talking about the IOM-generated proposals for MMR vaccines. I'll be talking on behalf of the MMR Working Group. My talk will cover three adverse events: febrile seizures, transient arthralgia, and measles inclusion body encephalitis, or I will say MIBE, for short.

First I will start off with febrile seizures. What are febrile seizures? Febrile seizures are very common convulsions that are associated with fever in infants or

small children. Most febrile seizures last a minute or two, although some can be as brief as a few seconds, while others can last more than 15 minutes. The natural history of febrile seizures is generally benign and typically do not indicate a long-term or ongoing problem.

The 2011 IOM committee concluded that the evidence convincingly supports a causal relationship between MMR vaccine and febrile seizures. This information is not new, with literature going back to 1989.

The next two slides will list relevant literature that contributed to the weight of evidence. The first study by Farrington involves 157 cases of febrile seizures and found an increased risk of febrile seizures within 6-11 days of MMR vaccination.

The second study, which is Miller, also contributed to the epidemiologic evidence. It has a study population of 894 children, and concluded that there was an increased risk of febrile seizures during the 6-11 days following vaccination.

Most of the literature that contributed to the evidence actually contributed to the epidemiologic evidence. There were only four mechanistic reports, and they did not isolate vaccine strain, but the IOM still felt that it was convincing.

On the next slide I'll just discuss the Chen study, which is a Vaccine Safety Datalink, VSD, study of more than 500,000 children from zero to six years. This showed that there was an increased risk of seizures 8-14 days after MMR vaccination, but they did not specify the seizure type.

The studies also supported that febrile seizures after MMR vaccination hold no long-term consequences. Patients who had febrile seizures after MMR vaccination had no higher risk of subsequent seizure or neurodevelopmental disability than either children with febrile seizures in the absence of vaccine administration. The long-term rate of epilepsy was not increased in children who had febrile seizures following MMR vaccination compared with children who had febrile seizures of a different etiology.

In comparison, 7.1-9.9 percent of post-vaccination syncope episodes can lead to serious adverse events such as life-threatening illness or permanent disability as a result of trauma from fainting. Although febrile seizures can be very alarming, the majority of children who have febrile seizures do recover quickly and have no lasting effects.

Rarely, febrile seizures can lead to serious injury or disability. Because febrile seizures generally

have no long-term consequences, this condition is not being proposed for inclusion on the Table. However, the program will consider any such claims for febrile seizures leading to serious injury or death on a case-by-case basis.

The next slide talks about the supporting literature. The study by Barlow is the VSD study of over 600,000 children, which confirmed the Chen study and also talked about the increased risk of febrile seizures 8-14 days after MMR vaccination and found no higher risk of neurodevelopmental disability in follow-up.

The Vestergaard study concluded that MMR vaccination was associated with transient increased rate of febrile seizures, but there the long-term rate of epilepsy was not increased in follow-up, which was the followed up children for up to eight years.

MR. KRAUS: Did you say how many they studied in that?

DR. RUBIN: I did not mention that, but I will say it. The Vestergaard study mentioned over 537,171 children.

MR. KRAUS: Half a million.

DR. RUBIN: I'm going to switch gears and talk about transient arthralgia.

MS. WILLIAMS: What is arthralgia?

DR. RUBIN: I will talk about that. Transient arthralgia is joint pain without swelling. It's a symptom and a complaint and has no long-term effects, as the word says it's transient. The 2011 IOM committee concluded that the evidence favors acceptance of a causal relationship between MMR vaccine attributable to the rubella component in transient arthralgia in women and children.

The 2011 IOM committee also concluded that the evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthralgia. Since transient arthralgia generally has no long-term effects, just as I talked about in the febrile seizures section, there are no proposed changes to the table.

This slide also lists references contributing to the weight of evidence. The Tingle 1997 study is actually what they based most of their studies with. The rest of them they considered evidence, but it wasn't as strong.

This one was the strongest study because it was a double-blind randomized controlled trial where they had post-partum women enrolled, and then randomly assigned them to receive rubella virus vaccine. The result was that receipt of the rubella vaccine was significantly associated with development of acute arthralgia in post-partum women, but they concluded that there wasn't much difference in

persistent arthralgia or chronic arthralgia. There wasn't significance.

I will now talk about the vaccine-strain measles viral disease.

MR. KRAUS: As just a process point, if we have questions about each of these distinct adverse reactions for MMR, are we going to address them at the end? I'm having a hard time keeping everything in my head going from adverse reactions.

MR. KING: Discuss it as needed.

MR. KRAUS: I have a question about the febrile seizures. I didn't want to stop the momentum of the presentation. There's no issue about the causation with febrile seizures and the MMR vaccine. The concern that you would have in adding it to the Vaccine Injury Table is that in most cases it's not going to have long-term consequences or sequelae. What you're saying is in some cases it might, and those cases would be properly handled not by a Vaccine Injury Table case, but by proving causation in fact.

DR. JOHANN-LIANG: Febrile seizures is such a common event for pediatrics. It happens not just with vaccination, but when kids have fevers all the time. As Elizabeth went over before, part of what goes in the Table is that you have to have some sort of a residual effect.

Febrile seizures, by definition, for the vast majority there's no residual effect.

What I think Dr. Rubin was trying to articulate was that once in a while that febrile seizure event may lead to -- for example, it could even be similar to syncope. What if the child had a febrile seizure and the mom, because of the seizure, let the baby go and the baby had some trauma?

There's always an unusual situation that may have a long-term consequence. For those situations we would consider them case-by-case basis. For the majority we just don't have the requirements, even with all the Guiding Principles, to be able to add that to the Table as a presumption of causation.

MR. KRAUS: Okay, thanks.

MS. WILLIAMS: How about transient arthralgia? Any questions before we move on to MIBE?

DR. VILLAREAL: You are putting both the transient and the chronic together with that slide. Is that correct?

DR. RUBIN: Yes. The reason why I did that was just to say that transient arthralgia is transient, but also the IOM also reviewed chronic arthralgia. At that time

the evidence right now is inadequate really to accept or reject.

DR. VILLAREAL: The only issue I have with MMR is, is it a paradigm only for women? Because when you do transient, it says women and children. I assume the children include boy children. Then when you do chronic, really looking at chronic women.

DR. RUBIN: The IOM actually had many different populations, and they divided it. They had chronic arthralgia for women, for children, and for men, then the transient for women and children. They divided the population. But they found inadequate to accept or reject for the men. But for children they did not specific gender.

MS. WILLIAMS: On the list of the literature, that includes what the IOM looked at plus what you all in the task force looked at, correct?

DR. RUBIN: For anything that was up from 2011.

DR. JOHANN-LIANG: Up to the time when the task force started in September of '11.

MR. KRAUS: Back to the febrile seizure, I think the other thing that's rattling in my head is that if there's no dispute about causation, if somebody bothers to file a claim for compensation, it's only going to be

compensable if the sequelae last for six months or longer or if it requires hospitalization and surgery.

DR. JOHANN-LIANG: Three things: six months, death, or hospitalization with surgical intervention. That's what the requirements are.

MR. KRAUS: If you have a situation where somebody is filing a petition because a febrile seizure caused something that is otherwise compensable, why wouldn't it make sense, if the science supports causation, to put it on the Table and then weed the cases as not otherwise compensable not because of causation, but because it's basically not serious enough?

DR. JOHANN-LIANG: We actually had a lot of discussion. It's a very good question. It really comes down to when you get presumption and you want to put something on the table, there is some specificity involved. For example, if you just got needled and you have a bursitis and it meets all the criteria, that's very specific to what happened.

Even in situations where we just talked about with varicella, if you identify the vaccine strain, it doesn't matter if it was 12 years later and it's a reactivation. It's very specific to that. Within that

specificity we want to be overly generous in Guiding Principles.

The problem with febrile seizures, like arthralgia, people have aches in their joints all the time. Kids have febrile seizures all the time. We think it will boggle the system down, our system. The whole point behind Guiding Principles is how do we move things forward. The point behind Table is how do we get presumption and not have all this litigation and just concede and move forward.

We think putting something like that, which is so common in kids that can occur with so many things than a vaccine, even though there is causality with that event, it doesn't rise to the residual effect requirement, and it will boggle the system down. We could do it the way you want, but it would really be counterproductive.

It's sort of like fainting, if we say fainting, but we make a requirement that the fainting has to result in a long-term sequelae. She made the contrast that in febrile seizures 99.99 percent of the time there's no sequelae, as opposed to fainting following needling. It has to be a needle. It is 9-10 percent there's some sort of a serious injury, so in that effect we want to put it on the Table because it's more specific to that event. We want to put it on the table. We get these claims. They faint,

there's no long-term effect. We weeded those out and said that's not compensable, whereas if there is an effect, it's going to now be under the Table.

That's kind of the yin and the yang. Do you see that, the logic system behind it? We really do have specificity with our thoughts, otherwise we're going to end up sort of having unintended consequences of bogging the system down even more.

DR. RUBIN: To put things in perspective with how Ro was saying how the febrile seizures are very common, it actually occurs in 3-4 percent of young children between 3 months to 5 years. I looked up the data in terms of MMR and febrile seizures and what they thought was attributable, and it happens between 25-34 per 100,000 children. That's the contrast.

DR. JOHANN-LIANG: That's just having febrile seizures. Out of those, how many are really going to have a long-term consequence? It's going to be contrary to our Guiding Principle. That was our logic.

The contrast between what we're proposing for syncope, which you'll hear about, versus something like febrile seizures or transient arthralgia -- people have transient arthralgia all the time, and to attribute that to have specificity to the vaccine at hand without having the

long-term consequence. IOM said even chronic arthritis is on the Table. We're not proposing to take it out. But they actually came down with an inadequate evidence at the current time. We really did a lot of thinking to make sure that we're getting this right.

DR. FEEMSTER: I guess another way to think about it is if you had a child who came and got their one-year immunizations including MMR and they happened at the same time that they developed a viral illness resulting in a high fever and they have a febrile seizure, they would be potentially more likely to have had the febrile seizure from fever due to virus rather than MMR. It's just too difficult to establish and attribute it to the vaccine itself. Another way to explain it is to operationalize your thinking.

DR. JOHANN-LIANG: Just to drive that home again, contrast that clinical scenario with someone who just got vaccine and faints. That's very specific to that. We feel very comfortable actually proposing to get presumption and put that on the table, given about 9 percent or so of serious sequelae from that event. Does that make sense?

MR. KRAUS: It does make sense. Just as a follow-up, when you really dig down in the literature, is there any time period for a febrile seizure to occur that gives

you a greater confidence? For example, if it was a febrile within 72 hours, does that start to --

DR. RUBIN: For the MMR vaccine, the science actually shows that it's between 7-14 days.

MR. KRAUS: Because the virus needs to replicate. So that window creates too many opportunities for other factors, potentially.

DR. JOHANN-LIANG: Again, it goes to the non-specific nature of the issue at hand. Yes, you're right. The closer the temporal to the vaccination, it would be more specific, given the different diseases at hand that we're talking about.

MR. KRAUS: That's why it's not inconsistent to put syncope on the table and leave off febrile seizures.

DR. JOHANN-LIANG: And work from the other perspective of presumption, and then febrile seizures and transient arthralgia. Again, our whole thought process behind this is to start with the best science, but then really look at the Guiding Principles and how to get these cases to completion, whether to compensate or not to compensate, so that we can move the system along, because we don't want to get bogged down.

DR. EVANS: It's a vexing question and one that previous commissions have struggled with because febrile

seizures, as it's defined in the literature reviews for the first two major IOM reports, these were thought to be benign febrile events, some lasting longer than others. Children with 4 percent of birth cohort will exhibit this at some time in the first couple years, and all but 2 percent never have any further seizures.

The question then becomes is if these are kids that will have a seizure related to fever, no matter what the fever's caused by, and then go on and just have a normal course and outgrow them versus the ones that have a preexisting potential for epilepsy, what do you do in terms of how the program should address those children?

In the first two rulemaking efforts we had a situation where DTP vaccine epidemiologists showed a causal relationship with febrile seizures, but did not show epilepsy, did not show febrile seizures, so we took off residual seizure disorder because there were no continued effects for the febrile seizures after vaccine. Similarly, in '97 we took off residual seizure disorder for measles/mumps rubella vaccine because of the same epidemiologic findings. They can possibly trigger with fever, but really no long-lasting effects.

This has been an issue for the program in terms of what's fair, what makes sense scientifically. Where does

the benefit start and end? You have so many children who are simply having a fever-related seizure event that this time the fever could be a virus, the next day could be whatever, another illness two weeks later.

It really calls into question whether this should be a presumptive injury in our program, unless there's some other reason, some other extraordinary circumstances surrounding the scenario that happens. That's why we say it's better to do this on a case-by-case basis. There's no reason to think that in the far majority of these cases, that the vaccine is causing the continued effects that may occur. Does that help?

MR. KRAUS: You answered my question all as a group. Thanks.

DR. SHIMABUKURO: I just want to also add to the discussion that febrile seizures are age-related. There's a risk period. They can occur in children up to six years old. They're very rare after a certain age, and the highest risk is 6-18 months, maybe a little bit longer.

It's just sort of the natural history of febrile seizures, is that kids in a certain age are at relatively high risk for febrile seizures. That's when they're getting MMR and other vaccines. If an older child is having

seizures, those probably aren't febrile seizures. That's from residual seizure disorder or a neurological condition.

DR. RUBIN: Now I will talk about vaccine-strain measles viral disease. In 2011 the Institute of Medicine, following an extensive review of scientific and medical literature, concluded that the evidence convincingly supported a causal relationship between MMR vaccine and measles inclusion body encephalitis, or MIBE, in individuals with demonstrated immunodeficiencies.

We are proposing changes to the Vaccine Injury Table because the current Vaccine Injury Table has the injury "vaccine-strain measles infection in an immunodeficient recipient" for vaccines containing measles virus. I'll define measles inclusion body encephalitis. It is a rare, slowly progressive encephalitis caused by the chronic infection with the measles virus. It's confined mainly to immunodeficient patients. Since MIBE is one type of measles-associated disease, the proposal involves revision of the current injury to include MIBE.

In terms of our proposal to change the time interval, this is based on reports that actually have been reviewed by the IOM, but also what we reviewed outside, because the IOM just reviewed MIBE, and we also reviewed other vaccine-strain measles disease.

Based on three case reports that the IOM reviewed, which were all mechanistic, the time interval for the onset of symptoms for MIBE was four to nine months. But then a case report of Goon in 2001 describes a patient with vaccine-strain measles with onset of symptoms eight days after vaccination. Another case report by Angel describes a patient with vaccine-associated measles pneumonitis with onset of symptoms 11 months after vaccination.

Our proposal would be a broad interval of less than to equal to 12 months for those cases in which the typing of vaccine strain was not performed, following the Guiding Principles. We felt that because it was a long time period and it actually involved up to a year and months, it was hard to parse out days, which is different from the 7-14 days that we discussed with the vaccine strains.

We just decided less than or equal to 12 months, rather than have to go to 1 day or 3 days. I know that it's not necessarily biologically plausible. Most of them occurred about six weeks, two months after vaccination, but the eight days was basically an outlier. It was with an AIDS patient. If the vaccine strain is identified, no timeframe will be applicable.

DR. JOHANN-LIANG: Not to confuse you, there is a difference as to why Mary's group is proposing less than

and equal to 12 months with no lower limit as opposed to what you heard from varicella, where we very carefully went to see what the lower limit would be. The reason for that is that is presumption given for anybody. This is presumption given only for immunocompromised people.

When people actually meet the definition for "immunodeficient patient," in medicine all bets are kind of off. It's very hard for us to really determine what's happening. That's why for measles, we're proposing a generous outlying month, which is 12 months, based upon the literature, with a no lower limit bound, because it's hard for us to really get a good handle on the lower bound. We've got a very handle on the varicella based upon all the information available. Not so over here. That's why there is a difference. There is a rationale behind what we're proposing.

MS. BERNSTEIN: I was just curious in practice how often the typing of the vaccine strain is typically performed.

DR. RUBIN: I will go over this, actually. In terms of the cases I reviewed with this, most of the cases did not type the vaccine strain.

The first three cases are actually the cases that the IOM reviewed, and these were cases of MIBE. Only the

first case of Bitnun is actually the one that describes where the vaccine strain was typed. The rest of them just isolated measles virus or saw the histopathologic findings consistent with the disease.

The next slide are case reports of other disseminated measles disease, such as in Mihatsch, which is the second article. This describes a nine-month-old boy who developed non-specific symptoms three weeks post-vaccination and died of respiratory failure. The autopsy findings were consistent with giant cell pneumonia and thymic atrophy, which is a deficiency of lymphocytes in the lymph nodes, spleen, and thymus, and makes the patient susceptible to invasive disease.

The next slide is a snapshot of what the changes will be. Basically, as we mentioned before, I will be talking about proposed changes that affect B. This is what it looks like right now with the vaccines containing measles virus. I will talk about this in detail, but B is what my talk will be talking about.

The current Vaccine Injury Table shows the vaccines containing measles virus in any combination, shows the injury of vaccine-strain measles viral infection in an immunodeficient recipient with a time interval of zero to six months.

Our proposal will state vaccine-strain measles viral disease in an immunodeficient recipient, and if a vaccine-strain virus is identified, then no time interval will be applicable. But if determination is not done, or if laboratory testing is inconclusive, then the time interval will be less than or equal to 12 months.

This is the current Qualification and Aids and proposed Qualification and Aids side by side. We will be replacing the green text with the blue text. The current Qualification and Aids states that the vaccine-strain measles viral infection is a disease caused by the vaccine strain that should be determined by vaccine-specific monoclonal antibody or polymerase chain reaction tests.

Our proposed Qualification and Aids will state that this is a term defined as a measles illness that involves the skin and/or other organs such as the brain and lungs, and that the measles virus must be isolated from the affected organ or histopathological findings characteristic of the disease must be present.

Measles viral strain determination may be performed by methods such as polymerase chain reaction test and vaccine-specific monoclonal antibody. If strain determination reveals wild-type measles virus or another non-vaccine-strain virus, the disease shall not be

considered to be a condition set for in the Table. But if strain determination is not done or if the strain cannot be identified, onset of illness in any organ must occur within 12 months after vaccination.

MR. KING: Why would a strain determination not be done? What you're saying here is you're unable to identify the strain, is really what you're saying. It's not that it's not done. Is that correct?

DR. RUBIN: Either. Sometimes they're not done.

DR. DOUGLAS: You don't always have access to PCR test.

MR. KING: Just so that I understand that, some areas are going to be able to have the medical reach to determine or to at least do the test for the strain and other areas will not have that?

DR. RUBIN: Yes, and actually this test is not necessarily available for all areas.

MR. KING: Here is my concern. If it is done, would this lead people to say we're not doing a strain test?

DR. JOHANN-LIANG: We hope not, if the doctors are taking care of the patients without thinking about compensation.

DR. RUBIN: It is very complicated with these diseases. They are very rare, and most of them, unfortunately, die. There is confirmatory testing. When someone has measles giant pneumonitis, for example, they can actually look at the lungs and it will show measles inclusion bodies in it. Most of the time they will say that looks like measles. Sometimes the testing stops there.

But for those that have the availability, they will say let's go isolate this and let's put monoclonal antibodies on this and see if it is the vaccine strain. But for all the studies that I looked at, I said the ones that the IOM looked at, out of the three, only one actually isolated and identified it was the vaccine strain.

The rest of them said it looks like measles and it looks like the disease, and then all the rest of the disseminated ones actually there was three out of the four had the vaccine strain. The measles inclusion body encephalitis, a little complicated because it involves the brain. I talked to someone who was involved with measles, and it says that it's not necessarily the PCR is widely available, I guess.

MS. SAINDON: I just wanted to clarify that you've seen this language already in the varicella proposal. In terms of the consistency, that's exactly what

we were trying to do to sort of say if you can type it or you can type it successfully, then we're going to treat you differently, but if you cannot, then we're going to treat -- but for each of these, the measles and the varicella, we're setting out the guidelines exactly the same.

MS. DELA ROSA: I am glad that you are taking into consideration that the viruses are actually very difficult to culture. They may get as many blood samples from you. They can test you as many times. If they cannot grow it, they cannot type it.

DR. RUBIN: There are limitations to testing.

MS. SAINDON: And they do get the presumption at that point.

DR. JOHANN-LIANG: Also remember, we're not talking real time. The patient has already been taken care of. We are reviewing backwards some years later, and when we're looking at the records, we may not find the vaccine strain or whatever, but we still want to get presumption of causation for disease such as this. Even if it was wild-type, we still want to give the presumption.

MS. BERNSTEIN: I just wanted to get back to your question for a moment. I know we talked about this a little bit when looking back at the varicella discussion where presumably we want to have the strain identified, but it

could be advantageous to the petitioner not to have the strain identified. Do you see what I'm asking?

MR. KING: Yes, and I don't know the answer.

MR. KRAUS: I think that is correct. The idea of this sort of theoretical perverse incentive exists, but I think it exists only in theory, because in my experience, thankfully, doctors treat patients based on their medical conditions and have concern appropriately for -- I shouldn't say appropriately because sometimes it stings you if you're trying to represent a petitioner down the line. I think, as you pointed out, that the timing is such that treatment decisions are made long before there's any potential for that perverse incentive to be a problem.

DR. RUBIN: The justification study showed that the isolation of measles virus from the affected organ and/or characteristic histopathologic findings. Some studies do show identification of the vaccine-strain measles virus by PCR or specific monoclonal antibody, and all the case reports involve patients with immunodeficiencies.

Under the ACCV Guiding Principles, we are giving presumption of causation to cases in which the vaccine strain is undetermined or testing is inconclusive. As I mentioned earlier, only one out of three of the MIBE cases

showed vaccine-strain virus, and three out of the four isolated in vaccine-strain virus in disseminated measles disease.

This is the slide of the proposed Table, what we are changing on the Table. I did not list all the sections for that MMR Section Five, which I talked about the languages in the Table and the Qualifications and Aids.

MR. SMITH: I was going to make a motion to ACCV to recommend moving forward with the proposed changes to the Table for vaccines containing measles virus, as outlined in Dr. Rubin's presentation.

DR. DOUGLAS: Second.

MR. KING: Is there any discussion?

MR. KRAUS: I had another point that I wanted to ask. You earlier said that the MIBE cases are mainly confined to immunodeficient --

DR. RUBIN: Actually, that's what, by definition, MIBE is.

MR. KRAUS: So basically all these cases of MIBE involve individuals who have immunosuppression.

DR. RUBIN: Actually, when they diagnose a case of MIBE, they then look for immunodeficiency because it only happens in immunodeficient -- and then the disseminated measles, all the other ones too.

MR. KRAUS: So sometimes they don't even know about the immunosuppression until the MIBE surfaces.

DR. JOHANN-LIANG: Or other disseminated measles disease.

MR. KING: Any discussion, comments, additional?

DR. VILLAREAL: A quick clarification for Dr. Douglas. In the rural communities, especially with us with Native Americans and Hispanics, we're always concerned that the immunodeficiency is hiding and that when we give that shot, especially with the Navajo kids, we are concerned that this is where you'll get the diagnosis. We try to send the PCR. Those kids aren't taken care of in our community. They're shipped out to the regional tertiary centers where we can get all the appropriate labs. So yes, with rural communities we're fully aware of the potential problems of pre-diagnosis. When you give the measles shot, then you know that the kid is immunodeficient.

MR. KING: Any other discussion? Let's take it to a vote.

(Whereupon, on motion duly made and seconded, the Commission approved the recommendation of proposed Table changes related to MMR vaccine.)

MR. KING: People are probably starving. We'd probably like a break, and I think we need to recess. We'll take one hour for lunch.

(Lunch break)

AFTERNOON SESSION

MR. KING: So it's Dr. Tom Ryan. Dr. Ryan is going to speak to us about proposed table changes related to injection-related for multiple vaccines.

We need to rearrange the agenda slightly? I have no objection to rearranging this to accommodate a schedule. I'm absolutely fine with that. We're going to have Dr. Atanasoff, and you're going to be speaking about anaphylaxis and the proposed Table changes for multiple vaccines on that. Thank you.

**Agenda Item: Proposed Table Changes -
Anaphylaxis (multiple vaccines)**

DR. ATANASOFF: First off, I just want to say I'm presenting on behalf of four different work groups. I want to just make sure that they're included in this. It wasn't just my work, certainly; it was the work of four different groups. The vaccines we're going to discuss as far as adding anaphylaxis as a Table injury or trivalent influenza vaccine -- and that includes the LAIV, or FluMist -- meningococcal vaccine, varicella vaccine, and the human papillomavirus virus vaccine.

As far as trivalent influenza, the summary of justification for proposed changes to the Table is basically that there are multiple well-documented reports

in the literature as well as reports of related laboratory and clinical evidence to support that anaphylaxis occurs after receipt of trivalent influenza vaccines.

Based on the reports that the IOM found, they felt that the evidence convincingly supported a causal relationship between trivalent influenza vaccines and anaphylaxis. We feel that the conclusion that it was a causal relationship was felt to be scientifically and medically credible.

Here's some of the literature for flu. I was the team lead for that group, and I found it convincing as well. It was primarily mechanistic evidence. There was one epi study, but they did not find any statistical increase of influenza causing anaphylaxis in two different years of seasonal vaccine administration. However, the mechanistic evidence, there was quite a bit of that.

Just to point out a couple of these, the Coop study was a case report of a 37-year-old male with developing systemic symptoms 15 minutes after influenza vaccine. He was treated and recovered. But then they went on to do some testing.

He tested positive for skin prick testing for the vaccination, as well as they performed an IgE immunoblot that showed that they were bands corresponding to the

molecular weights of three different items: gelatin, hemagglutinin from flu vaccine, as well as ovalbumin from eggs. I thought that was pretty significant.

Chung is a retrospective chart review in egg-allergic patients. This was from two different vaccine seasons. In one set of seasons 91 of 146 of the patients developed positive response to skin testing after flu vaccination. The other set of two separate seasons, 24 of 115 demonstrated localized or systemic reaction following the two-dose vaccine scheduled for influenza.

The next vaccine is meningococcal vaccine. Again, the IOM found after doing extensive review of the medical literature, did conclude the evidence convincingly supported a causal relationship between meningococcal vaccines and anaphylaxis. Their conclusion regarding the causal relationship we found to be scientifically and medically credible.

A little difference in the number of references cited. There were no epi studies that they felt contributed to the weight of the evidence, however they did find one study. This is a retrospective study of a passive surveillance system, and they found one case of anaphylaxis in a 12-year-old girl occurring 30 minutes after receipt of vaccination. They also considered the clinical symptoms

that she experienced, including low blood pressure despite two doses of adrenalin given, dyspnea, and bronchospasm.

The next vaccine is varicella vaccine. Again, multiple reports in the literature that anaphylaxis occurring after varicella vaccine. Based on those reports, the IOM found that the evidence convincingly supports a causal relationship between varicella vaccine and anaphylaxis. Again, we found that conclusion to be scientifically and medically credible.

With varicella literature, the Kumagai reported two cases of anaphylaxis after vaccination occurring less than 15 minutes. Both cases demonstrated positive antiagglutinin IgE. The Ozaki had 32 cases with anaphylaxis in less than an hour after vaccination. They tested nine of them for these antiagglutinin IgE antibodies, and they were all positive.

The fourth vaccine that we proposed adding anaphylaxis to the Table is HPV vaccine. Again, this vaccine, they did find multiple cases in the literature of anaphylaxis following receipt of the vaccination, and based on that, they found the evidence favors acceptance rather than convincingly supports -- that was an update that I made to my slide today -- of a causal relationship between

HPV vaccine and anaphylaxis. We found that conclusion to be scientifically and medically credible.

As far the relevant literature for HPV, this is mainly mechanistic evidence. We didn't find any epi studies that contributed to the weight. The two studies that they did look at -- and they didn't explain entirely why they said favors acceptance versus convincingly supports.

But I think it may have to do with the fact that out of the two studies, one was actually telephone interviews where they found eight cases of anaphylaxis occurring within 15 minutes after HPV. Then the other study was basically looking at VAERS reports. I think it may be that the liability of the case information, that may have been taken into consideration. They didn't really spell that out.

In addition to that, HPV working group found that out of the publication that came out of DVIC, there were a number of cases of anaphylaxis occurring after vaccination, which also included a case of anaphylaxis occurring after HPV that met the Brighton criteria. Combined with the IOM material and our own case study, we felt that this should move forward, and we were convinced that this is something that we would like to propose putting anaphylaxis on the injury for HPV.

Currently there are no injuries on the Table for these vaccines. The anaphylaxis is not currently an injury listed.

This is the proposed Table for all the vaccines. In the end, it'll have a different look to it. This just includes the current injury that we're talking about. It would essentially be anaphylaxis occurring within four hours of receipt of vaccination, but would also include any acute complication or sequelae, including death from anaphylaxis.

The current QAI is here. I'm not going to read through the entire thing, but if you want, you can refer to the color-coded version. That will show you what was there, what we're proposing to change.

The proposed QAI -- I'll read through this -- is defining anaphylaxis as an acute, severe, and potentially systemic reaction that occurs as a single discrete event with simultaneous involvement of two or more organ systems. Most cases resolve without sequelae. Signs and symptoms begin minutes to a few hours after exposure. Death, if it occurs, usually results from airway obstruction caused by laryngeal edema or bronchospasm and may be associated with cardiovascular collapse.

Other significant clinical signs and symptoms may include the following: cyanosis, hypotension, bradycardia, tachycardia, arrhythmia, edema of the pharynx and/or trachea and/or larynx with stridor and dyspnea. There are no specific pathological findings to confirm a diagnosis of anaphylaxis.

Essentially going over what we changed, anaphylactic shock, we removed it as a condition because it's already within the overall diagnosis of anaphylaxis. Some people who have anaphylaxis can develop shock, others may not, but it's included already using just the term "anaphylaxis."

Then we removed the word "allergic" because allergic actually excludes anaphylactoid reactions, which are non-allergic anaphylaxis. It's from degranulation of mast cells, and it can look exactly the same as anaphylaxis, but it's not considered allergic from a technical standpoint, so we took out the word "anaphylaxis." Anaphylaxis does include these anaphylactoid reactions.

Then we simplified the wording regarding the pathology findings, since there are no specific autopsy findings that you would see to be able to confirm that anaphylaxis occurred.

This is both how the Table would appear as far as the anaphylaxis and the acute complications as well as the new proposed QAI for anaphylaxis.

PARTICIPANT: For the HPV vaccine, was there any distinction made in the data between which in the series, like whether it was the first in the series or later in the series of the vaccine?

DR. ATANASOFF: I did not see that.

DR. SHOBACK: This is Barbara Shoback. I'm a medical officer. I was part of the working group on the HPV vaccine. They did in the surveys list the dose that it was. Unfortunately, not everyone who was included had completed all the doses, so I don't have the distribution, but many of the people in these studies had not completed. So it would have been the first two just based on that.

DR. VILLAREAL: Is there any way to isolate sole vaccine besides -- say you have a teenager who got the flu and a mening and an HPV and they have anaphylaxis. I didn't see that in the studies.

DR. ATANASOFF: From my perspective, the only way you might be able to do it is if you test for the antihemagglutinin that's specific for influenza, maybe gelatin if gelatin is in all three. But if all three are covered, it wouldn't. As long as there's one vaccine that's

a covered vaccine, I think they would be given the presumption, unless there was some other alternate cause that it was from the vaccine.

MS. LINGUITI PRON: I understand that the results from the IOM for hepatitis A and anaphylaxis are inconclusive. I think that's what I see on that multicolored chart of Rosemary's. Did the people reviewing that issue of anaphylaxis have any ideas about why that is?

Just about almost every other vaccine now -- I think there's one other one that doesn't have it -- has anaphylaxis now as an adverse event. It's just kind of counterintuitive as to why not all of them would be likely to cause that. Is there something specific about that vaccine?

DR. ATANASOFF: I'm going to let Dr. Marco answer that. I believe he's listening in. If he doesn't respond, we can address that.

OPERATOR: Dr. Marco, if you are on the line, hit star-zero.

DR. ATANASOFF: His group did look into the hepatitis A vaccine. It's not given as frequently as a lot of the other vaccines, so that may be the reason why there aren't case reports. But essentially their group found nothing in the literature to support that it does occur,

and so keeping in line with how we're treating the vaccines and whether or not putting them on the Table, there's no epi support and no mechanistic support at this time.

DR. JOHANN-LIANG: That is a very good question. The work groups discussed this at length, because you're absolutely right. We're proposing that the majority of the vaccines that are now on the Table will get anaphylaxis listed, so hep A kind of stands out.

Like Sarah was just saying, IOM could not find either epi or mechanistic evidence, and the work groups also went in to look for any evidence to support it. They couldn't find it, and they also looked through all the ingredients trying to come up with some way to make this work. Hep A, as it turns out, I've been told -- and Dr. Milo's not on the call -- has a pretty clean profile as far as ingredients are concerned in comparison to other vaccines.

Lastly, in the more recently published literature from our group that did not get included at the IOM report because it was published in 2011 we analyzed all the anaphylaxis experienced from the claims that have come in in the last 10 years. There actually is a case that has hep A listed, but it was in conjunction with other vaccines.

We do have to set some sort of a bar starting with some sort of a scientific evidence, and therefore if we had a case that was solely HAV, one case, from even our experience, we would have proposed to put it in the Table because, in fact, that's what we're doing for HPV.

HPV was assessed at the end of the day more than HAV. They said there is some evidence, and they favor acceptance. But in our case series we actually had a case of anaphylaxis with sole HPV, and therefore we're able to definitively propose that we add it to the table. But we just couldn't do that with HAV. Does that make sense?

MS. LINGUITI PRON: It does. I'm glad that you check it out. That's the important part. Thank you.

MR. KRAUS: I have a question not necessarily about whether we approve it, the merits of the changes. When it's anaphylaxis reaction, is it typically to the vaccine additive or adjuvant, or could it be to the vaccine itself, or do we not know?

DR. ATANASOFF: In the influenza data they found IgE antibodies not only to gelatin, but also to egg components, but also the specific hemagglutinin that's found in the influenza vaccine. So it can be either for that vaccine. I haven't come across anything that's found

antibodies toward other vaccine components for other vaccines.

DR. FEEMSTER: I just had a question about the distinction between anaphylactoid reaction and anaphylaxis. I just wanted to understand the reasons you kind of take away the term "allergic" and include both anaphylactoid reaction and anaphylaxis, because a lot of the evidence that you cited, the mechanistic evidence, talks about IgE and things that support an allergic reaction. I just wondered what led to the decision to make that distinction.

DR. ATANASOFF: It came up in discussions on whether or not we should make a distinction between anaphylaxis and anaphylactoid. They can look exactly the same, and they're rarely, if ever, tested for to actually see the distinction between the two. So we felt that it'd be best and in the spirit of the guidelines to basically leave it as an overarching anaphylaxis and including these anaphylactoid reactions, which can occur after administration of certain drugs. It's just technically not allergic.

MS. WILLIAMS: I just want to ask, because I'm not medical, looking at the entitlement to compensation, clearly I know enough to know anaphylaxis is extremely severe. Looking at the entitlement to compensation slide,

you can die, clearly covered. It's not going to be one of these six-month things that we were talking about this morning. But if there's no death and it's not a six-month residual, in order for compensation, would it have to require inpatient hospitalization and surgery?

DR. ATANASOFF: It could be six months.

DR. EVANS: It could be six months. It could be sequelae.

MS. WILLIAMS: My question is if it's not within the six months and it's not a death, does it get captured by the inpatient hospitalization and surgery?

MS. SAINDON: Any one of those will serve as the severity prong, but there have been cases where they had an anaphylactic reaction and were administered epinephrine and were covered. If they filed, they would not be compensated. But I think what you're asking is, is this more similar to the febrile seizure kind of case or to the syncope kind of case, and I think that there's plenty of evidence to show that there can be a severe reaction in enough cases to merit inclusion on the Table.

DR. JOHANN-LIANG: Aside from death as a sequelae to anaphylaxis, you can actually have issue arising from anaphylaxis that can result in a bad outcome. You can have anaphylaxis leading to other organ collapse that results in

sequelae. You can have anaphylaxis and found to be allergic to some components, and then that becomes a sequelae issue. There are many ways to satisfy the residual effects criteria.

However, it's a good thing if someone is trying to anaphylax and there is a healthcare provider right there, so you sort of circumvent the spiral down to something bad. If that person recovers, is perfectly fine and back to baseline, that would not satisfy the requirements for compensation.

MS. WILLIAMS: I guess where I was going with this is you survive and it's zero to six months and you have hospitalization, but you may not have surgery, but it's clearly an issue. But they would not be compensated.

DR. JOHANN-LIANG: Usually they go to the ER and then they leave. They don't even really get admitted because most people get treated and they do fine. But no, that wouldn't satisfy the --

DR. ATANASOFF: But if he had an anoxic event due to lack of oxygen during the anaphylaxis, if they didn't treat you in time and you ended up with encephalopathy, that would be covered.

MS. WILLIAMS: You could have a very severe event, not have surgery, not die, not last long enough to

make the six months, but still have a very severe reaction with lots of hospital bills, but you would not be eligible for compensation.

DR. JOHANN-LIANG: We rarely see cases like that. Usually, if there is a severe sequelae, it will meet the six months.

MS. WILLIAMS: That's the answer to my question, if you survive.

DR. JOHANN-LIANG: If you survive. Thankfully, though, many of these cases, when you review them, there is suggestion of stopping it, which is a good thing, I would think.

DR. DOUGLAS: Just as I've looked through these handouts, I know six months from the previous set of slides, but we are clear that in this set of slides we're just talking about the occurrence happening within four hours.

DR. JOHANN-LIANG: That's not been changed. The current one has four. I'm going to come back and do another talk with Dr. Stacy Stryer, and we'll go over the color-coded version in depth. One of the things we did is that we felt that just four hours -- it's the way it's currently listed -- is a little bit ambiguous, and we're just putting

less than or equal to. That's the interval of onset. That's the only change, actually.

MR. KRAUS: I would move that we accept the changes proposed in the report related to anaphylaxis in flu vaccine meningococcal, varicella, and HPV vaccine.

MR. SMITH: Second.

MR. KING: The motion has been seconded. Is there any discussion, other than what we've already done? Are there any questions?

(Whereupon, on motion duly made and seconded, the Commission approved the recommendation of proposed Table changes related to anaphylaxis.)

MR. KING: Thank you very much. I appreciate that. Dr. Tom Ryan, thank you for your flexibility. We will go to the proposed Table changes - injection-related (multiple vaccines).

Agenda Item: Proposed Table Changes - Injection Related (multiple vaccines)

DR. RYAN: Good afternoon, or good evening. I'm excited to be here today and talking to you because I get to talk about something brand new for the Table. First we had vaccine-specific injuries, and we've been talking about that, but what we're going to talk about now is a proposal

for injuries related to vaccine administration rather than the specific components of a vaccine.

What this really means is that these particular injuries will show up on the Table under every injectable vaccine. The only ones that wouldn't be covered would be the rotavirus, which is an oral vaccine; the influenza nasal spray; and, of course, oral polio, but we don't really use that anymore, so it wouldn't really be applicable anyway.

The IOM, as they did for all of these other injuries, looked at the information and found that there was convincing evidence supporting a causal relationship between vaccination and deltoid bursitis. I'll get into why this is titled shoulder injury related to vaccine administration.

One of the papers that they read was the paper that was written by Dr. Atanasoff, who just left. At any rate, when they read that paper, the IOM believed that the cases that were described in that paper met the definition of deltoid bursitis.

The literature on this is fairly limited. The first three bullets are the literature that was looked at by the IOM. The fourth bullet, Bodor, was not really identified by IOM, however it's sort of an interesting

story because this was really the seminal paper that was written on this.

Bodor had described two patients who developed shoulder pain and limited range of motion beginning about two days after vaccination. They hypothesized that this occurred due to inflammation from injection of the viral antigen into the bursa or the other synovial tissues under the deltoid muscle in the shoulder.

Vellozzi, just as an aside, that was a look at trivalent influenza vaccine and its safety. As a part of that, they identified three patients that developed shoulder pain and limited range of motion within a day after being vaccinated.

We here at the DVIC started looking through. We realized some of you have been on the committee long enough to know that we have done a presentation here on SIRVA in the past. But we looked through our database and found 13 cases in which an individual had developed shoulder pain and limited range of motion.

The vast majority of those, of the 13, 12 of them occurred within 24 hours of vaccination, the onset of symptoms. So we wrote a paper on this, in part to report our experience, but in part to inform the IOM that we felt

that this was a valid injury. That's the literature with regard to it.

We get right into the proposed QAI. I'm just going to read this lengthy document for you. Shoulder injury related to vaccine administration, SIRVA, manifests as shoulder pain and limited range of motion occurring after the administration of an injected vaccine. The pain and other symptoms are thought to occur as a result of unintended injection of vaccine antigen or trauma from the needle into and around the underlying bursa of the shoulder, resulting in an inflammatory reaction.

SIRVA is caused by an injury to the musculoskeletal structures of the shoulder, for instance, tendons, ligaments, bursae. SIRVA is not a neurological injury, and abnormalities on neurological examination or nerve conduction studies and/or electromyographic studies would not support SIRVA as a diagnosis, even if the condition causing the neurological abnormality is not known.

A vaccine recipient shall be considered to have suffered SIRVA if such recipient manifests all of the following: no prior history of pain, inflammation or dysfunction of the affected shoulder prior to vaccine administration; the pain occurs within the specified

timeframe; pain and reduced range of motion are limited to the shoulder in which the vaccine was administered; and no other condition or abnormality is present that would explain the patient's symptoms, for instance, EMG/NCV, the electrodiagnostic or clinical evidence of radiculopathy, brachial neuritis, mononeuropathies, or any other neuropathy.

MR. SMITH: Two questions. The first is I noticed the vaccine recipient shall be considered to have suffered SIRVA with the following conditions. The second bullet, is it deliberate that no reduced range of motion does not have to occur within the specified timeframe? In other words, it's just the pain that would have to occur within the 48 hours, not a limited range of motion.

DR. RYAN: Right.

MR. SMITH: The second one is the injury to the shoulder musculoskeletal structure is not a prerequisite to having a presumption of SIRVA. In other words, I could have a pain, but maybe not a musculoskeletal injury in the shoulder, and still be presumed, if I satisfy the other criteria --

DR. RYAN: If you satisfy these other criteria. Right.

DR. VILLAREAL: Just a hypothetical. This is limited only to the shoulder anatomically. It does not involve any femoral or leg pain in young infants. Is that correct? This is solely the shoulder.

DR. RYAN: Solely the shoulder. The only literature that's available is with regard to the shoulder.

DR. KING: Like a football player or baseball player who had a shoulder injury -- let's say they dislocated the shoulder half a million times and they eventually had surgery on it -- would that preclude?

DR. RYAN: That would not meet the Table definition in that they had a prior history of problems with that shoulder. While it wouldn't be a Table injury, still it would be an injury that would be looked at on a case-by-case basis. If the petitioner were able to make the case that what's going on now is unrelated to what's going on with his shoulder before, then they would be compensated.

This is the Table. This would appear under every injectable vaccine, that the injury would be shoulder injury related to vaccine administration. The time interval is up to 48 hours, so up to two days following vaccination.

MS. LINGUITI PRON: I understand the scientific information, but I'm still concerned about this issue in

general. How will we present this? Obviously if it's going to be a Table injury, then there's going to be compensation, but you also would like to prevent the situation in the first place.

Is there anyone at the CDC, or I'm not sure who would be in charge of that, looking into maybe changes to the way injections are given in the arm or whatever? I know once before they talked about the patient had to be seated and you had to do it a certain angle. We all were taught certain things certain ways, and it sounded like maybe we had to make changes.

DR. SHIMABUKURO: Providers who receive training on how to give injections should receive the proper training on how to give an intramuscular injection into the deltoid. In our immunization program we have a branch which does outreach and education, and they do provide education and training on proper technique. This is really a technique issue.

Just from our monitoring, we realize that this probably happens more than we had thought in the past. We are looking into engaging the immunization program to maybe develop some more specific messaging around proper injection techniques and the importance of proper training

and continued training, especially now that vaccines are being given in multiple settings.

MS. LINGUITI PRON: I recall in the past when I remember looking at the data that it seemed to be only an adult problem. Is that correct?

DR. RYAN: Yes. The series that we reported and all of the other cases occurred in adults.

MR. KRAUS: Does this injury, in theory at least, not occur if proper vaccine administration technique is employed?

DR. RYAN: I don't think I can answer that. In the paper by Atanasoff we did recommend paying attention to body size and proper needle length and proper technique, as Tom was talking about. We recommended against injection in the upper third of the deltoid simply because the subacromial bursa, that fluid sac, can extend down the shoulder, and there's a higher risk if it's given high in the shoulder. In fact, some of the patients in our series, that was their complaint. It was given higher than it usually was, and they had immediate pain when the injection was given. But I don't think I can answer your question directly.

MS. DELA ROSA: My question regards the word "severe" persistent. Will the person who has the problem

then be considered disabled in terms of other stuff like Social Security and all the stuff. Will they qualify for that depending on the severity of the injury?

DR. RYAN: Some people with this injury actually have qualified for Social Security disability. In others it clears up with time and they improve. Frequently people with this condition will see an orthopedist, they'll get an injection of corticosteroids, sometimes several injections of corticosteroids. Several of the patients went on to require surgery. I'm trying to think back now, but I would say that about half of our patients who had applied were still having symptoms a year or two following this injury, so it can be long-lasting in terms of disability.

I guess I'm on the slide I want to be on, and I wanted to talk a little bit about the decision to call this SIRVA rather than deltoid bursitis, as the IOM had found the evidence to support. Of course, we understand that this is related to the unintentional injection of the vaccine into the tissues and structures underneath the muscle.

The Atanasoff article was the article that reported the bulk of cases. The IOM felt that the description of those cases fit with the diagnosis of deltoid bursitis. However, our actual program experience is that a number of different injuries were related to

shoulder pain following vaccination. Deltoid bursitis was one of them, but tendonitis, impingement syndrome, frozen shoulder, adhesive capsulitis. Even a flare in a symptomatic rotator cuff injury could be the diagnosis that was actually made when they saw somebody and had an appropriate workup done.

So our work group really felt that deltoid bursitis was far too narrow a term and chose to use the term "SIRVA" to create a broader umbrella, to open this to more patients so that if someone had an MRI of their shoulder done and it didn't show deltoid bursitis, but perhaps it showed one of these other conditions, they're still eligible to be a Table injury and to move forward from there. We talked about this in our group. This was simply applying the ACCV Guiding Principles to choosing a name that was more inclusive.

In terms of the time interval, we've talked about the cases that were reported. Bodor had two. They occurred within 48 hours. Vellozzi had three. They occurred within 24 hours. The Atanasoff article, DVIC, we had 13, and of those, 12 occurred within 24 hours.

The literature is limited on this subject, and so we felt that we would go with the upper limit of the reported cases that really included 93 percent of all

cases. So 14 of 15 of the reported cases occurred within this time period, and we felt that that was supported by the science and, again, felt that it would provide a wider window for petitioners, most of whom, as I said, either had a pain immediately -- and over 50 percent of them had pain immediately after getting their injection, or 93 percent within 24 hours.

MR. KRAUS: Do you know the timeframe for the fifteenth person?

DR. RYAN: The fifteenth person was four days after injection. What our feeling was there is that it was difficult to arrive at where do you cut this off. If you say four days, should it be six days? We went by what we could see from the papers and articles that have been written on this that would bring the vast majority of the patients that have been injured in this way into a presumption of causation while still recognizing that patients that presented later -- my pain started in four days, my pain started in seven days, my pain started two weeks later -- could still be looked at on a case-by-case basis.

DR. FEEMSTER: I think this question was already asked, but I think I just missed the last part of it. The case definition is pain and limited range of motion. Is

that correct? The onset of symptoms may just be pain by itself, but it is both pain and limited range of motion.

DR. RYAN: Pain and limited range of motion.

DR. FEEMSTER: So that's a necessary condition for the diagnosis.

DR. RYAN: Exactly. Yes. Thank you, Kristen. If a person just presents with pain and never at any point during their course has a limited range of motion, that, again, would not be a Table injury.

We're at the voting page.

DR. JOHANN-LIANG: We're going to actually do these separately, even though we have the same presenter, because they're kind of different. Is that okay?

DR. KING: I think that makes sense.

DR. DOUGLAS: I move that we add shoulder injury related to vaccine administration, SIRVA, to the Injury Table with the provisions provided.

MR. SMITH: Second.

MR. KING: That's been seconded. So any discussion on this motion?

MR. KRAUS: I completely understand what you are saying, and my perspective is representing injured petitioners. I'm wondering if it would make more sense to increase the 48 hours to either 72 or 96. Here's why. I

understand what you're saying. You feel that you've captured the majority, 93 percent, but pain -- if the symptom that you're looking to trigger the timing from is pain, pain can be a little bit subjective, a little bit harder to pin down.

I know that you're working hard to try to stay true to the Guiding Principle of sort of petitioner-friendly interpretation. We're only talking about 15 cases, and if one of them occurred within 96 hours, I would propose, suggest, or at least inquire, as to why not make it within 96 hours.

DR. RYAN: I was simply going to repeat what we had talked about before, which I know you already understand, that we were looking at it as trying to be inclusive and realizing that there was such limited literature on this.

I guess the other point that I'd make at this point is that shoulder injuries are really common. They are common in adults. It's a complex joint. It's easily injured. The further that you get from the time of possible causal vaccination, the more likely that it is that something else other than the vaccination is causing the pain.

For instance, rotator cuff injuries in adults, older adults particularly, are very common, and many of them are asymptomatic. But it doesn't take much. Reaching wrong, reaching too fast, reaching too high can trigger that off, and it starts to hurt.

We were trying to pick a timeframe where we could say nothing else has intervened here. There seems to be a clear causal association between vaccination and onset of the pain, whereas when you start getting further from that, less likely, less certain.

MR. KRAUS: Of course, the way the Table functions, all this is doing is shifting the presumption so that it would make it the respondent's burden to do what you just said, to identify some other intervening cause that happened on the third or fourth day after vaccination.

DR. JOHANN-LIANG: This really comes back to that issue of specificity again. The problem is that we have such limited -- this is sentinel information. Instead of waiting for more information, we want to go right in there and put it in. But it comes with a little bit of a caveat, because just as we talked about with febrile seizures, shoulder injury is just very common, especially as we have more and more adult claimants.

Giving the presumption and under the Guiding Principles of including the structures around the bursa, not just the bursa, we felt was really consistent with our application of the Guiding Principles. To go out to four days, the specificity of this relationship really starts to fall out. It's possible as more data accumulates in the future to see what the time interval may be, but right now we're just saying it's pain occurring in the specified timeframe, not anything else, because I think that person was pain with some range of motion issues.

We could apply other, but we thought it was more in the Guiding Principles to apply pain within those hours because what we saw in these reports -- and it was a fascinating thing because cases hit your desk and you start to say what is going on here? What you start to recognize is that pain comes immediately, but all the other associated symptoms, it takes a little bit of time. We wanted to give pain as the only thing to cover within those 48 hours and qualify. That's why it was written this way.

But it's also sort of a balance act to make sure that we are operating under the Guiding Principles, but not stray so far away from the very initial science, and we want to be fair across other adverse events and issues as

well. But that's very good. Your points are very well taken.

MR. KING: Are there any other comments, questions, discussion?

(Whereupon, on motion duly made and seconded, the Commission approved the recommendation of proposed Table changes related to SIRVA.)

DR. RYAN: Number two, vasovagal syncope. Before I go on, I really want to the Injection-Related Work Group. As you can tell from my previous presentation on SIRVA, they did a tremendous amount of work on this. The same was true of syncope.

Syncope means fainting. Vasovagal syncope is a condition which there is a transient decrease in blood flow to the brain that results in a brief loss of consciousness, typically, and loss of muscle tone along with that. It's the most common cause of syncope, and being the most common, it's the most common in adolescents.

When we talk about syncope -- and I'll be reinforcing this as we go through -- we're not talking about the actual fainting; we're talking about what happens after you faint, because those are where the injuries occur. They may be dental injuries. They may be lacerations. They may be broken bones. Or they may be, as

in one of our cases, that somebody is released from their doctor's office immediately after getting the shot, and then jumps in a car and drives and faints while they're driving and had horrible injuries as a result of that.

There are lots of things that can occur, and that's what we're really talking about. Mary Rubin had already told us that close to 10 percent of syncopal episodes after a vaccination may have a serious sequelae or a serious result.

Once again, the IOM looked at the literature and found that the evidence convincingly supported a causal relationship between injection of a vaccine and syncope. They based this on 35 case series or individual case reports.

They noted that it was the injection, and not the contents of the vaccine, that contributed to the development of syncope. Once again, this is an injection-related injury rather than being specific to a single vaccine.

They also noted that both the latency, the fact that in the majority of the case reports the onset was within 15 minutes, and that many of the patients had typical prodromal symptoms for vasovagal syncope. They felt lightheaded. They turned white as a sheet. They started

sweating. They felt nauseated before they passed out. Those things really suggested that vasovagal syncope was the mechanism that triggered this fainting after receiving an injection.

There was lots of literature, but as I mentioned, most of this was either individual case reports or they were reviews of the VAERS data or other surveillance data. D'Souza was probably the largest case series. They reported on 21 patients who developed syncope within one hour of being vaccinated. Braun reported on another six patients, again, who had syncope within an hour of vaccination.

Most of the rest of these, as I mentioned, were individual case reports or just general reviews of the safety data that identified syncope as a risk factor after vaccination. That comes as no surprise to most physicians who are very aware that this is definitely a risk for vaccination as well as for having your blood drawn.

Our proposed Qualifications and Aids for vasovagal syncope. Vasovagal syncope, also sometimes called neurocardiogenic syncope, means loss of consciousness, fainting, and postural tone caused by a transient decrease in blood flow to the brain occurring after the administration of an injected vaccine.

Vasovagal syncope is usually a benign condition, but it may result in falling and injury with significant sequelae. Vasovagal syncope may be preceded by symptoms such as nausea, lightheadedness, diaphoresis, which is sweating, and/or pallor. Vasovagal syncope may be associated with transient seizure-like activity, but recovery of orientation and consciousness generally occurs simultaneously with vasovagal syncope.

Loss of consciousness resulting from the following conditions will not be considered vasovagal syncope: organic heart disease, cardiac arrhythmias, transient ischemic attacks, hyperventilation, metabolic conditions, neurological conditions, and seizures. Episodes of recurrent syncope occurring after the applicable time period are not considered to be sequelae of an episode of syncope meeting the Table requirements.

This is what it would like for all injectable vaccines on the Table. Vasovagal syncope up to an hour after injection.

MS. WILLIAMS: But in order to be compensable, there would have to be an injury associated with it that would meet one of the three criteria. So someone who fainted, fell, had three stitches, not going to be compensable.

DR. RYAN: Yes or no.

MS. WILLIAMS: There's no hospital. There's no death. There's no hospitalization and surgery and there's no six-month sequelae.

DR. RYAN: But there could be scarring depending on where the stitches were and depending on the response to their stitches. Perhaps they developed a keloid or got a secondary infection or they just had obvious scarring from that. That's six-month sequelae. But fortunately, the vast majority of people who faint do just faint and they're fine.

MR. KRAUS: Can you concisely what about the administration of the vaccine causes this transient blood flow loss?

DR. RYAN: It's felt to be a reflex, and it's felt to be a response to either a painful or stressful situation. Lots of adolescents receiving vaccines are feeling both stressed and experiencing pain with that. The reason that it's called vasovagal is that it affects the vagus nerve and can cause a slowing of the heart or pooling of the blood and a drop in blood pressure. Those things translate into less oxygenated blood getting to the brain, which clicks off until you assume a horizontal position, at which point everything comes back again.

DR. EVANS: For those of us who've had the pleasure of working on a blood drive, if you work past the half a day, you're going to have someone who says I faint every time they stick a needle in me.

MR. KRAUS: So it's really not specific to vaccine administration; it's any injectable or any needle.

DR. RYAN: It's really the needle that does it.

DR. FEEMSTER: Any pain can do it in some people. It doesn't even have to be an injection. It's more a response to pain, I think. Some people tend to be more susceptible than others.

DR. JOHANN-LIANG: For the purposes of our discussion, we are talking about needles because there's no other evidence otherwise.

DR. FEEMSTER: I'm sorry. I was just talking about vasovagal responses in general, but that's correct.

DR. VILLAREAL: Is there any data as to the blood pressure of the patient before you put a needle in them? Are they hypotensive? Have they fasted? Are they pregnant? Elizabeth is kicking me over here. Are they a girl? The boys do faint, but it's mostly the girls.

DR. RYAN: It is true. At least in our experience, we have a series of eight cases in our program,

and all of those were women. The vast majority of them were teenagers.

In most cases there were no pre-vaccination blood pressures or pulses done. The person was usually there to get the vaccine, and that isn't standard protocol for most people. They say you're here for the vaccine. Do you feel well? Do you have any contraindications to getting this vaccine? If not, they go ahead and give it. No, we didn't have any information like that.

DR. SHIMABUKURO: At a recent ACIP meeting where they voted on HPV vaccine for boys they did an extensive safety review of HPV in general and also HPV in boys, because at the time it was a permissive recommendation. It was pretty clear that boys are good fainters too. It's not exclusive to adolescent girls.

DR. JOHANN-LIANG: The reason why all our cases are girls is because HPV was only given in girls in adolescence.

MR. KING: It seems to be related to the injection. Is there anything that can be done to prevent the syncope from occurring?

DR. RYAN: I know that Tom will back me up on this. The things that they recommend is the person be seated when they receive the vaccine, and ideally the

person administering the vaccine is sitting also so that they don't cause SIRVA by injecting in the upper third of the deltoid muscle, but then that they're observed for 15 minutes afterwards.

Most of the literature that you read about this, the Pink Book talking about administering vaccines says keep the person under observation for 15 minutes afterwards, have them sitting down rather than wandering around and doing things. Of course, that always makes you think about the drive-up influenza vaccine places. Did you have anything more to add to that, Tom?

DR. SHIMABUKURO: No. There is a recommendation to observe for 15 minutes. I think some of the feedback we've gotten is that that's in practice that's sometimes difficult to observe every patient in your busy practice for 15 minutes after they get a vaccination, but that is the recommendation.

MR. KING: Is what we are really doing here the cause of the practicality and the fact that we do want people to have vaccines, but because of the practical application of following instructions that would prevent syncope, that what we're saying is that to relieve that responsibility, we'll absorb it here on the Vaccine Injury Compensation Table so that people will have redress for not

doing what they should have done? That's the question I have.

DR. RYAN: Or perhaps we're unaware that they should have done it.

DR. EVANS: It is a no-fault compensation system. Who knows how often and what circumstances people can really follow and do what is recommended in terms of the amount of time. It could be they have to leave. A patient says they have to leave right away. If they do and they fall, it's still the same case, and so on. That's not relevant to what we're trying to do.

MR. KING: Maybe it is relevant to some degree. I'm not really taking a position one way or the other, but I think we ought to and talk about what we're doing because what we do sets precedent, potentially, later on. So some of what we should begin to think in terms of possibly, or at least have a conversation and dialogue around, is are we saying -- vaccine injury compensation oftentimes, especially when it first started out as childhood vaccines, was because we were dealing innocence.

What we were basically saying is we need to vaccinate people, and they need the vaccination, and every now and then something may occur, and what we need to do to prevent the pharmaceutical companies from having to be

liable in dealing with that is that we can help out and provide something.

In this particular case what we're saying is we can't expect people, because of the way our society maybe is, to successfully monitor and follow a process to prevent injury. So therefore through what we're saying is that if we don't do what we know we should do, we're going to give an opportunity to get compensation if you get injured, even though we all know that it could have been prevented if we had done something else.

MR. SMITH: Dave, to your point, and very well taken, I don't think the discussion's much different than what we just voted on with respect to SIRVA, that mistakes are made. If the injury follows the vaccination, to Michelle's earlier point as far as approaching these buckets, I think --

MS. SAINDON: Just to clarify, the Act does provide liability protection for vaccine manufacturers, but it also, by statute, protects vaccine administrators. We are trying to prevent litigation against those providers because this is the program where they're supposed to come and bring that.

MR. KING: That actually resolves a big question. Thank you.

MS. WILLIAMS: Just to clarify, but not restart the consistency discussion, the syncope and the SIRVA were how I got to the issue of consistency being a good value, because if you're not going to compensate the administrator/provider who may be engaged in a poor practice or not best practice with the administration, then your liability will go against the nurse or the doctor administrator.

Then you're having these patients be subject to all 50 states' medical malpractice laws, which could result in inconsistency where one patient would get medical malpractice laws' liability in a state that has a cap of \$100,000, but somebody for the same injury with the same bad practice could get \$1 million, whereas here everybody gets access to the same. This was the root of the consistency question this morning. We're taking it out of the state hands and the medical malpractice vagaries and putting it into a federal system.

MS. LINGUITI PRON: I just want to speak to the issue of protecting the provider as well, because the issue is to try to make sure that as many kids and adults as possible get vaccinated against vaccine-preventable diseases. If folks are going to be more liable because they're giving vaccines than if they weren't, then that

will be an impediment for children and adults to be properly vaccinated. It's my understanding, at least, that that's part of the intent of the Vaccine Act, just like it protects the immunization companies.

MR. SMITH: Not all of the cases, despite the CDC recommendation, occur within the first 15 minutes. I think two of the eight occurred in a timeframe longer than the 15. So even a provider that were to follow the recommendation, someone who would have received the vaccine could have been injured and have long-term sequelae may otherwise qualify under the program.

MR. KING: One other comment for thought -- and it would really be something for much later down the road -- is will we see an increase in these types of injuries if people realize that they don't have to follow best practice anymore because there's no discipline around it to do so? Probably not, but who knows.

DR. SHIMABUKURO: Even if doctors are covered, I don't think they want people losing teeth in their office.

MR. KING: I wasn't really thinking so much in terms of the doctors, but I'm thinking more in terms of the mass shots that occur and those types of things where it's just occurring, and today is flu day and everybody's going to get their flu shot, and we're just wheeling them in and

going on to corporate campuses or university campuses and it's just flowing it through. I just think human beings have a tendency, if we don't have to worry, we don't.

DR. SHIMABUKURO: I think those mass vaccinators are even more concerned with bad PR because they're out there in the public doing what they do. It's in their best interest to make sure that people are vaccinated safely.

DR. JOHANN-LIANG: We will continue to monitor and see what happens. You never know.

DR. RYAN: Basically we've talked about this being a response to a painful or stressful stimulus, that really the case reports occurred within 60 minutes, most of them within 15 minutes, but there were some that even fell outside. Let me back up. There were not some that fell outside. Of the cases reported, 27 of the 35 cases occurred within 60 minutes. There were some case reports that didn't include timing information.

In our case series six of the eight cases that we had -- and as I mentioned, six of the eight were also teenagers -- the time interval for those range from 1-15 minutes. Then finally, the IOM noted that the latency period of 15 minutes or less for the majority of the cases that they reviewed, plus the fact that there were prodromal

symptoms there, backed up vasovagal syncope as the mechanism for this.

You noticed on the QAI we said, "Episodes of recurrent syncope occurring after the applicable time period are not considered to be sequelae of an episode of syncope meeting the Table requirements."

This was basically to acknowledge that there are people who faint fairly frequently, however we wanted to clarify that the fact that they may faint frequently and have an episode of vasovagal syncope as a result of a vaccination were not two parts of the same condition, that it's something different that's going on if they're fainting more frequently, and that that needs to be evaluated to determine what's going on, that there's really not any literature or accepted mechanism that would suggest that vasovagal syncope from a shot is going to lead to recurring fainting after that.

DR. DOUGLAS: There are 900 in a day, Fairfax County, with H1N1 we have entire rooms set aside for you to sit down for 15 minutes. On the George Mason campus it is the boys who drop like stones. It's basketball tall boys. Let's say big tall boy going down, catch him on the arm, lay him down, recovers, nothing's hit, just went down and got back up. Is that a file-able injury?

DR. RYAN: Again, would need to have that six-month sequelae. The simple act of fainting is not a Table injury. It needs to meet those legislatively set requirements.

DR. DOUGLAS: I keep looking for that six months through here.

MS. SAINDON: It is in the statute. I would disagree with that answer. I think you can talk to the petitioners. There might be somebody who would file it. There may not be. We hope that there wouldn't be, but my answer would be that it wouldn't be compensable. There's a difference. You can do what you want to do, but we don't have to pay.

DR. RYAN: That's a better answer.

MR. KRAUS: What if it's the healthcare provider and it's a really tall big guy who causes an arm injury? I'm just kidding.

DR. RYAN: Actually, that has come up in different situations. In fact, I think even our group talked about the fact what if the brother or sister is in the room watching their brother get a vaccination and faints because of that? That happens in medical school. People are standing there watching the surgery, and you can count on the first year students, somebody's going to

faint. So the question comes up, is that compensable? I think I'm correct in saying no, that it's the vaccine recipient.

MR. KING: We will entertain a motion.

DR. DOUGLAS: I move that vasovagal syncope be added to the Vaccine Injury Table with provisions as stated.

MR. SMITH: I second.

MR. KING: The motion is seconded. Any discussion or further discussion, comments, questions, clarification points?

(Whereupon, on motion duly made and seconded, the Commission approved the recommendation of proposed Table changes related to vasovagal syncope.)

MR. KING: Thank you, doctor. We are moving to proposed changes to the Qualifications and Aids to Interpretation. We have Dr. Rosemary Johann-Liang, and is Dr. Stacy Stryer joining us?

DR. JOHANN-LIANG: Yes.

**Agenda Item: Proposed Changes to the
Qualifications and Aids to Interpretation**

DR. JOHANN-LIANG: We're going to tag-team. This is Dr. Stacy Stryer and myself, and we're going to do this

together. This is the time now to really look at the color-coded document. We're going to walk through it together.

Up to now, you guys concurred on our proposed changes to the Table and its related Qualifications and Aids to Interpretation. But we're also doing some additional things to the QAI, and that's what you're going to be voting on later.

We're taking this opportunity to do this because I think Elizabeth or somebody mentioned before that the current QAI is a little bit disorganized, and it doesn't quite flow. There are things in there that are a little bit missing, things that are redundant, things that are in the wrong place. As we went to work on the Table and the QAI, we really thought this would be a good opportunity to try to harmonize and make it sort of flow a little better, as far as you can flow a VIT. I'll do a little bit of talk about that.

I organized this to make sense. We're not going to go letter by letter; we're going to do this in a conceptual thing of organizing and expanding, the definitions that are proposed, how we're harmonizing. Then there's a section on encephalitis that's missing altogether from the current VIT and QAI that Dr. Stryer is going to

talk about as representing the work group for the tetanus-containing task force members.

Let's start with the organizing part. Now we're in section (a). Section (a) is the actual Vaccine Injury Table. In the first row you can see that purple that says "Any acute complication or sequelae, et cetera, with no applicable timeframe." That is going to be actually under every row. It just makes the table just long.

We are proposing that we move that down to section (b), which is now on page four. It is now a little section (b), provision that applies to all vaccines listed. It says here purple means moving, moved here from each row of the table.

It's exactly the same as before -- any acute complication or sequelae, including death, of the illness, disability, injury, or condition listed in subparagraph A. Remember, (a) is the section that's the actual Table, and defined in subparagraphs (c) and (d), the sections that are coming up now, qualifies as Table injury under subparagraph (a). This is Elizabeth's language. I take no responsibility for that, except when the definition in subparagraph, requires exclusion. We just moved it. That's all.

Then the next thing that I want to tell you is if you go to the last page, which is page eight, we set up a

glossary, which was not there before at all. The glossary really is for the purposes of helping you with Sections (b) and (c). Throughout this QAI there are a number of things that get kind of repeated or concepts that get repeated. We thought rather than trying to repeat them, why don't we have a glossary section so that it can be referable? It's like a dictionary. It's only applicable to what we mean when we say Table.

Injected, for example, what we means as injected, number two, refers to intramuscular or subcutaneous needle administration of a vaccine. But in fact, injected, as a general rule, could mean the bio-injector. We just don't have any evidence of bio-injectors causing SIRVA or anything. Or you could be injecting a vaccine through the nose for nasal administration. We wanted to just make it clear that for the purposes of the Table, we mean needle. That's why the glossary was set up.

MR. KING: Can you just put "only" on that so that you don't have someone come back someday and say it really means all of this? Does it matter? It seems to me you've got it, but then since you made the point that there are other ways to be injected, might someone come someday and not know the true understanding, and by putting in the word "only," it just says this is what we mean.

DR. JOHANN-LIANG: That's fine. We thought this was okay because the glossary is for the purposes of the Table only, so it's a given that we only mean for the Table. That's what the glossary is for.

DR. SHIMABUKURO: Given that there's no intradermal flu vaccine -- you can barely even see the needle, but that's an injectable vaccine too.

DR. JOHANN-LIANG: There were really no reports of that, right?

DR. SHIMABUKURO: It's new. It's only been in use this past season.

DR. JOHANN-LIANG: We don't have any literature to back it up, but conceptually speaking, like hepatitis A vaccine, for example. It's possible. We could include it or we could add it later. Something for the committee to think about as we go through this. Thank you. That's a good point.

Then let's go to number three, says moved from section (c)(2) to glossary. Now that you know what the glossary is, what I want to tell you is that significantly decreased level of consciousness, that definition, chronic encephalopathy, seizure, and sequelae definitions are already on our current QAI, but we've moved them to the glossary because they're referred to more than just once.

For example, chronic encephalopathy is what actually gives you the compensation, because you have an acute encephalopathy or an acute encephalitis, but you need to kind of move on and have a chronic encephalopathy of six months or more in order to be compensated. It applies to both encephalopathy and encephalitis. So rather than repeating it under both sections, we just moved it to the glossary. It's just organizing purposes. Nothing really changes.

Next is expansion. I talked about this before. The current VIT has, under section (c), which is the Qualifications and Aids and to Interpretation section now, nine subsections, 1-9. We are expanding it to 13 because, as you just heard, we're adding things like SIRVA and syncope. These are totally new things, and we end up with 13 sections. And encephalitis, we're defining that. So it's now 13 sections.

If you look at the current VIT that you received before, encephalitis is always kind of together with encephalopathy. But when you actually go to the QAI to figure out what do you mean by that, there's nothing there. This has been a struggle when we're adjudicating cases from our end, as well as down the line for litigation purposes, special master, et cetera, for everybody. So we really took

sort of the posture here that we're defining things so that we're all clear as to what we mean, as far as we can be with the current evidence. That's what's being added.

We added the shoulder injury related to vaccine administration. That's subsection 10 now under (c). We added disseminated varicella-strain virus disease -- that's a brand new thing, too, because there was nothing listed for varicella before -- under subsection 11. We added the varicella vaccine-strain viral reactivation disease as subsection. And we added, as you just heard, the vasovagal syncope as the final subsection, subsection 13. The QAI has been drastically expanded.

Proposed definitions. Aside from what you've heard throughout the day today and that you sort of concurred and did your votes on, there are some additional clarifications and definitions that we're proposing here.

We noticed that under the current chronic arthritis section that is not defined. That's now been defined as what we mean for the purposes of the table as persistent joint swelling with at least two additional manifestations of warmth, tenderness, pain with movement, or limited range of motion, lasting for at least six months. That's chronic arthritis.

You recall that when IOM reviewed this, they actually listed this under inadequate, however under the Guiding Principles we're not proposing to do anything about taking it out or anything. We just want to clean it up a bit and define it.

Next is the section that's already there again, the thrombocytopenic purpura for the MMR section. Let's all go to it. It's a good example to look at. Go to page seven under subsection 7. All the black lettering is what's in the current QAI. Currently it says thrombocytopenic purpura and it's got a bunch of stuff on it. It just says thrombocytopenic purpura is defined as serum platelet count less than 50,000. That's all it says as definition. Really that's kind of incorrect because thrombocytopenic purpura really is a disease state, not just a laboratory value. So we want to add the clinical definition to make this harmonized.

What we're proposing are in the additional language in blue, is defined by the presence of clinical manifestations such as petichiae, significant bruising -- petichiae is like little blood vessels bursting on your skin, so you see these red dots -- or spontaneous bleeding, and by a serum platelet count of less than 50,000 with normal red and white blood cell indices, because, by

definition, thrombocytopenia means very lowered clotting blood cells, not the red cells or the white cells. We did that.

Let's now go to more definitions that we've added, which is under the glossary. We already talked about the injected. This is the one that you should think about, intradermal. That's very reasonable. We just don't have the scientific evidence right now, but again, as Tom mentioned, that's because it's very new.

It doesn't make biological sense to say you would get a SIRVA from a bio-injector because you're not putting anything inside. We're electing not to define that as an injection because we just don't have any evidence. That's kind of how we're thinking. We need to have some evidence, and then we apply the Guiding Principles and go to the Table. If there's really no evidence because things are so new, it's probably not the right time yet, and it's something we can add in the future. That's something I'm thinking. I'm just thinking out loud, but you guys can think about it.

MS. WILLIAMS: Is bio-injector not injected?

DR. JOHANN-LIANG: No. It's an injection, but it's not with a needle. It's like a mechanical push. It's by actually force that goes in through the skin.

DR. SHIMABUKURO: They look kind of like air guns. The ones that you've probably seen they don't use anymore, where they're hooked up to a cylinder. Those were taken off the market because of safety reasons. But I think that the fact that FDA recently issued the guidance that you shouldn't use jet injectors for any vaccine other than ones in which they were licensed for use with a jet injector, which I think is just varicella -- there's just one vaccine that was used. It was used, but the guidances now don't use them for influenza vaccination, which is an IM. You're right. The chance that you would get a SIRVA from a jet injector would be extremely unlikely.

DR. JOHANN-LIANG: I guess my point is intradermal point is a good point, and we may want to add that in the future. But if we're applying the principle, like for hepatitis A, the reason why we're not including that at the current time is because even though it's totally biologically plausible, we just don't have any evidence to single out that vaccine. Then I guess the same logic should apply. We'll add that when we have the evidence, or a little bit of evidence, at least, to work on.

The next thing is definition of immunodeficient recipient. Immunodeficient recipient is under what Dr.

Rubin presented this morning, but it's not defined at all, so we elected to add this to section (d). There is a flavor of immunodeficiencies to varicella, but as we heard in Dr. Shaer's presentation, we really didn't include that as part of what the Table is. But we thought that this was a definition that we should spell out for the purposes of the Table, what do we mean by an immunodeficient recipient. So that's been included.

MR. KRAUS: I have a question about the immunodeficient recipient. The definition, I understand why you would do it that way, but I don't think that the second part is really necessary, the identifiable defects such as absent lymphocytes and severe combined immunodeficiency or decreased CD4 cell counts in acquired immunodeficiency syndrome must be demonstrated in the medical records.

Again, my perspective is petitioner's counsel. I think you covered what immunodeficient recipient is by saying it's an individual with an inherited or acquired disorder resulting from an identifiable defect in the immunological system which impairs the body's ability to fight infections. I think that's a sufficient definition.

I understand when you're reviewing this as your office and medical personnel, "identifiable defect" is going to be something you're going to look to the medical

records to find, but we talked about earlier how some immunodeficient recipients don't know they're immunodeficient until after they have the vaccination.

DR. JOHANN-LIANG: That is a slightly different point. We, in fact, had one like this where the child had a vaccine-strain varicella, but there was no identifiable immunodeficiency identified in the records at all. They did look -- they didn't do a very comprehensive look -- but they didn't find it. We did compensate that child because that was a vaccine viral strain.

That person, though, by definition, is not immunodeficient. Just because you're not found to be immunodeficient doesn't mean we would not look at it and say we wouldn't compensate. What we mean by this is that when you are an immunodeficient recipient, what do you mean?

We want to make sure that when we compensate somebody based upon what their immunodeficient status is, we want to make sure that that is really a disorder that has been identified if we're compensating that person based upon an immunodeficiency, not the other way around. We wanted to make sure that it's a clear definition. So if you're saying that if you go up to "impairs body's ability

to fight infections," period, that would be enough, is what you're saying. Right?

MR. KRAUS: That's what I'm saying.

DR. JOHANN-LIANG: The reason why we added the second part is "identifiable defect," that, again, may need to be clarified. So we are clarifying what we mean by identifiable defect, which means that it's in the records and it tells you what part of the immune system is actually immunodeficient.

MS. WILLIAMS: Then should it be identified? If you are requiring it to be already demonstrated, then it's identified.

DR. JOHANN-LIANG: Where would you want to do that? Resulting from an identifiable defect?

MS. WILLIAMS: I don't know what an identifiable defect is.

DR. JOHANN-LIANG: That's why we on to have the second sentence, to give you an example so that we don't spend time trying to say what do they mean, because a lot of times we don't want to --

MR. KRAUS: I understand what you're saying, but in response I would say that I don't think it adds further clarification. Unless I'm mistaken, there are all sorts of different identifiable defects in the immunological system.

I'm not a medical person, but I think of there being many. You've made the point in defining immunodeficient recipient that it has to be one that's identifiable. The purpose of the second part of that definition --

DR. JOHANN-LIANG: If you guys have a better word -- but we don't want somebody to say I have an immunodeficiency. It's identifiable. We wanted to make sure that it was in the records as articulating certain defect in the immunological defect. Yes, these are only just two examples of a whole array of immunodeficiencies that one may have. One is an example of an inherited disorder, and the other, AIDS, is an example of an acquired immune deficiency.

We're just giving two examples to illustrate what does the program mean when we say an identifiable defect, and that it's in the record. It's not like somebody just says I have an immunodeficiency. We want to make sure that we can actually see that it's there because we have those situations.

MS. DELA ROSA: If I interpreted Ed Kraus' comment, the second sentence is something to do with the litigation of the case itself, not the definition, because for it to be in the medical record, that means it's already on your desk, and you are going to have the case litigated

to determine whether it's compensable or not. If I understand him correctly, we're just looking at the definition of the word, whether it is part of the compensation program.

DR. JOHANN-LIANG: Everything we've looked at is after --

MS. DELA ROSA: I know, but am I understanding it correctly, that the second sentence does not really add to the definition; it adds to the fact that it can be compensable if it is in the records?

DR. JOHANN-LIANG: All these definitions in the glossary is for the purposes of the program and Table. What do we do? We compensate. You may define immunodeficient recipient in slightly different ways if you're a physician at the clinic, but this is for the purpose of our Qualifications and Aids to Interpretation for the purpose of the Vaccine Injury Table.

When we consider an immunodeficient recipient, this is what we mean. We want to be very clear. The whole point of the definition is to clarify. We don't want to try to do that by trying to clarify something, and then result in something even more unclear, such as an identifiable defect. If there's some other word, we're open, but we really went around and around. This is really the best we

can do. The second sentence is really there to give an example of an inherited immunodeficient that's identifiable and acquired and just to make very clear what we mean. That's all it is, is nothing more, nothing less.

MS. DELA ROSA: The thing is, the person who received it, to repeat what I understood, may not know they have the deficiency. It's only after they get disease.

DR. JOHANN-LIANG: Yes, but it would be in the records.

MS. DELA ROSA: It may not be in the records in the beginning.

DR. EVANS: It doesn't matter.

DR. JOHANN-LIANG: It doesn't matter. It's at the time that we review the records when the claim comes in. If the claim comes in saying they're immunodeficient recipient, we're saying that we need to have something to verify that.

MR. SMITH: I'm going to follow up Ed's point now. It may be belabored a little bit much. Maybe demonstration of whatever fact it is in the medical record, is it redundant or not? In other words, even the definition of "injection," for example, is the intramuscular subcutaneous needle administration of a vaccine. We don't say there that has to be demonstrated in the medical

records, but I would assume that as a reviewer, I want to see the medical record to show that, in fact, you were administered or injected with the vaccine. Is there something particular about immunodeficiency that would require that clause, which I think most people are reacting to, in this particular subparagraph versus maybe some of the other ones?

DR. JOHANN-LIANG: Yes and no. As you'll see later, some of the redundancy we found -- and this is a redundant thing. There is a section on page five where it says, "In determining whether or not an encephalopathy is a condition set forth in the Table, the court shall consider the entire medical record." We're proposing to remove that because it's assumed that, of course, we're reviewing the medical records.

The reason I say this in this particular immunodeficient recipient is we have had many cases where patients say I'm immunodeficient in their affidavits, but it's not per the record. We can't identify what that immunodeficiency is. The medical officers who we talked about this at length thought that for this particular definition, when we say "identifiable defect," where is it identified? What are you identifying?

What we need is in the records we must be able to verify either something that shows you had an inherited disorder or something that shows you that you had an acquired immune deficiency. That's why this was inserted. It's really up to you guys. If you think that it's very crystal clear based upon the whole set of QAI that we don't need to articulate that again, we don't have to.

DR. DOUGLAS: I would vote to have it in, especially since you have the two different kinds. I think that'll just help people up front.

MR. SMITH: Maybe for clarity, just listening to some of the comments, it doesn't matter if it's in the medical records either prior to or after the vaccine administration. It's just got to be in the records.

MR. KRAUS: My point would be that the examples you gave, those are not identifiable defects. My petitioner in an affidavit saying I'm immunodeficient, that, to me, if you're a medical person reviewing that and there's nothing in the medical records that shows any evidence of the immunosuppression, then it's not a Table injury.

Again, adding it, I can understand why you would think it provides additional clarity. Maybe it does. I think the concern I would have is that it implies a greater

level of proof or evidence that you need to provide than is being asked for in other definitions.

MS. WILLIAMS: It seems that if the identified defect seems to be precluded, that it could not be established by an expert. So if you had an expert who is willing to say this person has a defect, but we don't have anything in the medical record, but I'm an expert and that's my conclusion and I want to put that conclusion forth, that would be precluded.

DR. JOHANN-LIANG: That would not be an immunodeficient recipient. It gets very murky. We want the patient to show that they had immunodeficiency if they're claiming an injury because of immunodeficiency. Your point is very well taken. Do we really need to say those medical records again, especially since we're proposing to not be redundant and we're trying to harmonize? In this particular definition -- and we've actually had many meetings about this and thoughts -- we thought that this is the most clear that we can present what we mean when we say an immunodeficient recipient.

MS. DELA ROSA: Wouldn't it be when you give the response, that you're denying this because you're not able to prove that you are immunodeficient? Wouldn't the other party then proceed to have themselves tested to show that

they are or they are not? But it's still part of the litigation process.

DR. JOHANN-LIANG: If they can go in and show, it will be in the medical records then.

MS. DELA ROSA: I know, but it's part of the litigation process already. It's not part of the definition of who a immunodeficient person is. It's the simplest statement from them with no medical proof. Your part would simply be saying no, this is not compensable.

DR. JOHANN-LIANG: No, it doesn't go like that. We review the records, and there's very rarely where we have complete records. There are many opportunities to request further records. It's not like we look at whatever's before us and we're done and we have a decision. It doesn't really work like that.

MS. DELA ROSA: I am not saying that. All I'm saying is that in the process you'd say you're claiming you're immunodeficient, but you don't have the proof. So therefore you say at this point we can throw this case out because you don't have the proof. Then the other party, the petitioner, then will turn around and proceed and prove, get all the tests and whatnot. Then if they prove that they are immunodeficient, then it goes into their record. But I think our point here, if I understood you correctly, is

that second sentence there is part of the litigation process. It is not defining who an immunodeficient person is.

DR. JOHANN-LIANG: It's defining the identifiable defect, what we mean by that.

MS. DELA ROSA: Then you should then remove the medical presence of it in the medical record. You just simply define what that identifiable deficiency is, but it doesn't have to be in the medical record.

DR. JOHANN-LIANG: Where else would it be?

MS. DELA ROSA: You're just saying that the letters of the alphabet are a, b, c, d, e, but they don't have to be written anywhere at this point.

DR. JOHANN-LIANG: Let me direct you to page six. Under chronic arthritis look at the way the current chronic arthritis is written. It says there, too, medical documentation -- this is what's there currently -- recorded within 30 days after onset of objective signs and acute. We are talking about a medical legal program. When we define terms, we want to be clear, and when we define terms, it's for the purposes of adjudicating claims.

So because we have a claimant who say that they're immunodeficient of this and that and that, but based upon the review of the records, there is no proof

that they're immunodeficient, it's not fair for somebody else who's actually immunodeficient to have all sorts of other people claim they're immunodeficient without documentation. We wanted to make sure in that particular definition we were very clear as to what we mean when we have claimant that says they're immunodeficient recipient.

That doesn't mean if based upon our review of a certain case, even though there is no documentation, we, looking at it, say this person was injured by the vaccination, the fact that they did not get good care and somebody could just not figure out what's going on doesn't mean we can't compensate them. But when we define an immunodeficiency or immunodeficient recipient, we're telling that for the purposes of adjudication, this is what's required when you're coming in saying you're immunodeficient. That's a little different.

DR. EVANS: When you said twice, your case will then be dismissed.

MS. DELA ROSA: But you always get the response that you don't have the proof, so therefore the respondent would then try to move it to be dismissed.

PARTICIPANT: The responder is trying to move you to get the proper documentation as outlined in the Aids to Interpretation so your case can be adjudicated.

DR. DOUGLAS: I would like to add, this is an aid to interpretation, and I'm reflecting on two things. Someone referred to this process as a funnel, that it starts here and it goes down with people who apply and what actually gets adjudicated at the end.

Also, we've had in previous briefings how very long it takes. Even on average, it's a very long time. I see this as something that we'll just cut down some time of that turnaround, of that reapplication, of me not understanding, anything that we could do to cut down on that time. I'm thinking those four lines would be helpful to that end.

DR. EVANS: Absolutely, and from day one Chief Special Master Golkiewicz used the word "frontloading" repeatedly, meaning you give us all the information you possibly can from day one so we can get your claim through as quickly as possible.

MR. KING: Charlene, I think you kind of crystallized something there. Ed, I don't know if this is completely satisfactory to you, but I'm wondering if, by chance, that in this particular example, because we're naming such as and we don't really do that anywhere else, if we should just have it that the identifiable defect must be demonstrated in the medical records. I don't know

whether you say whether it be acquired or be a severe combined(?), in other words, if we want some consistency. But I don't think that's going to address what Ed's thinking, but I'm just wondering from a consistency point of view, should we eliminate --

DR. JOHANN-LIANG: To me, an identifiable defect for someone to be an immunodeficient recipient is very clear, but the purposes of having the examples there is so that we are all thinking about the same thing.

DR. DOUGLAS: Also, you defined arthritis. As I tell my students all the time, when I say immunocompromised, don't let your mind always run to HIV. That's not what I'm talking about. I'm talking about somebody with cancer. I'm talking about somebody who had cancer treatment. I'm talking about someone who just has a defective lymph system, someone who has a cancer of the blood. It could be a lot of things. I don't think we're trying to nail somebody with any one particular thing. I see it as a point of clarity similar to that definition given for arthritis. We can all say I've got a touch of arthritis, but you gave it in a couple of lines.

DR. EVANS: That's the point, a touch of arthritis, a touch of lumbago, a touch of this and that, and there are all kinds of definitions of what conditions

are. We're putting definitions that a room full of immunologists would agree are clear-cut diagnoses of immunodeficiency, whereas in our cases fairly often there are allegations of immunodeficiency where there are none.

DR. SHIMABUKURO: I think having that line in there where it says must be demonstrated in the medical records, I think that would help with the frontloading of the process. Somebody reading this, it puts them on notice that if you're going to claim that you're immunodeficient, it would behoove you to have this document in your records when you enter into the process, as opposed to getting that later on. I can see Ed's point that it maybe doesn't happen that much, but I think having this language in here about you need to have this demonstrated in your medical records would be helpful as far as that --

DR. JOHANN-LIANG: We could just say the identifiable defect must be demonstrated in the medical records and leave it at that. That's fine. These were only just given as, as I said, one as an example, one as an acquired example. It could be other examples. They were just given as a very common example of when we think about an immunodeficient person. That's fine too. Do you guys want to think about it as we keep going?

MR. KING: We should make a note if we're going to come back to it, I guess, unless you guys want to make a recommendation on that specific point now. I'm thinking that if we bypass it, we get confused with other issues. I'm thinking that we ought to just come to a conclusion on how we want that worded right there.

MR. SMITH: I agree with Tom. I think it switched for me when he explained it that way. In most cases, having not represented petitioners, but you would think that you have to bring the right documentation to justify your injury, the date of vaccination.

I think this provides some more clarity to the petitioners that if I'm going to make an allegation about my particular status as a vaccine recipient, I should bring forward very early on in the case documentation to support that as well. To me, I think it actually provides some clarity, and there's a reason why we identify it in this definition that Dr. Liang kind of described. I actually think it's good, having heard Tom.

MR. KING: So we keep the wording as it currently is?

DR. FEEMSTER: I support keeping the wording as it is, again, for clarity. I also think it can be helpful to provide some examples, recognizing that it's obviously

not any kind of exhaustive list. But I can think of examples of patients saying that I have a weak immune system because I have a history of having frequent infections or viral infections or something that doesn't necessarily pertain. I think providing some examples is helpful as well. I think clarity is important, so I support keeping the wording in as it is.

DR. SHIMABUKURO: If you want to clarify it even further that you're saying these are examples, you could just say an example of an inherited defect is SCID and an example of an acquired -- just specify it. An example of an inherited defect is this. An example of an acquired defect is this. And just make a separate statement about you need to have this document in your medical records.

DR. VILLAREAL: It's just wordsmithing, so what it would read is, "Defined as an individual with an inherited, such as absent T lymphocytes, or acquired, such as decrease CD4." Then the rest of the sentence, "the identifiable defect," you exclude all of that, and, "must be demonstrated in medical records." So you just give the example up front just like Tom's saying, and then you just end, because I think we're just into the semantics of when you've defined it.

MR. KING: Are we good with that? When we eventually get around to saying, that's the wording that we're going to want to work with. Has that been captured enough to where you've got it?

DR. JOHANN-LIANG: Yes.

MR. KING: Then let's move on.

MS. WILLIAMS: I have one more comment. I'm just contemplating that the defect has already been identified. To me, identifiable means it could be identified in the future. If you want something that's already been identified, isn't it just identified, not identifiable?

MS. WILLIAMS: It could happen after the vaccine, but it'll have to be identified --

MR. KRAUS: Your point is at some point it would have to be identified.

DR. DOUGLAS: But identified means it's already established, and we're saying it does not necessarily have to be established at the time of the vaccine.

MS. WILLIAMS: But it has to be identified the time of the petition.

DR. JOHANN-LIANG: We'll work with the wording. Shall we move on?

MR. KING: Let's move on.

DR. JOHANN-LIANG: We've done some organizing. We've done expanding. We've done definitions. Now we're going to try to harmonize. Under subsection (c), which is the QAI body, subsections 2 and 3, I talked about the fact that we're going to have acute encephalitis and acute encephalopathy be there, but then we've moved chronic encephalopathy because they both pertain to leading to chronic encephalopathy. That's that bullet.

The next one is that we are taking out some redundant wording that's on page five. We say this before under encephalopathy, and also that green stuff that's coming out is what the statute says about the preponderance of evidence. As we said, we don't need to articulate for every section, that everything must be identified in the records, because that's what we're going by.

On this we're talking about certain definitions, and when you define something, that claim really needs to be articulated in the records, as we just discussed, for the immunodeficient recipient. That's what that second bullet means.

The third bullet, let's go to page six, which is the brachial neuritis. Brachial neuritis is on the Table already, and nobody really talked about it today. But in the course of writing up SIRVA, everyone felt that this is

a section that really needed to be tweaked a bit, and so it has been tweaked to a similar kind of structure as SIRVA. None of the content really has changed. It's just been reorganized to look similar to subsection 10, which is the shoulder injury.

That's subsection (6), which is brachial neuritis. Do you see that? The green stuff is coming out, and then the blue stuff is being added and being organized. It's just to make it more clear and to spell out things like what the studies are, NCS, and what EMG and all that is, and that it harmonizes with the SIRVA. Do you want me to read through it? What would you like for me to do? Or is it okay for you guys to take a look?

Actually, Dr. Ryan worked on this part, too, because he was a SIRVA person, so he took the task of reorganizing brachial neuritis. Tom Ryan, do you want to add anything regarding brachial neuritis section, as you reorganized it.

DR. RYAN: No. I don't think so. I think our intention was to clarify what is already there and lay it out in a systematic fashion.

MS. WILLIAMS: Is (i), (ii), (iii), (iiii), is there an "and?" Is it missing an "and"?

DR. JOHANN-LIANG: There is an "and" after the little iii. Do you see that on page seven?

MS. WILLIAMS: There should be a semicolon after --

DR. JOHANN-LIANG: That's a little subsection under (2).

The last bullet over here is that we actually we also did a little minor technical changes to update medical language as well as be mindful that we're no longer just in a child claim program, that we have a lot of adolescent and adult conditions. So for some of these exclusion criteria, we wanted to be mindful of things that matter that's not just the kid screening, but that there are symptoms of dementia was added, stroke, migraine, drug use for our adolescents.

Actually, under the chronic arthritis -- and now I'm talking about page six. If you look in the middle section under chronic arthritis, that juvenile rheumatoid arthritis now is being replaced with juvenile idiopathic arthritis because that's what the medical language is now. It's been changed.

We also added under the glossary the definition for seizure, the pseudo-seizures, because as far as we know the medicine currently, that is not something that's really

even a seizure; that's a part of a convergent disorder due to psychological or psychiatric issues. So we just did some technical changes with that rationale in mind.

What I propose to do now before we move on to acute encephalitis, just so that everybody can be clear, is let's briefly go through each of the sections of the QAI so that we're all synchronized and harmonized. Shall we? Let's go to our color-coded package.

On page four -- this is now at the end of the Table -- I reviewed with you why we did the (b), and under section (c), which is the body of the QAI, number one is anaphylaxis. You've already voted that that's okay. Number two is encephalopathy. Basically these are all just technical changes to make it word better. I shouldn't be doing this. Encephalopathy part is going to be gone over by -- so let's just skip the encephalopathy part and encephalitis and go to page six.

The intussusception, that came before you guys, is now being worked on in a separate NPRM, so we'll just leave it out for now. That's number four. Number five is a chronic arthritis, and we just talked about the fact that we added a definition and we changed rheumatoid to idiopathic, and at the very end we took out that green, but that we added -- it's just to make it words sound better.

Number six is brachial neuritis, and we talked about the fact that we took that kind of a mumbo-jumbo paragraph and organized it better into little sub-bullets. Number seven is thrombocytopenic purpura. Now I'm on page seven. We talked about the fact that we added the clinical definition to the platelet count requirement.

Number eight is a vaccine-strain measles viral infection that Dr. Rubin went over with you that you guys already voted to approve. Number nine we didn't say anything, except to write this term. You can see that that was a big contribution to that. Number ten is SIRVA, which you guys voted on already.

Moving on to page eight, number eleven and twelve were part of Dr. Shaer's presentation that you guys voted on already. Number thirteen is a vasovagal syncope that you guys voted on already. Then (d) is a section for the glossary that we talked about, and Dr. Stryer will talk about the chronic encephalopathy that moved over from -- nothing changed, it just moved here.

We talked about the injected definition. We talked about the immunodeficient recipient definition at length, and then the significant decreased level of consciousness. Again, nothing changed. We just moved that over here from encephalopathy.

That's really it. It looks like it's a lot, but mainly it's a lot of ads. It's, as we talked about, organizing, expanding, harmonizing, and definitions. Now I'm going to turn over to --

MR. KING: I'm thinking we might want to take a quick break here. Is 10 minutes enough time? We'll do a 10-minute break.

(Brief recess)

MR. KING: The meeting is picking up after the break, and we are getting started. It's a different speaker, but the same topic. We have Dr. Stacy Stryer speaking to us.

DR. STRYER: Thanks. Here we go. Although Dr. Johann-Liang actually spoke about some of this earlier, I'm going to talk about encephalopathy and encephalitis and how it pertains to acellular pertussis-containing vaccines. We heard earlier this morning that the 2011 IOM committee concluded that the evidence is inadequate to accept or reject a causal relationship between acellular pertussis-containing vaccines and encephalopathy or encephalitis.

There was much discussion and some debate in the early 1990s about whether to retain encephalopathy and encephalitis on the Vaccine Injury Table for pertussis-containing vaccines. In the end, the secretary decided to

keep it on the Table. This was based mainly on a 10-year National Childhood Encephalopathy Study that was done in 1979 and then a follow-up study that was published in 1994. More recently, in 1996, a large-scale study failed to show a relationship between whole-cell pertussis-containing vaccines and encephalopathy or encephalitis.

Acellular pertussis vaccines were developed because of concerns of neurologic events with whole-cell pertussis-containing vaccines. They were initially licensed in 1996 for use in infants who were less than 12 months of age, and today they've become the vaccine recommended and really the main vaccine used for all infants, young children, teens, adults, and even the elderly.

Toxicologists believe that the components in whole-cell and acellular pertussis vaccines should be treated as separate entities. Acellular pertussis-containing vaccines have pertussis toxin that has been inactivated to a toxoid. They also have a significantly reduced amount of other constituents, including known neurotoxins.

Whole-cell pertussis has 3,000 bacterial proteins, including endotoxin, that are not in acellular pertussis vaccines. There are also animal studies that show differences between these two types of vaccines. Clinical

studies with acellular pertussis-containing vaccines show a significant decrease in several side effects, including crying, fevers, fussiness, and febrile seizures.

A study that was included in the 2011 IOM report published by Yih et al. evaluated adolescents and adults who had encephalitis, encephalopathy, or meningitis within 42 days of Tdap vaccination. The number of cases of the adverse event in the acellular pertussis group was actually less than a historical Td cohort that contained no pertussis.

They looked at people between the ages of 10-64 years of age, and the number of subjects was 660,000 subjects. The number of cases of encephalopathy or encephalitis or meningitis in the group that had received the vaccine was 34, compared to the historic group that received the vaccine without the pertussis was 40.3.

Large-scale epidemiologic studies did not show an increased risk of these events, but their data was based mainly on a passive surveillance system. No appropriate epidemiologic study has been done that evaluates acellular pertussis-containing vaccines in infants and children.

We know that there's concern regarding severe neurologic effects after whole-cell pertussis-containing vaccines, and that that was a paramount reason for

developing the Vaccine Injury Table. So at the current time -- and following the Guiding Principles -- no changes are proposed to the Vaccine Injury Table. We are, however, proposing to add the definition for encephalitis.

If you look at the references, the first two studies by Miller are the National Childhood Encephalopathy Study and the 10-year follow-up. The third study by Ray et al. is a study that was published after the early 1990s where they had over 2 million cases that they reviewed, and found that of these 2 million cases, they did not see an increased risk of encephalopathy or encephalitis after receiving whole-cell pertussis or measles vaccine compared to a control group.

If you go to the next page, the last reference by Donnelly et al. is one of the animal studies that was done. In this study Donnelly et al. tested the hypothesis that seizures induced by whole-cell pertussis vaccine are mediated by interleukin B1 in the brain in response to active bacterial toxins that are present in whole-cell pertussis vaccine, but not in acellular pertussis vaccine.

They found that there was fever, seizure activity, and increased interleukin B1 activity in the brain of those mice who were injected with whole-cell

pertussis vaccine, but not in those who were injected with acellular pertussis vaccine.

I'm now going to briefly discuss encephalopathy and encephalitis and the MMR vaccine. The 2011 IOM committee assessed that based upon available evidence, the epidemiologic evidence is limited. The mechanistic evidence is weak, and it's based on our knowledge about both natural infection and a few case reports.

Natural or wild-type infection with measles, mumps, and/or rubella virus resulting in encephalopathy or encephalitis occurs through damage to the neurons by direct viral invasion. In vaccine-associated encephalopathy or encephalitis the mechanism is direct viral infection and/or viral reactivation, particularly in immunocompromised patients.

The publications that were available did not provide evidence linking these mechanisms directly to the MMR vaccine strains. There was detection of either viral antigens or antibodies, but the specific vaccine strain was not identified, and it's similar to what Dr. Shaer talked about earlier this morning with the varicella vaccine and the identification of strains.

The committee concluded that the evidence is inadequate to accept or reject a causal relationship

between MMR vaccine and encephalopathy or encephalitis. The task force working group for MMR, after reviewing the evidence from the IOM report, concluded that under the Guiding Principles, this adverse event should remain on the Table, again, with the definition added for encephalitis.

These references are the studies that were used by the IOM committee. If you look at the second one down, the Ray et al., this is the same study that I discussed with acellular pertussis with the 2 million records that were used to identify patients who had received either a DPT or an MMR vaccine within 90 days of developing encephalitis, encephalopathy, or meningitis. Again, the number of patients in this group did not differ from a control group. So there was no increased risk of developing any of these neurologic disease.

These three studies on the second page are what were used for the mechanistic evidence. As you can see, all of them are in immunocompromised patients. As one example, Bakshi et al. described a case report of a 16-month-old boy who presented with focal seizures, left-sided paralysis, and a left eye gaze preference 5 months after he received an MMR vaccine and 3 days after he underwent a bone marrow transplant.

He was given the vaccine five days before he was diagnosed with an immune deficiency. Mumps virus was found in urine, serum, and CSF, and the patient was diagnosed with meningoencephalitis. He died two months later.

Now I'm going to switch a little bit. We didn't make any changes to the Table, but we just kind of wanted to talk about what the IOM committee -- kind of look at the evidence they had and some of the evidence when we went searching through the data afterwards, some of the evidence we found and some of the studies we found. So we made no recommendations to remove anything or to change the Table itself, but we are making some recommendations for the QAI.

In terms of the encephalopathy QAI, turn to page four. As Dr. Johann-Liang discussed before, really we haven't changed the definition or the main substance for the encephalopathy QAI. We just chose to simplify it and clean it up to make it easier to understand and easier to read, and we moved things around to where it just seemed to make more sense. Instead of reading the actual QAI, I'm just going to go through what we did.

We removed repetitive themes and sentences. There was a statement that said, "Increased intracranial pressure may be a clinical feature of..." because it really had no impact on whether someone was diagnosed with encephalopathy

or not or whether it was a Table injury or not. We defined seizure in the context of encephalopathy and encephalitis and we put that in the glossary.

We added adult illnesses -- recognizing that this doesn't just occur in children, but that it occurs in adults -- that would lead to exclusion as a Table injury. A couple of examples are: transient ischemic attacks, stroke, complex migraines.

We moved the definitions for significantly decreased level of consciousness and chronic encephalopathy to the glossary, and really the only change we made in the definition was we added the term "encephalitis" to chronic encephalopathy. Are there any questions so far about any of this?

DR. VILLAREAL: When we're looking at the level of consciousness, do we use anything like a Glasgow scale? I assume in the literature there are parameters for us to know the level of consciousness.

DR. STRYER: No, we don't use a Glasgow scale; we use clinical criteria, so exactly what you see in the glossary here for decreased level of consciousness. If you guys look at the very end, page eight -- and this was in here before, so we didn't change it; we just moved it.

Significantly decreased level of consciousness is indicated by the presence of one or more of the following clinical signs: decreased or absent responses to the environment; responds, if at all, only to loud voice or painful stimuli; decreased or absent eye contact, does not fix gaze upon family members or individuals; or inconsistent or absent responses to external stimuli, does not recognize familiar people or things. This hasn't changed from previously.

As we discussed earlier, the current QAI lists the encephalitis as a Table injury, but it does not include a definition, so we've developed and are now proposing a definition for encephalitis. It's a very long -- not so long, hopefully -- definition on page five to six. Instead of reading the whole thing, I just want to talk about the major points, and then you can ask questions and take a look at it in the paper that you have.

In order to meet criteria for a Table injury for acute encephalitis, a petitioner must demonstrate two things. They must demonstrate an altered level of consciousness or other neurologic deficit by exhibiting either evidence of an acute encephalopathy, which we discussed already; or a neurologic sign that is referable to the central nervous system, including focal cortical

signs, cranial nerve abnormalities, visual field defects, primitive reflexes, or cerebellar dysfunction.

In addition, they must have evidence of an inflammatory process in the brain, which must include either cerebrospinal fluid pleocytosis, which means an abnormally high number of white cells in the spinal fluid, or at least two of the following: fever, which is defined as at least 100.4 degrees; electroencephalogram findings consistent with encephalitis; neuroimaging findings consistent with encephalitis or parenchymal inflammation. We gave in the definition examples of EEG or Neuroimaging findings that would be consistent with encephalitis, but it was just one example.

Encephalitis cannot be due to another cause as shown by a preponderance of evidence. To meet criteria for a Table injury, sequelae must persist at least six months or a chronic encephalopathy must ensue the illness.

We came up with this definition by looking at four major references. The first is Ford-Jones, and that's the Brighton criteria. We looked at that. We also looked at the Tunkel et al. article, which is the Clinical Practice Guidelines by the Infections Diseases Society of America.

The Ball et al. article was a development of case definitions for acute encephalopathy, encephalitis, and

multiple sclerosis reports to the VAERS system. Then we also found another supporting document by Johnson et al., Clinical Infectious Diseases.

MS. WILLIAMS: I defer to the litigators, but a preponderance of evidence, is that introducing now a legal standard into a medical definition?

DR. STRYER: That language was taken directly from the encephalopathy definition, so it's been in there forever.

MS. WILLIAMS: I still have a question. Does that mean that there has to be a legal determination in order to have that for the definition?

DR. DOUGLAS: As a provider, that doesn't sound legal to me. The fact that you're saying it's a legal standard of something is news. It says that as a review, on the whole, the case must be made using this.

DR. JOHANN-LIANG: That specific language is really taken directly from what's already there.

PARTICIPANT: I thought blue wording were additions.

DR. JOHANN-LIANG: Yes.

MS. WILLIAMS: So it's not already there.

MS. STRYER: The entire definition is new. It was taken from the encephalopathy definition. The encephalitis definition is a new definition, so all of this is blue.

MS. SAINDON: If you turn to page five, you'll see the exact same language under number (2)(i) in black. It's new and it's old.

DR. JOHANN-LIANG: If the question is, is it legal language that we're using, that's not what we had in mind. When we look at the entire record and we find that it was caused by something else, then we can get presumption that it's due to the vaccine. That's what we mean. But as far as what it means legally, that's up to you. We could just say the evidence shows.

MS. LINGUITI PRON: Change it. Take out the word.

MR. KING: If you take out the word "preponderance" and just say the evidence shows -- I think preponderance is saying that a significant amount of the evidence shows. If we just say the evidence shows, what we're really saying is it could be a little piece of the evidence.

MS. LINGUITI PRON: Find another word, if that's a legal word. If that's going to create a problem, just find a different word.

MS. WILLIAMS: It was just a question. I'm not making a suggestion, because I'm not a litigator, but I do know enough to know that "preponderance of the evidence" is a legal term that's now introduced into a medical definition. Maybe the suggestion would be to talk to the special master, to the litigators.

MS. SAINDON: I think we can bring that back to DOJ, because I think there are still other components that need to input into the draft, so we'll definitely provide that.

DR. SHIMABUKURO: If you say the evidence indicates or suggests, is that too weak?

DR. DOUGLAS: Once again, as a provider, this is news that that is a legal level of something, that it just speaks to the body of the evidence, on the whole, the case is made.

MS. WILLIAMS: What I'm trying to avoid is having this definition become something that has to be litigated as to what its meaning is every time you use it, because that would defeat the purpose.

MR. KRAUS: I think Michelle's got a good point. Regardless of whether it can be used outside the legal context, it does have a specific meaning. Since this is medical and legal, it would seem to me to be clearer to

just say if after evaluating the entire medical record, it is shown that -- it doesn't really add anything. It does stick out.

MR. KING: Can you just put the word "most" in, most of the evidence?

MR. KRAUS: I don't think you have to refer to the evidence, just it shall not be considered to be a condition set forth in the Table if, after evaluating the entire medical record, it is shown that it was caused by --

MS. WILLIAMS: I would make that same comment as to the encephalopathy.

DR. JOHANN-LIANG: The unintended consequences are something we can't predict, but from what we've learned thus far, if we could try to, as much as possible, not avoid it, then we tried. Point well taken.

MR. KING: Am I to gather that what we're saying here is that we want to remove the word "preponderance?"

MS. WILLIAMS: We're not going to do anything.

DR. JOHANN-LIANG: This is what we're proposing that you guys give us concurrence, obviously with comments, the section that we just talked about.

MR. KING: It is time for a vote.

DR. VILLAREAL: Just clarification. For your page-four encephalopathy versus the three encephalitis,

since I've been doing this for 30-some-odd years, we really got rid of increased intracranial pressure for anything? Because if you look at old data, that's the only way, because some of us didn't have MRIs when we went to med school. So really all it is now is this standard for the diagnosis of encephalopathy and encephalitis, not even ICP.

PARTICIPANT: It's not going to be a sole finding, just like a bulgy fontanel.

DR. VILLAREAL: Correct, but I'm just looking at evidence-based medicine. I'm trying to say what do you say to a clinician that meets these criteria? Because we got a point earlier in rural communities and do we have MRIs, and the answer is for some infants, no. Anyway, it's just a clarification. So that's been deleted. Thank you.

MR. KRAUS: I have always stumbled over the language that says in the definition of encephalopathy -- so this isn't new, but we are talking about it. Little (i) under encephalopathy, acute encephalopathy is one that's sufficiently severe so as to require hospitalization, whether or not hospitalization occurred.

DR. STRYER: That's been deleted. It just says acute encephalopathy, and then it's four children less than 18 months of age.

MS. WILLIAMS: Nobody gets hospitalized anymore.

DR. EVANS: The reason it made sense at the time is because the neurologist that was helping guide us through this, the neurologist that happened to be a commission member at the time, a national authority on DTP vaccine and adverse events, made very clear that any child who had acute encephalopathy would be sick enough that they would need hospitalization.

MS. WILLIAMS: That was before we had observation status.

MR. SMITH: I move that the ACCV recommend moving forward with proposed changes to the QAI PCV with consideration of the comments previously discussed.

MR. KING: Do we have a second to that motion?

MS. WILLIAMS: Second.

MR. KING: The motion is seconded. Is there any discussion or further discussion, comments, questions, regarding the motion?

(Whereupon, on motion duly made and seconded, the Commission approved the recommendation of proposed changes to the QAI PCV.)

MR. KING: Thank you very much. Well done. I'm prepared for us as a group to continue to press on on the day's agenda and work to complete. The additional task

force deliberations, including GBS/Influenza Vaccine. Dr. Tom Shimabukuro will be the speaker.

**Additional Task Force Deliberations - Including
GBS/Influenza Vaccine**

DR. SHIMABUKURO: I'm Tom Shimabukuro with the Immunization Safety Office at CDC. I'll be presenting on behalf of the entire task force. Before I begin, I just want to thank all my colleagues at HRSA, especially Ro who really shepherded us through this process, and thank my colleagues back at CDC -- some of them may be listening now -- for all of their contributions to this and also thank them for the work they're going to be doing in the future as well.

I'm going to be talking about vaccine/adverse event pairs where no action or limited action was taken in the case of GBS deferred following the phase two review. This is a snapshot of the vaccine/adverse event pairs that I'm going to go through, just to give you a preview. I'm going to go through most of these pretty quickly, with the exception of GBS, which is a little longer and a little more detailed.

I'll start off with the first one on the list. That was live attenuated influenza vaccine and exacerbation of reactive airway disease episodes in children less than

five years old. The IOM causality conclusion was the evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than five years of age.

The reason this went on to phase two review is there is some evidence from studies -- and this is really wheezing episodes -- that there was an increased risk of wheezing episodes in the youngest children, very young children, following administration of LAIV. There's no evidence that exposure to LAIV causes asthma or reactive airway disease. It's really that it was noted that there some wheezing episodes in the youngest children.

After our phase two review, we decided that no VIT revision was indicated. The justification for this was really the risk was limited to children in an age range, really less than two years old, for which LAIV is not currently licensed. The reason it wasn't licensed was largely on the basis of the data from the licensing studies, which will show this increased risk, and there really was not this increased risk for wheezing in older children or adults.

In addition, there was really no evidence of long-term sequelae from these wheezing episodes. Given that

the vaccine is not licensed, and therefore shouldn't be administered in this age group, with no evidence of long-term sequelae, we did not feel that this warranted a VIT revision.

The next vaccine/adverse event pairing that I'll get into is trivalent inactivated influenza vaccine and febrile seizures in young children. Actually, the last ACCV meeting I went over the data on this. The IOM causality conclusion was that the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and seizures. They look at seizures in general; they didn't look specifically at febrile seizures.

During our phase two review we noted that IOM had initiated its work prior to the 2010-2011 influenza season, which is really last season because we still are in influenza season, and therefore did not review the data from the 2010-2011 season.

During the season there were signals that were detected for febrile seizures in VAERS data mining and also a signal for seizures in general in the Vaccine Safety Datalink in young children. Further evaluation in the VSD indicated that these were febrile seizures.

The outcome for 2010-2011 was specifically febrile seizures in children six months to four years old.

That's what we were monitoring in VSD, and the signal in VAERS was in young children. This was not observed for prior seasonal TIVs.

Some additional information is that the risk was highest when TIV and PCV13 -- that's the 13-valent pneumococcal conjugate vaccine -- were co-administered, although there was some relatively small increased risk for TIV alone and for PCV alone, plus or minus other -- it's actually TIV plus or minus other vaccines without PCV13 and PCV13 plus or minus other vaccines, but not TIV.

The justification for the phase two decision was really the same justification for febrile seizures for MMR. I'm not going to get into that, but really these febrile seizures are no different. They're simple febrile seizures, no different than febrile seizures children experience following MMR. In fact, when we did the VAERS review, we reviewed 42 reports of febrile seizures in young children, and we documented that all of those 42 children fully recovered from their episode.

This is the graph. Again, I showed this previously, but this actually is a nice graph. It's from a paper on the VSD study. Tomorrow when I give the agency update, I'll give you the reference for this paper. I also

have a hard copy of this paper, which I can make copies for people who are interested in looking at it.

This is from the Vaccine Safety Datalink. You see on the y-axis the risk difference, which is similar to an attributable risk. On the x-axis you have age in months. You can see there that the highest risk is in that age group that I previously mentioned is at highest risk for febrile seizures in general.

You can also see that the risk is highest for concomitant TIV and PCV13, so when those two vaccines are given together. The excess risk is on the order of 45 excessive febrile seizures per 100,000 children vaccinated. Below the red dotted curve you can see the curves for TIV and for PCV13 when those two vaccines are not administered together.

Now I'm going to move on to influenza vaccine and GBS. IOM causality conclusion was that the evidence is inadequate to accept or reject a casual relationship between influenza vaccine and GBS. Issues that the task force considered was that the 1976 swine influenza vaccine was not included in this IOM report because the IOM had addressed that in a previous report back in 2003. This particular IOM committee was charged to consider seasonal influenza vaccines. I will say that IOM did conclude that

there was a causal relationship between 1976 swine influenza vaccine and GBS. It was on the order of excess risk of ten per million persons vaccinated.

The IOM initiated its work prior to the H1N1 pandemic, and therefore did not evaluate 2009 H1N1 monovalent vaccine pandemic H1N1 vaccine. I'll just refer to that as H1N1 vaccine from now on.

The H1N1 strain has been included in the seasonal influenza vaccine for 2010-2011 and for 2011-2012, the current season. VRBPAC recommended that it be included in the 2012-2013 seasonal influenza vaccine as well. So it will have been included in three seasonal vaccines, possibly even more, depending on the VRBPAC recommendations for subsequent seasons.

PARTICIPANT: What's VRBPAC?

PARTICIPANT: Vaccines and Related Biological Products Advisory Committee.

DR. SHIMABUKURO: It's an advisory body to FDA, and they make recommendations on what strains they believe should be included. Among other things, they make recommendations of what strains should be included in the seasonal influenza vaccine. Then FDA ultimately makes the decision, but they usually accept VRBPAC's recommendation.

Moving on, there are two studies using Emerging Infections Program data. There's the Vaccine Safety Datalink study, a PRISM study, and a study using Medicare and Medicaid data on GBS following H1N1 vaccine that have been submitted for publication, but are not published yet. There's also an HHS meta-analysis of GBS following H1N1 vaccine that uses data from these studies and some additional data from DOE and the VA, as well, that is in progress.

Let me back up a little bit. I don't want to get into discussion of what GBS is, but it's a fairly rare neurologic condition. It's a demyelinating disease. The nerves have basically a coating around them to allow for efficient transmission of neurologic signals, if you will. GBS is thought to be autoimmune in origin. What actually happens is there is a destruction of these myelin sheaths, which can lead to weakness, paralysis. There's a pretty broad range of severity of this disease.

There are some known risk factors, particularly gastrointestinal illness. Campylobacter, which is a very common cause of food poisoning, is a known risk factor. Also upper respiratory infections are known to be risk factors for GBS as well. It's extremely rare in children. It's rare in young people. It gets more common as people

get older, so it's more common in the elderly than in young people and, like I say, very rare in children.

This is a snapshot from a presentation at VRBPAC back in November of 2011 which basically goes through the different vaccine safety systems that we use to monitor H1N1 vaccine safety and some of the study designs for evaluating the association between H1N1 vaccination and GBS.

This is relative risk here. You've got the study design and the relative risk. There are actually a couple studies in EIP, and then these are single studies. But if you see this little end footnote here, that signifies a statistically significant increased risk of GBS following a vaccination.

You can see in the EIP data using one study design with unvaccinated controls and another using a self-controlled analysis -- self-controlled you basically serve as your own control and controls for a lot of confounding -- you can see two statistically significant increased relative risks.

In the CMS data in their secondary analysis they had a statistically significant increased risk, and then in the VSD and the self-controlled analysis a statistically significant increased risk. The case-centered, that's just

focusing on actual cases. That's a methodology focusing on cases. No increased risk. Then the PRISM, the DOD, and the VA data, increased relative risk, but did not rise to statistical significance.

I'm actually going to fast forward to an extra slide here at the end. The slide I just showed you, VRBPAC, is recent. It was updated version of this slide, but I just want to point out just focus on this column right here, "source," and you'll see that in EIP and VSD and CMS they used chart-confirmed data. What happens is they go through, using automated data they'll pluck out ICD-9 codes that are coded for GBS.

Then they will go in and they'll have reviewers review those, and based on criteria -- usually it's the Brighton criteria, that being the standard that we use -- they'll determine if these cases meet the criteria for GBS. If they do, they're included in the study. If they're not, they're not included.

The reason that is important is because ICD-9 codes, if you're just relying on automated data with ICD-9 codes, there's the potential for misclassification, so people who don't actually have GBS, but were coded for GBS, get included as a case. There's a phenomenon in coding where we have rule-out codes. So somebody gets a GBS

workup. They may be coded for an ICD-9 code for GBS, however when you go in and look at that chart, they did not meet the criteria, then they rule out and they're excluded. But again, an automated analysis basically includes all those cases. You don't do the chart review.

In our phase two review after looking at this data, we were able to review the preliminary data in some of the draft papers. In the unpublished data the increased risk for GBS following H1N1 inactivated influenza vaccine -- we're just talking about inactivated vaccine here -- tended to be relatively small. You see these relative significant risks in the range of one to two. We consider that a relatively small increased relative risk.

The risk for GBS following H1N1 inactivated influenza vaccine was similar to the risk observed for seasonal TIV in some past seasons when the sample sizes were sufficient to detect a small risk. In our current statements in the vaccine information statements and in the influenza statement that CDC puts out usually every year we use an excess risk, attributable risk, of one to two per million doses vaccinated.

That sort of is the range of the risk that we have in the information that we currently put out. This was

far less than that observed for the 1976 swine influenza vaccine, which was in the neighborhood of 10 per million.

There was no increased risk for GBS observed for 2009-2010 seasonal TIV. For the seasonal vaccine that was given during the pandemic season we did not observe an increased risk. There's no increased risk for GBS observed in 2010-2011 in the VSD surveillance or for 2011-2012 thus far. For the season after the pandemic and for this past season -- both vaccines have the H1N1 strain -- we're not seeing in VSD, which is really our gold standard for active surveillance, we're not seeing an increased risk.

There were no VAERS data mining signals in 2010-2011 or for 2011-2012 thus far. For VSD and for VAERS surveillance for this year and for CMS surveillance for this year, considering that well over 90 percent of the vaccine that's going to be administered has been administered, I don't anticipate that changing.

FDA analysis of 2010-2011 CMS data -- that's ICD-9, that's automated data, inpatient setting only. I guess it's not so important to get into cohort versus risk interval, but in one of their analyses they found a small increased relative risk of 1.25, which was statistically significant, and in their other methodology no statistically significant association. There's currently no

signal in FDA's analysis of the current season's CMS ICD-9 data.

The task force decision at the end of the day was to defer action, and really our justification for this decision is we want to allow completion of the peer review process. We want this data, which has been submitted for publication, to go through the referee process and to come out in the literature before we make a final assessment and make recommendations, basically go through our decision-making process. We think it's important that this go through the peer review process and come out in the published literature. Also, we would like the HHS meta-analysis to also come to its conclusion as well.

I'm actually going to stop and allow for discussion for GBS because I think this a fairly important topic, and it was the only one that we actually deferred.

MR. KRAUS: When the IOM did its study, they explained how they viewed the epidemiological evidence sort of on one side, and on the other side they looked at the mechanistic evidence. It seems like what you presented us with today is new developments in the epidemiological evidence. Are there developments in the mechanistic evidence, actual case studies where you have sort of a

medical consensus that you did have flu vaccine that did trigger the GBS, and are you taking those into account?

DR. SHIMABUKURO: We didn't find any additional mechanistic evidence.

MR. KRAUS: What about the mechanistic evidence that already existed?

DR. SHIMABUKURO: For seasonal? That the IOM looked at, you mean?

MR. KRAUS: Yes.

DR. SHIMABUKURO: I'd have to get my book, but I believe they had one case, and then they had some animal evidence. I believe their conclusion was that the mechanistic evidence was weak. Does that sound correct?

DR. JOHANN-LIANG: This is really an important concept. First of all, remember that even in the Guiding Principles there's a hierarchy of the strength of evidence. A mechanistic evidence which largely consists of things like animal studies or case reports, case series, these are very low down on the strength of evidence. If you have lots of epidemiologic evidence available, or even better yet, the highest strength, which is randomized controlled study, that's the evidence that you want to start with. That's concept number one.

In GBS and flu there was a 1976 epi assessment, but every season there is epidemiologic evidence that IOM went through. If you don't have epidemiological evidence like many of the things we proposed today, such as measles inclusion body, even SIRVA, you go with the mechanistic evidence, provided that you have a very good idea of what that mechanism is.

Measles inclusion body encephalitis, we're putting that on the Table. You see measles inclusion on microscopy or you isolate the vaccine strain from varicella. IOM does explain this, what they consider mechanistic evidence to stand alone versus what's not adequate. You really need to have some sort of a mechanism to be able to say mechanistic evidence.

The problem with GBS flu is that although there are a lot of theories, such as we see a lot of this molecular mimicry, T cell activation, bystander activation, et cetera, it really hasn't been worked out. We actually don't even have very good animal models to articulate what this type of mechanism would be.

Something new that has come up in the last 10 years understanding mechanism is what Tom talked about with ganglioside antibodies, which are similar to antibodies against campylobacter. So we know that that mechanism can

exist. We don't understand, though, how that's applicable to the flu vaccine. We haven't really identified the antigens or the antibodies against the antigens. If we actually had worked that out -- and we didn't have the epi evidence, then we had a series of case reports that said that may be okay.

But the problem right now is we have lots of epidemiological studies available, and they sometimes kind of contradict each other or they're very little risk, so we're not quite sure how certain that is. But we don't have enough of an actual mechanistic evidence in this instance to say case report will do. Does that help to explain what your question was?

MR. KRAUS: Yes.

DR. SHIMABUKURO: Another way to look at it is for the mechanistic evidence for measles inclusion body, if you find that evidence, it's pretty clear-cut that there's a causal relationship. We don't have that for GBS. The epidemiologic evidence, when you look at causality, one thing you like to see is consistency, being able to replicate studies. It looks like in some years in some studies using some surveillance systems there is a small risk. In others, sometimes even in the same year, there's

not. It's complicated by the fact that influenza vaccine potentially changes every year.

I brought this slide up because I think the footnote on here is very important. It says high degree of variability in the relative risk suggests that chance or uncontrolled confounding could contribute to the findings.

When you have multiple surveillance systems you're looking at and you're getting variable results, it makes you think are there reasons why you're seeing these variable results. Are there confounders? Are there things confounding that we haven't controlled for that we haven't recognized that are coming into play here? We've seen that for multiple seasons for influenza vaccine. It's just not consistent. The findings are variable.

DR. JOHANN-LIANG: But there is a prior, and the prior is very important. We do have the 1976 experience where there the attributable risk was pretty solid. We don't have that with the current evidence. We don't really even know exactly because we've got to wait for the publications to come out and for us to read it, et cetera. The current H1N1, even with the swine flu background, is very small. That's what we're thinking, so that's why we have a lot of thinking to do with this.

MR. KING: The defer action justification is we want to wait because we have to wait for the peer-reviewed material. Do you have a schedule, an idea of when that's coming, or is that we have no idea?

DR. JOHANN-LIANG: It's been coming for a while.

DR. SHIMABUKURO: These are at the journals, so we don't have much control about when the journals publish these. We're hoping it's relatively soon. I think that the actual writing and editing is largely done, but we need the peer review process to be completed before we can --

MR. KING: In your experience, from the time that they receive these and have it -- let's throw out the extremes. It'll be like the Olympics, the long weight goes, the short time goes. Typically, once they have it, there's got to be a typical of how long it takes.

DR. SHIMABUKURO: There's really none.

DR. EVANS: There's none, but there could be the circumstance that they're trying, as I understand it -- there are several articles, and they may wait for them so they can publish them against.

MR. KING: You're saying there's not a typical?

DR. EVANS: But this is a unique situation where they're trying to maybe get these done at once.

MR. KING: So we could have a six-month to a year wait here.

DR. JOHANN-LIANG: We are projecting that, most likely, we would like to come back to you this year to talk about it. We have a June and a September ACCV, and we're hoping that we can bring this to some sort of what should we do with this as far as our program is concerned, because let's face it, GBS flu confounds us every day. So we would like to have some sort of momentary closure. That would be nice.

DR. DOUGLAS: I have a question about the combined flu and pneumococcal vaccine. Is an attributable risk of 45 per 100,000 enough to say don't combine them?

DR. SHIMABUKURO: Actually, this issue went to the General Recommendations Working Group of the Advisory Committee on Immunization Practices. They looked at it. CDC's immunization program looked at it. The conclusion was that this excess risk did not rise to the level where there should be a change to the immunization schedule. I will say, though, there is a study in progress in VSD to look at febrile seizures following all vaccines, so we're looking into this.

DR. DOUGLAS: That wouldn't be on the Immunization Table. That's manufacturing, right?

DR. SHIMABUKURO: No, these are separate vaccines. This is when TIV and PCV13 are given as separate vaccines, but at the same time.

DR. EVANS: As I recall, the incidence rate was a little bit lower than what we were seeing with the MMRV situation, in which you had the choice of giving a combination vaccine, which had a higher rate of febrile seizures, versus separating them and giving MMRV, where there was a lower rate of febrile seizures.

MS. DELA ROSA: For clarification, the red dots there are actual numbers rather than the sum of those two curves below?

DR. SHIMABUKURO: Yes. These curves are not sums. The red curve is looking at when TIV and PCV13 and other vaccines are given at the same visit. The green one is when TIV is given without PCV13, but there may be other vaccines given as well. Then the dotted black line is when PCV13 is given without TIV, but possibly with other vaccines.

MS. DELA ROSA: It's seems the risk is more than doubled when you combine them. Would it be advisable, then, to change the schedule of when they are given? Would that be a better idea to solve this issue here?

DR. SHIMABUKURO: If you look at this curve, it looks like that risk is more than if you add the green

curve and the black curve. If, in fact, that is the case, then the risk is multiplicative as opposed to additive. However, statistically they have not been able with the data they have to make that determination or come to a conclusion on that, so we can't really say that this is multiplicative rather than additive. At this point we can't say that.

MS. DELA ROSA: Would changing the schedule of giving them affect the distribution? Because they peak at the same age when they give them, right? They all peak at about that same place.

DR. SHIMABUKURO: This is getting into complicated epi and statistics. If the risks are additive, it actually doesn't make sense to separate them, because either you have a certain amount of risk for one and a certain amount of risk for the other. If you give them together and you add the risk together, you have a certain amount of risk. That total risk is going to be the same whether you give them on one day or another day. If it's multiplicative, it's different. However, we can't say it's multiplicative yet based on the study we did.

The ACIP opined on this, and there are other risks not to giving vaccines at the same time, like you leave kids vulnerable to vaccine-preventable diseases.

Febrile seizures are a result of fever, and flu can cause fever and pneumococcal infections can cause fever too. You have to weight the risks and the benefits. I'm here just talking about the risk. I'm with Immunization Safety.

I'm just giving you the risk, and I don't want to get into a conversation about the risks and benefits, but when CDC looked at this, they essentially weighed the risks and benefits. Based on the risk, based on the benefits of simultaneous vaccination, they decided that they were not going to make any changes to the schedule. We're not going to recommend changes to the schedule.

Hepatitis A, we've touched on this. The IOM review, no studies were identified in the literature for the committee to evaluate the risk of anaphylaxis after hep A, so the evidence was inadequate to accept or reject a causal relationship between hepatitis A and anaphylaxis, and we did not find any additional data on our phase two review. Our decision was not to revise the VIT because the evidence just was not available to make any determination on that.

We just had the talk, so I'm actually going to just breeze through this slide just to say that for encephalitis and encephalopathy, the decision was to keep

these two conditions on the Table and update the Qualification and Aids to Interpretation.

The last one I'll talk about is injection-related complex regional pain syndrome. I'm glad Tom is here, so if anyone has any questions on what exactly CRPS is, I will defer to Dr. Ryan.

The IOM causality conclusion was that the evidence is inadequate to accept or reject a causal relationship between the injection of the vaccine and CRPS. The mechanistic evidence that the IOM reviewed was suggestive, but not sufficient to make a determination of a causal relationship.

In our phase two review we identified a small number of other published and unpublished case reports, a total of five, that met the International Association for the Study of Pain, IASP, criteria for the diagnosis of CRPS. These cases did exhibit a close temporal association to injection -- that's within 24 hours -- making an alternative unrecognized inciting incident unlikely and suggesting the mechanistic evidence supported a causal relationship.

Our phase two decision was no VIT revision was indicated at this time, and our justification was that the additional mechanistic evidence obtained during our

secondary review was suggestive, but yet still not sufficient to make a determination of a causal relationship. It was really similar to what the IOM concluded in that there are case reports out there. It's suggestive, but we really don't have sufficient information to make a determination of a causal relationship. CRPS is actually not that well understood of a condition. There's even some disagreement among experts about this condition as well.

MR. KING: What is the specific difference between SIRVA and the CRPS?

DR. RYAN: SIRVA is a musculoskeletal injury.

MR. KING: My second question is related to when we say "suggestive," are we really meaning there's a correlation? In other words, we know it's not causal, but is it correlated?

DR. SHIMABUKURO: I think suggestive means if you look at these cases and work, we're talking mostly about these are case reports, case series, case reports, which, as Ro was saying, in the hierarchy of evidence that sort of falls near the bottom, although if you look at these and you look at the temporal association and try to look at any alternative cause, the evidence from these case reports is suggestive. However, given the amount or the lack of the

amount of evidence and really the lack of epidemiologic evidence, we didn't think the evidence was sufficient to make a VIT change or an addition for CRPS.

MR. KING: So can I say that the answer is no, that's it's not a correlation?

DR. JOHANN-LIANG: "Correlation" is probably not the appropriate word.

DR. SHIMABUKURO: Usually you get a correlation or an association doing an epidemiologic study.

DR. JOHANN-LIANG: This would be based on mechanistic evidence, and as I said before, we're trying to work out the mechanism. If we have enough cases that you can wrap your hands around the mechanism and they all kind of fall in line, then we would move from suggestive to sufficient. We're kind of thinking things are falling in line or there's some, but there's just not enough there. We need more publications, basically.

DR. SHIMABUKURO: This is a pretty rare condition, so that makes doing epidemiologic studies difficult, and there are not that many case series to analyze as well. So we have to build the evidence base before we can make a determination.

DR. EVANS: But it has unique clinical features, which is promising.

DR. JOHANN-LIANG: Actually, the clinical picture is very difficult. That's the main problem. It's very hard to come up with a very good case definition. That's the main problem.

DR. VILLAREAL: I assume this is an adult issue, the data.

DR. EVANS: No, we have cases in children.

DR. DOUGLAS: I'm not familiar with TT vaccine, your slide number ten.

DR. SHIMABUKURO: Tetanus toxoid, I believe. Basically that's a diphtheria tetanus and tetanus or acellular pertussis.

MR. KING: So that's a typo.

DR. JOHANN-LIANG: It is not a typo, but it's just not relevant any more. It's what's in the current Table. We elected for tetanus toxoid -- all the stuff that's on the Table aside from adding these SIRVA and vasovagal syncope and stuff, not to really touch it at this time because IOM came back with inadequate. We just wanted to define encephalitis and clean up the QAI.

For example, we did discuss what do we do with this whole-cell pertussis. We don't give that anymore. Would we leave it in? What do we do? We really need to tackle this whole issue of diphtheria-, pertussis-,

tetanus-containing vaccines, and all the issues related to them at a later event, which is too much right now. IOM didn't say CS or FA, so we figure we'll just leave it.

DR. SHIMABUKURO: Tdap in adults is probably going to become a non-issue down the road.

MR. KING: We don't need a vote, because this is real informative.

DR. JOHANN-LIANG: We wanted to give a preview for things to come.

MR. KING: Thank you very much, Dr. Shimabukuro.

We already did the next steps, which was scheduled as one of the final components on the agenda, the summary. We don't know if there's really anything to summarize. We've done it. There is a public comment component, though, so what we need to find out is if there's anybody on the line who has a comment to make in a public forum. There are no questions. Public comment is what we have.

Agenda Item: Public Comment

OPERATOR: If you would like to make a public comment, please press star-one. To withdraw your comment, please press star-two. It looks like we have no public comments at this time.

MR. KING: We're not really adjourned; we're in recess until tomorrow. At the conclusion of 8 hours, 45 minutes, and 8 seconds on the Polycom here, we are recessed until --

DR. EVANS: We have an unfinished business section tomorrow morning.

MR. KING: We have welcome and unfinished business from day one. It starts at nine a.m. It's a nine a.m. start. We reconvene tomorrow morning at nine a.m., and I bid you all goodnight and adieu.

(Whereupon, the meeting was adjourned)