Advisory Commission on Childhood Vaccines

March 3-4, 2011

Day One

Minutes

Members Present
Charlene Gallagher, JD, chair
Sherry K. Drew, JD, Vice Chair
Magdalena Castro-Lewis
Margaret Fisher. MD
Thomas Herr, MD
Sarah Hoiberg
David King
Ann Linguiti Pron, MSN, CRNP, RN
Michelle Williams, JD

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Andrea Herzog, Principal Staff Liaison

Welcome, Report of the Chair and Approval of Minutes

Ms. Gallagher called the meeting to order and welcomed all in attendance in person and by teleconference to the 78th meeting of the ACCV. Since there were new commissioners in attendance, she invited introductions from all present. After calling for approval of the October 2010 meeting minutes, on motion duly made and seconded, the minutes of that meeting were unanimously approved. Although there were no additions or corrections, asked about her statement concerning rotavirus causing diarrhea, Dr. Fisher clarified that the condition is not always present as a result of rotavirus, but that it is a part of the spectrum of disorders that accompany the disease.

Report from the Division of Vaccine Injury Compensation
Dr. Geoffrey Evans, Director, DVIC

After reviewing the agenda for the two-day meeting, Dr. Evans provided a visual chart showing the total number of petitions filed since 2004. Autism filings, which were in the majority from 2004 until 2008, have decreased to less than 5 so far this Fiscal Year. Non-autism claim filings continue to remain brisk. Nearly half allege injury from influenza vaccines, which is administered to over 100 million individuals annually. Just over half of non-autism claims are filed on behalf of aults.

Dr. Evans noted that adjudications have increased over the last few years, with the expectation that this year's will equal or exceed the 463 reported for 2009. The number of claims settled has also increased, from about 50% in 2004 to about 80% last year. He added that the Department, upon review of the cases, concedes entitlement in about 10% of claims, meaning that there is a recommendation to award compensation. Claims not conceded are either adjudicated before the US Court of Federal Claims, or more often, result in a settlement. Approximately 80% of claims were compensated on the basis of a settlement in FY 2010.

Turning to awards, Dr. Evans noted the total amount awarded in FY 2010 dramatically increased to $179 million, more than double the several years before. It appears that that same level of awards may occur

in FY 2011. There are a number of reasons for the increase – the number of adjudications, the valuations arrived at by the parties, interest rates, and other factors in the the financial markets. Dr. Evans also noted that the Trust Fund was still increasing year-to-year, but the rate of increase had decreased mostly because of the significant increase in program awards. The Trust Fund stands at just under $3.3 billion.

Dr. Evans outlined DVIC activities since the last meeting. He and the ACCV chair, Ms. Gallagher, attended the National Vaccine Advisory Committee (NVAC) meeting in Washington, DC on February 15-16; and he attended the Advisory Committee on Immunization Practices (ACIP) in Atlanta on February 22-23. ACIP advises CDC and the Secretary on vaccine use and includes many non-federal liaison groups, such as the American Academy of Pediatrics, American College of Physicians, and American Academy of Family Physicians. During his program update, Dr. Evans briefed the ACIP on the recent Supreme Court decision in Bruesewitz v. Wyeth. Asked about possible VICP coverage of Japanese Encephalitis vaccine, he explained that only vaccines recommended by CDC for "routine use in children" are VICP-eligible. So called "travelers vaccines, such as JE vaccine, are not eligible. A vaccine would also have to have an excise tax approved before it could be part VICP-covered.

Report from the Department of Justice
Mark W. Rogers, J.D.
Deputy Director, Torts Branch, Civil Division, Department of Justice
Power Point Presentation Summary

Mr. Rogers referenced the Power Point materials, entitled March 3, 2011 Department of Justice Power Point Presentation (DOJ PP), as part of his presentation. Mr. Rogers welcomed the new committee members and said he hoped to give the ACCV a relatively recent snapshot of the litigation in the Program.

Personnel

Mr. Rogers announced that one trial attorney was leaving the office. Two replacement paralegals were recently hired.

Statistics

Mr. Rogers explained to ACCV members that the statistics in his presentation would differ slightly from the data in Dr. Evans's presentation because the two agencies use different time frames to track information. Additionally, DOJ tracks statistics based on the case judgment. After a Special Master issues a decision, the Court of Federal Claims enters judgment, signifying the end of the case. Judgment marks the final resolution of a claim. In the last reporting period (October 4, 2010 to January 31, 2011), there was one new autism claim filed. (DOJ PP, p. 3). Newly-filed autism claims are rare in the Program, and the focus has shifted to the processing of Omnibus Autism Proceeding (OAP) attorneys' fees and costs. There were 147 new non-autism claims filed in the last reporting period. (DOJ PP, p. 3). Of these claims, 103 were adult and forty-four were minors. Mr. Rogers commented that the percentage of adult claims is increasing. In this reporting period, there were 118 cases adjudicated, of which sixty-nine were compensated. Six of those were concessions by HHS, all resolved by a proffer. (DOJ PP, p. 4). Mr. Rogers explained that in a proffer, the two parties agree on the evidence in the case. The Special Master accepts the proffer and enters a decision that incorporates the terms of the proffer. Sixty-three cases were not conceded. (DOJ PP, p. 4). Of those cases, one was a decision by the Special Master awarding damages. Mr. Rogers speculated it was likely a case where the damages were set by statute, such as a death case. There were six decisions adopting proffers. Finally, fifty-six claims were resolved with a stipulation. Mr. Rogers explained that a stipulation is the agreement between the parties to settle the case, despite having different positions. The Special Master ultimately approves of this agreement in his decision. In this reporting period, forty-nine cases were dismissed without compensation. (DOJ PP, p. 4). Fifteen of those were non-autism cases, and thirty-four were autism cases. Finally, in this reporting period, seven petitions were voluntarily withdrawn. (DOJ PP, p. 5). Mr. Rogers explained that the Vaccine Act provides an avenue out of the Program for petitioners that doesn't result in a judgment against the petitioner. By withdrawing their petition under certain circumstances, petitioners can exit the

Program without prejudice and file a civil action. Of the seven cases that used this method to exit the Program, five were non-autism cases and two were autism cases. Mr. Rogers reviewed a glossary of terms for the benefit of the new members (DOJ PP,pp. 6-7). A petition that is "adjudicated" means judgment has entered and the case is closed. Mr. Rogers noted that judgments are generally final and are rarely re-opened. "Compensable" cases are claims in which petitioners have received compensation. These claims are awarded compensation in one of three ways. First, HHS can concede a claim, and the case proceeds immediately to determining the damages. Second, a case can be settled. Mr. Rogers emphasized that a settlement is a compromise, or "handshake" between the parties, supervised by the Special Master. Finally, in cases where the parties cannot reach a compromise, the Special Master resolves the issues with a decision. Regardless of whether the case is conceded, resolved with a settlement or proffer, or decided on its merits by the Special Master, the Special Master "stamps" all cases with a decision. That decision initiates a thirty-day waiting period in which either party can appeal the decision to the Court of Federal Claims. However, if a case is resolved by a settlement, it is rarely appealed. "Non-compensable/dismissed" claims can be dismissed for legal reasons, or because the Special Master determined that the injury was not caused by the vaccine. A "proffer" is like a settlement in that there is a "handshake" between the two parties. However, in a proffer situation, both parties agree as to what the evidence shows in the case. The most common situation for a proffer is when the life care planners for both sides agree as to what the medical needs are of the injured individual. The parties present their joint proffer to the Special Master, who approves it and makes it his decision. The distinction between settlements and proffers is important for DOJ's internal processing. A proffer doesn't require as much internal processing time at DOJ, so it can move slightly faster than a settlement. Mr. Rogers provided a flow chart showing the various pathways of petition processing in the Vaccine Program. (DOJ PP, p. 8). After the petition is filed, HHS reviews it and determines if it will concede the case. Cases that are conceded move immediately into determining the amount of damages to be awarded (the right side of the chart). Cases that are not conceded can be settled, if the parties can resolve the issues, or decided by the Special Master, if they parties cannot resolve the issues (the left side of the chart). Mr. Rogers commented that the most common pathway to compensation in the Program is through a final decision awarding compensation based upon a settlement (the pink box on the left side of the flow chart). Dr. Herr asked Mr. Rogers to comment on the trend of cases being resolved with a settlement (on the left side of the flow chart). Mr. Rogers remarked that there is a trend to the left, and when DOJ is forced to the right side of the chart, a proffer is often used. Dr. Fisher asked if conceded cases were mostly "Table" injuries. Dr. Evans estimated that three-quarters of concessions were "Table" injuries. Mr. Rogers stated that he sees non-Table conceded cases occasionally, but hadn't counted them. Dr. Fisher then asked if there could be a conceded case that didn't involve a Table injury. Mr. Rogers said yes.

Appeals

Mr. Rogers reviewed the status of appellate activity in the Program, noting there were three cases recently decided by the Court of Appeals for the Federal Circuit (CAFC), which is generally the highest court for Vaccine Act appeals. (DOJ PP, p. 9). The Davis case was a statute of limitations issue, and Rodriguez and Riggins dealt with the issue of fees and costs. All three appeals were brought forward by petitioners. At Dr. Herr's request, Mr. Rogers explained that the primary argument raised by petitioners in Davis was that the statute of limitations was unconstitutional. The CAFC ruled that petitioners had waived that argument, and that the statute of limitations is constitutional. Dr. Herr then asked for clarification about which party had raised the appeal. Mr. Rogers explained that "affirmed" means the higher court agrees with the court below. In this instance, petitioners appealed the decision of the Court of Federal Claims (CFC). The CAFC affirmed the CFC's decision. Dr. Herr also asked for clarification on which party appealed the Cloer case. Mr. Rogers explained the history of the appeal, stating that petitioners originally appealed the decision of the Special Master to the CFC. The CFC affirmed the Special Master's decision, and petitioners then appealed to the CAFC. Cases at the CAFC are evaluated by a three-judge panel. In Cloer, the CAFC overturned the CFC's decision. Respondent then took the step of petitioning for rehearing en banc. At Ms. Hoiberg's request, Mr. Rogers explained that rehearing en banc means the case is heard in front of all CAFC judges instead of a three-judge panel. Rehearing en banc is reserved for unusual cases, and is rarely granted. In this instance, the CAFC vacated, or removed, the three-judge

panel decision, and agreed to rehear the case with all CAFC judges. Mr. Rogers then highlighted the Vaccine Act cases pending before the CAFC. (DOJ PP, p. 10). Petitioners brought forward the appeal in all cases except for Knight (Rotoli) and Porter. Ms. Pron asked for an example of why respondent would appeal a case. Mr. Rogers answered that respondent will appeal a case if it is unhappy with the decision – if respondent feels that the law was misapplied, or that the judge's interpretation of the statute might affect other cases. There may also be policy considerations. Dr. Herr asked if decisions issued by Special Masters set up case law. Mr. Rogers that a Special Master's decision is not precedential to other Special Masters's decisions. Mr. Rogers commented that petitioners appeal more often than respondent. Three cases were recently decided by the CFC: Veryzer, Hammitt, and Simanski. (DOJ PP, p. 11). In all three cases, petitioner was the appellant. Mr. Rogers also discussed the cases pending at the CFC. (DOJ PP, p. 12). Of these, only Heinzelman was brought forward by respondent. Mr. Rogers noted that oral argument was scheduled for the Graves case. (DOJ PP, p.13).

Settlements

Mr. Rogers directed the ACCV's attention to a chart showing recent stipulations in the Program (DOJ PP, pp. 14-19). This chart was a response to the ACCV's request to see what kinds of cases are being settled and how quickly it takes to process them. Mr. Rogers offered the ACCV some general explanations for why settlements could take more than three years to process. He reported the predominant reason for the delay is an incomplete record. For example, additional records are needed, there was a search for an expert witness, petitioner made requests for more time to document the case. Occasionally, a case will appear to be headed to trial, and then shift over to settlement. Since the trial phase takes longer, switching gears can add time to the process. Also, cases with similar issues may be grouped in an omnibus proceeding, which can cause delay.

Bruesewitz Supreme Court Decision

Mr. Rogers discussed the recent Supreme Court Decision, Bruesewitz, explaining that the case involved a preemption issue and turned on the interpretation of one provision in Section 22(b)(1) of the Act: "No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings." Petitioners argued that the last clause was incidental, and that a vaccine manufacturer should be liable to a civil action following a Vaccine Act claim if it is shown the vaccine side effects were "avoidable." The vaccine manufacturer argued that the last clause was integral to the provision and therefore if the vaccine was properly prepared and accompanied by proper directions and warnings, the manufacturer should not be liable. Ultimately, the Supreme Court held that the Vaccine Act preempts design defect claims under state law. Ms. Hoiberg asked if the Supreme Court feared that by ruling in favor of the petitioners, a "Pandora's box" of autism cases would be filed in civil courts. Mr. Rogers responded that he was aware of that argument but had no opinion as to whether it influenced the Court's decision. Ms. Hoiberg stated that the decision was not unanimous, and Mr. Rogers agreed that it was not.

Questions and Comments

Dr. Evans asked Mr. Rogers about the Cloer case, and when a decision could reasonably be expected. Mr. Rogers replied that the argument had not yet been scheduled, and he would be surprised to see a decision before the end of the year. Ms. Gallagher asked Mr. Rogers to give a brief description of the issues in Cloer, for the benefit of the new ACCV members. Mr. Rogers explained that the issue is a question of when the statute of limitations starts running. The Vaccine Act states that the statue of limitations begins running "from the occurrence of the first symptom or manifestation of onset of a vaccine-related injury." The three-judge CAFC panel held that the statute of limitations doesn't begin running until the medical community relates the symptom with the vaccine. Respondent's position is that the statute of limitations begins running from the first symptom or manifestation of vaccine-related injury. Mr. King asked if the number of appeals filed by petitioners relating to fees and costs was increasing, and what may be driving that trend. Mr. Rogers affirmed that the trend is increasing, and

noted that one source of increased litigation is the Avera decision, which appears to authorize the award of interim fees, thus increasing the potential number of fee awards. Additionally, the Shaw decision rules that interim fee decisions are separately appealable, increasing the number of potential appeals. Mr. King asked if a possible explanation for the increase in these appeals was because the parties were arguing over fees. Mr. Rogers declined to generalize, stating there were a variety of reasons, but suggested the best way understand the issues is by reading the underlying decisions by the Special Masters. Mr. King followed up by asking if the Special Masters determine fees and costs. Mr. Rogers said yes, but only if the parties do not settle the issue.

Remarks and Presentations
Joyce Somsak, Associate Administrator, Healthcare Systems Bureau

Representing the Secretary, HHS, Ms. Somsak expressed appreciation to the retiring members of the Commission, Charlene Gallagher, the current Chair, Margaret Fisher, and Magdalena Castro-Lewis, past Chair. She added that the Secretary also recognized with appreciation the service of the absent retiring members, Jeffrey Sconyers, past Chair, Tawny Buck and Tammy Tempfer. Ms. Somsak presented a plaque recognizing their service and a letter of appreciation to each of those present, noting that those not present would receive the plaque by mail. Finally, she welcomed the incoming members of the Commission.

Review of Vaccine Information Statements
Jennifer Hamborsky and Skip Wolfe, Centers for Disease Control and Prevention (CDC)

Mr. Wolfe explained the requirements related to the creation and maintenance of the vaccine information statements (VIS) that must be published for every vaccine administered in the U.S. Within HHS, the CDC is charged with publishing the VIS. The initial draft for a new vaccine is prepared at CDC, relying on the ACIP recommendations and input from subject matter experts. Similarly, whenever there is a substantive change in the information related to an existing vaccine a revision is developed and reviewed by subject matter experts. That development process is followed by a consultation process in which the draft is reviewed by FDA, the ACCV and a panel of healthcare providers. When the recommendations from these reviewers are addressed and a final draft is prepared, it is published in the Federal Register for 60-day public comment period. When the consultation process is finished there is a final review by the CDC, final revisions, and an announcement of the availability of the VIS is published in the Federal Register.

Mr. Wolfe commented that the process imposes challenges to maintaining consistency that did not exist when the process was developed over twenty years ago, when there were only four vaccines which required only occasional updates. Now there are 21 vaccines covered by VIS's and changes are required much more often. To overcome this obstacle the CDC has devised an "interim VIS" that includes the first step of developing the initial draft in consultation with the technical experts. The "interim VIS" is published and made available to the health care community, parents and vaccine recipients, and the mandated process for a final VIS is pursued through to final announcement in the Federal Register.

Ms. Hamborsky invited comments on the draft of the hepatitis A VIS, noting that the main changes were recommendations related to contact with internationally adoption children and recommendations for post-exposure prophylaxis. Dr. Fisher commented that the revision was well written and acceptable. There was a question about the 2006 recommendation for universal immunization that was not clearly articulated in the VIS. Dr. Fisher noted that the "catch-up" immunizations for those not covered before that date was optional and not very well explained. Dr. Herr recommended changing the recommendation for who should receive the vaccine to "all children beginning at age one" rather than "all children one year of age," which suggests age 12 to 23 months of age only.

Ms. Drew reiterated previous recommendations suggesting that an individual may file a claim by contacting VICP by phone or a web site visit. The filing process cannot be completed with a phone call. Mr. Wolfe conceded that the recommendation had been made before and that the wording in the VIS under discussion was inadvertent and would be corrected.

Turning to the second VIS under review, for tetanus-diphtheria (Td) and tetanus-diphtheria-pertussis (Tdap), Ms. Hamborsky noted several changes – in the recommendations for ages, indications for children and adolescents, intervals between Td and Tdap, the risk of syncope (fainting) related to injections, and a recommendation that all healthcare personnel regardless of age receive Tdap. Dr. Fisher noted that, under risks, swelling, severe pain and tenderness are listed as both moderate and severe problems that may be associated with the vaccines. Ms. Hoiberg suggested that a localized reaction might be considered moderate and a generalized reaction, affecting a major part of the body might be considered severe. Mr. Wolfe agreed that it was an issue that should be referred to the subject matter experts for clarification. Finally, Dr. Herr suggested that information on infants and pertussis should be included in the VIS even though the focus is on adolescents.

Update from the National Vaccine Program Office
Dr. Dan Salmon, NVPO

Dr. Salmon explained that the National Vaccine Program (NVP) was created by the Public Health Service Act, PL Law 96-660, which spawned the Vaccine Injury Compensation Program, the National Vaccine Advisory Committee and the Advisory Commission on Childhood Vaccines. The NVP is comprised of all of the federal agencies involved in programs related to disease prevention through vaccines. Within the HHS that includes the Food an Drug Administration (FDA), the National Institutes of Health (NIH), Centers for Disease Control (CDC), Health Resources Services Administration (HRSA), Indian Health Service, the Centers for Medicare and Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ). Other federal Departments involved include USAID, the Veterans Administration and the Department of Defense. The NVP's mandate was to coordinate federal efforts to prevent infectious diseases through vaccines, and to reduce or eliminate adverse events related to vaccine administration. That charge is managed by the National Vaccine Program Office, a small policy office within the NVP.

The National Vaccine Advisory Committee provides recommendations regarding vaccine policy at the national level to the Assistant Secretary for Health, who is the director of the NVP. Issues such as the overarching challenge of disease prevention through vaccines and the reduction of adverse events associated with vaccines. The Advisory Committee on Immunization Practice gets into vaccine practice, including who should or should not receive immunizations, when and under what circumstances. The ACIP is concerned with practice whereas the NVAC is concerned with policy. Asked about the national vaccine stockpile, Dr. Salmon explained that the CDC is responsible for that aspect of the national vaccine program, but that the NVAC is concerned with a sufficient supply to meet the needs of the U.S. public, and the NVPO is concerned with how the stockpile may impact an adequate supply of vaccines.

The legislation that established the NVP included a requirement to create a National Vaccine Plan, which was developed by the NVPO in 1994 and included a strategic vision for coordinating the nation's vaccine programs. The latest version of the National Vaccine Plan was just released. The Plan has five major goals: to develop new and improved vaccines; to enhance the vaccine safety system; to support enhanced communications to improve informed vaccine decision making; to encourage efficient use of vaccines in the U.S. and to insure an adequate supply of vaccines; and to build global disease prevention to reduce mortality and morbidity resulting from diseases that can be prevented through the use of vaccines.

Dr. Salmon commented that the development of the plan took more than three years, involved extensive discussions with stakeholders, a number of public meetings, the engagement of the NVAC and an Institute of Medicine (IOM) review. He noted that the second and fourth goal were most germane to the ACCV's mission. Part of the second goal is focusing on high priority areas in a vaccine safety system, which includes developing a scientific agenda and recruiting the scientists and clinicians to carry out the agenda. There must also be advances in manufacturing technologies and new regulatory approaches to licensing. The second goal also includes enhancing the timely recognition and verification of safety signals that may come from surveillance programs, media reports, Internet blogs and even scientific publications. A concomitant objective is to improve the timeliness of evaluating signals, especially when new vaccine safety concerns emerge and when a new vaccine is recommended. When a safety concern is identified it is important to improve the causality assessment of adverse events following administration

of a particular vaccine. That is, determination of whether or not the adverse event was really caused by the vaccine.

Dr. Salmon noted that it is also important to improve the scientific knowledge about why adverse reactions occur and whether or not they occur more commonly in particular subgroups of vaccine recipients. That includes determining whether genetic, previous illness, or other factors are related to adverse events and vaccines.

Concerning one action that would contribute to achieving the objectives of the second goal, Dr. Salmon noted that the NVPO had supported a meeting to enhance the development of biobanks and repositories of clinical information. He added that one such repository is maintained by the Clinical Immunization Safety Assessment (CISA) Network, a group of six academic medical research centers that have developed a small biobank. One challenge to establishing a repository is the requirement to insure confidentiality of the personally identifiable information of those who contribute.

Dr. Salmon commented that the final objective under the second goal was to promote collaboration of vaccine safety activities among the various entities involved in the effort, an objective that is part of the NVPO's primary mission. Working with other agencies associated with the National Vaccine Program, Dr. Salmon stated than an implementation plan is being developed specifically to insure that the second goal objectives will be realized. Part of the input for the plan will come from comments received at a series of regional public meetings that are being conducted currently. Of course the implementation plan cannot cover all of the objectives equally so it will include a prioritization such that the highest priority objectives will be addressed first. The plan should be completed within about six months.

Ms. Hoiberg commented that there should be a way to invite parents who have vaccine-injured children to participate in research protocols, or even to be included as donors to the repositories. She conceded that the issue of confidentiality and consent would have to be addressed. Dr. Salmon agreed, adding that in addition to the donations of tissue, a medical history would be needed to support the research. The Federal Immunization Safety Task Force, established by Secretary Leavitt, is specifically concerned with vaccine safety and developing an infrastructure that would include a repository that would facilitate research on very rare vaccine side effects. As for recruitment of participants, Dr. Salmon identified a number of programs – the VICP, VAERS and other surveillance programs, CMS, the VA, and the DoD. The clinical trials conducted by the vaccine manufacturers could also provide information.

Asked whether there was consideration of analyzing the data that should be available from the approximately 2,500 VICP cases that have been settled in favor of the petitioners, Dr. Salmon agreed that the issue has been discussed for a number of years and that there would be a discussion of one aspect of that information resource on the Commission's second meeting day by the Chief Medical Officer, Dr. Rosemary Johann-Liang. Her Branch does small studies of VICP cases concerned with specific adverse events.

Dr. Salmon turned to the fourth goal, also germane to the ACCV mission, which relates to access to vaccines and more effective and efficient use of existing vaccines. One objective under that goal is to strengthen the VICP and its sister program, the Countermeasures Injury Compensation Program (CICP). Part of that objective is to increase public awareness of both programs; ensuring that the programs are responsive to the evolving science (including regular updates of the Injury Table); ensuring that valid vaccine injuries are fairly compensated; and improving the VICP adjudication process for injuries not on the Injury Table.

Discussing some of the groups that contribute to the NVP, Dr. Salmon explained that the NVAC is an advisory committee that makes policy recommendations to the Assistant Secretary for Health, who is the director of the National Vaccine Program. There are a number of working groups that develop those recommendations for final approval by the full committee. He discussed two of the working groups.

The H1N1 Vaccine Safety Risk Assessment Working Group was established to assess H1N1 safety data on a continuing basis. It is composed of representatives from five federal agencies that are officially involved with vaccine safety – ACIP, VRBPAC, NVAC, the National Biodefense Service Board, and the

DoD Health Board – and two non-federal experts who are members of the Institute of Medicine. All members are thoroughly vetted for conflicts of interest.

Focusing solely on vaccine safety, the working group meets biweekly by phone, looking at the most recent reports from several surveillance programs, summarizing the data and submitting a monthly report to the NVAC at meetings that are open to the public. In addition to general risks, the reports address Guillain Barre syndrome (GBS) and pregnancy outcomes when expectant mothers receive H1N1 vaccine.

Dr. Salmon discussed a second working group, the Vaccine Safety Working Group, which includes four federal advisory committee representatives, a number of non-federal members who have expertise in a variety of scientific specialties including immunology, neurology, epidemiology, biostatistics, genetics and others. The working group has reviewed the CDC's Immunization Safety Office's research agenda that was based on a report by the IOM. In the process the working group held several public meetings, a few smaller stakeholder meetings, and issued a report to CDC that included suggestions for the prioritization of the agenda. That task was completed in 2009. The working group's current project is to look at the vaccine safety system more broadly and to create a white paper that will provide guidance on how to take advantage of new science and technology as it might impact vaccine safety in the 21st century. In April the draft of the white paper will be submitted to a broad range of stakeholders to elicit comments and recommendations, after which a final draft will be submitted to the NVAC at the June meeting. It is anticipated that the final white paper will be released in September 2011.

Finally, Dr. Salmon announced that a guide to the national vaccine safety system had been prepared and released. The system is exceptionally complex, with, many programs in the various federal agencies involved with vaccines. The guide is a 70-page document that is available on the CDC web site.

Update on the Immunization Safety Office (ISO) Vaccine Activities
Dr. Jane Gidudu, ISO, CDC

Dr. Gidudu discussed the ISO, beginning with an explanation that, like drugs, no vaccine is absolutely safe or absolutely effective. Monitoring for adverse events is part of the pre-licensure process that begins with Phase I trials that enroll only a few subjects (usually between 10-50) to assess safety, continues with the Phase II trials (may enroll 100-1000) to look at both safety and whether or not the vaccine is effective, Phase III trials assess more individuals (typically 1000-10,000) and finally includes post-licensure data collection potentially involving the larger number of individuals who receive the vaccine. It is in the post-licensure phase when very rare side effects are revealed; a process that is supported by the various surveillance systems that collect data after a vaccine has been licensed in the US.

Dr. Gidudu noted that these rarer adverse events are a challenge to define since some conditions may occur in the population with or without the presence of vaccines. When these rare adverse events are detected they often constitute only a potential signal that such a side effect might be related to a vaccine, and significant follow-on investigation is required to try to determine whether or not the adverse event is related to the vaccine. Vaccines are given to healthy individuals (including children), unlike drugs that are administered in therapeutic doses to ill individuals. It is extremely important to ascertain the safety of each vaccine made available to the public.

The vaccine safety effort of the federal government involves a number of agencies – the National Vaccine Program Office is responsible for interagency coordination of vaccine safety programs; the CDC conducts surveillance, research, prevention and education activities; the FDA is the regulatory and enforcement agency; and the NIH conducts basic research. The ISO is part of CDC and its mission is to assess the safety of vaccinations administered to every age group in the U.S. Responsibilities include monitoring newly licensed vaccines, reviewing changes in vaccine administration policy usually effected by a recommendation from the ACIP, and periodic monitoring of unique events such as the recent mass N1N1 vaccination program.

Dr. Gidudu described four main projects that the ISO is involved in (with other agencies) – the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the Vaccine Analytic Unit (VAU), and the Clinical Immunization Safety Assessment (CISA) Network. VAERS is a spontaneous

national reporting system that accepts reports of adverse events from anyone, but especially healthcare providers, manufacturers, individuals affected by adverse events, and parents. It is jointly administered by FDA and CDC, and receives over 30,000 reports annually. VAERS is valuable in detecting signals of potential adverse events related to a vaccine. These signals must be carefully analyzed since the information received may be inaccurate (anyone can report any event as a vaccine injury), may be over-reported because of media coverage on a vaccine event, or may be under-reported. There is also the limitation that analysis is hindered because there is no reliable denominator to obtain rates of adverse events in those immunized. There is, no way to ascertain how many doses of a vaccine were actually administered to result in the reported adverse events, and usually no information on the background rate of adverse events that would occur without the introduction of the vaccine. Although the VAERS report form requires certain information about the adverse event, the vaccine, the patient involved and so on, VAERS will accept incomplete reports.

On the positive side, VAERS has often identified very rare adverse events, and generates signals that provide a rationale for further investigation of possible side effects. For example, VAERS revealed the possibility of an increased risk of intussusception in infants related to the administration of the Rotashield vaccine, which was shortly proved true and the vaccine was taken off the market. Similarly, VAERS reports alerted the vaccine safety community to the risk of syncope related to immunizations, an issue that is currently being investigated further. Finally, when a report of a serious adverse event is received, VAERS conducts an immediate proactive investigation. A serious event is considered a death, a life threatening condition, hospitalization, or prolonged disability.

The Vaccine Safety DataLink is a cooperative effort among ten major managed health care organizations, caring for 9 million patients, that includes 3% of the U.S. population. Relying on the medical records generated in that population, the VSD monitors and analyzes data on several specific conditions. A significant advantage of the VSD is that all medical care for the subject population is available for analysis (except any care obtained outside the system, such as vaccinations at a local pharmacy). Background rates (illness clearly unrelated to vaccines) can be calculated, and there is an opportunity to survey the patients in the systems. However, the sample size is limited and the VSD population demographics differ from those of the entire country. Although not unique to the VSD, the size of the unvaccinated population is relatively small, so studies that compare vaccinated with unvaccinated may not be possible. The VSD can react fairly quickly, as it did in the investigation of reports of risk of febrile seizures related to the administration of the MMRV vaccine (measles, mumps, rubella, varicella); this investigation determined that one additional febrile seizure occurred per 2,300 MMRV doses administered compared to administering the MMR and varicella vaccines separately.

Dr. Gidudu described the VAU, which relies on the Defense Medical Surveillance System data on 1.4 million active duty personnel, and is focused on the adverse events related to current and future anthrax vaccines as well as other vaccines that may be administered to military personnel.

Finally, Dr. Gidudu discussed CISA, which conducts specific research on the pathophysiology of adverse events, individual risk factors, identification of genetic risk factors, and consultation for policies and on individual patients. CISA has established a bio-bank that will store specimens, particularly from individuals who experience rare adverse events, to facilitate future research. CISA's goals include an interest in becoming a resource for public health agencies involved in vaccine safety and to support policy makers in the US and globally. As examples, CISA collaborates with the World Health Organization, the Brighton Collaboration and other international organizations to advance the understanding of vaccine safety.

Dr. Gidudu concluded her remarks noting that the ISO had recently completed its scientific agenda, which should be released with a few weeks. The ISO also provided presentations to the ACIP at its February meeting, including a discussion of vaccines and febrile seizures. The latter involved a signal, currently being investigated, of an increased incidence of seizures among children who received both PCV-13 and influenza vaccines.

During discussion, asked about how the ISO was increasing public awareness of the VICP, Dr. Gidudu stated that most of the efforts are focused on providing educational webinars to vaccine safety coordinators at the state level, although information is also available on the CDC web site.

Communications and Outreach Workgroup Report
Sarah Hoiberg, ACCV Member

Ms. Hoiberg reported the contract with Banyan Communications resulted in an excellent report that put forth a number of promising proposals. Under Dr. Evans' direction, DVIC staff created a slide presentation entitled "Draft National Vaccine Injury Compensation Program," for the review of the Commission. It is intended to be a presentation that would be on a web site available to health care professionals groups that might find it appropriate as an educational tool to provide information about the program to their associates and clients. Ms. Hoiberg suggested that the draft be reviewed slide by slide. The following recommendations were agreed on:

Slide 2 – add the year 1986 under the bullet "Congress passes National Childhood Vaccine Act."

Slide 3 – revise the first bullet to read, "federal no-fault compensation system *for children and adults*." That revision would make the last bullet redundant so that it should be deleted (i.e., no age restrictions on who may file).

Slide 4 – add a specific description of the 2011 IOM report and provide a link to that report if possible.

Slide 5 – there was agreement to clarify the role of the Department of Justice, and to try to simplify the term for the Special Master, since most laymen would not understand that term -- perhaps judicial officer with Special Master in parentheses.

Slide 6 – In describing the claims process there was agreement that the illustrations could become difficult to follow and that a simplification of the presentation would be helpful. There was agreement to remove the description of witnesses (parents, experts, medical witnesses" as unnecessary, and emphasized that the "court may compensate claims" as a separate bullet for emphasis. There was a comment that the presentation might have a supporting script that could be read during the slide presentation to provide additional clarification. Ms. Hoiberg suggested that a perusal of the slides should give an individual a good idea of the program, and the script would allow a much more in depth understanding. With regard to the bullet describing the review of medical records, there was a suggestion to add "medical staff" to clarify that the review is scientific.

Slide 7 -- in defining the statute of limitations, there was agreement to use the statutory language for both injury and death, since that will not change, and leave the interpretation of the wording to the reader.

Slide 8 – VICP entitlement determination. There was agreement that the slide was very dense but that the detail was needed. There was a suggestion to divide the slide into two slides, with the notation "Continued" at the top of the second slide. With regard to lost wages and fees, there was agreement to simplify the wording to just "lost wages" and "attorney's fees and costs."

Slide 9 – VICP appeal – no changes

Slide 10 – VICP vaccines. There was agreement to simplify the slide, delete acronyms, and revise the wording to reflect "any vaccine recommended by CDC for routine administration in children even when used in adults." The second slide containing information about adding new vaccines would be deleted.

Slide 11 – Contact information. There was agreement that a notation should be added to the contact information that an individual can locate an attorney for VICP cases by going to the court web site. Dr. Evans reiterated that the VICP and his office cannot provide specific information about attorneys. Only a referral to the court web site can be included in the contact page information. There was a recommendation to put the HRSA VICP URL on the first slide of the series.

There was a brief discussion about whether the ACCV should be credited or mentioned on the slides, and Dr. Evans commented that there would be nothing to prevent that if that was the wish of the Commission.

Finally, Ms. Hoiberg invited Commission members to join the working group, and to submit any afterthoughts to her after the meeting adjourned.

Update on the National Institute of Allergy and Infectious Diseases. NIH Vaccine Activities. Dr. Barbara Mulach, NIAID, NIH

Representing NIH, Dr. Mulach explained that the NIH mission is the pursuit of scientific knowledge related to improving human health, including research on new and improved vaccines and vaccine safety. A number of the institutes are specifically involved in vaccine research, including NIAID, NICHD, NIMH, MCI and others. The mechanism by which most of the research is conducted is through the award of grants and contracts to researchers, for the most part not a part of the NIH, who perform the research at academic institutions and in public sector research and pharmaceutical firms. Typically the institute publishes an invitation for proposals to address a particular or a general research question under its extramural program. Individual researchers submit proposals that describe a specific research plan. After a vetting process the most promising plans are funded. The proposals may be submitted by any qualified researcher in the world. NIH is also committed to building the research community by providing training at NIH to scientists who may participate in such programs on a temporary basis. Finally, each institute has its own intramural program in which scientists employed by NIH conduct research.

Dr. Mulach noted that since the NIAID is primarily responsible for infectious diseases, most NIH vaccine research is funded by the Institute. That research is focused on developing new and improved vaccines and diagnostics, development of innovative vaccine technologies and a more complete understanding of human immune response. Although there are few infectious disease threats in the U.S. not already covered by existing vaccine programs, vaccine research at NIH has an international purview since disease threats in other countries may find a vector into the U.S. through international travel.

Much of the research is conducted outside of NIH, relying on the extramural research mechanism already mentioned. The grants are often awarded to researchers who have built a long-standing relationship with NIH and whose expertise and response to NIH requirements are established. Because of this relationship it has been possible on short notice to pull together a research team to address immediate health issues, such as the recent H1N1 pandemic, and arrive at valid conclusions in a relatively short period of time. In the longer term, these researchers are looking at new strategies in vaccine development and safety, including the creation of a “universal flu vaccine,” for example, that will be effective for longer periods of time against a wider range of flu strains.

Dr. Mulach explained that most often the proposals sent to the research community describe a general research issue, but the proposals returned are usually focused on a specific scientific question that is part of the general research issue. For example, one proposal in response to an invitation to look at vaccine safety looked only at metabolic and immune responses to vaccines given to subjects with mitochondrial disorders. Another project looked only at one specific vaccine (chicken pox zoster vaccine) and how it affected immune response. Dr. Mulach added that, although valuable research came from the two projects, once an invitation is published NIH must wait for proposals which may or may not be forthcoming, and may or may not be fully responsive to the original research question. The group of research scientists interested in vaccines is relatively small and stimulating interest to address specific questions of interest to NIH is challenging. She commented that, although NIH is mainly concerned with basic research, in some areas, like drugs and vaccines, the interest continues through the clinical evaluation phases.

For the benefit of the newly appointed commissioners, Dr. Mulach described a recent issue presented to the Commission for its consideration. She noted that the ACCV was regularly informed of the 2009 effort to understand the H1N1 flu pandemic at the beginning of which there was a multi-agency response to create and implement a vaccine program. Because seasonal influenza presents in a variety of strains each year, experts try to predict which strains will be the most damaging during the regular flu season. Then a trivalent vaccine is developed in an attempt to reduce the aggregate infection from any and all of the strains that may be active during the flu season. The appearance in April 2009 of the H1N1 influenza strain imposed a complication on this process. It was a new strain and its effects were much more serious than the seasonal flu strains. The process of developing a flu vaccine usually takes more than nine months, but the threat of H1N1 forced a much more rapid response. By October 2009 involved

agencies, working with vaccine manufacturers, had developed a vaccine, established the dosage, estimated how much vaccine would be required to immunize the at risk population, and identified which groups would be most vulnerable. Since then follow-on studies have been conducted to assess the impact of the flu and the vaccine in smaller special populations, like pregnant women and individuals with compromised immune responses (such as HIV-infected patients).

Dr. Mulach mentioned a second issue previously presented to the ACCV, the establishment of phenotyping centers through research grant awards that would characterize individuals who are and who are not infected with a virus for which a vaccine exists and, for the former group, who are immunized against that virus, to begin to understand the human immune response in the two groups.

Finally, Dr. Mulach described the Human Microbiome Project that is characterizing the trillions of microbes that reside in the human body. Most are beneficial or neutral in effect; some are not; and some may or may not be helpful or harmful. An important consideration is the intake of an antibiotic that may kill both bad and good microbes, which may cause side effects, including perhaps a delayed full recovery.

During discussion, Ms. Hoiberg raised the issue of utilizing the data accumulated in the VICP from cases that have resulted in settlement, and the fact that many parents of vaccine-injured children would be willing to participate in research protocols. Dr. Mulach agreed that there was valuable information in those records, but that issues of confidentiality impede direct contact with the parents. Then it becomes an issue of communications, looking at the challenge of a researcher who might be interested in such participation being unable to directly contact the parents or even reach those parents through indirect communication.

Update on the Center for Biologics, Evaluation and Research (CBER) Vaccine Activities
Dr. Marion Gruber, CBER, FDA

Dr. Gruber provided an overview of preventive vaccine development and regulation. These products are regulated by the Office of Vaccine Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER). CBER/OVRR is responsible for regulating vaccines in the United States. OVRR has three divisions, an applications division responsible for processing all regulatory applications; project management, clinical and toxicology review; and two research based divisions responsible for performing research supporting regulatory decision making as well as responsible for the review of chemical, manufacturing and control information for the vaccines and submitted by applicants and sponsors.

Dr. Gruber explained that preventive vaccines are delivered to healthy individuals, mainly to children, placing special emphasis on the safety of these products. The laws that govern vaccine regulation and approval are the Public Health Service Act (Section 351) and certain sections of the Federal Food, Drug and Cosmetic Act. The laws state that a vaccine must be safe, pure and potent (which is a term that implies effectiveness). Because safety can never be absolute, the “safety” determination of a vaccine is based on a risk-benefit analysis – do the benefits of receiving the vaccine clearly outweigh the risks.

A sponsor who wants to study a vaccine candidate in the clinic must submit an Investigational New Drug application (IND) to FDA. This document describes the vaccine, manufacturing process, and quality control tests for release. Also included are information about the vaccine's safety and ability to elicit a protective immune response (immunogenicity) in animal testing, as well as the proposed clinical protocol for studies in humans.

Pre-licensure vaccine clinical trials are done in three phases, referred to as Phase 1 (safety studies performed in a small number of closely monitored subjects), Phase 2 studies (dose-ranging safety and immunogenicity studies that may enroll hundreds of subjects) and Phase 3 trials (typically enrolling thousands of individuals and providing data of effectiveness and safety required for licensing). At any stage of the clinical development of the product, if data raise concerns about either safety or effectiveness, FDA may request additional information or studies, or may halt ongoing clinical studies.

If successful, the completion of the clinical development can be followed by the submission of a Biologics License Application (BLA) providing all relevant data demonstrating efficacy and safety. This document is reviewed by a team of FDA experts who recommend approval or other regulatory actions. The BLA includes a post-licensure pharmacovigilance plan that outlines how the vaccine is further studied for safety, once approved. During the BLA review, the proposed manufacturing facility undergoes a pre-approval detailed inspection of the vaccine production process.

The sponsor and the FDA may present their findings from the BLA review to FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). This non-FDA expert committee provides advice to the Agency regarding the safety and efficacy of the vaccine for the proposed indication.

After licensure, monitoring of the product and production activities, including periodic facility inspections, continues as long as the manufacturer holds a license for the product. If a problem is identified the manufacturer is asked to address this immediately.

With regard to recent FDA vaccine approvals, Dr. Gruber announced that Menveo, an approved vaccine for individuals 11 to 55 years of age to prevent invasive meningococcal disease, was approved for children 2 to 10 years of age. Gardasil, a human papillomavirus vaccine approved for individuals 9 through 26 years of age, was approved for an additional indication, prevention of anal cancer. Finally, Dr. Gruber mentioned that the VRBPAC had considered the composition of the seasonal flu vaccine for the 2011/12 influenza season. Recommendations were made not to change the influenza strain composition, i.e. to use the same strains included in the flu vaccine that was used during the 2010/11 season. Manufacturers have submitted proposal for quadrivalent influenza vaccines. There was discussion that children have different susceptibility to the influenza B strains and there is discussion of a supplemental B strain vaccine that would potentially result in two different vaccines for adults and children. Dr. Mulach noted that neither monovalent nor quadrivalent vaccines are included in the vaccine injury table, which may require further consideration in the near future. Ms. Hoiberg commented that approval of vaccines for nearly universal coverage, and the fact that flu vaccines are available in a wide variety of venues, most of which are not medical offices, suggests there should be consideration of issues such as proper storage and administration. Dr. Gruber agreed, but noted that the issue was not under the purview of the FDA. Dr. Fisher added that if vaccine administration was restricted to medical offices it would thwart the goal of universal coverage.

During discussion, asked about approval for use in children, Dr. Gruber explained that if a vaccine is proposed for use in a particular pediatric subgroup, the vaccine must be studied in clinical trials to ensure safety and effectiveness of the product in the particular pediatric population. Asked about the review process, Dr. Gruber explained that it is exceptionally thorough, involving 20 to 30 reviewers from a wide variety of specialties – epidemiologists, microbiologists, biologists, statisticians, clinicians, etc.

Petition to Add Injury to Vaccine Injury Table
Ms. Charlene Gallagher, Chair, ACCV, and Dr. Geoffrey Evans, Director DVIC

Ms. Gallagher announced that, on August 27, 2010, a petition was received by the Chief Special Master from a member of the public to add Guillain Barre syndrome to the vaccine injury table. The petition was referred to the ACCV on October 28th, 2010. Ms. Gallagher explained that the National Childhood Vaccine Injury Act of 1986, as amended, authorizes the Secretary HHS, after consultation with the ACCV, to create and modify a list of injuries, including death, related to specified vaccines that are included on the table. There is also a provision that any person may petition the Secretary to amend the table. Unless clearly frivolous or initiated by the ACCV (which may also petition the Secretary for a revision) the petition must be submitted to the ACCV for review and recommendation. Following the receipt of such a petition, within 180 days, the Secretary must conduct a rulemaking proceeding or publish in the Federal Register a rationale for not initiating a rulemaking proceeding.

Dr. Evans, representing the Secretary, stated that the Department takes seriously any valid petition to revise the table, including this petition from a member of the public, the first such petition to be received

by the Secretary since the establishment of the VICP. He noted that, in the past, before making decisions related to vaccine injury table revisions, the Secretary has relied on Institute of Medicine reviews of the medical and scientific literature on adverse events following vaccination. He noted that such a report is anticipated from the IOM in the early summer, which will cover influenza-related adverse events, including GBS. Dr. Evans stated that the Secretary will consider changes to the table after review of that report and would prefer to defer consideration of this particular petition until that information is made available. In compliance with statute, any changes under the authority of the Secretary would first be reviewed by the ACCV. The recommendation of the ACCV on this particular matter, including the vote on a formal motion, will be published in the Federal Register later in the year.

Dr. Evans stated that the Secretary requests that the Commission advise and consent concerning the matter of the petition.

Ms. Gallagher commented that the IOM review would include consideration of GBS as a possible side effect of influenza vaccines, a study that is already under way. During the discussion Dr. Evans stated that based on previous IOM reports on vaccines and adverse events, he expected this next one to have a summary table showing the weight of evidence associated with each vaccine and adverse event. The Secretary will consider the report and make decisions on all adverse effects covered in the report, including GBS. He noted that the IOM does not make recommendations for changes in the Vaccine Injury Table; that is left to the Secretary. Dr. Evans added that the petition does not mention any specific vaccine to which GBS should be related in the table, not any timeframe for the adverse event to occur.

After discussion of the issues Ms. Gallagher invited a motion.

On motion duly made and seconded, to support the Secretary's decision not to go forward with rulemaking to amend the vaccine injury table in response to this petition, the motion was unanimously approved.

Public Comment

Ms. Gallagher announced the opportunity for members of the public to comment during the proceeding. There were no requests for time to comment.

Ms. Gallagher ordered a recess until the following day.

(The meeting recessed at 5:30 p.m., to reconvene the following morning, March 5, at 9:00 a.m.)

Advisory Commission on Childhood Vaccines

March 3-4, 2011

Day Two

Minutes

Members Present
Charlene Gallagher, JD, chair
Sherry K. Drew, JD, Vice Chair
Magdalena Castro-Lewis
Margaret Fisher. MD
Thomas Herr, MD
Sarah Hoiberg
David King
Ann Linguiti Pron, MSN, CRNP, RN
Michelle Williams, JD

Executive Secretary

Geoffrey Evans, M.D., Director, DVIC

Staff Liaison

Andrea Herzog, Principal Staff Liaison

Welcome, Ms. Charlene Gallagher, Chair.

Ms. Gallagher called the meeting to order and introduced the first presentation by Dr. Rosemary Johann-Liang.

DVIC Clinical Case Update
Dr. Rosemary Johann-Liang, Chief Medical Officer, DVIC
Dr. Barbara Shoback and Dr. Tom Ryan, Medical Officers, DVIC

Dr. Johann-Liang stated that she would discuss the recently completed review of non-autism medical claims, provide an update on rotavirus vaccines, human papillomavirus (HPV) and meningococcal vaccine claims, and the analysis of claims for anaphylaxis, and syncope, and cover the steps being taken by the medical staff to prepare for release of the IOM report. She reminded the Commission that the reviews and comments refer to aggregate cases and not individuals, whose personally identifiable information must be protected.

Looking at the history of non-autism petitions filed, Dr. Johann-Liang noted that from 2001 to 2007 less than 200 claims were filed each year. Since 2008, the caseload has increased significantly, close to tripling the number of filed cases by 2010. This increase in non-autism claims is due mainly to the increase in influenza (flu) and human papillomavirus (HPV)claims. She also provided some information on the denominator, showing that the number of doses of flu and HPV vaccine distributed increased in a similar ratio, doubling from 2005 to 2008 to over 100 million doses. Doses distributed in 2010 were further increased projecting around 160 million. She explained that there is a 2-3 year lag time in cases filed from the time of vaccination because of the statute of limitations for filing a non-fatal event. She also reminded the Commission that doses distributed cannot be directly translated into doses administered.

There is no national count of flu doses administered. Dr. Johann-Liang explained that her office reviews each case filed and that in the first three months of the fiscal year, from October to December 2010, 137 claims were handled by her office, 122 of which were non-autism cases. Most of the autism cases were claims that were reactivated following the omnibus autism proceedings. The number of claims is different from the total reviewed because her reviewers can only review claims which have enough records to make a recommendation.

Dr. Johann-Liang described the change in age distribution of individuals for whom claims were filed, noting that from 1998 to 2010 the percentage of pediatric (through age 17) claims fell from over 70% of all claims to 20%, while claims for adults rose from less than 20% to about 60%. Results from the National Health Interview Survey (NHIS) supports these numbers, showing a similar proportional increase in those interviewed who reported having received an influenza vaccination. The NHIS is an annual survey of a randomly selected cohort that collects information about health-related matters, and the periods reported cover the same years mentioned earlier, 2005 to 2007.

Turning to medical reviews, Dr. Johann-Liang reported the proportion of case reviews submitted to her office in the first quarter of FY 2011: 39% were flu vaccines, 26% HPV, 10% tetanus, 7% the infant multiple vaccine group; the others were between 2% and 4% each and included meningococcal vaccines, varicella, hepatitis A and B, MMR and rotavirus. A primary purpose of the medical review is to confirm that the condition or injury reported in the claim was an accurate diagnosis, which is accomplished by reviewing the medical records submitted with the claim. In a significant proportion of claims the diagnosis after the review of the records is actually different from what injury was alleged. In the final analysis the following conditions were identified after medical review of the records: GBS (30%), other neurologic (19%), other demyelinating (15%), genetic and underlying disorders (13%), and a few that were in the 2%-4% range – infectious diseases, rheumatologic conditions, toxins (conditions caused by drugs or chemicals), and death. There was also a catch-all category for miscellaneous conditions that amounted to 10% of the claims (heart, skin, gastrointestinal, blood, cancer and psychiatric). Dr. Johann-Liang mentioned that the genetic disorders, which showed an increase from earlier review periods, were interesting because they may provide clues to specific populations that might be at increased risk for specific vaccine injury.

Dr. Johann-Liang briefly discussed rotavirus vaccines. She showed a summary slide of the current safety information known regarding Rotateq and Rotarix. Rotateq is mainly used in the U.S., Rotarix outside of the U.S. There is insufficient information at this time to confirm that increased risk of intussusception exists for these two newer vaccines above what occurs in the general population. Intussusception was the reason that an earlier vaccine, Rotashield, was removed from the market.

Dr. Johann-Liang discussed the activities in her office to respond to the results of the Institute of Medicine study that will be received in a few months. The charge is to support the DVIC's development of possible revisions to the Vaccine Injury Table based on the IOM concluions. The IOM has been asked to review specific adverse events, including a review of biological mechanisms associated with those adverse events. The review will look at eight vaccines – HAV, HBV, HPV, influenza, meningococcal, MMR, tetanus-containing vaccines, and varicella. There are also special projects in DVIC to review injuries related to vaccine administration (SIRVA), anaphylaxis, GBS and syncope claims.

At the September meeting, a VICP case series was presented on Shoulder injury Related to Vaccine Administration (SIRVA), a new adverse event related to immunization. At that time, the study was in progress that has now been completed. For the benefit of the incoming Commissioners, Dr. Atanasoff, briefly outlined the results of the study. In response to a few reports of significant side effects that appeared to be related to the way vaccines were administered, the office initiated a review of records that revealed 13 cases of post-vaccination pain or disability in the area of the vaccination, the shoulder. No specific vaccine was involved; onset of pain immediately followed the injection in some cases accompanied by limited range of motion of the joint. Many of the individuals required subsequent treatment; some underwent surgery. In two cases ultrasound scans indicated that the needle could have penetrated the sub-deltoid bursa leading to an immune response that caused the symptoms described.

To cause the physical injury the needle might be too long, or the angle of injection could be improper (e.g., a seated recipient and a standing provider). Dr. Evans commented that the report is a success story in that a new medical condition has been identified from the review of claims cases.

Dr. Johann-Liang continued the discussion, turning to anaphylaxis, and stating that a search of the medical records from 2000 to 2009 (10 years review), identified 53 unique cases alleging anaphylaxis or anaphylaxis shock as a vaccine injury. For the review, the definition of anaphylaxis was taken from a Brighton Collaboration study in 2007 to insure consistency in the diagnosis. Cases were categorized as true anaphylaxis when the Brighton Collaboration definitions were met; allergic reaction not meeting the specification of anaphylaxis; and the third was not meeting the specifications for either anaphylaxis or allergic reaction. Of the 53 cases, which accounted for 3% of the total 1,819 non-autism claims filed, the review confirmed only 9 cases of true anaphylaxis occurring within four hours of inoculation. Five of those cases resulted in death. Four cases fell into the second category of allergic reaction but not anaphylaxis. The remaining 36 proved not to be anaphylaxis or allergic reaction. The causes of the adverse event included 15 sudden deaths (SIDS, asphyxia, pneumonitis, cardiac event, homicide and hyperglycemia); and several other conditions including neurological response, dermatologic reaction, respiratory distress, psychiatric response and syncope. Eight different vaccines containing 11 different antigens were involved in the anaphylactic reactions, some of which are on the vaccine injury table. Dr. Johann-Liang indicated that the study will be helpful to updating the vaccine injury table.

Presentation: Human Papillomavirus Vaccine, Dr. Barbara Shoback

Dr. Shoback explained that human papillomavirus is the most common sexually transmitted infection. There are over a hundred types of HPV, but types 16 and 18, which cause about 70% of cervical, anal and genital cancers, are the most serious. Types 6 and 11 cause about 90% of genital warts. Cervical cancer ranks eleventh in cancer among women in the U.S. it is much more common in developing countries as the second most common cancer.

Merck has an approved vaccine, Gardasil, which vaccinated against the four types of HPV mentioned. It is approved for use in women and men (for men mainly to prevent transmission of HPV). It was licensed in June 2006 for females 9 to 26 years of age and in October 2009 for males in the same age range. A warning was added to the label in June 2009 for syncope after administration. The vaccine is contraindicated during pregnancy, if an individual has had a previous allergic reaction to the vaccine, or has a severe allergy to yeast. A second vaccine, Cervarix, was licensed to GlaxoSmithKline in October 2009, for females 10-25 years of age. It is a bivalent vaccine that protects against HPV types 16 and 18.

HPV vaccines were added to the injury table in February 2007 without specific injuries. There have been 117 claims filed with the VICP; all women but one, a male with GBS. A majority of the claims alleged a neurological condition, over 20% of these named GBS. The remaining neurological claims were for seizures, headaches, and neuritis. A significant number (25%) alleged rheumatologic conditions. Other injuries included gastrointestinal, hematologic, and endocrine-related conditions. There were five cases of syncope with secondary injury, and one case of SIRVA. About 20% of claims had mental issues that contributed to the illness. Affective disorders was the most common. Finally, there were eight deaths, all in women, whose autopsies showed underlying genetic disorders or acquired conditions that could have contributed to the death.

Presentation: Meningococcal Vaccines, Dr. Tom Ryan

Dr. Ryan described meningococcal disease caused by Neisseria meningitides bacteria, which is believed to reside only in humans and not in other species in the animal world. The bacteria can be found transiently in up to 10% of the population, residing in the noses and throats of typically asymptomatic individuals. It may rarely invade the body leading to infections such as meningococcemia and meningococcal meningitis. The CDC has indicated that the background rate of infection is about 0.3 cases per 100,000 population, translating into up to 1,200 cases in the U.S. annually. Susceptibility to the bacteria is affected by genetics and the level of immune response, and to lifestyle (close contact with others as is usual in college dorms and the military). It is a leading cause of meningitis in young healthy individuals, and it results in up to 15% mortality regardless of timely antibiotic therapy in those who

become infected. A significant group infected each year are children under age two, and there is no licensed vaccine for this age group.

Dr. Ryan indicated that vaccines are available for four of the bacteria's sero-groups (A, C, Y and W-135), providing effective prevention in about 80% of vaccinated individuals. But there is no vaccine for sero-group B. The first vaccine was available in 1981, a polysaccharide called Menomune. That vaccine, although effective, has been replaced by two conjugate vaccines, Menactra (2005) and Menveo (2010). Although not yet proven, it was hoped that the vaccines would provide longer immunity and would induce a faster immune response to the bacteria. Dr. Ryan stated that meningococcal vaccines were added to the injury table in February 2007, although like HPV there are no specific injuries listed to date.

Dr. Ryan discussed recent ACIP recommendations. The conjugate vaccines did appear to have longer immunity, but it began to wane after about five years. This is a concern since twelve year olds typically receive the first inoculation, and the immunity begins to fade at about the time they enter college, a time of higher risk. ACIP recommended a booster at 16 years of age. ACIP also recommended a two-dose initial series for individuals 2 to 54 who were at increased risk for infection – those with compromised immune response, those lacking functioning spleens, adolescents with HIV, and lab workers exposed to N. meningitides

ACIP reviewed a 2006 CDC report that indicated a small increased risk of GBS following Menactra vaccination and therefore issued a recommendation that individuals with a past history of GBS should not receive the vaccine. However, in 2010 two large epidemiologic studies of more than 2.3 million doses of Menactra revealed no increased risk of GBS, and the original recommendation was rescinded. In response to a question about the advisability of such an action, Dr. Johann-Liang explained that GBS is rare even without the addition of Menactra to the formula. Therefore it is difficult to mount a study large enough to provide a definitive answer. Nonetheless, the surveillance systems will continue to look for signals that there may be a risk for GBS associated with the vaccines. Concerning revision of the injury table, Dr. Johann-Liang indicated that the IOM study would cover the scientific literature related to adverse events to meningococcal vaccines.

Moving to the claims history, Dr. Ryan reported that there have been 32 claims since the vaccine was added to the injury table. Nine of those claims were for adverse events after administration of the meningococcal vaccine alone, and 23 were claims that included other covered vaccines. Sixty percent of the claims alleged neurological conditions, GBS accounting for about a third of all claims and "other" accounting for about a third. Finally, Dr. Ryan noted that the average age at vaccination was 17 years of age, a result of the focus on college entrance, and the full age range was 11 to 49 years of age. The claims filed indicated onset of the alleged condition occurred from the time of vaccination to 105 days.

Presentation: Vaccine-Related Syncope, Dr. Tom Ryan

Dr. Ryan described syncope, or fainting, as a condition usually caused by decreased blood flow to the brain, a condition that is considered benign in that it does not lead to serious or chronic illness or death, although there is risk of injury from syncope-induced falls. There has been a slight increase in reports of syncope in adolescents following the release of Gardasil, Menactra and Tdap, although only Gardasil had a label warning that recipients be observed for 15 minutes after vaccination. ACIP has published a recommendation that patients should be seated or lying down when inoculated, observed seated or lying down for 15 minutes after inoculation, and should be observed until all symptoms resolve after an episode of syncope.

There have only been seven claims filed alleging injury from syncope. Four claims were filed for injury after Gardasil alone, two for Gardasil plus Menactra, and one for influenza vaccine. Onset was within 15 minutes, all were female aged 16 to 19. Dr. Ryan added that there are a number of articles about vaccination and syncope and that the incidence of injurious syncope could be dramatically reduced by following the warning included in those articles. He added that, although there is only one vaccine with a label warning. Menactra may be too new to the market to have accumulated sufficient evidence to prompt the manufacturer to add the warning. There was a brief discussion about the logistical implications of following the advice for preventing syncope injuries, including the facts that clinics may not have sufficient

space to allow every recipient to lie down for 15 minutes and may not have sufficient staff to observe the recipients for the recommended time.

General Discussion

In response to a question for clarification on the 2,500 claim awards since the inception of the program, Dr. Evans explained that there were about 4,000 cases filed for injuries before 1988. When the program began on October 1, 1988, two types of claims were filed – one for vaccines administered up until that date, and one for vaccines administered after that date. There was no statute of limitations on pre-1988 claims, but there was a deadline for filing, at which time about 4,200 claims had been filed. It took 14 years to adjudicate all of those claims, not all of which received awards. Of the 2,500 awards since the beginning of the program a significant proportion came from the pre-1988 claims. Dr. Evans indicated that it was not feasible because of limited resources to go through all of those cases to identify those that might contribute to an analysis of a particular adverse event. In addition, there are legal impediments to contacting the individuals involved.

Dr. Johann-Liang commented that there is activity, within the limits of resources, to gather some data on selected cases of, for example, encephalopathy, and conduct a study similar to the two presented on SIRVA and anaphylaxis. However, the condition must be shown to relate to vaccine safety. In addition, such a study may require a case approach rather than an aggregate approach, which involves institutional review boards, protection of human subjects, confidentiality of personally identifiable information and so on. In the VICP that means contacting the petitioner's attorney, who may or may not encourage the petitioner to respond. Dr. Johann-Liang suggested that it may require a statute to facilitate such a process, to identify cases that should be available for a research project. Ms. Williams noted that the DVIC is not really in the business of conducting extensive general research on conditions related to vaccine adverse events. She agreed that it was appropriate to conduct the kinds of limited research described by Dr. Johann-Liang in response to a question that the Commission members may present. Dr. Johann-Liang agreed, noting that there are collaborations with larger research entities, like Children's Hospital and Johns Hopkins University, that may contribute to the body of knowledge. She reiterated her suggestion that the whole process would be improved if there were a statutory way to inform parents about opportunities in the medical research community pertaining to the child's vaccine injury.

Ms. Gallagher proposed that the ACCV establish a workgroup to evaluate these ideas. Ms. Williams agreed to chair the committee, and Ms. Hoiberg, Mr. King, Ms. Pron and Ms. Drew agreed to serve on the committee. Dr. Evans suggested that the description of the committee charge should include "use of clinical information after claims review."

Future Agenda Items

Ms. Gallagher announced that Ms. Drew would chair the next meeting, at which time a new chair and vice chair would be selected. She invited volunteers to be on the agenda committee for that meeting and Dr. Herr, Ms. Hoiberg and Ms. Drew agreed to serve. Ms. Gallagher commented that one suggestion had been made to include a presentation on the increased level of the awards, and Ms. Williams suggested that some information about private sector and academic institution research would be helpful.

Public Comment

Ms. Gallagher invited comments from the public participants at the meeting or on the teleconference. There were no requests to comment.

Adjournment

There being no other business, on motion duly made and seconded, the meeting was adjourned by consensus at 10:50 a.m.

_____	_____
Charlene Gallagher, ACCV Chair	Sherry K. Drew, ACCV Vice-Chair
_____	_____
Geoffrey Evans, M.D. Executive Secretary, ACCV	Date