Advisory Commission on Childhood Vaccines (ACCV)
Meeting and Conference Call

March 9, 2006

Minutes

Members Present

Don L. Wilber, M.D., Chair
Suzanne H. Vaughn, Vice-Chair, via conference call
Robert P. Fuller, M.D., via conference call
Loren G. Cooper, J.D
Jaime Deville, M.D., via conference call
William P. Glass, Jr., J.D.
Robin Stavola
Marguerite E. Willner

Ex-Officio Members Present

Marion Gruber, Ph.D. for
Norman Baylor, Ph.D., Center for Biologics and Evaluation Research, Food and Drug Administration (FDA)
Robert L. Davis, M.D., M.P.H., Director, Immunization Safety Office, Centers for Disease Control and Prevention (CDC)
Barbara Mulach, Ph.D., for
Carole Heilman, Ph.D./National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) (via conference call)

Executive Secretary

Geoffrey Evans, M.D., Director, Division of Vaccine Injury Compensation (DVIC), Healthcare Systems Bureau (HSB), Health Resources and Services Administration (HRSA)

Staff Liaison

Cheryl Lee, DVIC, HSB, HRSA

Introduction

Dr. Don Wilber convened the 63rd quarterly meeting of the Advisory Commission of Childhood Vaccines (ACCV) and welcomed all participants. The minutes of the September 14 and December 12, 2005 meetings were approved.

Report from the Division of Vaccine Injury Compensation (DVIC): Geoffrey Evans, M.D., Acting Director

Dr. Evans welcomed Dr. Robert Davis to the ACCV as the new Centers for Disease Control and Prevention's (CDC) ex-officio member. He has replaced Dr. Frank DeStefano as Director, Immunization Safety Office, Office of the Chief Science Officer. Previously, Dr. Davis served as an Epidemic Intelligence Service Officer with CDC, and as an epidemiologist with the state of Washington's Department of Health. While serving on the Group Health Cooperative in Seattle, he was one of the original project officers for the Large-Linked Database project, which is currently called the Vaccine Safety Datalink. He is an acknowledged leader in the field of immunization safety.

Dr. Evans reported that the National Vaccine Injury Compensation Program (VICP) Post-1988 Statistical Report has been changed based on feedback from the public. The Awards Paid section has been changed to report separate totals for petitioners'awards and attorneys' fees for compensable cases. Previously, this section incorporated attorneys fees and costs into the petitioners' award total. More footnotes have been included in the new report to aid in understanding the new format.

The VICP's Claims Filed and Compensated or Dismissed by Vaccine Report has also been changed. The new format consolidates data on the number of claims filed for injuries and deaths and the number of claims compensated and dismissed by vaccine as reported by petitioners. Previously, this information was provided in two separate reports. Hopefully, this change will make it more user-friendly. Footnotes have been provided to explain the changes.

Dr. Evans provided program statistics from the March 8 Monthly Statistics Report. Currently, the trend of autism filings has continued to decrease, and the non-autism claims have increased slightly from 180 to 190. This is likely due to the addition of influenza vaccines to the VICP, which became effective on July 1, 2005.

The average award paid for Fiscal Years (FY) 1990 – 2006 is approximately $61 million for petitioners, and $4 million annually for attorneys fees and costs. As of December 31, 2005, the balance in the Vaccine Injury Trust Fund (Trust Fund) was over $2.2 billion. Currently in FY 2006, the Trust Fund has received approximately $35 million in revenue, of which $15 million was excise tax collections, and $20 million in interest.

Dr. Evans reported on the recent approval of a vaccine license this year. On February 3, the Food and Drug Administration approved a new live oral rotavirus vaccine that will be administered to infants in a three dose series between the ages of 6 to 32 weeks. RotaTeq ® is the trade name, and is manufactured by Merck. Rotavirus infection is the leading cause of diarrhea in infants and young children causing about 20 – 60 deaths per year in the U.S. A previous rotavirus product, Rotashield®, was withdrawn from the U.S. market in 1999, due to cases of intussusception found associated with the vaccine. There is no

indication that this adverse event is associated with Rotateq after being confirmed by the largest clinical trial leading up to vaccine licensure in many years.

As a general category, rotavirus vaccines are already covered under the VICP under category XI with no corresponding injury or condition specified. On the Vaccine Injury Table (Table) there is a second category XII for the live oral rhesus-based rotavirus vaccine, Rotashield, with the corresponding injury of intussusception.

HRSA has revised the VICP website to make it more user-friendly. The new website address is http://www.hrsa.gov/vaccinecompensation. The old website address, www.hrsa.gov/osp/vicp, will also allow access to the updated website.

Dr. Evans reported on meetings attended by DVIC staff. On February 21-22, he represented HRSA as an ex-officio member at CDC's Advisory Committee on Immunization Practices (ACIP) meeting in Atlanta. The ACIP endorsed universal immunization of U.S. infants with the newly licensed oral rotavirus vaccine, Rotateq. In addition, they unanimously recommended the expansion of the routine use of influenza vaccines in children from 6 to 23 months to 6 to 59 months of age. Household contacts of children up to age 5 years are included in this recommendation.

Several ACIP members expressed strong support for approving a recommendation that influenza vaccine be given to healthy individuals of all ages. There are programmatic, logistical, financial, and other factors at this time that make this change unfeasible. However, language is included in the current recommendation that a strategy of universal influenza immunization vaccination be evaluated by ACIP in the future.

Dr. Evans provided additional information on adding vaccines to the Table. When a new vaccine is added to the Table, there is a two-year window in which to file a claim for injuries that occurred up to eight years before the effective date of coverage for the newly added vaccine. When hepatitis B vaccine was added to the VICP in 1997, nearly 350 claims were filed in 1999. Since the influenza vaccine will be given to larger numbers of people, it is expected that many more influenza claims could be filed with the VICP. The filing deadline is July 1, 2007.

On February 21-22, Dr. Robert Weibel served as the HRSA representative to the National Institutes of Health's Autoimmune Diseases Coordinating Committee at the Conference on Developing New Standards of Autoantibody Measurement at the National Institute of Standards and Technology in Gaithersburg, Maryland. The conference reviewed current assays for determining rheumatic and vascular diseases and auto-antibodies for diabetes mellitus, cancer, cardiovascular and celiac disease. The goal of the conference was to establish new standards for measuring autoantibodies for prevention, diagnosis and treatment of these diseases.

Update on the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Activities: Barbara Mulach, Ph.D.

Last fall, NIAID completed the H5N1 avian influenza vaccine study, which involved evaluating the vaccine in healthy adults. At the end of March, the results of this study will be published in the *New England Journal of Medicine.* (http://content.nejm.org/http://content.nejm.org/cgi/content/abstract/354/13/1343)

NIAID has also been involved in the avian influenza vaccination studies on healthy elderly and children to get preliminary data on the immunogenicity and safety of this vaccination for these populations.

This week, several clinical trials of this vaccine with and without different adjuvants are beginning in order to determine if there is a way to boost the immune response and the ability to extend the vaccine as much as possible. Recruitment for these trials is underway at several sites, including the University of Maryland. More information on the trials can be viewed at http://clinicaltrials.gov/

Report from the Department of Justice (DOJ): Vincent Matonoski, J.D., Acting Deputy Director for the Torts Branch, Civil Division

Staffing and Hiring

Mr. Matanoski noted that Deputy Director Mark Rogers remains on active duty with the Marine Corps, in Africa. He announced that the Office of Vaccine Litigation has recently hired two attorneys, who will replace two attorneys who left the office in August 2005. One is already onboard and the other attorney should be entering on duty in April or May 2006. These new hires are important to the office because the Court of Federal Claims (CFC) has hired three new special masters, which will increase that office's ability to handle cases by about 40 percent. The Department of Justice (DOJ) wants to make sure that the office has resources available so that cases can continue to move quickly through the system.

Litigation

Autism

DOJ continues to see a trend downward in the number of autism cases filed. It is anticipated that there will be less than 20 cases filed per month by the end of this Fiscal Year (FY). There were 42 autism cases filed between December 1, 2005 and February 28, 2006. This is out of a total of 75 cases filed during the aforesaid period. Approximately 4700 autism cases have been filed in the Program.

Petitioners' interests in the Omnibus Autism Proceeding are represented by a steering committee of several attorneys. The committee has filed a brief in which it has been

requested that petitioners be allowed until the end of 2006 before being required to put on their cases.

In January 2006, the steering committee presented a preliminary list of 15 potential experts they may use to assist them in proving causation. These experts come from a variety of fields, including epidemiology, biostatistics, chemistry, and pediatrics. The committee has indicated that the number of experts may be increased or decreased.

Influenza vaccine

There were 8 influenza (flu) vaccine cases filed between December 1, 2005 and February 28, 2006. A slight increase in the number of flu vaccine-related cases is being seen, but it is expected that the bulk of such cases will be filed in July 2007, two years from the date the flu vaccine was added to the Vaccine Injury Table.

Other case activity

Of the remaining cases filed during the above time period, four were hepatitis B vaccine-related cases and 25 were related to other vaccines. There were 39 dispositions of cases during this period, and 15 of those resulted in decisions finding petitioners entitled to compensation. In 4 of those cases, respondent had contested petitioners' entitlement to compensation, but the court found entitlement anyway. In the remaining 11 cases, the disposition resulted from either a stipulation of settlement, or a proffer by respondent of an award of compensation, or a concession of entitlement by respondent. Twenty-four cases were dismissed without compensation. The bases for the dismissals varied. Many of them occurred because petitioners requested that the special master decide the case on the record as it stands. In most of those instances, petitioners felt that they did not have enough evidence to go forward and obtain compensation, but they wanted a decision nevertheless – the petitioners understood that the decision was probably going to result in decision against them, but they preferred to have the decided at that time, rather than continue further with the litigation of their claim.

Appeals

During the aforesaid period, there were 8 appellate decisions in the CFC. Five of these decisions were in cases that had been dismissed by the special master, and these dismissals were affirmed by the CFC. In the three other appeals, the CFC reversed the special master's dismissals of the cases and remanded the cases to the special master for further findings in light of the CFC's decision.

Settlements

Many vaccine cases are resolved through mutually agreed upon settlements. In FY 2006, there have been 18 settlements. There are 13 settlements currently pending final approval. In every case settled, the 15-week time frame established for finalizing

settlements and sending a stipulation to the petitioner has been met, which is good news for everyone concerned.

Vaccine Safety Datalink (VSD)

Pursuant to an agreement between petitioners' counsel in the autism cases and respondent, petitioners have been given permission to look at certain VSD data concerning the Thimerosal Screening Analysis. This data is resident in the Research Data Center in Greenbelt, Maryland, and is handled by the National Center for Health Statistics. Petitioners have identified 2 experts who will perform the research on this data. The research will not be done until petitioners and their experts sign an agreement not to disclose any personal information found during the research.

In January 2006, several petitioners' counsel met with members of CDC, including Dr. Robert Davis and Dr. Tanya Popovich, the Associate Director for Science at the CDC, both of whom have experience with and are knowledgeable about the VSD. They presented a great deal of information about how the VSD works, the type of information it contains, and how quickly it can be used to do research. Mr. Matanoski feels that the conclusion to be reached based on the information presented at the meeting is that the VSD is not a "real time" research tool – one cannot use the VSD to pose a scientific question and receive an answer in a short period of time. Rather, it would take several years to get an answer using the VSD as a research tool. The VSD is not something that is feasible for a petitioner under the Act to use to get evidence to support a case that already has been filed and which is subject to statutory deadlines.

The VSD can be used to set a research agenda by determining the types of research questions that may be posed to the VSD. Information gleaned from Vaccine Act cases and the kinds of questions that are coming up in vaccine cases would be funneled into the decision-making process in setting the research agenda. This could be another piece of information that those who are setting the research agenda could consider in deciding which questions to put to the VSD data. While the VSD will not give an answer for a case that is currently pending, it could give answers out into the future.

Snyder v. HHS

The CFC decision in Snyder has the potential to affect the litigation of vaccine cases. In that case, petitioner's medical records contained entries noting a potential vaccine association with an injury. Petitioner went forward with the case without presenting any medical expert evidence. Respondent did present a medical expert to address petitioner's claim. The special master found that petitioner had not proven that the vaccine caused her alleged injury and dismissed the case. On appeal to the CFC, the judge found that the medical record entries were more compelling to him than was the expert opinion of the respondent. This is a very unusual decision, in that an appellate judge does not normally step in and do his or her own fact finding. The decision will affect respondent's litigation of other vaccine cases because medical records are often seen which contain conclusory

assertions of a connection to a vaccine for a patient's illness or condition. Sometimes these assertions are based on a temporal association alone. The petitioner may come in and say to the treating physician, "I was injured by rubella vaccine," and the physician writes this statement in his records. That is what happened in Snyder. In the past, it has been left up to the special master to consider such entries and determine whether they should be given any weight.

Based on the weight given, such entries by the CFC judge in Snyder, respondent may be compelled to look behind medical record entries and investigate them by deposing or interviewing the individual who made the notation to determine the basis for it. Did the person really believe that the vaccine caused the problem or were they noting something based solely on the patient's report? Was the association based solely on the temporal relationship or was there some other reason? Was there a clinical sign or reason that was thought to be compelling in that particular case? Respondent may be forced to investigate such entries in the medical records to ensure that they are not misinterpreted, either by the parties or the court. One of the ways that Snyder has already affected the litigation of vaccine cases is that recently, a petitioner's attorney who was under a court order to provide an expert opinion to support a petitioner's claim, instead filed a report stating that he was going to rely solely on petitioner's medical records, and would not be providing an expert opinion in the case, citing Snyder. It remains to be seen how the litigation of vaccine cases will be affected by the Snyder decision, given that it just came down in early February 2006, but Mr. Matanoski wanted to make the ACCV aware of the potential effect.

Capizzano v. HHS

The Federal Circuit has not issued its decision yet in Capizzano. The case was argued in the beginning of November 2005. Dr. Evans asked Mr. Matanoski to discuss the significance of the case, in light of the Circuit's decision in Althen. Mr. Matanoski explained that Althen did not, in respondent's view, change the actual causation standards under the Vaccine Act. In fact, it could not change those standards because a panel sitting alone cannot change the existing precedent of the Circuit. That would require an *en banc* decision. If the language of Althen is parsed, one can see that the standard articulated in that decision is word-for-word the standard that was used in Grant v. HHS, which was a 1992 Federal Circuit decision that set the standard for actual causation cases. Althen reiterated that standard.

What has been taken away from Althen is perhaps something read between the lines of the holding based on comments in the decision. There are comments such as "close calls go to petitioner." That seems to have been interpreted to mean that the standard of causation may have eased a bit for petitioners. Clearly the standard that was articulated is the same one that has been in place for 14 years. Also, by saying that "close cases go to the petitioner" the Circuit cannot mean that petitioners can meet their burden of proof by less than a preponderance of the evidence, which is the legally applicable standard in causation in fact cases filed under the Act.

Capizzano involved the dismissal of a petition because the special master found that petitioner failed to meet her burden of proving causation in fact. It was decided before the Circuit's decision in Althen, but after the CFC's decision in that case, which struck down the so called "Stevens standard." The special master did not use that standard in deciding Capizzano.

In respondent's view, the decision in Capizzano determined whether or not petitioner had satisfied her burden of proving causation in fact by applying the precedent set in Grant, and so it should not be disturbed in light of Althen. The result would not have been any different if Althen had been decided before the decision was made in Capizzano. Mr. Matanoski believes that the decision ought to withstand scrutiny at the appellate level, but it remains to be seen how the Circuit will decide the case.

Vaccine Injury Compensation Programs Worldwide: Geoffrey Evans, M.D.

Dr. Evans provided information on worldwide vaccine injury compensation programs. His research began by individually surveying existing vaccine injury compensation programs in preparation for a VICP-sponsored workshop held in 2000. Managers from over a dozen programs in Canada, Western Europe and Asia attended the 2-day workshop in Washington. Survey results were presented the following year at the European Vaccine Manufacturer's Association in Brighton, UK. More recently, Dr. Evans contacted each of the programs to update the 2000 survey information. This updated information was presented in November 2005 at the 3rd Congress of the Asociacion Espanola de Vacunologia in Madrid. One additional program, Finland, came to his attention while obtaining the new data. Today's presentation mirrors what was presented at the Madrid meeting.

There are many similarities and differences in the various programs. They came about because of important public policy questions. First, what do you do when there are victims of unpredictable reactions to properly manufactured and administered vaccines? Second, who is responsible for compensating people who experience vaccine injuries? Should they be compensated? If so, who should pay for it? Should it be the vaccine company who may have manufactured the product correctly, but unanticipated the adverse effects of product, or the government who is responsible for protecting public health, or other sources (private health insurance or excise tax on vaccines)?

In the U.S., medical injuries and malpractice claims were handled in the civil tort system where negligence needs to be proven. Either the product was inadequately made, or it was administered negligently, or the patient was not warned of the possible side effects. However, the problem arises when there is no fault on the part of the manufacturer or the administrator.

Historically, outside the U.S., adult victims were commonly covered in most industrial accident programs which did not contain coverage for disability compensation. Children,

however, were not covered under these programs, and there was no compensation for severe disabilities, loss of future earnings, and permanent injury or death.

Dr. Evans provided information on 14 vaccine injury compensation programs in other countries which were detailed by category in a 2-page table handout. In 1953, the German Supreme Court ruled that people who were injured by compulsory vaccine (at that time it was smallpox vaccine) were entitled to compensation. In 1960, Germany and France were providing compensation for the vaccine injured. In the 1970s, the following countries established compensation programs due to DTP vaccine concerns: Japan, Switzerland, Denmark, New Zealand, Sweden, and United Kingdom. In the 1980s, Finland, Quebec, United States, and Taiwan started compensation programs, and in 1990, Italy and Norway formed programs.

The reasons for the enactment of compensation programs varied. Basically, programs were created because people believed that the government had a responsibility to compensate those who were injured by vaccines. Another reason these programs were created was that injuries caused by vaccines are unique and should be dealt with separately from other types of injuries (i.e., from industrial accident injuries). In the U.S., Japan, and the U.K., concerns over injuries from the DTP vaccines resulted in public pressure to create a compensation program. Other reasons included trying to avoid costly trials, and providing more consistency in liability law outcomes and compensation. In Italy and some other countries, the medical community pressured the government to create a compensation program.

All countries, except Sweden and Finland, were enacted through administration on the national level. Germany and Switzerland enacted their programs on the state level which is responsible for determining eligibility in compensation outcome decisions, and deciding which vaccines are recommended for use. Japan enacted their program on a state and local level. New Zealand has a compensation system that requires its citizens to participate and give up their rights to sue for injuries, whether from drugs, vaccines, or other products or services. Participation in this program is mandatory. Individuals in high-risk professions pay more to the "Accident Rehabilitation and Compensation Insurance Corporation," which is setup as a quasi-governmental private enterprise.

Sweden's compensation program called the "Pharmaceutical Insurance" started in 1978 by companies marketing pharmaceutical products. Compensation is not decided under their judicial system. Finland has a program similar to Sweden. Denmark switched to a private insurance system in 2004.

The eligibility criteria for the compensation programs varies from country to country. The criteria reflects the specific needs and vaccine recommendations found in these countries. Most countries specify the type of vaccines that are given, whether it is compulsory, recommended, or voluntary; the date of vaccination, injury, or filing of the claim; and the type and severity of the continued effects of the injury. Some specify the setting where the vaccine is given, such as public, clinic, doctor's office, type of employment of healthcare worker, and citizen requirements.

The vaccines covered in these programs are usually recommended for routine use. Few countries have compulsory immunization. Most of the compensation programs covered vaccines given to children or those who are required to get vaccines for certain occupations and travel. France provides coverage for specific vaccines required for healthcare workers and health profession students. In Italy, persons who received the typhoid vaccine for professional reasons, and who traveled outside the country became eligible for compensation due to the 1992 legislation enacted which covered contaminated blood products.

In the U.S., there are no Federal vaccination mandates. There are 50 different state laws and nearly all of the 14 vaccines covered under the VICP are mandated in these states.

Some of the countries have different filing deadlines and limit coverage to a certain time period. In the U.K., claims could at one point be filed for injuries dating back to 1948. In the U.S., a pertussis vaccine claim was filed with the VICP dating back to 1918. There were also cases filed from vaccines administered in the 1930s and 1940s. Japan and Norway have no time limits for filing, and Germany's deadlines are determined by their Cantons.

In terms of compensable injuries, most countries are not very specific other than the U.S. In Taiwan, they used the U.S. Vaccine Injury Table to compensate injuries until two years ago. Currently, they require that the injury have a certain level of severity and have lasting effects. Often the decision to compensate is based on temporal association as well as current knowledge of vaccine reactions.

In most countries, claims are usually filed with the administrative entity at the national level and eligibility for compensation is determined at the same level. Decisions about compensation are done through an administrative process using internal reviews with some outside consultants. Some countries employ more formal evaluations bodies consisting of health and legal professionals as prescribed by law to evaluate their claims. In Quebec, the process for reviewing a claim consists of each party choosing a physician who will support their causation theories, and then both of these physicians choose a third physician in order to obtain a majority vote.

Most programs do offer flexibility in making causation decisions. Other than that, Dr. Evans was not able to determine more precisely the criteria upon which these decisions are made. Usually, if there is a suggestion in the literature of some significance and there is a reasonable temporal association, causation will be determined in favor of the injured party. Many of the western European countries have very different healthcare systems than in the U.S. Many have universal health insurance that covers people from when they are born until they die.

All programs allow claimants the right to appeal decisions against compensation. Almost all provide four categories of basic compensation similar to the benefits listed under industrial accident programs. The U.K. is the exception and has a provision for tax free

lump sum payment of 100,000 pounds to ease the present and future burdens of those suffering from vaccine damage and their families. The types of benefits covered by most programs include: (1) medical costs for laboratory testing, therapy, hospital care; (2) disability pensions that can be based on lost earnings and long-term care costs, or based on the severity of the injury; (3) lost earnings for adults to care for a disabled child; and (4) damages for pain and suffering.

France is very specific about compensation for emotional distress and loss of consortium. Other programs provide additional benefits based on the severity of the injury and degree of inconvenience and discomfort. They all provide some type of death benefit, either for the family to pay funeral costs or for loss of income. Germany and Denmark apply provisions of their industrial injury pension laws to vaccine injury victims. Some countries also allow individuals to supplement payments obtained from other forms of social assistance, while others disallow such practices. Japan allows an individual to obtain both government and social assistance benefits and private insurance if available. In the U.S., individuals are compensated for unreimbursed expenses.

The funding sources for vaccine injury compensation programs differ among countries. About half are funded from the national treasuries. Private insurance provides funding for programs in Sweden, Finland, and Denmark. Some programs are funded by vaccine manufacturers.

Most of these programs allow the filing of civil actions in addition to obtaining compensation. However, some programs preclude individuals from obtaining benefits from both systems or reduce the amount of benefits obtained through civil action by the amount of benefits received under governmental programs. Denmark, Germany, U.K., and Switzerland do not allow civil suits to be filed.

There is great variability in the number of claims filed. In the U.K. and Japan, public awareness was high and affected the number of claims filed. The data from Japan reflects an increase in claims due to more public awareness and the Urabe mumps vaccine causing cases of aseptic meningitis, which has lead to a significant percentage in compensation. Other factors affected the number of claims filed including population size, numbers of vaccines administered, the types of injuries covered, and the willingness of the public to utilize government programs versus other options.

Dr. Evans concluded that vaccine injury compensation programs outside of the U.S. are working well, but there is not much awareness of their existence. All exist solely in industrialized countries. The Pan American Health Organization has expressed interest in creating compensation programs for developing countries. However, in order to have a compensation program, a country must be able to afford to buy vaccines.

Update from the National Vaccine Program Office (NVPO) and the Interagency Vaccine: Kenneth Bart, M.D., M.P.H., Consultant

Dr. Bart submitted the following summary after the ACCV Meeting.

Advisory Committee on Immunization Practices (ACIP)

On February 21-22, the ACIP conducted their meeting in Atlanta, Georgia. Agenda items that were discussed included general recommendations on immunization, the status of Tdap vaccine recommendations, the status of human papillomavirus vaccine, recommendations for the rotavirus vaccine, and influenza activities. Hepatitis B vaccine recommendations were published in the Morbidity and Mortality Weekly Report on December 25, 2005. Major updates to the recommendation include implementation of universal vaccination of newborns before hospital discharge, and vaccination of children and adolescents who were not previously vaccinated.

National Vaccine Advisory Committee (NVAC)

On February 7-8, NVAC met and presentations were made by CDC and FDA staff on the supply and demand of influenza vaccine, vaccine safety, and vaccine financing. Helen Darling, President, National Business Group on Health made a presentation on immunization coverage and insurance coverage for vaccination. Harry Hull, an epidemiologist with the State of Minnesota provided a talk about the recent polio outbreak among unvaccinated populations. Dr. Robert Davis, Director of the Immunization Safety Office at the CDC, spoke about vaccine safety and the prevention of adverse events and how genomic medicine could change the way in which medical professionals and the public evaluate the safety of vaccines. The genomic approach to vaccine safety determination is modeled on the method utilized by pharmaceutical manufacturers in identifying predisposing genetic factors that could be exacerbated by the use of a particular medication. John Agwunobi, Assistant Secretary of Health, HHS spoke about the increasing burden of vaccine financing and discussed strategies with ACIP. The Subcommittee on Safety heard a presentation from the National Institutes of Allergy and Infectious Diseases on current research to identify nucleotide polymorphisms that could predispose a vaccine recipient to an adverse event.

Cost Effectiveness of Vaccine

An economic evaluation of the impact of seven vaccines (DTap, Td, Hib, polio, MMR, hepatitis B, and varicella) routinely given as part of the childhood immunization schedule found that vaccines are very cost effective. Routine childhood vaccination with these seven vaccines, which prevent over 14 million cases of disease and over 35,500 deaths over the lifetime of children born in any given year, resulted in annual cost saving of $10 billion in direct medical costs and over $40 billion in indirect societal costs. (Published in the *Archives of Pediatric and Adolescent Medicine* in December 2005).

Vaccine Liability 50 years After the Cutter Incident: Paul A. Offit, M.D.

Dr. Paul Offit is a virologist in the Division of Infectious Diseases, Children's Hospital of Philadelphia, University of Pennsylvania, School of Medicine. He provided a discussion of his book entitled, “The Cutter Incident: How America’s First Polio Vaccine Led to the Growing Vaccine Crisis.”

In the 1940's and 1950's, polio disease was a highly contagious and occasionally fatal disease. In 1952, 58,000 cases of polio were reported, and 65 percent of these cases occurred in children between 5 and 9 years of age. The polio virus affected the central nervous system, specifically the cells that are responsible for the motion in the enervating muscles. Usually, children became paralyzed in their legs, and occasionally, it caused paralysis in their arms. The virus also affected the cranial nerves that are necessary for breathing. Children who experienced breathing problems from this condition were place in iron lungs, which were negative pressure ventilators. They typically died from aspiration pneumonia. As a consequence, there was a tremendous amount of public and private interest to develop a vaccine to prevent polio.

Jonas Salk, M.D. developed the first polio vaccine based on research done by John Enders of Harvard University. He grew the polio virus in monkey kidney cells, and then purified it using formaldehyde. Hence, the vaccine was referred to as the formaldehyde-inactivated polio vaccine. In Dr. Salk's theory of inactivation, he reasoned that there were a million of infectious particles per dose, which is per milliliter. He found that if a million particles were treated with formaldehyde at a certain acidity level at a certain temperature, then over 3 days, the amount of infectivity would be reduced from a million infectious particles to one infectious particle. He thought that if you treated the virus with formaldehyde for another three days, there would be another million fold reduction in the virus leading to only one infectious particle per million milliliters. If you treated the virus for another 3 days there would be one infectious particle per trillion milliliters resulting in complete inactivation of the virus.

With the help of Eli Lilly and Parke-Davis, in 1954, a polio vaccine was created for a large clinical trial that was headed by Thomas Francis, University of Michigan. Three doses of vaccine were given to 420,000 children, and 200,000 children were inoculated with placebo, and 1.2 million children served as observed, uninoculated controls. This was the largest clinical trial of a vaccine ever performed. About 1.8 million children participated in the trial. The polio vaccine proved to be effective. However, it was not effective against type one polio virus because the Federal government at the time required a substance called merthiolate (currently called thimerosal) to be added to the vaccine. Merthiolate destroyed type one virus and made it less effective against the virus.

On April 12, 1955, the Salk vaccine was released, and merthiolate was removed from the vaccine. At that time, the Laboratory of Biologists Control within the National Institutes of Health (NIH) was responsible for the release of vaccines. The following vaccine companies distributed the Salk vaccine: Eli Lily, Parke-Davis, Wyeth, Pitman-Moore, and Cutter. The polio vaccines were released and never tested pre-licensure.

On April 28, 1955, the *New York Times* published an article entitled, "One Firm's Vaccine Barred; 6 Polio Cases Are Studied." This article discussed polio cases that involved paralysis which occurred in the arm that was inoculated within two weeks of receiving this vaccine. All of the cases occurred following inoculation with the vaccine from one company. This vaccine was made at the Cutter Laboratories in Berkeley, CA.

A study by Neal Nathanson, was published in the *American Journal of Hygiene*, examined eight lots of polio vaccine that were released by Cutter Laboratories and found that two of the lots were high-risk and the instance of paralysis following the administration of this vaccine was about eight fold greater than in other lots.

In Idaho, polio vaccines were made available free of charge to all first and second graders by the National Foundation for Infantile Paralysis who funded the 1.8 million children clinical trial and is currently known as the March of Dimes. Thirty-two thousand school children were immunized in two weeks, and 20 children were paralyzed, and 3 were killed by the Cutter vaccine.

Dr. Manley Shaw, an orthopedic surgeon, provided retrospective examination of medical records and conducted interviews with parents of 425 children who received the Cutter vaccine in Boise, Lewiston and Pocatello, Idaho. Thirty-two percent of the children had symptoms of abortive polio (i.e., headaches, stiff neck and back, residual paralysis), which is roughly the rate of abortive polio that occurs after natural infection. Therefore, it is likely that every dose in the two high risks lots administered in Idaho contained live polio virus. About 120,000 children were inoculated with the vaccine that contained the live polio virus, because these children excreted the virus in their stools resulting in another 100,000 family members and community contacts being infected. At least 70,000 developed abortive polio; at least 164 people were permanently paralyzed, and 10 people were killed by the vaccine.

Within 3 months, investigators determined that the problem with the Cutter virus was caused by the filtration method used to separate the cells from the virus. The polio virus and cell debris would come through a tube and then Cutter would try to filter out the cell debris in the porous glass. The filtered virus would come out of another tube. In this case, the filtration was not good enough and some dead cells or cell debris actually ended up in the final preparation before it was treated with formaldehyde. Then, the polio virus particles hid within that cell debris and was not accessible to the killing effects of formaldehyde. Some of the dead polio cells were found in the final vaccine batch, and were not effected by or killed by the formaldehyde process.

In essence, Dr. Salk's theory of straight line inactivation that was based on studies used in his laboratory did not come true in practice. It is possible that the line did not remain straight, but that it curved up toward the baseline. There were some good things that resulted from this medical tragedy. Second, the safety tests on vaccines were improved. Better test results revealed whether there was live virus in the vaccine, and there were better filtration requirements.

The first was the birth of vaccine regulation in the U.S. Vaccine regulation within NIH moved from the Laboratory of Biologics Control to the Division of Biologics Standards. The number of professional regulators increased from 10 part-time to 150 full-time people. In the early 1970s, the control of the vaccine regulation was transferred from NIH to the FDA, at the Centers for Biologics Evaluation and Research.

One of the first assignments of the Epidemic Intelligence Service (EIS), CDC was the first national response to the medical emergency resulting from the Cutter incident, which gave tremendous credibility to the EIS. As a result, more funds were quickly garnered to the CDC.

In 1955, the Salk vaccine was released in the U.S. and uptake was very slow. The immunization rate was only about 40 percent because the U.S. was not very good at immunizing its citizens and of fear resulting from the Cutter incident. Nevertheless, the Salk vaccine reduced the number of cases of polio during the years it was used. The Salk vaccine was replaced by Sabin's oral polio vaccine which was a live, weakened form of the virus itself and caused people to get polio in rare instances. Therefore, in 1998, the U.S. switched to a fully inactivated polio vaccine schedule.

Anne Gottsdanker was five and a half years old when she was paralyzed after receiving the Cutter polio vaccine. Her mother, Josephine Gottsdanker, sued Cutter Laboratories for damages caused by their vaccine. The attorney who handled her case was Melvin Belli, probably the most famous tort attorney at the time. Mr. Belli sued Cutter for negligence because they failed to exercise ordinary care in manufacturing that vaccine. He also sued them for breach of an implied warranty because it was implied that a vaccine designed to prevent paralysis shouldn't have caused paralysis.

The jury in the Gottsdanker case was provided with information that Cutter Laboratories was not the only vaccine company experiencing problems inactivating the virus. Records provided in the case through the Freedom of Information Act revealed that the following vaccine companies had live virus in their vaccines when they thought they had fully inactivated the virus: Eli Lilly, Parke-Davis, Wyeth, and Pitman-Moore. Eli Lilly and Parke-Davis were the biggest companies, and it took them a while to figure out a way to inactivate the virus in the vaccine. The other companies (Wyeth, Pitman-Moore, and Cutter) were smaller companies.

Wyeth's polio vaccine also caused more cases of polio than expected in the normal population. A study written by Neal Nathanson, Alexander Lang, and Bill Jackson at CDC, called "An Epidemiological Analysis of the Occurrence of Poliomyelitis in Association with Certain Lots of Wyeth Vaccine," was never published. Wyeth made a lot of vaccine – lot 236 – that caused paralysis and the death of at least one child in Buck's County, PA. For this reason lot 236 was quietly withdrawn from the market.

On April 28, 1955, Cutter withdrew all of its polio vaccines from the market. A couple of weeks later all polio vaccines were withdrawn and more re-tested based on more sensitive tests. However, Wyeth's vaccine lot #236 continued to be withdrawn from the market, even after the other vaccines were returned.

In the case of Gottsdanker v. Cutter Laboratories, the jury found Cutter not guilty of negligence, but guilty of breech of implied warranty. The jury based their verdict on the view that in the process of medical advances, especially commercial scale manufacturer,

there is expected to be trial and error in creating a safe vaccine. The rationale was that Cutter, as well as other vaccine companies were experiencing the same problems with there vaccines. However, the judge in the case stated that if the vaccine was the proximate cause of harm, then you must find Cutter liable for their vaccine.

This case was a precedent for liability without fault or negligence for pharmaceutical companies. This was the first time that liability without fault was extended to a pharmaceutical company. The thought was why Anne Gottsdanker should have to buy insurance to protect her from paralysis caused by polio vaccine. An article was published in the *Yale Law Journal* by Guildo Calabresi. He stated that society will be better off if vaccine companies could be held liable without fault for their products. He reasoned that vaccine companies are in a better position to provide insurance by increasing their price for the vaccine. However, difficult vaccines continued to be developed, tested, and sold. The measles-mumps-rubella vaccine experienced many trials and error before it became a safe vaccine.

In 1974, the Kulenkampff paper was published in the *Archives of Diseases of Children* in London. Thirty-six pertussis vaccine cases were reported, of which 22 cases were children who had received the whole cell pertussis vaccine. They subsequently developed brain damage (mental retardation and seizure disorder). Kulenkampff argued that the whole cell pertussis vaccine could cause permanent brain damage. This caused many lawsuits in the U.S., and the pertussis vaccine was blamed for unexplained coma, Sudden Infant Death Syndrome, Reye Syndrome, retardation, seizure disorders, and paralysis.

The results of the lawsuits caused the price of the pertussis vaccines to increase from .17 cents per dose to $11.00 per dose. The increase was due to the cost of liability. The number of vaccine companies producing pertussis vaccine decreased from eight to one, which was Lederle Laboratories.

In the mid-1980s, the parents of a child, Kevin Toner claimed that the pertussis vaccine caused transverse myelitis, and filed suit against Lederle Laboratories. The jury was responsible for determining causality, and had difficultly doing so because there was no evidence that the pertussis vaccine increased the incidents of transverse myelitis. They ended up awarding the parents of Kevin Toner $1.3 million dollars. At that time, pertussis vaccine business in the U.S. was only $3 million dollars.

In other vaccine cases, juries continued to awarded big settlements against vaccine manufacturers. They determined that the drug, Bendectin, an anti-nausea drug used in the 1950 – 1970's, caused birth defects. Twenty seven studies did not show a causal relation. However, the jury awarded a $4.7 billion dollar settlement. They found that breast implants can cause cardiovascular disease, even though six studies have shown that is does not. In the Fen-phen case, a jury awarded $21 billion, and in the Vioxx case, the award the jury recommended caused Merck to lose about two-thirds of their capitalization.

To assist vaccine companies with liability protection, the Federal government created the "National Childhood Vaccine Injury Act of 1986, as amended." The Vaccine Injury Table was established and it lists injuries/conditions that are presumed to be caused by vaccines. The program is funded by revenues in the Vaccine Injury Trust Fund, which are earned by excise taxes on vaccines.

Dr. Offit explained how several vaccines were taken off the market due to fears from the public that it caused a condition that was not supported by scientific studies. GlaxoSmithKline developed a vaccine to treat Lyme disease. Lyme disease is a bacterial infection that can cause permanent joint, central nervous system, or heart abnormalities. It affects about 23,000 people a year in the U.S. The vaccine contained the outer surface protein of Lyme bacteria.

The Lyme vaccine was tested pre-licensure on 20,000 people who were followed for 2 years. The vaccine was recommended for use in only adolescents and young adults living in high risk areas (New Jersey, Pennsylvania, etc.) who engaged in high risk activities.

There were a number of lawsuits filed against the Lyme vaccine. One lawsuit filed in Philadelphia alleged that the vaccine caused chronic arthritis. There were no pre-licensure studies to support the causal relationship. Tremendous negative publicity about the perception that the vaccine caused chronic arthritis drove the vaccine off the market. Children who acquired Lyme disease would have to endure it since there was no vaccine available to treat the disease. Dr. Offit stated that he feels that this vaccine would be available if it was covered by the VICP.

The Group B Strep vaccine was also removed from the market. Group B Strep disease is a bacterial infection that affects about 2,000 children per year in the U.S. It has caused about 100 deaths. The disease causes meningitis, which is an inflammation of the lining of the brain and spinal cord. It typically attacks children in the first week of life.

In the late 1980s, studies were conducted on Group B Strep by Carol Baker at Baylor University in Houston, Texas. The results of the study revealed that if the complex sugar is stripped from the Group B strep, the level of antibodies in the serum could be transferred from mother to child, therefore, protecting the baby against Group B Strep. A vaccine was never developed.

In conclusion, Dr. Offit expressed concern that the many autism claims being filed in Federal and state court will be decided by juries that will rule in the petitioners favor. He worries that the parents who sue vaccine companies for loss of consortium and medical monitoring may be successful one day. Currently, there are trace amounts of thimerosal in a number of vaccines, and Dr. Offit believes if these claims are successful it would cause vaccines companies to re-formulate their vaccines with even less amounts of thimerosal, which may cause some vaccine manufacturers to go out of business.

Dr. Offit stated that certain vaccines that would protect against diseases are off the market because they are not covered in the VICP. He believes that if someone files a claim in the program, they should not be able to opt out to file a claim in state court.

Public Comment Period: Argument to Amend the VICP to Toll the Statute of Limitations to the Age of Majority for Vaccine Injured Children: Clifford J. Shoemaker, J.D.

Clifford J. Shoemaker, J.D. is an attorney with the law firm of Shoemaker & Associates, Vienna, VA. He has represented a number of individuals filing claims with the VICP over the years. Mr. Shoemaker stated that he is a vaccine advocate, and is in favor of safe and effective vaccines. His sister contracted paralytic polio when she was nine years old, and is in a wheelchair today because there were no vaccines available.
Mr. Shoemaker's vaccine litigation career began during his last year in the Marine Corps in 1977. He represented people injured after receiving the swine flu vaccine.

Mr. Shoemaker feels that the VICP has improved since its inception, and that it should be a model for tort reform. However, he is requesting that the current statute of limitation be amended to allow for tolling to the age of majority for vaccine injured children. Specifically, he is proposing to amend the National Childhood Vaccine Injury Act of 1986, as amended, section 300aa-16(a) (2) to add the following language at the end of the paragraph after the word "injury": "provided, however, that if the injured party is a minor, then the 3-year limitation of actions shall be tolled until the injured party reaches 18 years of age."

Currently, the statute of limitations for filing a claim in the VICP is within three years after the first symptom of the vaccine injury. For a death, a claim must be filed within two years of the death, and four years after the start of the first symptom of the vaccine-related injury from which the death occurred. When a new vaccine is covered by the VICP, or when a new injury/condition is added to the Vaccine Injury Table (Table), claims must be filed within two years from the date the vaccine or injury/condition is added to the Table for injuries or deaths that occurred up to 8 years before the Table change.

Mr. Shoemaker stated that he is recommending that the statute be amended because it is difficult to identify vaccine-related injuries in babies and infants. In some cases it takes years to diagnose a condition where the symptoms may have started years earlier. There are times when the child's doctor specifically tells the parents that an injury is not related to a vaccine, even in cases that are conceded by HHS.

He also stated that children should not be punished for the failure of their parents to bring a claim on their behalf, especially when the parents are often overwhelmed with the job of caring for an injured child. Every state has a tolling provision for minors and the disabled. For instance, Agent Orange and radiation exposure cases have no deadlines for filing a claim.

Mr. Shoemaker mentioned that the goals of the VICP are to prevent civil litigation by providing compensation for all injured children, and assuring public confidence and trust in vaccination programs. Mr. Shoemaker also stated that his goal is to have kids diagnosed with autism compensated by the VICP.

One of the first efforts at tort reform in vaccine cases was started by Secretary Califano of the Department of Health, Education, and Welfare who provided compensation to individuals who experienced Guillian Barre Syndrome after receiving the Swine flu vaccine. These individuals did not have to prove a theory of liability. At the time, the Federal government was sued instead of the vaccine manufacturers and these cases were filed in Federal court. Trials were handled by only judges. This program laid the groundwork for the vaccine program established today.

NOTE: After reviewing the minutes of his presentation, Mr. Shoemaker requested the following "afterthought" be included: Almost all of the countries that have vaccine compensation programs (as reported by Geoff Evans, MD) have more liberal statutes of limitations than the United States. This represents a black mark on the way the United States is handling these unfortunate, but rare, victims of childhood vaccinations.

Report from the ACCV Workgroup on Standards for Adding Injuries to the Vaccine Injury Table: Loren Cooper, J.D.

Ms. Loren Cooper reported that since the December 12, 2005 ACCV meeting, the Workgroup has continued its discussions on the "ACCV Resolution Regarding Periodic Review of the Vaccine Injury Table (Resolution)" and "Guiding Principles for Recommending changes to the Vaccine Injury Table (Guiding Principles)" and held meetings on January 18 and February 15. Ms. Cooper reminded the group of the discussions that took place at the December 12 ACCV meeting regarding the draft documents. She stated that said discussions were helpful to the Workgroup.

Since the December meeting, the Workgroup received comments on the Resolution and Guiding Principles from individuals who were not members of the Workgroup. In a letter to Ms. Robin Stavola, ACCV member, dated January 20, Robert E. Schiappacasse, J.D., of the Fox, Rothschild law firm, expressed his views on the Resolution and Guiding Principles. His comments were submitted at the request of Ms. Stavola. Clifford Shoemaker, J.D., Shoemaker & Associates, Ms. Kathi Williams, National Vaccine Information Center, and Kevin Conway, J.D., Conway, Homer & Chin-Caplan, P.C. also provided feedback to the Workgroup. As Mr. Conway's letter was not received until March 7, only two days before this meeting, the Workgroup had no opportunity to fully review or discuss his comments, as it had with other reviewers. However, Ms. Cooper stated that all other comments have been reviewed and considered by the Workgroup when preparing the documents presented to the ACCV for consideration at the March 9 meeting. Ms. Cooper thanked the Workgroup for its hard work in developing these documents and everyone else who provided comments on the documents.

ACCV Resolution Regarding Periodic Review of the Vaccine Injury Table

Ms. Cooper stated the Resolution was developed to recommend to the Secretary of Health and Human Services (Secretary) that the Department of Health and Human Services appoint a standing scientific panel of external experts to periodically review the scientific and medical evidence – whether it be published in the literature or otherwise – concerning vaccine safety and then come back to the ACCV to recommend proposed changes to the Vaccine Injury Table ("the Table"). To goal is to keep the Table as current as possible. Ms. Cooper stressed that the role of the panel of experts would be to advise the ACCV, which ultimately decides what recommendations it will make to the Secretary regarding changes to the Table. Ms. Cooper further emphasized that the panel may recommend the addition and removal of injuries from the Table, but the establishment of the panel is absolutely not intended to be simply a mechanism by which injuries are removed from the Table.

Ms. Cooper noted, for the benefit of those who had not yet read Mr. Conway's letter, that he had suggested removing a pediatrician and epidemiologist from the list of disciplines included in the scientific panel (in the February 23rd draft) and adding a pharmacologist and a vaccinologist and asked the ACCV members to keep this in mind during its deliberations.

Dr. Wilber asked if there were additional comments on the Resolution. Mr. Glass invited Vincent Matanoski, DOJ and Mr. Cliff Shoemaker, a petitioners' attorney, to comment on the Resolution. Mr. Shoemaker opined that one of the problems with the Table is that it is not a scientific or medical document; it was created as a political compromise. It was not intended to say anything about scientific certainty or medical probability; rather, it was a mechanism designed to make the program run more efficiently. Mr. Shoemaker stated that, if there must be a Table, he favors one without injuries because whenever an injury is listed, a presumption is created against any injuries not listed.

However, as long as there is a Table with injuries, Mr. Shoemaker recommended always erring toward adding injuries to the Table, not only when a vaccine has been scientifically proven to cause the specific injury, but even when it is suspected of doing so. He suggested the creation of a public relations campaign designed to inform the public that injuries are added to the Table in deference to the public, not because we believe the injuries are caused by vaccines. Mr. Shoemaker stated that if we err on the side of helping people and explain properly what the Table is and is not, we will bolster public confidence in the vaccine program.

Mr. Matanoski replied that it is not really the place of DOJ to tell the ACCV how to do its job with respect to the Resolution and Guiding Principles. He asked, "if you are not going to look at science at least in part for what is going to go into the Table, what are you going to look at? He stated that science should play a part. In Mr. Matanoski's view, when Congress passed the Act, they did expect that the Secretary would look at science. Congress initially created the Table, but charged the Secretary to consult with scientific bodies who would provide research so that the Table could be reviewed and

amended. From a litigation perspective, Mr. Matanoski expressed his view that having certain injuries on the Table which are presumed to be caused by the vaccine does not translate into a presumption against causation for injuries not on the Table. He confirmed that cases for injuries that are not on the Table are compensated. From December 1, 2005 to February 28, 2006, 15 cases were compensated and some of those were for injuries not on the Table. He stated that the Table should exist and should be based on science as Congress intended.

Dr. Wilber requested a motion to pass the Resolution. Ms. Cooper reminded the ACCV that in his letter, Mr. Conway had recommended that a pharmacologist and vaccinologist be added to the disciplines represented on the panel. Dr. Evans replied that he is not clear what a vaccinologist is and thought it was an umbrella term for scientists who do vaccine research, which could be an epidemiologist or microbiologist.

Ms. Cooper made a motion to pass the Resolution. Dr. Robert Fuller seconded the motion. Dr. Wilber called for a vote on the Resolution. The following ACCV members voted in favor of the Resolution: Dr. Robert Fuller, Marguerite Willner, Loren Cooper, J.D., Dr. Jaime Deville, and Dr. Don Wilber. Paul Glass, Jr., J.D. and Robin Stavola voted against the Resolution.

Guiding Principles for Recommending Changes to the Vaccine Injury Table

Ms. Cooper reported that the Guiding Principles were developed to provide a framework to assist the ACCV in their decision making process for deciding if changes should be made to the Table. She explained that the Guiding Principles reflect the Workgroup's view that they should incorporate both policy and scientific considerations. Ms. Cooper further explained that the Guiding Principles are not intended to be standards that dictate any kind of outcome but are intended, instead, to provide an analytical framework, recognizing that many who serve on the ACCV do not have any formal training in science or medicine.

Specifically, Ms. Cooper suggested the Guiding Principles would help ACCV members put into context the different sources of information that exist. Responding to feedback that not all of the sources of data listed are always available when discussing changes to the Table, Ms. Cooper stated that the document should only be used as a framework. For example, if clinical data does not exist, the other types of data listed should be considered. All available data should, under the Guiding Principles, be considered.

Mr. Glass asked if the Secretary decides on the option for establishing the panel and who decides on the funding. Dr. Evans replied that the Program operates within the Health Resources and Services Administration (HRSA) and the Secretary would work with HRSA to decide how it will be funded. Mr. Glass asked if the ACCV has to develop an estimate of the cost of it. Dr. Evans responded that there is information on the cost of the IOM contracts in the past, and the cost of this project would be similar.

Ms. Cooper opened the floor for ACCV comments on the Guiding Principles. Robert L. Davis, M.D., M.P.H, ACCV ex officio member, stated that the framework proposed in the Guiding Principles is similar to an already established framework evaluating scientific evidence developed by the U.S. Preventive Services Task Force (USPSTF). Dr. Davis suggested that the ACCV may want to refer to the USPSTF framework. He also stated that the USPSTF framework has guiding principles and a panel of epidemiologists in place to review scientific evidence.

Robin Stavola commented that she does not agree with the Resolution and Guiding Principles. She expressed concern that the panel of experts would be biased, and she does not agree with the proposed hierarchy of scientific data sources. In particular, Ms. Stavola suggested that the data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD) should be higher in the hierarchy list because these data are used more often to come to a conclusion on a vaccine injury.

Ms. Cooper agreed that VAERS and VSD data have been helpful in drawing conclusions about certain issues. She also acknowledged that there will be instances where one or more listed source is unavailable. In these instances, the ACCV would look to the sources that are available. Moreover, Ms. Cooper pointed out that even if some of the data sources listed at the top of the proposed list do exist, there may be policy considerations (such as potential biases) that need to be taken into consideration when assessing such data sources.

Ms. Cooper reported that the hierarchy of sources in the Guiding Principles is a generally accepted hierarchy that is used within scientific and medical communities. Nevertheless, she invited further discussion, recognizing the importance of reaching a consensus among ACCV members on the Guiding Principles.

Ms. Stavola asked why guiding principles are needed to assist the ACCV in their decision making process for making changes to the Table.

Ms. Cooper stated that the Workgroup decided to come up with a panel of experts to assist the ACCV in understanding what is involved in making changes to the Table. At the February 15, 2005 meeting of another ACCV workgroup, Dr. Vito Caserta, an ex DVIC employee, gave a presentation on the various types of scientific evidence, and a hierarchy of data sources based on the reliability of findings. The Workgroup used the information from his presentation as a framework for developing the hierarchy of scientific data sources included in the Guiding Principles.

Ms. Stavola asked if the Secretary would be reviewing the Guiding Principles and Resolution. She also asked about the status of the proposed injuries for hepatitis A and varicella vaccines that the ACCV approved and voted on at the March 10, 2005 ACCV meeting.

Dr. Evans replied that the Secretary has not made a decision on the injuries, and that the process for reviewing injuries for the Table can be deliberative. He stated that the

Secretary will be notified of the Guiding Principles and Resolution via a recommendation letter from the ACCV.

Mr. Paul Glass, Jr., J.D. asked what would be the next step after sending the Guiding Principles and Resolution to the Secretary. He also asked who would provide the funding to set up the panel of experts.

Dr. Evans stated that the Secretary would review the recommendation and consult with the program. Thereafter, there will be discussions on what type of panel of experts will be established. Dr. Evans stated that the panel could be modeled after the Institute of Medicine (IOM) scientific committees, or the Secretary could pick experts for the panel. The Secretary will determine what type of panel is needed, and the funding source to establish the panel. In the past, funding for IOM committees to study certain vaccine issues has been requested but not granted. Dr. Evans stated that the important goal is to have in place a set of principles for the ACCV members to use as a guide for making changes to the Table.

In the context of understanding the merits of the recommendation for a scientific panel to review literature to consider making changes to Table, Mr. Glass inquired about the current process in place for making changes to the Table.

Dr. Evans stated that the first set of Table changes for pertussis and rubella vaccines became effective March 10, 1995, while the second set of changes for the remaining Table vaccines, plus hepatitis B, Hib, and varicella became effective March 24, 1997. Congress requested that the Secretary have the IOM study all of the vaccines listed on the Table. Changes were made to the Table based on studies reviewed by the IOM. After this process, there was no statutory authority in place for guidance in making future Table changes for vaccines on the Table.

Effective August 26, 2002, intussusception was added as an injury to the Table for rotavirus vaccine. The science reviewed for this change came from epidemiologic studies provided by CDC.

Dr. Evans reported that published reports and studies are currently being used as a basis for making future changes to the Table. He stated that having an independent scientific panel will be beneficial to the program to provide an objective analysis of published scientific sources, and include the public in discussions on the decision making process for making changes to the Table.

Mr. Glass asked what led up to the development of the Guiding Principles. Ms. Cooper explained that in the past, the ACCV had discussions about which injuries should be associated with new vaccines added to the Table. The Workgroup realized that there was no mechanism in place for a comprehensive review of the Table. She explained that the Workgroup wanted to provide guidelines to ensure that the injuries listed on the Table are consistent with current medical and scientific information.

Dr. Davis suggested as a future ACCV agenda item is to have Al Berg, University of Washington, Department of Family Medicine and ex Chair of the USPSTF provide a presentation on their process of weighing scientific evidence.

Mr. Glass expressed concern that the Guiding Principles were an effort to prescribe the manner in which the ACCV is to weigh and prioritize sources of medical evidence. He recalled that Ms. Tamara Overby informed the Workgroup at the November 18, 2005 Workgroup meeting that DVIC has a review process in place for injuries on the Table and asked for further explanation on this process.

Dr. Evans replied that there is no formal process in place for reviewing injuries listed on the Table. He stated that in addition to other duties, DVIC physicians search the scientific literature to see if there is supporting evidence available to suggest making a Table change. Ms. Cooper stated the Workgroup recommended a panel of scientific experts to periodically review the Table so that it could provide an additional review process on a regular process.

Dr. Marion Gruber (filling in for ex officio member Dr. Norman Baylor) asked what would be the consequences if the panel makes a recommendation for adding a certain injury to the Table, and the ACCV disagrees with its recommendation.

Ms. Cooper stated that the Workgroup developed the Guiding Principles to assist the ACCV in understanding scientific evidence from various scientific data. She also stated that if the principles are adopted, she does not foresee the ACCV disagreeing with the panel if they find data that supports an association between a vaccine and an adverse event. She explained that the more likely scenario is that the panel will conclude there is inadequate scientific evidence to justify a change (because there is both supporting and opposing data). In such instances, Ms. Cooper stated that the Guiding Principles encourage the ACCV to recommend whatever is in the best interest of the petitioners.

Dr. Evans stated that the Secretary has never charged the IOM Vaccine Safety Review Committee with recommending policy changes to the Table. He stated that the charge of the scientific panel would be to research and categorize vaccines and hypotheses, and to put the findings into categories of causation.

Dr. Wilber asked if anyone had comments on the Guiding Principles. Dr. Deville provided comments to the Workgroup on February 10. He suggested that data from passive surveillance systems should be listed higher than “uncontrolled observational studies such as ecological studies” and “case series” on the list of scientific sources. He stated that editorial articles on scientific presentations, and non-peer reviewed publications are too weak to be listed, and should be deleted from the list. He suggested adding the following language in parenthesis after clinical laboratory data (such as PCR confirmation of vaccine strain virus following immunization against varicella), which has been added to the Guiding Principles.

Ms. Cooper reported that the Workgroup had not incorporated Dr. Deville's suggestion of moving up the data from passive surveillance systems on the list of scientific sources because it wanted to discuss the issue at the meeting. Ms. Cooper questioned Dr. Deville's rational and indicated that it is her understanding that passive surveillance systems such as VAERS are less likely to contain medically confirmed reports. In contrast, she suggested that data in VSD, uncontrolled observational studies, and case series often involved medically-confirmed reports. She explained that while these other data sources may be similar in weight with passive surveillance systems, the lack of medical confirmation of data within passive surveillance systems led the Workgroup not to change the proposed hierarchy. Dr. Wilber asked Dr. Deville if he would accept the hierarchy of data sources as it is currently listed. Dr. Deville agreed.

Ms. Cooper called for a motion to pass the Guiding Principles, and Ms. Willner seconded the motion. The following ACCV members voted to approve the Guiding Principles: Loren Cooper, J.D., Marguerite Willner, Dr. Robert Fuller, Dr. Jaime Deville, and Dr. Don Wilber. Paul Glass and Robin Stavola voted against the Guiding Principles.

VICP Program Assessment Rating Tool Results: Tamara Overby, MBA

Ms. Tamara Overby and Ms. Alexis Babcock of DOJ provided the results of the Program Assessment Rating Tool (PART) on the VICP.

Ms. Overby began her presentation by providing information on the history of PART. In 2001, the President announced his agenda to improve the management of the Federal government. It is called the "President's Management Agenda" (PMA) and it includes the following five elements: (1) Strategic Management of Human Capital; (2) Budget and Performance Integration; (3) Competitive Sourcing; (4) Expanded E-government; and (5) Improved Financial Management. The PMA is implemented by the U.S. Office of Management and Budget (OMB). OMB's primary responsibility is implementing the policies and regulations of the Executive Branch of the Federal government, and administering the President's budget.

Ms. Overby discussed the PMA's budget and performance integration for Federal programs. The President wanted to ensure that performance results were linked to budget decisions since this had not been done in the past. OMB decided to use PART to link program performance results to budgets. PART also assesses the performance of program activities in the Federal government. Federal agencies are currently required to link performance results to budget requests. Using this information, the President and/or Congress will reinforce high performing programs, and reform or terminate low-performing programs. If programs perform well their budgets could be increased. If programs do not perform well, their budgets could be terminated or cut.

Since 2002, OMB has used PART, a diagnostic tool, to make budget decisions. PART assesses the performance of program activities across the Federal government and is actually used to improve program performance using an action plan. The PART consists of 25 questions which assess different aspects of program performance. The questions

are divided into the following four sections and each section is weighted: (1) Program Purpose and Design (20%); (2) Strategic Planning (10%); (3) Program Management (20%); and (4) Program Results/Accountability (50%).

The numeric scores are weighted, tallied, and translated into overall qualitative ratings of effective (85-100), moderately effective (70-84), adequate (50-69), ineffective (0-49), and results not demonstrated. As part of the process, programs are expected to develop long-term and annual performance measures and targets, and action plans to improve program performance. In addition, programs have to track their progress toward achieving targets.

In April 2005, the OMB requested that DVIC and DOJ go through the PART process together. This was the first time that two agencies were assessed at the same time. Both agencies provided responses to 25 questions that were sent to OMB. They reviewed the responses, and agreed with some of the answers, and had questions about the other responses. The OMB met with officials at the U.S. Court of Federal Claims (Court) and vaccine companies. The Court was not involved in the PART assessment, because it is part of the Judicial Branch of the Federal government, and OMB only oversees the Executive Branch of the Federal Government. In September 2005, OMB finalized the responses to the questions. In December 2005, DVIC and DOJ completed the improvement plan for the VICP.

Long-term performance measures and targets were developed for the VICP and DOJ to track progress towards achieving the VICP's goals. One of the goals of the VICP is to prevent vaccine liability cases from being filed in civil court, and the first long-term measure, which is the percentage of eligible claimants who opt to reject their awards, tracks this goal. This measures how well the VICP is keeping individuals who are eligible for compensation in the VICP. The baseline for this measure of zero percent was established in 2004. In 2004 and 2005, the VICP met the target of zero percent. In other words, no one who was eligible for compensation rejected their award. In 2006, the target is zero percent, and the actual data will not be available until October 2006.

The second long-term measure is the average claim processing time, which tracks the VICP's goal of compensating claims quickly. In 2004, the baseline was 738 days to process a claim. In 2005, the target was 990 days, and the VICP exceeded this target by processing claims on average in 894 days. In 2006, the target is 1005 days, and the actual processing time will be available in October. The 2006 target number is higher due to the hepatitis B cases that have been pending in the VICP since 1999. Decisions on these cases are expected soon.

The annual performance measures and targets are subsets of the average claim processing time. The annual measures are processing measures which track the long term measure of reducing the average claim processing time. The first annual measure is decreasing the average time that lump sum only awards are paid from the receipt of a DOJ clearance letter. In 2004, the baseline was six days to pay lump sum only awards from the receipt of DOJ letter, and in 2005, the target was five days, but the VICP did not meet this target

because it took an average of 11 days to pay these awards. The 2006 target is five days and the actual data will be available in October. The VICP is putting mechanisms in place to meet the 2006 target.

The second annual measure is to decrease the average time settlements are approved from the date of the receipt of the DOJ settlement proposal. In 2004, the baseline was 11 days. In 2005 and 2006, the targets were 10 days. In 2005, the average time settlements were approved was 18 days. For 2006, the actual data will be available in October. The VICP is instituting mechanisms to meet the 2006 target.

Ms. Alexis Babcock discussed the third annual performance measure, which is the percentage of cases in which case settlements are completed within the court-ordered 15 weeks. This annual measure concerns the period of time between a tentative settlement agreement between the parties and when DOJ provides the actual settlement stipulation to petitioners. In 2004, the baseline was 80%. In 2005, the target was 85%, and DOJ met this target with an actual percentage of 95%. For 2006, the target is 90%, and the actual data will be available in October.

The fourth annual performance measure is the percentage of cases where the deadline for the Rule 4(b) report is met once the case has been deemed complete. The Rule 4(b) report is the equivalent of the government's answer in VICP cases and states whether or not a case should be compensated and why. In 2004, the baseline was 75.3%. In 2005, the target was 78% which was met with 83.7% compliance. For 2006, the target is 80%, and the actual data will be available in October.

The last annual performance measure is the median time to process an award for damages. This measures the median time after there is a determination that a petitioner is entitled to compensation until the damages process is completed. In 2004, the baseline was 529.5 days. In 2005, the target was 529.5 days, and the actual median time was 483.9 days. In 2006, the target is 500 days, and the actual data will be available in October.

Ms. Overby stated that the VICP received a rating of adequate, which translates to a "C" average. The VICP scored 80% for program purpose and design; 63% for strategic planning; 72% for program management; and 47 % for program results and accountability.

How does the VICP compare to other Federal programs? Currently, the OMB has assessed approximately 800 Federal programs or about 80% of all Federal programs. About 15% of these programs were rated effective; 29% were moderately effective; 28% were adequate; 4% were ineffective; and results were not demonstrated in 24% of the programs. Programs whose results were not demonstrated do not have the data to support any of the categories mentioned above.

The OMB rated the VICP adequate because of several factors. OMB stated that the program's design contains inherent legislative flaws that hindered its ability to satisfy

claimants and vaccine manufacturers. They also stated that the program has made progress in achieving its annual performance goals, but its performance on long-term goals has been inconsistent. They agreed that DVIC and DOJ effectively collaborate to administer the VICP.

The OMB recommended several areas that need to be improved. OMB recommended that long-term and annual measures be included in the Strategic Plan and other planning documents. The VICP will be taking the steps required to include long-term and annual measures in these documents. The OMB also recommended that the VICP meet or exceed the long-term and annual targets. The VICP is planning to do this by reducing claims processing time through the increased use of electronic file sharing. In addition, the VICP is attempting to track its progress toward meeting targets on a quarterly basis.

The OMB also requested that the VICP inform the ACCV of the measures and targets, which was done at this meeting today. OMB also stated that the VICP needs to conduct independent evaluations of sufficient scope and quality. Over the years, there have been a number of evaluations on specific aspects of the VICP. In 1995, the HHS Office of the Inspector General published a report on the timeliness of processing claims in the VICP. There was another report conducted that reviewed the processing of settlements; however, there has never been a comprehensive evaluation of the VICP.

The VICP has contracted with Health Systems Research to examine the feasibility of conducting a comprehensive evaluation on the VICP. The outcome of the evaluation will determine which aspects of the VICP can be evaluated. The contract was awarded in September 2005, and the contractors are in the process of developing the methodology that will be used to conduct this study.

Finally, OMB stated that the VICP needs to tie budget requests to achieving performance goals. In 2006, the VICP submitted their budget request and has linked it to performance results.

Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention: Robert Davis, M.D., M.P.H

As of January 23, Dr. Robert Davis became the new Director of the Immunization Safety Office, Office of the Chief Science Officer, CDC. The ISO is charged with doing risk assessment activities, (i.e., assessments of vaccine safety issues). Currently, the ISO has been focusing on policy issues and communication activities. Ms. Brooke Berry has been hired to handle the policy issues; the position is vacant for someone to handle the communications activities. In the interim, Ms. Beth Hibbs, RN, M.P.H. is handling the communications issues.

In the ISO, the primary studies underway are addressing thimerosal issues. Four studies are underway and one is in the active planning stage. First, the analyses from the thimerosal and neurodevelopmental outcomes cohort study will be completed this month, and the manuscript will be written shortly. Second, the ISO is also involved in the

beginning stages of recruiting for an autism thimerosal study, which involves looking at various levels of thimerosal received in early life and subsequent risk for developing autism. Third, there has been analysis on Italian data of DTP or DTaP vaccines given to children who participated in a randomized clinical trial. The vaccines given contained different levels of thimerosal, and they were able to compare the effects of thimerosal in the children who received these vaccines.

Fourth, the ISO is also planning to conduct a study looking at trends in autism in the U.S.A. In this study, an article entitled, "Early Downward Trend in Neurodelopmental Disorders Following Removal of Thimerosal-Containing Vaccines" by David A. Geier, B.A. and Mark R. Geier, M.D., Ph.D., which discusses the decrease in autism since the removal of thimerosal from vaccines will be addressed.

The ISO is committed to a new process of conducting active surveillance on new vaccines. They would like to institute a way to perform routine weekly surveillance of safety signals in the new vaccines. They plan to use this new process on the new rotavirus vaccine, RotaTeq®.

The ISO is also planning to address the potential association between the meningococcal conjugate vaccine and the Gullain-Barre Syndrome (GBS). Another area of interest to the ISO is the question of individual predisposition to vaccine adverse events. This is a new long-term direction for the office that will allow ISO to attempt to identify people who might have a specific predisposition to vaccine events or for some reason maybe prone to not responding in the normal fashion to vaccines.

On February 10, 2005, the FDA released Menactra, a new conjugate meningococcal vaccine that was released towards the end of last year. Menactra is recommended for routine use in children 11 -12 years old, students entering high school and college freshman living in dormitories. It is a high efficacious vaccine to prevent a common type of invasive, very serious meningococcal disease which is most commonly seen in adolescents and adults. Shortly after the release of this vaccine, there were reports of GBS cases among adolescents reported to the Vaccine Adverse Event Reporting System. CDC mobilized the Vaccine Safety Datalink immediately in addition to one other very large managed care organization.

Subsequently, CDC released a Morbidity and Mortality Weekly Report article on a public health alert to inform the medical community of the problem. No additional cases of GBS had been reported. In determining the safety of Menactra, CDC had calculated that the rate of GBS in approximately 3 million vaccine recipients and the number of observed cases of GBS were about the number of expected cases that would be anticipated to occur in a natural background rate among 3 million people. There is reasonable evidence to suggest that the individuals who contracted GBS were simply coincidental cases. The vaccine stayed on the market. The ISO plans to release another update on the continuing observance of GBS and Menactra. A follow-up epidemiologic study is being planned with VSD and other managed care organizations.

The last project ISO is involved with is creating an external oversight committee that would assist annually in formulating its Vaccine Safety agenda as recommended by the February 17, 2005 Institute of Medicine report entitled, "Vaccine Safety Research, Data Access, and Public Trust." The recommendation called for CDC to create a new subcommittee of the National Vaccine Advisory Committee (NVAC) to enable stakeholders to review and provide input on the vaccine safety research plan every year. The ISO has been in communication with NVAC, and the National Vaccine Program Office about setting up this committee, and they have scheduled a full day meeting for early April.

Update on the Center for Biologics and Evaluation Research, Food and Drug Administration: Marion Gruber, Ph.D.

Dr. Gruber reported that a new vaccine called Rotateq was licensed on February 3. It is a live, oral, pentavalent vaccine to prevent gastroenteritis in infants. The FDA has a biologics license applications under review for a combination diphtheria and tetanus toxiods and acellular pertussis, inactivated poliovirus, haemophilus influenza type b vaccine (Pentacel), human papillomavirus recombinant vaccines (Gardasil), and zoster vaccine (Zostavax).

On February 17, FDA's Vaccines and Related Biological Products Advisory Committee met to consider which influenza virus strains should be included in the vaccine for use during the 2006 – 2007 season in the U.S. Based on surveillance data and the availability of strengths of reagents, the Committee recommended that the influenza vaccine for the upcoming season should again be trivalent, which means that it should consist of three types of viruses. The committee recommended the following: retaining the current A/New Caledonia/20/99 (H1N1)-like virus; replacing the current strain with an A/Wisconsin/67/2005 (H3N2)-like virus (A/Wisconsin/67/2005 and A/Hiroshima/52/2005 strains); and replacing the current strain with a B/Malaysia/2506/2004-like virus (B/Malaysia/2506/2004 and B/Ohio/01/2005 strains). A recommendation was also made for the FDA to convene a workshop to discuss the possibility of having the annual influenza vaccine comprised of two B strains rather than the current one. The influenza vaccine recommendation for the 2006 -2007 season is identical to what the World Health Organization recommended for the season at their February 15 meeting.

For the 2006 – 2007 season, it is projected that approximately 120 million doses of the influenza vaccine will be available. Sanofi Pasteur will provide 50 million doses. Chiron will provide about 40 million doses, and GlaxoSmithKline will provide 30 million doses, after they purchased ID Biomedical, which is an unlicensed vaccine manufacturer. The number of doses has increased since last season. However, the supply is still less than the CDC recommendation that about 180 million individuals receive the influenza vaccine annually. Dr. Gruber noted that 80 to 90 million doses were available this current flu season.

On March 2, the FDA published two guidances for industry documents entitled, "Clinical Data Needed to Support the Licensure of Trivalent Influenza vaccine," and "Clinical Data Needed to Support the Licensure of Pandemic Flu Vaccines." These documents were prepared to address the influenza shortage issue by outlining a clinical development path for the licensure of the influenza vaccines to hopefully expedite and facilitate licensure. Guidance is needed on the clinical data and clinical trials needed to support licensure for the trivalent and pandemic influenza vaccines. It is hoped that these documents will assist in increasing the amount of vaccine doses available.

Future Agenda Items

Ms. Marguerite Willner requested a discussion at the next ACCV meeting on adding a sentence to the Qualifications and Aids to Interpretation that the Vaccine Injury Table is a scientific and policy document. Ms. Willner suggested that a workgroup be formed to look at making changes to the Program. She also suggested that discussion be held on Clifford Shoemakers' request of tolling the statute of limitation to the age of majority for vaccine injured children.

Mr. William P. Glass, Jr. suggested that a presentation be held on vaccine liability in rebuttal to Dr. Offit's presentation on "Vaccine Liability 50 years After the Cutter Incident."

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Don Wilber, M.D. ACCV Chair	Marguerite Willner ACCV Vice-Chair
_____	_____
Geoffrey Evans, M.D. Executive Secretary, ACCV	Date