

Advisory Commission on Childhood Vaccines

December 8, 2017

104th Meeting

Members Present

Karlen E. Luthy, D.N.P., Interim Chair, ('18)

John Howie, J.D. ('19)

H. Cody Meissner, MD, ('19)

Dino Sangiamo, J.D. ('19)

Alexandra Stewart, J.D. ('18)

Martha Toomey ('18)

Division of Injury Compensation Programs (DICP), Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services (HHS)

Narayan Nair, M.D., Director, DICP

Andrea Herzog, Principal Staff Liaison, ACCV

Welcome and Report from Beth Luthy, Interim Chair

Ms. Luthy called the meeting to order. After the introduction of Commission members present, Ms. Luthy invited public comment on the meeting agenda. Public comment on agenda items:

1. A member of the public, Janet Cakir, requested time to comment on several issues that would be discussed during the meeting, including: comments on methyl mercury and tics, the petition related to adding Pediatric Autoimmune Neuropsychiatric Syndrome (PANS), Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders (PITANDS), and Pediatric Autoimmune Neuropsychiatric Disorders (PANDAS) to the Vaccine Injury Table, and the petition related to adding acute demyelinating encephalomyelitis (ADEM) to the Vaccine Injury Table (Table). Ms. Luthy reminded her that this opportunity to comment related only to the relevance of the agenda items as topics for discussion, and not for substantive discussion of those topics. Ms. Luthy offered assurance that members of the public would have the opportunity to comment after the discussion of each agenda item. In addition, she explained that each petition would be presented separately, followed by public comment limited to the substance of the petition, followed by Commissioners' discussion, followed by a vote of the Commission on the petition.
2. Ms. Theresa Wrangham, Executive Director of the National Vaccine Information Center (NVIC), noted a minor error in the September minutes. The title of NVIC was inaccurately described as the National Vaccine Injury Center. Ms. Wrangham expressed concern that representatives of HRSA usually make presentations on

agenda items and discussion of issues is usually limited to ACCV members and staff, and the public has little opportunity to participate in a give-and-take conversation. She added that the National Academy of Medicine (NAM) (formerly Institute of Medicine (IOM)) relies on a format of providing a “report card” that includes considerations of the quality of evidence from scientific literature, epidemiological data, causality rationale and so on. Ms. Wrangham felt it would be helpful to follow the NAM model in making presentations such as those concerning Table revisions.

Approval of September 8, 2017 ACCV Meeting Minutes

Ms. Luthy invited approval of the minutes of the September 2017 meeting, noting that the NVIC name would be corrected to read National Vaccine Information Center, not Injury Center. A motion to approve the minutes was made and it was seconded. However, a vote by Commission to approve the minutes did not occur until later in the meeting. At that time, there was a motion to approve the minutes and it was seconded. Then, the Commission voted to approve the minutes.

Report from the DICP, Dr. Narayan Nair, Director

Dr. Nair welcomed the Commission members, staff and members of the public. He especially welcomed the new members who were participating in their first ACCV meeting. Dr. Nair reviewed the agenda for the meeting, which included presentations of petitions to add injuries to the Table. Beginning with statistical information, Dr. Nair announced that 401 petitions were filed in 2012 and the number of petitions filed annually has increased significantly every year since 2012. The number of petitions filed in FY 2017 was 1,243. To date, there have been 215 petitions filed in FY 2018, indicating there will be more petitions filed in FY 2018 than there were in FY 2017. The petitioners’ awards in FY 2017 totaled \$252 million (nearly \$30 million to attorneys’ fees/costs), and for the first two months of FY 2018 the awards were \$31 million (\$5.7 million for attorneys’ fees/costs). Finally, the total cases adjudicated in FY 2017, which may have been filed in a prior fiscal year, were 836 (683 compensable, 153 dismissed), and thus far in FY 2018, 90 cases were adjudicated (53 compensable, 37 dismissed). Of the 686 non-autism cases adjudicated in FY 2017, HHS conceded 26%, the court decided 7%, and the majority, 67%, were settled by agreement between the parties involved.

Dr. Nair reported that the Vaccine Injury Compensation Trust Fund had a balance of \$3.7 billion at the end of FY 2017, and had received total income of \$331 million from excise taxes (\$270 million), interest income (nearly \$57 million), and a refund from prior year of \$5 million.

A significant activity since the last report to the Commission was the vote on revised language to the Table. A Notice of Proposed Rulemaking published in the Federal Register regarding that change is being developed. DICP presented information about SIRVA (shoulder injuries related to vaccine administration) at the Advisory Committee on Immunization Practices (ACIP) in October 2017. Dr. Nair noted that the Commission would discuss several pending petitions.

During the discussion, there was clarification that the Court’s web site publishes specific case decisions for those interested.

Report from the Department of Justice, Ms. Catharine Reeves, Deputy Director, Torts Branch

Ms. Reeves welcomed the commissioners. Ms. Reeves noted that the reporting period for the Department of Justice (DOJ) is different from that of the Division of Injury Compensation Programs. Ms. Reeves referenced the DOJ Power Point materials as part of her presentation for the three-month period from August 16, 2017 to November 15, 2017. During this reporting period, 396 petitions were filed, compared to 355 petitions filed during the same period last year. Of those 396, 33 were filed on behalf of children (8%) and 363 were filed by adults (92%). (DOJ PP at 2). Ms. Reeves noted that majority of these petitions involve claims for shoulder injury related to vaccine administration (SIRVA).

With regard to total cases adjudicated, Ms. Reeves noted that most cases—approximately 80%—continue to resolve by settlement. Ms. Reeves noted that 196 claims were adjudicated this quarter, compared to 222 for the same period last year. (DOJ PP at 3). There were 141 cases compensated. Of those 141 cases, 56 were conceded by HHS. Of those 56 conceded cases, 54 were resolved by a decision adopting a proffer and 2 were resolved by a decision awarding damages. There were 85 cases compensated but not conceded by HHS. Of those, all 85 cases were resolved by a decision adopting a settlement stipulation. (DOJ PP at 3). There were 55 cases dismissed. Of those, 36 non-OAP cases were resolved by decisions dismissing the petition, and 19 were dismissed from the OAP. (DOJ PP at 3). There were 5 petitions voluntarily withdrawn. (DOJ PP at 4).

Turning to appeals, two appeals filed by petitioners at the U.S. Court of Appeals for the Federal Circuit (CAFC) were affirmed. (DOJ PP at 5). *H.L. v. HHS* involved entitlement. In *Simmons v. HHS*, the CAFC discussed when it is appropriate for a special master to award attorneys' fees and costs when a petitioner is not compensated, and provided more guidance on what constitutes reasonable basis. Four appeals regarding entitlement remain pending in *D'Tiole v. HHS*, *Anderson v. HHS*, *Oliver v. HHS*, and *Depena v. HHS*. (DOJ PP at 6).

Ms. Reeves discussed appeals at the CFC, and noted that four appeals filed by petitioners were decided by the CFC. (DOJ PP at 7). Two of the four appeals concerned attorneys' fees and costs and two concerned entitlement. The court affirmed the special master's decisions in the cases concerning entitlement and in one of the cases regarding attorneys' fees and costs. In *Cottingham v. HHS*, the CFC remanded and the case remains pending before the special master for further proceedings. Fourteen cases remain pending at the CFC. (DOJ PP 8-9).

No oral arguments are scheduled at the CAFC. An oral argument in *Santacroce v. HHS* before the CFC was scheduled for December 12, 2017. (DOJ PP at 10).

Ms. Reeves noted the history of adjudicated settlements, which are listed in order of the time they took to resolve. (DOJ PP at 11-18). Most of the cases involved injuries related to Guillain-Barré Syndrome and SIRVA, and most cases resolved within two years of filing, which is notable considering the increasing case load.

Dr. Meissner remarked that it was interesting that 10% or fewer petitions were filed on behalf of minors with the remainder being adults, and that among adults the flu vaccine was the most alleged vaccine. He noted that we should be educating people about administering vaccines to prevent SIRVA injuries. Dr. Nair responded that SIRVA is the only theoretically preventable vaccine injury, that HHS had recently presented at ACIP with the CDC's Immunization Safety Office about SIRVA, and that he believed that CDC was conducting outreach activities regarding vaccine administration.

Mr. Sangiamo asked for further clarification about *Simmons v. HHS*. Ms. Reeves responded that *Simmons* held that reasonable basis cannot be based on the actions of the attorney filing on the eve of the statute of limitations. She noted that previously special masters and the CFC have looked at the totality of the circumstances, including a looming statute of limitations, to determine whether reasonable basis exists, and that the CAFC held in *Simmons* that a looming statute of limitations by itself is insufficient. Ms. Reeves is hopeful that attorneys will be more careful about filing petitions, especially considering the limited resources at the Court, DOJ, and HHS, but it remains to be seen how *Simmons* will impact the filing of cases.

Mr. Howie asked what measures have been implemented to move cases faster and more efficiently. Ms. Reeves noted that DOJ attorneys have more than 100 cases on their dockets, and while DOJ was allowed to hire six more attorneys who are in the hiring pipeline, there is a learning curve once they start. Ms. Reeves also noted that HHS does not have funding to increase resources and the Court cannot increase the number of special masters without an act of Congress. Ms. Toomey noted that the ACCV had submitted a recommendation to the Secretary requesting increased funding, but that recommendation had not been acted upon.

Petition to Add Injuries to the Vaccine Injury Table - Introduction, Dr. Nair, Director, DICP

Dr. Nair briefly described the purpose of the Table, which, in accordance with section 312(b) of the National Childhood Vaccine Injury Act of 1986, title III of Pub.L. 99–660, 100 Stat. 3779 (42 U.S.C. 300aa–1 note) and section 2114(c) of the Public Health Service Act (42 U.S.C. 300aa–14(c)), authorizes the Secretary of HHS to create and modify/update/revise the Table. The Table lists vaccines covered by the VICP and the injuries, disabilities, illnesses, conditions, (including death), resulting from the administration of the listed vaccines. The Table also includes the timeline in which the first symptom or manifestation of onset or of the significant aggravation of such injuries, disabilities, illnesses, conditions, or death is to occur after vaccine administration for purposes of receiving compensation under the Program. The Table also is a legal mechanism for defining complex medical conditions and permits “presumption of causation” if no other cause is found. Dr. Nair noted that, although any claim that fits all criteria is eligible for compensation, a claim for an injury not on the Table may be filed by anyone, and will be heard based on the merits of each case and the preponderance of evidence submitted.

Several years ago, the Commission developed “Guiding Principles for Recommending Changes in the Vaccine Injury Table.” The Commission believed that the Table must be scientifically and medically credible, and the final decision about accepting or rejecting a recommendation must be made for the benefit of the petitioner. The Guiding Principles recognize that some data is more valuable in assessing causality than other data and the Commission established a hierarchy to assign weight to various data (briefly listed in descending order of weight):

- Clinical laboratory data
- Challenge/re-challenge/de-challenge data involving non-re lapsing symptoms or diseases controlled clinical trials
- Controlled clinical trials (including, but not limited to, double-blind, placebo controlled

- clinical trials)
- Controlled observational cohort and case-control studies and studies based on Vaccine Safety Datalink (VSD) database.
- Uncontrolled observational studies such as ecological studies
- Case series
- Data from passive surveillance systems (e.g., Vaccine Adverse Event Reporting System (VAERS))
- Case reports
- Editorial articles on scientific presentations
- Non-peer reviewed publications

Dr. Nair reiterated that several petitions to add injuries to the Table would be discussed during the meeting, including:

- Asthma, Food Allergies and Autism (Food Allergies/Autism will be addressed separately) (vaccines not specified)
- Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders (PITANDS); and/or Pediatric Autoimmune and Neuropsychiatric Syndrome (PANS); and Pediatric Autoimmune Neuropsychiatric Disorder Associated with group A Streptococcus (PANDAS) for pertussis, pneumococcal conjugate and Haemophilus influenza type b (Hib) vaccines
- Experimental Autoimmune Encephalomyelitis for pertussis vaccines
- Tics (vaccines not specified)

Dr. Nair explained that the process for preparing the petitions for Commission consideration included a review of the Institute of Medicine report, described above, and an independent literature search with support from the NIH National Library of Medicine, focusing on English-language peer reviewed publications.

Dr. Nair began a discussion of the petition to add food allergies to the Table, reminding the Commission that a private citizen has submitted a request to add food allergies to the Table. A request to add food allergies to the Table was previously received from the same individual in 2016, that petition was reviewed at the December 2016 ACCV meeting, and the ACCV voted to not add food allergies to the Table. The individual resubmitted an expanded request in April 2017 to include food allergies, asthma and autism to the Table. After additional research, no new information was found concerning food allergies.

Responding to the autism claim in the request, Dr. Nair recalled that the CFC ordered Omnibus Autism Proceedings in July 2002 due to about 5,600 claims alleging autism. These claims were addressed in a two-phase discovery process that lasted until 2006. During the 2002, Omnibus Autism Proceedings petitioners submitted over 200,000 pages of documents and the issue was processed in entitlement hearings in 2007 and 2008. Decisions were handed down in 2009 and 2010, affirmed on appeal, that there was no evidence that the measles-mumps-rubella (MMR) vaccine, with or without thimerosal, causes autism. Current scientific evidence continues to support those decisions.

In addition, Dr. Nair explained that, in 2011, the National Academy of Medicine reviewed evidence and found no causal relationship between MMR vaccine and autism. The ACCV heard that report in September 2011 and March 2012. The DICP reviewed medical

literature from peer reviewed English language clinical publications and determined that there was no publications that concluded that other vaccines cause autism. Additionally, a number of national and international medical associations, academies and institutions have conducted independent studies that arrived at the same conclusion. HHS affirmed the position that autism is not caused by any vaccines in the Final Rule amending the Table (82 FR 6294, 6298).

At the end of his comments, Dr. Nair reviewed the provisions of the Guiding Principles. He concluded that the Commission would consider two options with regard to the autism Table revision – either add autism as an injury to the Vaccine Injury Table, or not add autism as an injury to the Table. Ms. Luthy stated that the Commission could ask questions regarding the presentation, followed by an opportunity for public comment, and a final vote on the options.

During the discussion, Martha Toomey, a Commissioner, asked who paid for the various studies. Dr. Nair responded that the studies were financed through various sources. There was an observation that, contrary to a statement made about reports from other national and international health entities; there are studies in the literature that indicate that autism can be caused by vaccines. Ms. Luthy invited public comment.

1. A member of the public commented that the DTaP (Diphtheria-Tetanus-Acellular Pertussis) vaccine package insert contains a statement that autism can be a complication from vaccination. She made a technical comment about the Stephano case (cited in a presentation) concerning the density of lipopolysaccharides in whole cell and acellular pertussis, which could affect the number of antigens present, which in turn can influence the effect of vaccine as causative of autism. The private citizen also mentioned an allegation that African- American children from Georgia develop autism at a higher rate than the general population; she felt this is a research question that should be addressed.
2. Theresa Wrangham, Executive Director of the NVIC reiterated the opinion that the DICI data lacks the weighting or ranking of the NAM data, mentioned previously. She added that the NAM only expressed a position on MMR vaccine, asserting that there was inadequate data to make valid conclusions about other vaccines. Ms. Wrangham reiterated that the presentations appear to be prepared only by HRSA, which could introduce bias. Ms. Wrangham reiterated NVIC's position that petitioners should be invited to present their petitions to the ACCV. Ms. Toomey, citing the court decision that her son's autism was a vaccine injury eligible for compensation, stated that this action belies any claim that a vaccine cannot cause autism.

Prior to the final vote, Ms. Luthy invited questions or comments from the Commission members. Asked about the package insert comment, Dr. Shimabukuro indicated that that question should be directed to the Food and Drug Administration, the agency responsible for package inserts. LCDR Marshall stated that mention of adverse events in a package insert does not necessarily support a direct association. Ms. Luthy invited each member of the quorum to submit an oral vote:

Option 1 – Add autism to the Table.

Option 2 – Do not add autism to the Table.

The result of the vote was five in favor of Option 2 and one in favor of Option 1. Ms. Stewart, Mr. Howie, Mr. Sangiamo, Dr. Meissner and Ms. Luthy voted for Option 2. Ms.

Toomey voted for Option 1.

Ms. Luthy invited Dr. Rubin to discuss the petition requesting that tics be added as an injury to the Table.

Petition to Add Tics as an Injury to the Vaccine Injury Table, Dr. Mary Rubin, Medical Officer, DICP

Dr. Rubin stated that a private citizen submitted a formal request to HHS and the ACCV to add tics as an injury to the Table as a disorder resulting from vaccination based on a claim made by two CDC employees. Dr. Rubin explained that tics are sudden, rapid, non-rhythmic recurrent movements or vocalizations (brief sounds or more complex utterances and with Tourette's syndrome, may include involuntary obscenities). Tics typically diminish during sleep, and can be controlled, at least temporarily, in some cases. Tics usually develop in 5-10% of early school age children (4-6), with peak severity between 10-12 years of age, and decline during adolescence. Tics are believed to be caused by abnormal chemical reaction in the brain. Tics may be exacerbated by stress, excitement and exhaustion. Males are affected more frequently than females; otherwise, the disorder is similar in both.

Diagnosis is symptom-specific, and four categories are typically identified: Tourette's disorder (not attributed to the physiologic effects of a substance or other medical disorder); persistent motor or vocal tic disorder (criteria never met for Tourette's); and provisional tic disorder (criteria not met for either Tourette's or persistent disorder); and other specified or non-specified tic disorder. Diagnosis of tic disorder is complex and only specialists can make reliable diagnosis. Treatment is variable, and includes education and managing disabling tics; there are also cognitive-behavioral therapies and medication in severe cases.

Dr. Rubin reviewed the ACCV Guiding Principles discussed previously. There was no supporting citation provided in the private citizen's request, but a literature search revealed a paper published in the Journal of Pediatric Psychology, entitled "Thimerosal exposure in early life and neuropsychological outcomes 7-10 years later." (J.P. Barile et al). The article described research related to thimerosal exposure in early life. Researchers measured seven neuropsychological outcomes, one of which was tics. The researchers found no statistically significant responses in six of the seven outcomes. However, there was a statistically significant response in the outcome measuring tics in boys, although additional confirmation is needed to develop a more reliable and valid measure of tics. There were significant limitations to the results – training of the clinical observers was brief (about 30 minutes focused on diagnosis of Tourette's); although tics run in families, the lack of response in girls needs further explanation; and the response/participation rate was low (only 30% of eligible subjects chose to participate, which could introduce bias).

The private citizen's petition did not identify the vaccine types or whether the vaccines contained thimerosal. Thimerosal is a mercury-based preservative. Dr. Rubin discussed two types of mercury, methyl mercury and ethyl mercury. Methyl mercury is formed in the environment and is typically found in food. Ethyl mercury is found when the body breaks down thimerosal, and is cleared from the blood more quickly than methyl mercury. There is no evidence of harm from thimerosal in vaccines; however, the compound was removed from vaccines in 2001. MMR, varicella, pneumococcal vaccines, and inactivated polio vaccines, never contained thimerosal. Influenza vaccines are manufactured with and without thimerosal, and no vaccines recommended for children contain thimerosal.

Dr. Rubin reviewed a study by S. Iqbal et al, looking at the number of antigens in early childhood vaccines and neuropsychological outcomes at age 7 to 10 years; and as described previously, there were seven outcomes, one of which was tic disorder. The children showed no adverse response for antigens in vaccines during the first two years of life, and neurological outcomes in later life. The analysis assumed that levels of immune response were similar for all antigens, which was an oversimplification. In addition, enrollment was less than 30%, which could introduce selection bias. There were also recall issues related to self-reporting. Finally, antigen exposure in that early (1990s) trial were considerably greater than antigen exposure in the current vaccination schedule.

In a search for additional data on tic disorders, very few papers were found. The few that were found included substantial data on thimerosal, a compound that is no longer included in vaccines for children. A study by Leslie, D. L., R. A. Kobre, et al. (2017), entitled “Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination of Children and Adolescents: A Pilot Case-Control Study,” (Front Psychiatry) concluded that the onset of some neuropsychiatric disorders (obsessive compulsive disorder, anorexia nervosa, anxiety disorder, chronic tic disorder, attention deficit hyperactivity disorder, major depressive disorder and bipolar disorder) may be temporally related to prior vaccinations. There were a number of limitations related to the Leslie study. There is limited literature on tics and tic disorders, and vaccinations. The tic symptoms are usually part of a complex diagnosis. Further research on tics alone is required.

Dr. Rubin reviewed the Guiding Principles for revising the Table, and noted that the options that the Commission must consider are:

Option 1 - Add tics/tic disorders to the Table.

Option 2 - Do not add tics/tic disorders to the Table.

Dr. Rubin invited comments or questions from Commission members. There was a question regarding the funding source for the studies mentioned and Dr. Shimabukuro reiterated that the studies were funded under the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink (VSD) program. There was a request that Dr. Thompson, whose papers the petition discussed, be invited to discuss the issues with the Commission. There was a comment that the articles were not peer reviewed and must therefore be considered in that light. Martha Toomey, a commissioner, commented that because of a lack of peer reviewed literature and research, the Commission may not have sufficiently reliable information to make a decision about adding or not adding tics to the Table. There was a brief discussion about whether there was sufficient reliable information about tics and causation to choose an option. There was no consensus concerning the ability to vote, but the Commission agreed to invite public comment. Public comments:

1. A public participant (Katherine) confirmed that Dr. Thompson was still at CDC and should be able to participate. She played a recording, allegedly of Dr. Thompson stating, that the Barile paper replicated the fact that vaccines cause tics and that there were efforts by CDC to hide association between vaccines and tics.
2. A public participant (Janet Cakir) commented that the Thompson, Iqbal and Barile studies relied on the same database. She observed that the information/data was manipulated to facilitate analysis. For example, data concerning encephalitis, a brain

inflammation, was removed prior to analysis. Similarly, all data regarding low birth weight babies was removed, which diluted the impact of thimerosal since the effect is dose dependent (the smaller the baby, the greater the drug effect). Finally, all adverse outcomes were not necessarily reported. She cited a number of papers that compared the effects of methyl and ethyl mercury, which appear to be similar.

3. There was a comment from Theresa Wrangham, acting as a private citizen, who said that thimerosal was suggested for the National Toxicology Program, although the resolution or outcome of that recommendation is not clear. She also noted that a manufacturer of multi-dose thimerosal, which contains mercury, could convert that product to mercury-free thimerosal if there was a demand for the mercury-free product, which there apparently is not.

Ms. Luthy invited Commission comment about the motions on the floor to decide on options. There was a question about whether the commissioners could rely on knowledge accumulated from any sources or from personal experience, or only on information presented at the meeting. Dr. Nair stated that the purpose is to obtain input broadly from the members, and from all valid information sources. He felt the Commission could make a determination about the options based on their personal knowledge and on the information heard during the meeting. By a voice vote, the members agreed to vote on the options:

Option 1 - Add tics as a vaccine injury to the Table.

Option 2 - Do not to add tics as an injury to the Table.

Ms. Luthy invited each member of the Commission to vote. The result of the vote was five in favor of Option 2 and one in favor of Option 1. Ms. Stewart, Mr. Howie, Mr. Sangiamo, Dr. Meissner and Ms. Luthy voted for Option 2. Ms. Toomey voted for Option 1.

After a recess for lunch, the Commission reconvened and Ms. Luthy invited Dr. Stryer to discuss the petition requesting that asthma be added as an injury to the Table.

Petition to Add Asthma as an Injury to the Vaccine Injury Table, Dr. Stacy Stryer, Medical Officer, DICP

Dr. Stryer stated that on April 3, 2017, a private citizen petitioned HHS and the ACCV to add asthma to the Table because the injection of food allergen-contaminated vaccines causes sensitization and subsequently asthma. Asthma is a respiratory disorder that results in difficulty breathing and other physiological problems. There is a wide variety of causative factors including genetic predisposition, underdeveloped lungs, exposure to environmental contaminants, viral infections, obesity, allergies, and others, including atopy (the production of immunoglobulin E (IgE) antibodies). When an individual is exposed to a specific allergen, these antibodies bind to the allergen, causing an allergic reaction. This results in breathing difficulties, for example, and may effect permanent changes in the bronchial airway.

Dr. Stryer reviewed the Guiding Principles for recommending changes to the Table, discussed previously. The private citizen who submitted the petition supported his claim by referencing a non-peer reviewed article that he wrote and self-published online and citing 15 references. The article was entitled, "Medical Muddles that Maim our Children with Allergies, Asthma and Autism". He asserts that individuals may develop IgE-mediated sensitization by

injection of food proteins in vaccines. Then when they inhale the sensitized food particles, they can suffer asthma symptoms. Individuals can also become sensitized to “pathogen associated vaccine antigens” via IgE. Upon inhalation of these particles, such as influenza viral particles, pertussis bacteria particles, etc., they will develop asthma symptoms. Dr. Stryer described all of the articles submitted by the petitioner that related to vaccine-induced IgE, and the implication that it leads to asthma. However, there is no evidence in publications submitted that vaccination leads to IgE antibody or the most common causes of wheezing in childhood, namely respiratory syncytial virus and human rhinovirus. There is no evidence that individuals develop IgE sensitization by injection of food proteins in vaccines and that subsequent inhalation of these particles causes symptoms of asthma. In addition, there is no evidence that inhalation of vaccine antigens triggers asthma symptoms via an IgE mechanism.

Dr. Stryer explained that after reviewing the petitioner’s submission, she looked at the scientific literature, starting with the 2012 IOM Report, “Adverse Effects of Vaccines: Evidence and Causality”. The report reviewed studies of asthma exacerbation or reactive airway disease episodes in children and adults after both live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine in children younger than 5 years of age and in persons 5 years of age or older. The IOM deemed the evidence inadequate to either accept or reject a causal relationship between either vaccine and asthma exacerbation or reactive airway episodes in individuals of any age. Dr. Stryer stated that the IOM does not support adding asthma to the Table with regard to influenza vaccine and did not evaluate evidence related to other vaccines. .

A search of other literature focused on an important 2007 “Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma”, sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Neither this report, nor four additional reports identified in the search, mentioned vaccines as a potential cause or risk factor in the development or exacerbation of asthma. Further literature searches did not result in the identification of peer reviewed articles that mentioned food allergen-contaminated vaccines or pathogen-associated vaccine antigens in the development or exacerbation of asthma. The search identified numerous studies that evaluated the development of asthma after vaccination. The overwhelming majority found no causality between vaccination and the development of asthma.

Dr. Stryer briefly mentioned 15 studies that evaluated vaccines and asthma which showed no association between vaccines and asthma. Many of the studies were from the International Study of Allergies and Asthma in Children (ISAAC), established in 1991. ISAAC proposed a standardized methodology and approach to the research. Some of the studies came from the CDC VSD, which looked at high-risk infants. Sample sizes varied from a few hundred, to several hundred thousand, to one that evaluated all online studies which included millions of children.

Finally, Dr. Stryer discussed four studies that showed mixed (mainly negative) results between vaccines and asthma. One study (McDonald, 2008) showed a delay in onset of asthma in subjects who received four or more doses of DPT when the vaccination was delayed by six months. Dr. Stryer reviewed the Guiding Principles again.

There was a brief discussion among Commission members, with regard to the homogeneous Manitoba population and in the case of more delay, less risk of DTP vaccine/asthma, the indication of a dose-dependent relationship is clear, and the effect of an urban versus non-urban setting is probably irrelevant. Ms. Luthy invited public comment before voting on the options. Public comments:

1. Janet Cakir, commented on the Manitoba study. In response to the presentation of the study and limitations of the study, Ms. Cakir commented that the participants of the study would have the same environmental exposure if they were all from Manitoba, Canada and a comparative (urban vs. suburban) sample isn't necessary.
2. Ms. Wrangham, Executive Director of the NVIC, endorsed using data from the VICP awards for any petition as a resource to consider when making decisions about Table revisions. Ms. Wrangham cited the addition of Guillain-Barré as an example.

Martha Toomey, a commissioner, commented that there are enough challenges to adding an injury to the Table such that the Commission should encourage simplifying the process rather than making it more adversarial.

Ms. Luthy invited each member of the Commission to submit an oral vote.

Option 1 – Add Asthma to the Vaccine Injury Table.

Option 2 – Do not add Asthma to the Vaccine Injury Table.

The result of the vote was unanimous, six in favor of Option 2 and none in favor of Option 1. Ms. Stewart, Ms. Toomey, Mr. Howie, Mr. Sangiamo, Dr. Meissner and Ms. Luthy voted for Option 2.

Petition to Add Pediatric Autoimmune Neuropsychiatric Syndrome (PANS), Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorder (PITAND), and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Group A Streptococcus (PANDAS) as Injuries to the Vaccine Injury Table, Dr. Mark Ditmar, Medical Officer, DICP

Ms. Luthy commented that there were several e-mails concerning the next petition, indicating a higher than usual interest in PANS, PITAND and PANDAS. Dr. Ditmar stated that a private citizen submitted petitions on February 20, 2017 and March 20, 2017, to add PANS, PITAND and/or PANDAS to the Table. The petitions assert that components of pertussis present in vaccines cause the development of PANS and/or PITAND and that components of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) present in vaccines cause or enable the development of PANS and/or PANDAS.

Dr. Ditmar explained that PANS, PITAND and PANDAS might develop from an autoimmune response. These disorders may produce a physical movement abnormality and a behavioral or psychiatric disorder. The immune response may cause antibodies to affect various parts of the body including the heart (carditis), joints (arthritis), skin (rashes) and potentially the brain that results in involuntary movements.

In 1995, a disorder was identified in four individuals that would become known as PITAND, which was successfully treated with plasmapheresis, intravenous immunoglobulin (IVIG) or prednisone. Then a larger cohort was diagnosed with a complex disorder that would become PANDAS, with five similar symptoms--1) presence of obsessive compulsive disorder (OCD) or tic disorder; 2) prepubertal symptom onset, 3) acute symptom onset and episodic (relapsing-remitting course); 4) temporal association between group A strep infection and symptom onset/exacerbation; and 5) neurologic abnormalities (particularly hyperactivity and

choreiform movements). Shortly thereafter, the same researchers refined the nomenclature to add PANS.

In the first petition, to support the claim that pertussis-containing vaccines cause PANS and/or PITAND, the petition outlines a mechanism of molecular mimicry and autoantibody-mediated neuronal cell signaling. In the second petition, which involved pneumococcal and Hib vaccines, not pertussis, the petitioner described a slightly different mechanism that resulted in the same disorders. The 2012 IOM study did not address PANS, PITANDS or PANDAS; nor did it recognize any possible association between pneumococcal conjugate vaccines and *Haemophilus influenzae* type b (Hib) vaccines or any other vaccine and PANS and/or PANDAS.

Dr. Ditmar commented that the petitions raised questions. Specifically,

- Is PANS and/or PITAND and/or PANDAS mechanistically established as an autoimmune process via molecular mimicry and autoantibody mediated neuronal cell signaling, and is PANS and/or PANDAS mechanistically established as a result of blood brain barrier disruption that results in the same effect?
- Do pertussis-containing vaccines or pertussis infections generate antibodies that could result in acute neuropsychiatric symptoms?
- Do pneumococcal vaccines or pneumococcal infections and Hib vaccines or Hib infections cause or enable the development of acute neuropsychiatric symptoms?
- Do natural pertussis infections or pertussis-containing vaccines trigger PANS and/or PITAND?
- Do natural pneumococcal infection or Hib infection, or conjugate pneumococcal vaccines and Hib vaccines trigger PANS and/or PANDAS?
- Are PANS and/or PITAND and/or PANDAS generally accepted as independent disease entities?

Dr. Ditmar stated that an extensive review of the literature was conducted and he discussed the results of the review. He said:

- No published study that examines anti-neuronal antibodies including anti-dopamine receptor 1 (DR1), anti-dopamine receptor 2 (DR2), anti-tubulin, anti-lysoganglioside – GM1 or antibody-mediated activation of calcium calmodulin dependent protein kinase II (CaMKII) in children suspected of PANS and/or PITAND following pertussis infection or following pertussis immunization was found.
- No published case report of conjugate pneumococcal vaccines or pneumococcal infections and Hib vaccines or Hib infections causing or enabling the development of acute neuropsychiatric symptoms via a mechanism of blood-brain barrier disruption with GAS antibody-mediated CNS cross-reaction in a susceptible child were found.
- No published case report of PANS, PITAND and/or PANDAS following pertussis vaccination or during or following pertussis infection were found.
- No published case report of PANS, PITAND and/or PANDAS following either pneumococcal conjugate or *Haemophilus influenzae* type b (Hib) vaccination or pneumococcal or *Haemophilus influenzae* type b infection were found.
- The diagnoses of PANS, PITAND and/or PANDAS are controversial and are not validated as an officially-recognized independent disease entity. Dr. Ditmar added that

he categorized PANS, PITAND and PANDAS as investigational diagnoses and not as established or universally accepted diagnoses.

Dr. Ditmar reiterated the options for the Commission to consider.

With regard to Petition 1:

Option 1 - Add PANS and/or PITAND as injuries associated with the pertussis vaccine to the Vaccine Injury Table.

Option 2: Do not add PANS and/or PITAND as injuries associated with the pertussis vaccine to the Vaccine Injury Table.

With regard to Petition 2:

Option 1: Add PANS and/or PANDAS as injuries associated with pneumococcal conjugate vaccine and *Haemophilus influenzae* type b (Hib) vaccine to the Vaccine Injury Table.

Option 2: Do not add PANS and/or PANDAS as injuries associated with pneumococcal conjugate vaccine and *Haemophilus influenzae* type b (Hib) vaccine to the Vaccine Injury Table.

Ms. Luthy invited discussion from Commission members. There was a discussion of the food issues mentioned in the presentation, particularly in light of the lack of certitude of the defined diagnostic criteria for each condition. There was a comment from Commissioner Martha Toomey, that many in the health care community have little faith in the reality of PANDA and that calling PANDA controversial is adversarial and shouldn't be used in the discussion. There was also a comment that the medical community's response to a PANDA diagnosis can be, frankly, dangerous treatments, like plasmapheresis. Ms. Luthy invited comments from the public. Public comments:

1. A participant from the public, a parent (Daniel Humphreys) expressed concern over the number of references to the VSD, which is only accessible to individuals who are mainly pro-vaccine. He was also concerned that autism is not on the Table, which is a significant issue among those with vaccine-injured children. He noted that a positive vaccine response is for the immune system to attack itself, which is not discussed. Mr. Humphreys discussed the lack of public knowledge about the Table and expressed concern that the VICP's three-year time limit to file a claim is insufficient. He also commented that, contrary to Food and Drug Administration (FDA) recommendations, there is a tendency for doctors to administer multiple pathogens, up to dozens.
2. Another public participant, a parent (Janet Cakir), referring to diagnostic criteria and whether or not PANDAS exist, noted that on the NIH web pages there is a clear list of symptoms – the presence of clinical obsessions, compulsion, or tics. She mentioned that her children exhibited one or more of these symptoms and, on advice of medical experts,

treatment with immunoglobulins essentially cured the conditions, but it was very expensive. These children need to be able to rely on the Table.

3. An audio recording allegedly of Dr. Thompson, CDC, expressing his belief that vaccines can cause tics was played.
4. A participant from the public, a parent (Joel Troyer) told his personal story of his child's diagnosis of autism and PANS, which he believes is a result of childhood vaccinations. Mr. Troyer discussed current proposed state level legislation requiring insurance companies to cover PANS/PANDAS treatments. He also expressed his opinion that PANS/PANDAS should be added to the Table.
A participant from the public, a parent (Karen McMillan), related her personal experience with her child's injury, which she believes was vaccine-related. Ms. McMillan, suggested that physicians be required to share information about vaccine injury programs with parents when a child has an illness following a vaccination. She also recommends that physicians be required to comply/assist with a parent's decision to file a vaccine injury claim.
5. Theresa Wrangham, Executive Director of the NVIC, commented that the IOM reported for 25 years on the lack of evidence of vaccine related injuries and that there needs to be more research.

Ms. Luthy invited each member of the quorum to submit an oral vote. On Petition 1, the result of the vote was five in favor of Option 2, one in favor of Option 1. Ms. Toomey voted in favor of Option 1.

On Petition 2, the result of the vote was five in favor of Option 2, one in favor of Option

1. Ms. Stewart, Mr. Howie, Mr. Sangiamo, Dr. Meissner and Ms. Luthy voted in favor of Option
2. Ms. Toomey voted in favor of Option 1.

Petition to Add Experimental Autoimmune Encephalomyelitis (EAE) and/or Acute Demyelinating Encephalomyelitis (ADEM) as Injuries to the Vaccine Injury Table, Dr. Terry Dalle-Tezze, Medical Officer, Pediatric Team Lead, DICP

Dr. Dalle-Tezze set a framework for the discussion, noting that encephalopathy is already on the Table for the pertussis vaccine. Acute Demyelinating Encephalopathy (ADEM) is a type of encephalopathy, but it was neither specifically included nor excluded in the Table until 2017, when ADEM was excluded as an encephalopathy diagnosis. The decision for the Commission is whether to include or exclude ADEM for the pertussis vaccination. Dr. Dalle-Tezze stated that the following wording was included in the petition:

- "I...petition for the addition of Experimental Autoimmune Encephalomyelitis (EAE)...and provide a scientific review in support of my petition."
- "Experimental Autoimmune Encephalopathy (EAE), sometimes called acute disseminated encephalomyelitis...can be triggered by pertussis-containing vaccines. On January 19, 2017, the Secretary at the time clarified this disorder and excluded it from the Injury Table because it involves demyelination."
- "With this petition, I am requesting that the Secretary list Experimental Autoimmune Encephalomyelitis as an adverse event following pertussis vaccination"

Dr. Dalle-Tezze further quoted the petitioner:

- “Combination of pertussis vaccine and amyloid beta open the blood brain barrier allowing entry of anti-MOG antibodies resulting in monophasic inflammatory disease with sparse perivenous demyelination”
- “EAE following pertussis vaccination is a recognized disorder routinely initiated in laboratories using pertussis vaccinations”
 - “Documented to have occurred in a case-control study”
 - Specific study not mentioned (cited) in petition.
 - “VAERS database revealed 7 reports within the last decade”
 - Source/citations for this information not mentioned in petition.

Providing some background for EAE, Dr. Dalle-Tezze explained that EAE is not a disease, illness or injury in humans. EAE is an inflammatory demyelinating condition of the central nervous system (CNS) induced in the laboratory by the generation of an immune response against myelin epitopes. EAE is an experimental model used for studying autoimmunity. Animals are injected with antigens that have similar epitopes to CNS neural tissue. Antibodies are formed which attack the CNS and cause demyelination. CNS neural tissues (from rabbit brains) were used in the production of vaccine. CNS neural tissue antigens were unknowingly injected along with the vaccine. Vaccines with lower concentrations were less effective, and when concentrations of vaccine were increased, meningoencephalomyelitis occurred. With regard to pertussis, Dr. Dalle-Tezze explained that pertussis antigen (particles from pertussis bacteria) have been used in EAE studies because of its immunogenicity. Acellular pertussis vaccinations do not contain pertussis antigen. Finally, EAE has been critical to understanding CNS demyelinating conditions including ADEM and multiple sclerosis (MS).

Dr. Dalle-Tezze stated that the petitioner submitted 12 articles in support of his petition. Summarizing, he stated that the articles present a strong argument for the validity of the importance of EAE research. EAE is an instrumental tool in the study of demyelinating CNS conditions, including MS and ADEM. The experimental EAE studies have no relevance to pertussis vaccinations and/or ADEM. They do not provide any evidence or support to the allegations that pertussis vaccinations cause ADEM. These studies on EAE do not provide any support that ADEM should be added to the Table.

Dr. Dalle-Tezze continued with a discussion of encephalopathy. Dr. Dalle-Tezze stated that the Table covers acellular pertussis vaccination and encephalopathy/encephalitis when onset is within 72 hours, and there is evidence of acute encephalopathy as well as evidence of chronic encephalopathy, and no evidence of an alternate cause and/or other conditions as set forth in the Qualifications and Aids to Interpretation (QAI). In 2017, the QAI was revised regarding ADEM to reflect the following language:

“Exclusionary criteria for encephalitis. Regardless of whether or not the specific cause of the underlying condition, systemic disease, or acute event (including an infectious organism) is known, encephalitis shall not be considered to be a condition set forth in the Table if it is shown that the encephalitis was caused by:

acute disseminated encephalomyelitis (ADEM). Although early ADEM may have laboratory and clinical characteristics similar to acute encephalitis, findings on

MRI are distinct with ADEM displaying evidence of acute demyelination (scattered, focal, or multifocal areas of inflammation and demyelination within cerebral subcortical and deep cortical white matter; gray matter involvement may also be seen, but is a minor component).”

Dr. Dalle-Tezze summarized the issues related to pertussis vaccinations and encephalopathy:

- Critical review of literature does not support vaccine causation between whole cell pertussis vaccinations and encephalopathy/encephalitis
- Critical review of literature does not support vaccine causation between acellular pertussis vaccinations and encephalopathy/encephalitis

Dr. Dalle-Tezze explained that the Secretary’s and ACCV’s decisions in 2015 on acellular pertussis and encephalopathy/encephalitis was published in the Federal Register on July 29, 2015. Despite the lack of literature to support vaccine causation with acellular pertussis and encephalopathy/encephalitis, the Secretary made the decision to keep encephalopathy/encephalitis on the Table for acellular pertussis. This decision was supported by the ACCV.

Dr. Dalle-Tezze continued his presentation addressing ADEM . Pathologically ADEM is an autoimmune condition of the central nervous system with hallmark symptoms of encephalopathy and demyelination in the CNS. ADEM etiology is unclear, but infectious etiology is suspected. In general terms, ADEM is a disease of the brain that alters brain structure and function. ADEM is a type of encephalopathy. Because of its autoimmune etiology, the timeframe for the Table is 7-10 days (versus 72 hours for acellular pertussis). The IOM failed to find a causal relationship between the pertussis vaccine and ADEM. Dr. Dalle-Tezze summarized his conclusions related to pertussis and ADEM:

- Most current literature does not support a relationship between whole cell pertussis and encephalopathy/encephalitis.
- Most current literature does not support a relationship between acellular pertussis vaccination and encephalopathy/encephalitis.
- ADEM is a very distinct condition from other forms of encephalopathy/encephalitis.
- The distinction was large enough that the IOM 2011 Report considered ADEM separately from encephalopathy/encephalitis.
- ADEM has a distinct autoimmune etiology.
 - Onset of 72 hours is not supported by the medical literature (hence the 7-10-day criterion).
 - ADEM is strongly associated with prodromal symptoms.
 - ADEM exhibits characteristic CNS demyelination.
- The 2012 IOM report does not support vaccine causation.
- Literature provided by the petitioner does not support vaccine causation.
- Current medical literature does not support vaccine causation.

Dr. Dalle-Tezze concluded his remarks and reminded the Commission of the options:

Option 1 - Add EAE/ADEM as an injury associated with acellular pertussis vaccines to the Vaccine Injury Table.

Option 2 - Do not add EAE/ADEM as an injury associated with acellular pertussis vaccines to Vaccine Injury Table.

If an injury is not on the Table or if the alleged injury and/or condition does not satisfy the Table's requirements, the petitioner must show that the vaccine caused the injury and/or condition. In addition, no other cause for the injury can be found. Many non-Table injuries are compensated by the program each year, typically through negotiated settlement between the parties in which HHS has not concluded, based upon review of the evidence, that the alleged vaccine caused the alleged injury.

Ms. Luthy invited comments from the Commissioners. There was a question of whether or not it would be acceptable to omit consideration of EAE, and vote only on the ADEM options. Dr. Dalle-Tezze agreed that that would make sense. Ms. Luthy invited comment from the public. Public comments:

1. A member of the public, Janet Cakir, expressed concern that ignoring or minimizing the importance of EAE research would be a mistake. She also expressed concern that pertussis toxin is in the acellular pertussis vaccine, which suggests that more research on the composition of the vaccine would be in order.
2. There was a comment from a member of the public, Jerry, who took exception to the predominance of physicians on the panel. The commenter expressed the opinion that doctors, albeit with medical degrees, may not have the depth of experience necessary to make recommendations on this narrow issue and related the opinion that many medical professionals and parents are not adequately educated on vaccines. The commenter expressed his belief that the Commission should vote for Option 1.

Following the public comment session, some Commission members noted that there had been significantly more participation from the public in this meeting than in previous meetings.

Ms. Luthy invited each member of the Commission to submit an oral vote. The result of the vote was four in favor of Option 2 and one in favor of Option 1. Ms. Stewart, Mr. Sangiamo, Dr. Meissner, and Ms. Luthy voted in favor of Option 2. Ms. Toomey voted in favor of Option 1.

Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities, Dr. Tom Shimabukuro, CDC

Dr. Shimabukuro provided a summary of the proceedings of the October 2017 meeting of the Advisory Committee on Immunization Practice, which addressed the herpes zoster vaccine, the hepatitis B vaccine (Dynavax), live attenuated influenza vaccine (LAIV), a mumps outbreak, and a report of shoulder dysfunction following immunization. He also briefly discussed selected publications since the last ACCV meeting.

The FDA recently licensed the herpes zoster adjuvant subunit (HZ/su) vaccine. There is strong evidence that the vaccine is efficacious and durable, with minimal waning of efficacy in

the first four years after receiving the vaccine. In clinical trials, it had an acceptable safety profile, although it was locally reactogenic. About 20% of all herpes episodes occur in the age group 50 to 59, and the cost effectiveness of the vaccine is similar or better than most adult vaccines. HZ/su (inactivated) is one of two herpes vaccines available; the other is ZOSTAVAX, a live vaccine, ZVL.

The two vaccines have not been studied in a head-to-head trial, but HZ/su efficacy is considerably higher than ZVL, over 90% in adults over the age of 60. The effectiveness of ZVL is 64% for adults in their sixties, dropping to only 18% for those who reach 90. There is also significant waning of effectiveness after the first year. Neither vaccine was associated with serious adverse events in immunocompetent individuals, although HZ/su is more reactogenic. HZ/su leads to more disease prevention and decreased overall costs.

Three votes were taken at the ACIP meeting: ACIP recommended HZ/su for immunocompetent adults age 50 and older (unanimous); ACIP recommended HZ/su for individuals previously vaccinated with ZVL after a minimum interval of at least 8 weeks (12 in favor, 3 opposed); and ACIP recommended HZ/su be preferred over ZVL (8 in favor, 7 opposed). Dr. Shimabukuro stated that there is limited safety data on HZ/su so safety monitoring will be important during the uptake period, with enhanced VAERS surveillance and rapid cycle analysis in CDC's Vaccine Safety Datalink (VSD).

Dr. Shimabukuro commented that a new hepatitis B vaccine is available, HEPLISAV-B, licensed after the ACIP September meeting. It is a two-dose series completed in one month (versus the previous 3-dose, 6-month series). It has shown higher protection in adults than other available hepatitis B vaccines.

Dr. Shimabukuro discussed influenza. LAIV has not been recommended for immunization during the past two flu seasons, but additional data on LAIV effectiveness will be available in December 2017. Dr. Shimabukuro also described the final results of a recently published VSD study looking at inactivated influenza vaccine (IIV) and spontaneous abortion or miscarriage. This case-control study showed that miscarriage was significantly associated with IIV receipt in the 28 day exposure window. A similar VSD study before 2009 pandemic and other studies have not found an association between IIV and miscarriage. In the current study, the association between IIV and miscarriage was significant in the 2010-11 influenza season, but not in the 2011-12 season. In both seasons, the association was elevated only in the 28-day window and only in women who received influenza A H1N1pdm09-containing vaccine in the prior season. A follow-up study is underway, and no policy change has been proposed.

Dr. Shimabukuro pointed out there have been several mumps outbreaks since 2015, mainly in university settings. An ACIP workgroup had reviewed and discussed evidence on MMR vaccination in outbreak settings that a 3rd dose of MMR would improve protection for those at increased risk due to an outbreak.. ACIP voted unanimously that persons previously vaccinated with 2 doses of MMR and who are at increased risk of mumps due to outbreak should receive a 3rd dose.

Dr. Shimabukuro discussed an ACIP session on shoulder dysfunction following influenza immunization based on VAERS reports submitted between 2010 and 2016. The familiar term SIRVA was not used because the term implies a causal relationship and VAERS is a passive reporting system and not designed to determine causality. The number of reports ranged from 128 to 223 per year, with a higher percentage of reports among females. Of the reports, 70% were about individuals 19 to 59 years, and only a few were in younger individuals (0 to 18

years). The most commonly reported possible contributing factor was vaccine given too high on the arm. Most commonly reported places of vaccination were pharmacies and doctors' offices and hospitals. There does not appear to be an increase in shoulder dysfunction reports following IIV and recent influenza seasons. The shoulder dysfunction reports amounted to about 2% of all IIV VAERS reports during the analytic period.

Finally, Dr. Shimabukuro told the commission there were ACIP sessions on human papillomavirus vaccine, an adult and child/adolescent immunization schedule vote, Japanese encephalitis vaccine, and pneumococcal vaccines.

Finally, Dr. Shimabukuro commented on selected published papers, reporting on two of the thirteen papers provided in PDF format to Commission members.

A VSD study by McCarthy and colleagues addressed recommendations for a study topic from the IOM 2013 report on the childhood immunization schedule. Specifically, is there a risk of death following childhood vaccination?

McCarthy et al. Patterns of childhood immunization and all-cause mortality. *Vaccine*. 2017. pii: S0264-410X(17)31442-1.

- Although there were few deaths, the results do not indicate a difference in risk of all-cause mortality among fully vaccinated versus under vaccinated children.
- Findings support the safety of the currently recommended immunization schedule with regard to all-cause mortality.

Another study by Woo and colleagues looked at the safety of trivalent recombinant influenza vaccine in VAERS. The recombinant vaccine is not an egg-based vaccine. It is made using an insect vector and does not contain residual egg protein, which has been suspected to be implicated in anaphylactic reactions.

Woo et al. Post-marketing safety surveillance of trivalent recombinant influenza vaccine: Reports to the Vaccine Adverse Event Reporting System. *Vaccine*. 2017; 35(42): 5618-5621.

- Allergic reactions following recombinant influenza vaccine were reported.
- Occurrence of anaphylaxis and other allergic reactions in some individuals may reflect an underlying predisposition to atopy that may manifest itself after an exposure to any drug or vaccine, and it does not necessarily suggest a causal relationship with the constituents specific to the vaccine product administered.

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

Responding to an earlier question, Ms. Schuster announced that NIH is supporting trials for several Zika vaccine candidates. Two papers were published in *Lancet* for two Phase 1 trials of different candidate vaccines.

Ms. Schuster began her presentation talking about influenza and the fact that NIH is focusing research efforts on seasonal and pandemic influenza preparedness. She discussed a specific strain, H7N9, which first appeared in China in 2013. Most cases of H7N9 influenza occur through contact with infected poultry or contaminated environments, including live poultry

markets. There have been five waves of the virus, involving over 1,600 total human cases resulting in more than 600 deaths.

The most recent wave accounted for over half of the total cases. In response to the first wave, NIAID launched two Phase 2 trials in 2013 to assess an investigational H7N9 vaccine made from inactivated virus; results were published in JAMA in 2014 and 2015. The research showed efficacy and the need for two doses of vaccine and the H7N9 vaccine was added to the U.S. emergency stockpile of vaccines. In 2017, the H7N9 vaccine was tested and found to be inadequate in providing protection against the most recent H7N9 strain. A new vaccine is needed. Researchers are working on a universal influenza vaccine that would protect against most flu strains. In June 2017, NIAID organized a workshop, The Pathway to a Universal Influenza Vaccine. Scientists are working on a vaccine that would target parts of the influenza virus that remain relatively unchanged from year to year. The workshop report was published in Immunity on October 17, 2017.

Ms. Schuster continued her presentation discussing Ebola. Results from a large randomized clinical trial in Liberia show that two experimental vaccines pose no major safety concerns, and can elicit an immune response within a month of immunization that lasts for a year or more. This NIAID-sponsored research was published on October 12, 2017 in the New England Journal of Medicine.

Ms. Schuster discussed a new seven-year initiative on Environmental Influences on Child Health Outcomes (ECHO). It will look at multiple studies of cohorts of women and children who have previously participated in other studies. The focus is on upper/lower airway, obesity, pre-, peri- and post-natal outcomes, and neurodevelopment. In October 2017, NIH announced a new study, named ACT NOW, looking for treatment options for newborns with opioid withdrawal syndrome, a disorder caused by exposure to opioids during pregnancy.

Ms. Schuster announced a new NIAID Now blog, that includes a post on an NIAID-funded study that focuses on biological mechanisms underlying immune responses to the flu vaccine and how these change with age. Describing immune profiles measured prior to vaccination may predict a person's antibody response to the seasonal flu vaccine.

Finally, Ms. Schuster announced that experts from NIAID and the World Health Organization Collaborating Centre for Reference and Research on Influenza (Australia) discussed how preparing vaccines in eggs may contribute to limited effectiveness. Mutations occurring in these vaccines may have contributed to decreased vaccine effectiveness during the 2016-2017 influenza season in the U.S. and 2017 flu season in Australia. The researchers emphasized the importance of targeted vaccine research and development of a universal flu vaccine.

Update on the Center for Biologics, Evaluating and Research (CBER), Food and Drug Administration (FDA) Vaccine Activities, LCDR Valerie Marshall, CBER, FDA

CDR Marshall stated that the FDA approved two vaccines, both of which Dr. Shimabukuro mentioned by in his presentation. The FDA approved zoster vaccine recombinant, adjuvanted (Shingrix), in October 2017. Glaxo Smith Kline (GSK) manufactures the vaccine, and it is intended for prevention of herpes zoster (shingles) in adults aged 50 years and older. The trial excluded individuals with a history of herpes zoster. After the age of 50, a person's risk for shingles increases. Shingles typically present as a painful, itchy rash that develops on one

side of the body and can last for two to four weeks. Even if the rash disappears, a person can experience post herpetic neuralgia (PHN), pain lasting from at least three months up to several years. Shingrix is a non-live, recombinant adjuvant subunit vaccine given intramuscularly in two doses.

In November 2017, the FDA approved Hepatitis B Vaccine, Recombinant, Adjuvant (Heplisav), manufactured by Dynavax Technologies Corporation, for prevention of infection caused by all known subtypes of hepatitis B virus in adults age 18 years and older. Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV). Heplisav contains hepatitis B surface antigen with Dynavax's proprietary Toll-like Receptor (TLR) 9 agonist adjuvant to enhance the immune response and is administered intramuscularly in two doses.

CDR Marshall commented that the Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on November 7, 2017 to discuss the clinical development plan of Pfizer's investigational *Staphylococcus aureus* vaccine (SA4Ag), intended for pre-surgical prophylaxis in elective orthopedic surgical populations. Invasive *Staphylococcus aureus* infections (SSIs) are a serious complication after elective surgeries and cause significant morbidity and mortality. It is the most common infection related to surgical settings. To address this unmet medical need, Pfizer has proposed a clinical development plan to support traditional approval of their investigational SA4Ag vaccine for use in adults undergoing elective orthopedic surgery. Pfizer initiated a large double-blind, placebo controlled clinical trial to evaluate the safety and efficacy of a single dose of the vaccine to prevent postoperative *Staph aureus* infection in adults 18 to 85 years of age scheduled to undergo spinal fusion surgery.

The purpose of this VRBPAC meeting was to seek input regarding the clinical data needed to support an indication for use in adults undergoing elective orthopedic surgery, with a focus on the extent to which safety and efficacy data accrued in a spinal surgery population can be generalized to other elective orthopedic surgical populations. The consensus of the committee members was that, if the trial succeeds, it may be valid to generalize the safety and efficacy to other orthopedic surgical procedures. Experts expressed varied opinions about whether the results could be broadly generalized, or whether the results should apply only to similar surgical procedures, such as knee and hip replacements.

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

Dr. Bok described a meeting in August 2017, on vaccine confidence sponsored by the NVPO and Emory University. Preliminary discussions settled on several focus areas: measuring and tracking vaccine confidence; communication and community strategies to increase vaccine confidence; health care provider strategies to increase vaccine confidence; developing policy strategies to increase vaccine confidence; and continued support and monitoring of the state of vaccine confidence. The meeting convened researchers, government agencies, and healthcare organizations to learn more about the work being done to address: vaccine confidence, hesitancy, and acceptance; to share new research and identify gaps; to strengthen the community of professionals working to increase vaccine confidence; and to discuss issues with leaders in related fields. Several studies were described:

- The NVPO conducted a poll of parents in 2016, which revealed that most parents surveyed consented to vaccines for their children as recommended, and most parents trusted their child's doctor as a reliable source of vaccine information, although there was concern about the number of vaccines, ingredients, and potential side effects.
- There was a mother's longitudinal study that showed that vaccine decisions were typically made before a child is born and seldom changed. Vaccine confidence typically increased over time and with experience, and with discussion with the family doctor often at the two-month office visit.
- Another study included interviews with vaccine-hesitant parents, who typically sought more details on side effects of vaccines and the potential consequences of not vaccinating. Finally, confidence levels of parents varied more than in the highly confident parents who were polled in 2016, described above.

Dr. Bok described a study from the Hennepin County Public Health Department that looked at communications planning and implementation during an outbreak. The study population was mainly Somali-Minnesotan. There were 70 measles cases, mainly in unvaccinated Somali children. A major outreach program of more than 150 visits by trusted health community leaders resulted in 25,000 vaccinations in a short period of time, which included an eightfold increase in vaccination of Somali-Minnesotan children. Dr. Bok briefly described another study using digital and social media in support of vaccine communication, and other efforts to improve confidence in HPV and zoster vaccination programs, and to improve healthcare providers' communication skills about HPV vaccines. Finally, there was a discussion about vaccine laws as they apply to school vaccination programs, including discussion of the various exemption options available to parents.

Public Comment

Ms. Luthy invited public comment.

1. A public commenter, Janet Cakir, a parent submitted a power point presentation and discussed the progress of the Commission's work on the statute of limitations, which began in December 2013 with an ACCV recommendation to extend the statute of limitations from three years to eight years after the first symptom of injury or death. Ms. Cakir's presentation discussed the timeline of the ACCV's recommendation. Written recommendations were submitted to Secretary Sebelius in 2013. The Secretary replied in 2014, pledging to consider extending the statute of limitations; however, in April 2014, Secretary Sebelius resigned. Secretary Burwell followed, but there was no action on the recommendation by 2015. Ms. Cakir observed no apparent contact between HHS and the responsible congressional committee that would have addressed the recommendation. Ms. Cakir observed that there has been a breakdown in the functioning of the VICP in that petitioners apparently are not being heard. She expressed the opinion that the examples of the petitions previously discussed and voted on are witness to the fact that the program designed to compensate them for injuries is accommodating too few petitioners. Petitioners face a long process of proving their injury; by a more effective process to list injuries in the Table could

reduce the length of the process in many situations. Ms. Cakir also expressed concern over the objectivity of the Commission and the people who decide to add injuries to the Table.

Ms. Luthy discussed the time limitations and invited individuals to submit written comments via e-mail, which would be published in the minutes of the meeting. Alternatively, a telephone comment would be acceptable if limited to no more than two minutes.

2. There was a comment from a member of the public, Andrea Woodruff, asking about the rate of the excise tax, suggesting that it should be reviewed since it has not changed in many years.

Ms. Luthy noted that there were no other requests for public comment.

Future Agenda Items/New Business, Ms. Beth Luthy, Interim Chair

Ms. Luthy and others mentioned several future agenda items suggested during the course of the meeting, including:

- Revisit the ACCV subcommittees (there were previous subcommittees, one of which was the Process Working Group, which discussed the statute of limitations),
- Discuss including as a member of the committee, an individual who has had a vaccine injury, preferably an adult,
- Discuss allowing a substitution for the general public commission member or a parent of a vaccine-injured child,
- Election of a permanent (not interim) chair and vice chair,
- Consider inviting advocates like Bobby Kennedy to make a presentation, and
- Discussion of the resource issues that negatively affect the work of the DOJ and the Court.

Adjournment

There being no further business, on motion duly made and seconded, the Commission unanimously approved adjournment.