Advisory Commission on Childhood Vaccines

September 4, 2014

93rd Meeting

Members Present

David King, Chair ('14)
Michelle Williams, J.D., Vice Chair ('14) (via telephone)
Charlene Douglas, Ph.D. ('14)
Kirsten Feemster ('14) (via telephone)
Edward Kraus, J.D. ('15)
Ann Linguiti Pron, DNP, CRNP, RN ('14)
Luisita dela Rosa, Ph.D. ('15)
Sylvia Fernandez Villareal, M.D. ('15)

Division of Injury Compensation Programs (DICP)

A. Melissa Houston, MD., Director, DICP
Andrea Herzog, Staff Liaison

Welcome, Report of the Chair and Approval of Minutes
Mr. David King, ACCV Chair

Mr. King called the meeting to order and invited a roll call of Advisory Commission on Childhood Vaccine (ACCV) members and representatives of federal agencies. He congratulated Dr. Houston on her appointment as permanent director of the DICP. Mr. King noted that several members have reached the end of their terms as commissioners, in particular the chair and vice chair. Therefore it is incumbent on the Commission to select individuals who will serve in those positions for the next term. He added that a number of candidates had been nominated for membership on the Commission, pending Office of White House review and approval.

Mr. King reiterated his longstanding admonition that the Commission's mission is to protect those who are vaccine injured and that recommendations should be developed keeping in mind the importance of protecting their interests. He introduced Ms. Cheryl Dammons, Associate Administrator, Healthcare Systems Bureau (HSB), Health Resources and Services Administration (HRSA), and invited her comments.

Welcome by the Associate Administrator, HSB, Ms. Cheryl Dammons.

Ms. Dammons expressed appreciation on behalf of the agency for the time and effort contributed to the Commission's work. She announced the permanent appointment of Dr. Houston to head newly-named division, the Division of Injury Compensation Programs, which replaces the Division of Vaccine Injury Compensation. The division houses two additional programs, the Countermeasures Injury Compensation Program (CICP) and the Medical Claims

Review Panel. She added that Dr. Houston regularly reports the Commission's activities to her. Also, she assured the commissioners that their recommendations are promptly forwarded to the Secretary of Health and Human Services (Secretary) and that their recent recommendations are under review. Finally, she pointed out how valuable the Commission's help is in reviewing the Vaccine Information Statements (VIS), especially those recently addressed, including hepatitis A and B, tetanus, and diphtheria.

Ms. Dammons invited questions and comments. She was asked about claims that may have been filed under the CICP, and what effect that program might have on the National Vaccine Injury Compensation Program (VICP). Ms. Dammons indicated that the two are different and independent programs. She added that she did not have data on CICP claims. She was asked about the organizational structure of HRSA. Ms. Dammons indicated there was an organization chart on the HRSA web site. HSB is one of five bureaus in the agency and within the HSB there are 11 programs. Three of those programs, all claims related, are under the aegis of Dr. Houston.

Mr. King asked if the Bureau can affect the Commission's interest in having face-to-face meetings. Ms. Dammons stated that the budget is one of the many considerations that influence decisions about whether or not such face-to-face meetings are scheduled. There have been across the board reductions in travel, which directly affects the scheduling of meetings.

Before continuing to the next agenda item, Mr. King mentioned the ethics review that might impact members on an individual basis. He stated that questions could be directed to Laura Ridder who agreed to respond to general questions. There being no other questions, Mr. King moved to the next agenda item.

Public Comment on Agenda

Mr. King invited public comment specifically related to the agenda. There were no comments.

Approval of June 2014 ACCV Meeting Minutes

Mr. King invited approval of the minutes of the June 2014 Commission meeting. Ms. Pron commented that there had been a number of discussions at the meeting and at previous meetings about whether the term "healthcare provider" should be used rather than simply "doctor," since there are a number of patient contacts in the health care environment – nurse practitioner, pharmacist, etc. She stated that there had been an agreement to consider changing the language in the VIS to broaden the term. Mr. King recalled that discussion and Ms. Herzog stated that the revision would be made.

On motion duly made and seconded, the minutes of the June 2014 meeting minutes, including the revision as described in the preceding discussion, were unanimously approved.

Report from the Division of Injury Compensation Programs, Dr. A. Melissa Houston, Director, DICP

Dr. Houston commented that the VICP is co-administered by three federal agencies – the Department of Health and Human Services (HHS), the Department of Justice (DOJ) and the U.S. Court of Federal Claims (CFC). Noting that Mr. Vince Matanoski would make a formal presentation later in the meeting, Dr. Houston introduced Chief Special Master of the CFC, Denise Vowel, who would be participating in the meeting. She introduced the new Chief Medical Officer, Dr. Narayan Nair, who would also be present for the meeting.

Dr. Houston previewed meeting highlights agenda, which included a discussion of proposed changes to the Vaccine Injury Table, an update from the DOJ, a report from the ACCV Process Workgroup, a briefing on the proposed VAERS Form 2.0 that will eventually replace the current hard copy reporting form, safety presentations on pneumococcal vaccine (Pneumovax23) and zoster (singles) vaccine, as well as reports from the ex officio members.

Concerning the activities of the DICP since the last ACCV meeting, Dr. Houston announced that 451 claims had been filed as of August 1, which projected that approximately 541claims would be filed for the year, slightly up from the previous fiscal year. There had been 375 claims adjudicated and 349 non-autism claims adjudicated. It was projected that 450 claims would be adjudicated by the end of FY 2014 which would be slightly down from the same time last fiscal year and 418 non-autism claims would be processed for this fiscal year which would be about the same as FY 2013. Awards of $177 million have been made as of August 1 to petitioners, and petitioner attorneys have received $17.4 million. The Vaccine Injury Compensation Trust Fund (Trust Fund) stands at $3.4 billion, with revenues of $127 million from excise taxes and $45 million from interest earned on investments.

Dr. Houston stated that two significant meeting were held since the last ACCV meeting. The National Vaccine Advisor Committee (NVAC) met on June 10-11 and the Advisory Committee on Immunization Practices (ACIP) met on June 25-26. She added that the division had been responding to inquiries from the General Accountability Office (GAO) concerning the Trust Fund, outreach, claims processing data, and the process for making changes to the Vaccine Injury Table. The GAO has indicated that a draft report should be provided to DICP to review in mid-September.

Dr. Houston provided contact information for the division – Annie Herzog, Parklawn Building, Room 11C-26, 5600 Fishers Lane, Rockville, Maryland 20857, at telephone number 301-443-6634, and by e-mail at aherzog@hrsa.gov.

Clarification of Proposed Changes to the Vaccine Injury Table, Dr. A. Melissa Houston, Director, DICP

Mr. King explained that the next section was affected by the ethics regulation of HHS and that Ms. Pron would limit her participation to asking clarifying questions and would recuse herself from any decisions made as a result of the discussion. There was a review of ethics practices that resulted in a decision by the HHS to impose certain restrictions on participation in

discussions by individual commission members based on reviews of each member's financial disclosure statements. The division may request a waiver of that restriction but it would not be approved until the next ACCV meeting.

Dr. Houston stated that the DICP is currently updating the Vaccine Injury Table (Table) and that the Commission approved proposed revisions to the table in March 2012 and in June 2014. The VICP has also revised some of the language previously approved by the ACCV in the Qualifications and Aids to Interpretation (QAIs). The last formal revision to the table was made in 1997 after which nine vaccines were added to the table although no specific injuries were identified for any of the vaccines. Those nine vaccines were: haemophilus influenza type B polysaccharide conjugate, pneumococcal conjugate, hepatitis A and B, varicella, meningococcal, human papillomavirus, trivalent influenza, and rotavirus vaccines.

The HHS commissioned an Institute of Medicine (IOM) expert committee to review certain vaccines and related adverse events and the results of that study were, in turn, reviewed by a HHS task force. As a result, it was recommended that several vaccine-associated injuries be addedto the Table.

The IOM found that measles inclusion body encephalitis (MIBE), a rare encephalitis caused by chronic infection with the measles virus, mainly in immune deficient individuals, was associated with the measles, mumps, and rubella (MMR) vaccine. MIBE was added as an injury to the Table. Injuries listed on the Table usually include a time frame within which symptoms following inoculation must occur. The timeframe for MIBE was 4 to 9 months. However, there would be no time limitation if MIBE was confirmed by lab tests.

The IOM also confirmed there was a causal association between the varicella vaccine and disseminated vaccine viral disease on the skin and in other organs. The proposal was to add the disorder if the vaccine was confirmed by lab testing or within 7 to 42 days if lab testing was not performed or was inconclusive. The IOM also stated that there was convincing evidence of a casual association between varicella vaccine and vaccine strain virus reactivation, which is the appearance of the rash months to years after vaccination, with or without infection in other organs. The brain and meninges could also be involved in vaccine strain reactivation, usually in immune compromised individuals, but the proposal did not limit the involvement to those two organs. That was in keeping with the second overarching ACCV Guiding Principles which states where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the table, the change should, whenever possible, be made to the benefit of petitioners.

These proposals associated with multiple vaccines were approved in March 2012. Any acute complication or sequela was deleted from the individual vaccines and placed in a separate paragraph. The IOM concluded there was a causal relationship between any injected vaccine and deltoid bursitis, not related to the specific vaccine. It could also affect other similar injuries. Therefore the program proposed that injury of Shoulder Injury Related to Vaccine Injury (SIRVA) be added to the table, to include more than only deltoid bursitis, if they occurred within 48 hours. The IOM also found a causal relationship between vaccine injection and syncope,

usually within 15 minutes. In keeping with the ACCV Guiding Principles, the DICP recommended a timeframe of one hour.

The IOM found a causal relationship between the vaccine for trivalent influenza, meningococcal, human papilloma and varicella vaccines with episodes of anaphylaxis. Usually the onset was less than an hour and the DICP recommended adding the injury to the Table with an onset of four hours.

The QAIs were expanded from 9 to 13 to provide definitions for the additional adverse events. There was also a revision to the paragraph on brachial neuritis to harmonize with the new language for SIRVA, since the conditions are similar. The proposed definition for disseminated varicella vaccine strain virus disease clarified the requirement for laboratory testing and time frames, defined the illness as one that involved the skin beyond the dermatome where the immunization was administered, and stated that clear evidence of disease in an organ must be present.

The QAI language regarding varicella strain reactivated disease states that there is no applicable time frame associated with this condition. With regard to syncope, the QAI states that loss of consciousness clearly related to causes other than an injection would not be considered a table injury. With regard to anaphylaxis, minor changes were made that eliminates the description of autopsy results since autopsy findings do not confirm a diagnosis of anaphylaxis.

The QAI section on vaccine strain measles viral disease was expanded to provide more detail with regard to the definition, the involvement of skin and other organs, testing and exclusions. With regard to encephalopathy and encephalitis, the IOM rejected a causal relationship with acellular pertussis-containing or MMR vaccines. The definition of encephalopathy was revised and a definition was developed for encephalitis. For clarity, a revised definition of chronic arthritis was proposed, although it was no revision to that condition was proposed. The definition of thrombocytopenic purpura was expanded to make it compatible with medical diagnostic language, instead of just the laboratory test result definition.

Finally, Dr. Houston stated that the glossary was revised to include the definition of "chronic encephalopathy", the technical definition of "injection" and the definition of an "immune deficient recipient". Two definitions previously described in other sections of the table were moved unchanged to the glossary – the definitions of "significantly decreased level of consciousness," "seizure" and "sequela".

During discussion, Dr. Tom Shimabukuro, Immunization Safety Office, Centers for Disease Control and Prevention, commented that, in the glossary, concerning injection, there is an intradermal injection now in use. Also there has been a device recently approved for a non-needle injection, an intramuscular subcutaneous "diffusion" that does not involve a needle stick.

Mr. King commented that the preceding review addressed ACCV action taken in March 2012. Dr. Houston discussed recommendations approved by the Commission at its June 2014 meeting. She noted that all seasonal trivalent flu vaccines were covered under the program in July 2005. Quadrivalent vaccines became available during the 2013-2014 flu season and are

covered by the program as of November 12, 2013. Congress passed Public Law 113-15 on June 25, 2013 that authorized an excise tax on all flu vaccines changing the previous vaccine category known as "trivalent influenza vaccines" to "seasonal influenza vaccines".

Haemophilus influenza polysaccharide type B conjugate vaccines were first licensed in 1987 and have been recommended by the CDC for routine use in children since 1991. The category was changed to haemophilus influenza type B vaccine as a technical change to harmonize with the terminology in the excise tax law.

Mr. King invited discussion. Hearing none, he invited Dr. Houston to discuss proposed changes to the QAI language previously approved in March 2012. After the discussion, Dr. Houston indicated that the Commission would be requested to either approve or not approve the revisions. Mr. King commented that Dr. Pron would continue to be limited in her participation in the discussion.

Dr. Houston stated that the first change would make the definition of encephalopathy less restrictive, such that if it could be shown that the exclusions were related to the vaccine, the presumption of causation would continue to apply. She added that a reference in the original recommendation requiring evaluation of the entire medical record was deleted because it is in the statute, which would make the language unnecessary. That is, there is an assumption that the evaluation takes place in all circumstances.

Mr. Kraus commented that, when the 2012 changes were approved, most of the commission members were relatively new to the Commission, and the consideration of the changes was felt to be very important and somewhat urgent. He conceded that staff made clear presentations justifying the changes and the Commission approved them. Then there was no discussion until the December 2013 meeting, when the Commission approved adding Guillain-Barrè Syndrome (GBS) following flu vaccination to the table. Then in June 2014 the Commission approved changes to the 2012 recommendations, most of which were clarifying revisions. Mr. Kraus commented that the entire process prompted him to review the original 2012 recommendations, which in turn raised some issues in his mind that he proposed discussing – that is, it would re-open the discussion of the 2012 recommendations, and not just the subsequent changes that were approved since that original Commission action.

Asked for specifics, Mr. Kraus commented that he had concerns about the recommendation regarding the definition of encephalopathy in the QAI. He explained that the wording in the 2012 version seemed to place the onus of proof on the petitioner to show that the conditions listed were unrelated to the vaccine or were underlying conditions of a systemic disease. Secondly, Mr. Kraus expressed concern that the definition of anaphylaxis had been expanded to require simultaneous involvement of two or more organ system, making it more restrictive. Dr. Houston assured the Commission that the medical definition of anaphylaxis required the involvement of two or more organ systems. Mr. Kraus summarized his concern that the revisions seem to require the petitioner to take on more of the burden of proof than existed before the revisions were approved.

There was a brief discussion concerning the responsibility for substantiating a claim that is filed as a table injury. Dr. Houston noted that the table prior to 2012 had exclusions, which are similar to those in the 2012 recommended language. There was agreement that the initial burden rests with the petitioner, but once established as a table injury, it would become the HHS's obligation to disprove the assumption. Mr. Kraus made a motion to reconsider the 2012 recommendation concerning encephalitis. The motion failed because of a lack of a second to that motion.

Resuming the discussion of QAI revisions, Dr. Houston commented that the QAI was revised from encephalopathy "symptoms within six months of vaccination" to "at least six months from first symptoms or manifestation of onset or of significant aggravation of acute encephalopathy or encephalitis."

Another proposed revision would change the definition of thrombocytopenic purpura making the definition less restrictive – if culture or serologic testing was performed and the viral illness was attributed to the vaccine strain measles virus then the presumption of causation would remain in effect. Finally, in the case of SIRVA injury, the wording was refined to clarify that the injection referred to in the QAI was presumed to be intramuscular, which involves a longer needle than the subcutaneous injections, which are far less likely to cause a SIRVA-type injury.

Mr. King noted that the Commission would address the disposition of the recommendations – that is, to concur with the recommendations or not to concur with the recommendations. He suggested addressing each recommendation individually, as had been done at the March 2012 meeting. Asked about the Commission's options in terms of the charge to issue a decision with regard to the proposed revisions, Dr. Houston explained that the Commission is allowed 90 days to review the revisions and arrive at a decision to concur or not concur. The Commission could also not make any recommendations.

The first revision related to the new wording for the encephalopathy definition in the QAI, and on motion duly made and seconded, the Commission approved the revision, six in favor, one abstention, and one member recused and did not vote.

The second revision related to the new wording for the thrombocytopenic purpura definition in the QAI, and on motion duly made and seconded, the Commission approved the revision, six in favor, one abstention, and one member recused and did not vote.

The third revision related to the new wording for the chronic encephalopathy definition in the QAI, and on motion duly made and seconded, the Commission approved the revision, seven in favor and one member recused and did not vote.

The fourth revision related to the new wording for the SIRVA definition in the QAI, and on motion duly made and seconded, the Commission approved the revision, seven in favor and one member recused and did not vote.

Report from the Department of Justice. Mr. Vince Matanoski, Deputy Director, Torts Branch

Mr. Matanoski referenced the Department of Justice PowerPoint materials (DOJ PP), dated September 4, 2014, as part of his presentation. Mr. Matanoski reported that 168 petitions were filed since the last report to the Commission (DOJ PP at 2), which extrapolates to over 500 for the fiscal year. The number of claims is increasing each year. Nearly 80 percent of the claims were filed by adults. The number of cases filed is mainly a function of the number of seasonal influenza vaccinations. Those vaccinations also account for the increase in GBS and SIRVA claims. Some of the increase in claims could be the result of a more active petitioner's bar, which makes information about the program more available to the public.

Mr. Matanoski stated that adjudications this reporting period, which totaled 152, slightly lagged behind petitions filed (168), a trend that would be concerning if it continues because it could forecast an increasing backlog of pending claims (DOJ PP at 3). The numbers suggest that adjudications could exceed 600 for the fiscal year, which is a significant increase over past years. About two-thirds of the adjudicated cases were compensated through settlement. Mr. Matanoski added that nine cases were voluntarily dismissed (DOJ PP at 4).

Regarding appeals, the U.S. Supreme Court dismissed petitioner's *writ of certiorari* on June 30, 2013, in *Tembenis v. Sebelius* (DOJ PP at 5). *Tembenis* has been discussed at prior meetings and involved a claim for compensation to a deceased child's estate for unearned wages. Three cases were decided during this reporting period by the U.S. Court of Appeals for the Federal Circuit (CAFC). Petitioners' appeals in *Graves v. HHS* and *Price v. HHS* were denied because they were filed outside the statute of limitations (DOJ PP at 6). In *Dobrydnev v. HHS*, an appeal by respondent, the Court reversed the holding of the CFC, finding that the judge erroneously substituted her factual findings for those of special master's, which is only permitted if the special master made a legal error (DOJ PP at 6). The petitioner has moved for *en banc* review. The other listed cases currently pending before the CAFC were discussed at the last Commission meeting, and no new cases were added to that docket (DOJ PP at 7).

Turning to the CFC, two cases were decided this reporting quarter (DOJ PP at 8). In *Bast v. HHS*, the CFC affirmed the special master's decision that respondent's expert witness was more reliable than petitioner's expert witness. In *Scanlon v. HHS*, the CFC vacated the special master's denial of attorneys' fees and costs and remanded the claim to the special master for an award even though the underlying petition for compensation alleged an injury from a vaccine (shingles vaccine) that is not covered by the National Childhood Vaccine Injury Act of 1986, as amended, (Vaccine Act). Several appeals are pending before the CFC with four new appeals filed by petitioners during the reporting period (DOJ PP at 9). *Castaldi v. HHS* involved statute of limitations and entitlement issues. In *Mosley v. HHS*, the special master found that the appearance of transverse myelitis occurred too soon after the tetanus toxoid vaccination (the day following the vaccination). In *Godfrey v. HHS*, petitioner alleged that human papillomavirus (HPV) vaccine and meningococcal conjugate vaccines caused juvenile rheumatoid arthritis. The special master found respondent's experts more reliable in a battle of the experts on causation. In *Harris v. HHS*, the special master found that petitioner failed to satisfy prong one of *Althen* in

that there was no reliable evidence that the HPV vaccine could cause lupus, and, further, there was evidence that petitioner's symptoms of lupus began prior to vaccination.

Turning to settlements, Mr. Matanoski discussed the compilation of settlements adjudicated during the preceding quarter (DOJ PP at 11-19). There were 90 settlements finalized in the quarter, which is impressive in a three-month period. Of those, Mr. Matanoski noted that 40% of cases were settled within the first year of the date they were filed. An additional 33% were adjudicated in the second year and an additional 11% in the third year. In all, 88% of cases reported were settled in three years or less. That number has been relatively stable for the last several reporting periods. In the more distant past, significantly lower percentages were settled within three years of filing. Mr. Matanoski explained that the office is becoming more efficient, learning to adjudicate similar cases more quickly, and the Office of Special Masters has supported efforts to expedite the settlement process.

He was asked the ratio of on-table injury adjudications versus off-table injury adjudications. Mr. Matanoski responded that a majority of the adjudications were off-table claims, but that trend might change if injuries such as GBS and SIRVA are added to the Table. He was asked about DOJ's approach to processing cases meeting the criteria for proposed Table changes, Mr. Matanoski acknowledged that accommodations are being made such as identifying cases for "fast-track" that have been and are continuing to be implemented. Finally, when asked about the current caseload, Mr. Matanoski indicated there were about a 1,000 cases on the docket. He warned that although there have been impressive improvements in efficiency, case processing is subject to the limited resources available.

Mr. Matanoski expressed appreciation for being able to update the Commission.

VICP Outreach Plan, CAPT Narayan Nair, M.D., DICP

Dr. Nair began by discussing the background related to outreach efforts. He explained that the Vaccine Act stated that the public should be informed about the program. In the past, there were two groups involved in outreach: the ACCV Outreach Workgroup and the Communications Liaison Outreach Group who was concerned mainly with participation in professional meetings. The VICP contracted with Banyan Communications to develop a marketing and communications plan, which was presented to the ACCV in 2010.

Dr. Nair then discussed the objectives and strategy related to outreach. He noted that the present objectives of the outreach program are to increase awareness in the public arena about the VICP, how the program works, and to develop partnerships with organizations that can support the outreach effort. These organizations could include HRSA grantees such as community health centers; Healthy Start Programs; and maternal, infant, and early childhood home visit programs. Partnerships can also be developed with other HHS agencies and professional organizations.

Dr. Nair concluded by discussing current and future outreach efforts. Currently, a toll-free number is maintained to answer questions about the program and written inquiries are

promptly answered. In the future, the VICP web site will be significantly improved to enable easier navigation and make it more user-friendly. The printed material will be improved and made more available and partners will be recruited to distribute VICP information materials.

Ms. Williams noted that a former Commission member, Sara Hoiberg, had indicated an interest to support the outreach process.

Public Comment

Theresa Wrangham, representing the National Vaccine Information Center (NVIC), endorsed the face-to-face meeting format. In addition, she stated that there was a report from an outside group, the Banyan Communications that revealed some deficits in the outreach process. This report mentioned the value of television and radio public service announcements. Also, the report recommended a satisfaction survey of petitioners for which response was limited, perhaps because of timing of the survey. Such a survey should be made on a timely basis when memories are fresh.

Concerning the discussion about encephalopathy, the discussion was thoughtful, but changes have been made in the table that may not be fully responsive to changes made outside the recommendations of the IOM. She stated that the NVIC is opposed to the changes made with regard to encephalopathy. Because the provision in the table is too narrow and restrictive to potential claims related to encephalopathy.

Adjournment

Mr. King recessed the meeting until 9:00 a.m. the following day.

Advisory Commission on Childhood Vaccines

September 5, 2014

93rd Meeting

Members Present

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Charlene Douglas, Ph.D. ('14)
Kirsten Feemster ('14)
Edward Kraus, J.D. ('15)
Ann Linguiti Pron, DNP, CRNP, RN ('14)
Luisita dela Rosa, Ph.D. ('15)
Jason Smith, J.D. ('15) (via telephone)
Sylvia Fernandez Villareal, M.D. ('15)

Division Injury Compensation Programs (DICP)

A. Melissa Houston, MD., Director, DICP
Andrea Herzog, Staff Liaison

Welcome, Report of the Chair and Approval of Minutes, Mr. David King, ACCV Chair

Mr. King called the meeting to order. After introductions, he noted that Kristen Feemster was en route to the meeting and that Theresa Wrangham, in her capacity as director of the National Vaccine Information Center (NVIC), submitted a letter from the NVIC requesting that it be included in the official record of the Advisory Commission on Childhood Vaccines (ACCV) meeting. He indicated the letter was relatively long and would require some review before specific action could be taken with regard to including it in the minutes.

Report from the Process Workgroup, Ms. Luisita dela Rosa, ACCV Member

Ms. dela Rosa reported that the Workgroup met by telephone on May 8 and discussed a statistical table provided by Ms. Theresa Wrangham of the NVIC that included historical data on vaccine injury cases filed with the National Vaccine Injury Compensation Program (VICP) over the past few years. The Workgroup discussed how the information was different from that made available on the VICP web site. Ms. Wrangham described how the DICP could prepare a similar presentation that would respond to the needs of parents about the kinds of claims being filed. She also reminded the Workgroup of the U.S. Court of Federal Claims' requirement to submit an annual report on vaccine cases.

Ms. dela Rosa reported that the DICP staff had reviewed the information and stated that creating such a table would require additional staff support since much of the information

required is not located within DICP. The information would have to be gleaned from other sources. It was noted that determining why cases were or were not filed, why filed cases may have been dismissed, or reasons for compensating, or not compensating a claim, requires review of individual cases, which is a labor intensive process. The Workgroup agreed that it was important for such information to be made available and for the DICP to respond to non-governmental advocacy groups such as the NVIC. The Workgroup requested that Dr. Houston follow up on the feasibility of creating the table.

At the Workgroup's September 4th meeting Dr. Houston reported that the program had reviewed the statutory and regulatory reporting requirements and that DICP was comfortable that the published information adequately describes program operations. Information about individual cases is provided on the U.S. Court of Federal Claims (Court) web site as well. Some information, such as reported injuries after vaccination, is provided by the Centers for Disease Control and Prevention (CDC).

The Workgroup also discussed the possibility that the ACCV might invite individuals to testify about personal experiences with the statute of limitations when that part of the law might have presented an impediment to timely filing of a claim. In addition, the Vaccine Injury Petitioners Bar could be invited to provide information. The Workgroup agreed that such information might be just as well collected through a survey process. However, there is a lengthy process involving U.S. Office of Management and Budget (OMB) approval when such surveys are undertaken. The Workgroup asked Dr. Houston to provide information about what the approval process entails.

Finally, the Workgroup asked for an update on the appointment of new commissioners since the nominations have apparently been submitted to the Office of the White House for review and approval. Ms. dela Rosa concluded her report.

During discussion there was a question about whether the Commission had received certain information pertaining to cases that the Court had handled, and it was noted that there was information provided in a report related to cases from 2012 and 2013. Chief Special Master Vowell commented that information under Tab 3 was taken from annual reports to Congress and that information was not under her control. The Commission was interested in exploring that area of the report further and the Clerk of the Court should be contacted. Mr. King noted that the information received at the meeting was not identified by tabs, and Chief Special Master Vowell stated that it was submitted in that format and if the information was re-sent it should be organized in tabular format. Mr. King stated that unless the issue is clarified the information received will not be disseminated to the public. There was a brief discussion that clarified that information sent to the Commission or any of its subcommittees would be available through a formal Freedom of Information Act (FOIA) request.

Mr. King noted that Dr. Feemster had joined the meeting.

Election of Succeeding Chair and Vice Chair

Mr. King noted that with all of the commissioners present the issue of electing the next chair and vice chair would be addressed. He stated that a number of commissioners were at the end of their tenure, including the present officers and Ms. Pron, and that it would probably be necessary to extend the terms of the next group of commissioners, including Dr. Feemster, Mr. Smith, and Ms. Douglas (the second 2014 cohort).

Mr. Kraus nominated Dr. Feemster to be chair, seconded by Ms. Williams. Mr. King, noting that there were no other nominations, called for the election to occur. There was unanimous approval of the nomination.

Calling for nominations for vice chair, there were nominations for Ms. Douglas and Mr. Smith. A secret ballot was taken and Mr. Smith was elected by a vote of five versus four votes for Ms. Douglas.

Update on Vaccine Activities of the Immunization Safety Office (ISO), CDC by Dr. Tom Shimabukuro

Dr. Shimabukuro outlined his report stating that he would provide a follow-up on the 2010-2011 febrile seizure signal for trivalent inactivated influenza (TIV) and pneumococcal 13-valent conjugate vaccines (PCV13) and discuss the June 2014 ACIP meeting.

Dr. Shimabukuro reported that there was a Vaccine Adverse Event Reporting System (VAERS) data mining signal during the 2010-2011 flu season for febrile seizure following Fluzone, a TIV that is approved for children six months and older. At the same time there was a Vaccine Safety Datalink (VSD) rapid cycle analysis signal for febrile seizures in infants 6-59 months of age following TIV administration. A follow-on VSD study found that there was increased risk for febrile seizure primarily when TIV and PCV13 were administered during the same healthcare visit. The risk peaked at about 16 months of age with an additional 45 cases per 100,000 children vaccinated. In a Clinical Immunization Safety Assessment (CISA) Project study, children aged 6-23 months who received the vaccines at the same time were about three times as likely to have fever on day 0 or day 1 post vaccination. Fever precedes a febrile seizure. CDC posted information on its web site communicating these findings and stating that no changes in the childhood immunization schedule were necessary. Information was also added to the Vaccine Information Statement (VIS) regarding the risks.

In addition, Dr. Shimabukuro described the VSD and a Post-licensure Rapid Immunization Safety Monitoring System (PRISM) studies that looked at multiple vaccines. The results were that when looking at independent risk for febrile seizures when TIV is given alone there was of no evidence of increased risk of febrile seizure. The updated VSD analysis for 2010-11 season suggests that the relative risk increased about three-fold when TIV was given with PCV and/or DTaP compared with unexposed periods, with similar result for prior seasons from 2006 to 2009. The Food and Drug Administration (FDA) PRISM study looked at one flu season, 2010-2011, same day versus separate day vaccinations of TIV and PCV13 and found no increased risk in either circumstance.

In summary, Dr. Shimabukuro stated that the VSD analysis over several flu seasons showed that the risk of febrile seizure is not increased when TIV is given alone, but when TIV is given with PCV and/or DTaP that risk is increased, and the highest risk occurs when all three vaccines are administered together at age 15 months. That risk is about 38 additional febrile seizures per 100,000 vaccinations, which is similar to the risk seen in measles-mumps-rubella vaccine. Simultaneous administration of TIV with PCV and/or DTAP appears to increase risk of febrile seizure, but the risk is transient (same day or following day), and although seizures can be alarming to parents they typically do not have lasting effects.

During discussion, Dr. Shimabukuro assured the commissioners that febrile seizures, of which 3-5% of children experience, do not increase the risk of developing epilepsy or similar seizure disorders. He deferred a question about non-physical effects to the pediatricians on the Commission. Dr. Villareal commented that when parents experience a child's febrile seizure, it can cause a lasting impact in terms of increased anxiety when a child gets fever or when a child is scheduled to receive a further vaccination. Dr. Pron added that parents often become opposed to any further vaccinations for their children and can become advocates opposing mandatory vaccinations. Mr. King was concerned the words "lasting effect" might not be accurate in that instance. Dr. Shimabukuro assured the commission that although a child may be more or less likely to have additional similar seizures related to fever, the child's risk of developing a seizure disorder after a febrile seizure is not increased because of the initial event.

Turning to his report on the June 24 Advisory Committee on Immunization Practices (ACIP) meeting, Dr. Shimabukuro reported that there was an influenza session that reviewed the 2013-2014 flu season that confirmed there were no new safety concerns and the formulation for the 2014-2015 season would remain the same. He described safety monitoring activities, including an enhanced surveillance of children with incidents of asthma or wheezing after live attenuated influenza vaccine quadrivalent (LAIV4) since the vaccine may be administered to younger children. The specific recommendation is to give children live attenuated influenza vaccine (LAIV) preferentially, if available, but give inactivated influenza vaccine (IIV) if LAIV is not available.

Mr. Smith interjected a comment that his company, Pfizer, markets Prevnar, a PCV13 vaccine and is also developing a meningococcal serogroup B vaccine and for that reason, for the record, he recused himself from the discussion.

Dr. Shimabukuro commented that the ACIP discussed adding a dose of PCV13 following the currently recommended dose of pneumococcal polysaccharide vaccine (PPSV23) at age 65 and up. The Committee also discussed replacing a dose of PPSV23 with a dose of PCV13 at age 65 and up. Concerning the meningococcal vaccines, the Committee discussed publication of interim guidance for the use of a serogroup B meningococcal vaccine under a CDC-sponsored expanded access investigational new drug (IND). Updates to CDC's comprehensive meningococcal disease outbreak guidelines will be published once the vaccines are licensed in the United States.

Dr. Shimabukuro mentioned several recent publications. Nordin et al. found no acute safety signals within six weeks of vaccination in a large cohort of pregnant women who received

monovalent 2009 H1N1 (pandemic) inactivated influenza vaccine. Stokley et al. reported in the Morbidity and Mortality Weekly Report (MMWR) that post licensure monitoring of Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) recombinant vaccine (HPV4) vaccine continued to confirm safety with a commentary that appropriate practice patterns for physicians should include consistent encouragement for patients to take advantage of the human papillomavirus (HPV) vaccine. Grohskopf et al., also in MMWR, updated the recommendations for seasonal influenza vaccines. Also in the MMWR, Markowitz et al. described HPV vaccine recommendations. Dr. Shimabukuro concluded his report.

During discussion, Mr. Kraus expressed concern, notwithstanding the CDC recommendation that administering vaccines on the same visit may have significant advantages, that parents should be given full information about the increased risks of febrile seizure when vaccines are administered simultaneously.

Discussion of Proposed Revisions to VAERS Form 2.0

Dr. Shimabukuro explained that VAERS receives about 30,000 reports annually. Anyone can submit an adverse event (AE) report to VAERS – health care workers, public health personnel, individuals including parents, relatives and others. He noted that manufacturers are required by law to submit AEs to VAERS that come to their attention. VAERS is administered jointly by the CDC and FDA and is authorized by the National Childhood Vaccine Injury Act of 1986. VAERS is national in scope and can rapidly detect potential safety problems and rare AEs. The reports are accepted without judging clinical importance or causality. VAERS provides for rapid signal detection, contains information concerning the vaccine and adverse event as well as information about the individual vaccinated. The data, with personal identifiers removed, is posted on the VAERS web site and is available to the public. Limitations of VAERS include reporting bias, varying data quality and completeness, and a general inability to determine cause and effect. Reporting for pregnant women is inconsistent. Rates of AE occurrence cannot be calculated using VAERS data and therefore, relative risk cannot be estimated, nor can vaccination coverage.

The current method for submitting a non-online VAERS report is manual. The report form (VAERS-1) can be downloaded from the VAERS web site, printed and filled in by the person making the report, then mailed or faxed to the VAERS contractor who manually processes reports and conducts data entry and coding. A report may be made verbally to a VAERS customer service representative who fills in the form with the information provided on the phone. The process is resource and labor intensive.

The objective for the proposed VAERS 2.0 reporting form is to provide a fillable/savable electronic form that can be completed on a computer and submitted through an electronic upload process. Secondary objectives include adding new information fields that will improve surveillance and eliminating fields that are no longer relevant or useful, updating and clarifying language, giving the form a more modern easy to use appearance, and insuring that data entered on the new form is compatible with historical data so that historical comparisons are possible. The electronic format facilitates consistency in the entries (e.g., dates and phone number formats), allows pop-up reminders if a field is left blank, and eliminates human errors, such as

illegible handwriting, illogical answers and other errors. However, Dr. Shimabukuro assured the Commission that incomplete forms and even forms with errors in some fields could be submitted. The electronic format should eliminate a large amount of the manual processes for the VAERS contractor.

The proposed VAERS 2.0 form partially addresses the problem of getting "timed out" on the online reporting tool. The fillable/savable VAERS 2.0 would allow the form to be saved and completed in stages, by multiple persons, if necessary. The form can be partially filled out and saved for later completion, then uploaded to the VAERS contractor via the VAERS web site. The contractor would transfer the reported data to the VAERS database. As before, for those not comfortable with computers or otherwise not able to report via computer, there is a third option to make a phone call to the VAERS customer service representative and dictate a verbal report. Finally, Dr. Shimabukuro reviewed the specific changes in the new form as listed on the presentation. He noted that there have been several levels of review, including interviews with potential reporters and testing of this process will continue as the form is finalized.

Dr. Shimabukuro discussed next steps. The "smart form" with electronic smart features will be created and tested. The proposed VAERS 2.0 will also be presented to the NVAC and ACIP at the next scheduled meetings. The VAERS 2.0 form will be published in the Federal Register inviting public comment and final revisions will be made to the form based on those comments and the ongoing computer testing of the form. The final platform that will enable acceptance of the electronic VAERS Form 2.0 and online reporting tool will updated to reflect the new data elements.

During discussion, Dr. Shimabukuro stated that there are no capabilities for reporting in other languages at this time. He added that the English language version has been made as simple as possible while still insuring that the data needed can be collected. Asked about who submits reports, Dr. Shimabukuro commented that about 25% of the reports come from parents and patients, about 30% from providers, but there is an "Other" category that may contain some parents and some providers. There was a question about how long it takes to fill out the form and Dr. Shimabukuro stated that it depends on the individual submitting the report and the adverse event, but that the amount of data required is about the same in the current VAERS-1 form.

Asked about the roll-out of the new form, Dr. Shimabukuro stated that there would probably be an initial period when a report could be submitted either the current manual method or by electronic reporting.

Pneumococcal Polysaccharide (Pneumovax 23) Vaccine Safety Presentation, Ms. Elaine Miller, R.N., MPH, CDC

Ms. Miller provided background about the disease burden of pneumococcal infections that annually cause 3,000 to 6,000 cases of meningitis, 50,000 cases of bacteremia and as many as half a million cases of pneumonia in the U.S. Deaths from meningitis may exceed 30% in younger victims and up to 80% in the elderly. The fatality rate for bacteremia is about 20% (up

to 60% in the elderly) and pneumonia claims up to 7% of individuals with the infection, more in the elderly. The pneumococcal polysaccharide vaccine, Pneumovax 23, is effective in preventing disease caused by the 23 serotypes contained in the vaccine and is recommended for adults 50 years of age and older, and for children ages 2 years and up who are at increased risk for pneumococcal disease. Those children may have chronic conditions (such as heart disease or diabetes mellitus), lack of a functioning spleen, or congenital or acquired immunodeficiency (e.g., HIV, chronic renal failure, or similar conditions). Children under two do not develop an effective immune response. The 23 serotypes in the vaccine cause approximately 88% of bacteremic pneumococcal disease. Pneumovax 23 is an inactivated vaccine and cannot cause the disease.

Pneumovax 23 was licensed in 1983 and is now the only pneumococcal polysaccharide vaccine on the market in the US. There have been several ACIP recommendations over the years, which will now be harmonized into a single set of recommendations. The ACIP recommendation for adults is the same as for children, except that all over age 65 should receive the vaccine regardless of prior history. Ms. Miller noted that certain adverse events were common though non-serious, mainly localized reactions at the injection site (pain, swelling, erythema) and systemic reactions like headache, fatigue, and myalgia.

A VAERS review was completed. The strengths and weaknesses of VAERS were outlined in the previous discussion by Dr. Shimabukuro. The VAERS reports for pneumococcal polysaccharide vaccines received from 1990-2013 were summarized, not including those of Pnu-Immune, a vaccine used from 1983 until 2002 comprising about 10% of VAERS reports. Another analysis known as empirical Bayesian data mining was conducted, which detects disproportional reporting for a vaccine and an adverse event. It does not necessarily demonstrate that a vaccine has an increased risk for an adverse event. Data mining findings may indicate the need for further analysis. There were over 25,000 AE reports. Slightly over 2,000 were considered serious. The majority of reports came from health care providers (10,462), mainly concerning individuals in the 19-64 age group (11,040), followed by reports about those 65 and older (10,546). There were 66 deaths reported, four of which occurred in children.

Ms. Miller reported that 144.2 million Pneumovax doses were distributed in the U.S. from January 1991 to December 2013 (no way to tell how many were actually administered to individuals). That works out to 17.7 VAERS reports per 100,000 doses distributed. Mr. King observed that since fewer doses are actually given than distributed the percentages related to actual AEs would be higher than the number of reports. He was asked about whether Pneumovax can be stored over a long period of time and therefore, should have a higher actual use rate than vaccines with relatively short expiration date. Dr. Shimabukuro stated his belief that the vaccine probably does have a longer shelf life than some others that expire and must be destroyed. Nonetheless there is no data on actual number of doses administered. He added that when a vaccine is first introduced there may be a higher level of reporting of adverse events than after the vaccine has been in use for a period of time. The same thing occurs when a vaccine is substantially changed and the new version is put on the market.

Ms. Miller provided statistics about co-administered vaccines in children included in the VAERS reports. Pneumovax alone was administered in 45% of the reports, and flu vaccine

(TIV) was mentioned in an additional 28%. In adults the numbers were similar. Ms. Miller also briefly discussed the reported deaths in children (4) and in adults (61), which did not appear to be causally related to the vaccine.

In summary, Ms. Miller stated that from 1990-2013, VAERS received 25,168 Pneumovax reports, 92% of which were non-serious. Fever was the most commonly reported adverse event (47%) in children followed by injection site issues. Death reports among children were very rare and cause of death did not suggest any causative relationship to the vaccine. In adults the most commonly reported adverse event was injection site erythema and pain (57%) and fever (24%). No concerning patterns were detected through VAERS for Pneumovax 23 for children or adults. A 2008 World Health Organization (WHO) position paper confirmed most of the findings discussed.

Zoster (Shingles) Vaccine Safety Presentation, Ms. Elaine Miller, R.N., MPH, CDC

Noting that the presentation for the herpes zoster vaccine parallels the previous Pneumovax presentation, Ms. Miller commented that she would focus on the information that has not been presented the Commission. An individual with a history of the varicella zoster virus (chicken pox) could have a reactivation of the virus. Those individuals, usually the elderly and those immunosuppressed, experience herpes zoster, also known as shingles. Also at risk are persons who had varicella at less than 18 months of age and those who had intrauterine exposure to varicella zoster virus. Symptoms occur in a specific area related to a sensory nerve and complications include post-herpetic neuralgia (persistent pain after the rash disappears), vision loss if the shingles occur near an eye, and other neurologic problems. In the U.S., up to a million individuals experience the condition annually and the lifetime exposure risk is about 32%.

The zoster vaccine, Zostavax, is a live attenuated vaccine given in a single dose and currently licensed for individuals 50 years of age and older. The ACIP limited its recommendation to individuals 60 and older partly because the condition mainly affects older individuals and partly in consideration of the possibility of a limited vaccine supply. Since it is a live, although weakened virus vaccine, it is contraindicated for those who are immune suppressed and women who are pregnant. Also, it should not be given to individuals who have had an anaphylactic reaction to any component in the vaccine.

The vaccine reduced the risk of developing shingles by approximately 51%, which is a lower rate than most vaccines, but the efficacy is higher in preventing post-herpetic neuralgia at 62% and increases to approximately 73% in preventing episodes of post-herpetic neuralgia lasting 182 days or more. In prelicensure studies, the most common adverse event was injection site reaction occurring in 48% of recipients. Far behind were headaches affecting 1.4% of the recipients. A prelicensure safety study showed that Zostavax recipients experienced a higher number of cardiovascular events (20 or 0.6%) than those receiving placebo (12 or 0.4%).

The VAERS surveillance system was discussed during the Pneumovax presentation as was the empirical Bayesian data mining study procedure. The results for the VAERS Zostavax data received May 2006 to February 2014 revealed that 15,930 reports were received 723 of

which (5%) were considered serious adverse events. Women were the subject of 11,500 (72%) reports. As in the Pneumovax VAERS data manufacturers and healthcare providers accounted for the majority of reports, amounting to 73% of the total reports filed.

Most of the reports were for older adults, 60 years of age and up (12,486 or 78%), with an additional 1,541 (10%) filed for individuals 50 to 59 years of age. There were 638 reports for individuals under age 50 (4%) for whom the vaccine is not recommended and most were medication errors. Finally, there were 51 deaths reported (0.3%) none of which were in children or younger adults.

Between 2006 and 2013, 18.4 million doses of Zostavax were distributed in the U.S. The rate for all reports was 82.6 per 100,000 doses distributed and only 3.9 serious reports per 100,000 doses distributed. By MedDRA-codes, the most common symptoms among non-serious reports were injection site erythema, injection site swelling, and development of herpes zoster (shingles). Among serious reports, the most common symptoms based on MedDRA codes were shingles, pain and rash. Zostavax was the only vaccine mentioned in 90% of the reports, followed by three vaccines also mentioned— TIV (5%), pneumococcal polysaccharide (3%) and Tdap (2%). There were only 15 reports related to pregnant women, of which seven were pregnant vaccine administrators (usually a vaccine spill on the body of the vaccine recipient), and eight involved pregnant vaccines.

Ms. Miller outlined the conclusion of her report. From 2006 to 2013, VAERS received 15,930 reports, 95% of which were non-serious. In the 50-59 age group, the most commonly reported symptoms were injection site erythema (36%), injection site swelling (23%), generalized erythema (17%), and injection site warmth (16%). In the 60 and older age group, the most commonly reported symptoms were injection site erythema (25%), shingles (17%), injection site swelling (15%), and rash (14%). Death reports were rare and did not suggest a causal relationship with the vaccine. No concerning patterns were detected in VAERS for Zostavax.

Update on the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Activities, Ms. Claire Schuster, MPH, NIAID, NIH

Ms. Schuster stated that NIAID is responsible for responding to emerging infectious disease threats, among which the recent Ebola outbreak is of especially urgent concern. NIAID supports Ebola research, including the development of vaccine candidates to protect against the disease. Currently there is a Phase I clinical trial taking place on the NIH campus in Bethesda, Maryland, to assess an investigational vaccine co-developed by NIAID and GlaxoSmithKline. The study is assessing the vaccine's safety and ability to stimulate an immune response in healthy volunteers. There is an experimental vaccine developed in Canada that will also be tested in healthy controls in a separate trial. NIAID is also collaborating with partners in the United Kingdom to test an Ebola vaccine candidate in West Africa.

Another emerging threat is chikungunya virus which is spread through the bites of infected mosquitos, resulting in high fever, joint and muscle aches, and headaches. Although

rarely fatal, the disease can cause long-term chronic pain. It has been reported in a number of Asian countries and arrived in the Western Hemisphere last year. As of August 29, 2014, there were more than 659,000 cases reported in the Americas, 696 cases in the continental U.S. including six cases in Florida that are thought to have been locally acquired. Therapy has not been developed and the best prevention is to avoid mosquito bites.

In August, NIAID reported on an experimental chikungunya vaccine that appeared to elicit a robust immune response in 25 healthy volunteers who participated in an early clinical trial conducted by NIAID. The antibodies persisted in the volunteers, even those who received the lowest dose, for up to nine months suggesting that the vaccine could provide protection against the disease.

NIAID recently established the NIAID Centers of Excellence for Translational Research to support early research, testing, licensure, and use of diagnostics, new therapies, and vaccines for emerging and re-emerging infectious diseases. There are 14 multi-project centers across the United States. Five of the centers are engaged in Ebola-related research.

Finally, Ms. Schuster mentioned several meetings of interest. NIAID and FDA co-sponsored a meeting on the development of new antibacterial products on July 30-31. A meeting will be held on September 22-23 entitled "Overcoming Bottlenecks in Antibacterial Product Development." Also on September 23-24, the "Coordinated Development of Diagnostics and Therapeutics Workshop" will be held at NIH.

Update on the Center for Biologics, Evaluation, and Research (CBER), FDA, Vaccine Activities, LCDR Valerie Marshall, CBER, FDA

LCDR Marshall reported that in July 2014, the FDA approved a supplement to the biologics license application for diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed and inactivated poliovirus vaccine. The brand name is Kinrix and the marketing will include revised package insert to include safety and immunogenicity data to support co-administration of Kinrix with varicella virus vaccine, and to update the pharmacovigilance plan.

In July 2014, the FDA approved a supplement to the biologics license application for human papillomavirus bivalent (types 16 and 18) vaccine, recombinant (Cervarix) to include efficacy and immunogenicity data from an end-of-study analysis in the package insert and to update the pharmacovigilance plan.

In July 2014, the FDA approved supplements to the biologics license application for licensed influenza vaccines to include 2014-2015 United States formulations. Influenza vaccine lots that have been released by FDA are available for distribution by the manufacturers.

In July 2014, the FDA (CBER, CDER, CDRH) released draft guidance intended to provide information for institutional review boards, clinical investigators, and study sponsors about FDA's informed consent regulations.

In August 2014, the FDA approved a supplement to the biologics license application (BLA) for influenza vaccine, Afluria, to include data in the labeling for the use of Afluria with the PharmaJet Stratis Needle-Free Injection System for use in persons 18 through 64 years of age.

The FDA received biologic license applications from Pfizer and Novartis for vaccines to protect against meningococcal B disease.

Finally, a conference will be held on September 22-23, cosponsored by NIAID, entitled "Translational and Laboratory Science of Polio Vaccines and Antivirals." The purpose is to bring together stakeholders to identify gaps in scientific knowledge on developing and introducing new vaccines and antivirals against polio virus.

Update from the National Vaccine Program Office (NVPO), Dr. Karin Bok, NVPO

Dr. Bok reported that NVPO completed a study, which they funded through Agency for Healthcare Research and Quality (AHRQ), in which the Rand Corporation reviewed the published literature on the safety of vaccines currently recommended in the U.S. for both children and adults including pregnant women. This study was meant to be a follow-up to the Institute of Medicine (IOM) study. A manuscript detailing the results of the study in children was published in the Journal of Pediatrics. Dr. Bok mentioned adverse events associated with certain vaccines including hepatitis A (minor reports of purpura), influenza (TIV, febrile seizures), PCV 13 (also febrile seizures), and rotavirus vaccine, which has a very low risk of intussusception.

NVPO is investing in vaccine safety research including a new collaboration with CISA following infants born to mothers who received the Tdap vaccination while pregnant. There will also be a pilot program announced in early 2015 to fund vaccine safety studies focusing on pregnant women.

Public Comment

Mr. King invited members of the public to comment. There were no comments.

Future Agenda Items/New Business

Mr. King invited recommendations for future agenda items or submission of items that could be considered new business. Dr. Houston noted that in the past there had been comments about whether or not adult vaccines should be considered for addition to the program, which could be a potential agenda item for the next meeting. Tamara Overby, Acting Deputy Director, DICP commented that the presentations on Pneumovax and Zostavax, the latter of which is not recommended for children, were included in the meeting agenda to give the Commission an opportunity to consider adult vaccines. Incoming Chair, Kristen Feemster, suggested either referring the topic to a work group or adding it to the agenda for the next meeting.

Dr. Shimabukuro commented on the distinction between vaccines that are recommended for routine use in children which, when given to adults (like the influenza vaccines), may cause injury. Those injuries are covered by the program for adult recipients, versus vaccines that are routinely recommended for adults but not children, which are not covered when an adult is injured.

Dr. Feemster recommended establishing a working group to consider these issues. Mr. King agreed, noting that recruitment to the workgroup could be deferred. Ms. Williams commented that the Commission could also recommend that legislation be pursued to include adults in the program whether or not the vaccines are routinely recommended for children.

Adjournment

Mr. King and Ms. Williams both expressed appreciation for the opportunity to serve as chair and co-chair, and for the support the members had shown during their tenures. Mr. King invited a motion to adjourn and, on motion duly made and seconded, adjournment was unanimously approved.

National Vaccine Information Center

www.NVIC.org

***** VIA EMAIL*****

August 27, 2014

Mr. Dave King, Chairman
Advisory Commission on Childhood Vaccines (ACCV)
Division Of Vaccine Injury Compensation (DVIC)
Parklawn Building, Room 11C-26
5600 Fishers Lane
Rockville, MD 20857
Email: dking@salesmotion.com

Re: Request for ACCV to reconsider encephalopathy definition recommendation relating to the Vaccine Injury Table

Dear Mr. King,

Acute and chronic encephalopathy is one of the most serious vaccine adverse events on the Vaccine Injury Table (VIT) eligible for compensation under the federal Vaccine Injury Compensation Program (VICP). The Secretary of the Department of Health and Human Services (DHHS) is the legal respondent in the vaccine injury compensation process, is defended by the Department of Justice (DOJ) in claims proceedings and DHHS officials determine eligibility, administer the Trust Fund and make compensation payments awarded by the U.S. Court of Claims. Any revision of the definition of encephalopathy by DHHS officials is of great concern to the National Vaccine Information Center (NVIC), whose co-founders worked with Congress on the National Childhood Vaccine Injury Act of 1986 [1] to help ensure that the VICP would be a non-adversarial, expedited, less traumatic and more reliable alternative to a vaccine injury lawsuit in civil court.[2] [3] [4]

NVIC requests that ACCV carefully reconsider pending recommendations to change the definition of encephalopathy, which will be used as a guide by officials at DHHS and Department of Justice (DOJ), as well as by special masters in the Claims Court, to either award or deny compensation to plaintiffs filing vaccine injury and death claims. We make this request in hopes that ACCV will reaffirm and maintain the spirit and intent of the National Childhood Vaccine Injury Act, which is to err on the side of the petitioner in order to provide an economic safety net for those for whom the risks of vaccination are 100% and to address eroding public trust in the integrity of the vaccination system.

First, it is important to put NVIC's objections to changing the definition of encephalopathy in context by reviewing the history of the 1986 National Childhood Vaccine Injury Act and the VIT.

NVIC's History with the National Childhood Vaccine Injury Act of 1986

NVIC co-founders Jeffrey Schwartz, Barbara Loe Fisher and Kathi Williams, whose children had suffered serious reactions to DPT vaccine, founded the charitable non-profit Dissatisfied Parents Together (DPT) in the spring of 1982 with the mission of "preventing vaccine injuries and deaths through public education." Subsequently, they worked for four years with parents and Congress on the

1986 law at the request of congressional legislative staff.[5] In 1989, they established the National Vaccine Information Center (NVIC) and expanded the mission to include defending the ethical principle of informed consent to medical risk-taking, including vaccine risk-taking. For the past 25 years, NVIC has called for the institution of informed consent protections in U.S. vaccine policies and laws.[6]

The participation of parents of vaccine injured children during the legislative process creating the 1986 National Childhood Vaccine Injury Act was to ensure that the legislation would balance ***prevention*** of vaccine injuries and deaths with ***compensation*** for children suffering serious injury and for families of children who died after receipt of government recommended and mandated vaccines.

Importantly, the key to creating a no-fault, non-adversarial federal compensation alternative to a civil lawsuit was that the VICP would avoid compelling most plaintiff's to prove "causation in fact," which is the standard used in personal injury and product liability lawsuits filed in the tort system. There was to be a "presumption" of causation in the absence of a more biologically plausible explanation for the child's injury or death. Compensation was also to be awarded if there was evidence that a vaccination significantly aggravated a pre-existing health condition in the child leading to a substantial deterioration of health.[7]

Presumption of causation was key to making the VICP primarily an administrative, rather than an adversarial, system in order for:

(1) parents to want to select the no-fault, non-adversarial federal compensation alternative as the preferred legal option for obtaining compensation for their vaccine injured children, thereby reducing product liability and malpractice lawsuits; and

(2) to make the VICP less burdensome than a long, contentious, expensive and emotionally draining lawsuit for families caring for a severely vaccine injured child.

In addition to securing important vaccine safety informing,[8] recording and reporting provisions[9] in the 1986 law, among the unique contributions that NVIC parent co-founders made to the Act was to secure a provision in the Act that Congress would ask the Institute of Medicine (IOM), National Academy of Sciences, to review the medical literature and publish reports evaluating evidence regarding federally recommended vaccines and brain dysfunction, immune system disorders and death.[10] Parents of vaccine injured children participating in the legislative process were very concerned that those evaluating vaccine safety science be independent from influence by pharmaceutical corporations marketing vaccines in the U.S. and federal health agencies responsible for developing, regulating, making policy for and promoting state mandated vaccine use.

The IOM was selected as the entity included in the Act for conducting review and analysis of the vaccine safety science for several important reasons. While IOM receives funding from government and industry, IOM has a history of making efforts to assemble committees with broad representation utilizing a deliberative process that includes transparency and public engagement when addressing scientific and controversial public policy issues, unlike other government and industry funded organizations.[11]

Development of the VIT

The Vaccine Injury Table (VIT) included in the 1986 law was created primarily based on published scientific evidence in the medical literature and through a collaborative process that included participation by medical trade associations, whose memberships administer vaccines to children, such as the American Academy of Pediatrics. At the time the VIT was created, there were only seven vaccines federally recommended and state mandated for children and administered between the ages

of two months and six years: diphtheria, tetanus and pertussis (DPT); measles, mumps and rubella (MMR); and oral polio vaccine (OPV).[12]

The VIT incorporated clinical symptoms of vaccine reactions, injuries and deaths published in the medical literature and time periods within which most symptoms generally appeared following receipt of DPT, MMR and OPV vaccines. The purpose of the VIT was to provide officials at DHHS, DOJ and the U.S. Court of Claims with an administrative guideline for awarding no-fault, non-adversarial compensation to those children filing claims with evidence of serious health deterioration after receipt of government recommended and mandated vaccines or to families whose children died following vaccination. Causation is presumed for conditions listed in the VIT.

Encephalopathy: The VIT Centerpiece

The centerpiece of the VIT was a list of clinical symptoms associated with acute and chronic encephalopathy because encephalopathy[13] is one of the most serious complications of vaccination and can lead to permanent brain dysfunction. Acute encephalopathy or brain inflammation (encephalitis,[14] [15] encephalomyelitis[16]) and chronic encephalopathy (persistent brain dysfunction) has been a long acknowledged serious reaction to vaccination since the first vaccines for smallpox and rabies[17] [18] were developed and used in humans.

Acute and chronic encephalopathy also has been an acknowledged reaction to pertussis vaccine, a vaccine originally developed in 1912 and administered as a single component vaccine[19] before being combined with diphtheria vaccine[20] and tetanus vaccines (DPT) in the late 1940's[21] and recommended by federal health and AAP officials for children since the early 1950s.[22] [23] [24] Acute and chronic encephalopathy is also an acknowledged reaction to measles vaccine and measles containing vaccines (MR, MMR)[25] and has been reported following receipt of other federally recommended vaccines.[26] [27]

Many of the children most in need of vaccine injury compensation have experienced acute encephalopathy with or without brain inflammation (encephalitis, encephalomyelitis) following vaccination[28] [29] [30] [31]because brain inflammation or acute encephalopathy – irrespective of the cause - can lead to chronic encephalopathy (permanent neurological dysfunction).[32] [33] [34] [35] [36] Encephalopathy or chronic brain dysfunction can result in the most serious manifestations of brain injury, including physical and mental regression and failure to meet developmental milestones; dramatic personality and behavior changes; loss of muscle control, speech and other abilities; multiple learning disabilities and ADHD/ADD; medication resistant seizure disorders; behavior disorders and profound mental retardation.

The scientific literature has long recognized that neurological symptoms of acute encephalopathy can include:

- the sudden onset of convulsions (seizures);
- high pitched screaming *(cri encephalique*) resulting from cerebral irritation;
- and altered state of consciousness.

The literature has also historically recognized that seizures may be a manifestation of acute encephalopathy and that chronic encephalopathy can include residual seizure disorders that over time can cause irreversible brain damage. Chronic encephalopathy can render the child incapable of functioning independently in society as an adult, requiring lifelong economic support. Families caring for vaccine injured children with severe brain injury have little money, time or physical and emotional energy to spend on expensive and drawn out legal proceedings and the VIT was one mechanism for making the VICP a less burdensome legal alternative for petitioners.

Below is the original VIT that was included in the 1986 National Childhood Vaccine Injury Act with definitions for encephalopathy. The original VIT definition of encephalopathy and clinical signs and symptoms indicating encephalopathy remain consistent with the definitions of encephalopathy in past and current scientific literature.

VACCINE INJURY TABLE [37]

I. DTP; P; DTP/Polio Combination; or Any Other Vaccine Containing Whole Cell Pertussis Bacteria, Extracted or Partial Cell Bacteria, or Specific Pertussis Antigen(s).	
Illness, disability, injury, or condition covered:	Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration:
A. Anaphylaxis or anaphylactic shock	24 hours
B. Encephalopathy (or encephalitis)	3 days
C. Shock-collapse or hypotonic-hyporesponsive collapse	3 days
D. Residual seizure disorder in accordance with subsection (b)(2)	3 days
E. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable
II. Measles, mumps, rubella, or any vaccine containing any of the foregoing as a component; DT; Td; or Tetanus Toxoid.	
A. Anaphylaxis or anaphylactic shock	24 hours
B. Encephalopathy (or encephalitis)	15 days (for mumps, rubella, measles, or any vaccine containing any of the foregoing as a component). 3 days (for DT, Td, or tetanus toxoid).
C. Residual seizure disorder in accordance with subsection (b)(2)	15 days (for mumps, rubella, measles, or any vaccine

		containing any of the foregoing as a component). 3 days (for DT, Td, or tetanus toxoid).
	D. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable
III.	Polio Vaccines (other than Inactivated Polio Vaccine).	
	A. Paralytic polio	
	—in a non-immunodeficient recipient	30 days
	—in an immunodeficient recipient	6 months
	—in a vaccine-associated community case	Not applicable
	B. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable
IV.	Inactivated Polio Vaccine.	
	A. Anaphylaxis or anaphylactic shock	24 hours
	B. Any acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above which illness, disability, injury, or condition arose within the time period prescribed	Not applicable

(b) Qualifications and aids to interpretation

The following qualifications and aids to interpretation shall apply to the Vaccine Injury Table in subsection (a) of this section:

(1) A shock-collapse or a hypotonic-hyporesponsive collapse may be evidenced by indicia or symptoms such as decrease or loss of muscle tone, paralysis (partial or complete), hemiplegia or hemiparesis, loss of color or turning pale white or blue, unresponsiveness to environmental stimuli, depression of consciousness, loss of consciousness, prolonged sleeping with difficulty arousing, or cardiovascular or respiratory arrest.

(2) A petitioner may be considered to have suffered a residual seizure disorder if the petitioner did not suffer a seizure or convulsion unaccompanied by fever or accompanied by a fever of

less than 102 degrees Fahrenheit before the first seizure or convulsion after the administration of the vaccine involved and if—

(A) in the case of a measles, mumps, or rubella vaccine or any combination of such vaccines, the first seizure or convulsion occurred within 15 days after administration of the vaccine and 2 or more seizures or convulsions occurred within 1 year after the administration of the vaccine which were unaccompanied by fever or accompanied by a fever of less than 102 degrees Fahrenheit, and

(B) in the case of any other vaccine, the first seizure or convulsion occurred within 3 days after administration of the vaccine and 2 or more seizures or convulsions occurred within 1 year after the administration of the vaccine which were unaccompanied by fever or accompanied by a fever of less than 102 degrees Fahrenheit.

(3)(A) **The term "encephalopathy" means any significant acquired abnormality of, or injury to, or impairment of function of the brain**. Among the frequent manifestations of encephalopathy are focal and diffuse neurologic signs, increased intracranial pressure, or changes lasting at least 6 hours in level of consciousness, with or without convulsions. The neurological signs and symptoms of encephalopathy may be temporary with complete recovery, or may result in various degrees of permanent impairment. Signs and symptoms such as high pitched and unusual screaming, persistent unconsolable crying, and bulging fontanel are compatible with an encephalopathy, but in and of themselves are not conclusive evidence of encephalopathy. Encephalopathy usually can be documented by slow wave activity on an electroencephalogram.

(B) If in a proceeding on a petition it is shown by a preponderance of the evidence that an encephalopathy was caused by infection, toxins, trauma, or metabolic disturbances the encephalopathy shall not be considered to be a condition set forth in the table. If at the time a judgment is entered on a petition filed under section 300aa–11 of this title for a vaccine-related injury or death it is not possible to determine the cause, by a preponderance of the evidence, of an encephalopathy, the encephalopathy shall be considered to be a condition set forth in the table. In determining whether or not an encephalopathy is a condition set forth in the table, the court shall consider the entire medical record.

(4) For purposes of paragraphs (2) and (3), the terms "seizure" and "convulsion" include grand mal, petit mal, absence, myoclonic, tonic-clonic, and focal motor seizures and signs. If a provision of the table to which paragraph (1), (2), (3), or (4) applies is revised under subsection (c) or (d) of this section, such paragraph shall not apply to such provision after the effective date of the revision unless the revision specifies that such paragraph is to continue to apply.

Department of Health & Human Services (DHHS) Changes VIT Definition of Encephalopathy

In 1995, the Secretary of DHHS removed long recognized symptoms of acute and chronic encephalopathy, including seizures, from the VIT[38] *despite* (1) an IOM report published in 1991, which acknowledged that DPT vaccine can cause acute encephalopathy[39] and is associated with clinical symptoms such as seizures, collapse and protracted inconsolable crying (includes high pitched screaming or *encephalitic cry*) and (2) an IOM report published in 1994 that acknowledged DPT vaccine can cause chronic encephalopathy.[40]

When the 1986 law was enacted, encephalopathy was defined in the VIT as "*any acute or chronic significant acquired abnormality of, or injury to, or impairment of function of, the brain*". In 1995, DHHS rewrote the VIT definition for acute encephalopathy as "*a significantly decreased level of consciousness lasting for at least 24 hours*" and specifically excluded clinical signs and symptoms of acute encephalopathy that have been reported in the medical literature for a century.

Contrary to the IOM's definition of encephalopathy, the new VIT definition re-written by DHHS in 1995 and still in effect today states:

> "*The following clinical features alone or in combination do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness: sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy.*"

Encephalopathy Defined: Institute of Medicine Reports (1991-2012)

1991: IOM Report on Adverse Effects of Pertussis and Rubella Vaccines

The 1991 IOM committee report *Adverse Effects of Pertussis and Rubella Vaccines*[41] identified a causal relationship between DPT vaccine and acute encephalopathy. This report went into great detail when describing clinical symptoms and scientific definitions of encephalopathy, with the committee noting that "acute or subacute encephalitis, encephalomyelitis and encephalopathy" were used in various published studies to describe a "constellation of symptoms and signs reflecting a generalized disturbance in brain function" that may include:

- altered levels of consciousness;
- confusion;
- irritability;
- headaches;
- changes in behavior;
- screaming attacks;
- neck stiffness;
- sudden onset of convulsions;
- visual, auditory or speech disturbances;
- motor and sensory deficit;
- other neurological abnormality of the brain.

Knowledge Gaps: The 1991 IOM report also for the first time pointed out to the medical community and the public that there is a serious lack of quality basic science research and methodologically sound epidemiological studies evaluating the biological mechanisms and frequency of vaccine adverse events and natural history of conditions, such as encephalopathy. These knowledge gaps hampered the IOM committee's investigation into reported serious health problems associated with the two federally recommended childhood vaccines (DPT, rubella). The committee stated:

> *"In the course of its review the committee found many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. Such shortcomings relate, for*

example, to pathologic mechanisms of specific infectious agents, the molecular basis for vaccine injury, and the natural history of conditions such as ***encephalopathy****, mental retardation and chronic arthritis."* [42]

1994: IOM Report on Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality

The Institute of Medicine issued two important reports in 1994 and both fell within the congressional vaccine research mandate under the 1986 law for IOM to review medical literature and other evidence that there are health risks to children associated with federally recommended vaccines.

Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality was a report that reviewed evidence related to seven federally recommended childhood vaccines: diphtheria, tetanus, measles, mumps, polio, hepatitis B and H. influenza type b (Hib) vaccines.[43]

Continuing Knowledge Gaps: For more than 30 reported serious brain and immune system problems associated with the seven federally recommended vaccines under examination, the 1994 IOM committee was unable to come to a conclusion about *whether or not* there was a causal relationship, including for **encephalopathy and residual seizure disorders** related to several vaccines. Once again, an IOM committee was frustrated by gaps in vaccine safety science and made statements such as:

> *"For the vast majority of vaccine-adverse event relations studied, the data came predominantly from uncontrolled studies and case reports."* [44]

This 1994 report echoed concerns expressed in the 1991 IOM report about lack of scientific knowledge about vaccine adverse events and why there is individual susceptibility to suffering vaccine harm:

> *"The lack of adequate data regarding many of the adverse events under study was of major concern to the committee....The committee was able to identify little information pertaining to why some individuals react adversely to vaccines when most do not."* [45]

In a concluding chapter "Need for Research and Surveillance," the committee stated:

> *"The committee found that a judgment regarding causality was often limited by the absence of background data for the occurrence of the pathologic condition (the putative adverse event) in apparently normal individuals not recently exposed to the vaccine."* [46]

This lack of background data for the occurrence of acute encephalopathy in unvaccinated children or those receiving fewer vaccines, such as learning disabilities, ADD/ADHD, seizure disorders, developmental delays and other chronic brain and immune disorders, continues today to hamper causality conclusions about encephalopathy and vaccination.

1994: IOM Report on DPT Vaccine & Chronic Nervous System Dysfunction

The second report issued by IOM in 1994, *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* was groundbreaking.[47] This report affirmed the conclusions of the *National Childhood Encephalopathy Study (NCES)* published by the British government in 1981.[48]

More than three decades after *NCES* was published, it remains the largest well-conducted prospective, case controlled study of neurological disorders in children. The *NCES* included evaluation of cases of

acute and chronic encephalopathy that developed after children received DPT or measles vaccines and, in 1981, *NCES* authors concluded that receipt of DPT vaccine was causally related to the development of acute encephalopathy (encephalitis, encephalomyelitis) and permanent brain damage in some previously healthy children enrolled in *NCES*, as well as those with underlying brain or metabolic disorders after the DPT vaccine "triggered" expression of the underlying disorder.

Attributable risk estimates in for participants in *NCES* were that:

- **1 in 110,000 DPT shots was followed by an acute encephalopathy within seven days of administration of the vaccine**; and

- **1 in 310,000 DPT shots was followed by persistent neurological damage one year later.**

It is notable that in 1981, the same year that the *NCES* was published confirming that DPT vaccine can cause acute and chronic encephalopathy, an FDA-sponsored case controlled study conducted at UCLA was published reporting the results of a head-to-head comparison of the reactivity of whole cell DPT vaccines and DT vaccines.[49] That U.S. study found that DPT vaccine was far more reactive than DT vaccine and estimated that 1 in 1,750 DPT shots was followed by a convulsion or a hypotonic-hyporesponsive episode (HHE).

In 1993, *NCES* authors published a 10-year follow up of the children, who had developed an acute encephalopathy after DPT vaccination during the study.[50] They found that many of the children were continuing to suffer clinical symptoms of neurologic, behavioral, educational, motor, sensory and self care dysfunctions, including:

- low scores for global educational abilities assessed by intelligence, vocabulary, spelling, reading and arithmetic tests;
- epilepsy/seizure disorder;
- tremor;
- fine or gross motor incoordination;
- muscle weakness or spasticity in one or more limbs;
- hearing and vision problems;
- behavioral dysfunction (problem, hyperactive or unsociable behavior);
- lack of bladder or bowel control.

The *NCES* authors said:

> ***"Our results provide good evidence that illnesses such as those studied in the national childhood encephalopathy study, including a variety of encephalopathies and severe convulsions, both febrile and afebrile, can have lasting sequelae as measured by various indices of brain function. This seems to be true for cases associated in time with diphtheria, tetanus and pertussis immunization as for other cases."*** [51]

The 1994 IOM Committee to Study New Research on Vaccines reviewed the 10-Year follow up of *NCES* and determined that, in addition to the evidence about acute and chronic encephalopathy they had collected for the 1991 IOM report on DPT vaccine, there was compelling scientific evidence to conclude that children with or without underlying brain or metabolic abnormalities can experience an acute encephalopathy within 7 days after receipt of DPT vaccine and go on to suffer chronic neurological dysfunction.

The IOM committee stated:

> ***"The NCES data are consistent with the possibility that some children without underlying brain or metabolic abnormalities might experience serious acute neurologic illness within 7 days after receiving DPT and that acute illness could have chronic nervous system sequelae. The NCES data are also consistent with the possibility that some children with underlying brain or metabolic abnormalities (which foster a "triggering" by DPT of an acute neurologic illness) might go on to develop chronic neurological dysfunction due to a DPT-triggered acute illness. Therefore, the committee concludes that the balance of evidence is consistent with a causal relation between DPT and the forms of chronic nervous system dysfunction described in the NCES in those children who experience a serious acute neurologic illness within 7 days after receiving DPT vaccine."*** [52]

[In September 2006, DHHS officials and four health maintenance organizations (HMOs) participating in the DHHS-operated Vaccine Safety Datalink Group published a retrospective study that concluded DPT and MMR vaccines do not cause encephalopathy.[53] The study has never been replicated and part of the reason may be that non-DHHS, independent scientists are unable to get access to raw data used in Vaccine Safety Datalink Group studies to confirm VSD vaccine safety findings.

In 2005, the IOM Committee on the Review of the National Immunization Program's Research Procedures and Data Sharing Program published a report, *Vaccine Safety Research, Data Access, and Public Trust*. [54] The IOM Committee concluded that there is "limited ability of independent external researchers to conduct high quality corroborative studies or studies of new hypotheses" [55] using VSD data:

> ***"There are legitimate concerns about the independence and fairness of the implementation of review procedures applied to VSD data sharing proposals and of determination about the release of preliminary findings from VSD analyses. The lack of transparency of some of the processes also affects the trust relationship between the National Immunization Program Office (NIP) and the general public."*** [56]

Prospective studies, such as NCES, are superior to retrospective studies and replication is a gold standard in science. The DHHS-conducted 2006 study rejecting a causal association between DPT and MMR vaccines and encephalopathy, a study which has never been replicated and contradicts conclusions of more transparent studies adhering to higher scientific standards, should not influence the revision of the VIT definition of encephalopathy or be used to deny compensation to those suffering encephalopathy following receipt of MMR or pertussis containing vaccines.]

The 1991 and 1994 IOM reports reaffirmed the evidence base for the definition of encephalopathy embedded in the original VIT in the VICP, including acknowledgement of the fact that some children have pre-existing identified and unidentified genetic or biological risk factors that can be triggered by administration of vaccines or have pre-existing medical conditions that can be significantly aggravated by vaccination. Appropriately, there have been vaccine injury compensation awards made to children, who were born with genetic or biological high risk factors, such as an undiagnosed brain or metabolic disorder, that increased their susceptibility to suffering harm from federally recommended vaccines.[57]

2012: IOM Report on Adverse Effects of Vaccines: Evidence and Causality

In 2012, two decades after the first congressionally mandated 1991 IOM report was published, the IOM published a report *Adverse Effects of Vaccines: Evidence and Causality*[58] again reviewing the medical literature for scientific evidence that federally recommended vaccines can cause brain and immune system dysfunction and death. The report reviewed a total of 158 vaccine-related adverse events - including **encephalitis, acute disseminated encephalomyelitis (ADEM) and encephalopathy** - reported following receipt of varicella zoster (chickenpox) vaccine; influenza vaccines; hepatitis B vaccine; human papillomavirus vaccine (HPV); tetanus toxoid-containing vaccines other than those containing the whole cell pertussis component; measles, mumps and rubella vaccines; hepatitis A vaccine; and meningococcal vaccines.

In 2009, the Health Resources and Services Administration (HRSA) had contracted with IOM to conduct what would become the largest assessment of epidemiologic, clinical and biological mechanism evidence about vaccine adverse event outcomes conducted by IOM since the 1986 Childhood Vaccine Injury Act became law and IOM published the 1991 and 1994 reports requested by Congress under the Act. The CDC and National Vaccine Program Office (NVPO) also contributed funding for the 2012 IOM study.[59]

The stated purpose of the 2012 IOM study was to provide scientific basis for review and adjudication of claims of vaccine injury by the VICP. At the study outset, HRSA presented a list of specific adverse events for the committee to review, which HRSA indicated represented the majority of adverse events listed in VICP petitioner claims. During the course of its review of the medical literature, the IOM committee added to the report the following adverse events for which epidemiological studies or case reports were identified:

- all cause mortality and seizures following influenza vaccine;
- optic neuritis following MMR, influenza, hepatitis B and DTaP vaccines;
- neuromyelitis optica following MMR vaccine;
- erythema nodosum following hepatitis B vaccine;
- stroke and small fiber neuropathy following varicella vaccine.

The 2012 IOM Committee to Review Adverse Effects of Vaccines concluded that "the evidence convincingly supports" or "favors acceptance of" a causal relationship between:

- varicella vaccine and Oka varicella zoster vaccine reactivation;
- MMR vaccine and measles inclusion body encephalitis;
- MMR vaccine and febrile seizures;
- Anaphylaxis and MMR, varicella, influenza, hepatitis B, meningococcal, HPV and tetanus toxoid vaccine;
- MMR vaccine and transient arthralgia in female adults and children;
- Any of the vaccines and syncope (sudden loss of consciousness)
- Any of the vaccines and deltoid bursitis;

However, significantly for 135 (85%)[60] of serious adverse health outcomes associated with one or more of the federally recommended vaccines under examination there was either an absence of or too little biological mechanism evidence and/or methodologically sound epidemiologic studies related to the vaccine and reported serious adverse health outcome for the committee to make a causation conclusion. This lack of enough scientific evidence to make a causation

determination between a number of the vaccines being studied and a wide range of brain and immune system disorders included:

- **Encephalitis; encephalopathy; acute disseminated encephalomyelitis (ADEM);** meningitis; traverse myelitis; optic neuritis; chronic inflammatory disseminated polyneuropathy; Bell's palsy; small fiber neuropathy; Guillain Barre Syndrome GBS); afebrile seizures; infantile spasms; opsoclonus/myoclonus syndrome; ataxia; first demyelinating event in children and adults; multiple sclerosis in children and adults.

Like the previous IOM committees, this committee was unable to come to conclusions about causation for the majority of vaccine-related adverse health outcomes because of continuing gaps in scientific knowledge about the biological mechanisms for vaccine adverse effects. Chapter 3 "Evaluating Biological Mechanisms of Adverse Events" is a thoughtful description of the outstanding biological mechanism questions that need to be answered before there can be a better understanding of how and why vaccines can cause acute and chronic brain and immune system dysfunction and death.

The 2012 report highlights the lack of understanding of biological, genetic, environmental and other high risk factors, which increase an individual's susceptibility to vaccine reactions:

> ***"Both epidemiologic and mechanistic research suggest that most individuals who experience an adverse reaction to vaccines have a pre-existing susceptibility. These predispositions can exist for a number of reasons – genetic variants (in human or microbiome DNA), environmental exposures, behaviors, illness or developmental stage, to name just a few, all of which can interact. Some of these adverse reactions are specific to the particular vaccines, while others may not be. Some of these predispositions may be detectable prior to the administration of vaccine; others, at least with current technology and practice, are not."*** [61]

In the Preface of the published 2012 study, the IOM committee chair, Ellen Wright Clayton, M.D., stated that the committee "had a herculean task, requiring long and thoughtful discussions of our approach to analyzing the studies culled from more than 12,000 peer-reviewed articles." She said "some issues simply cannot be resolved with current available epidemiological data" and emphasized that scientific conclusions about cause and effect relationships between vaccines and reported adverse events requires a combination of biological mechanism and epidemiological evidence, particularly when it comes to identifying individual susceptibility risk factors:

> *"Even very large epidemiologic studies may not detect or rule out rare events. Subgroup analysis or more focused epidemiologic studies, informed by as yet incomplete knowledge of the biological mechanisms of vaccine-induced injury, may be required....The value of dialogue between both epidemiologic and mechanism approaches cannot be overstated. Epidemiologic studies can identify particular high risk groups, who can then be examined with more in depth testing to explore predisposing factors. The findings of such studies can then inform more focused epidemiologic research as well as efforts to reduce risks. These conversations between different types of research can be difficult, but the results are worth it."*

While the 2012 IOM Committee noted recent discoveries relating to SCN1A mutations, Dravet syndrome and encephalopathy, they were cautious in drawing any conclusions and stated:

> "This list of factors that are known to confer susceptibility is by no means definitive or exhaustive. Rather, we hypothesize that continued study of alleged vaccine-related injuries, the committee informed by epidemiologic studies that identify vulnerable populations and exploration of underlying mechanisms of susceptibility, will provide greater insight into these and other mechanisms and will identify more factors that contribute to vaccine susceptibility." [62]

More recent studies with regard to Dravet syndrome have noted de novo genetic mutations of SCN1A may occur at any time, from the embryonic premorula stage to adulthood[63] and the syndrome "encompasses different epileptic and cognitive phenotypes that probably result from both genetic and epigenetic factors."[64] Coupled with the 2012 IOM Committee's acknowledgement that fever induced by vaccines may trigger Dravet syndrome, these studies indicate that there are as yet unidentified genetic, biological and environment factors involved in expression of Dravet syndrome in some individuals and leaves open the possibility that individuals may go through their whole lifetime without exhibiting symptoms of Dravet syndrome.

In the IOM 2012 report the following statements were made regarding Dravet syndrome and whole cell pertussis vaccine:

> *"In some metabolically vulnerable children, receiving vaccines may be the largely nonspecific "last straw" that leads these children to reveal their underlying genotype. It was recently discovered that a large majority of children who developed encephalopathy after receiving whole cell pertussis vaccine have mutations in SCN1A, which are associated with Dravet syndrome or severe myoclonic epilepsy of childhood (Berkovic et al., 2006; McIntosh et al., 2010). While it seems likely that the vaccine triggered symptoms in these children by causing high fever, the particular vaccine antigens do not appear to alter the course of the disease. Rather, the ensuing phenotype could and probably would have been precipitated by multiple other fever-inducing triggers (McIntosh et al., 2010; Wiznitzer, 2010)."* [65]

At issue is the implication that "a large majority of children" who develop encephalopathy after receiving whole cell pertussis vaccine have mutations in SCN1A, when the 2006 Bercovic et al study examined only 14 patients and the 2010 McIntosh study examined 40 patients. This dataset is not large enough to make that sweeping conclusion and certainly not enough justification to change the definition of encephalopathy for the purpose of denying vaccine injury compensation to those children with that genotype.

In 2011, a study by Tro-Baumann et al retrospectively examined the relationship between vaccination and occurrence of seizures in 70 children with Dravet syndrome. The authors pointed out that 27% of patients suffered seizures post-vaccination (primarily after DPT vaccine) and in 58% vaccine-related seizures represented the first clinical manifestation. Appropriately, the study authors called for "preventive measures for seizures triggered by vaccination or fever in these children." [66]

There can be no assumption that *all* individuals with SCN1A mutations associated with Dravet, who develop encephalopathic symptoms after vaccination, including seizures, would have developed encephalopathy even if no vaccines had been given. Children born with SCN1A mutations, who develop acute and chronic encephalopathy after vaccination, should not be precluded from receiving vaccine injury compensation simply because of the genes they were born with, genes which may or may not have been expressed had one or more federally recommended vaccines not been given.

Definitions for Encephalopathy Align with IOM Findings

The IOM is not alone in their acknowledgment of signs, symptoms and definitions of encephalopathy long recognized in the medical literature.

- **The National Institutes of Health's National Library of Medicine** states encephalitis complications can lead to permanent brain damage with symptoms that can include mild fever, mild to severe headache, low energy, poor appetite, clumsiness, unsteady gait, confusion, disorientation, drowsiness, irritability, light sensitivity, stiff neck and back, vomiting, fontanel bulging (infant), loss of consciousness, stupor, coma, muscle weakness, paralysis, seizures, flat mood, inappropriate mood, memory loss that may be caused by the following vaccines: MMR, Polio, Varicella.[67]

- **The National Institute of Neurological Disorders and Stroke (NINDS)** uses the following definitions and symptoms for the following conditions:
    - **Encephalitis** is an inflammation of the membranes surrounding the brain and spinal cord with symptoms that can include sudden fever, headache, vomiting, light sensitivity, stiff neck and back, confusion and impaired judgment, drowsiness, weak muscles, clumsy and unsteady gait, irritability, loss of consciousness, seizures, muscle weakness, and/or sudden severe dementia. Complications can include permanent impairment or death.[68]
    - **Encephalopathy** is a condition that results in the altering of the structure or function of the brain that may include the following symptoms: altered mental state, progressive loss of memory and cognition, involuntary muscle twitching, subtle personality changes, rapid involuntary eye movement, tremor, muscle atrophy and weakness, dementia, seizures, apraxia (loss of speech), and/or inability to swallow. This condition may cause permanent changes and irreversible damage to the brain and can be fatal. [69]
    - **Acute Disseminated Encephalomyelitis** is characterized as an attack of inflammation of the brain and spinal cord that damages the protective covering of nerve fibers. This condition can result from the MMR vaccine with encephalitis-like symptoms appearing rapidly that can include fever, fatigue, headache, nausea, vomiting, seizures and coma. The damage to nerve fibers typically lead to neurological symptoms that can include vision loss, paralysis, muscular coordination difficulties. Some ADEM patients will have lifelong impairment such as cognitive difficulties, weakness, loss of vision, numbness, and can be fatal.[70]

Current VIT Language Under Consideration

The current language the ACCV is being asked to approve relating to the VIT and encephalopathy and are additions to the QAI that would stating

> "Individuals who return to their baseline neurologic state, as confirmed by clinical findings, in **less than** 6 months **from the date of vaccination** shall not be presumed to have suffered residual neurologic damage from that event..."
>
> and
>
> "...an encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by: (A) An underlying condition or systemic disease

shown to be unrelated to the vaccine (such as a malignancy, structural lesions, psychiatric illness, dementia, genetic disorder..."

This restrictive and exclusionary encephalopathy guideline change unfairly discriminates against children and adults born with certain genes or pre-existing medical conditions that may be triggered or significantly aggravated following receipt of government recommended and mandated vaccines. There is no ethical, scientific or legal justification for denying compensation to susceptible individuals because of the genes they were born with, especially in light of the fact that significant knowledge gaps about the biological mechanisms and high risk factors for vaccine injury remain. The VICP cannot and should not be a vehicle for discrimination against those most vulnerable to vaccine injury and death.

Knowledge Gaps, Biodiversity & Individual Susceptibility Being Ignored

Science is not static but continually evolves. In the coming years, there will be more information about genetic and other high risk factors that predispose some individuals to suffering vaccine induced encephalopathy and other serious, life altering brain and immune system disorders. The emerging new microbiome and epigenetics science, which is focusing on biodiversity and how it affects individual health outcomes, will change the practice of medicine.

Microbiome Individual Differences: Resident microbes add another 100 trillion cells to the 10 million cells that make up the human body and contributing 8 million genes that interact with 21,000 human genes to help our body grow, digest food, develop and mount immune responses and perform many other normal bodily functions.[71] [72] [73] In 2014, researchers in Ireland studying the microbiome, stress, health and disease observed that the microbiome is established during the first three years of life but that it evolves throughout our lives as we constantly respond to our environment and there are microbiome differences between individuals:

> *"The microbiome is a dynamic entity that is under continuous evolution throughout the host's lifetime in particular during the first three years of life during which time a stable microbiome is established. It is sensitive to a whole array of manipulations such as diet, stress, infection, pharmacological interventions and thus is it clear that the composition of the microbiota is distinct at different milestones of life."* [74]

Epigenetics & Individual Differences: Together with a better understanding of the complexity of the microbiome, the new field of epigenetics is highlighting the importance of respecting biodiversity.[75] Epigenetics, which can be defined as stimuli-triggered changes in gene expression that are inheritable and occur independent of changes to the underlying DNA sequence[76] provides compelling evidence for the urgent need to fill in knowledge gaps about individual susceptibility to vaccine reactions. Scientists have discovered that differing external environmental exposures (such as nutrients, chemicals, infections) and individual responses to trauma and fear, for example, can trigger changes in chromatin structure and gene expression to uniquely affect each individual's susceptibility to certain illnesses and disorders and these susceptibilities can be passed on to future generations.[77] [78]

Microbiome and epigenetics science highlights why there is an urgent need to acknowledge and adjust for individual differences in responses to vaccines and to respect individual susceptibilities, not ignore or punish those with them when considering awards for development of encephalopathy after vaccination. Hopefully the new science will lead to a move away from the current one-size-fits-all approach to vaccine policies and in the future fewer individuals will need to apply for vaccine injury compensation.

In the meantime, vaccine manufacturers protected from civil liability by the 1986 law should make greater efforts to better define the biological mechanisms for adverse events and potential genetic,

biological and environmental high risk factors that place some individuals at higher risk than others for suffering encephalopathy and other types of brain and immune system damage from both existing and new vaccines being developed so fewer children and adults will become vaccine injured VICP claimants.[79] [80]

NVIC urges the ACCV to vote against the DHHS recommendations for the revision of the definition of encephalopathy because it is not based on sound science and will unfairly discriminate against those most susceptible to vaccine injury and death, as well as further erode parent and public confidence in the integrity of the vaccine system.

Sincerely,

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/s/Theresa Wrangham
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[5] See References 2-4.
[6] NVIC.org. About National Vaccine Information Center (NVIC).
[7] Title 42 – The Public Health and Welfare Chapter 6A – Public Health Service – Subchapter XIX – Vaccines Part 2 – National Vaccine Injury Compensation Program subpart d – Sec. 300aa-33 – Definition (4) *The term "significant aggravation" means any change for the worse of a pre-existing condition which results in markedly greater disability, pain or illness accompanied by a substantial deterioration of health.*
[8] Ibid. National Vaccine Injury Compensation Program subpart c – assuring a safer childhood vaccination program in the United States – Sec. 300aa-26 – Vaccine Information.
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