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P R O C E E D I N G S (9:00 A.M.)

Agenda Item: Welcome and Unfinished Business from Day One, Ms. Sherry Drew, Chair

MS. DREW: Good morning. Welcome to our meeting. We reported the number of Commissioners that were here yesterday. We are all here again today, other than Michelle Williams, who will be slightly late. I am wondering if we have any unfinished business from yesterday that anyone would like to raise.

There being no unfinished business, we will move onto Dr. Rosemary Johann-Liang, DVIC, Clinical Update on the Institute of Medicine Report, Generated Task Force Update.

Agenda Item: DVIC Clinical Update/Institute of Medicine Report Generated Task Force Update, Dr. Rosemary Johann-Liang, chief Medical Officer, DVIC

DR. JOHANN-LIANG: Good morning everybody. The way the agenda has it s that I'm going to be talking about IOM and other folks will be talking about rotavirus. We're going to be actually doing this all together.

You know, when we usually do the every three month update, I give you guys a quarterly update on the medical review and analysis, going over how many claims came in, what the claims were about, what were the vaccines, some interesting issues, et cetera.

But because we have an hour and a lot of slides to cover, and some thinking involved this morning, I am going to just do that next time, and we'll bring it together and give you guys an updated review of the medical update. Today I want to just give you a brief update on the IOM report.

Remember, last ACCV, when you guys met, Dr. Clayton, the Chair for the IOM Committee, gave you guys a full briefing on the report. I believe everybody received, the ACCV members, and I know we have new members, so we've got to get, Annie, we've got to get the pre-pub copy to them as well. We have ordered the IOM hard copy. It comes in a book for all of you at the ACCV.

But they apparently take a long time going through their editing and copying thing and going to wherever the books go to get bound, et cetera. And so it probably will be some time in the spring that those books will be available for everyone. So we'll make sure that everyone has a pre-pub copy available. That's what we are working off as well for now until we have the full publication available.

I am going to just give you a little bit of a background, because we have some new members joining, and then give you an update of where we are with this. And then the most of this hour we want to spend on the

rotavirus vaccine and intussusception and proposal for changes to the injury table.

I am going to be doing that with my colleagues from the rotavirus Vaccine Working Group. As it turned out, we really did not plan this, we are all in sort of black and red today. So you can see that we're all synchronized in our thinking. It's government at its best.

The members from the working group who will be speaking today will be Ms. Anna Jacobs. She is our Office of General Counsel, Counsel to our VICP, and member of our working group. And Dr. Mary Rubin, who is a pediatrician and one of the medical officers in our division.

So let's just talk about IOM vaccine adverse event review history. The contract actually to the IOM started in the fall and the winter of 2008. It took some time to get all the paperwork in order for them to look for the committee members that would be totally no conflict of interest, et cetera.

And so it took until April of 2009 for us to meet the committee, the initial committee, and give them the charge from the government as to what we would like for them to do. And really, this was the first time, I think, it was a HRSA-generated IOM contract.

There were a number of vaccines that had been added to the table that had no adverse events listed on

them. Our goal was to really try to get an outside independent assessment of the current science so that we can update the injury table.

And to do so, we asked them not only to look at certain vaccines and certain adverse events, but to really give us some sort of a framework of doing causality assessments, because there are many different ways people look at causality, but it was really important for us to all work by the same sort of framework.

And even after IOM was done, there are other vaccines that we just couldn't ask them to review, because there are only limited funds. So we would need to go back and do some of that causality assessment for other vaccines, other adverse events. We really wanted to know what framework to work off of. That was a really major issue.

But then we also gave them a list of adverse events that really were generated by us talking to our sister agencies throughout the government, especially CDC, the Immunization Safety Office, where we are currently working with.

The list of adverse events was generated for four vaccines initially. Mainly the criteria for why those four out of the 16 that we have covered in the program, is because those were ones that were newer, that did not have

adverse events listed. And then thirdly, really, the vaccines that had a lot of claims coming into our program and there was media attention.

So the initial ones were really varicella, which was added a long time ago, but there was nothing listed on the table, influenza, which was a big vaccine in the sense that we were getting a lot of claims, meningococcal and HPV, because these were newer vaccines. That's all we had resources for.

And then thankfully, after the initial charge went out we were able to get additional funding through the ARRA stimulus funding through CDC, and add four more vaccines for review. And this was really fortuitous because it only needed a little bit of resources to add more vaccines, because the sitting of the committee is what was so costly.

And then after all of that, the final release of the report was this August. You all heard the presentation by the Chair in the last ACCV. So these were the vaccines that were reviewed. And they were reviewed together. It shows that it really makes up 92 percent of VCIP claims. So we thought that was really helpful for us to get a good sense of how we can go and modify the Vaccine Injury Table.

Remember that the working list of adverse events were generated from our staff, based upon our statistics,

and what the current science as we understood they were. And then we presented it publicly during the charge, and IOM put the working list up on their website, so it was open to the public. And the public had all of that time to add their comments and their recommendations to the list.

The IOM was not going to take away anything that we had asked for, but they were open to, and they did, add further adverse events to the list. And because this is really supposed to be an independent review by them, we gave them a general concept. It was really up to them to figure out the framework and how they were going to put the adverse events together, and what the final list and the final review was going to be.

As you saw from the report, the final working list constituted 76 different adverse events, 157 adverse event vaccine combinations. So as you saw on the report, they had the causality framework as we asked them, as we charged them, with a three-pronged approach. They looked at not only the weight of the epidemiologic evidence, at the four levels, but also the weight of the mechanistic evidence, and they put that together for an overall causality assessment.

And the conclusions that they had also were in four different categories, and it lists here what convincingly supports, what favors acceptance, what is

inadequate to accept or reject, and then what favors rejection. Those were causality conclusions. We will really spend a lot more time on this once we bring what our thoughts are, based upon their review, before you.

Currently, the members of the HHS, the Task Force for this, which constitutes Immunization Safety Office, our Office of General Counsel and HRSA reviewers, are working very hard. So everything is under review. Our goal is, at the risk of being called a taskmaster, our goal is to really try to at least bring the initial thoughts before you for the next ACCV meeting.

The nine working groups -- it is the eight vaccines, but we also have a general category which we charge the IOM for, which is the actual injection and administration adverse events. That is the ninth category, and that is what we are all very, very busy working on right now.

I'm going to just move right along unless somebody has a burning question about the first part of this. So rotavirus -- I'm going to actually ask my speakers here to come up and join me, and then we can do this as a team. This is Anna Jacobs and Mary Rubin, and we are going to be talking to you about rotavirus vaccines and intussusception.

Agenda Item: Intussusception: Proposal to Add to the Vaccine Injury Table for rotavirus Vaccines, Ms. Anna Jacobs, Office of General Counsel

DR. JOHANN-LIANG: Now this is something you have heard a lot of, because we have kept you abreast as we have learned things too, as to what we are doing. But we have come to a time where we are actually going to ask you what your thoughts are.

I want to make sure that all of you in your binders have not only the slide set but the proposed reg. Do you have all that? And the voting folks are eight, and Michelle, nine, right? So if you can make sure that you have the regs with you. It is the one that looks like a lawyerly kind of thing. It has the table, it has a little blurb and there is a table. It is really important that you guys all have the regs with you.

So the IOM did not include -- we did not ask them to include the rotavirus because at the time when we gave the charge, rotavirus issues were pretty quiet. So we only could ask them to get the big ticket items at that time.

But as the IOM review was ongoing, we had some recent post-marketing surveillance publication come up, which led us to establish our rotavirus working group and the intussusception issue. And today we are finally proposing a draft regulation regarding this adverse event.

So these are the members of our working group. Dr. Shaer is sitting here as well. And Dr. Smith, I believe is on an open line. Remember, she is the one that gave you guys a very comprehensive talk on rotavirus and all of that data, preclinical, the thoughts about the shedding and all that which we don't have time to go into today. I am just going to briefly just give you a summary so that we can all come to speed.

The outline is that Anna Jacobs is going to give you some of our legal history and what ACCV came up with some years ago, the Guiding Principles about how we go about changing the Vaccine Injury Table.

I will summarize some of the data because that has already been extensively discussed. And then Dr. Rubin will talk about there is an ongoing study in the US right now that I think it is important that you guys know that that is ongoing. And then the actual proposed changes to the table. I will come back, summarize and ask you guys what your thoughts are.

We may need a little bit of a -- this is a really good practice going into the IOM. We may need to figure out a little process issue of how we are going to query the members for their input.

rotavirus disease, just to start off, is very common. I am sure that if you have young children, most

young children have rotavirus. In the winter months is when it comes the most. They have vomiting, fever, gastroenteritis, and almost everyone gets this by age five.

The mortality is not such an issue in the US, but in developing countries there are many deaths actually caused from this due to dehydration, et cetera. And even in the US there are many rotavirus induced, disease-induced hospitalizations. Although now with the vaccinations in place the hospitalizations are decreasing.

Then, talking about what intussusception is, the picture is worth a thousand words, right? It shows you how one segment of the bowel sometimes, for various reasons, actually sort of telescopes into the next segment of the bowel. You can imagine all those blood vessels sort of get pulled with it. And so you start to get less blood flow, and then swelling of the gut. And then eventually you will actually get obstruction and the child can really get into trouble.

It is quite uncommon, the intussusception part. It is about 1,400 kids in the US per year. Just so that we can have a common denominator for you to put things into context, that translates to something in the US on the order of like 30 to 60 cases per 100,000 kids per year.

PARTICIPANT: That's pre-rotavirus. That's just the baseline incidence.

DR. JOHANN-LIANG: This is background, background incidence of intussusception, so just so that you can put it in the context of intussusception, what the numbers look like when you have the RotaShield, which Anna is going to talk about. And then I will come back and talk about what the numbers are with the second generation rotavirus vaccines, because I think it's important for you guys to know the magnitude of the issue.

So you don't really see this too much in little, little babies. It really sort of starts to peak about, earliest maybe at two months, and it goes up to peak at like six months. You can have intussusception even in an older child, but the peak really is that the babies, when they are really cute, you know that four to six months, that time. It is really pathetic when they --

So naturally occurring -- there is a little bit more information. So this is intussusception as a baseline. It is interesting that this adverse event really varies by region. For example, you are going to see the new study that was published in Mexico and South America. Even as a background, in South America the incidence of this adverse event, intussusception, is much higher, on the order of doubling what we see in the US.

So there are region variances. And Mary is going to talk about all the different issues of why IS occurs

naturally, without the vaccine. It is usually diagnosed with, if you have stool that is we call currant jelly stool, you have the diagnostic thing right there clinically.

But sometimes you need to use radiological tests to diagnose it, which we do with the barium contrast. But also just putting the barium through sometimes reduces and actually corrects for the intussusception. That is different than children who actually end up having surgical intervention.

It seems that the data shows it really is not that there is any difference between these kids. But if you don't treat or reduce the telescoping with the barium or by natural happenstance -- I remember having a patient, getting them through the ambulance. We hit a pothole -- boom, the pothole hit, the kid reduced. So you can have a natural reduction. But usually you need a barium reduction.

But if you don't get to the child, and you end up -- yes, I got a standing ovation when I got off the ambulance -- but when you don't get to reducing them, then they can go on in their disease. And you can see that the more you obstruct, it just becomes to a point where the child has to undergo surgery, and the surgical intervention.

So that is the different way to treat it. It looks like it's about 50/50 in how the patients get treated with this illness. So morbidity and mortality from this adverse event is very low in the US, just like rotavirus mortality is very low in the US. And recurrences do happen. I am going to turn now over to my colleague here.

MS. JACOBS: I am Anna Jacobs, and I am an attorney with the Office of the General Counsel, and I advise the VICP with Elizabeth Saindon, my colleague. Today I will just go over again the basics of the Vaccine Injury Table and how that is revised and what your role is in all of this. And then we will walk through the history of rotavirus as it relates to the table and the program.

So as you are well aware, the program has a Vaccine Injury Table, and claims that fit within the parameters of the table receive a presumption that the vaccine caused the injury. And the petitioner is entitled to compensation unless the government can prove that something else caused the injury.

And so if the claim does not fit within the parameters of the table, then the petitioner can receive compensation if he or she proves that the vaccine did in fact cause the injury.

And so how do you fit within the parameters of the table? The petitioner has to prove three things. The

petitioner has to prove that she received a vaccine set forth in the table, sustained or significantly aggravated an injury listed on the table in association with that vaccine, and sustained the injury, or the onset of the injury occurred within a time frame listed on the table.

And so the injuries are defined in a section that is called the qualifications and aids to interpretation. And the statute says the following qualifications and aids to interpretation shall apply to the Vaccine Injury Table. We also call them the QAI.

And so Congress recognized that science is not static. It changes. And so they wanted the table to also be able to change along with science. But they didn't want to leave that up to the legislative process because the legislative process moves a lot slower than science does. So they gave the Secretary the authority to change the table by way of the regulatory process.

So by regulation, the Secretary can modify the table by adding or deleting vaccines, adding, deleting or modifying injuries. And that includes the definitions of those injuries. And can also change the time periods listed and add those.

And that regulatory table is found in the Code of Federal Regulations in Title 42 in Part 100.3(a). And so by statute modifications to the table apply only with

regard to petitions that are filed after the revision.

Just to go through the general basic process of the regulatory process, basically, the Secretary would publish a Notice of Proposed Rulemaking, and then the Secretary would have to afford at least 180 days of public comment and provide a public hearing on the proposal. And then after that period closes the Secretary can move forward with publishing a final regulation.

What is your role in all of this? The Secretary cannot propose a regulation until she first provides you with a copy of the proposed reg text, which is what you have before you in your materials, and requests comments and recommendations, and affords you at least 90 days to come up with a recommendation.

So what standard should guide you in considering the proposal? Unfortunately, there isn't a whole lot set out in the statute. The statute does give a standard for when the Secretary should add a vaccine to the table. And the Secretary should do that when the CDC recommends a vaccine for routine use in children, the Secretary shall add that vaccine to the table within two years. But there is no standard for adding injuries, modifying or deleting injuries.

And so, in 2006, the ACCV at that time developed a set of Guiding Principles. And I believe you also have

this document in your materials, and you are welcome to pull that out. I am going to just walk through them and summarize them for you. I should say these principles are not legally binding on you. They are just helpful, it's a helpful set of guidelines that you are welcome to use.

So in essence, the ACCV then believe that the table should be scientifically and medically credible, and where there is credible scientific and medical evidence, both to support and reject a proposed change, then the change should really tend toward benefiting the petitioners.

So what is scientifically and medically credible? The ACCV said that conclusions in IOM reports are deemed to be credible, but of course that should not limit your discussions. For data sources other than IOM reports, you will need to assess the relative strength of the evidence. Consistency across multiple sources is an indication of strength of the evidence.

And so they set out a hierarchy of data sources ranging from the strongest sources to the weakest sources. And I won't go through all of them, but the strongest sources are going to be the clinical laboratory data, challenge/re-challenge data involving non-relapsing symptoms or diseases in controlled clinical trials. And the weakest source is going to be more like your case

reports, editorial articles on scientific presentations and non-peer reviewed publications.

And also consider whether there are methodological limitations in the studies, is there any potential bias or confounding factors, and is there biologic adherence in the conclusions.

Do not worry, though, if you are not a scientist and you don't regularly assess the strength of evidence, because you are welcome to seek the assistance from the Division of Vaccine Injury Compensation. And you can ask them to guide you through the evidence to help you assess the strength.

And of course, the ACCV recommended that you should remain aware of the policy considerations underlying the table. Congress basically intended that awards to vaccine injured persons should be made quickly, easily, with certainty and generosity. And they also intended to compensate the very serious injuries. And so if there is a perfect split down the middle in the evidence, then you should tend toward adding or retaining the injury.

So now I'm going to walk through the history of rotavirus in the program as it relates to the table. Rotavirus vaccine is not new. On August 31, 1998, the FDA licensed the live, oral, rhesus-based rotavirus vaccine, and that was under the trade name of RotaShield. This was

the only US-licensed rotavirus vaccine on the market at that time.

And so the CDC then recommended this vaccine be routinely administered to children, and so on October 22, 1998, the Secretary added the general category of rotavirus vaccine to the table, with no condition specified, or no timeframe. So around this time, VAERS had been receiving reports of intussusceptions occurring after the first dose in infants.

So July 16, 1999, the CDC then recommended that parents and health care providers suspend the use of RotaShield, and they continued to conduct studies to determine an association. And the manufacturer voluntarily ceased distribution of RotaShield. And then on October 15, 1999, they voluntarily withdrew the vaccine from the market and requested immediate return of all doses.

Shortly after that, October 22, 1999, the ACIP concluded that intussusceptions occurred with significantly increased frequency in the first 14 days following the administration of RotaShield, and withdrew their recommendation for use of RotaShield in infants, and the CDC adopted that as their recommendation.

And so in 2001, July 13, the Secretary published a Notice of Proposed Rulemaking to revise the table. And the Secretary found that intussusceptions could reasonably

be determined in some circumstances to be caused by vaccines containing live, oral, rhesus-based rotavirus.

The Secretary proposed to add a specific category of vaccines containing live, oral, rhesus-based rotavirus, with the associated injury of intussusception with a timeframe of zero to 30 days. The Secretary then published the final rule on January 25, 2002, and it became effective on August 26, 2002.

And so basically, what the table then looked like was, there was this general category of rotavirus vaccines, no conditions specified and no time frame. And there was also this specific category of live, oral, rhesus-based rotavirus vaccine with injury of intussusception, with a timeframe of zero to 30 days.

And that injury only applied to vaccines administered on or before the effective date of the regulation. And you will recall, though, that the vaccines had been long since withdrawn from the market, and they weren't being distributed.

So if you fast forward then to October 9, 2008, the Secretary removed then the specific category of vaccines containing live, oral, rhesus-based rotavirus and the associated injury. And her reasoning for this was that RotaShield was removed from the market on October 15, 1999, and the CDC withdrew their recommendation for routine use

of the vaccine shortly after that.

So really the claims could likely only been for injuries sustained from vaccines that were administered before that time, because they were not being administered after that time.

So if you take that into consideration, and the fact that the table required the injury to have occurred within 30 days after the vaccination, and you consider the statute of limitations, which in the case of table revisions, for injuries that occurred before the revision, the petitioner has two years to file a claim, and the onset of the injury needed to have occurred within eight years preceding the revision.

So doing the math, if the date of table revision was August 26, 2002, then the date that the last claim could have been filed would have been August 26, 2004. And the onset of injury or the death needed to have occurred between August 26, 1994 and August 26, 2002.

But that filing deadline of August 26, 2004 is the key date. And so by 2008, the Secretary believed that any potential claim under this specific table category would have been time barred. But the Secretary did retain the general category of rotavirus vaccine with no condition specified, no timeframe.

And that is where we are today. And I will turn

the platform over to my colleague, Ro.

DR. JOHANN-LIANG: Ro needs to speak very fast because we are in a time crunch here. This is a slide that you all saw already. I believe this was given to you – update 3/20/11, it must have been in March. I say it right up there on the slide here. March you got this slide. And what I tried to do here was, because you did get an extensive review from, I believe, the FDA representative in October 2010, when all of this was being presented to ACIP.

I just did a summary slide for you at that time, showing what the difference between the RV1 and RV5 is, and then what pre-licensure studies showed. So the way the pre-licensure studies for these second generation vaccines were powered, the numbers needed was based upon what they saw with RotaShield.

If the RotaShield was -- if they thought there was maybe one in 11,000 they wanted to rule that out, and that is why it was powered to have about 30,000, 35,000. That is a huge safety study. As a pre-licensure study goes, you just don't see that, and that is why you see the numbers like that. And really, there was nothing seen, so it was ruled out for IS, for intussusception.

And the post marketing, remember, you have seen all this before, and I'm going to go over this again. But this is what was shown to you in March as a summary slide,

and then in June, the New England Journal publication came out about the South American studies.

And what they showed was a slight increase in attributable, meaning there is a background. And remember I told you, there's more of intussusception down in South America. But on top of that, they also thought there was a little bit of an attributable risk from the vaccination, mainly with the first dose, one to seven days post the first dose.

And there was a commentary also written about this, talking about the background of RotaShield. Really, for safety we look at the totality of the evidence, all the different things, the background, what is happening. It is kind of like that kind of editorial.

So given this coming out in June, this is a further updated slide of what you saw before. And I just took out the pre-licensure and expanded on the post marketing a little bit. So that study, the Patel, et al, from the New England Journal, was Mexico, the incidence rate of 5.3, one to seven days after first dose, not after dose two.

In Brazil a little bit different. And Dr. Smith went through this with you last time. It was actually after dose two, not after dose one. Again, one to seven days after the vaccine. And the thought behind it, nobody

really knows but the thought behind that is that in Brazil oral polio is co-administered. And the thinking was that the oral polio -- and I guess what is happening in your gut may take precedence over what needs to happen immunologically for rotavirus vaccine.

So it is not really until dose two that you see this effect, that small attributable risk on top of -- and then also for Rotarix. And when we talk about Rotarix right now, there is the Australian surveillance which looked at what was happening with the kids against the expected. So it is not a concurrent control, it is really an expected number.

And they did a relative risk and then again saw something a little bit above one to seven days post after first dose, and not after second dose. That is Rotarix. RotaTeq, the data is even not -- the issue is, Rotarix is where we have better data. I think there is a little bit of an attributable risk.

It is really in the order. If you think about it like this. So baseline is something like 30 to 60 in the US per 100,000. So the RotaShield was really like an additional five to 10 cases per 100,000. For these second generation vaccines, very simply, probably if there was something there, something in the order of one or two extra cases per 100,000.

We are talking about much lower magnitude of attributable risk. But it looks like for Rotarix, because you have seen it in a couple of different places outside of the US data, that something is really there. RotaTeq is a little bit difficult because the only thing we really have is the article by Buttery et al. in Vaccine that talks about, again, the Australian data.

We don't really have anything that is what we call a positive study in the sense of an attributable risk in the US at all. And RotaTeq is actually the vaccine that is being most utilized in the US. Now I am told by CDC that Rotarix will have an uptake, and we will see Rotarix use in the US as well, moving into the future. But currently it is really RotaTeq that we use in this country.

Dr. Rubin is going to talk about because of this, because this is uncertain data sets and there is really nothing in the US, the FDA has started a study on this issue. And she will talk about this.

DR. RUBIN: Good morning, everybody. Again, my name is Mary Rubin and I am a pediatrician. And I work as a medical reviewer at DVIC. I know the important thing is the proposal, but I will first discuss the ongoing study which is part of the FDA's Postlicensure Rapid Immunization Safety Monitoring program, which is PRISM.

PRISM was actually established as one of the

several 2009 H1 influenza vaccine safety surveillance efforts. And then PRISM was incorporated into the mini Sentinel to focus primarily on vaccines. The mini-sentinel is one piece of the Sentinel Initiative, which is a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance.

So this PRISM study on rotavirus vaccines in the US will assess the risk of intussusception after Rotarix and/or RotaTeq vaccines. So this is actually both the second generation rotavirus vaccines.

Now a detailed protocol is found in the mini-sentinel website, which is on www.mini-sentinel.org, for those people on the phone. It is also on the slide set. This analysis will use what is usually used in the Vaccine Safety Datalink studies. Self-controlled, case centered and sequential methods. And the total study population is estimated to be greater than one million infants, during a maximum study period of January 2004 to a point in 2011 that is undetermined

The investigators are hopeful to have preliminary results by the fall of 2012. So this data is not available to us right now. But based on the available data, which I will go back to Dr. Johann-Liang's slide, as you can see the increased rate of rotavirus intussusception, there is a

small increased rate within one to seven days after the first dose. And most of the data that is available is with Rotarix vaccines.

So we will go back to our proposal. We do propose amendment to the general category of rotavirus-containing vaccines, which involves the injury of intussusception, with a time period of zero to 21 days. Now as the publications show, one to seven days is the risk window. And we are proposing zero to 21 days, to be consistent with the ACCV Guiding Principles. As Ms. Jacobs mentioned earlier, RotaShield intussusception data showed a one to 14 days window. And the Vaccine Injury Table listed zero to 30 days for that rotavirus vaccine.

So what is intussusception? I know you have heard a lot about it already. But intussusception, as Rosemary, Dr. Johann-Liang mentioned, is the invagination or telescoping of the proximal segment of an intestine into the distal segment of the intestine. This can result in obstruction of the bowel passage, constriction of the mesentery and obstruction of the venous blood flow.

This can be characterized by sudden onset abdominal pain. As Ms. Jacobs mentioned, there is a section in the Code of Federal Regulations, that the following Qualifications and Aids to Interpretation shall apply to the Vaccine Injury Table, to paragraph A of the

section and Code. So we are proposing to add this paragraph that defines the injury of intussusception.

This slide is actually just a snapshot of the specific Vaccine Injury Table line. But you have the full Vaccine Injury Table with the regs in your handouts. So it just shows the vaccines containing rotavirus and injury intussusception in zero to 21 days.

Now in addition, the proposed paragraph for Qualifications and Aids to Interpretation, or QAI, as I will call it from now, gives presumption of causation to intussusception occurring after the first or second dose. As publications show, association after the first dose. And actually, some of the studies of RotaTeq show that the third dose is protective, or does decrease risk, and in the absence of alternate factors.

Now while in most intussusceptions, the cause is unknown, a proportion of naturally-occurring intussusceptions have been associated with infectious disease, conditions causing lead points, anatomic abnormalities and underlying conditions or systemic diseases.

I will discuss each of these factors in a little more detail in the following slides. And for each section you will find references to articles of medical literature. The credits go to Dr. Chris Liacouras, who is the Pediatric

Gastroenterologist from the Children's Hospital of Philadelphia, for literature review and reference.

So infectious disease secondary to both enteric and nonenteric strains of adenovirus enterovirus, and other viruses are linked to intussusception, as well as bacterial enteritis such as those due to campylobacter or salmonella typhi, as well as parasitic diseases such as ascaris, could be examples.

Intestinal masses like polyps and tumors and cystic structures like Meckel's diverticulum and duplication cysts, and also increased lymphoid tissues such as lymphoma, may actually protrude into the intestine, or create a weakness in the wall. So these can act as what is called lead point, which causes the intussusception.

And then congenital anatomic abnormalities such as malrotation, anatomic changes after surgery, and abnormal intestinal blood vessels such as hematoma or hemangiomas are also attributable factors.

Finally, systemic illnesses such as inflammatory bowel disease, namely Crohn's Disease and ulcerative colitis, also cystic fibrosis and celiac disease have been associated with intussusception. As an example, in cystic fibrosis the stools in these patients can become very dehydrated and putty like in consistency, and adhere to the bowel wall. And this actually can act as a lead point.

Also, there are other conditions that have small vessel tissue inflammation, which have been associated with intussusception as well, such as Henoch-Schonlein purpura and Kawasaki disease. So putting all of these together, here is a slide of the proposed language of the QAI, which you also have in your handout. I guess I will stop here.

DR. JOHANN-LIANG: You guys all have this in front of you? This is the Qualifications and Aids at the bottom of the proposed regulation change. And basically Dr. Rubin just went over the definition of intussusception. And that is followed by, basically this is laid out as what really doesn't qualify to give you presumption of causation under the table if you have a baby with an intussusception. So that is what you have before you.

I am just going to go on to just give you an update. I gave you an update about so what does it mean for our program really, to kind of put that in perspective. The last time we met I believe I gave you a brief synopsis of 12 cases that we had gotten claims for. That number is up to 15 now, at the end of fiscal year 2011. These were 15 RotaTeq intussusception claims.

And this is sort of a demographic breakdown, 11 males, four females, age range from eight to 31 weeks, and you can see that these are all you would see in the background IS population. And it breaks down really, there

are five after dose one, five after dose two, and five after dose three. That is how it broke down.

And many of these children really did have serious sequelae in the sense that they ended up in the hospital and had to actually undergo surgery. Eighty percent actually have surgical intervention, not just barium enema. And about half of them had -- if you look at the listings in the QAI that Dr. Rubin was going over -- about 50 percent of those kids actually had one of those qualifications for alternate factors. That is kind of what we have.

So this is not by any means the flu generated claims that we see. This is a small percentage of what we are reviewing in the program. But certainly given the new information, and under really the Guiding Principles that Ms. Jacobs went over, we really felt that we wanted to proactively bring this before you and propose a regulation change.

So in summary, some but not all studies suggest the possible very low risk of intussusception caused by the second generation rotavirus vaccines, mainly the studies on Rotarix. And it is after the first dose, within the one to seven days post-window.

The level of observed risk, I talked about the numbers with you and sort of gave you a side by side

comparison background to what we saw on RotaShield and what we are seeing with the second generation rotavirus vaccines. And possibly, if there really was an attributable risk, there will be an additional one case per 100,000 infants.

We do know that the benefits continue to outweigh the risk, and so the rotavirus vaccines are still being recommended by CDC, by ACIP. It is a very different story than what RotaShield attributable risk was shown at that time in the history you heard from Ms. Jacobs.

So given, as I said, the background of the RotaShield experience that we had in intussusception, given the new intussusception information, mainly coming from literature inside of the United States, but given that we have the Guiding Principles which you already have, this is what we are proposing.

Keep in mind, though, as Dr. Rubin went over, there is a study that is ongoing right now, and it is a US study, the PRISM study. So we don't know what the answers are to that yet. That's an unknown. We also gave you the hard copy of the proposed regulation changes, because that is what the statute requires for the ACCV members to have. And we also are asking you for your recommendation.

And the choices are as follows as to what we want to do with the proposed regulation. You can concur with

the proposed amendment to the table. And what that would mean is that we would bring together a Notice for Proposed Rulemaking, NPRM, which we have already started to draft. And we have to get that out to the public. There will be a six-month comment period for the public to give their input, and then we can move ahead to a final rule. That is what number one is.

Number two is that you don't concur with the proposed amendment and you don't want to move forward, you don't think there is enough evidence here, you think that the numbers of claims coming into the program are not that much. I don't know what your reasons are, but that would be one choice.

Number three would be you have the regulation in front of you and you want to think about it, sleep on it, and you want to make recommendations to changes for the next meeting. That's a choice.

And number four, because we have this US PRISM study that is ongoing right now, that you would like for us to wait until the data from that study is final. Which we think that at best the preliminary answers will be end of next year, 2012, and then the final answers probably won't be until sometime in 2013. It takes forever for the end product of publications to come out. I don't know, it depends. But it's some time to go. But that is a choice

you have.

Keep also in mind that from the summary that Dr. Rubin was showing you, the denominator is about a million there, too. And I am not quite sure how much of that is going to be Rotarix or RotaTeq. And remember, in the US, Rotarix is just not used. So even if you were to try to do the study, you can't really get the charts to review RotaTeq, so depending on how the denominators for those two vaccines work out, we are not quite sure, because the VSD study was also approaching a denominator of about a million. And they didn't see anything.

So at the end of the day you may be still left with, we don't see anything here but our denominator is still just right there. So I am not quite sure. If we thought, if the working group thought that this was a definitive study that would give us a definitive answer in the United States, we may make that a choice number one and say let's just wait. This is what we have now, we are going to continue to wait for the answers to come in and adjudicate claims as they come in.

But given that we are not quite sure at the end of waiting two years how those answers will actually help us to go one way or another -- this is just full transparency, that's what our thinking is -- but we still wanted to give you that option as a recommendation choice.

So those are the four choices that we thought you want to consider. I guess at this point in time how do we want to do this? Should we go around?

DR. HERR: Do we have any anticipation of any change in vaccine production from the manufacturers, in the sense that we anticipate that RotaTeq is not going to be as available as it has been in the past? Because we have had this with other vaccines where all of a sudden they are not making it. Or, do we anticipate any change in purchase in the sense that VFC authorization, does VFC purchase now both RotaTeq and Rotarix?

Or do we have a preference of one versus the other? In the sense of, if the predominant use in this country is RotaTeq and the increased risk is primarily through what we know so far from the Mexican study is Rotarix, are there things that we could do purchase wise? That we would have VFC authorize only RotaTeq purchase versus Rotarix that would modify that while we wait for the study?

If the makeup of the vaccine use in this country stays the same, we're not really going to see much, and we shouldn't see as much. And that might in many ways still be a safer, responsible thing to do while we look at more information.

MS. PRON: What is the safety thing?

DR. HERR: The Rotarix, by the studies, is a little bit riskier vaccine. And it may be just because of the data and what data information we don't have.

DR. JOHANN-LIANG: Right. If Mexico and Brazil actually -- the manufacturers compete for the country to buy, and Rotarix just won out, that was all. But if RotaTeq had won out, who knows what the data would be, right? So I totally know what you are saying.

In answer to your question, number one, do we know if there have been any shortages for either secondarily? Not that I know of. Do you know, Tom, from CDC?

DR. HERR: Not that I know of.

DR. JOHANN-LIANG: We have talked to the rotavirus people at CDC pretty recently. I don't think they anticipate there is going to be any shortage issues. But you are right, we don't know. Maybe there is some contamination with RotaTeq and then Rotarix is available and Rotarix gets the big uptake. Anything is possible. But right now we don't know anything in the future.

Number two, to answer your question about do we know whether either one is preferred to be used, RotaTeq came before Rotarix and that is why it sort of stayed.

DR. EVANS: Market share.

DR. JOHANN-LIANG: But according to CDC, although

I am not really sure what the exact information source for them to say, but they do think that Rotarix, the company will try to be more competitive as far as pricing, et cetera, and they will try to market it in this country more, and that the uptake of Rotarix will go up.

I don't know what the timeframe is, but the market share right now is mainly all RotaTeq and a little bit of Rotarix. But over time, it will come up. Rotarix will come up. That is their feeling. But I don't really know. This is company, probably financial information that we are not privy to, so we don't really know.

DR. HERR: Wouldn't a responsible thing now be for us, while we study, to put more governmental preference on purchase of the safer vaccine? I mean again, it is not our purview, so to speak, here, because we are talking about the table. But again, our responsibility here is to look at facts in utilization and safety of the vaccine.

DR. JOHANN-LIANG: Right, but I guess the general thinking behind this is that you have the background of RotaShield. You have two different second generation vaccines. And granted that they are different, a reassortment, et cetera, and we do think that we have more information on Rotarix, but, again, that is because of who studied it and what the denominator was.

We don't really know whether there is a

difference in safety between these two vaccines. The data is what we have. It really depends on how many people you study in what sort of a population. The study does not assure us that RotaTeq is safer than Rotarix, or Rotarix is safer than RotaTeq or anything like that. We just don't have enough data to say.

But given the background of RotaShield, given the Guiding Principles, we thought the best thing to do is to give presumption of causation. Not that there is causation per se, but presumption of causation for second generation rotavirus vaccines in general, and propose to put that on the table, with a qualification saying that if you have a child with a lymphoma, if you have a child that had an adenovirus infection within the right time, that that is really not a qualifier for presumption. Because that would be much more likely as an event to an IS than a rotavirus vaccine.

So we are not saying one vaccine is safer than the other, we're saying we are kind of looking at it in total. Does that make sense to you?

MS. HOIBERG: My question is, we talk about how if the shot aggravates a pre-existing condition. Yet here, you are excluding pre-existing conditions, children with pre-existing conditions you are excluding from really it being a presumption of causation, if I am using that

correctly.

It says onset in a person with a pre-existing condition, which causes lead to intussusception, such as intestinal masses and cystic structures. Who is to say that the vaccine didn't aggravate that condition?

DR. JOHANN-LIANG: It is really important to remember that when we put something on a table it is a presumption of causation. We are just saying, without going through all the litigation, someone comes in with intussusception within this timeframe, they get the presumption, unless it's blah blah blah blah.

That doesn't mean -- what you are talking about is an aggravation. We are not defining what would be an aggravation to the underlying disorder. I mean, that just gets way too -- but if you have a case and let's say the person has an underlying disorder and you get the vaccine, we can still look at that and do causation in fact. It's not like we can't give them compensation. Does that make sense?

This is just saying, when you are presuming something, when you are saying okay, nothing else, we look at it, it meets the facts, go, we have to have certain rules of engagement. That's what we are laying out here. And as I told you, the numbers, the naturally occurring intussusception as opposed to the possible small

attributable risk from second generation rotavirus, it can't be but that it's these things, if somebody has a clearly defined leading point, et cetera. That's what would define the qualification.

MS. JACOBS: Let me just add something. So Congress' original table that they created, it did the same thing. They basically inserted exclusions of basically pre-existing conditions. So it's not like the program is trying to do this de novo. So they have precedence for that.

MR. JASON SMITH: The QAI, the first presumption is the onset occurs after the third dose of the rotavirus vaccine?

MS. SAINDON: No, that's the opposite. That is an exclusion.

MR. JASON SMITH: Exclusion, I'm sorry, I said it the wrong way. So in other words that would not be a presumption of causation.

DR. JOHANN-LIANG: The studies actually showed that when you look at the total, there doesn't seem to be any difference in the incidence of intussusception of kids, looking at the first year. So it looks like there may be a small attributable increased risk for the first dose, definitely. Maybe the second dose. We are just doing that as a Guiding Principle, give the second dose.

But the third dose, the data really looks like it may be protective, which is just to say that at the end of the year everybody sort of ends up in the same place. So for us to say that would be a presumption of causation, would be really too much of a stretch. So that's why it's not --

MR. JASON SMITH: It is? So you feel comfortable that the data is supporting this exclusion from a presumption --

DR. JOHANN-LIANG: Yes.

MR. JASON SMITH: Okay.

DR. JOHANN-LIANG: Dr. Smith, Candace? Are you on the call?

DR. CANDACE SMITH: Hi.

DR. JOHANN-LIANG: On the West Coast. Do you want to elaborate a little bit more on the third dose issue? That is a question that came up.

DR. CANDACE SMITH: We have a study. Even from the very beginning, the pre-marketing studies, it looks like we were protective at the end of a year. You know, as they did those pre-marketing studies they looked at the end of a year and they were very protective against intussusception. So as the post-marketing studies have gone on, they have actually looked at first dose, second dose, third dose, the risk with each one.

And what they noticed is that the risk is well below one. Which means that it is protective by the third dose. I think the most recent data is that you are at a risk of .2, and a risk of one is, all things being equal, there is no risk. So when you get to a risk of .2, that means you are actually more likely to be protected against intussusception than to get an intussusception after a third dose.

And the reasoning behind that is, I guess the best way to say it is the vaccine has kind of primed your intestine and protected it against it. So that if you were to have some sort of trigger for an intussusception, your intestine is now primed and it is not going to have it. I hope that makes sense.

MR. JASON SMITH: So it did show then, with each administration of the vaccine the relative risk decreases from first, second, third?

DR. CANDACE SMITH: Yes, we drop a lot. So I think the Australian data was the most important. The first dose was a relative risk of about five, the second one was about 1.5, and the third one was .2.

DR. JOHANN-LIANG: So it would be very hard for us to do that as a presumption. So that is why it would be very hard for us to put that, just lump it all together. We really struggle with this. We really think that this

is, under the Guiding Principles, the most generous way to do it, including the second dose into the presumption, but really making sure that we say, a third dose, if the vaccine is actually protective, we don't want to say that is presumptively causal for intussusception.

DR. CANDACE SMITH: And I think it is important to also say that just the natural intussusception, that third dose time is the time when you should be at the highest risk, the peak time for intussusception. So it is really remarkable that you are seeing such a drop in the people who receive their rotavirus vaccine, for that timing of the third dose. So the science definitely points to the third dose as protective.

DR. DOUGLAS: You noted a one in 100,000 occurrence. How does that match up against other injuries in the table?

DR. JOHANN-LIANG: That's a good question. Was GBS, if you look at GBS, in the background, it is probably one in 100,000. So that would be like a natural GBS occurring. So that's not on the table, but I am just trying to think about the things, the claims that were coming in. Thrombocytopenia, about one in 50,000, one in 40,000.

PARTICIPANT: So this is good. This is very good.

DR. JOHANN-LIANG: This is very, very low risk. We had a discussion about even mitochondrial incidents. This is just diseases. We are talking about some things on the table. And something in one in 4,000, that's what he was talking about. So we are talking about a very, very, very small risk.

MR. DAVID KING: That would be 10 in a million though, right?

DR. JOHANN-LIANG: Right.

MR. DAVID KING: And how many vaccines are administered?

DR. JOHANN-LIANG: For rotavirus?

DR. CANDACE SMITH: About 30 million to date. For RotaTeq, right?

DR. JOHANN-LIANG: 30 million, Candace, or less?

DR. CANDACE SMITH: Sorry, I didn't hear that.

DR. JOHANN-LIANG: For RotaTeq.

(overlapping voices, off microphone)

DR. JOHANN-LIANG: 30 million. Flu is what, like 160 million last year, per year. I don't want to give numbers without actually having it in front of me. And I have that data, so again, get that to me.

MR. DAVID KING: On the actual number of vaccines that are given.

DR. JOHANN-LIANG: Distributed.

MR. DAVID KING: Distributed, right. We don't actually know how many are given. We have gone through that, yes, I remember that.

MS. PRON: My question is, if we decide to go with the proposed amendment and the study that comes out suggests something different, which may be not for another two years before we really get the final count and we decide it's really going to say what we want, we can change it again, right?

DR. JOHANN-LIANG: Yes. But it is about two years to go. So that's a question. We could wait. If it was a claim that is coming in a lot it may be really nice to have a presumption so we could move cases along. But as I have shown you, the experience, it is not a huge number of claims.

So we could wait. That is one of the choices that we have, wait for the study to come in. The other side of that is that there is no assurance that that study will be definitive, either. We may still be uncertain at that point.

MR. DAVID KING: I know there's not a great number of claims. But based upon current data in terms of the number of claims that we have, a third of those claims are occurring after the third dose.

DR. JOHANN-LIANG: Third dose, yes.

MR. DAVID KING: Right. And we are excluding the third dose here.

MS. PRON: That's just for the automatic, you know.

DR. JOHANN-LIANG: That's a presumption of causation.

MS. PRON: Presumption of causality. It doesn't mean that they are not going to get compensated down the line.

MR. DAVID KING: Understood. But I would suspect that if it isn't on the table, the case would be made if one were to say. they'd say, well, it's not on the table. I think it will be a lot harder for someone to make their case if the table doesn't reflect it. It makes it more difficult for the petitioner.

And, since we are supposed to be, according to the Guiding Principles, more aligned with weighing more heavily on the petitioner's side of the table than on the other side of the table, that we would --

DR. JOHANN-LIANG: But you have to have some sort of a -- you are not just going to, everybody who has an IS, you are not going to be compensating. You want to try to tease out who possibly is injured due to vaccine, and want to be very generous about that. That's, i.e., the interval, the dose, the second dose, et cetera.

But if the vaccine really looks like it is something that is protective against an adverse event following that dose, it would really not be -- it doesn't make sense to say --

MR. DAVID KING: No, we might not know. The research is not 100 percent complete. And we don't have the adjudication of these claims yet, so there is no determination yet, I suspect, on a third of the claims already that are saying that it happens after dose five.

DR. JOHANN-LIANG: Dose three?

MR. DAVID KING: Dose three, excuse me. So there are questions. I am afraid to rush into decision-making here without some lengthy understanding discussion related around to things that answer, like, the number of vaccines. The Vaccine Information Statement that currently exists would be useful for us to be reviewing, so that we could compare it in case there is anything here that might --

So there is a lot of information, I think, that we would still need to have to have a conversation about, before we rush to any judgment. So I am thinking more in terms of cautiously moving forward, but I am not yet prepared to throw a motion out on the table here on that, because I think we should discuss this a little bit further.

MS. DREW: I am in agreement with Dave, but I

need a little clarification on B, where we have onset within one month after an infectious disease. Does that mean any infectious disease? Does that mean a child who is vaccinated while he's got the sniffles isn't going to be covered under this? I don't really know what that means.

DR. RUBIN: The qualification has the examples, as I have talked about and discussed, that the main infectious diseases were the viral diseases and the bacterial enteritis, and also parasitic infections.

MS. DREW: But what it says is, an infectious disease, including -- and then it goes on to say without regard to whether the organism of the infectious disease is known. The way I read that is, if the child has any infectious disease including the sniffles, which we can probably presume is a virus, when the child is immunized, that is within a month, that child is not going to be subject to the table. It is not going to be a table injury.

DR. RUBIN: When a claim comes to our program, the medical reviewers do review this. Most of the time all of us are really, we would do a literature search. And most of the literature doesn't necessarily show a strong association with just, as you call it, the sniffles.

MS. DREW: But that is what the statute is going to say. Irrespective of what your review may show, this is

what the statute says. So maybe that needs to be reworked and make it clear that you are talking about something intestinal as opposed to what it says now. I've got a real issue with that.

DR. JOHANN-LIANG: When you look at the literature, mainly the one month comes from exactly what is listed there, which is the antiviral disease, which actually is not just enteric antiviral disease but can be a systemic antiviral disease. Some of the bacterial enteritis, as well as parasitic infestations of the gut, basically. And they are acting like a lead point, which we don't really see in the US very much.

So if the concern is that the language is too broad so that it may make things like viral infections, upper respiratory tract infections as an alternate factor, then that's something we can try to -- yes, we are open to that. We are talking about infectious diseases that really we know as causal for intussusception, that is well known to be causal for intussusception.

There is a lot of literature even on using antibiotics could be intussusception association, or ear infections. So those are not what we were thinking of as we were listing the --

MS. DREW: Also the word, within one month. Is this within a month of the first manifestation of an

enteric disease? Or within a month after it is over? This is so vague that I can just see all kinds of litigation being sparked by this, litigation that isn't necessary if you folks clarify it before you put it into the statute.

MS. WILLIAMS: This is Michelle Williams. Are there additional studies other than the PRISM study? Are there still post marketing studies going on?

DR. JOHANN-LIANG: My understanding is that VSD study, which is a US study that was presented at ACIP in 2010, it is kind of closed. And they are either preparing or have already prepared for publication. And the denominator for that, again -- and it's mainly RotaTeq, because it is US-based -- the denominator for that is just under a million.

They see nothing. There is no attributable risk at all in the US to the RotaTeq vaccine. Now I don't know, because it is not published, but this is personal communication with the CDC person. So that is pretty much done. It is my understanding in the US.

There is probably other, outside the United States ongoing, with surveillance, et cetera, particularly in Australia. I think that there is an ongoing study in Australia with rather than doing -- remember I told you the Buttery study was really looking at intussusception happening over the expected background from historical

background in different provinces of Australia.

The one that is ongoing, that's my understanding, is actually doing this more self controlled, which is thought to be a better quality study. So the Australians are ongoing. But in the US I believe, Michelle, the only thing we have is the PRISM. And we wouldn't have any preliminary results until end of next year, at best.

MS. WILLIAMS: And you had said -- I'm trying to get a timing question to go to Dave's and Sherry's comments, trying to move forward but maybe get additional information at the same time. You started your notice, you are drafting your notice. And when would the notice have to go in? If we were to vote on it, when would the notice go in? Would we see that notice before it got published?

DR. JOHANN-LIANG: Sure.

DR. EVANS: You will vote and make a recommendation to the Secretary, and that will be taken under consideration with the Department, and then the notice will be published. And, as everyone else will, you will have public comment, a six-month period of public comment in which it can further be amended. And it will be in the form of a final report.

MS. WILLIAMS: That was my question. If we voted now and then the Notice of Proposed Rulemaking would be drafted. But if there was additional information that

Sherry and Dave think need to be elicited, that would be able to be done at the same time? Or would that require a new recommendation?

DR. EVANS: It can always be adjusted and tweaked, but there wouldn't be a formal -- at least we have not done that in the past -- a formal reconsideration before it is published. But again, there can always be changes after it is published because that is the whole purpose of public comment.

MS. WILLIAMS: Just to try to figure out if we are kicking the can or if we are going to expand or if we are going to delay, if there is additional information that could be incorporated into the Notice of Proposed Rulemaking as comments?

DR. JOHANN-LIANG: Right. The Notice of Proposed Rulemaking, it will take us some time to get that draft together even though we have started drafting it. It's a regulation. It has to go through multiple clearances through the agencies. That's going to all take time. 2012 is an election year, we have been told. So any rulemaking will take time.

We don't want to delay too much. But let's say that during the process of proposing to NPRM -- and we can always make changes, of course. And then even when the NPRM goes out, it goes out for six months for public

comment and everybody is free to comment. That's what we are supposed to do, the Secretary, and hearing.

MS. SAINDON: Just to clarify one other thing. By law you have 90 days. So you do not need to --

MR. DAVID KING: I was going to get a clarification on that from you, if I could. On the slide it says at least 90 days. So do we have more than 90 days? Or do we only have 90 days?

MS. SAINDON: I think we can cut it off at 90 days, because the Secretary has --

MR. DAVID KING: That doesn't answer my question actually, if we can cut it off at 90 days.

MS. SAINDON: 90 days, you have 90 days.

MR. DAVID KING: So the at least 90 days is an incorrect statement on the slide?

DR. JACOBS: No. It says the Secretary has to afford the ACCV at least 90 days. So if they afford you 90 days --

MR. DAVID KING: Then they can do what they want.

DR. JACOBS: Yes.

MR. DAVID KING: Thank you. Now I have the understanding, thank you, perfect. So we would have till March 9th? Is that accurate? Or because we do have 29 days in February --

DR. JOHANN-LIANG: I don't know, we have to look

at the calendar. Is that including business days or weekends?

DR. JACOBS: I guess not. 90 days is 90 days.

MR. DAVID KING: That's what I would do, 90 days. So we meet on March 8th, and on March 9th. So we would be within the timeframe of the statute, to be able to give a recommendation if we were to review this at the next meeting, say. And it might be more than a 15-minute conversation.

DR. EVANS: Your comfort level is what is paramount. If you need additional time to consider this, that's fine.

DR. JOHANN-LIANG: And that's your choice here. If you'd like to review the proposal.

MR. DAVID KING: This is one man's opinion, though.

MS. PRON: At least in my understanding -- I need clarification here if it's not correct -- this is Ann Pron, for the people on the phone. Currently rotavirus, there is no table of injury for rotavirus. So in fact, by adding this, at least we are helping some folks, some parents, to move along quicker. But if we don't add it, everyone has to go through the long process. Am I correct?

DR. JOHANN-LIANG: Yes, that is correct.

MS. PRON: So it may be in the future, if more

data -- because right now the data for dose three is not really meaningful. There is not really anything in their research that showed that there is an association between dose three and intussusception. In fact, it goes in reverse is what they are saying. It is a decrease in intussusception after dose three rather than an increase in cases.

So that if we pass this, in some ways we are erring on the side of helping families rather than setting up obstacles. That's my read. Is that accurate?

MR. DAVID KING: I think that is one interpretation. But I think that we may also be impeding if we move too quickly because of the wording that Sherry has brought up, in terms of what specifically does that mean. So I think that we may be creating a litigation nightmare and dragging things out. But I do think that we need to be sensitive, though, to the fact that nothing is on the table.

So I have a couple of questions, then, that will help me in my thinking here. One of the questions is, if we were to not wait till the next meeting to do this, and to do this today, what material difference would that make to getting it onto the table, as opposed to waiting till March 8th or 9th?

In terms of what is the real timeframe, is it

going to make any significant difference? Or is it still going to be the same time period?

DR. JOHANN-LIANG: It is really unclear, because the timing of clearances is really not in our control. But I can tell you that you guys have a lot of work ahead of you with IOM. We are working really hard to try to bring stuff to you next year, so we have got a lot of work to do to move things forward.

The idea behind this is to take a program that is so much off table, and so as you heard yesterday there is a lot of litigation involved, to try as best we can with the current size, with the Guiding Principles in mind, to add things to the table so that we could give presumption of causation. The medical folks are all here for presumption of causation. That will really cut down on the time clock, and we want to move things forward.

So the idea of waiting is fine. That is one of the choices that we have, because it really is up to your recommendation as to what you want to do. But I think next year, personally, we are going to be in a lot of time crunch. I am not sure. This is off of IOM, and we have these signals from outside of the US coming in. We should try to bring this to you. But it is really up to you.

MS. WILLIAMS: Let me ask another timing question, then. Would your Notice of Proposed Rulemaking

go in to start the clearance process before our next meeting?

DR. JOHANN-LIANG: We would like to.

DR. EVANS: To add on to what Rosemary said, in a shorter version, the IOM track is going to be thick, long, wide, lots of things on it. We had the perhaps idealistic notion that we could have a quick, narrow short track to get this done, as separate, get it within the Department and they could clear it sooner, and not be as involved as we are facing with the other rulemaking. And we got the agreement to do it that way, which is a little different.

Normally people like to lump things together and just do it all at once. We said no, this is different, this was not IOM, and we think this is much more condensed and simplified. But, as a great philosopher once said, nothing is ever simple. I think the questions raised today are legitimate questions, if somehow we can come to some agreement and some answers. But if this could go forward sooner than later I think it is better.

DR. FEEMSTER: I have one question about the data. One thing that I noticed, for RotaShield the rule very specifically referred to rhesus-containing, they really talked about the components of the vaccine. This time it doesn't. Really, the data is quite different. There is some suggestion that we may or may not end up

finding a definitive signal as studies are ongoing, particularly in the US, for RotaTeq.

Was there any thought about -- I am not saying that we shouldn't add this to the table -- but about being specific about the vaccine components? Because if down the line, the PRISM study doesn't show a signal with RotaTeq, for example and we may make a decision to change the rule.

But Rotarix -- I mean, they are both quite different, and you could argue that they may act a little bit differently in the gut. One is human-based, one is bovine-based. I just wondered if that was something that you did talk about, because it was so specific with RotaShield.

DR. JOHANN-LIANG: That is a very good point.

DR. FEEMSTER: And the data, especially now that I hear that the Buttery study was comparing historical data, that really makes it less powerful in my mind, if we are weighing the strength of evidence.

DR. JOHANN-LIANG: I have to tell you, preliminary data, although nothing is published yet, of the self-controlled, the better, it seems to be in line with what they have already shown. It is not contradictory. Yes, Dave, go ahead.

MR. DAVID KING: So --

DR. JOHANN-LIANG: This is in regards to her

query, right? Otherwise I am going to respond and then you can say.

MR. DAVID KING: You are going to respond to the query here?

DR. JOHANN-LIANG: Yes, are you responding to her query?

MR. DAVID KING: No.

DR. JOHANN-LIANG: Can I just respond to it then? You are absolutely right. We could do what we did before with the RotaShield, which is, you leave the rotavirus vaccine blank, and then add another row that specifically says only for the RV1 or the human-based, whatever. Not the bovine-based, but the human-based. We could do that.

But the struggle that we had was, because Rotarix is underutilized in the US, although we don't know what the uptake will be, we don't even have one claim for it actually. So we decided that, let's say that Rotarix, RotaShield, that's two of three vaccines already, why don't we just do the general characteristics? Again, applying the general principle. We are trying to be overly generous at every turn here.

DR. FEEMSTER: I can see that. It's just there seems to be such a differential at least. It seems like the stronger data is associated with the bovine-based vaccine. But I understand that as well.

DR. JOHANN-LIANG: You see it's a lot of levels.

DR. FEEMSTER: It's not easy.

MR. DAVID KING: So there is a consensus I think that we want to do something because we should. The question is on timing. But there may be a way to make the timing happen. Could there be changes made to the proposal now, as we are speaking, that incorporated the concerns that Sherry raised?

In other words, can we change the wording of this right here and do some things along that nature to tweak this as we sit in this meeting, it changes it, and then we might be able to give you something that you can move with today?

DR. JOHANN-LIANG: I am not sure if time is going to allow us to word something right now. If they vote to move this forward, can we have them make comments to the --

MS. SAINDON: Yes, the law requires, we are seeking your comments and your recommendations. So if your recommendation is to move forward and incorporate as many of your comments as we can reasonably do, that is a totally reasonable recommendation.

MR. JASON SMITH: Dave, can I suggest along the same lines -- and I am in complete agreement, I think Sherry's concerns are good ones. Could we possibly recommend that we move forward, but ask the Secretary to

consider some of the concerns raised by Sherry so that it doesn't appear to be from a language standpoint overly restrictive in terms of that Paragraph B?

DR. JOHANN-LIANG: And that is precisely why we provided you with all the references that we use for each qualification, so that you can actually take a look and see what your thoughts are on the matter. So we really welcome that. That is why we are asking.

But as far as recommending what you want to do, if you are concerned that if you recommend to move this forward now it has got to go exactly the way it is, it is going to take a lot of time to get it to --

DR. HERR: You can't change any words at all on it.

DR. EVANS: No, of course you can. In other words, specify the kinds of changes you would like to make.

DR. JOHANN-LIANG: I didn't hear what Tom said.

DR. HERR: I was just, you were making the statement, it has to go as it is.

DR. JOHANN-LIANG: No. The recommendation is to say, we want to do the table change. And I think what I am hearing relevant to this is, that we welcome, and that's why we provided you with every slide with the references, et cetera.

MR. DAVID KING: Just so I understand, because I

don't want a motion to get on the table and we all go down the road with a motion that we think means something but it means something else. So before we make those motions, let's very quickly make sure we understand what we are talking about here.

Which is, if we were to recommend that we wanted to go forward with the change to the table, could we in that recommendation specifically state, subject to certain changes in this, and then that would then be the recommendation so that it would be the recommendation is that we want some of these changes? Can that be done?

DR. EVANS: Yes. For example, the Commission years ago voted to add GBS for tetanus vaccine and for the Secretary to develop an Aids to Interpretation to accurately identify cases of vaccine-related GBS. Well that was not possible, and the Secretary decided not to add GBS to the table. That was the ACCV's recommendation. The Secretary didn't take it. So you can recommend --

MS. SAINDON: But your recommendations will be included in the preamble to the Notice of Proposed Rulemaking, and we take them very seriously. So we are seeking your comments.

MS. WILLIAMS: I think Dave's question is, will the Notice of Proposed Rulemaking have this paragraph just the way it is? Or will the Notice of Proposed Rulemaking

be changed to have the paragraph be changed?

DR. EVANS: It is likely to be changed, and it may be changed in 100 percent the way that you all are describing, or there may be variations on the theme. But the point is, you are voting to both add something to the table as well as comment and endorse changes to the Aids to Interpretation that will describe the injury that is being added to the table.

MR. DAVID KING: Which is not exactly the same thing as making the actual change. Is that correct?

DR. EVANS: Yes, there are two things. You are adding under the general category of rotavirus vaccines, you are adding intussusception with an onset of zero to 21 days. That is the first recommendation. And then the second would be pertaining to the Qualifications and Aids to Interpretation.

DR. JOHANN-LIANG: I just want to add, though, if we didn't have the IOM things coming down the line, we may have much more, just practically speaking, much more time. But because we want to start tackling those things starting the next ACCV meeting, as I told you in the beginning of the slides, it would be helpful if you guys, for that second motion, if there was some sort of a timeline that you would bring your recommendations and suggestions and comments to us.

So that we can try to do the NPRM, try to get that out, at least before March. We can't promise anything, but we are really trying to move things forward. Does that make sense? We don't want to be just waiting. It's another way of saying that we really want to hear from you and incorporate what you want to say to the NPRM. But we do have timeframes here, for us to move forward.

MR. DAVID KING: There is a saying, though, haste makes waste. Let us be careful.

DR. HERR: This really is simple. But in your alternate underlying conditions, on your slide you thought it was important enough and during your presentation, to say inflammatory bowel disease. But it is not in the statute recommendation changes. Should it be there?

DR. JOHANN-LIANG: The inflammatory bowel disease, really to be complete. It is more adults that can actually have something like intussusception, or bigger people. Usually babies, babies at six months, really there is no diagnosis of Crohn's or ulcerative colitis. We really geared it more towards that and that was the logic behind it.

DR. HERR: I just thought, you thought enough of it to put it on your slide.

DR. JOHANN-LIANG: I think she was trying to be very comprehensive.

DR. HERR: Okay, that's fine.

DR. DOUGLAS: But in terms of advocacy for parents who are looking for remedy, the best move for them would be to have this on the table.

DR. JOHANN-LIANG: We are always trying to see what would be best. Because it will help the presumption to move forward. We would be doing everything else the same way we are doing right now. It will cut down on the amount of time, but again, we really want to hear from you, and this is really good, the discussion that we are having, because there is a science and there is a policy, and then there is the patient advocacy. And those all have to kind of merge.

That's what is very different about this, that pure science will logically say, we wait. But the program and what our goals are, is a little bit different than that. It is more over-arching than that. So that is why we have before you. If it was purely left up to science, Dr. Tom, we would wait. Right? Absolutely.

DR. HERR: This is Tom Herr. I would like to move that we approve it.

MS. PRON: I will second it.

MS. WILLIAMS: When you say I approve it, I don't know what it is.

MR. DAVID KING: Your motion is to approve

exactly --

DR. HERR: As distributed. With the underlying assumption, a realization that the Secretary can change this as she wants.

(overlapping voices)

DR. HERR: What we are doing is approving that we would like to move forward on the issue. And the issue is to make a table of injuries, to facilitate taking care of the kids who have qualifications specified on the table. And move it on.

If there are some things that are sort of in between the need to be fixed, that can be done. And the assumption is that the Secretary will do that. And if it doesn't, it will come back and people will argue about it, and we will say we want more.

MR. DAVID KING: So there is a motion on the table that was seconded. So we should vote on that.

(Whereupon, the motion to go forward with the recommendations for a change to the Table, with the understanding that comments have been made concerning wording on the Aids and Qualifications, and with the hope that the Secretary will re-read the wording and consider the suggestions and comments made by the Commission, was duly seconded and unanimously approved.)

DR. HERR: We don't need the second motion based

on that.

DR. JOHANN-LIANG: That is perfect.

MR. JASON SMITH: Sherry, can I just add one other suggestion, just as a general commentary to some of the language?

MS. DREW: Please.

MR. JASON SMITH: With various other vaccines on the table, and some of the injuries listed, there is a section, Section C, for example, for vaccines containing tetanus toxoid, vaccines containing wholesale pertussis, Section C, where it is this generic language about any acute complication, the sequelae of an illness, disability, injury. Sort of along the lines that Sara suggested before.

It seems that it is listed for every injury except for this vaccine. If we can also suggest that the Secretary consider that.

DR. JOHANN-LIANG: Very good. So we really look forward to -- it is very helpful to have people's comments, second look, third look. Do you guys want to have a general discussion about when you want to bring the comments to the Secretary?

DR. EVANS: The comments are on the record. We will look at the transcript.

DR. JOHANN-LIANG: There is nothing else?

DR. EVANS: There is nothing else we need to do.

MR. DAVID KING: The only thing is that when we talk about the Vaccine Information Statements, I would think that where they talk about when can you get it, or who should not get it, or things like that, it should be consistent with the wording that you have in here, with all that. That is really what we are talking about.

DR. JOHANN-LIANG: Those are good comments.

MS. PRON: That would be for the next agenda, for the next meeting maybe, to re-review the rotavirus? Is that what you want to do?

MR. DAVID KING: No.

MS. DREW: No, the VIS.

MR. DAVID KING: Oh, the VIS, to review the VIS on it?

MS. PRON: Because that is what you are making reference to, the VIS now?

MR. DAVID KING: Yes, but that was more in terms of the actual comments on it.

MS. PRON: But I don't think we can add anything unless we come here.

MS. DREW: We are running really late. So I think we need to move on.

(Brief recess)

Agenda Item: Update on the Immunization Safety

Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities, Dr. Tom Shimabukuro, CDC

DR. SHIMABUKURO: In the interests of time, I will move through my presentation fairly quickly. But before I start I just want to acknowledge the contributions of Dr. Jane Gidudu, who is my predecessor. I am pretty sure that I will be here with everyone who is going to be on ACCV three-year terms before I eventually rotate off as well. But it is a pleasure to join you.

One update which I don't have on my slides, I was able to confirm yesterday that there is a clinical trial going on. It is called Immune Responses in Adults to Revaccination with Adacel 10 Years After Previous Dose. So that work is underway, to look at that as a 10-year booster.

I am going to cover some highlights from the October ACIP meeting. The two I will is the Gardasil safety review and the ACIP vote. And then just an update on the VSD febrile seizure investigation. I would just mention our role in supporting HRSA in the IOM-generated task force, and then some recent selected publications.

There was a very extensive review of Gardasil during the last October ACIP meeting, which was the lead in to the vote on males. And the data sources for this review were from pre-licensure studies, data from VAERS for both

males and females, data from vaccine rapid cycle analysis in females, and then two manufacturer sponsored studies. This is the Nordic long-term follow-up study, and the long term study of Gardasil in adolescents.

That information was presented during a previous ACIP meeting, and that is available. Actually this presentation, this comprehensive review and those two manufacturer sponsored studies, those presentations are available on the ACIP website. I am actually not going to go into details. I recommend you do look at the Gardasil Safety Review by Julianne Gee, an epidemiologist in our office. It is very thorough.

Before I get into this actual summary, I will just say that there was data presented on males specifically in Julianne's presentation, because there was a vote on males. And just going through some of the numbers there is a total of 569 reports for males, and most of these over 500 were post-licensure reports. So there were a few pre-licensure reports in there.

The breakdown for serious and non-serious is roughly 94 percent non-serious and six percent serious. That is consistent with what we see in VAERS. If you looked at what we call the MedDRA Preferred Terms -- so these are codes we look at in VAERS, they are not mutually exclusive, so an individual could be coded to have multiple

MedDRA Preferred Terms with a single report -- for serious reports we did not see any pattern, which is reassuring.

There were two death reports, verified death reports for males. One was a case of myocarditis in a 10-year-old with no past medical history. The other was a death in a 15-year-old, 25 days after vaccination, who had a known congenital heart disease. This is all available on the ACIP presentation, which is on line at the ACIP site. So no new adverse event concerns or clinical patterns were identified in this VAERS review.

The VSD rapid cycle analysis confirmed no significant risks for pre-specified adverse events after vaccination for females nine to 17 years and 18 to 26 years. You can see the pre-specified adverse events there. Of note in the VSD rapid cycle analysis study, there was a non statistically significant increase relative risk for venous thromboembolism among nine to 17 year old females. This study was just in females.

It is important to note that there was a pattern that many of these cases had known risk factors for VTE, like obesity, smoking, oral contraceptive use. Which is not to say that the vaccine couldn't have aggravated an underlying condition. But there is further work in VSD to assess this finding, to include looking at other vaccines other than just HPV4.

Further evaluation of VTE post-vaccination is ongoing through other studies. And the long-term follow up of adolescents have not identified any safety concerns. Those are from the two manufacturer studies.

So ACIP voted on vaccination for males, and their vote was a routine recommendation for HPV4 for males 11 to 12 years. And this series can start as early as nine years of age. Males age 13 to 21 years who have not been vaccinated should be given catch up vaccination. And males 22 to 26 may be vaccinated, but there is not a recommendation for routine use.

Moving on to the VSD febrile seizure investigation, I know Jane briefed you on this investigation. So the previous flu season, 2010, 2011, VSD was monitoring nine outcomes, to include seizures. And looking at inpatient and emergency department settings, because the coding for outpatient seizures in VSD is not really good. But the coding for inpatient, the positive predictive value, is fairly high.

So VSD detected a possible increased risk of febrile seizures on days zero to one, post vaccination, in this age group, six to 59 months, who received a first dose of TIV. After chart review and confirmation, it looked like the risk was highest in the six to 23 month age group. And most had received other vaccines, most commonly

pneumococcal conjugate vaccine and DTaP.

So the VSD investigators in CDC have presented this a couple of times to ACIP. And what you see here on this chart is actually the updated, what we think is going to be the final updated results. This has been provisionally accepted, this paper is provisionally accepted to the journal Vaccine, and hopefully will be published fairly soon.

What the investigators did for reasons which are more into statistical methodology, they transitioned from an age stratified analysis, to a statistical model. So previously you may have seen these breakdowns -- six to 11 months, 12 to 23, 24 to 59 -- and seen the relative risks in those age groups. And the decision was made to go with a statistical model looking at the entire age group, but it really didn't change the bottom line.

As you can see here, there is a slight increased risk in febrile seizures in this age interval for inactivated influenza vaccine, without pneumococcal conjugate vaccine. That is also plus or minus other vaccines. And also a slight increased risk for PCV13, without TIV, but with other vaccines.

But really the risk is highest when TIV was given concomitantly with PCV13, and other vaccines, still in this roughly 12 to 23 month age group, peaking at about 16

months of age at an attributable risk of 45 per 100,000. If you flip that over that is about, in the age group, one additional febrile seizure for every 2,000 to 3,000 vaccines administered.

So the recommendations after CDC and ACIP looked at this, was that there are no changes in the immunization schedule that were necessary at this time; giving recommended childhood vaccines during a single health care visit has important health benefits, and timely vaccination can prevent influenza and pneumococcal disease and may actually prevent febrile seizures from fevers from these infections.

In our communications piece we also noted that scientific evidence -- scientific studies have not shown that fever reducing medicines like Tylenol or Motrin prevent febrile seizures. So there is no recommendation to use those prophylactically. And of course aspirin and aspirin containing products should not be used to reduce fever in children, because of the increase in Reye Syndrome. There is a more comprehensive study underway in the Vaccine Safety Datalink to assess febrile seizures in general, and the contribution of other vaccines.

So I just want to point out that we have 16 ISO staff that are currently supporting HRSA as members of this task force that is reviewing the IOM report and generating

recommendations to update the Vaccine Injury Table.

A couple of quick notes on publications. We recently had a publication come out, Duderstadt et al., which looked at data in the defense medical surveillance system. The bottom line on this study was there was no increased risk of diagnosed type I diabetes in any of the study vaccines. And you can see those vaccines there. Some of those are not really used that much in the civilian world.

We had a study come out from the Vaccine Safety Datalink on wheezing lower respiratory disease and vaccination of premature infants. And there was no evidence of increased wheezing lower respiratory disease following routine vaccinations of premature infants.

And wheezing lower respiratory disease among non-fragile premature infants appeared to be reduced for a few weeks after live attenuated vaccinations. This did not include LAIV. These live vaccines were MMR, varicella, OPV and I think those are the live vaccines they looked at.

The top paper is just the HPV4 VSD rapid cycle analysis paper that I discussed. And then the last paper, Huang et al, was a survey of physicians looking into really knowledge, attitudes and behaviors around the ACIP recommendations to prevent injuries from post-vaccination syncope.

And the take home message on this paper was that few physicians are aware of the recommendations for post-vaccination observation for syncope, and even fewer adhere to them. So there is room for improvement in that arena. That is all I have and I will be happy to answer questions if you have any.

MS. DREW: Thank you. We are going to go out of order a little bit on our agenda, and call for Dr. Salmon, who needs to give his report, his update from the National Vaccine Program Office as soon as possible. Dr. Salmon, are you there?

Agenda Item: Update from the National Vaccine Program Office (NVPO), Dr. Dan Salmon, NVPO

DR. SALMON: (off microphone) Yes, I am on the line. Thank you for allowing me to go out of turn. I appreciate it. The update that I give, I want to focus on an upcoming NVAC, National Vaccine Advisory Committee meeting February 7th and 8th.

PARTICIPANT: Can you speak a little louder?

DR. SALMON: Can you hear me okay?

PARTICIPANT: No.

MR. DAVID KING: Slowly and louder, please.

DR. SALMON: Let me try again. This is Dan Salmon from the National Vaccine Program Office. The update I would like to give is on our next NVAC meeting,

the National Vaccine Advisory Committee, which gives advice to the Assistant Secretary for Health on vaccine policy. Our next meeting is February 7th and 8th. Can you hear me okay now?

MS. DREW: Yes, thank you.

DR. SALMON: Okay, good. There are a number of items on the agenda which I can go through briefly but I think one in particular which will be of interest to this group. So the draft agenda which is still being finalized includes topics such as the Adult Immunization Working Group Health Care Personnel Influenza Vaccine Subgroup, discussions of 317 funds and vaccine financing.

There will be updates from each of the agencies and liaisons. There will also be international discussion of immunizations in the international arena. And lastly, not on the agenda but in terms of what is most important to this group, we expect to file a report from the Vaccine Safety Risk Assessment Working Group.

The ACCV has heard of this group before. This was the working group that was set up for H1N1, and it looked at all the safety data from the many systems that were monitoring the safety throughout the vaccine program. At this point they have been reviewing all of the end of season analyses.

They have put together a final report, which will

be presented to and deliberated upon by the NVAC at the February meeting. This will be a summary of what we know about the 2009 H1N1 vaccine. Let me stop there, and I am happy to answer any questions.

MS. DREW: No questions. Thank you Dr. Salmon.

DR. SALMON: Thank you.

MS. DREW: Is Dr. Barbara Mulach on the line?

DR. MULACH: Yes, I am here, and I am ready, if you are ready for my update.

MS. DREW: Thank you. Just one second. You will be giving an update on the National Institute of Allergy and Infectious Diseases, National Institutes of Health and Vaccine Activities. Thank you for waiting for us. We are a little late, but please go ahead.

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

DR. MULACH: Sure. I just have one main thing that I wanted to make sure that everyone was aware of. I have spoken at previous ACCV meetings about the program announcement that NIH and CDC co-sponsor. And that was originally intended to expire in September, and then it was extended through January.

In late November we were able to extend the

program announcement for three more years, which is very exciting. And so just to remind you a little bit about what this program announcement entails, it is called Research to Advance Vaccine Safety. And the purpose is to support research that will contribute to the overall understanding of vaccine safety, wherever there are scientific questions, where we don't have enough information.

I wasn't available for the full morning session but I am sure that one of the topics that was discussed as part of the IOM discussion is that there still are a lot of scientific questions that need to be addressed. And this is one way in which scientists can propose ideas for how to get more information in that area. So like I said, this is the second iteration of that announcement.

It was sort of slow in getting the attention of scientists at first, but I am very encouraged by the number of people who have shown interest in seeing this new announcement that came out in late November. I am very hopeful we will be able to encourage people to look at some of the ideas in the IOM report, and propose ways to try to address those questions and get us more answers.

I will be happy to send the links, for those who are interested in seeing the announcement. Again, we are sharing it with the scientific community as well.

MS. DREW: Thank you. Does anyone have any questions or want the links? Thank you, Dr. Mulach. Lieutenant Valerie Marshall is here to give an update on the Center for Biologics, Evaluation and Research, Food and Drug Administration Vaccine Activities.

Agenda Item: Update on the Center for Biologics, Evaluation and Research (CBER), Food and Drug Administration (FDA) Vaccine Activities, Lt. Valerie Marshall, CBER, FDA

LT. MARSHALL: Good morning. My name is Lieutenant Valerie Marshall. I will replace Dr. Marion Gruber as the FDA representative to this committee. Marion Gruber is currently the Acting Director of the Office of Vaccines, Research and Review. The former director, Dr. Norman Baylor, has since retired from the position as director.

Since the last ACCV update of September 2, 2011, there were no new original biologic license applications approved. However, there are several vaccines currently under review, including a vaccine to prevent infants age 2 to 16 months of age from meningococcal disease types A, C, Y and W134 [SIC -- w135?], a vaccine to prevent pneumococcal disease in adults 50 years and older, and an influenza vaccine containing four strains.

The Vaccine and Related Biological Products

Advisory Committee met on November 16, 2011 to discuss and make recommendations on the safety and immunogenicity of the pneumococcal 13-valent conjugate vaccine in adults, aged 50 years and older, using an accelerated approval.

On September 16, 2011, the FDA and the National Institutes of Health, the Institute for Allergy and Infectious Diseases, held a public workshop entitled The Development and Evaluation of Next Generation Smallpox Vaccines. The purpose of the public workshop was to identify and discuss the key issues related to the development and evaluation of next generation smallpox vaccines.

The workshop included presentations on the human response to smallpox vaccines, and the development of animal models for demonstration of effectiveness of next generation smallpox vaccines. And that's all I have for FDA.

MS. DREW: Thank you very much, and welcome to our meetings. We look forward to seeing you in the future.

LT. MARSHALL: Okay, thank you, my pleasure.

MS. DREW: That ends our presentations for the day. Our next agenda item is the nomination and election of a new Chair and Vice Chair for the Commission.

Agenda Item: Nomination/Election of New Chair and Vice Chair, Ms. Sherry Drew, Chair

MS. DREW: Annie, do you have paper for us? Paper ballots? I am not exactly sure how you want to proceed with this. In the past we have had nominations made and then just, if there was more than one nomination we just made a secret vote. I don't know if it will come to that or not, but I am wondering if we could have nominations for the Vice Chair now.

MS. HOIBERG: I would like to nominate Michelle Williams.

DR. DOUGLAS: I would like to nominate Kristen.

MS. DREW: I don't know if you want to say anything. Hopefully the two nominees will be present for most of the meetings. That's probably the biggest qualification. Do you want to say anything?

DR. FEEMSTER: I would be honored to serve as Vice Chair and do plan to attend all upcoming meetings and to work with the Chair to help make sure that we discuss all that needs to be discussed and facilitate a smooth meeting.

MS. DREW: Thank you. Michelle?

MS. WILLIAMS: The same. Top that. If asked to serve I would be pleased to serve, and I do plan to attend all the meetings.

MS. DREW: All right. Now we are looking for nominees for the Chair.

MS. HOIBERG: Dave King.

MS. DREW: Second?

(Seconded)

MS. DREW: Any other nominations? I think that one is easy. And I don't think we need a secret ballot, given we have only one nominee. We still have to vote, but I thought we could do a show of hands. Show of hands for Dave?

(Show of hands -- unanimous.)

MS. DREW: Dave has been elected unanimously the new Chair of the Commission. I will turn this over to you in a minute. If you want to just write down Michelle or Kristen.

PARTICIPANT: Do we have the same length of time of service spanning? Are we on the same term?

MS. DREW: You serve for a year, or however long you choose to serve. You just have to be elected. There isn't any real term.

(Paper ballots collected and tabulated)

MS. DREW: Michelle has been elected our Vice Chair.

MS. WILLIAMS: And may I say it was an honor to run against Kristen a worthy honor.

Agenda Item: Future Agenda Items, Ms. Sherry Drew, Chair

MS. DREW: I am still Chair here, and we are looking for future agenda items now. Tom brought up a subject yesterday, the packaging of vaccines, there should also be something on the label. I think that needs some further discussion. And I don't even know who might address that.

DR. EVANS: Well, we will work on it. It is certainly an FDA issue. Also this issue of a CDC safety, but also has some -- we will work with our colleagues on that.

MS. DREW: Okay. Is there anything --

MS. PRON: It looks like we need something about the VIS for rotavirus, possibly.

MS. DREW: Possibly the VIS for rotavirus.

MR. DAVID KING: Right. We need to determine whether or not -- so the question I have on that, because I do think that it needs to be reviewed, is, is it premature to review it yet, though, if we don't have it on the table? So I don't know if it is necessary for the next meeting or not. I guess we need to figure that out.

MS. PRON: And we need to have an ongoing list of things that will need to come up, even if it is not at the next meeting.

MR. DAVID KING: I will do that. I'll have that. (laughs)

MS. WILLIAMS: There is no reason why it couldn't be included in the packet, even if we didn't have --

MR. DAVID KING: I would agree. That's fair.

DR. DOUGLAS(?): Most of the concerns are not things that would be on the VIS. Most of the kind of background concerns with the wording and the injury table, that would not be on the VIS.

MR. DAVID KING: The future science meeting. Are we going to have a report from them at the next meeting? Michelle? Will there be a future science meeting report at the next meeting?

MS. WILLIAMS: Yes, we can do that.

MS. DREW: All right, future science on the next agenda.

MR. DAVID KING: There was one yesterday, wasn't there?

MS. WILLIAMS: That I didn't attend.

(overlapping voices)

MS. DREW: I think now we need volunteers for the agenda workgroup committee. Dave and Michelle will be on it automatically. Probably we need one or two more folks to meet once or twice prior to the next meeting to clarify the agenda. Kristen? All right, Kristen will be on the agenda meeting. Anybody else?

MS. PRON: I'm not sure how easy it will be for

me to call in. If it's not hard, I will do it.

MR. DAVID KING: So why don't we invite you, and if you can make it, you will.

MS. DREW: And perhaps one of the new people might even volunteer after they have been sworn in. They could be drafted at that point.

MS. PRON: May I suggest another item then, for the ongoing list on the agenda which we said from the minutes? And I said it, but I wasn't sure, because we were all sort of talking at once. But injection practices, changes to injection practices, recommendations about changes to injection practices from the shoulder injury reports that we had.

That was a carryover from the minutes from the last time that we said we would talk about it, put it in as an agenda item. But I don't think we talked about it.

MS. DREW: Okay.

MR. SMITH: Maybe we could fold it into that general topic during the CDC presentation, about this concept of 15 minutes after the vaccination administration, and if it is there to go ahead and try to educate more about the importance of doing that, because of syncope. At some point in the future, probably not the next meeting.

MS. PRON: Follow up to that research study that you mentioned.

DR. HERR: We are currently doing analysis on vaccine errors or administration injuries. Would you be interested in just seeing the actual data on that? Or is this more of an outreach? Are you more interested in outreach and education to vaccinators and how to give proper injections?

MS. PRON: I think that is an issue. That seems to have come up in your study that the ACIP recommendation hasn't been implemented.

DR. SHIMABUKURO: You are talking about the server paper?

MS. PRON: Yes. And the syncope issue.

DR. SHIMABUKURO: The way this works, this goes through the ACIP General Recommendations Workgroup. And I am actually on that workgroup. And this subject has come up from time to time and there was no big light bulb that went on with the servers so far, but that is certainly something that we can pursue because that is recent information.

Syncope they have discussed before. And as I understand it, when you start making recommendations for doing things it becomes a standard of care. And when it becomes a standard of care, then it becomes possibly something that involves litigation. So they are careful about how prescriptive they are about how long and what you

are supposed to do, et cetera.

But this is something that is discussed. Everyone is aware that there is certainly a risk in some children and adults, of having syncope after vaccination. It's something that we can certainly bring back to the General Recs Workgroup and just see what their current thinking is, as far as this issue.

MS. WILLIAMS: Despite being a lawyer, I recognize that it does become a standard of care. And then ensuing civil litigation on a malpractice front. But that is not our concern. Our concern is patient safety.

MS. SAINDON: In fact, the vaccine program covers both vaccine administrators and manufacturers. So even if it is the standard of care, the requirement would be that they come to the VICP. So I think it is absolutely within the purview.

DR. EVANS: This has been pointed out.

MS. PRON: Well, we have already compensated for that, right?

DR. EVANS: And we have compensated, both injection injuries as well as things like post-injection syncope.

MS. WILLIAMS: Why shouldn't it be a standard of care?

DR. EVANS: And the practicalities of 15 minutes

in a busy clinic where there are very few places to wait and so on. It's a lot easier said than done when you put it in a recommendation. So again, we will see what the latest thinking is at the workgroup.

MS. HOIBERG: That goes back to what I have said that the major problem is that the vaccines aren't given the respect that they deserve. They are given out just really willy-nilly. And so especially with the flu vaccine and all, I feel like there needs to be a step back and a re-education of the practitioners and the people who are giving out the vaccines, to be like, hey, listen, you need to take care.

You are injecting something foreign into a body and you don't know how they are going to react, whether they are going to faint, whether they are going to have a -- you have got to be careful how you give it. They are not careful. And so I think that re-education is something that is very necessary.

DR. DOUGLAS: When I was an educator of the initial practitioners, we take it very seriously. And during my first meeting I noted that the large injuries that come when you inject way up here, and my thought was, no one in life has ever been taught to inject way up there. So I just reiterated that we are educating properly initial practitioners.

I know the older I get and the more gray hair I have, the more babyish they look. And they look like absolute children. But they graduate at 21 years old, and professionals with a license. And we can't call them babies or honey or sweetie any more. (laughter)

And I have run clinics in malls and I have run clinics in storefronts. And I have run clinics in incredibly busy clinics and on military bases. We are mindful. We have our little section with the little seats. Especially even what I have learned here, just to reinforce for me that if you shoot a teenager, they are going to drop like a stone.

On that side of the table it is not a void, that we are preparing people who must take a license, and they must know. And so we are working very hard on that end.

MS. DREW: Any more future agenda items? Can we go to public comment? Operator, do you have anybody waiting for public comment?

Agenda Item: Public Comment

OPERATOR: We are showing no public comments at this time.

MS. DREW: Thank you, the public comments session is done. I think the meeting is complete.

DR. EVANS: What I wanted to do is just to reflect on the sad fact that we are saying goodbye to three

people who have been part of the ACCV family for the last three years, and I know at times probably they were going to be part of the family for several generations -- Tom, Sara and Sherry.

I was wondering if any of you would like to give us some parting thoughts, as you sail off, ride off.

DR. HERR: It's been a real honor and it's been an education to be here. I came in with certain expectations and certain ideas about things. You learn, you modify. So it's important, it has been a growth in my being in education. It has been well worth it.

And seeing people who work hard for this, and for the kids and now adults in all phases, whether they be as parents or whether they be as attorneys trying to fight for them, or mobilizing the Justice Department, and Rosemary, the things that they do to try to make things straight and keep things in order.

It is a daunting task. As well as Geoff, trying to keep all of us organized and keep himself in his job. It is hard not being able to always realize what you are trying to do and be fair to everybody. But it has been something I have appreciated. Thank you very much.

MS. DREW: I agree with Tom. It has been an education. I have always tried as an attorney to see both sides to every issue. Here I have seen there has been at

least 10 sides to every issue. I have enjoyed working with the people here. I have made some very good friends, and I thank you for bringing me on, Geoff. I will miss you guys.

MS. HOIBERG: It's been fun. Very educational. Just keep up the work.

DR. EVANS: Well, it's auf wiedersehen, it's not goodbye. But there are various ways that you can help us, and please stay in touch with the program. And maybe we will have televideo, tele meetings in the future and you can always, if you have the time, tune in.

You are one of the select few that has a reasonably good understanding of what this is all about, and a reasonably good understanding is quite a lot to say. Because there is a lot to understand about this program and its ins and outs and so on.

So when you hear someone make a comment about the compensation program from what they have heard or read in the paper, whatever, you have this insight. It will serve us, as you can be our ambassador to try to help people understand what it is we are trying to do, and trying to do the best we can at it.

I want to particularly thank Annie. Give Annie a round of applause. She really has been just great getting everything together. She really singlehandedly has put all this together with a smile on her face.

We have the business to adjourn and we also have business after we adjourn.

Agenda Item: Adjournment of the ACCV December Quarterly Meeting

MS. DREW: Do I hear a motion?

(Motion to adjourn)

MS. DREW: Do I hear a second?

(Seconded)

MS. DREW: The meeting is adjourned, I will bang the hammer for the last time.

(Whereupon, at 11:45 p.m., the meeting was adjourned.)