ADVISORY COMMISSION ON CHILDHOOD VACCINES
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September 4 & 5, 2014

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ADVISORY COMMISSION ON CHILDHOOD VACCINES

Agenda

DRAFT August 14, 2014

ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV)
Parklawn Building, 5600 Fishers Lane, Rockville, Maryland
Conference Room 10-65
September 04 & 05, 2014
(1:00pm – 4:25 pm Eastern Daylight Time)
(9:00 am – 1:15 pm Eastern Daylight Time)
Dial: 1-877-917-4913
Passcode: ACCV

Thursday, September 04, 2014

Time	Agenda Item	Presenter
1:00 PM	Welcome and Chair Report	Mr. David King, Chair
1:10 PM	Welcome	Ms. Cheryl Dammons Associate Administrator, HRSA
1:15 PM	Public Comment on Agenda Items	
1:20 PM	Approval of June 2014 Minutes	Mr. David King, Chair
1:25 PM	Report from the Division of Vaccine Injury Compensation	Dr. A. Melissa Houston Acting Director, DVIC
1:55 PM	Clarification on Proposed Changes to the Vaccine Injury Table	Dr. A. Melissa Houston Acting Director, DVIC
2:55 PM	Report from the Department of Justice	Mr. Vince Matanoski, Deputy Director, Torts Branch, DOJ
3:25 PM	VICP Outreach Plan	
4:25 PM	Public Comment (follows the preceding topic and may commence earlier or later than 4:25 pm)	
4:40 PM	Adjournment of the 1st Day of the ACCV Quarterly Meeting	

Friday, September 05, 2014

Time	Agenda Item	Presenter
9:00 AM	Welcome & Unfinished Business from Day 1	Mr. David King, Chair
9:15 AM	Report from the Process Workgroup	Ms. Luisita dela Rosa, ACCV Member
10:00 AM	Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities	Dr. Tom Shimabukuro CDC
10:15 AM	Discussion of Proposed Revisions to VAERS Form (2.0)	Dr. Tom Shimabukuro CDC
11:15 AM	Pneumococcal Polysaccharide (Pneumovax 23) Vaccine Safety Presentation	Ms. Elaine Miller, R.N., MPH CDC
11:45 AM	Zoster (Shingles) Vaccine Safety Presentation	Ms. Elaine Miller, R.N., MPH CDC
12:15 PM	Update on the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) Vaccine Activities	Dr. Barbara Mulach NIAID, NIH
12:45 PM	Update on the Center for Biologics, Evaluation and Research (CBER), Food and Drug Administration (FDA) Vaccine Activities	Ms. Valerie Marshall, Ph.D CBER, FDA
1:00 PM	Update from the National Vaccine Program Office (NVPO)	Dr. Karin Bok, NVPO
1:15 PM	Public Comment (follows the preceding topic and may commence earlier or later than 1:15 pm)	Mr. David King, Chair
1:30 PM	Future Agenda Items/New Business	Mr. David King, Chair
1:45 PM	**Adjournment of the ACCV Quarterly Meeting**	

Charter

CHARTER

ADVISORY COMMISSION ON CHILDHOOD VACCINES

Authority

42 U.S.C. 300aa-19, Section 2119 of the PHS Act. The Advisory Commission on Childhood Vaccines (hereinafter referred to as the "Commission") is governed by the provisions of Public Law 92-463 (5 U.S.C. App. 2), which sets forth standards for the formation of advisory committees.

Objectives and Scope of Activities

The Secretary of Health and Human Services is mandated under Section 2119 of the Public Health Service (PHS) Act to appoint an advisory commission to give advice regarding the National Vaccine Injury Compensation Program (the Program), which provides compensation for certain vaccine-related injuries or deaths.

Description of Duties

The Commission shall: (1) advise the Secretary on the implementation of the Program; (2) on its own initiative or as the result of the filing of a petition, recommend changes in the Vaccine Injury Table; (3) advise the Secretary in implementing the Secretary's responsibilities under Section 2127 of the PHS Act regarding the need for childhood vaccination products that result in fewer or no significant adverse reactions; (4) survey Federal, State, and local programs and activities relating to the gathering of information on injuries associated with the administration of childhood vaccines, including the adverse reaction reporting requirements of Section 2125(b), and advise the Secretary on means to obtain, compile, publish, and use credible data related to the frequency and severity of adverse reactions associated with childhood vaccines; (5) recommend to the Director of the National Vaccine Program research related to vaccine injuries which should be conducted to carry out the Program; and (6) consult regarding the development or revision of vaccine information materials as required by Section 2126 of the PHS Act.

Agency or Official to Whom the Commission Reports

The Commission shall advise and make recommendations to the Secretary on matters related to the Program responsibilities.

Support

Management and support services shall be provided by the Division of Vaccine Injury Compensation, Healthcare Systems Bureau, Health Resources and Services Administration.

Estimated Annual Operating Costs and Staff Years

Estimated annual cost for operating the Commission, including compensation and travel expenses for members, but excluding staff support, is approximately $39,795. The estimate of annual person-years of staff support required is 1.5 at an estimated annual cost of $256,377.

Designated Federal Official

HRSA will select a full-time or permanent part-time Federal employee to serve as the Designated Federal Official (DFO) to attend each Commission meeting and ensure that all procedures are within applicable, statutory, regulatory, and HHS General Administration Manual directives. The DFO will approve and prepare all meeting agendas, approve all of the Commission or subcommittee meetings, adjourn any meeting when the DFO determines adjournment to be in the public interest, and chair meetings when directed to do so by the official to whom the Commission reports. The DFO or his/her designee shall be present at all meetings of the full Commission and subcommittees.

Estimated Number and Frequency of Meetings

The Commission shall meet no less than four times per year and at the call of the Chair. Meetings shall be open to the public except as determined otherwise by the Secretary or designee in accordance with the Government in the Sunshine Act 5 U.S.C. 552b(c) and the Federal Advisory Committee Act. Notice of all meetings shall be given to the public. Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and departmental regulations.

Duration

Continuing.

Termination

Unless renewed by appropriate action prior to its expiration, this charter will expire two years from the date the charter is filed.

Membership and Designation

The Secretary shall select members of the Commission. The members of the Commission shall select a Chair and Vice Chair from among the members. Appointed members of the Commission shall be appointed for a term of office of 3 years.

The Commission shall be composed of the following:

(1) Nine members appointed by the Secretary as follows:

(A) three members who are health professionals, who are not employees of the United States, and who have expertise in the health care of children, the epidemiology, etiology, and prevention of childhood diseases, and the adverse reactions associated with vaccines, of whom at least two shall be pediatricians;

(B) three members from the general public, of whom at least two shall be legal representatives of children who have suffered a vaccine-related injury or death; and

(C) three members who are attorneys, of whom at least one shall be an attorney whose specialty includes representation of persons who have suffered a vaccine-related injury or death and of whom one shall be an attorney whose specialty includes representation of vaccine manufacturers.

(2) The Director of the National Institutes of Health, the Assistant Secretary for Health, the Director of the Centers for Disease Control and Prevention, and the Commissioner of the Food and Drug Administration (or the designees of such officials), each of whom shall be a non-voting ex officio member.

The nine members appointed by the Secretary shall serve as Special Government Employees. The ex officio members and the DFO shall be Regular Government Employees.

Subcommittees

Subcommittees may be established with the approval of the Secretary or designee. Subcommittee members may be members of the parent Commission. The subcommittee shall make recommendations to be deliberated by the parent Commission. The Department's Committee Management Officer will be notified upon the establishment of the each subcommittee and will be provided information on the subcommittee's name, membership, function, and estimated frequency of meetings.

Recordkeeping

The records of the Commission, formally established subcommittees, or other subgroups of the Commission, shall be handled in accordance with General Records Schedule 26, Item 2 or other approved agency records disposition schedule. These records shall be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

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Filing Date

July 21, 2014

Approved:

JUL 1 2014

Date

Bahar Niakan
Acting Director, Office of Management

Roster

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2014 & 2015 Meeting Dates

ADVISORY COMMISSION ON CHILDHOOD VACCINES

2014 MEETING DATES

September 4 & 5, 2014
December 4 & 5, 2014

2015 MEETING DATES

March 5 & 6, 2015
June 4 & 5, 2015
September 10 & 11, 2015
December 3 & 4, 2015

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Advisory Commission on Childhood Vaccines

June 5, 2014
92nd Meeting

Members Present

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

Division of Vaccine Injury Compensation (DVIC)

A. Melissa Houston, MD., Acting Director, DVIC
Andrea Herzog, Staff Liaison

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

Mr. King called the meeting to order and, after introductions, noted that Commission members Mr. Krause and Dr. dela Rosa, would join the meeting later in the morning. He stated that the meeting was again being held via teleconference and not in person, which is less desirable in terms of effective discussion than an in-person meeting would be. He reiterated his conviction that the Commission should approach the issues to be discussed with an understanding that the Commission represents those who are injured by vaccines and decisions and recommendations should be made such that the interests of those injured parties are best protected.

Public Comment on Agenda

Mr. King invited public comment specifically related to the agenda.

Theresa Wrangham, Executive Director of the National Vaccine Information Center, spoke to two agenda items – the discussion of the Vaccine Injury Table (Table) and the review of Vaccine Information Statements (VISs). With regard to the Table, injury claims based on underlying conditions and genetic predispositions and susceptibilities should not be barred because it is not in consonance with the Institute of Medicine's (IOM) study report's comments on epidemiological study limitations. In individuals who may have such predispositions, if a vaccine triggers an event that might have otherwise occurred because of the predispositions, that

individual should not be barred from the benefits of the Vaccine Injury Compensation Program (VICP). That would be in harmony with the chair's statement that decisions should be made to protect the injured persons.

Ms. Wrangham commented that the vaccine information statements to be considered, again referring to the IOM report, take into account the report's reference to the many unknowns that exist in the research and in the state of the science as it is now understood. She also referred to the vaccine product insert that is often referred to in the VIS that contains a significant amount of information, much of which the consumer may not be aware of. Pertinent information in the inserts should be included in the VIS.

Approval of March 2014 ACCV Meeting Minutes

Noting no further comment from the public, Mr. King invited approval of the minutes of the December 2013 meeting. On motion duly made and seconded, the minutes were unanimously approved.

Report from DVIC, Dr. A. Melissa Houston, Acting Director, DVIC

Dr. Houston briefly reviewed the day's agenda, noting that the Commission would consider changes to the Vaccine Injury Table (including a petition to add diabetes mellitus as an injury for MMR), hear presentations from the Department of Justice and the ACCV Process Workgroup, review certain Vaccine Information Statements, and hear the regular reports from the ex officio representatives of the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH) and National Vaccine Program Office (NVPO).

With regard to program statistics through May 6, 2014, Dr. Houston reported that with seven months' data, there were 311 petitions filed, which would extrapolate to about 533 for the fiscal year, a slight increase over the past year, perhaps because of the dramatic increase in influenza immunizations in adults. There were 246 adjudications handled by the Department of Justice, which projects to about 421 for the fiscal year. Although that is a slight decrease from the previous year, that could be the result of adding four new special masters and the concomitant additional time required for them to get up to speed in handling claims.

At this point, 18 minutes into the meeting, Dr. dela Rosa joined the meeting.

Dr. Houston continued with a report on adjudications, noting the types of adjudications to date and the estimated total in each category for the year:

Compensable	148	Projected for the fiscal year	253
Concessions	19	Projected for the fiscal year	32
Court decisions	17	Projected for the fiscal year	29
Non-compensable	64	Projected for the fiscal year	109

Finally, Dr. Houston noted that there had been awards in the amount of $128 million to petitioners, and $12.8 million to attorneys, which extrapolates to $219 million and $21 million respectively for the fiscal year. As of March 2014, the Trust Fund stands at about $3.4 billion, with a net income of $125.5 million (24% of which was derived from interest come on the corpus of the trust).

Dr. Houston described recent activities, including the second and final public hearing for the NPRM to add intussusception to the Table as an injury related to rotavirus vaccination. There were no public comments provided during the second hearing and the draft Final Rule to add the injury should be completed shortly. A Federal Register Notice was published on November 12, 2013 to add seasonal influenza vaccines to the Table, which would permit petitioners to file for all such vaccines not already covered by the program.

Dr. Houston noted that a Government Accountability Office (GAO) study of the VICP was initiated at the request of the U.S. House of Representatives Committee on Oversight and Government Reform. The GAO will look at the timelines for processing claims; changes in the Table and criteria for such changes; expenditures of funds from the Trust Fund; experiences of petitioners who file VICP claims; and efforts to publicize the VICP. The study began in March and the GAO has met with HRSA and DOJ representatives, had conversations with selected ACCV members and representatives of the Court. The study should be completed by August.

Turning to proposed changes to the Table, Dr. Houston explained that the trivalent flu vaccines were covered by the program in July, 2005 and all other flu vaccines (mainly the quadrivalent vaccines) were added in November 2013. The Department of Health and Human Services (HHS) Secretary has proposed changing the description of the category of vaccines from trivalent to seasonal. The Commission was asked to consider this recommendation and decide either to modify the category as recommended by the Secretary, or to not modify the category as recommended by the Secretary. Dr. Houston added that a pandemic vaccine would not be covered by the VICP, but injury claims for pandemic vaccines can be filed with a separate program, the Countermeasures Injury Compensation Program.

During discussion, Dr. Houston clarified that the Secretary's recommendation in effect combines the coverage provided under two sections in the Table, Category XIV and Category XVII, simplifying the Table. Asked if there was any argument in favor of rejecting the Secretary's recommendation, Drs. Houston and Shimabukuro both concurred that the recommendation was positive and there was no downside to endorsing the Secretary's recommendation. Dr. Houston also clarified that there are no injuries related to the flu vaccines on the Table, but that a proposal to add certain injuries was in the rulemaking stage. She reviewed the fairly lengthy process to complete the rulemaking process. She also reviewed the process by which a claim maybe filed for a flu-related vaccine injury.

Mr. King proposed that, when a recommendation is made to add a vaccine injury to the Table, that the DHHS should relax the process by which a petition is considered; that is, that the existing litigated causation in fact process be waived to expedite the final ruling for the claim. There was a recommendation that the issue be discussed at the end of the meeting under agenda item Future Agenda Items/New Business.

Dr. Houston continued her presentation of proposed changes, noting that the Secretary has recommended modifying Category IX Haemophilus influenza type b (HIB) polysaccharide vaccines to be categorized as simply Haemophilus influenza type b, to conform to the language in the Internal Revenue Code that imposes excise taxes on certain vaccines. It is a technical change that applies only to the nomenclature. As before, the Commission must recommend or not recommend approval of the Secretary's proposal.

Mr. .Kraus announced his presence at the meeting, noting that he had only been available for the discussion of the HIB vaccine change.

Dr. Houston continued the discussion, referring to the proposed clarifying language that would be added to the Qualifications and Aids to Interpretation. With regard to encephalopathy, a list of conditions is now included in the Table as examples of conditions that would be disallowed as an underlying systemic disease. The new wording proposed would eliminate some of the conditions that were deemed to be disallowable: An encephalopathy shall not be considered to be a condition set forth in the Table if it is shown that the encephalopathy was caused by an underlying condition or systemic disease shown to be unrelated to the vaccine *(change is underlined).* A list of conditions was included as examples, some of which were eliminated by the meaning of the new wording, which in effect reduced the number of exclusions (conditions) listed in the original wording.

Dr. Houston reiterated that the proposed change is based on scientific findings and not on suppositions that a vaccine might or might not trigger the onset of a condition. In addition, she clarified that the changes being discussed are changes to a previous change that was submitted to the ACCV for review at an earlier meeting. All of the changes are intended to make the criteria for filing claims less restrictive. She added that even if an underlying condition is specified as an exclusion, an individual would still be able to file a claim under the causation in fact provision.

Although the Commissioners attempted to conduct a discussion of the issues, because of difficulties in distributing all of the germane documents needed for proper consideration, there was consensus to consider the issue as an agenda item at a later meeting. The Commission agreed to take action on the first two issues discussed and, on motion duly made and seconded, the Commission unanimously approved the modification of Table Category XIV from "trivalent influenza vaccines" to "seasonal influenza vaccines;" and the modification of Table Category IX from "haemophilus influenza type b polysaccharide conjugate vaccines" to "haemophilus influenza type b vaccines."

Further discussion was deferred. Dr. Houston expressed appreciation for the commissioners' participation and provided the DVIC contact information.

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

Mr. Matanoski referenced the Department of Justice PowerPoint materials (DOJ PP), dated June 5, 2014, as part of his presentation. He commented that DOJ has also seen an increase in the number of cases filed versus the historical average since 2009, an increase of about 25%. There were

122 cases filed in the three-month reporting period, including 40 minors and 82 adults (DOJ PP at 2), which projects out to about 530 cases for the fiscal year. He advised that the increase in petitions filed should not be correlated to the number of vaccine injuries that may have occurred. Analysis of the filings shows that flu-related Guillain-Barré Syndrome (GBS) and shoulder injury related to vaccine administration (SIRVA) injuries are the main drivers in the increase. It appears that the increase will be sustained in the near future. Additional resources to process the claims will be needed to meet the increased case filing.

Mr. Matanoski noted that there were 120 adjudications in the three-month reporting period (DOJ PP at 3), versus 122 new claims filed, which is a good balance with little net increase in the number of pending petitions, but he observed that the proposed Table changes for SIRVA and flu could affect that balance as case filings increase. Mr. Matanoski noted a wide variety of petitioner's law firms filing petitions. During a discussion about the Table recommendations, Mr. Matanoski reiterated that some of the proposed Table changes are based on policy reasons and cast a wider net in terms of potential concessions. Discussing how cases that fall into the new Table criteria are treated pending the implementation of the recommendations, Mr. Matanoski offered that, as a practical matter, those cases become candidates for settlement early on in the process. Citing flu vaccine and GBS cases, Mr. Matanoski explained that the Court is already taking the proposed Table recommendations into account when the case is filed, and considers the strength of a petitioner's claim in terms of proposed damages. Mr. Matanoski pointed out that, of the more than 60 adjudicated claims in the current reporting period, half were for flu vaccine and GBS-related injuries (DOJ PP at 11-17). Although scientific evidence is the most important determinant of the outcome of a claim, the fact that the condition is on track to be added to the Table facilitates the settlement process, including the determination of damages. In fact, as the administrative process to add to the Table occurs in parallel with the judicial process of arriving at settlements, there is often very little dramatic impact when the condition is officially added to the Table.

Turning to appellate proceedings, Mr. Matanoski briefly reviewed a few cases. *Tembenis v. Sebelius* is pending before the U.S. Supreme Court (DOJ PP at 5). This was discussed at the last meeting. Briefly, the U.S. Court of Appeals for the Federal Circuit (CAFC) reversed the lower court and special master to find that the estate of a child who suffered an alleged vaccine related injury and death is not entitled to future damages based on expected lifetime earnings. Petitioners filed a *writ of certiorari* asking the Court to hear the issue. HHS filed a brief in opposition on May 21, 2014. The CAFC resolved two claims during the reporting period. In *Price v. HHS*, the CAFC affirmed *per curiam*, denying the motion for review because it was filed after the deadline (DOJ PP at 6). In *LaLonde v. HHS*, the CAFC in a 2-1 decision affirmed the dismissal of petitioner's case where petitioner suffered an episode of anaphylactic shock, but did not suffer six months sequelae. Respondent appealed two cases, *Paluck v. HHS* and *Dobrydnev v. HHS* (argued on June 4, 2014). Both appeals involved a question of deference by the U.S. Court of Federal Claims (CFC) of the special master's decision.

Turning to the CFC, Mr. Matanoski discussed *Tompkins v. HHS* (DJ PP at 8). The CFC affirmed the Special Master's dismissal of a petition alleging that the flu vaccine caused GBS based on evidence that there was a pre-existing respiratory infection shown to be the cause of petitioner's GBS. Mr. Matanoski mentioned this case because it was related to the earlier discussion about adding GBS to the Table where the case would be likely be defended even though GBS would be listed as a Table injury, if there was evidence that petitioner's GBS was due to a factor unrelated to the vaccine.

Responding to questions posed to Dr. Houston about how cases are being processed pending Table recommendations, Mr. Matanoski reiterated that the Court, petitioner's bar, and DOJ are sensitive to Table recommendations that are "in the works." Responding to Mr. King's question about whether or not science is being pushed too hard, Mr. Matanoski reiterated that claims are processed with the recognition that the Table may be more generous in terms of proving entitlement because the Table construct is based on policy considerations, as opposed to a petitioner having to prove cause-in-fact, which is based on science.

Petition to add diabetes mellitus as an injury for measles, mumps and rubella vaccine to the Vaccine Injury Table, Dr. Mary Rubin, Medical Officer, DVIC

Dr. Rubin stated that this petition was coming before the Commission because it was initiated by a public citizen and, by law, the Secretary must conduct a rulemaking proceeding on the terms of the petition or publish in the Federal Register an explanation for why such a proceeding was not conducted.

Dr. Rubin explained that diabetes mellitus is a common disease, often afflicting children. There are two forms. Type 1, an autoimmune disease, is most common in children and expresses itself by an insulin deficiency. Type 2 exhibits insulin resistance, an impairment in insulin secretion, is typically associated with hyperglycemia, and frequently affects obese individuals. The petition does not distinguish between the two types.

In the current scientific literature, which includes a 2012 Institute of Medicine study, there appears to be no causal relationship between measles-mumps-rubella (MMR) vaccine and Type 1 diabetes. There is also no apparent mechanistic evidence of any such relationship. Also in 2012, the Cochrane Collaboration assessed the administration of MMR vaccine in children to age 15 and found no likely association with Type 1 diabetes mellitus onset. Finally, also in 2012, Duderstadt et al., reviewed a cohort of military personnel in a retrospective study looking for initial diagnosis of Type 1 diabetes in the years 2002 through 2008 versus various vaccine exposures. The study found no increased risk in any vaccines studied, including MMR vaccine. Dr. Rubin noted that there were no studies of Type 2 diabetes. Dr. Rubin noted that she had provided a number of published studies to the Commission staff prior to the meeting, mainly related to diabetes in children.

Dr. Rubin invited discussion of the petition to add MMR-diabetes mellitus to the Table. Asked whether an individual with mumps may be more likely to become Type 1 diabetic, Dr. Rubin commented that there is no evidence that the live vaccine for mumps causes diabetes mellitus.

Mr. King confirmed that the individual who proposed the addition of diabetes mellitus to the Table was from the general public. Dr. Villareal observed that the Merck package insert includes a description of adverse events. Dr. Feemster added that the adverse events were listed in no rank order and included all adverse events that occurred during the drug trials. Mr. Kraus observed that there did not appear to be a rationale for adding the condition to the Table, and that there did not appear to be any basis for creating a presumption of causation of diabetes following MMR vaccination.

There was a motion, duly seconded, to recommend not adding diabetes mellitus to the Table. The motion was unanimously approved by the Commission.

Report from the Process Work Group, Dr. Luisita dela Rosa, ACCV Member

Dr. dela Rosa reported that the work group met by telephone on March 8 and focused discussion on two issues: consideration of the statistical table proposed by member of the public, Theresa Wrangham, on cases filed and adjudications; and a process by which the Commission could encourage action on recommendations submitted to the Secretary of HHS.

On the first topic, the work group looked at the differences in the table provided by Ms. Wrangham and the information published on the HRSA DVIC web site, which is updated monthly. The work group came to the following conclusions:

- Ms. Wrangham should be invited to a future Process Work Group meeting to discuss her proposal and related issues.
- In Ms. Wrangham's proposal, construction of the table requires detailed analysis of individual claims filed to determine facts related to the category "Not Compensable."
- All claim decisions are published on the CFC web site, including damages (but not attorney's fees), and various Internet search engines also provide access to case records. Cases decided by proffer or settlement are not usually described in detail.
- It appears that when a claimant attempts to engage an attorney to file a claim for which the statute of limitations has passed, the attorney is often reluctant to pursue the matter.

On the second topic, the work group agreed that the Secretary should respond to each recommendation submitted by the Commission, beyond the simple recognition that the recommendation was received. The work group recommends that the Commission discuss how to encourage action by the Secretary in at least making the recommendations public, especially those that would require legislative action for implementation.

The work group focused on extending the statute of limitations, a recommendation recently submitted to the Secretary. There was agreement that there are several circumstances that hinder timely submission of claims:

- There is an apparent lack of awareness of the program in spite of its being mentioned in the VISs.
- Health care providers often advise patients that a vaccine could not be a causative factor in an injury after vaccination.
- Attorneys may discourage claims by stating that a case has "no merit."
- Parents of vaccine-injured children may be so distracted by dealing with the injury that they become unaware of the passage of time.

Mr. King stated that the Commission had agreed to address the issue of the statute of limitations at the face-to-face meeting scheduled for September. At that time individuals from different interest groups will be invited to testify. He suggested that the work group consider that agenda item at their July work group meeting. Dr. dela Rosa agreed, but noted that it had been difficult to arrange meetings because of work group member scheduling conflicts. There was a suggestion that one individual on the work group, or a subgroup made up of the attorneys on the Commission, could act as coordinator of suggestions from the Commission members, which could be submitted by e-mail. Ms. Williams, Mr. Kraus and Mr. Smith agreed to be on the subgroup. Finally, Mr. King suggested that Ms. Herzog coordinate a July meeting of the work group, to which Ms. Wrangham could be invited.

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

Ms. Mulach reported on three NIAID activities, including a small study looking at immune response to tetanus-diphtheria-acellular pertussis (Tdap) vaccination in pregnant women, which showed safety and a positive immune response effect in women and newborns. A second intramural effort was undertaken to model human immune response to flu vaccine, and to predict the level of flu-specific antibodies after vaccination. The study might develop a potential framework for predicting an individual's responsiveness to vaccination.

The third activity, the Centers of Excellence for Influenza Research and Surveillance (CEIR) was begun about ten years ago. In addition to global surveillance in South America, Europe, Africa and the Far East, the program has a goal of developing a universal flu vaccine.

Finally, Ms. Mulach mentioned two planned meetings in June, one co-sponsored by NIAID and FDA on Common Barriers in Vaccine Research and Development; and a second under the NIAID Meeting Report umbrella looking at dengue fever and Staphylococcus aureus.

Review of Vaccine Information Statements, Mr. Skip Wolfe, CDC

The Commission first considered the VIS for Gardasil human papillomavirus vaccine (HPV). In the first section -- "Why get vaccinated?"—there was agreement that the vaccine should be described as preventing "many" types of cancer, which is more accurate than the phrase "Gardasil prevents cancer caused by HPV." There was also agreement to put the prevention of genital warts in both sexes under its own bullet. There was an observation that to emphasize that the infection comes from sexual contact, even though a correct statement, is often unsettling to parents of children of the age recommended for the vaccination – 11-12 years old. The final paragraph in Section 1 should begin, "Most people will become infected at some point in their life," and then mention the primary cause (sexual contact) later in the paragraph. Some parents may feel that their abstinent children would not need the vaccine.

Mr. Wolfe explained that Section 2 had been simplified by omitting the scheduling of HPV vaccinations and simply advising individuals that HPV vaccine is usually initially given at about age 11 or 12 and may be given up to age 26. There was a recommendation to add that the HPV series usually involves three doses, since without that information patients may not be aware of the number or finish the course.

Mr. Wolfe moved to Section 3, noting that, since individuals may not know they are allergic to yeast, that allergy was specifically mentioned in this VIS. He added that the word "severe" and "life threatening" may be redundant, and there was an observation that the parentheses could be removed. Finally, although there was a comment that the last sentence about whether or not to accept vaccination if one has a mild or moderately severe illness is vague, there was agreement to leave it unchanged since the physician would be in the best position to advise the patient.

Under Section 4, Risks of a vaccine reaction, there was a comment about the missing warning about the most serious side effects, such as death, and Mr. Wolfe stated that the wording of that warning was under review, including legal counsel review, but that it would eventually be added.

Dr. Shimabukuro noted that the three statements in the section about serious side effects may be contradictory (serious side effects are very rare, serious problems have been associated with HPV, severe allergic reactions from a vaccine are very rare). He explained that if the statement was worded to indicate that no serious adverse reactions were causally associated with HPV vaccine, then the statement would be more accurate. However, adding a reference to Vaccine Adverse Event Reporting System (VAERS) might be inappropriate since any reaction can be reported to VAERS without any substantiation regarding causation.

Ultimately the Commission agreed that the following sentence should be removed from the VIS: No serious problems have been associated with HPV vaccine.

Mr. Wolfe noted that there had been no changes in Sections 5, 6 and 7, although in Section 6 wording about the statute of limitation will be added once that wording is finalized. Dr. Houston noted that there was a general statement in the VIS being reviewed that a time limit exists, and Mr. King suggested that the actual time limits of the statute should be included in the VIS. Mr. Wolfe commented that there is a line between providing enough information and too much information, such that individuals reading the VIS may be overwhelmed by the volume of information. Mr. King also suggested that the order of the VIS might be reversed, beginning with risks. After discussion, there was agreement that putting risks, including risk of death, at the beginning might first, unnecessarily intimidate patients, and second, might suggest that the risks are the most important consideration, rather than the benefits. There was also agreement that the natural chronology of the experience would be most appropriate – the reasons for the vaccine, contraindications, adverse reactions and responses to adverse reactions, and the final administrative information about the VICP and sources of information.

Mr. Wolfe turned to the VIS for Cervarix. With a few exceptions the text is the same for both Gardasil and Cervarix. A difference is that Cervarix is recommended only for women and

the predominant risk is for cervical cancer. There is also no yeast in the Cervarix formulation so there is no mention of yeast effects in the VIS. Mr. Wolfe confirmed that the changes agreed on for Gardasil would also be made in the Cervarix VIS.

Finally, Mr. Wolfe described the VIS that covers multiple newborn vaccines. The structure of the VIS is similar to the individual VISs in that information about each of the six vaccines is covered in condensed form under the same major headings: (1) Why get vaccinated; (2) Some children should not get certain vaccines; (3) Risks of vaccine reactions; (4) Problems that could happen after any vaccination; (5) What if there is a serious reaction; (6) The VICP; and (7) Sources of additional information.

Asked why the consolidated VIS was developed, Dr. Wolfe explained that the single VIS replaces multiple forms that repeat most of the information, thereby reducing the time it takes for a parent to read and understand the content. The response from providers has been positive. There have been requests for a similar VIS for adolescents.

Mr. King noted that 15,000 individuals died before the universal vaccination program in the US and there was a brief discussion about the importance of the herd effect, which effectively eliminated fatalities. However, it was noted that publicizing herd immunity might cause people to bypass vaccination and lead to deterioration in herd immunity. There was agreement that the wording in the second paragraph following the description of rotavirus should not include the reference to "generations of parents who made sure their children were vaccinated," since it could be interpreted an indictment of parents who do not allow their children to be vaccinated, some or many of whom could have legitimate reasons.

Referring to the table of information describing the vaccines that are intended for newborns, doses in the series, ages and comments, Mr. Wolfe asked for consensus that the table was appropriate to the VIS. The Commission agreed that the information in the table would be helpful. Mr. Wolfe stated that the explanatory sentence following the table would serve to allow the provider to limit the vaccines to the six described.

There was a brief discussion about including some reference to the parents' role in deciding whether or not a child receives a vaccination, and the importance of the health care provider's recommendations. Under Section 2, *Some children should not get certain vaccines,* Mr. Wolfe agreed to review the list of specific conditions described under *"Talk to your doctor,"* to make sure that each is a true contraindication that would indicate that the child should not receive a vaccine.

Mr. Wolfe stated that the statute of limitation language would be added to this VIS, and Dr. Shimabukuro commented that the wording on the rare risk of death was being worked on and would be submitted for review when available. There was an observation that the incidence of death related to a vaccination is so rare that it would be impractical, if not impossible, to provide any statistical risk information. Mr. King suggested putting the reference to death risk in the VICP section, adding the simple statement that the reports are extremely rare without getting involved with the statistics and causation. Dr. Shimabukuro suggested: In these rare instances

the contribution of the vaccine to the condition can be difficult to determine. Mr. King commented that the wording was an improvement and should be considered for the VIS.

Update on the vaccine activities of the of the Center for Biologics, Evaluation and Research (CBER), FDA, LCDR Valerie Marshall, CBER, FDA

LCDR Marshall reported that in January 2014, the FDA approved three supplements to the biologics application for pneumococcal 13-valent conjugate vaccine, Prevnar13®, to include text in the US Prescribing Information (USPI) for the use of Prevnar 13® in HIV-infected adults 50 years of age and older, preterm infants less than 37 weeks of gestational age, and children and adolescents age 6 to less than 18 years of age with sickle cell disease.

In March 2014, the FDA approved a supplement to lower the age indication for Adacel (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed) from 11 to 10 years of age.

In March and April 2014, the FDA granted breakthrough therapy designation, which is an expedited review program, respectively, to Pfizer's candidate type B meningococcal vaccine, and to Novartis' type B meningococcal vaccine.

In May 2014 the FDA approved a supplement to the Biologics License Application (BLA) for the rotavirus vaccine, live, oral, trade name Rotarix, to include a summary of post-marketing surveillance data suggestive of an increased risk of intussusception in the seven days following the administration of the second dose.

In May 2014, the FDA published an update to earlier FDA/CDC communications, which described increased VAERS reports of febrile seizures following vaccination with Fluzone during the 2010-2011 flu season. Results from an FDA Post-Licensure Rapid Immunization Safety Monitoring (PRISM) study demonstrated no statistically significant association between trivalent influenza vaccine (TIV) and febrile seizures in children during the 2010-2011 influenza season.

On June 4, 2014, the Science Board of the FDA discussed and made recommendations on the draft final report from CBER's Post-Marketing Safety Review Subcommittee.

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

Dr. Bok, a vaccine safety specialist at NVPO, reported that NVAC would meet in the week following the ACCV meeting, and would review and possibly approve recommendations to reduce patient and provider barriers to maternal vaccine administration. A number of public comments were received. A group B strep support group expressed concern that litigation in matters involving adverse vaccine outcomes might become barriers to health professionals in promoting maternal vaccine administration.

The American Academy of Pediatrics supported broadening the eligibility of the VICP to include infants injured in utero. It is important for VICP to define which fetal outcomes are related to vaccines. The Academy supported the NVAC report recommendation 5.

The National Vaccine Information Center expressed concern for the lack of credible research on vaccines for pregnant women. The NVIC is not in favor to providing legal protection under the VICP to vaccine manufacturers for liability for vaccine-related injury.

The final report from NVAC should be available after the meeting.

Update on the Immunization Safety Office (ISO), CDC, Dr. Tom Shimabukuro, CDC.

Dr. Shimabukuro previewed his presentation in which he would recap the February 2014 Advisory Committee on Immunization Practices (ACIP), and preview the upcoming June 2014 ACIP meeting, and look at several recent publications.

The Committee voted to accept the recommendations for the influenza vaccine formulation for the 2014-2015 flu season based on the same recommendations made for 2013-2014. The Committee also approved the updates for HPV – to consolidate recommendations for males and females; to consolidate bivalent and quadrivalent vaccine recommendations; to harmonize wording; and to add a section on history of sexual abuse or assault.

There was an interim vaccine safety update for live attenuated (LAIV) and inactivated (IIV) influenza vaccines (quadrivalent and trivalent), based on VAERS and Vaccine Safety Datalink (VSD) data through the end of last year in persons 18 years of age and younger, which revealed no safety concerns. Dr. Shimabukuro noted that the trivalent live attenuated vaccine had been replaced by quadrivalent vaccine for the 2013-2014 flu season. There was also a comparison analysis for LAIV and IIV in children aged two to eight which suggested a slightly higher efficacy for LAIV over IIV, but no significant differences in hospitalizations, flu-like illness or acute respiratory illness requiring medical attention. There was a slightly increased transient fever after LAIV versus IIV.

Dr. Shimabukuro reported on a presentation on Tdap in pregnancy based on VAERS that showed no new safety concerns for women who received Tdap (or their infants), but there were few reports on women who received repeated doses (CDC will continue to monitor reports with special focus on repeated vaccinations). There was also a presentation of VSD data that showed no increase in risk after Tdap vaccination of pregnant women for adverse birth outcomes, although there was a very slight increased risk of chorioamnionitis, a factor in increased risk of preterm birth that merits further study. However, there was no actual increased risk of preterm birth in the VSD data.

In the HPV session, epidemiologic data was discussed. With regard to cervical intraepithelial neoplasia grade 2 and 3 lesions: 50% were attributable to HPV 16/18 (which is in the HPV vaccine) and 25% were attributable to 5 additional types in investigational 9-valent vaccine. For cancers associated with HPV, about 62% were attributable to HPV 16/18 and about

11% were attributable to 5 additional types in 9-valent vaccine. Merck, manufacturer of the 9-valent version, made the presentation for that vaccine, which is under FDA review with licensure anticipated in 2015.

Dr. Shimabukuro previewed the agenda for the June 25-26, 2014 ACIP meeting. There will be two sessions, one an update on the 2013-2014 influenza season, and the other a vaccine safety session that will include reports on the PRISM system that evaluated the discovery of febrile seizures related to the 2010-2011 influenza season; and a VSD study of safety issues related to administration of multiple vaccines, also related to the 2010-2011 signal for febrile seizures.

Turning to publications, Dr. Shimabukuro mentioned the following:

- Hambidge et al, on timely versus delayed early childhood vaccinations ad seizures, showed that delaying MMR vaccine until the second year of life does increase the risk of febrile seizures, but Dr. Shimabukuro noted that the risk of febrile seizures in the first year of life it typically low, increasing in the second year.
- Haber et al, analysis of a post-licensure VAERS surveillance of trivalent live attenuated influenza vaccine in children 2-18, showed no new or unexpected adverse event patterns.
- Naleway et al, looking in two studies at the safety of influenza vaccine given during pregnancy showed no association between inactivated influenza vaccination and gestational diabetes, gestational hypertension, preeclampsia/eclampsia, or chorioamnionitis. The analysis should reassure women with regard to vaccination for influenza during pregnancy.
- Nordin et al, looked at maternal influenza vaccine and risks for preterm or small for gestational age birth. Receipt of trivalent inactivated influenza vaccine during pregnancy was not associated with increased or decreased risk of preterm or small for gestational age birth.

Public Comment

Ms. Wrangham expressed appreciation for the Commission's work on recommendations concerning the Table, noting however that the documents distributed at the meeting to Commission members were not available on the VICP web site. She requested that the Commission staff provide copies of those documents if possible.

Ms. Wrangham reiterated her remarks made at the outset of the meeting, that an individual who may have genetic predisposition or susceptibilities to a condition may not see the manifestation of those conditions unless triggered by an outside circumstance. A vaccine could be the trigger, and if that is demonstrated, that individual should be eligible for the protections of the VICP.

Ms. Wrangham commented that the statements made with regard to herd immunity were not completely accurate, and that the VISs must include a description of the three risks related to

vaccines – that the vaccines may fail to protect, that the vaccines may cause injury, that the vaccines may result in death. The VIS is less detailed than in the past and does not now fully explain these risks. Nor does the law require that parents read the VIS or that health care providers explain the contents of a VIS before administering a vaccine.

Ms. Wrangham stated that the first section of the VIS, "*Why get vaccinated,*" is inappropriate. Since the VIS is an informational document, the data should be factual and not designed to encourage an individual to be vaccinated. The VIS should be more effective in explaining the importance of the time limits related to filing an injury claim. The gaps in research are not well understood by the general public, and explaining the known and unknown risks of a vaccine should be included in the VIS. A list of vaccine ingredients should be included to allow consumers to identify possible allergic components in a vaccine.

Ms. Wrangham stated that the ACCV should meet in person, as do the other important vaccine advisory committees.

Future Agenda Items/New Business

Mr. King recalled that recommendations to the Secretary should be supported by the other interested agencies. If the ACCV makes a recommendation about an issue that involves federal enforcement, that interested agencies should respond to the recommendation with a sense of cooperation – for example, if an ACCV recommendation is to add an injury to the Table, HHS and the Department of Justice should relax its position with regard to granting concessions for that injury and be more liberal in considering the petition. Dr. Villareal suggested that the Table be carefully reviewed at the September in-person meeting. Noting the problems encountered earlier in the meeting concerning the wording and formatting of the various versions of the Table language, Dr. Houston suggested that, before the next meeting, those issues should be fully reviewed and corrected so that the Commissioners will be dealing with the correct drafts.

Mr. King reiterated his concern that the new Commission members be added such that the entire Commission is not changed at a single time. It would adversely affect the continuity of the Commission's deliberations.

Adjournment

Mr. King called for a motion to adjourn. On motion duly made and seconded, the Commission approved adjournment.

3

Vaccine Injury Compensation Trust Fund

Balance as of June 30, 2014

$3,441,236,922.07

Figures for October 1, 2013 – June 30, 2014

Excise Tax Revenue: $127,241,986
Interest on Investments: $45,740,737
Net Income: $172,982,723
Interest as a Percentage of Net Income: 26%

Source: U.S. Treasury, Bureau of Public Debt
August 11, 2014

4

4.1

Petitions Filed

Fiscal Year	Total
FY 1988	24
FY 1989	148
FY 1990	1,492
FY 1991	2,718
FY 1992	189
FY 1993	140
FY 1994	107
FY 1995	180
FY 1996	84
FY 1997	104
FY 1998	120
FY 1999	411
FY 2000	164
FY 2001	216
FY 2002	957
FY 2003	2,592
FY 2004	1,214
FY 2005	735
FY 2006	325
FY 2007	410
FY 2008	417
FY 2009	397
FY 2010	449
FY 2011	386
FY 2012	400
FY 2013	503
FY 2014	451
Total	**15,333**

Adjudications[1]

Fiscal Year	Compensable	Dismissed	Total
FY 1989	9	12	21
FY 1990	100	33	133
FY 1991	141	447	588
FY 1992	166	487	653
FY 1993	125	588	713
FY 1994	162	446	608
FY 1995	160	575	735
FY 1996	162	408	570
FY 1997	189	198	387
FY 1998	144	181	325
FY 1999	98	139	237
FY 2000	125	104	229
FY 2001	86	87	173
FY 2002	104	103	207
FY 2003	56	99	155
FY 2004	62	233	295
FY 2005	60	121	181
FY 2006	69	191	260
FY 2007	82	121	203
FY 2008	147	134	281
FY 2009	134	231	365
FY 2010	180	293	473
FY 2011	265	1,370	1,635
FY 2012	261	2,439	2,700
FY 2013	367	627	994
FY 2014	236	139	375
Totals	**3,690**	**9,806**	**13,496**

[1]Generally, petitions/claims are not adjudicated in the same fiscal year as filed. On average, it takes 2-3 years to adjudicate a petition/claim after it is filed.

U.S. Department of Health and Human Services
HRSA
Health Resources and Services Administration

Awards Paid[1]

Fiscal Year	Compensated[2]			Dismissed		Interim Fees		Total Outlays
	# of Awards	Petitioners' Award Amount	Attorneys' Fees/ Cost Payments	# of Payments to Attorneys	Attorneys' Fees/ Costs Payments	# of Payments to Attorneys	Attorneys' Fees/ Costs Payments	
FY 1989	6	$1,317,654.78	$54,107.14	0	$0.00	0	$0.00	$1,371,761.92
FY 1990	88	$53,252,510.46	$1,379,005.79	4	$57,699.48	0	$0.00	$54,689,215.73
FY 1991	114	$95,980,493.16	$2,364,758.91	30	$496,809.21	0	$0.00	$98,842,061.28
FY 1992	130	$94,538,071.30	$3,001,927.97	118	$1,212,677.14	0	$0.00	$98,752,676.41
FY 1993	162	$119,693,267.87	$3,262,453.06	272	$2,447,273.05	0	$0.00	$125,402,993.98
FY 1994	158	$98,151,900.08	$3,571,179.67	335	$3,166,527.38	0	$0.00	$104,889,607.13
FY 1995	169	$104,085,265.72	$3,652,770.57	221	$2,276,136.32	0	$0.00	$110,014,172.61
FY 1996	163	$100,425,325.22	$3,096,231.96	216	$2,364,122.71	0	$0.00	$105,885,679.89
FY 1997	179	$113,620,171.68	$3,898,284.77	142	$1,879,418.14	0	$0.00	$119,397,874.59
FY 1998	165	$127,546,009.19	$4,002,278.55	121	$1,936,065.50	0	$0.00	$133,484,353.24
FY 1999	96	$95,917,680.51	$2,799,910.85	117	$2,306,957.40	0	$0.00	$101,024,548.76
FY 2000	136	$125,945,195.64	$4,112,369.02	80	$1,724,451.08	0	$0.00	$131,782,015.74
FY 2001	97	$105,878,632.57	$3,373,865.88	57	$2,066,224.67	0	$0.00	$111,318,723.12
FY 2002	80	$59,799,604.39	$2,653,598.89	50	$656,244.79	0	$0.00	$63,109,448.07
FY 2003	65	$82,816,240.07	$3,147,755.12	69	$1,545,654.87	0	$0.00	$87,509,650.08
FY 2004	57	$61,933,764.20	$3,079,328.55	69	$1,198,615.96	0	$0.00	$66,211,708.71
FY 2005	64	$55,065,797.01	$2,694,664.03	71	$1,790,587.29	0	$0.00	$59,551,048.33
FY 2006	68	$48,746,162.74	$2,441,199.02	54	$1,353,632.61	0	$0.00	$52,540,994.37
FY 2007	82	$91,449,433.89	$4,034,154.37	61	$1,692,020.25	0	$0.00	$97,175,608.51
FY 2008	141	$75,716,552.06	$5,191,770.83	73	$2,511,313.26	2	$117,265.31	$83,536,901.46
FY 2009	131	$74,142,490.58	$5,404,711.98	36	$1,557,139.53	28	$4,241,362.55	$85,345,704.64
FY 2010	173	$179,387,341.30	$5,961,744.40	56	$1,886,239.95	22	$1,978,803.88	$189,214,129.53

Awards Paid[1]

Fiscal Year	Compensated[2]			Dismissed		Interim Fees		Total Outlays
	# of Awards	Petitioners' Award Amount	Attorneys' Fees/ Cost Payments	# of Payments to Attorneys	Attorneys' Fees/ Costs Payments	# of Payments to Attorneys	Attorneys' Fees/ Costs Payments	
FY 2011	251	$216,319,428.47	$9,736,216.87	402	$5,425,243.19	28	$2,001,770.91	$233,482,659.44
FY 2012	250	$163,511,998.82	$9,104,488.60	1,017	$8,621,182.32	37	$5,420,257.99	$186,657,927.73
FY 2013	375	$254,666,326.70	$13,333,179.53	703	$6,970,278.84	50	$1,454,851.74	$276,424,636.81
FY 2014	283	$177,021,428.49	$9,194,846.05	462	$6,107,799.29	32	$2,115,589.48	$194,438,663.31
Total	**3,683**	**2,776,928,746.90**	**114,546,802.38**	**4,836**	**63,250,314.23**	**199**	**17,329,901.86**	**2,972,054,765.39**

[1]"Compensated" are claims that have been paid as a result of a settlement between parties or a decision made by the U.S. Court of Federal Claims (Court). The # of awards is the number of petitioner awards paid, including the attorneys' fees/costs payments, if made during a fiscal year. However, petitioners' awards and attorneys' fees/costs are not necessarily paid in the same fiscal year as when the petitions/claims are determined compensable. "Dismissed" includes the the # of payments to attorneys and the total amount of payments for attorneys' fees/costs per fiscal year. The VICP will pay attorneys' fees/costs related to the claim, whether or not the petition/claim is awarded compensation by the Court, if certain minimal requirements are met. "Total Outlays" are the total amount of funds expended for compensation and attorneys' fees/costs from the Vaccine Injury Compensation Trust Fund by fiscal year.

[2]Due to the populations receiving vaccines added to the VICP in recent years, the proportion of adults to children seeking compensation has changed. Since influenza vaccines (vaccines administered to large numbers of adults each year) were added to the VICP in 2005, many adult claims related to that vaccine have been filed.

4.2

U.S. Department of Health and Human Services
HRSA
Health Resources and Services Administration

National Vaccine Injury Compensation Program (VICP) Adjudication Categories by Vaccine for Claims Filed Calendar Year 2006 to Present[1]

Vaccine Alleged by Petitioner[2]	No. of Doses Distributed US CY 2006 - CY 2012 (Source: CDC)[3]	Compensable			Compensable Total	Dismissed/ Non-Compensable Total	Grand Total
		Concession	Court Decision	Settlement			
DT	592,707	1	0	3	4	4	8
DTaP	68,113,573	10	17	71	98	70	168
DTaP-Hep B-IPV	38,347,667	4	6	18	28	35	63
DTaP-HIB	1,135,474	0	0	0	0	1	1
DTaP-IPV-HIB	46,633,881	0	0	5	5	11	16
DTP	0[4]	0	1	2	3	3	6
Hep A-Hep B	10,405,325	0	0	8	8	0	8
Hep B-HIB	4,621,999	1	1	1	3	1	4
Hepatitis A (Hep A)	110,596,300	1	4	18	24	18	42
Hepatitis B (Hep B)	116,853,062	2	10	35	47	34	81
HIB	70,755,674	0	1	4	5	4	9
HPV	55,168,454	10	0	61	71	80	151
Influenza[5]	809,000,000	30	68	701	799	156	955
IPV	52,439,162	0	0	3	3	2	5
Measles	135,660	0	0	1	1	0	1
Meningococcal	51,173,032	1	1	22	24	3	27
MMR	65,864,745	15	13	52	80	67	147
MMR-Varicella	8,073,618	8	0	7	15	8	23
Nonqualified[6]	N/A	0	0	0	0	21	21
OPV	0	1	0	0	1	3	4

National Vaccine Injury Compensation Program (VICP) Adjudication Categories by Vaccine for Claims Filed Calendar Year 2006 to Present[1]

Vaccine Alleged by Petitioner[2]	No. of Doses Distributed US CY 2006 - CY 2012 (Source: CDC)[3]	Compensable			Compensable Total	Dismissed/ Non-Compensable Total	Grand Total
		Concession	Court Decision	Settlement			
Pneumococcal Conjugate	123,606,306	0	1	5	6	13	19
Rotavirus	61,336,583	1	3	15	19	6	25
Rubella	422,548	0	1	0	1	0	1
Td	53,009,015	4	5	49	58	15	73
Tdap	133,744,203	11	6	72	89	11	100
TETANUS	3,836,052	3	0	16	19	10	29
Unspecified[7]	N/A	1	0	2	3	540	543
Varicella	82,534,257	3	5	19	27	10	37
Grand Total	**1,968,399,297**	**107**	**143**	**1,190**	**1,441**	**1,126**	**2,567**

DEFINITIONS:

• Compensable – The injured person who filed a claim was paid money by the VICP. Compensation can be achieved through a concession by the Department of Health and Human Services (HHS), a decision on the merits of the claim by a special master or a judge of the United States Court of Federal Claims (Court), or a settlement between the parties.

• Concession: HHS concludes that a petition should be compensated based on a thorough review and analysis of the evidence, including medical records and the scientific and medical literature. The HHS review concludes that the petitioner is entitled to compensation, including a determination either that it is more likely than not that the vaccine caused the injury or the evidence supports fulfillment of the criteria of the Vaccine Injury Table. The Court also determines that the petition should be compensated.

• Court Decision: A special master or the court, within the United States Court of Federal Claims, issues a legal decision after weighing the evidence presented by both sides. HHS abides by the ultimate Court decision even if it maintains its position that the petitioner was not entitled to compensation (e.g., that the injury was not caused by the vaccine).

• For injury claims, compensable court decisions are based in part on one of the following determinations by the court:

• The evidence is legally sufficient to show that the vaccine more likely than not caused (or significantly aggravated) the injury; or

- The injury is listed on, and meets all of the requirements of, the Vaccine Injury Table, and HHS has not proven that a factor unrelated to the vaccine more likely than not caused or significantly aggravated the injury. An injury listed on the Table and meeting all Table requirements is given the legal presumption of causation. It should be noted that conditions are placed on the Table for both scientific and policy reasons.

- Settlement: The petition is resolved via a negotiated settlement between the parties. This settlement is not an admission by the United States or the Secretary of Health and Human Services that the vaccine caused the petitioner's alleged injuries, and, in settled cases, the Court does not determine that the vaccine caused the injury. A settlement therefore cannot be characterized as a decision by HHS or by the Court that the vaccine caused an injury. Claims may be resolved by settlement for many reasons, including consideration of prior court decisions; a recognition by both parties that there is a risk of loss in proceeding to a decision by the Court making the certainty of settlement more desirable; a desire by both parties to minimize the time and expense associated with litigating a case to conclusion; and a desire by both parties to resolve a case quickly and efficiently.

- Non-compensable/Dismissed – The injured person who filed a claim was ultimately not paid money.
  - Non-compensable Court decisions include the following:
    - The Court determines that the person who filed the claim did not demonstrate that the injury was caused (or significantly aggravated) by a covered vaccine or meet the requirements of the Table (for injuries listed on the Table).
    - The claim was dismissed for not meeting other statutory requirements (such as not meeting the filing deadline, not receiving a covered vaccine, and not meeting the statute's severity requirement).
    - The injured person voluntarily withdrew his or her claim.

[1]The date range for this table was selected to reflect the status of the current Program since the inclusion of influenza in July 2005, which now constitutes the majority of all VICP claims.

[2]This is the first vaccine listed by the petitioner in the claim, and other vaccines may be alleged or may form the basis of compensation.

[3]Vaccine doses are self-reported distribution data provided by US-licensed vaccine manufacturers. The data provide an estimate of the annual national distribution and do not represent vaccine administration. In order to maintain confidentiality of an individual manufacturer or brand, the data are presented in an aggregate format by vaccine type.

[4]Whole cell pertussis vaccines were not distributed during this time period.

[5]Flu doses are derived from CDC's FluFinder tracking system, which includes data provided to CDC by US-licensed influenza vaccine manufacturers as well as their first line distributors.

[6]Claims filed for vaccines which are not covered under the VICP.

[7]Insufficient information submitted by petitioner to make an initial determination. The concession was for multiple unidentified vaccines that caused abscess formation at the vaccination site(s), and the settlements were for multiple vaccines later identified in the Special Master's Decisions.

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5.1

The National Vaccine Injury Compensation Program (VICP)

Division of Injury Compensation Programs Update

Advisory Commission on Childhood Vaccines
September 4, 2014
A. Melissa Houston, M.D., M.P.H., F.A.A.P

Department of Health and Human Services
Health Resources and Services Administration

ACCV Meeting Highlights

- Clarification on Proposed Changes to the Vaccine Injury Table
- Update from the Department of Justice Vaccine Litigation Office
- VICP Outreach Plan
- Report from the ACCV Process Workgroup
- Discussion on Proposed Revisions to VAERS Form (2.0)
- Vaccine Safety Presentations on Pneumococcal Polysaccharide (Pneumovax 23) and Zoster (Shingles)
- Updates from ACCV Ex Officio Members — FDA, CDC, NIH, NVPO

Number of Petitions Filed as of August 1, 2014

Average annual number of petitions filed during FY 2009-2013 = 427

Fiscal Year	Total
FY 2009	397
FY 2010	449
FY 2011	386
FY 2012	400
FY 2013	503
FY 2014	451

Number of Adjudications as of August 1, 2014

Fiscal Year	Compensable	Dismissed	Total
FY 2009	134	231	365
FY 2010	180	293	473
FY 2011	265	1,370	1,635
FY 2012	261	2,439	2,700
FY 2013	367	627	994
FY 2014	236	139	375

Adjudication Categories for Non-Autism Claims FY 2012 – FY 2014 as of August 11, 2014

Adjudication Category	FY 2012	FY 2013	FY 2014 As of 8/11/14
Compensable	261 (100%)	367 (100%)	249 (100%)
❖Concession	13 (5%)	21 (6%)	24 (10%)
❖Court Decision (includes proffers)	30 (11%)	21 (6%)	20 (8%)
❖Settlement	218 (84%)	325 (88%)	205 (82%)
Not Compensable	144	88	100
Adjudication Total	405	455	349

Award Amounts Paid as of August 1, 2014

Fiscal Year	Petitioners' Award	Attorneys' Fees & Costs
FY 2009	$74,142,491	$11,203,212
FY 2010	$179,387,341	$9,826,786
FY 2011	$216,319,428	$17,163,229
FY 2012	$163,511,999	$23,148,927
FY 2013	$254,666,326	$21,758,308
FY 2014	$177,021,428	$17,418,234

Vaccine Injury Compensation Trust Fund

- Balance as of June 30, 2014
  - $3,441,236,922.07

- Activity from October 1, 2013 to June 30, 2014
  - Excise Tax Revenue: $127,241,986
  - Interest on Investments: $45,740,737
  - Net Income: $172,982,723
  - Interest as a Percentage of Net Income: 26%

Source: U.S. Treasury, Bureau of Public Debt (August 11, 2014)

Significant Activities

- National Vaccine Advisory Committee
  - June 10 & 11, 2014

- Advisory Committee on Immunization Practices
  - June 25 & 26, 2014

Significant Activities

- Since the last ACCV Meeting, DVIC has been responding to requests for information from GAO.
- GAO has asked questions about the Vaccine Injury Compensation Trust Fund, outreach efforts, process for making changes to the Vaccine Injury Table and claims processing data.
- GAO plans to submit its draft report to DVIC in mid-September.

Public Comment/Participation in Commission Meetings

Annie Herzog
Parklawn Building, Room 11C-26
5600 Fishers Lane
Rockville, Maryland 20857
Phone: 301-443-6634
Email: aherzog@hrsa.gov

5.2

5.3

Report from the Department of Justice

September 4, 2014

Vincent J. Matanoski
Deputy Director, Torts Branch

1

Statistics

Reporting Period: 5/16/14 – 8/15/14

I. **Total Petitions Filed in the United States Court of Federal Claims this reporting period: 168**
   A. Minors: 43
   B. Adults: 125

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Statistics

Reporting Period: 5/16/14 – 8/15/14

II. Total Petitions Adjudicated this reporting period: 152

A. Compensated: 104

i. Cases conceded by HHS: 14

1. Decision awarding damages: 0
2. Decision adopting Proffer: 12
3. Decision adopting Settlement: 2

ii. Cases not conceded by HHS: 90

1. Decision awarding damages: 0
2. Decision adopting Proffer: 2
3. Decision adopting Settlement: 88

B. Not Compensated/Dismissed: 48

i. Decision dismissing Non-OAP: 44

ii. Decision dismissing OAP: 4

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Statistics

Reporting Period: 5/16/14 – 8/15/14

III. Total Petitions Voluntarily Withdrawn this reporting period (no judgment will be issued): 9

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Appeals: U.S. Supreme Court

- *Tembenis v. Sebelius*
- Petitioners' petition for a writ of certiorari was denied on June 30, 2014

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Appeals: U.S. Court of Appeals for the Federal Circuit

Recently Decided Cases

Appeals by Petitioner:

- *Graves v. HHS*: Affirmed
- *Price v. HHS*: Affirmed; petition for *en banc* rehearing denied

Appeals by Respondent:

- *Dobrydnev v. HHS*: Reversed; petition for panel rehearing filed

All decisions are available on the CAFC's website: http://www.cafc.uscourts.gov

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Appeals: U.S. Court of Appeals for the Federal Circuit

Pending Cases

Appeals by Petitioner:

- *Simanski v. HHS* (Entitlement)
- *Flores v. HHS* (Entitlement)
- *Koehn v. HHS* (Entitlement)

Appeals by Respondent:

- *Paluck v. HHS* (Entitlement)

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Appeals: U.S. Court of Federal Claims

Recently Decided Cases

Appeals by Petitioner:

- *Bast v. HHS*: Affirmed (Entitlement)
- *Scanlon v. HHS*: Vacated, Remanded (Attorneys' Fees and Costs)

All decisions are available on the CFC's website: http://www.uscfc.uscourts.gov

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Appeals: U.S. Court of Federal Claims

Pending Cases

Appeals by Petitioner:

- *Castaldi v. HHS** (Statute of Limitations, Entitlement)
- *Mosley v. HHS** (Entitlement)
- *Godfrey v. HHS** (Entitlement)
- *Harris v. HHS** (Entitlement)
- *Somosot v. HHS* (Statute of Limitations)
- *Griffin v. HHS* (Entitlement)
- *Crutchfield v. HHS* (Entitlement)
- *D'Angiolini v. HHS* (Entitlement)
- *Stillwell v. HHS* (Entitlement)

*Yellow cases are new this reporting period 9

Scheduled Oral Arguments

U.S. Court of Appeals for the Federal Circuit:

- None scheduled at this time

U.S. Court of Federal Claims:

- None scheduled at this time

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Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Guillain-Barré Syndrome	1 year, 8 months
Flu	Transverse myelitis	1 year, 7 months
Flu	Guillain-Barré Syndrome	11 months
Flu	Guillain-Barré Syndrome	11 months
Tdap	Guillain-Barré Syndrome	8 months
Flu	Brachial neuritis	2 years, 8 months
Tdap	Chronic Inflammatory Demyelinating Polyneuropathy	2 years, 2 months
Flu	Guillain-Barré Syndrome and small fiber neuropathy	1 year, 9 months
Tdap	Guillain-Barré Syndrome	2 years, 2 months
Flu	Brachial plexus neuropathy	1 year, 3 months

*Terms of settlement are memorialized by Stipulation

(continued . . .) 11

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu, Td	Guillain-Barré Syndrome	7 months
Varicella, Flu	Immune Thrombocytopenia Purpura	3 years, 10 months
Flu	Guillain-Barré Syndrome	3 years, 2 months
Flu, MCV	Transverse myelitis	2 years, 6 months
Flu	Brachial neuritis	8 months
Flu	Guillain-Barré Syndrome	8 months
Tdap	Parsonage-Turner syndrome; or significant aggravation of Parsonage-Turner Syndrome	7 months
Tdap	Transverse myelitis	8 months
Flu	Guillain-Barré Syndrome	6 months
Flu	Mononeuropathy of the 6th cranial nerve and esotropia	4 years, 6 months

*Terms of settlement are memorialized by Stipulation

(continued . . .) 12

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Chronic Inflammatory Demyelinating Polyneuropathy	3 years, 10 months
Flu	Guillain-Barré Syndrome	1 year, 6 months
Flu	Bilateral upper extremity swelling, paresthesias, and arthritis	10 months
Flu	Shoulder injury related to vaccine administration and rheumatoid arthritis	10 months
Flu	Left optic neuritis with permanent vision loss	1 year, 8 months
Flu	Guillain-Barré Syndrome	1 year, 2 months
Flu	Guillain-Barré Syndrome, Bell's palsy, and hypertension	9 months
Flu	Left arm and shoulder injury	9 months
Flu	Guillain-Barré Syndrome	9 months
Flu	Guillain-Barré Syndrome	9 months

*Terms of settlement are memorialized by Stipulation

(continued . . .)

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Guillain-Barré Syndrome	8 months
Tdap	Psoriatic arthritis	7 months
Flu	Guillain-Barré Syndrome, death	1 year, 8 months
Flu	Transverse myelitis	9 months
Flu	Chronic Inflammatory Demyelinating Polyneuropathy	1 year, 9 months
Flu	Guillain-Barré Syndrome	2 years, 7 months
Tdap, Flu	Guillain-Barré Syndrome, death	1 year, 1 month
Flu	Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyneuropathy	7 months
Tdap	Sensory neuropathy	1 year, 9 months
Flu	Brachial neuritis and/or a similar condition	9 months

*Terms of settlement are memorialized by Stipulation

(continued . . .)

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Guillain-Barré Syndrome	2 years
Flu	Neurological injury	8 months
Flu	Anaphylaxis, a non-anaphylactic reaction, or an asthma attack that caused death; or significant aggravation of pre-existing exercise-induced asthma which caused death	1 year, 9 months
Tdap, Flu	Guillain-Barré Syndrome	1 year, 2 months
Flu	Brachial neuritis, and/or a complex regional pain syndrome, and/or carpal tunnel syndrome	2 years, 8 months
Tetanus	Guillain-Barré Syndrome	1 year
Flu	Encephalomyelitis and neuromuscular problems	11 months
Varicella	Encephalitis, intractable seizure disorder, and personality and behavior changes	4 years, 11 months
RV	Intussusception	1 year, 5 months
Flu	Granuloma annulare, and left arm and shoulder tingling, numbness, pain and itchiness	1 year, 4 months

*Terms of settlement are memorialized by Stipulation

(continued . . .) 15

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Shoulder injury	9 months
Flu	Acute disseminated encephalomyelitis	2 years, 9 months
Flu	Guillain-Barré Syndrome	1 year, 10 months
Flu	Chronic Inflammatory Demyelinating Polyneuropathy	1 year, 3 months
Tdap	Guillain-Barré Syndrome	1 year, 2 months
Tdap	Shoulder injury related to vaccine administration	1 year
Flu	Shoulder injury related to vaccine administration	11 months
Flu	Guillain-Barré Syndrome and/or a peripheral neuropathy	9 months
Flu	Guillain-Barré Syndrome	9 months
Flu	Guillain-Barré Syndrome	4 years

*Terms of settlement are memorialized by Stipulation

(continued . . .) 16

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Shoulder injury related to vaccine administration, to include upper brachial plexopathy, Parsonage-Turner syndrome, nerve pain, low-grade strain, subacromial bursitis, and subdeltoid bursitis	5 months
Tdap	Shoulder injury related to vaccine administration	8 months
Flu	Guillain-Barré Syndrome	2 years, 2 months
Flu	Shoulder injury related to vaccine administration	1 year, 9 months
Varicella	Idiopathic Thrombocytopenia Purpura	1 year, 2 months
Flu	Guillain-Barré Syndrome	1 year
PCV, Hep A, DTaP	Transverse myelitis	10 months
Flu	Guillain-Barré Syndrome, death	9 months
Flu	Guillain-Barré Syndrome, death	2 years, 5 months
Flu	Left-sided pain, numbness, tingling, swelling and difficulty ambulating	2 years, 1 month

*Terms of settlement are memorialized by Stipulation

(continued . . .)

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Shoulder injury related to vaccine administration	1 year, 3 months
Flu	Trigeminal sensory neuropathy and vertigo	1 year
Flu	Guillain-Barré Syndrome	10 months
Flu	Injection-related shoulder injury	8 months
IPV, DTaP	Guillain-Barré Syndrome and/or Chronic Inflammatory Demyelinating Polyneuropathy	4 years
Flu	Chronic Inflammatory Demyelinating Polyneuropathy	11 months
Flu	Guillain-Barré Syndrome	1 year, 6 months
Flu	Guillain-Barré Syndrome	1 year, 5 months
Flu	Transverse myelitis	9 months
Flu	Guillain-Barré Syndrome	1 year, 10 months

*Terms of settlement are memorialized by Stipulation

(continued . . .)

Adjudicated Settlements*

Reporting Period: 5/16/14 – 8/15/14

Vaccine(s)	Alleged Injury(ies)	Petition Filing to Settlement Filing
Flu	Guillain-Barré Syndrome	1 year, 10 months
Flu	Guillain-Barré Syndrome	7 months
MCV, Hep A	Neurologic injuries, to include chronic inflammatory demyelinating polyneuropathy	4 years, 6 months
Flu	Guillain-Barré Syndrome	4 years
Flu	Guillain-Barré Syndrome, and/or polymyalgia rheumatica, and/or giant cell arteritis	3 years, 9 months
Flu	Guillain-Barré Syndrome	1 year, 11 months
HPV	Chronic autoimmune hepatitis	1 year, 5 months
Hep A	Rheumatologic injuries	1 year, 5 months
Flu	Peripheral neuropathy	8 months
Flu	Guillain-Barré Syndrome	1 year, 8 months

Total Number of Judgments Adopting Settlement this reporting period: 90

*Terms of settlement are memorialized by Stipulation

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Appendix

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Glossary of Terms

- **Petitions Adjudicated:** Final judgment has entered on the petition in the United States Court of Federal Claims.
- **Final Judgment:** Clerk of Court, United States Court of Federal Claims, enters judgment awarding or denying compensation.
- **Compensable:** Petitioner received an award of compensation, which can be achieved through a concession by HHS, settlement, or decision on the merits by the special master, United States Court of Federal Claims.
- **Conceded by HHS:** HHS concluded that a petition should be compensated based on review and analysis of the medical records.

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Glossary of Terms

- **Settlement:** Petition is resolved via a negotiated settlement between the parties, and results in the filing of a stipulation that memorializes the terms of the settlement.
- **Decision:** Special Master issues decision on the merits of the petition.
- **Non-compensable/Dismissed:** Petition dismissed.
- **Proffer:** After discussions between the parties regarding a reasonable amount of damages, respondent will file a suggested award of compensation, known within the Program as a "Proffer," which is also agreed to by petitioners and their counsel. The Proffer is reviewed by the presiding special master to determine that it represents a reasonable measure of the amount of the award and describes compensation pursuant to 42 U.S.C. § 300aa-15(a). The special master issues a final decision consistent with the terms of the Proffer.

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Glossary of Terms

- **Affirmed:** Case has been reviewed on appeal, and the court on appeal agreed with the decision of the lower court.
- **Reversed:** Case has been reviewed on appeal, and the court on appeal disagreed with the decision of the lower court. The court on appeal typically provides reasons for reversing, and that decision becomes the law of the case, absent further appeal.
- **Remanded:** Case has been reviewed on appeal, and the reviewing court has a problem with the decision, and sends it back to the lower court. Typically, a case is remanded with a specific question or issue for the lower court to address.
- **Vacated:** Case has been reviewed on appeal, and the reviewing court has voided the lower court's decision.

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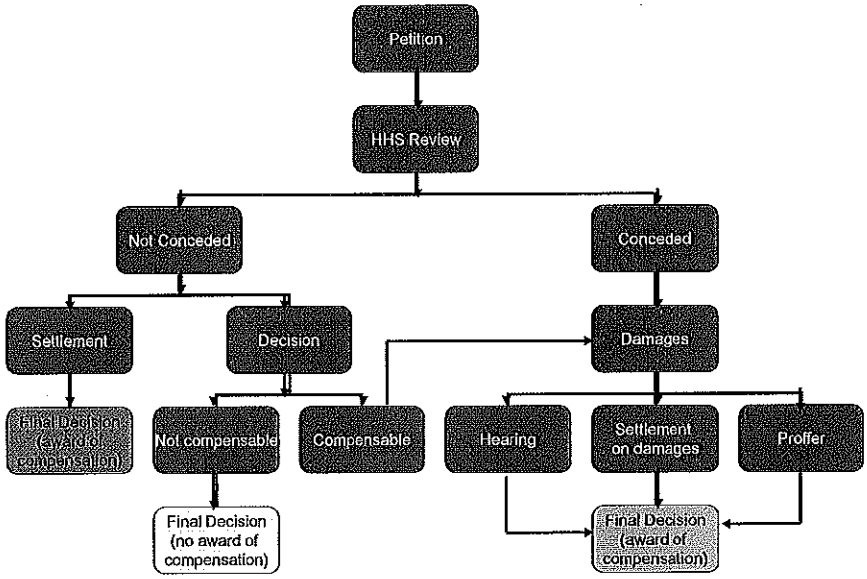
Petition Processing in the Office of Special Masters



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Levels of Appeal in Vaccine Act Cases

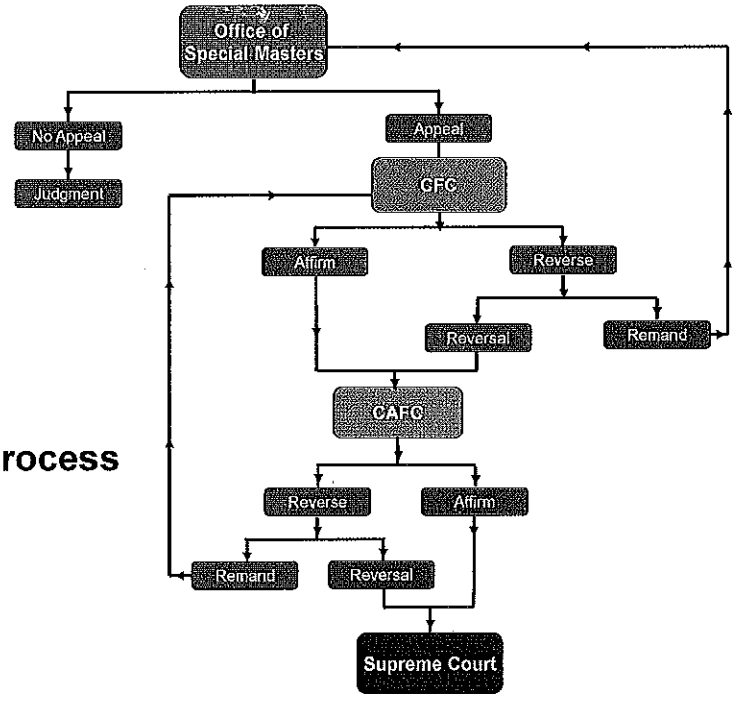
U.S. Supreme Court

U.S. Court of Appeals for the Federal Circuit

U.S. Court of Federal Claims

Office of Special Masters

Appeals Process



Updated for the September 2014 ACCV Meeting
Prepared by the U.S. Department of Justice (DOJ)
U.S. Court of Appeals for the Federal Circuit (CAFC) / U.S. Supreme Court

Entitlement

CASE NAME CITATION	HOLDING
STONE and HAMMITT 676 F.3d 1373 (Fed. Cir. 2012)	In a consolidated appeal, the CAFC reiterated prior precedent and held that the special master was not precluded from considering respondent's evidence of a genetic mutation as part of examining the record as a whole to determine whether or not petitioners met their burden of proof in establishing a prima facie case merely because that evidence was also relevant as to whether or not respondent had satisfied her burden of showing an alternate cause. Because the special master found that the genetic mutation was the sole cause of the children's condition, there was no need to analyze the question of superseding causes. The CAFC also found that the special master was not arbitrary or capricious in his fact finding and that petitioners failed to show that the DTaP vaccine was the more likely cause of the children's seizure disorder.
ROTOLI and PORTER 663 F.3d 1242 (Fed. Cir. 2011)	The CAFC found that the Claims Court judge incorrectly read Andreu to prohibit a special master from using credibility determinations to reject a petitioner's theory of causation. Rather, in Moberly, Broekelschen, and Doe 11, the CAFC had "unambiguously explained" that special masters are expected to consider credibility of expert witnesses in evaluating vaccine claims. Further, the Claims Court's blanket approach of setting aside the special master's findings of fact without ever determining whether the findings were arbitrary and capricious was legal error. Because the special master's decision contained a thorough and careful evaluation of all of the evidence, including records, tests, reports, medical literature, and expert's opinions and their credibility, the CAFC found that the special master's decision was not arbitrary, capricious, an abuse of discretion or otherwise not in accordance with law. The CAFC reversed the findings of the Claims Court and remanded with instructions that a decision be entered affirming the special master's denial of compensation.

CEDILLO 617 F.3d 1328 (Fed. Cir. 2010)	The CAFC affirmed the Court of Federal Claims' decision sustaining the special master's determination that thimerosal containing vaccines combined with the measles-mumps-rubella (MMR) vaccine do not cause autism. In this appeal, appellants argued that the special master improperly based his decision on evidence derived from litigation in the United Kingdom that should have been excluded, and disregarded other evidence that should have been considered. The CAFC disagreed and found that the special master committed no legal error, properly considered all relevant and reliable evidence, and appropriately exercised his discretion in weighing that evidence. Of particular note, the CAFC held that the special master's use of Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), was an appropriate tool to assess the reliability of the parties' evidence, particularly the expert testimony.
HAZLEHURST 604 F.3d 1343 (Fed. Cir. 2010)	The CAFC found that the special master acted consistent with principles of fundamental fairness by admitting and considering respondent's expert's testimony and reports criticizing petitioners' evidence and offered petitioners ample time and opportunity to rebut respondent's evidence. Further, the special master did not commit legal error by according little weight to petitioners' evidence from a research facility, which the special master found to be unpublished, preliminary, and incomplete. The special master further committed no error in discounting testimony by petitioners' expert regarding causation because that opinion was based on studies that were unreliable.
DOE 11 601 F.3d 1349 (Fed. Cir. 2010)	The CAFC found that the special master correctly considered "the record as a whole" in determining whether compensation is warranted, and that the Government is not restricted by proving a "factor unrelated" as the burden never shifted from petitioner to establish a prima facie case. The Government may present evidence of an alternate cause and the special master is not limited or precluded from considering such evidence when deciding whether petitioner has established a prima facie case. Petitioners' failure to meet his burden of proof as to the cause of an injury or condition is different from a requirement that he affirmatively disprove an alternate cause.
MOBERLY 592 F.3d 1315 (Fed. Cir. 2010)	The CAFC found that the special master correctly interpreted and applied the traditional tort "preponderance" standard applicable in Vaccine Act cases, and that the petitioners' argument for a more relaxed standard was not consistent with the Act. The Court also held that a close temporal association and the lack of an identifiable alternative cause, standing alone, are insufficient to prove causation. The Court further held that when evaluating an expert's medical theory, a special master is expected to evaluate both the reliability and credibility of the expert's testimony.

ANDREU 569 F.3d 1367 (Fed. Cir. 2009)	The CAFC found that if a petitioner satisfies the first and third prongs of Althen, the second prong (whether there exists a logical sequence of cause and effect between the vaccination and the injury alleged) can be met through the testimony of a treating physician. The CAFC further found that the special master's determinations regarding the credibility of witnesses are distinct from determinations of the reliability of scientific evidence, and the special master must clearly differentiate between these determinations to allow appropriate review on appeal.
DE BAZAN 539 F.3d 1347 (Fed. Cir. 2008)	The CAFC found that as part of petitioner's evidence in establishing a prima facie case of actual causation, petitioner has the burden of proving a medically appropriate time frame between vaccination and the onset of injury. The Government, like any defendant, may offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief, and a special master is obliged to consider all evidence when deciding whether or not petitioner has met his burden of proof.
WALTHER 485 F.3d 1146 (Fed. Cir. 2007)	The CAFC found that the Vaccine Act does not require petitioners to bear the burden of eliminating alternative causes where the other evidence on causation-in-fact is sufficient to establish a prima facie case.
PAFFORD 451 F.3d 1352 (Fed. Cir. 2006)	The CAFC found that petitioners must prove by a preponderance of the evidence that the vaccine, and not some other agent, was the actual cause of the injury, when petitioners' other evidence of causation-in-fact is insufficient to establish a prima facie case.
CAPIZZANO 440 F.3d 1317 (Fed. Cir. 2006)	The CAFC found that a claimant could satisfy prongs one and two of the three-prong Althen test but fail to satisfy prong two when medical records and medical opinions do not suggest that the vaccine caused the injury or where the evidence shows that the probability of coincidence or another cause prevents petitioner from establishing causation by a preponderance of the evidence. The CAFC found that statements in the medical records by treating physicians are relevant and should be afforded significant evidentiary weight.
ALTHEN 418 F.3d 1274 (Fed. Cir. 2005)	The CAFC found that in order to prove causation-in-fact, a petitioner must prove by a preponderance of the evidence: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury. Lack of peer reviewed literature does not, in and of itself, preclude a finding of causation-in-fact.

Statute of Limitations

CASE NAME CITATION	HOLDING
CLOER 654 F.3d 1322 (Fed. Cir. 2011)	On August 5, 2011, the CAFC, in an 8-4 en banc decision, held that the Vaccine Act does not contain a discovery rule, nor can a discovery rule be read by implication into the Act. Rather, the statute of limitations begins to run on a specific statutory date: the date of the occurrence of the first symptom or manifestation of onset of the injury for which a claimant seeks compensation. In addition, the Court overruled its prior precedent and further held that equitable tolling applies to the Vaccine Act, although it determined that the statute of limitations is not tolled due to unawareness of a causal link between an injury and administration of a vaccine.
WILKERSON 593 F.3d 1343 (Fed. Cir. 2010)	The CAFC found that, consistent with its holding in Markovich, the 36 month statute of limitations period under 42 U.S.C. § 300aa-16(a)(2) begins to run with ***either*** the occurrence of the first symptom of or the manifestation of onset of an alleged vaccine-related injury, whichever is first. The Court held that the Act's time for filing runs from "the date of the occurrence of the first symptom or manifestation of onset," not the date the medical profession recognizes that a symptom is related to an alleged vaccine-related injury, and the Court held that an expert's determination of the first symptom or manifestation of onset may be made in "hindsight," i.e., a medical professional need not have appreciated the significance of the symptom at the time it occurred.
MARKOVICH 477 F.3d 1353 (Fed. Cir. 2007)	The CAFC found that the determination of when the 36 month statute of limitations period under 42 U.S.C. § 16(a)(2) begins to run is made by an objective standard, that is, even if the petitioner reasonably would not have known at the time that the vaccine had caused injury.

Death Benefits/Survivorship

CASE NAME CITATION	HOLDING
ZATUCHNI (SNYDER) 516 F.3d 1312 (Fed. Cir. 2008)	The CAFC found that a petitioner who establishes vaccine-related injuries and a vaccine-caused death is entitled to recover the compensation for vaccine-related injuries and vaccine-related death benefits under 42 U.S.C. § 300aa-15(a)(1)(B), (a)(3), (a)(4), and the death benefit provided under Section 15(a)(2). This applies where petitioner filed a claim for vaccine-related injuries, received a favorable ruling that the injuries were vaccine-related, and then died before receiving compensation for those injuries.

Attorneys' Fees and Costs/Interim Fees Requests

CASE NAME CITATION	HOLDING
CLOER 133 S. Ct. 1886 (2013)	The U.S. Supreme Court affirmed the judgment of the CAFC, finding that a person whose petition under the National Vaccine Injury Compensation Program is dismissed as untimely may recover from the United States an award of attorneys' fees and costs.
RODRIGUEZ 632 F.3d 1381 (Fed. Cir. 2011)	The CAFC affirmed the special master's decision rejecting the Laffey matrix as prima facie evidence of a forum rate for petitioners' counsel. The issue was whether the reasonable hourly rate for attorneys handling Vaccine Act cases should be determined by applying the Laffey matrix, a schedule of rates maintained by DOJ to compensate attorneys prevailing in "complex federal litigation," or whether the rate should be determined by considering a variety of factors, which may or may not include the Laffey matrix. The CAFC held that Vaccine Act litigation, while potentially involving complicated medical issues and requiring highly skilled counsel, is not analogous to "complex federal litigation" as described in Laffey, so as to justify use of the matrix. Distinguishing between the type of litigation the Laffey matrix is designed to compensate, the CAFC stated that a party need not prevail under the Vaccine Act in order to receive an attorneys' fees award, that attorneys are practically assured of compensation in every case without regard to whether they win or lose and the skill with which they presented their clients' cases, and that the attorneys' fees provisions under the Act "were not designed as a form of economic relief to improve the financial lot of lawyers." Further, the CAFC noted that Vaccine Act proceedings are an alternative to the traditional civil forum, apply relaxed legal standards of causation, have eased procedural rules compared to other federal civil litigation, do not have formal discovery and thus avoid discovery disputes, do not apply the rules of evidence, and are tried in informal, streamlined proceedings before special masters well-versed in the issues commonly repeated in Vaccine Act cases.

RIGGINS 406 Fed. App'x. 479 (Fed. Cir. 2011)	The CAFC found that the special master appropriately reduced the amount of attorneys' fees and costs sought by petitioner's counsel for the general development of Hepatitis B vaccine cases from the requested sum of $204,619.18 to an award of $79,782.81. In doing so, the CAFC affirmed the special master's decision to reduce the $97,443.43 in fees and costs associated with the consulting work of two experts to $10,000.00. Among other things, the CAFC agreed with the special master's finding that a hypothetical client would not pay for costly travel by petitioner's counsel and his consultants to France for personal consultation with foreign experts and lawyers, or for time and expenses related to the consultants' attendance at a professional conference in Italy.
KAY 298 Fed. App'x. 985 (Fed. Cir. 2008) per curiam, affirmance, Nov. 10, 2008	The CAFC denied an award of attorneys' fees and costs where the petition was found to be time-barred under Markovich and dismissed for lack of jurisdiction, precluding an award of attorneys' fees in a case that was untimely filed.
AVERA 515 F.3d 1343 (Fed. Cir. 2008)	The CAFC affirmed that, in general, the forum rule should be used to calculate reasonable hourly rates for petitioners' attorneys in claims brought under the Vaccine Act, and found that Washington, DC is the forum for vaccine cases because it is where the CFC, which has exclusive jurisdiction over vaccine cases, is physically located. In applying the forum rule, the CAFC recognized and applied an exception derived from Davis v. U.S. E.P.A., 169 F.3d 755 (D.C. Cir. 1999). Applying Davis, the CAFC found that an exception to the forum rule applies where 1) the bulk of the work was done outside DC and 2) there is a very significant difference between the DC rates and the attorneys' hometown rates. The CAFC found that the appellants' vaccine attorneys hailing from Cheyenne, Wyoming were not entitled to forum rates in this case. The CAFC also held that interim attorneys' fees are permitted under the Vaccine Act. The CAFC considered an award of interim fees particularly appropriate when cases are protracted and costly experts must be retained. The CAFC found that there was no basis for an award of interim fees here because the petitioners only sought an award of interim fees pending an appeal; made no showing of undue hardship; the amount of fees was not substantial; no experts had been employed; and there was only a short delay in the award pending the appeal.

5.4

5.5

Immunization Safety Office Updates

Centers for Disease Control and Prevention

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention (CDC)

Advisory Commission on Childhood Vaccines (ACCV)
September 4-5, 2014

Topics

- Follow-up on the 2010-11 febrile seizure signal for trivalent inactivated influenza and pneumococcal 13-valent conjugate vaccines (presented at the June 2014 ACIP meeting)
- June 2014 Advisory Committee on Immunization Practices (ACIP) meeting highlights
- Selected publications

Follow-up on the 2010-11 febrile seizure signal for trivalent inactivated influenza and pneumococcal 13-valent conjugate vaccines

(presented at the June 2014 ACIP meeting)

http://www.cdc.gov/vaccines/acip/meetings/slides-2014-06.html
https://www.youtube.com/watch?v=KmGI-JtK6WQ&feature=youtu.be

3

Febrile seizures in young children following TIV and PCV13 (background/key events)

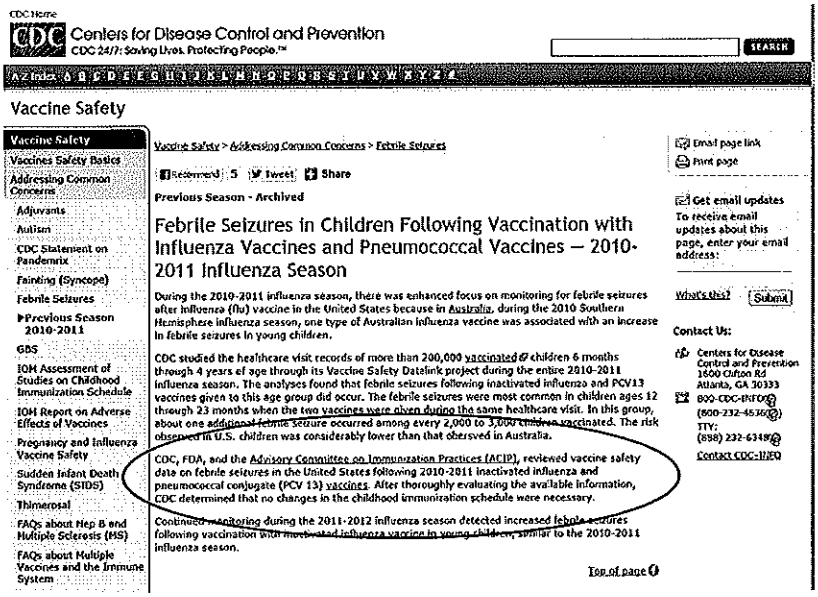
2010-11
- ❑ VAERS data mining signal for Fluzone®; clinically relevant age group was in children 6-23 mo.*
- ❑ VSD Rapid Cycle Analysis (RCA) signal for TIV in children 6-59 mo.
- ❑ VSD TIV-PCV13 febrile seizure study**
  - Attributable risk for concomitant TIV+PCV13 peaked at 16 mo. with 45 additional febrile seizures per 100,000 children vaccinated

2011-12
- ❑ VSD RCA signal for TIV persisted (same formulation as 2010-11)
- ❑ Clinical Immunization Safety Assessment (CISA) Project TIV-PCV13 fever study***
  - Children 6-23 mo. who received TIV and PCV13 together at the same visit were about 3 times as likely to have a fever on days 0-1 compared with children who received TIV or PCV13 without the other product

2012-13
2013-14
- ❑ No VSD RCA signal for TIV (formulation change(s) from 2010-11)

*Leroy et al. Vaccine. 2012;30(11):2020-3; **Tse et al. Vaccine. 2012 Mar 2;30(11):2024-31; ***Stockwell et al. JAMA Pediatr. 2014;168(3):211-9 4

CDC web posting on febrile seizures following TIV and PCV13*



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SEARCH

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Vaccine Safety

Vaccine Safety
Vaccines Safety Basics
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Autism
CDC Statement on Pandemrix
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IOM Assessment of Studies on Childhood Immunization Schedule
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Vaccine Safety > Addressing Common Concerns > Febrile Seizures

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Febrile Seizures in Children Following Vaccination with Influenza Vaccines and Pneumococcal Vaccines – 2010-2011 Influenza Season

During the 2010-2011 influenza season, there was enhanced focus on monitoring for febrile seizures after influenza (flu) vaccine in the United States because in Australia, during the 2010 Southern Hemisphere influenza season, one type of Australian influenza vaccine was associated with an increase in febrile seizures in young children.

CDC studied the healthcare visit records of more than 200,000 vaccinated children 6 months through 4 years of age through its Vaccine Safety Datalink project during the entire 2010-2011 influenza season. The analyses found that febrile seizures following inactivated influenza and PCV13 vaccines given to this age group did occur. The febrile seizures were most common in children ages 12 through 23 months when the two vaccines were given during the same healthcare visit. In this group, about one additional febrile seizure occurred among every 2,000 to 3,000 children vaccinated. The risk observed in U.S. children was considerably lower than that observed in Australia.

CDC, FDA, and the Advisory Committee on Immunization Practices (ACIP), reviewed vaccine safety data on febrile seizures in the United States following 2010-2011 inactivated influenza and pneumococcal conjugate (PCV 13) vaccines. After thoroughly evaluating the available information, CDC determined that no changes in the childhood immunization schedule were necessary.

Continued monitoring during the 2011-2012 influenza season detected increased febrile seizures following vaccination with inactivated influenza vaccine in young children, similar to the 2010-2011 influenza season.

Top of page

*http://www.cdc.gov/vaccinesafety/Concerns/FebrileSeizures-archived.html

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Language added to the inactivated influenza vaccine Vaccine Information Statement (VIS) following the CDC, FDA and ACIP review of the 2010-11 data*

Moderate problems following inactivated flu vaccine:

- Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time may be at increased risk for seizures caused by fever. Ask your doctor for more information. Tell your doctor if a child who is getting flu vaccine has ever had a seizure.

*http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.html

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Febrile seizures in young children following TIV and PCV13

- Follow-up studies to the 2010-11 febrile seizure signal
  - Febrile Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) Study*
    - Question: Did vaccines other than PCV13 given concomitantly with TIV affect the risk of febrile seizure following receipt of TIV?
  - Assessment of febrile seizures after trivalent influenza vaccines during the 2010-2011 influenza season in PRISM**
    - Question: Was exposure to TIV or PCV13 associated with a greater risk for FS when compared to unexposed periods?
    - Question: Assuming children received both TIV and PCV13, did administering them on the same day lead to a greater risk for FS when compared to separate days?

* Duffy et al. Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) study. June 2014 ACIP meeting (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-02-Duffy.pdf)

** Kawai. Assessment of febrile seizures after Trivalent Influenza Vaccines during the 2010-2011 influenza season in the Post Licensure Rapid Immunization Monitoring (PRISM) system. June 2014 ACIP meeting (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-03-Kawai.pdf)

7

Febrile seizures in young children following TIV and PCV13

- Independent effect of TIV on risk of febrile seizures
  - PRISM analysis* found no statistically significant independent increased risk of febrile seizure associated with TIV during the 2010-11 influenza season
  - Updated VSD analysis** found
    - No statistically significant independent increased risk of febrile seizure associated with TIV during the 2010-11 influenza season
    - No independent increased risk of febrile seizure for TIV given without PCV or DTaP during 2006-2009 influenza seasons*

* Kawai. Assessment of febrile seizures after Trivalent Influenza Vaccines during the 2010-2011 influenza season in the Post Licensure Rapid Immunization Monitoring (PRISM) system. June 2014 ACIP meeting (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-03-Kawai.pdf)

** Duffy et al. Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) study. June 2014 ACIP meeting (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-02-Duffy.pdf)

8

Febrile seizures in young children following TIV and PCV13

- Risk of febrile seizure when TIV was given with PCV and/or DTaP
  - Updated VSD analysis for 2010-11 season suggests that the relative risk increased about 3-fold when TIV was given with PCV and/or DTaP compared with unexposed periods*
    - Similar results seen for the 2006-2009 influenza seasons*
- PRISM analysis did not find any greater risk of febrile seizures for same day vs. separate day vaccination with TIV and PCV13 during the 2010-11 influenza season**

* Duffy et al. Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) study. June 2014 ACIP meeting (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-02-Duffy.pdf)

** Kawai. Assessment of febrile seizures after Trivalent Influenza Vaccines during the 2010-2011 influenza season in the Post Licensure Rapid Immunization Monitoring (PRISM) system. June 2014 ACIP meeting (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-03-Kawai.pdf)

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Febrile seizures in young children following TIV and PCV13

- The weight of the evidence and the consistency of the findings from the VSD analysis over several seasons suggest that:
  - When TIV is given alone, risk of febrile seizure is not increased
  - When TIV is given with PCV and/or DTaP, however, risk of febrile seizure is increased
  - Highest risk is when TIV + PCV + DTaP given together at 15 months of age
    - Attributable risk = 38 additional febrile seizures per 100,000 children vaccinated
    - Similar to febrile seizure risk seen with measles-mumps-rubella (MMR) vaccine*

* Barlow et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med. 2001;345(9):656-61.

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Conclusion: febrile seizures in young children following TIV and PCV13

- Simultaneous administration of TIV with PCV and/or DTaP vaccines appears to be associated with an increased risk for febrile seizures in young children
- This increased risk is transient (the day of to the day after vaccination [days 0-1])
- Although frightening for parents and caregivers, febrile seizures do not have lasting effects
- Getting recommended childhood vaccines during a single healthcare visit has important benefits
  - On-time vaccinations keep children protected against many infectious diseases, and providing multiple vaccinations in a healthcare visit minimizes the number of healthcare visits that parents, caregivers, and children must make

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June 2014 ACIP meeting update*

- Influenza
  - No new safety concerns detected for IIV or LAIV during the 2013-2014 influenza season
  - Influenza vaccine virus composition for 2014-15 unchanged from 2013-14
  - Surveillance for the 2014-2015 influenza season will include enhanced safety monitoring for:
    - Quadrivalent IIV and LAIV vaccines
    - Cell culture-based IIV
    - Recombinant IIV
    - Pregnancy reports
    - Reports in persons with history of egg allergy after IIV and LAIV
    - Reports with history of asthma/wheezing after LAIV4

* http://www.cdc.gov/vaccines/acip/meetings/slides-2014-06.html; http://www.cdc.gov/vaccines/acip/meetings/live-mtg-2014-06.html 12

June 2014 ACIP meeting update, cont.

- **Influenza, cont.**
  - Assessing fever rates in children following LAIV and IIV
    - No significant difference in fever rates in the 3-10 days post-vaccination after LAIV vs. IIV
  - New recommendation regarding use of LAIV and IIV for healthy young children where either is available and appropriate*
    - LAIV should be used if both available
    - IIV should be used and not delayed if LAIV not available

*http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm

June 2014 ACIP meeting update, cont.

- **13-valent pneumococcal conjugate vaccine (policy options under consideration)**
  - Add a dose of PCV13 at age ≥65 years to currently recommended PPSV23 regimen
    - PCV13 dose followed by dose of PPSV23 at age ≥65 years
    - Risk-based recommendations for PCV13 and PPSV23 use remain unchanged
  - Replace a dose of PPSV23 at age ≥65 years with a dose of PCV13
    - PCV13 at age ≥65 years
    - Risk-based recommendations for PCV13 and PPSV23 use remain unchanged

June 2014 ACIP meeting update, cont.

- **Meningococcal vaccines**
  - Publication of interim guidance planned for the use of a serogroup B meningococcal vaccine under a CDC-sponsored expanded access IND
  - Updates to CDC's comprehensive meningococcal disease outbreak guidelines will be developed once serogroup B meningococcal vaccines are licensed in the United States

Selected publications

- Nordin et al. Monovalent H1N1 influenza vaccine safety in pregnant women, risks for acute adverse events. Vaccine. 2014 Jul 18. [Epub ahead of print]
  - In a large cohort of pregnant women in the Vaccine Safety Datalink, no acute safety signals were identified within 6 weeks of receipt of monovalent 2009 H1N1 inactivated influenza vaccine.
- Stokley et al. Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006-2014 - United States. MMWR Morb Mortal Wkly Rep. 2014;63(29):620-4.
  - Postlicensure monitoring data continue to confirm the safety of HPV4 vaccine
  - Improving practice patterns so that clinicians use every opportunity to recommend HPV vaccines and address questions from parents can help realize reductions in vaccine-preventable infections and cancers caused by HPV.

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Selected publications

- Grohskopf et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) - United States, 2014-15 Influenza Season. MMWR Morb Mortal Wkly Rep. 2014;63(32):691-7.
  - This report updates the 2013 recommendations by the Advisory Committee on Immunization Practices (ACIP) regarding use of seasonal influenza vaccines. Updated information for the 2014-15 influenza season includes 1) antigenic composition of U.S. seasonal influenza vaccines; 2) vaccine dose considerations for children aged 6 months through 8 years; and 3) a preference for the use, when immediately available, of live attenuated influenza vaccine (LAIV) for healthy children aged 2 through 8 years, to be implemented as feasible for the 2014-15 season but not later than the 2015-16 season. Information regarding issues related to influenza vaccination not addressed in this report is available in the 2013 ACIP seasonal influenza recommendations.

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Atlanta, GA

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion – Immunization Safety Office

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National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion -- Immunization Safety Office

5.6

The Vaccine Adverse Event Reporting System (VAERS) form Version 2.0 (proposed)

Tom Shimabukuro, MD, MPH, MBA

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Advisory Commission on Childhood Vaccines (ACCV)
September 4-5, 2014

Topics

- Background on VAERS
- TBD
- TBD

Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events after US-licensed vaccines
  - In recent years, received around 30,000 U.S. reports annually
  - Accepts reports from healthcare providers, manufacturers and the public
  - Signs/symptoms of adverse event coded (using MedDRA terms) and entered into database
- Jointly administered by CDC and FDA
- Authorized by National Childhood Vaccine Injury Act of 1986

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Vaccine Adverse Event Reporting System (VAERS) (co-managed CDC and FDA)[1]

Strengths	Limitations
❑ National data; accepts reports from anyone	❑ Reporting bias
❑ Rapid signal detection; rare adverse events (AE)	❑ Inconsistent data quality and completeness
❑ Collects information about vaccine, characteristics of vaccinee, AE[2]	❑ Lack of unvaccinated comparison group
❑ Data available to public	❑ Generally cannot assess if vaccine caused an AE
	❑ Pregnancy inconsistently reported

1. VAERS website: http://vaers.hhs.gov
2. Some reports have no adverse event

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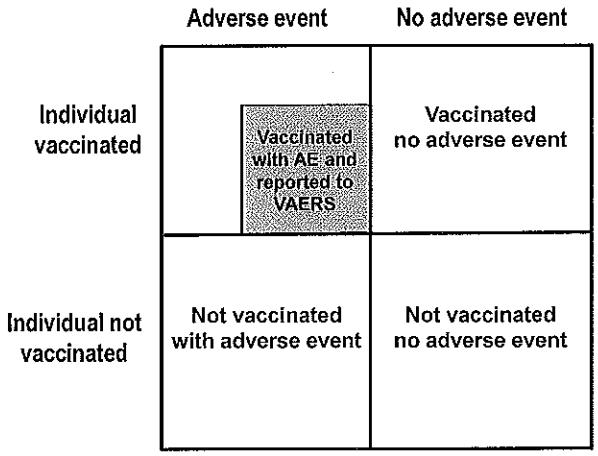
Limitations of VAERS data



- VAERS only contains partial data in pink cell (incomplete population data)
  - Not able to calculate rates of occurrence of adverse events
  - Not able to determine increased risk for adverse events
  - Not able to calculate vaccination coverage

5

Submitting a VAERS report (currently)

- Secure online submission (~30% of reports in recent years, but has plateaued)
- Mailed written hardcopy of paper form
- Faxed hardcopy
- Via telephone through a VAERS customer service representative

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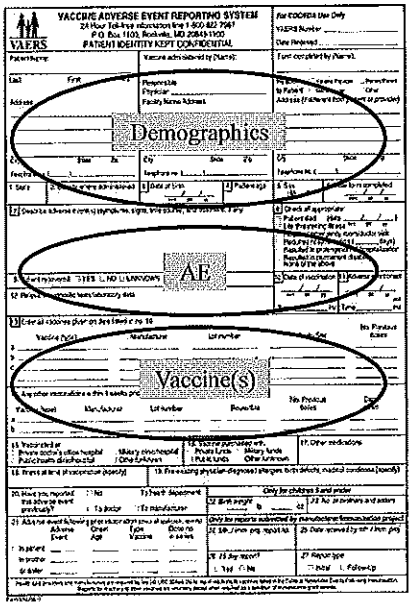
VAERS-1 report form*

- Pure paper form; must be completed by hand or using a typewriter
- Mailed or faxed to VAERS contractor
- Requires manual receipt, processing and data entry procedures
- Hardcopies scanned and uploaded to the VAERS image database
- Resource intensive to manage paper reporting



*Online reporting form has same fields in a different presentation

7

Objectives for the VAERS 2.0 form (proposed)

- Update data fields to address current vaccine safety information needs and changes in vaccination practices over time
- Modernize the appearance and format of the VAERS form
- Modernize reporting procedures (implement electronic document upload capability)
- Ensure data collected on the VAERS 2.0 form allows for comparisons to be made with older data (i.e., historical comparisons between VAERS-1 and VAERS 2.0 data)

8

Why revise the VAERS form? (content changes)

- Some fields on the current VAERS form (VAERS-1) have limited public health and/or regulatory value
  - Other important information isn't being collected
- Some fields are no longer relevant due to changes in the immunization program
- The language in some fields is confusing and needs clarification
- Fields used in paper reporting and for manual processing will no longer be necessary (e.g., manufacturer fields after the transition to the the ICH E2B(R3) message standard)
- Federal advisory committees and other stakeholders have expressed interest in collecting information on pregnancy status, race and ethnicity

9

Why revise the VAERS form? (format changes)

- The VAERS form would benefit from a more modern appearance with breaks and headers to clearly define sections or groups of data elements
- Electronic forms allow for features such as
  - Standardized dates, times, phone numbers, etc.
  - Drop down menus
  - Check boxes (mutually exclusive and "all that apply")
  - Logic checks
  - Pop-up instructions and reminders

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Why revise the VAERS form? (process changes)

- Handwritten and mailed/faxed copies of paper reports is an inefficient way to conduct vaccine safety surveillance
- Paperless reporting using an electronic form would
  - Eliminate most manual receipt and processing activities
  - Mitigate problems with poor handwriting and sloppy reporting
  - Mitigate the problem of illogical answers
  - Allow for standardized data elements
  - Eliminate most manual data entry
  - Addresse the complaint of getting "timed out" on the online reporting tool
- Using technology to improve the efficiency of VAERS reporting will allow CDC to shift resources to other priority activities
- Manufacturers will be transiting to fully electronic reporting using the ICH E2B(R3) message standard

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VAERS 2.0 form development

- Actions that have already occurred
  - Initial VAERS 2.0 development by CDC, FDA and VAERS contractor staff
  - Internal (CDC, FDA and VAERS contractor) review and revision; review and revision is an ongoing activity
  - Initial external review by immunization partners (CDC immunization program, NVPO, HRSA, DoD, ACIP liaison representatives, state immunization program officials, other partners)
  - Cognitive interviews with potential reporters (physicians, nurses, pharmacist, parents, patients)
  - Major revisions based on results of cognitive interviews
  - Presentation to internal and selected external partners (CDC immunization program, state Vaccine Safety Coordinators, others)
  - Presentation to the Federal Immunization Safety Task Force (ISTF)
  - Follow up interviews with a sample of individuals that completed cognitive interviews to test the revised form

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VAERS 2.0 electronic form reporting (proposed)

1. Reporter downloads the VAERS 2.0 form from the VAERS website
2. Reporter completes a VAERS 2.0 form on a computer (form is a fillable/savable PDF document)
3. Reporter saves the VAERS 2.0 report as an electronic document in a secure environment per instructions
4. Reporter uploads saved VAERS 2.0 report to the VAERS contractor through the VAERS website
5. VAERS contractor electronically extracts the data from the VAERS 2.0 report into the VAERS database (also reviews, redacts and performs Q&A on data)
6. VAERS contractor generates an individual report for the VAERS image database

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Successful transition to VAERS 2.0

- ❑ Access to computers and to the internet among the public is fairly high and expected to increase with time
- ❑ Healthcare facilities are increasingly becoming connected to the internet and connectivity is becoming a requirement for modern healthcare
- ❑ Familiarity with electronic forms and electronic data submission among the public is increasing
- ❑ Electronic reporting for public health surveillance has broad acceptance and support in the public health community
- ❑ Efficiency gains should free up resources for other priorities such as:
  - Shifting resources to rapidly follow-up on serious reports
  - Focusing on coding quality and consistency
  - Exploring automated reporting options from EHRs and IISs

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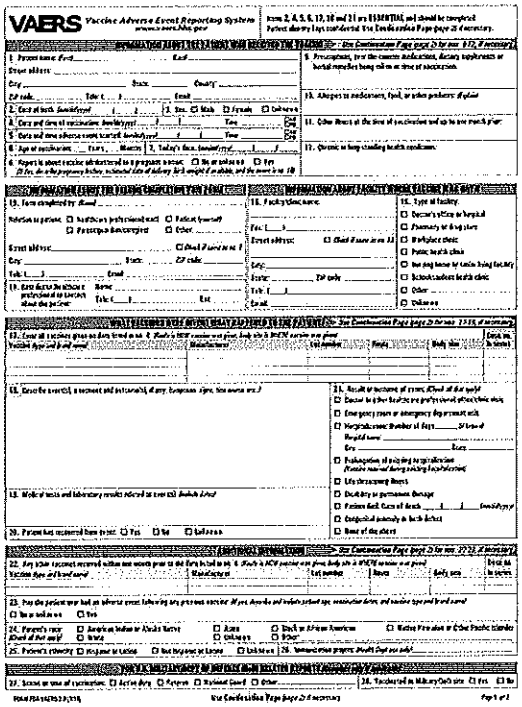
VAERS 2.0 form (proposed)



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Specific changes

- Removed (from VAERS-1)
  - For CDC/FDA Use Only box
  - 16. Vaccine purchased with:
  - 20. Have you reported this adverse event previously?
  - 21. Adverse event following prior vaccination….. (in tabular form)
  - 22. Birth weight
  - 23 No. of brothers and sisters
  - Only for reports submitted by manufacturer/immunization project (24, 25, 26, 27); however, we keep "Immunization project" in VAERS 2.0

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Specific changes

- Added to VAERS 2.0*
  - Email
  - 8. Report is about vaccine administered to a pregnant woman:
  - 10. Allergies to medications, food, or other products: (Explain)
  - 24. Race:
  - 25. Ethnicity:
  - FOR U.S. MILITARY/DEPT OF DEFENSE (DoD) RELATED REPORTS
    - 27. Status at time of vaccination:
    - 28. Vaccinated at Military/DoD site:

*Some of the original language in the VAERS-1 fields has been modified slightly for VAERS 2.0 to provide clarification and is not included as a specific change

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VAERS 2.0

- Review of VAERS 2.0
  - Slide 15
  - VAERS-1 form available for comparison at https://vaers.hhs.gov/resources/vaers_form.pdf

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Next steps

1. Create "smart" electronic form
2. Computer test form on potential reporters
3. Present the VAERS 2.0 form to ACIP, NVAC and ACCV
4. Post the VAERS 2.0 form on the Federal Register
5. Make final revisions based on computer testing results and comments
6. Develop the platform to accept electronic VAERS 2.0 submissions and update the online reporting tool
7. Implement the VAERS 2.0 form
8. Evaluate completeness and quality of VAERS data (pre-post comparison)

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Discussion

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5.7

Safety of Pneumococcal Polysaccharide Vaccine (Pneumovax® 23) in the Vaccine Adverse Event Reporting System (VAERS)

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Advisory Commission on Childhood Vaccines (ACCV)
September 4, 2014

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of CDC

Purpose

- Provide the Advisory Commission on Childhood Vaccines (ACCV) with a review of the safety of Pneumococcal Polysaccharide Vaccine (Pneumovax® 23) as it considers making a recommendation for the Vaccine Injury Compensation Program to cover adult immunizations

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Outline

- Pneumococcal polysaccharide vaccine (Pneumovax® 23) background
- VAERS analysis
- Summary and conclusions

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Background: Pneumococcal Disease as a Public Health Issue [1-2]

- Pneumococcal infections cause US annual estimated
  - 3,000 to 6,000 cases of meningitis
    - Case fatality rate ~30%, up to 80% in elderly
    - Neurologic sequelae common among those who survive
  - 50,000 cases of bacteremia
    - Case fatality rate ~20%, up to 60% in elderly
  - 500,000 cases of pneumonia annually in the US [1-2]
    - Case fatality rate 5-7%, higher in elderly

1. Willis, et al. Improving influenza, pneumococcal polysaccharide, and hepatitis B vaccination coverage among adults aged <65 years at high risk. *MMWR* 2005 Apr.1;54(RR05): 1-11.
2. CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* Atkinson W, Hamborsky J, Wolfe S, eds. 12th ed., second printing. Washington DC: Public Health Foundation, 2012

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Background: Pneumococcal Polysaccharide Vaccine (Pneumovax® 23)

- Indication
  - For prevention of pneumococcal disease caused by the 23 serotypes in the vaccine
  - Approved for persons ≥50 years, and for persons ≥2 years at increased risk for pneumococcal disease
  - Not approved for use in children less than 2 years of age since they do not develop an effective immune response
- Antigen content
  - 25 micrograms of 23 capsular polysaccharide types of *Streptococcus pneumoniae* (pneumococcus)
  - Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F*
    - Cause 88% of bacteremic pneumococcal disease and provide cross-reactivity for additional types that account for 8% of bacteremic disease

*13-valent pneumococcal conjugate vaccine (PCV13) contains serotypes in yellow above as well as 6A and 19A

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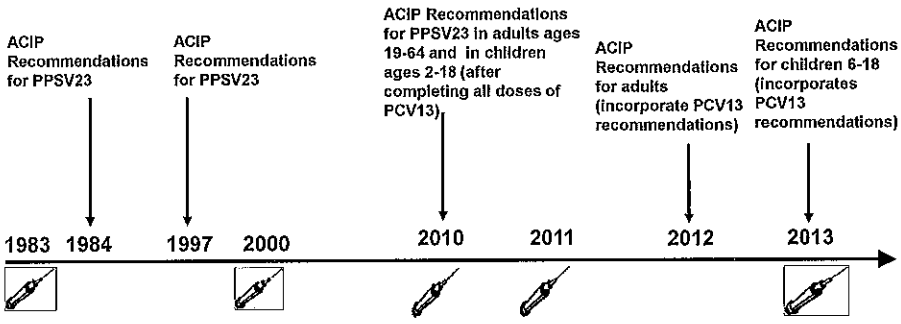
Timeline for Pneumococcal Polysaccharide Vaccine Recommendations in the U.S.



1983
Pneumovax® 23 (Merck) licensed for ages ≥2

Pnu-Immune (Wyeth Lederle) licensed 1983 till 2002

2000
PCV7 (Wyeth) licensed for infants and young children (2, 4, 6,12-16 mo. age)*

2010
PCV13 licensed for children 6 weeks to 5 years

2011
PCV13 licensed for adults ≥50 years

2013
PCV13 licensed for children 6-17 years old

ACIP=Advisory Committee on Immunization Practices

*Pneumococcal conjugate vaccines were developed because polysaccharide vaccines are not adequately immunogenic in young children to protect against pneumococcal disease.

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Pneumovax® 23 Pediatric Recommendations[1,2]

- Children ages 2 to 18 years
  - Immunocompetent with chronic conditions (1 dose)
    - Chronic heart or lung disease, diabetes mellitus, cerebrospinal fluid leaks, cochlear implants
    - Alcoholism, chronic liver disease, cigarette smoking (in children ages 6-18 years)
  - Functional or anatomic asplenia (2 doses, 5 years apart)
    - Sickle cell disease/other hemaglobinopathies; congenital or acquired asplenia
  - Immunocompromised (2 doses, 5 years apart)
    - Congenital or acquired immunodeficiencies, HIV, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma

1. CDC ACIP Recommendations June 28, 2013 at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6225a3.htm
2. CDC ACIP Recommendations Dec. 10, 2010 at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5911a1.htm

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Pneumovax® 23 Adult Recommendations[1,2]

- **Adults ages 19-64**
  - **Immunocompetent with chronic conditions (1 dose)**
    - Chronic heart disease, chronic lung disease, diabetes mellitus, cerebrospinal fluid leaks, cochlear implants
    - Alcoholism, chronic liver disease including cirrhosis, cigarette smoking
  - **Functional or anatomic asplenia (2 doses, 5 years apart)**
    - Sickle cell disease/other hemaglobinopathies; congenital or acquired asplenia
  - **Immunocompromised (2 doses, 5 years apart)**
    - Congenital or acquired immunodeficiencies, HIV, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma
- **All adults ≥ 65**
  - **One dose regardless of previous history**

1. CDC ACIP Recommendations Sept. 3, 2010, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5934a3.htm
2. CDC ACIP Recommendations Oct. 12, 2012 available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm

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Adverse Events from Prelicensure Studies Summarized in Package Insert (Pneumovax® 23)*

Most common adverse events, reported in >10% of subjects

Adverse Event	Initial Vaccination	Revaccination
Local Reactions		
Injection-site pain/soreness/tenderness	60%	77%
Injection-site swelling/induration	20%	40%
Injection-site erythema	16%	35%
Systemic Reactions		
Headache	18%	18%
Asthenia and fatigue	13%	18%
Myalgia	12%	17%

*http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM257088.pdf

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Selected Post-Marketing Studies

Study (year)	Design	Vaccine	Study Group	Main Safety Findings
Jackson, et al. (1999)[1]	Prospective comparative intervention study	Pneu-Immune (Lederle)	> 1400 participants of a group health cooperative. Ages of participants were 50 to 74.	Revaccinated vaccinees more likely than primary to report large local injection site reaction (≥ 10.2 cm within 2 days of vaccination: 11% (55/513) vs. 3% (29/901) (relative risk [RR], 3.3; 95% confidence interval [CI], 2.1-5.1). These reactions resolved by a median of 3 days following vaccination. No serious adverse events reported in either group.
Törling, et al. (2003)[2]	Prospective revaccination study	PPSV23 (brand not stated)	61 persons (ages 56-88) with history of hospitalization for pneumonia and previous PPSV23. No comparison group.	Local reactions occurred in 63%. 10% of total stated local reactions affected daily activity. No serious adverse events reported.
Lin, et al. (2005)[3]	Prospective vaccination study	2 doses of PCV7 and 1 dose of PPSV23 (controls-1 dose of PCV7 and 1 dose of PPSV23). Either Pnu-Immune or Pneumovax	25 pediatric solid organ transplant recipients between 2 and 18 years of age and 23 healthy age matched controls	Systemic and injection-site reactions were comparable between the 2 groups. 17 to 21% of transplant recipients reported fussiness, headache, loss of appetite after 23V, somewhat more than the control subjects.

1. Jackson LA, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* 1999 Jan 20;281(3):243-8.
2. Törling J, et al. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. *Vaccine* 2003 Dec. 8;22(1):96-103.
3. Lin PL, et al. Safety and immunogenicity of the American Academy of Pediatrics–recommended sequential pneumococcal conjugate and polysaccharide vaccine schedule in pediatric solid organ transplant recipients. *Pediatrics*. 2005 Jul;116(1):160-7.

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Selected Post-Marketing Studies (continued)

Study (year)	Design	Vaccine	Study Group	Main Safety Findings
Abzug, et al. (2006)[1]	Multicenter prospective	2 doses PCV & 1 dose PPSV23	263 children ages 2 to <19 receiving HAART* for HIV. No comparison group.	Two PCVs and 1 PPSV23 were immunogenic and safe in HIV-infected children 2 to <19 years who were receiving HAART[2]
Burwen, et al, (2007)[3]	Retrospective database	Flu & PPSV23	Medicare Administrative Databases	Pneumococcal vaccinees had a statistically significant increased rate of hospitalizations for cellulitis and abscess of arm with an incidence rate of 2.5 cases per 100,000 vaccinees. Cellulitis and abscess of arm incidence rate was 5.4 per 100, 000 persons vaccinated if had a previous pneumococcal vaccine within 5 years.

1. Abzug MJ, et al. Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and pneumococcal polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J.* 2006 Oct;25(10):920-9.
2. HAART-highly active antiretroviral therapy
3. Burwen DR, et al. Evaluating adverse events after vaccination in the Medicare population. *Pharmacoepidemiol Drug Saf.* 2007 Jul;16(7):753-61.

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VAERS Review

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Objective

- Describe the safety profile of Pneumovax® 23 in the Vaccine Adverse Event Reporting System (VAERS)

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Vaccine Adverse Event Reporting System (VAERS) (co-managed by CDC and FDA)[1]

Strengths

- National data; accepts reports from anyone
- Rapid signal detection; rare adverse events (AE)
- Collects information about vaccine, characteristics of vaccinee, adverse event[2]
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Generally cannot assess if vaccine caused an AE
- Lack of unvaccinated comparison group
- Cannot calculate rates of occurrence of adverse events
- Pregnancy status not included on VAERS form

1. VAERS website: http://vaers.hhs.gov
2. Some reports have no adverse event

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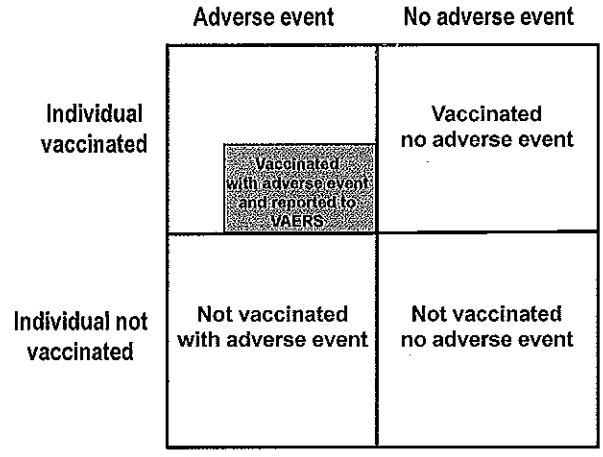
Limitations of VAERS Data



- VAERS only contains partial data in pink cell (incomplete population data)
  - Not able to calculate rates of occurrence of adverse events
  - Not able to determine increased risk
  - Not able to calculate vaccination coverage

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Methods

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Methods

- Included US VAERS reports following Pneumovax® 23 or pneumococcal polysaccharide vaccine (PPSV23) brand unknown after 2002
- Reports received from January 1, 1990 – January 31, 2014
- Dates vaccinated January 1, 1990 – December 31, 2013
- Excluded PPSV23 brand name "Pnu-Immune"
  - Pnu-Immune has not been used in the US since 2002 and constitutes ~10% of PPSV23 reports in VAERS
- Signs, symptoms, or diagnosis coded using Medical Dictionary for Regulatory Activities (MedDRA)[1]
- Descriptive statistics: age, serious[2], non-serious, deaths

1. http://www.meddra.org/

2. Serious reports classified based on Code of Federal Regulations: death, life threatening, hospitalization, prolonged hospitalization, permanent disability

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Empirical Bayesian Data Mining in VAERS

- Identify events after Pneumovax® 23 that have been reported disproportionately compared to all other US licensed vaccines
  - Empirical Bayesian data mining is used by FDA to detect disproportional reporting in the VAERS database
  - A vaccine-adverse event pairing "signals" when a statistical threshold is reached (referred to as a data mining finding)
- A data mining finding does NOT demonstrate the vaccine is associated with increased risk for the adverse event or that a new safety problem exists
  - Some findings may be due to biases in reporting or to chance or other factors not related to an actual safety problem
  - Some adverse events are known, expected and accepted side effects (e.g., runny nose after live attenuated influenza vaccine)
- Data mining findings may prompt further assessment to evaluate association

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Results

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Pneumovax® 23 VAERS Reports – All Ages

Characteristics	N (%)
Number of reports	25,168
Serious	2129 (8)
Female	16,871 (67)
Type of reporter	
Healthcare provider	10,462 (42)
Other	6,319 (25)
Manufacturer	5152 (20)
Patient/Parent	2576 (10)
Age groups (years)	
0<2 (not approved for this age group)	940 (4)
2-5	427 (2)
6-12	550 (2)
13-18	390 (2)
19-64	11,040 (44)
65+	10,546 (42)

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Pneumovax® 23 VAERS Reports by Age Groups and Serious Status[1,2]

Age	Deaths N (%)	Serious non-fatal[2] N (%)	Non-serious N (%)	Total N (%)
2 to 18 years	4 (0.3)	234 (17)	1129 (83)	1367 (100)
2 to 4 years	0 (0)	55 (16)	280 (84)	335 (100)
5 to 18 years	4 (0.4)	179 (17)	849 (82)	1032 (100)
19 to 64 years	23 (0.2)	997 (9)	10,020 (91)	11,040 (100)
65+ years	38 (0.4)	696 (7)	9812 (93)	10,546 (100)
Total	66 (0.3)	2063 (8)	23,039 (92)	25,168 (100)

1. Not shown: 1275 (5%) reports with age not reported/unknown and 940 (4%) report with age 0 to <2 years
2. Includes life threatening illness, inpatient hospitalization, prolongation of an existing hospitalization, or permanent disability

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Pneumovax® 23 Doses Distributed and Adverse Event Reporting Rates to VAERS

- 142.2 million Pneumovax® 23 doses distributed in the United States from January 1, 1991 to December 31, 2013
- Reporting rate
  - All reports - 17.7 per 100,000 doses distributed
  - Serious reports - 1.5 per 100,000 doses distributed
  - Anaphylaxis reports - 0.04 per 100,000 doses distributed

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Top 10 MedDRA Terms[1,2] in Children ages 2 to 18 Years

MedDRA Codes Non-serious reports	N=1129 (%)
Pyrexia	476 (42)
Injection site erythema	344 (30)
Injection site pain	269 (24)
Injection site swelling	219 (19)
Erythema	183 (16)
Pain	167 (15)
Injection site oedema	123 (11)
Injection site warmth	105 (9)
Oedema peripheral	101 (9)
Vomiting	93 (8)

MedDRA Codes Serious reports	N=238 (%)
Pyrexia	172 (72)
White blood cell count increased	95 (40)
Cellulitis	93 (39)
Injection site pain	87 (37)
Injection site erythema	82 (34)
Injection site swelling	67 (28)
C-reactive protein increased	49 (21)
Erythema	46 (19)
Blood culture negative	44 (18)
Vomiting	44 (18)

1. MedDRA terms are not mutually exclusive.
2. These symptoms or related symptoms are listed in the package insert except "blood culture negative."

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Co-administered Vaccines with Pneumovax® 23 in Children 2 to 18 years (N=1367), VAERS

Vaccine	N (%)
Pneumovax® 23 administered alone	*613 (45)*
Trivalent inactivated influenza (TIV)	377 (28)
DTaP	78 (6)
H1N1 inactivated influenza	18 (1)
DTaP-IPV-Hib (Pentacel)	10 (0.7)
DTP	9 (0.7)
DT	8 (0.6)
Live attenuated influenza vaccine (LAIV)	8 (0.6)

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Pediatric Death Reports after Pneumovax® 23 in VAERS

Co-administered Vaccines	Age[1]	Sex	Onset interval	Cause of death or medical condition around time of death[2]	Medical History
None	3 years	Male	3.6 years	Sickle cell disease with fever; cause of death unknown May have developed pneumococcal sepsis around time of death	Sickle cell disease
Trivalent inactivated influenza (IIV3)	7 years	Female	3 days	Accidental asphyxiation	Lissencephaly - microcephaly Seizure disorder
None	~6 years	Female	5.8 years	Pneumococcal sepsis, hemoglobin sickle cell disease	Sickle cell disease
Meningococcal polysaccharide, IIV3, Hep B, MMR	18 years	Male	1 month	Neisseria meningitidis septicemia	No illnesses

1. Age is at time of vaccination, not at time of death
2. Cause of death is based on review of autopsy report, death certificate or medical record

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Top 10 MedDRA Terms* in Adults Ages 19 and Older

MedDRA Codes Non-serious reports	N=19,832 (%)
Injection site erythema	6119 (31)
Injection site pain	5161 (26)
Erythema	4498 (23)
Pyrexia	4418 (22)
Injection site swelling	4389 (22)
Pain	3795 (19)
Oedema peripheral	2624 (13)
Injection site warmth	2529 (13)
Pain in extremity	2522 (13)
Injection site oedema	1906 (10)

MedDRA Codes Serious reports	N=1754 (%)
Pyrexia	770 (44)
Injection site erythema	520 (30)
Cellulitis	515 (29)
Injection site pain	512 (29)
White blood cell count increased	454 (26)
Pain	373 (21)
Injection site swelling	369 (21)
Chills	353 (20)
Erythema	323 (18)
Pain in extremity	272 (16)

* MedDRA terms are not mutually exclusive. All of these symptoms or related symptoms are listed in the package insert.

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Co-administered Vaccines with Pneumovax® 23 in Adults ages 19 and older (N=21,586), VAERS

Vaccine	N (%)
Pneumovax® 23 administered alone	*11,286 (52)*
Trivalent inactivated influenza (TIV)	8,291 (38)
Hepatitis B	151 (0.7)
Hepatitis A	147 (0.7)
H1N1 inactivated influenza	141 (0.7)
Hepatitis A & B Combined	78 (0.4)
DTAP	71 (0.3)
DT	43 (0.2)

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Reports of Pneumovax® 23 Administered during Pregnancy

- 17 total reports
- Adverse events include
  - 2 spontaneous abortions
  - 5 cellulitis
  - 5 local reactions
  - 4 no adverse event
  - 1 gestational diabetes and chlamydia

Pregnancy Category C: Animal reproduction studies have not been conducted with Pneumovax® 23. It is also not known whether Pneumovax® 23 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pneumovax® 23 should be given to a pregnant woman only if clearly needed.

ACIP-Pregnancy is neither a contraindication nor a precaution to PPSV23. If someone has a recommendation for PPSV23, ACIP does not have a recommendation to withhold or delay the dose of vaccine even if they are pregnant.

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Death Reports in Adults ages 19 and Older Following Pneumovax® 23

- 61 total
  - Median age 69 years; range 27 to 98 years
  - 44 had cause of death confirmed with medical records, autopsy reports and/or death certificates
  - 17 had no records to confirm cause of death
- Body systems involved in the cause of death among the 43 confirmed reports
  - Cardiovascular (N=16)
  - Respiratory (N=9)
  - Other infectious (N=9)
  - Undetermined (N=2)
  - Other non-infectious (N=4)
  - Neurological (N=3)
  - Allergic (N=1)

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FDA Data Mining Results for Pneumovax® 23

- MedDRA Preferred Terms for which a statistically significant threshold was reached (EB05 > 2.0) as of July 7, 2014
  - Cellulitis, injection site cellulitis
    - Cellulitis and injection site cellulitis after PPSV have been documented in the literature (Burwen et al. Pharmacoepidemiol Drug Saf. 2007 Jul;16(7):753-61, Evaluating adverse events after vaccination in the Medicare population) and are commonly reported in VAERS. They are labeled events.
  - Leukocytosis, white blood cell count increased
    - Systemic signs and symptoms associated with the administration of PPSV, including fever, leukocytosis and increased C-reactive protein are commonly reported in VAERS and were added to the PPSV label in 2008 and 2009.

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FDA Data Mining Results for Pneumovax® 23 (cont.)

- MedDRA Preferred Terms for which a statistically significant threshold was reached (EB05 > 2.0) as of July 7, 2014
  - Local reaction, skin warm, injected limb mobility decreased, skin striae, local swelling, injection site streaking
    - Mild, moderate and severe injection site reactions have been observed in clinical trials and are commonly reported after PPSV.
  - Blood culture and blood culture negative
    - These preferred terms (PTs) from the MedDRA System Organ Class "Investigations" are usually reported in the context of severe injection site reactions or cellulitis.

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Summary and Conclusions: Pneumovax® 23

- From 1990 through 2013, VAERS received 25,168 reports following Pneumovax® 23
- Most reports (92%) were classified as non-serious
- Fever (47%) is most commonly reported adverse event in children followed by injection site erythema (31%), injection site pain (26%), and injection site swelling (21%)
- Deaths reports in children are rare (4 total) and listed cause of death and information from medical records do not suggest a pattern of concern
- Injection site erythema (31%) and injection site pain (26%) and fever (24%) are the most commonly reported adverse events in adults
- No concerning patterns were detected in VAERS for Pneumovax® 23 for children or adults

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WHO Position Paper: 23-valent Pneumococcal Polysaccharide Vaccine*—2008

"On the basis of decades of use, PPV23 is considered safe both in terms of severe immediate reactions and potential long-term adverse consequences. Minor adverse reactions, such as transient redness and pain at the injection site, occur in 30–50% of those who have been vaccinated, more commonly following subcutaneous administration than intramuscular administration; low grade fever occurs infrequently. Local reactions may be more frequent in recipients of a second dose of the vaccine..."

*http://www.who.int/wer/2008/wer8342.pdf

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Thank You

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National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion -- Immunization Safety Office

5.8

Safety of Varicella Zoster Vaccine (Zostavax®) in the Vaccine Adverse Event Reporting System (VAERS)

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September 4, 2014

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Purpose

- Provide the Advisory Commission on Childhood Vaccines (ACCV) with a review of the safety of Zoster Vaccine (Zostavax®) as it considers making a recommendation for the Vaccine Injury Compensation Program to cover adult immunizations

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Outline

- Background
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Herpes Zoster-Shingles*

- Herpes zoster or shingles occurs when a person with history of varicella zoster virus (chicken pox) infection has a reactivation of the virus
  - Associated with
    - Aging
    - Immunosuppression
    - Intrauterine exposure
    - Varicella at <18 months of age

  - Eruption usually occurs on one side in the area of a sensory nerve
  - Complications include postherpetic neuralgia, vision loss if shingles in or around an eye, other neurologic problems
  - 500,000 to 1 million US cases annually, lifetime risk ~32%

*Source-CDC. *Epidemiology and Prevention of Vaccine Preventable Diseases* (Pink Book) 12th edition, second printing, May 2012.

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Background: Zoster Vaccine (Zostavax®)

- Live attenuated, single dose subcutaneous injection
- May 25, 2006 - Initial FDA approval for use in persons ≥60 years of age
- March 24, 2011- Label change for use in persons 50-59 years of age
- Indicated for prevention of herpes zoster (shingles) in persons ages ≥ 50 years
- Contraindications
  - History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine
  - Immunosuppression or immunodeficiency
  - Pregnancy*

* It is not known whether Zostavax® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, naturally occurring VZV infection is known to sometimes cause fetal harm. Therefore, Zostavax® X should not be administered to pregnant women, and pregnancy should be avoided for 3 months following administration of Zostavax® (from package insert).

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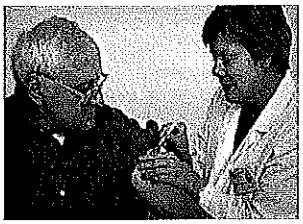
Advisory Committee on Immunization Practices (ACIP) Recommendations for Zoster Vaccine*

- Recommended for all persons ≥60 years
  - Administer as a single 0.65-mL dose subcutaneously in the deltoid region of the upper arm
- Declined to recommend the vaccine in adults ages 50 - 59
- Person with previous episode of zoster or persons with chronic medical conditions can be vaccinated unless those conditions are contraindications or precautions
- Contraindications
  - Primary or acquired immunodeficiency
  - Pregnancy



*CDC-Prevention of Herpes Zoster. Recommendations of the ACIP June 6, 2008. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

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Zostavax® Effectiveness*

Condition	Efficacy % and 95% CI
Shingles	51.3% (44.2-57.6)
Postherpetic neuralgia – lasting 30 days	58.9% (46.6-68.7)
Postherpetic neuralgia – lasting 60 days	60.4% (43.6-72.6)
Postherpetic neuralgia – lasting 90 days	66.5% (47.5-79.2)
Postherpetic neuralgia – lasting 120 days	68.7% (45.2-83.0)
Postherpetic neuralgia – lasting 182 days	72.9% (42.1-88.6)

*CDC-Prevention of Herpes Zoster. Recommendations of the ACIP June 6, 2008. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm

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Adverse Events from Prelicensure Studies Summarized in the Zostavax® Package Insert

Adverse Event	Shingles Prevention Study Ages ≥ 60 Zostavax® vs. placebo	Zoster Efficacy & Safety Trial Ages 50-59 Zostavax® vs. placebo
Injection Site[1]		
Any injection site adverse reaction	48% vs. 17%	64% vs. 14%
Systemic[2]		
Overall systemic adverse experiences		35% vs. 34%
Headache	1.4% vs. 0.8%	9% vs. 8%
Noninjection-site zoster-like rashes	0.1% vs. 0.2%	
Noninjection-site varicella like rashes	0.1% vs. 0.1%	
Confirmed Case of Herpes Zoster	<0.1% vs. 0.1%	
Death	0.1% vs. 0.1%	
Serious Adverse Events	1.4% vs. 1.4%	0.6% vs. 0.5%
Serious adverse event --in substudy	1.9% vs. 1.3% RR 1.5 (95% CI, 1.0 to 2.3)	
Adverse event substudy[3]		
Hospitalization	34% vs. 34.1%	
Death	4.1% vs. 4.1%	

1. Monitored for 5 days post vaccination; 2. Monitored for 42 days post vaccination; 3. Monthly surveillance for hospitalization was conducted through the end of the study, 2 to 5 years post vaccination; * indicates a statistically significant difference

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Adverse Events from Prelicensure Studies Summarized in Package Insert (Zostavax®)

- Pre-licensure clinical trail: Shingles Prevention Study (~38,000)
  - Injection site reactions and headaches were the most common adverse events
  - In a safety substudy (~6,600) serious cardiovascular events were more frequent in those receiving Zostavax® (20 [0.6%]) than in placebo (12 [0.4%])

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Selected Post-Marketing Studies

Study (year)	Design	Study Group	Main Safety Findings
Murray et al[1] (2011)	Randomized double blind clinical trial: 5,983 received zoster vaccine and 5,997 received placebo. Subjects followed for serious adverse events (SAEs) for 42 and 182 days after vaccination.	Adults ≥ 60 years old. Study targeted 15% enrollment ≥ 80 years old	The relative risk of SAEs within 42 d for ZV vs. placebo, was 1.26 (95% CI: 0.91, 1.73). During the 182-day follow-up period, the relative risk of SAEs for ZV vs. placebo was 1.13 (95% CI: 0.98, 1.32). ZV & placebo groups had similar safety profiles for SAEs during the 42 day and 182 days follow-up periods.
Parrino et al [2] (2011)	Randomized double blind clinical trial: 309 adults were randomized to receive either zoster vaccine or placebo.	Adults ≥ 60 who were taking Prednisone 5-20 mg daily dose prior to vaccination and expected to continue for 6 weeks	Serious adverse events within 42 days of vaccination: 5% among Zostavax® vs. 6% among placebo. Serious adverse events within 6 months of vaccination: 10% among ZV vs. 11% among placebo recipients. Zostavax® was generally well tolerated in adults ages ≥ 60 on chronic steroids.
Baxter, et al[3] (2012)	Retrospective cohort study, compared rates of clinical events in 29,010 adults resulting hospitalizations or emergency room visits for 42 days post vaccination compared with day 91 to 180 post vaccination	Adults ≥ 60 years old in a managed care organization. Vaccinees served as their own controls.	No clear increase in health events observed in the 42 day risk period as compared to the later 91 to 180 day risk period. No safety concerns identified.
Tseng, et al [4] (VSD study) 2012	2 self comparison approaches: case-centered approach and self-controlled case series using computerized data to look at pre-specified adverse event categories	193,083 adults ≥ 60 years receiving zoster vaccine from January 1, 2007 to December 31, 2008 from a large managed-care cohort	Risk of allergic reaction was increased within 1-7 days of vaccination [relative risk = 2.13, 95% confidence interval (CI): 1.87-2.40]. No increased risk was found for the following adverse event groupings: cerebrovascular events; cardiovascular events; meningitis; encephalitis and encephalopathy; Ramsay-Hunt syndrome and Bell's palsy. Other than allergic reactions within 7 days after vaccination, no safety concerns.

1. Murray, AV, et al. Safety and tolerability of zoster vaccine in adults ≥60 years old. *Hum Vaccine* 2011 Nov;7(11):1130-6.
2. Parrino, J, et al. Safety, tolerability and immunogenicity of zoster vaccine in patients on chronic/maintenance corticosteroids. (abstract). *Arthritis Rheum* 2011; 63 Suppl 10:2071.
3. Baxter, R et al. Safety of Zostavax-a cohort study in a managed care organization. *Vaccine* 2012 Oct 19;30(47):6636-41.
4. Tseng, et al. Safety of zoster vaccine in adults from a large managed-care cohort: A Vaccine Safety Datalink Study. *J Intern Med.* 2012 May;271(5): 510-20.
11

VAERS Review

12

Objective

- Describe the safety profile of Zostavax® in the Vaccine Adverse Event Reporting System (VAERS)

13

Vaccine Adverse Event Reporting System (VAERS) (co-managed by CDC and FDA)[1]

Strengths

- National data; accepts reports from anyone
- Rapid signal detection; rare adverse events (AE)
- Collects information about vaccine, characteristics of vaccinee, adverse event[2]
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Cannot calculate rates of occurrence of adverse events
- Generally cannot assess if vaccine caused an AE
- Pregnancy status not included on VAERS form

1. VAERS website: http://vaers.hhs.gov
2. Some reports have no adverse event

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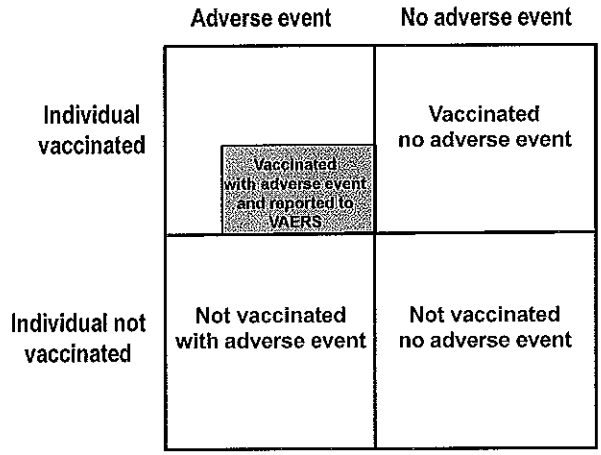
Limitations of VAERS Data



- VAERS only contains partial data in pink cell (incomplete population data)
  - Not able to calculate rates of occurrence of adverse events
  - Not able to determine increased risk
  - Not able to calculate vaccination coverage

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Methods

16

Methods

- Included US VAERS reports following Zostavax® or zoster vaccine brand unknown
  - Reports received from May 1, 2006 – February 28, 2014
  - Dates vaccinated May 1, 2006 – January 31, 2014
- Signs, symptoms, or diagnosis coded using Medical Dictionary for Regulatory Activities (MedDRA)[1]
  - Internationally standardized terminology
  - Clinically validated
- Descriptive statistics: age, serious[2], non-serious, deaths

1. http://www.meddra.org/

2. Serious reports classified based on Code of Federal Regulations: death, life threatening illness, hospitalization, prolongation of an existing hospitalization, permanent disability

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Empirical Bayesian Data Mining in VAERS

- Identify events after Zostavax® that have been reported disproportionately compared to all other US licensed vaccines
  - Empirical Bayesian data mining is used by FDA to detect disproportional reporting in the VAERS database
  - A vaccine-adverse event pairing "signals" when a statistical threshold is reached (referred to as a data mining finding)
- A data mining finding does NOT demonstrate the vaccine is associated with increased risk for the adverse event or that a new safety problem exists
  - Some findings may be due to biases in reporting or to chance or other factors not related to an actual safety problem
  - Some adverse events are known, expected and accepted side effects (e.g., runny nose after live attenuated influenza vaccine)
- Data mining findings may prompt further assessment to evaluate association

18

Results

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Zostavax® VAERS Reports – All Ages*

Characteristics	N (%)
Number of reports	15,930
Serious	723 (5)
Female	11,507 (72)
Type of reporter	
Manufacturer	6408 (40)
Healthcare provider	5192 (33)
Other	2824 (18)
Patient/Parent	1506 (9)
Age groups (years)	
0-18 (not approved for this age group)	390 (2)
19-49 (not approved for this age group)	248 (2)
50-59	1541 (10)
60+	12,486 (78)

* Not shown: 1265 (8%) reports with age not reported/unknown

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Zostavax® VAERS Reports by Age Groups and Serious Status[1,2]

Age	Deaths N (%)	Serious non-fatal N (%)	Non-serious N (%)	Total N (%)
0 to 18 years	0 (0)	1 (0.3)	389 (100)	390 (100)
19 to 49 years	0 (0)	5 (2)	243 (98)	248 (100)
50 to 59 years	2 (0.1)	37 (2)	1502 (97)	1541 (100)
60+ years	47 (0.4)	593 (5)	11,846 (95)	12,486 (100)
Total	51 (0.3)	672 (4)	15,207 (95)	15,930 (100)

1. Not shown: 1265 (8%) reports with age not reported/unknown

2. Includes death, life threatening illness, inpatient hospitalization, prolongation of an existing hospitalization, or permanent disability

21

Zostavax® Doses Distributed and Adverse Event Reporting Rates to VAERS

- 18.4 million doses of Zostavax® distributed in the US from licensure in 2006 to December 31, 2013
- Reporting rate to VAERS
  - All reports — 86.2 per 100,000 doses distributed
  - Serious reports — 3.9 per 100,000 doses distributed

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Top 10 MedDRA Terms[1] in Adults Ages 50 to 59 Years

MedDRA Codes Non-serious reports	N= 1502 (%)
Injection Site Erythema	550 (37)
Injection Site Swelling	355 (24)
Erythema	265 (18)
Injection Site Warmth	238 (16)
Injection Site Pain	234 (16)
Injection Site Pruritus	181 (12)
Pruritus	166 (11)
Pain	151 (10)
Rash	151 (10)
Headache	123 (8)

MedDRA Codes Serious reports	N=39 (%)
Injection Site Erythema	10 (26)
Pyrexia (fever)	9 (23)
Dyspnoea (difficulty breathing)	7 (18)
White Blood Cell Count Increased[2]	7 (18)
Chills[2]	6 (15)
Headache	6 (15)
Injection Site Swelling	6 (15)
Injection Site Warmth	5 (13)
Red Blood Cell Count Decreased[2]	5 (13)
Blood Culture Negative[2], Blood Glucose Increased[2], Cellulitis[2], EKG abnormal[2], Erythema, Haematocrit Decreased[2], Neutrophil % Increased[2], Rash	4 (10)

1.MedDRA terms are not mutually exclusive.
2.These adverse events are not listed in the package insert.

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Top 10 MedDRA Terms[1] in Adults Ages 60 and Older

MedDRA Codes Non-serious reports	N= 11,846 (%)
Injection Site Erythema	3083 (26)
Herpes Zoster	1997 (17)
Injection Site Swelling	1822 (15)
Rash	1620 (14)
Erythema	1552 (13)
Pruritus	1430 (12)
Pain	1319 (11)
Injection Site Pain	1316 (11)
Injection Site Pruritus	1186 (10)
Injection Site Warmth	1138 (10)

MedDRA Codes Serious reports	N= 640 (%)
Herpes Zoster	167 (26)
Pain	117 (18)
Rash	96 (15)
Pyrexia	87 (14)
Asthenia	84 (13)
Dyspnoea	82 (13)
Headache	72 (11)
Nausea	72 (11)
Dizziness[2]	61 (10)
Pain in Extremity, & White Blood Cell Count Increased[2]	61 (10)

1. MedDRA terms are not mutually exclusive.
2. These adverse events are not listed in the package insert.

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Co-administered Vaccines with Zostavax® in Adults Ages 50+ (N=14,027), VAERS

Vaccine	14,027 (%)
Zostavax® administered alone	12,675 (90%)
Trivalent inactivated influenza (TIV)	700 (5%)
Pneumococcal polysaccharide vaccine	414 (3%)
Tdap	262 (2%)
Td	49 (0.3%)
Tetanus toxoid	23 (0.2%)
Varicella	21 (0.1%)
Hepatitis A	17 (0.1%)

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Reports of Zostavax® during Pregnancy

- 15 total reports
  - 7 reports among pregnant vaccine administrators (nurse or pharmacist)
    - 1 oral numbness (vaccine splashed in mouth)
    - 2 eye irritation (vaccine splashed in eyes)
    - 2 needle sticks
    - 2 splashes on skin
  - 8 reports among pregnant patients vaccinated with Zostavax®
    - 2 spontaneous abortions (1 in a 50 y/o)
    - 1 cleft lip in newborn
    - 1 uncontrolled blood sugars in preexisting diabetic patient
    - 1 injection site erythema
    - 3 no adverse event

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Death Reports in VAERS Following Zostavax®

- 51 total death reports
  - Median age 74 years old; range 56 to 90 years old
  - 41 confirmed with autopsy reports or death certificates
  - 10 had no records
- Body systems[1] involved in the cause of death among the 41 confirmed death reports in adults
  - Cardiovascular (N=25)
  - Other infectious (N=9)
  - Respiratory (N=3)
  - Other non-infectious[2] (N=3)
  - Other Gastrointestinal (N=1)

1. Vellozzi, et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010. *Vaccine* 2010. 28 (45).

2. Cause of death includes metastatic inflammatory breast cancer, subdural hematoma due to a fall, and acute renal failure & Creutzfeldt-Jacob Disease.

27

FDA Data Mining Results for Zostavax®

- MedDRA Preferred Terms for which a statistically significant threshold was reached (EB05 > 2.0) as of July 7, 2014
  - Herpes zoster, ophthalmic herpes zoster, oral herpes, post herpetic neuralgia, varicella, varicella virus test positive
    - Zoster- and varicella-like rashes were observed in the clinical trials. Conditions relating to varicella-zoster vaccine and herpes viruses are commonly reported and may represent confounding by indication, as well as general confusion about the virology of some of these clinical entities.
  - Blister, injection site pruritus, injection site rash, injection site vesicles, rash vesicular, scab, skin lesion
    - In addition to VZV- and HSV-related conditions (please see above), local rashes and other lesions of the integument are commonly reported.

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FDA Data Mining Results for Zostavax®, cont.

- MedDRA Preferred Terms for which a statistically significant threshold was reached (EB05 > 2.0) as of July 7, 2014
  - Accidental exposure to product, drug administered to patient of inappropriate age, no adverse event, secondary transmission, wrong drug administered
    - Medication errors are not necessarily adverse health events, but they are commonly reported for Zostavax®, partly because the product is a live viral vaccine and partly because of confusion regarding Varivax and Zostavax®.
    - The potential for transmission is listed in the Warnings and Precautions of the US package insert.

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Summary and Conclusions: Zostavax®

- VAERS received 15,930 reports following Zostavax® 2006-2013
- 95% were non-serious
- Injection site erythema (36%) most common AE in 50-59 y/o followed by injection site swelling (23%), erythema (17%), and injection site warmth (16%)
- Injection site erythema (25%) is the most common AE in ≥ 60 y/o followed by herpes zoster (17%), injection site swelling (15%), and rash (14%)
- Deaths reports are rare (51 total) and listed cause of death and information from medical records do not suggest a pattern of concern
- No concerning patterns were detected in VAERS for Zostavax®

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Immunization Safety Office/CDC

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FDA

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Jane Woo

31

Centers for Disease Control and Prevention
Atlanta, GA

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion – Immunization Safety Office

Thank You

For more information please contact Centers for Disease Control and Prevention
1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion – Immunization Safety Office

5.9

Vaccine Activities Update

National Institute of Allergy and Infectious Diseases, National Institutes of Health

Claire Schuster, MPH
Division of Microbiology and Infectious Diseases
NIAID, NIH, DHHS

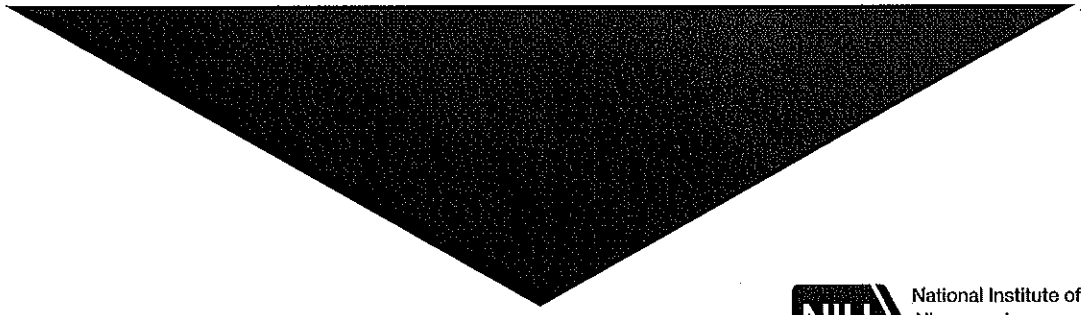
September 2014

National Institute of Allergy and Infectious Diseases

NIAID Infectious Disease Research: A Dual Mandate

Maintain and "grow" a robust basic and applied research portfolio in microbiology, immunology, and clinical research

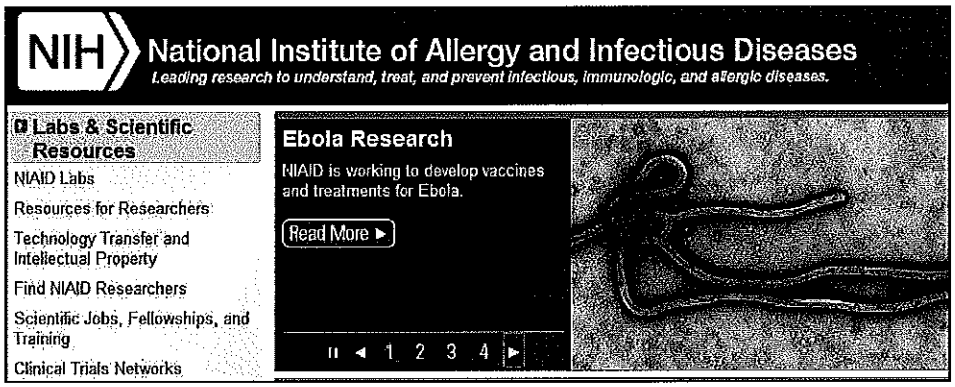
Respond rapidly to new infectious disease threats



National Institute of Allergy and Infectious Diseases

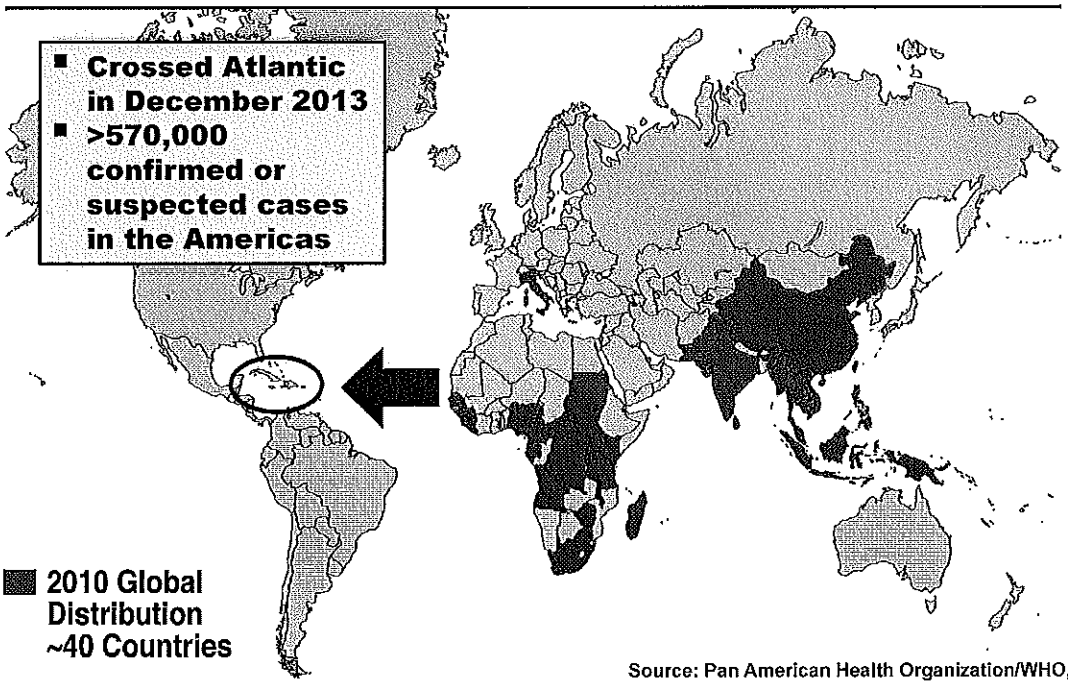
Slide Source: A. S. Fauci

Ebola Research



www.niaid.nih.gov/topics/ebolaMarburg/research/Pages/default.aspx

Chikungunya Virus: An Emerging Threat



Slide Source: A. S. Fauci

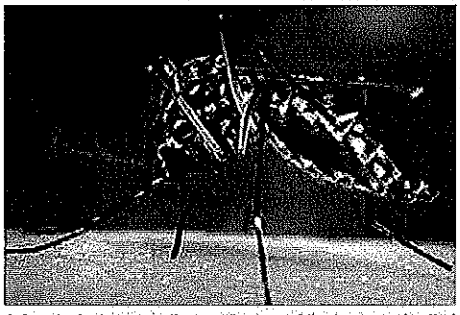
Source: Pan American Health Organization/WHO, August 8, 2014

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Allergy and Infectious Diseases (NIAID)

http://www.niaid.nih.gov
Thursday, August 14, 2014

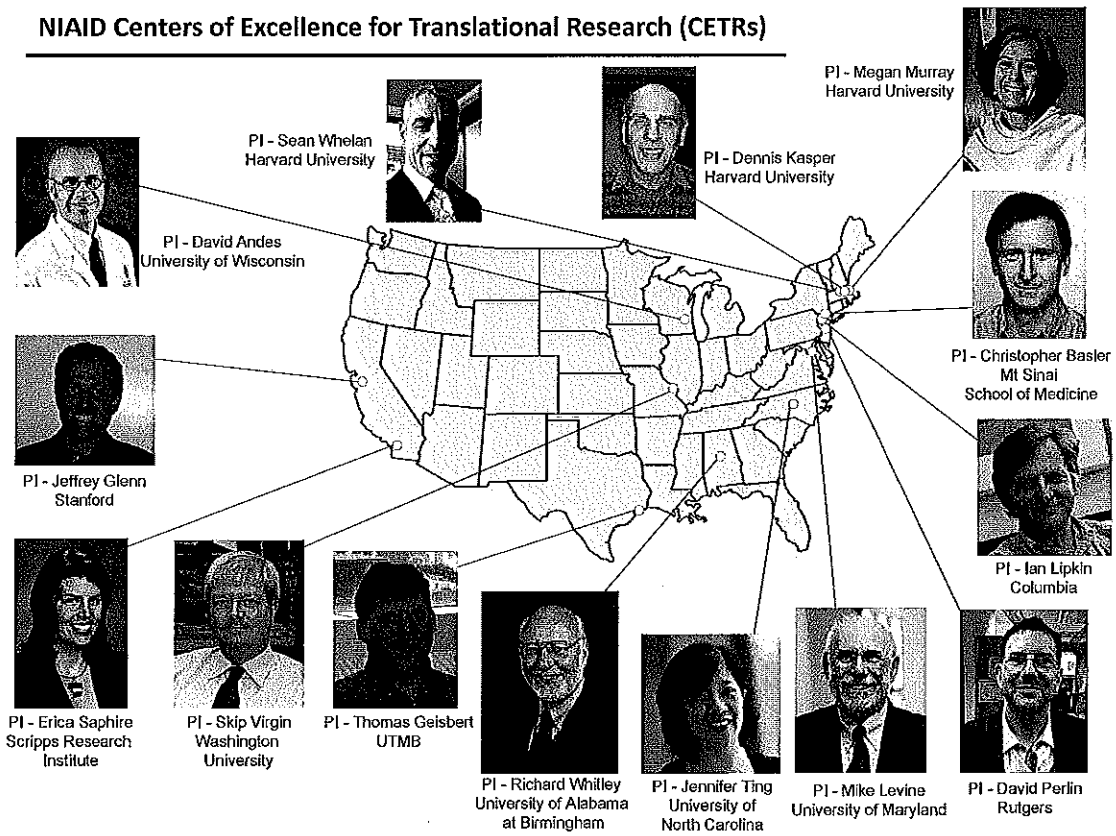
Experimental Chikungunya Vaccine Induces Robust Antibody Response



A female *Aedes aegypti* mosquito, one of the two species that spreads chikungunya virus, is shown feeding.
Credit: CDC

National Institute of Allergy and Infectious Diseases

NIAID Centers of Excellence for Translational Research (CETRs)



Meetings

- Development of New Antibacterial Products: Charting a Course for the Future (July 30-31, 2014)
  - Workshop sponsored by NIAID and FDA
- Overcoming Bottlenecks in Antibacterial Product Development (Sept. 22-23, 2014)
- Coordinated Development of Diagnostics and Therapeutics Workshop (Sept. 23-24, 2014)

National Institute of Allergy and Infectious Diseases

5.10

Food and Drug Administration Report for the September ACCV Report

LCDR Valerie Marshall

Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Vaccines Research and Review (OVRR)

- In July 2014, the FDA approved a supplement to the biologics license application for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed and Inactivated Poliovirus Vaccine, Kinrix, to revise the package insert to include safety and immunogenicity data to support co-administration of Kinrix with varicella virus vaccine and to update the pharmacovigilance plan.

- In July 2014, the FDA approved a supplement to the biologics license application for Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant (CERVARIX®) to include efficacy and immunogenicity data from an end-of-study analyses in the package insert and to update the pharmacovigilance plan.

- In July 2014, the FDA approved supplements to the biologics license applications for licensed Influenza Vaccines, to include the 2014-2015 United States formulation. Influenza vaccine lots that have been released by FDA and are available for distribution by the manufacturers.

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

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

5.11

National Vaccine Program Office Update

National Vaccine Program Office

ACCV, September 2014

Dr. Karin Bok

NVPO-funded review of vaccine safety in the U.S.

- AHRQ report (RAND research) on an extensive review of the safety of vaccines currently recommended in the U.S in adult and children, including pregnant women
- Publication in journal "Pediatrics" summarizing the results of the review of vaccine safety of childhood vaccinations

National Vaccine Program Office

VACCINES INCLUDED IN THE STUDY

Vaccine	Age
DTaP (diphtheria, tetanus, and acellular pertussis)	2 months–6 years
Hepatitis A	12 months and older
Hepatitis B	Birth and older
Hib (*Haemophilus influenzae* type b)	6 weeks–59 months
HPV (human papillomavirus)	9 years–21 years (male) 9 years–26 years (female)
Influenza (inactivated)	6 months and older
Influenza (live attenuated)	2 years and older
IPV (inactivated polio vaccine)	6 weeks and older
MCV (meningococcal conjugate vaccine)	2 years and older
MMR (measles, mumps, and rubella)	12 months and older
MPSV (meningococcal polysaccharide vaccine)	2 years and older in specific circumstances
PCV13 (pneumococcal conjugate vaccine)	6 weeks–18 years
Pneumococcal polysaccharide vaccine	2 years and older in specific circumstances
Rotavirus	6 weeks–8 months
Tdap (tetanus, diphtheria, and acellular pertussis)	7 years and older
Varicella	12 months and older

National Vaccine Program Office

HIGHLIGHTED ADVERSE REACTIONS

Vaccine	Adverse Reaction	Study Details
HAV	Moderate evidence of **purpura**	Mild and acute purpura in children 7-17 yo
Flu	Moderate evidence of association with **febrile seizures**	TIV (H1N1) associated with febrile seizures when administered with PCV13 in children <5y
PCV13	Moderate evidence of association with **febrile seizures**	In 16 mo patients at 13.7 cases/100,000 and 45 cases/100,000 when co-administered with TIV
Rotavirus	Moderate evidence of **intussusception**	1.1-1.5 cases /100,000 vaccinated

National Vaccine Program Office

NVPO SUPPORTING VACCINE SAFETY RESEARCH

- NVPO and ISO, CDC are collaborating on a study following up babies born from mothers vaccinated with Tdap

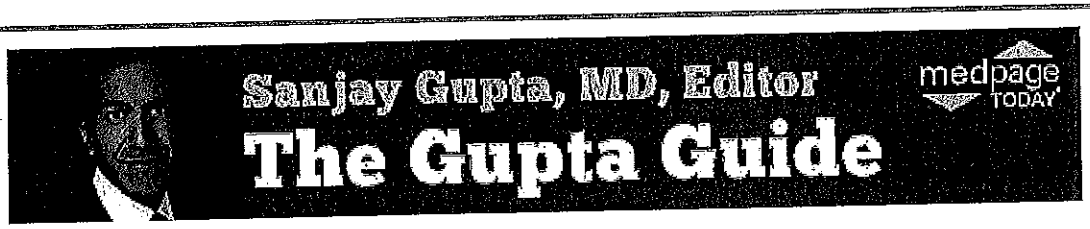
- NVPO is launching a pilot program to support vaccine safety research at any stage of vaccine development or licensure, with two competitive Cooperative Agreements.

Announcement will be out soon, for a total investment of $500,000.

National Vaccine Program Office

6

6.1



ACIP Urges Nasal Spray Flu Vaccine

Published: Jun 26, 2014

By Michael Smith, North American Correspondent, MedPage Today

Say goodbye to needles -- if there's a choice, doctors should give children their flu vaccine as a nasal spray rather than a shot, a CDC committee has urged.

The Advisory Committee on Immunization Practices voted 15-0 to recommend a preference for the inhaled live attenuated influenza vaccine, FluMist Quadrivalent, for healthy children 2 through 8.

The recommendation still must still be approved by the CDC director, incorporated into the flu prevention and control recommendations, and published in *Morbidity and Mortality Weekly Report* before it becomes official policy.

The recommendation was based on a data review that suggested the nasal spray vaccine provides better protection than flu shots against laboratory-confirmed, medically attended flu illness.

But the committee also said that if the nasal vaccine isn't available, children should get the flu shot rather than miss vaccination.

The recommendation is not likely to change practice, commented Catherine Dundon, MD, a Nashville-area pediatrician and consultant to MedImmune, the maker of FluMist Quadrivalent.

"Most pediatricians," she told *MedPage Today*, "are already using FluMist or at least have it in their offices."

"To know the one that's quicker, easier, and doesn't hurt is actually a preferred product and protects better -- and to have that stated by ACIP -- is wonderful," she said.

"The nurses love it because it's their job to stick all these kids," she said.

The American Academy of Pediatrics (AAP) will not make its own recommendations about flu vaccines until early fall, and a spokesman for the group was not immediately available for comment.

However, news reports quoted Michael Brady, MD, of Ohio State University, as saying FluMist Quadrivalent is more costly and most doctors have already vaccines for the fall flu season.

Brady is chair of the AAP's committee on infectious diseases.

According to the Associated Press, Brady said the committee made its decision based on studies done before flu vaccine was encouraged for most children, when vaccination rates were much lower, and newer research might not support the move.

6.2

California's pertussis epidemic escalates, health officials report

By ERYN BROWN

JUNE 27, 2014, 7:52 PM

California's pertussis epidemic has escalated, state health officials said Friday, with 4,558 cases reported this year as of Tuesday — 1,100 of those in the last two weeks.

"We are off to a really bad start in 2014," Dr. Gil Chavez, state epidemiologist with the California Department of Public Health, said during a phone call with reporters Friday.

Chavez delivered his comments as the health department released a report summarizing the latest data on this year's epidemic of pertussis, or whooping cough. Of this year's cases thus far, 3,614, or 84%, have occurred in patients 18 or younger. Out of 142 illnesses that required hospitalization, 89, or 63%, were in infants 4 months or younger.

Three babies have died from pertussis infections in 2014, Chavez said, although two of those will be attributed to 2013's case count because they initially became ill last year.

Because infants less than a year old are at the highest risk of hospitalization and death from pertussis — and because babies generally do not receive pertussis vaccinations until they are 8 weeks old — Chavez said that all pregnant women should receive the Tdap vaccine during their third trimester.

"Vaccination of pregnant women is the most important thing that can be done to protect infants," he said, because the mothers' antibodies can be passed along to their newborns.

Whooping cough cases peak on a three- to five-year cycle. Based on historical patterns, Chavez said, it is likely that disease activity will remain high through the summer. But he said it was too soon to know if this year would be worse than 2010, the last year pertussis peaked.

That year, more than 9,000 Californians contracted the disease.

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6.3

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

Margaret A. Maglione, Lopamudra Das, Laura Raaen, Alexandria Smith, Ramya Chari, Sydne Newberry, Roberta Shanman, Tanja Perry, Matthew Bidwell Goetz and Courtney Gidengil

Pediatrics 2014;134;325; originally published online July 1, 2014;
DOI: 10.1542/peds.2014-1079

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

AUTHORS: Margaret A. Maglione, MPP,[a] Lopamudra Das, MPH,[a] Laura Raaen, MPH,[a] Alexandria Smith, MPH,[a] Ramya Chari, PhD,[a] Sydne Newberry, PhD,[a] Roberta Shanman, MLS,[a] Tanja Perry, BHM,[a] Matthew Bidwell Goetz, MD,[b] and Courtney Gidengil, MD, MPH[a,c]

[a]RAND Corporation, Santa Monica, California; [b]VA Greater Los Angeles Healthcare System and David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California; and [c]Boston Children's Hospital, Boston, Massachusetts

KEY WORDS
evidence-based medicine, vaccine/immunization, infectious disease

ABBREVIATIONS
AEs—adverse events
AHRQ—Agency for Healthcare Research and Quality
CI—confidence interval
DTaP—diphtheria, tetanus, and acellular pertussis
H1N1—Swine Flu
Hib—*Haemophilus influenza* type b
ILI—influenza-like illness
IOM—Institute of Medicine
IPV—inactivated poliovirus
IRR—incidence rate ratio
LAIV—live attenuated vaccine
MMR—measles/mumps/rubella
Oka VZV—Oka strain varicella zoster virus
OR—odds ratio
PCV—pneumococcal conjugate vaccine
PRISM—Post-Licensure Rapid Immunization Safety Monitoring
Td—tetanus-diphtheria
TIV—trivalent inactivated vaccine
VSD—Vaccine Safety Datalink

Ms Maglione conceptualized and designed the study, oversaw the abstraction of data, interpreted the results, and drafted the manuscript; Ms Das abstracted data, interpreted results, and revised the manuscript; Ms Raaen abstracted data, interpreted results, and revised the manuscript; Ms Smith designed data collection instruments, analyzed data, and revised the manuscript; Dr Chari abstracted data, interpreted results, and revised the manuscript; Dr Newberry revised the manuscript for important content and approved the final manuscript as submitted; Ms Shanman developed the literature search strategy, conducted electronic literature searches, and acquired data; Ms Perry acquired data and designed screening and data abstraction forms; Dr Goetz contributed to the conceptualization and design of the study, interpreted results, and critically reviewed and revised the manuscript; Dr Gidengil participated in study design, interpreted the results, drafted part of the manuscript, and critically reviewed the manuscript, and all authors approved the final manuscript as submitted.

(Continued on last page)

abstract

BACKGROUND: Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical for population health. This study systematically reviewed the literature on the safety of routine vaccines recommended for children in the United States.

METHODS: Data sources included PubMed, Advisory Committee on Immunization Practices statements, package inserts, existing reviews, manufacturer information packets, and the 2011 Institute of Medicine consensus report on vaccine safety. We augmented the Institute of Medicine report with more recent studies and increased the scope to include more vaccines. Only studies that used active surveillance and had a control mechanism were included. Formulations not used in the United States were excluded. Adverse events and patient and vaccine characteristics were abstracted. Adverse event collection and reporting was evaluated by using the McHarm scale. We were unable to pool results. Strength of evidence was rated as high, moderate, low, or insufficient.

RESULTS: Of 20 478 titles identified, 67 were included. Strength of evidence was high for measles/mumps/rubella (MMR) vaccine and febrile seizures; the varicella vaccine was associated with complications in immunodeficient individuals. There is strong evidence that MMR vaccine is not associated with autism. There is moderate evidence that rotavirus vaccines are associated with intussusception. Limitations of the study include that the majority of studies did not investigate or identify risk factors for AEs; and the severity of AEs was inconsistently reported.

CONCLUSIONS: We found evidence that some vaccines are associated with serious AEs; however, these events are extremely rare and must be weighed against the protective benefits that vaccines provide.. *Pediatrics* 2014;134:325–337

Vaccines are considered one of the greatest public health achievements of the 20th century for their role in eradicating smallpox and controlling polio, measles, rubella, and other infectious diseases in the United States.[1] Despite their effectiveness in preventing and eradicating disease, routine childhood vaccine uptake remains suboptimal. Parent refusal of vaccines has contributed to outbreaks of vaccine-preventable diseases such as measles[2] and pertussis.[3] In addition, although multiple large studies have confirmed the lack of association between measles/mumps/rubella (MMR) and autism, parental worries about the safety of vaccines persist.

The Agency for Healthcare Research and Quality (AHRQ) requested an evidence report on the safety of vaccines recommended for routine immunization of adults (including pregnant women), children, and adolescents to be used by the Office of the Assistant Secretary of Health to identify the gaps in evidence. This article addresses the safety of vaccines recommended for routine use in children aged 6 years and younger: DTaP (diphtheria, tetanus, and acellular pertussis), hepatitis A, hepatitis B, *Haemophilus influenza* type b (Hib), influenza (live attenuated and inactivated), meningococcal (conjugate or polysaccharide), MMR, pneumococcal (conjugate or polysaccharide), rotavirus, and varicella. It represents the results of a comprehensive and systematic review of scientific evidence, describes statistical associations between vaccines and adverse events (AEs), and reports on any risk factors identified.

METHODS

In 2011, the Institute of Medicine (IOM) published a consensus report titled *Adverse Effects of Vaccines: Evidence and Causality*.[4] That report evaluated the scientific evidence for AEs potentially associated with varicella, influenza, hepatitis A, hepatitis B, human papillomavirus, MMR, meningococcal, tetanus, diphtheria, and pertussis vaccines. We report the IOM findings regarding children and update those findings by identifying and evaluating studies published after the IOM searches. We also identify studies and evaluate evidence on pneumococcal, rotavirus, Hib, and inactivated poliovirus (IPV) vaccines because these are recommended for children aged 6 years and younger.

The following databases were searched: DARE (Database of Abstracts of Reviews of Effects), the Cochrane Database of Systematic Reviews, CENTRAL, PubMed, Embase, CINAHL (Cumulative Index to Nursing and Allied Health), TOXLINE (Toxicology Literature Online), and TOXFILE. The IOM report, Advisory Committee on Immunization Practices statements, vaccine package inserts, and review articles were mined for studies. Using the IOM keyword search strategy, we updated their searches to identify more recently published studies. The following structure was used: "vaccine term" AND "health term," where vaccine terms include the technical vaccine name, general descriptions of the vaccine of interest (eg, rotavirus AND vaccine), or manufacturer names; health terms include a list of AEs potentially associated with the vaccine. We also added more general AE keywords to the list of health terms such as "safe" or "safety," "side effect" or "harm." We searched from a year before the publication of the IOM report through August 2013. Using this approach, we developed new search strategies for the vaccines not originally included in the IOM report and searched each database from its inception through August 2013. AE terms were based on AEs reported in systems such as the Vaccine Injury Compensation Program, Vaccine Adverse Event Reporting System, and the Food and Drug Administration's Mini-Sentinel Program. A Technical Expert Panel reviewed the draft list of AEs and suggested additional AEs of interest.

We included studies that used active surveillance and had a control mechanism; eligible designs were controlled trials, cohorts comparing a vaccinated with nonvaccinated group, case–control studies, self-controlled case series, and observational studies that used regression to control for confounders and test multiple relationships simultaneously (multivariate risk factor analyses). Common sources of data included medical records, health insurance claims, and government registries.

To maintain applicability to the current US context, we excluded studies of vaccine formulations never used or no longer available in the United States; examples include whole cell pertussis vaccine, oral polio vaccine, and pneumococcal conjugate vaccine (PCV)7 vaccine. The recent IOM report, *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies*,[5] makes recommendations for future research on childhood vaccine schedules and cumulative effect, so the current project focused on specific vaccines, rather than any cumulative effect.

Two researchers experienced in systematic review methodology independently reviewed the titles and abstracts identified. The union of their selections was retrieved. These researchers independently reviewed the full text of study reports and met to reach consensus regarding exclusion/inclusion. Disputes were settled by the lead investigators and team physician experts. Patient and study characteristics were abstracted by single researchers and confirmed by the project leader. If a study reported severity or if adequate information was

provided for our investigators to categorize severity, we used the Common Terminology Criteria for Adverse Events classification system[6] to characterize AEs. The definition of "serious" differs by AE type; each category of AE (ie fever, headache) is rated on a 5-point scale, with 1 being very mild and 5 being death due to the event.

The McHarm instrument[7] was used to evaluate the quality of the studies with regard to their assessment of AEs. Studies that reported timing and severity and defined AEs using standard, precise definitions were rated higher than those that did not. We assessed the overall strength of evidence by using guidance suggested by AHRQ for its Effective Health Care Program[8] as of 2013. (The guidance has since been modified slightly.) The method is based on one developed by the Grading of Recommendations Assessment Working Group[9] and classifies the evidence based on risk of bias, consistency, directness, precision, dose–response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. Possible ratings are as follows:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

It is important to note that the 2011 IOM report used different terminology to classify the strength of evidence; evidence was classified as either "convincingly supports," "favors acceptance," "inadequate to accept or reject," or "favors rejection" of a causal association. They also included mechanistic studies and individual case reports to assess the biological plausibility of AE and considered this in addition to any statistical association. For each vaccine discussed in the IOM report, we started with the IOM findings and modified them, if needed, on the basis of any additional evidence we identified.

RESULTS

As presented in Fig 1, 20 478 titles were identified through electronic literature searches; review of product inserts; review of Food and Drug Administration, Advisory Committee on Immunization Practices, and other Web sites; reference mining; and requests for Scientific Information Packets from drug manufacturers. Of those, 17 270 were excluded on review of abstract or title for reasons such as "not about a vaccine," "vaccine not within the scope of this project" (formulations never available in the United States, recommended only for travel), or because they were animal studies. Upon full text review of the remaining 3208 articles, 392 were identified as relevant background/theoretical materials and set aside as potential references for the Introduction; 2749 other articles were excluded. The most common reason for exclusion was lack of suitable study design (1549): individual case reports, nonsystematic reviews, and studies using passive surveillance were excluded. Many publications (458) discussed vaccines on the recommended schedule but did not report or assess AEs. Eighty-eight studies on adults or adolescents were excluded for this article, as were 11 studies of children with preexisting conditions such as HIV, juvenile arthritis, or cancer, which left 67 studies. These studies are in addition to those included in the 2011 IOM consensus report *Adverse Effects of Vaccines: Evidence and Causality*, which were not abstracted.

We present the results for each vaccine in alphabetical order. Results are summarized in Table 1.

DTaP

The IOM studied diphtheria toxoid, tetanus toxoid, and acellular pertussis-containing vaccines alone and in combination in both children and adults. The IOM committee did not find evidence that "favors acceptance" of causal relationships for any conditions. They found the evidence "favors rejection" of a causal relationship between type 1 diabetes and vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens.[10–14] We found no additional studies in children published after the IOM search date; our review of their assessment supports their conclusions.

Hib Vaccine

The IOM did not study the safety of Hib vaccine. We identified 3 controlled trials of the Hib vaccine in children[15–17]; 1 was set in the United States, the other 2 in Asia. Results of the US trial (N = 5190) indicated that Hib vaccination was associated with redness (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.57–4.67) and swelling (OR 9.44, 95% CI 4.90–18.19) but not with hospitalizations. Vaccination was not associated with high fever in either the US trial or a trial in the Philippines. A trial in Vietnam[15] found the vaccine was not associated with any serious AEs, including convulsion, diarrhea, fungal infection, or gastroesophageal reflux disease. No other AEs were associated with the Hib vaccination.

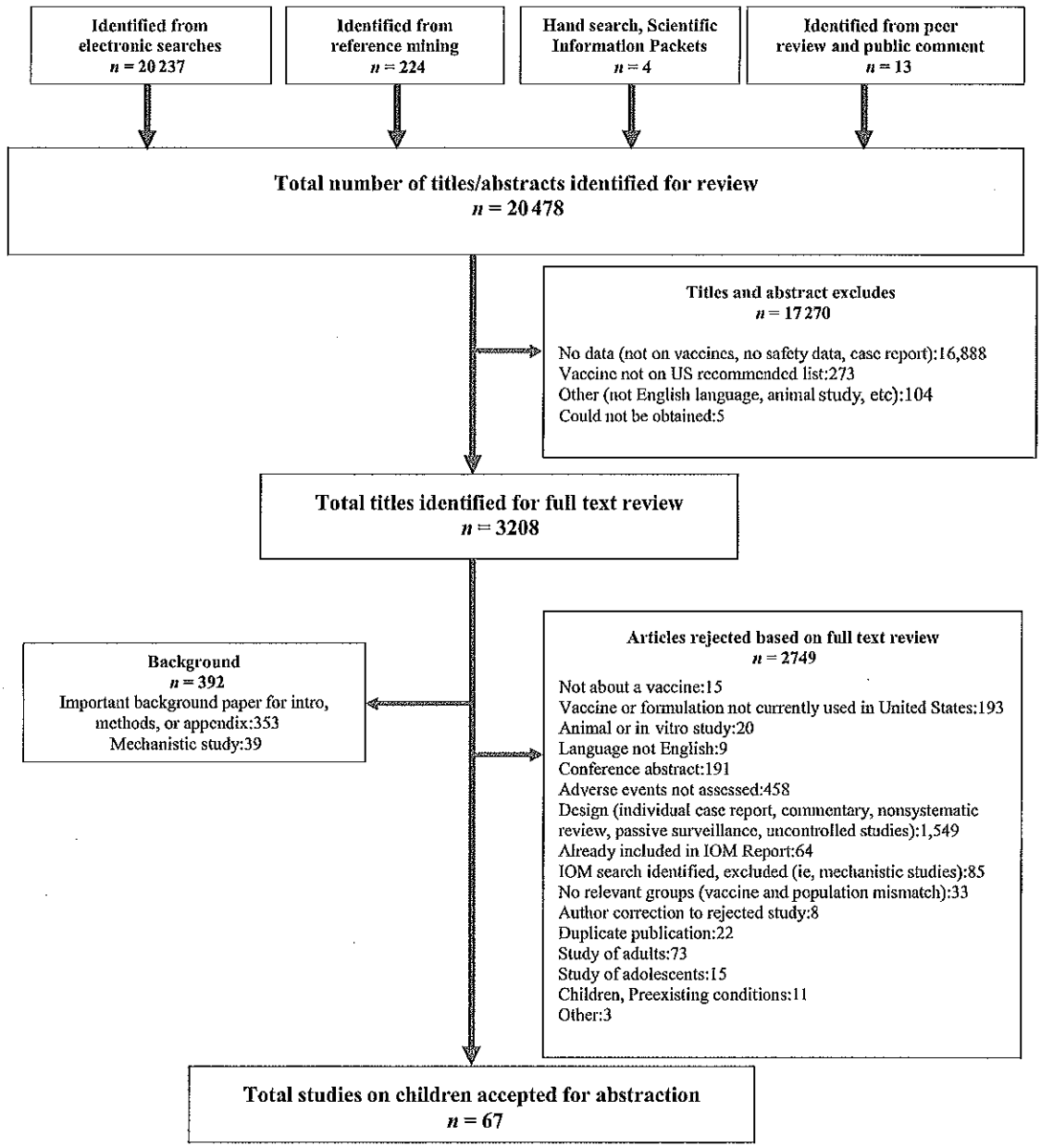

FIGURE 1
Literature diagram.

Hepatitis A

Hepatitis A vaccine was not covered by the IOM report on vaccine safety. We did not identify any studies of children that assessed the association of hepatitis A alone with AEs. However, we did identify a recent analysis that investigated possible relationships among Hib, PCV, MMR, DTaP, trivalent inactivated vaccine (TIV), hepatitis A, varicella, and meningococcal vaccines and immune thrombocytopenic purpura in children enrolled in 5 US health maintenance organizations.[18] Purpura was not associated with any of the vaccines in children aged 2 to 6 years but was associated with vaccination against hepatitis A in children aged 7 to 17 years (incidence rate ratio 23.14, 95% CI 3.59–149.30; findings related to other vaccines are reported in their respective sections). This study provides evidence for a moderate association between hepatitis A vaccine and purpura in children aged 7 to 17 years.

Hepatitis B

Although no epidemiologic studies were identified by the IOM, mechanistic evidence "favored acceptance" of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals. The 2011 IOM study found "insufficient" evidence of an association of hepatitis B vaccine with any short- or

TABLE 1 Results: Safety of Vaccines Used for Routine Immunization of Children

Vaccine	Conclusions and Strength of Evidence	2011 IOM Findings	New Findings
DTaP	Moderate: no association with type 1 diabetes	Evidence "favors rejection" of a causal relationship between vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens and type 1 diabetes.	No additional studies met inclusion criteria.
Hepatitis A vaccine	Moderate: purpura	Not covered.	In a large postlicensure study of >1.8 million vaccine recipients, purpura was associated with vaccination against hepatitis A in children aged 7–17 y. These results were based on 1 or 2 cases per vaccine type/age group. According to the authors, most cases were mild and acute.
Hepatitis B vaccine	Insufficient: food allergy	Although no epidemiologic studies were identified by the IOM, mechanistic evidence "favored acceptance" of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals.	Hepatitis B vaccine in the first 6 mo of life was associated with elevated total immunoglobulin E in a postlicensure study of children with a family history of food allergy but not with clinical allergy.
	Moderate: no association with MS	A 2002 IOM report "favors rejection" of a causal relationship with MS onset or exacerbation.	
Hib vaccine	Moderate: no association with serious AEs in short term	Not covered.	No serious AEs were associated in 3 high-quality clinical trials.
IPV	Insufficient: food allergy	Not covered.	One postlicensure study reported association between polio vaccine in newborns and sensitivity to food allergens.
Influenza vaccines (live attenuated and inactivated)	Moderate: mild gastrointestinal disorders, febrile seizures	Evidence was "inadequate to accept or reject" a causal relationship with any AEs investigated.	We identified 1 trial of seasonal influenza vaccine (including a strain of H1N1) and 1 cohort comparison study of 2009 monovalent H1N1 vaccine published after the IOM search dates; the studies found no evidence of an association of the vaccines with any AEs.
	Low: Influenza-like symptoms		Both seasonal influenza vaccines and monovalent H1N1 vaccine (administered only in 2009 season) were associated with mild gastrointestinal disorders, such as vomiting and diarrhea, in children in the short term in 2 large postlicensure studies. One of these studies found that younger vaccinated children (aged 5–8 y) were more likely to experience these symptoms than older vaccinated children (aged 9–17 y). (Children aged <5 y were not included in that study). Both live and inactivated seasonal influenza vaccines were associated with influenza-like symptoms in children in the short term in 1 new study. A large US postlicensure study of children aged <5 y found TIV associated with febrile seizures. Risk was increased if PCV13 was administered concomitantly.
MMR	High: no association with autism spectrum disorders	Evidence "convincingly supports" causal relationships anaphylaxis in allergic children and febrile seizures.	Five new postmarketing studies were identified. Vaccination was associated with thrombocytopenic purpura in the short term in 3; it was not studied in the other 2. In 1 study, MMR vaccination was associated with increased emergency department visits within 2 wk; this is indirect support of the IOM's findings that MMR vaccine is associated with febrile seizures.

TABLE 1 Continued

Vaccine	Conclusions and Strength of Evidence	2011 IOM Findings	New Findings
	High: anaphylaxis in children with allergies, febrile seizures	Evidence "favors acceptance" of a causal relationship between MMR and transient arthralgia	A new case-control study found MMR vaccine was unrelated to autism.
	Moderate: transient arthralgia	Evidence "favors rejection" of a causal relationship between MMR and autism.	
	Moderate: thrombocytopenic purpura		
Meningococcal vaccines (MCV4, MPSV)	Moderate: anaphylaxis in children with allergies	Evidence "convincingly supports" a causal relationship with anaphylaxis allergic children.	Two new trials of quadrivalent meningococcal conjugate vaccines found no association with any AEs assessed.
PCV13	Moderate: febrile seizures	Not covered.	The US VSD found an association with febrile seizures. Estimated rate for 16-mo-old patients is 13.7 cases per 100 000 doses for PCV13 without concomitant TIV and 44.9 per 100 000 doses for concomitant TIV and PCV13.
Rotavirus vaccines: RotaTeq and Rotarix	Moderate: Intussusception	Not covered.	In 31 clinical trials, there was no association between either of the current vaccines (RotaTeq and Rotarix) and any serious AEs, including intussusception, in the long or short term. A high-quality Australian epidemiologic study found RotaTeq associated with intussusception 1–21 d after the first of 3 required doses in infants 1–3 mo of age. Two case–control studies conducted in Latin America found an association of Rotarix with intussusception in children after the first of 2 required doses. Although 1 US epidemiologic study found no association, a recent analysis of the US PRISM program found both RotaTeq and Rotarix associated with intussusception in the short term. Estimated rate was 1.1–1.5 cases per 100 000 doses of RotaTeq and 5.1 cases per 100 000 doses of Rotarix.
Varicella vaccine	High: anaphylaxis; disseminated Oka VZV without other organ involvement; disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies; vaccine strain viral reactivation without other organ involvement; vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis.	Evidence "convincingly supports" causal relationships between varicella virus vaccine and the following: disseminated Oka VZV without other organ involvement; disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies; vaccine strain viral reactivation without other organ involvement; vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis; and anaphylaxis.	In a large postlicensure study of >1.8 million vaccine recipients, purpura was associated with vaccination against varicella in children aged 11–17. These results were based on 1 or 2 cases per vaccine type/age group. According to the authors most cases were mild and acute.
	Moderate: purpura		
Miscellaneous	High: no association of childhood leukemia with MMR, DTaP, Td, Hib, hepatitis B, and polio vaccines	Not applicable.	Four large epidemiologic studies conducted analyses to assess which, if any, of the following vaccines might be associated with childhood leukemia: MMR, DTaP, Td, Hib, hepatitis B, and polio vaccine. No association was found for any vaccine.

EPC, Evidence-based Practice Center; MS, multiple solerosis; MCV, meningococcal conjugate vaccine; MPSV, meningococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; VZV, varicella-zoster virus.

long-term AEs in children. A 2002 IOM review on hepatitis B vaccine and demyelinating neurologic disorders concluded that the evidence "favors rejection" of a causal relationship with incident multiple sclerosis or multiple sclerosis relapse.[19] We identified 1 study published after the IOM 2011 search: Gallagher and Goodman (2010)[20] conducted a secondary analysis of National Health Interview Survey data on 7074 boys born before 1999. Vaccination status and health outcomes were reported by parents. Results were significant for the risk of autism in children who received their first dose of hepatitis B vaccine during the first month of life (OR 3.00, 95% CI 1.11–8.13), compared with those who received the vaccination after the first month of life or not at all. Significant protective factors included non-Hispanic white ethnicity (OR 0.36, 95% CI 0.15–0.88) and belonging to a household with 2 parents (OR 0.30, 95% CI 0.12–0.75). It is unclear why the authors selected "first month of life" as the only vaccination time period studied, without presenting analyses for other time periods or comparing "ever vaccinated" with "never vaccinated." Because of high risk of bias and low quality, this study presents insufficient evidence that hepatitis B vaccine is associated with autism.

IPV: Inactivated Polio Virus

The IOM did not study IPV vaccine. Our search identified a case–control study of >2000 children with atopic dermatitis and a family history of allergy in 12 Western countries,[21] which found that newborns immunized against polio had higher odds (OR 2.60, 95% CI 1.08–6.25) of sensitivity to food allergens. This relationship did not hold for those immunized against polio later in life. A self-controlled case series of premature infants born in the United States[22] found no increased risk of wheezing and lower respiratory syndrome associated with DTaP, IPV, Hib, varicella, PCV7, MMR, or TIV vaccination. In sum, the strength of evidence is insufficient to determine an association between polio vaccine in newborns and sensitivity to food allergens.

Influenza Vaccines

Influenza vaccine is administered in 2 forms: live attenuated vaccine (LAIV), administered intranasally, and TIV, administered intramuscularly. The IOM found no evidence that "convincingly supports" causal relationships in the pediatric population for any AEs. We identified 1 trial of seasonal influenza vaccine (which included a strain of H1N1 [swine flu])[23] and 1 cohort comparison study of 2009 monovalent H1N1 vaccine[24] published after the IOM search dates; the studies found no evidence of an association of the vaccines with AEs.

Six observational studies also met our inclusion criteria.[25–30] A 2011 UK study of 2336 children[25] found no association between flu vaccines and febrile seizures; however, a recent study using the US Vaccine Safety Datalink (VSD)[26] found an association of flu vaccine with febrile seizures, which increased with concomitant administration of pneumococcal vaccine (PCV13). In the highest risk age group (16 months), estimated rate was 12.5 per 100 000 doses for TIV without concomitant PCV13, 13.7 per 100 000 doses for PCV13 without concomitant TIV, and 44.9 per 100 000 doses for concomitant TIV and PCV13. In large, high-quality postlicensure studies, both LAIV and TIV were associated with mild gastrointestinal disorders,[27,28] such as short-term vomiting and diarrhea in children. Strength of evidence is moderate for these AEs. One of these studies found that younger vaccinated children (aged 5–8 years) were more likely to experience these symptoms than older vaccinated children (aged 9–17 years). (Children <5 years of age were not included in that study). Finally, an Italian study[31] of children hospitalized for influenza-like illness (ILI) found those vaccinated with seasonal vaccine (OR 2.1, 95% CI 1.1–4.1) were significantly more likely to show symptoms of ILI than unvaccinated children, whereas those vaccinated for H1N1 were not at higher risk (OR 1.3, 95% CI 0.6–3.1). Strength of evidence is moderate for mild gastrointestinal events and febrile seizures and low for ILI.

MMR

The IOM committee found that mechanistic evidence "convincingly supports" causal relationships between MMR and measles inclusion body encephalitis in immunocompromised children and anaphylaxis in allergic patients. They also found epidemiologic evidence that "convincingly supports" a causal relationship between MMR vaccine and febrile seizures.[32–38] The IOM committee found the evidence "favors acceptance" of a causal relationship between MMR and transient arthralgia in the pediatric population.[39–45] They found the evidence "favors rejection" of a causal relationship between MMR and autism.[46–50] In addition, a causal relationship between the Urabe strain of mumps and aseptic meningitis has been shown; there is no evidence to link Jeryl Lynn strain, commonly used in the United States, to this AE.

We identified 5 postlicensure studies of childhood MMR vaccination published after the IOM searches. In a case–control study of 189 young adults with autism spectrum disorder and 224 controls, Uno et al[51] found that childhood receipt of MMR vaccine was not associated with an increased rate of new-onset autism (OR 1.10, 95% CI 0.64–1.90). In 3 studies,[18,52,53] MMR vaccination was associated with thrombocytopenic purpura in children in the

short term after vaccination. Strength of evidence is moderate because findings were consistent and ORs similar in 3 European countries, Canada, and the United States. Finally, 1 Canadian study found MMR vaccination was associated with increased emergency department visits within 2 weeks. This finding is consistent with the IOM's findings that MMR vaccine is associated with febrile seizures.

Meningococcal

The IOM found the evidence "convincingly supports" a causal relationship with anaphylaxis in children who may be allergic to ingredients. The IOM conclusion does not differentiate between meningococcal conjugate or meningococcal polysaccharide vaccines. We found 2 studies of quadrivalent meningococcal conjugate vaccine in children[54,55] published after the IOM report. A trial in Saudi Arabia found no statistical association with grade 2 or 3 fever, malaise, myalgia, or headache in the short term.[54] A trial in the United States and South America[55] found vaccination was not associated with severe change in eating habits, severe irritability, severe persistent crying, severe sleepiness, or urticaria in the year after vaccination.

Thus, the strength of evidence is moderate that meningococcal vaccine may cause anaphylaxis in children who are allergic to ingredients. Strength of evidence is insufficient to determine an association with less serious events such as headache, irritability, and urticaria.

PCV13

The IOM did not study the safety of PCV13. As noted earlier, the VSD[26] analyzed data on >200 000 US children aged <5 years and found that vaccine against pneumonia (PCV13) was associated with febrile seizures; importantly, administration of influenza vaccine at the same visit was associated with increased risk. For example, in the highest risk group, which was 16-month-old children, the estimated rate was 13.7 per 100 000 doses for PCV13 without concomitant TIV and 44.9 per 100 000 doses for concomitant TIV and PCV13. Risk difference estimates varied by age due to the varying baseline risk for seizures in young children. Thus the strength of evidence for an association between PCV13 and febrile seizures is moderate, and the risk is particularly high when coadministered with influenza vaccine.

Rotavirus Vaccines: RotaTeq and Rotarix

The IOM report did not address vaccines against rotavirus. Thirty-one trials of rotavirus vaccine[56–85] met our inclusion criteria. Participants in the accepted studies received 2 or 3 oral-administered doses of Rotarix (18 studies) or RotaTeq (13 studies). Neither Rotarix nor RotaTeq was associated with increased risk of AEs other than cough, runny nose, or irritability.

We identified 5 postlicensure studies on intussusception risk[86–90]; an earlier brand of rotavirus vaccine (Rotashield) was withdrawn from the market in 1999 due to concerns about risk for this condition. A high-quality epidemiologic study ($N = 296\,023$) conducted in Australia[86] found RotaTeq associated with intussusception in children 1 to 21 days after the first of 3 required doses but found no association with Rotarix. Two postlicensure studies were recently conducted in the United States. Shui et al[89] analyzed VSD data on 786 725 doses of RotaTeq and found no association with intussusception at any time after vaccination. However, a recent analysis of data from the US Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program[90] found that intussusception risk was increased after Dose 1 of RotaTeq and Dose 2 of Rotarix. The RotaTeq analysis had higher statistical power because that vaccine was administered to orders of magnitude more children than Rotarix. Estimated rate of intussusception was 1.1 to 1.5 cases per 100 000 doses of RotaTeq and 5.1 cases per 100 000 doses of Rotarix.

In addition, 2 case–control studies conducted in Latin America found an association with intussusception in children after the first of 2 required doses of Rotarix. One study estimated Rotarix increased risk by 3.7 additional cases per 100 000 person years in Mexico.[87] The other Latin American study estimated risk as 1 case per 51 000 vaccinations in Mexico and 1 case per 68 000 vaccinations in Brazil.[88] In sum, there is moderate strength evidence that vaccination against rotavirus is associated with intussusception, but the occurrence is extremely rare, and risk factors have not been investigated.

Varicella

The IOM committee found evidence "convincingly supports" causal relationships in children between varicella virus vaccine and the following: disseminated Oka strain varicella zoster virus (Oka VZV) without other organ involvement; disseminated Oka VZV with subsequent infection resulting in pneumonia,[91] meningitis, or hepatitis in individuals with demonstrated immunodeficiencies; vaccine strain viral reactivation without other organ involvement; vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis[92]; and anaphylaxis.[91]

We identified 1 study that investigated possible relationships among Hib, PCV, MMR, DTaP, TIV, hepatitis A, varicella, and meningococcal vaccines and immune thrombocytopenic purpura in children enrolled in 5 US health maintenance organizations.[18] Purpura was not

associated with any of the vaccines in children aged 2 to 6 years but was associated with vaccination against varicella in children aged 11 to 17 years (incidence rate ratio *R* 12.14, 95% CI 1.10–133.96; findings related to other vaccines are reported in their respective sections). This study provides evidence for a moderate association between varicella vaccine and purpura in children aged 11 to 17 years.

Studies Controlling for Multiple Vaccinations During Childhood

Four high-quality epidemiologic studies investigated the potential relationship between vaccinations and onset of childhood leukemia. Groves and colleagues[93] included 439 US children with lymphoblastic leukemia in a case–control analysis to investigate any possible relationship with oral or injected polio vaccine, diphtheria-tetanus pertussis vaccine, MMR, Hib, or hepatitis B vaccine. Controls were selected using random-digit dialing, which resulted in controls of higher socioeconomic status then the 439 cases. None of the vaccines were associated with leukemia. The relationship between vaccination and leukemia was also assessed in a case–control study of children in Northern California.[94] Cases were matched on date of birth, gender, and race/ethnicity. Analysis also controlled for maternal education and family income. None of the vaccines investigated (DPT, polio vaccine, MMR, Hib, hepatitis B vaccine) were associated with increased risk of leukemia. Similarly, the Cross-Canada Childhood Leukemia Study[95] found no association between vaccines against mumps, measles, rubella, diphtheria, tetanus, pertussis, polio, or hepatitis B and leukemia. Finally, a large case–control study of children born in Texas[96] found that several vaccines may have a protective effect against acute lymphoblastic leukemia.

DISCUSSION

This study updated the evidence presented in the 2011 IOM report and expanded the scope of that study by including additional vaccines such as those against Hib, hepatitis A, PCV13, rotavirus, and IPV. Findings related to these vaccines indicate that the Hib vaccine is associated with local discomfort such as redness and swelling but is not associated with serious AEs or hospitalization. Strength of evidence is moderate for the following associations: Hepatitis A vaccine and purpura in children aged 7 to 17 years, PCV13 and febrile seizures with an escalation of risk when coadministered with TIV, and rotavirus vaccine and intussusception. None of the vaccines studied here were associated with childhood-onset leukemia.

Our findings support the following IOM results: vaccine against hepatitis B is not associated with any long- or short-term AEs; the MMR vaccine is associated with febrile seizures; MMR vaccine is not associated with autism. In addition, our study found moderate evidence linking both LAIV and TIV forms of the influenza vaccines with mild gastrointestinal events; TIV was associated with febrile seizures. We also found moderate (but consistent) strength evidence of an association between the MMR vaccine and thrombocytopenic purpura in children; there was a similar association between the varicella vaccine and thrombocytopenic purpura in children aged 11 to 17 years.

Literature search procedures for this review were extensive; however, some unpublished trial results may not have been identified. An independent Scientific Resource Center under contract with AHRQ requested Scientific Information Packets from the vaccine manufacturers. (The research team was prohibited from contacting manufacturers directly.) Only 2 companies responded.

Our findings are based on only the most rigorous study designs to assess potential statistical associations; however, these designs have limitations that must be considered. Controlled trials often have insufficient sample size to identify rare AEs and do not have extended follow-up to identify long-term sequelae. In addition, trials may purposely exclude subjects who could be more susceptible to AEs. For this reason, any comprehensive review of vaccine safety must include post-licensure studies, but these also have limitations. Large epidemiologic studies sometimes include any available formulation of vaccines against a particular disease and may not stratify results by dosage or formulation. For example, the relationship between the "seasonal influenza vaccine" and an AE could be studied over several years of data without considering the changes in formulation over the seasons or differentiating between live or inactive vaccine. In addition, people who avoid vaccinations (whether purposely or not) may differ from those who receive vaccinations in terms of race, gender, age, socioeconomic status, and preexisting medical conditions, and these differences may be associated with health outcomes. Observational studies may attempt to control for such potential confounders by using matched cohorts or multivariate regression analysis; still, some factors such as environmental exposures may be unmeasured or challenging to adequately control for.

The self-controlled case series was developed specifically to assess the safety of vaccines; this method eliminates confounding by all time-independent variables by using cases as their own controls and predefined "time windows" before and after vaccination. This design has been used to study purpura, febrile seizures, intussusception, and autism

in children. However, the assumption of no temporal shifts in this model is difficult to justify in very young children because any patient characteristics that change with time will not be adequately controlled for.

Importantly, some AE signals that warrant future research may not have been identified by this project. Passive surveillance systems such as the US Vaccine Adverse Event Reporting System[97] are crucial in identifying signals regarding AEs post licensure, but they are not designed to assess a statistical association, so they were excluded as sources of data.

CONCLUSIONS

Our findings may allay some patient, caregiver, and health care provider concerns. Strength of evidence is high that MMR vaccine is not associated with the onset of autism in children; this conclusion supports findings of all previous reviews on the topic. There is also high-strength evidence that MMR, DTaP, Td, Hib, and hepatitis B vaccines are not associated with childhood leukemia.

Evidence was found for an association of several serious AEs with vaccines; however, these events were extremely rare: absolute risk is low. For example, strength of evidence is moderate for association of vaccines against rotavirus with intussusception. Although 1 large US epidemiologic study found no association, a recent analysis of the US PRISM program[90] found both RotaTeq and Rotarix associated with intussusception in the short term. Estimated rates were 1.1 to 1.5 cases per 100 000 doses of RotaTeq and 5.1 cases per 100 000 doses of Rotarix.

Few studies were powered to detect patient characteristics associated with increased risk of rare AEs. Advanced health information technology systems that contain both vaccination and health outcome records may be used to conduct such investigations. In the United States, the VSD contains data from such systems at 9 large managed care organizations. In addition, the PRISM program also conducts active surveillance using electronic health care databases from managed care organizations. Nations with single-payer health care systems often have electronic registries that allow large epidemiologic studies of entire populations. Future analyses should be stratified by formulation and brand of vaccine whenever possible.

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Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

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6.4

Centers for Disease Control and Prevention
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Morbidity and Mortality Weekly Report (*MMWR*)

Interim CDC Guidance for Polio Vaccination for Travel to and from Countries Affected by Wild Poliovirus

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In the prevaccine era, infection with wild poliovirus (WPV) was common worldwide, with seasonal peaks and epidemics in the summer and fall in temperate areas. The incidence of poliomyelitis in the United States declined rapidly after the licensure of inactivated polio vaccine (IPV) in 1955 and live oral polio vaccine (OPV) in the 1960s (*1*). The last cases of indigenously acquired WPV in the United States occurred in 1979, the last WPV case in a U.S. resident traveling abroad occurred in 1986, and the last WPV imported case was in 1993 (*2,3*). Since 2000, the United States has exclusively used IPV, resulting in prevention of 8–10 vaccine-associated paralytic poliomyelitis cases annually. In 2005, an unvaccinated U.S. adult traveling abroad acquired vaccine-associated paralytic poliomyelitis after contact with an infant recently vaccinated with OPV (*4*).

The Global Polio Eradication Initiative has made great progress in eradicating WPV, reducing the number of reported polio cases worldwide by >99% since the late 1980s. Only three countries remain in which WPV circulation has never been interrupted: Afghanistan, Nigeria, and Pakistan. However, polio could be brought into the United States from countries where WPV is circulating. During the last 6 months, 10 countries have had active transmission of WPV, and four of these countries have exported WPV to other countries. In the last 10 years, at least 40 polio-free countries have been affected through international travel (*5*).

In 2012, the completion of polio eradication was declared a programmatic emergency by the World Health Assembly (*6*). On May 5, 2014, the director-general of the World Health Organization (WHO) declared the international spread of polio to be a public health emergency of international concern under the authority of the International Health Regulations (*7*) and issued temporary vaccination recommendations for travelers from countries with active WPV transmission to prevent further spread of the disease (*8*). On June 2, 2014, CDC issued a health alert providing guidance to U.S. clinicians regarding new WHO polio vaccination requirements for travel by residents of and long-term visitors to countries with active poliovirus transmission (*9*). This report provides an update on CDC policy for polio vaccination of travelers for health protection. It also provides additional interim guidance for physicians whose U.S. resident patients will travel to or reside in affected countries for >4 weeks, to ensure those patients will have evidence of administration of polio vaccine (IPV or OPV) within 12 months of travel that might be required when they depart from countries with active poliovirus transmission. This interim guidance is to ensure compliance with WHO International Health Regulations temporary recommendations for countries designated as "polio-infected" to reduce the risk for exportation of WPV from those countries.

Vaccine Recommendations and Requirements

Advisory Committee on Immunization Practices (ACIP) and CDC recommendations are evidence-based and provide public health recommendations to the general public on the basis of the best available epidemiological and scientific data to prevent poliovirus infection. This includes recommendations for travelers visiting countries with WPV circulation in the last 12 months or countries and provinces where they will be in situations with a high risk for exposure to persons with imported poliovirus infection.

Three countries are still endemic for polio (Afghanistan, Nigeria, and Pakistan). Countries where WPV has circulated during the previous 12 months include those endemic countries and those with polio outbreaks or environmental evidence of active WPV circulation during this time (Cameroon, Ethiopia, Equatorial Guinea, Iraq, Israel, Somalia, and Syria). Travelers working in health-care settings, refugee camps, or other humanitarian aid settings in these and neighboring countries might be at particular risk for exposure to WPV.

Recommendations for vaccination under the International Health Regulations differ from ACIP and CDC recommendations and include exit requirements for proof of polio vaccination when leaving the country at borders or through airports. If implemented by a country, these requirements could be mandatory and are intended to prevent exportation of WPV.

Vaccine Recommendations for Travelers to Countries with WPV Circulation

Persons at greatest risk for acquiring polio are unvaccinated persons. In the United States, infants and children should be vaccinated against polio as part of a routine immunization series. Before traveling to areas with WPV circulation, all travelers should ensure that they have completed the recommended age-appropriate polio vaccine series and have received a booster dose, if necessary.*

Infants and Children

In the United States, all infants and children should receive 4 doses of IPV at ages 2, 4, and 6–18 months and 4–6 years (*10*). The final dose should be administered at age ≥4 years, regardless of the number of previous doses, and should be given ≥6 months after the previous dose. A fourth dose in the routine IPV series is not necessary if the third dose was administered at age ≥4 years and ≥6 months after the previous dose (*11*). Infants and children traveling to areas where there has been WPV circulation in the last 12 months should be vaccinated according to the routine schedule. If the routine series cannot be administered within the recommended intervals before protection is needed, an accelerated schedule can be used as follows: 1) the first dose should be given to infants aged ≥6 weeks, 2) the second and third doses should be administered ≥4 weeks after the previous doses, and 3) the minimum interval between the third and fourth doses is 6 months.

If the age-appropriate series is not completed before departure, the remaining IPV doses to complete a full series should be administered when feasible, at the intervals recommended for the accelerated schedule. If doses are needed while residing in the affected country, the polio vaccine that is available (IPV or OPV) may be administered.

Adults

Adults, who are traveling to areas where there has been WPV circulation in the last 12 months and who are unvaccinated, incompletely vaccinated, or whose vaccination status is unknown should receive a series of 3 doses: 2 doses of IPV administered at an interval of 4–8 weeks; a third dose should be administered 6–12 months after the second. If 3 doses of IPV cannot be administered within the recommended intervals before protection is needed, the following alternatives are recommended:

- If >8 weeks are available before protection is needed, 3 doses of IPV should be administered ≥4 weeks apart.

- If <8 weeks but >4 weeks are available before protection is needed, 2 doses of IPV should be administered ≥4 weeks apart.
- If <4 weeks are available before protection is needed, a single dose of IPV is recommended.

If <3 doses are administered, the remaining IPV doses to complete a 3-dose series should be administered when feasible, at appropriate intervals, if the person remains at increased risk for poliovirus exposure. If doses are needed while residing in the affected country, the polio vaccine that is available (IPV or OPV) may be administered.

Adults who have completed a routine series of polio vaccine are considered to have lifelong immunity to poliovirus, but data are lacking (*12*). As a precaution, persons aged ≥18 years who are traveling to areas where there has been WPV circulation in the last 12 months and who have received a routine series with either IPV or OPV in childhood should receive another dose of IPV before departure. For adults, available data do not indicate the need for more than a single lifetime booster dose with IPV.

Interim Vaccination Guidance to Comply with WHO International Health Regulations Temporary Recommendations for Countries Designated as "Polio-infected"

U.S. clinicians should be aware of possible new vaccination requirements for patients planning travel for >4 weeks to the 10 countries identified by WHO as polio-infected (Figure) (*13*). Four countries (Cameroon, Equatorial Guinea, Pakistan, and Syria) are now designated as "exporting wild poliovirus." Those countries should "ensure" recent (4–52 weeks before travel) polio boosters among departing residents and long-term travelers (of >4 weeks). An additional six countries (Afghanistan, Ethiopia, Iraq, Israel, Nigeria, and Somalia) are designated as "infected with wild poliovirus." Those countries should "encourage" recent polio vaccination boosters among departing residents and long-term travelers. This list might change when the public health emergency of international concern is reassessed at the end of July, and, for some countries, these measures could extend beyond the 3 months validity of these temporary recommendations.†

Long-term (staying >4 weeks) residents of polio exporting or infected countries, including potential immigrants and refugees migrating to the United States, and travelers to those countries might be required to show proof of polio vaccination when departing the country. The polio vaccine must be received between 4 weeks and 12 months before the date of departure. As of June 12, 2014, Pakistan has implemented exit requirements for polio vaccination and the remaining exporting countries are expected to implement these requirements. The remaining countries with active WPV transmission might also implement exit requirements.

To ensure that U.S. travelers are properly prepared for any vaccination requirements they might face departing polio-exporting or polio-infected countries, CDC provides the following additional guidance:

- All polio vaccination administration should be documented on an International Certificate of Vaccination or Prophylaxis (often referred to as the WHO "yellow card").§
- For children and adolescents who are up to date with IPV vaccination, including those who have completed the routine IPV series and who will be in a polio-exporting or polio-infected country for >4 weeks and their last dose of polio vaccine was administered >12 months before the date they will be departing that country, an additional dose of IPV should be given. Children who receive this additional dose as a fourth dose between ages 18 months and 4 years will still require an IPV booster dose at age ≥4 years.
- For adults with documentation of a polio vaccine series and an adult IPV booster dose who will be in a polio-exporting or polio-infected country for >4 weeks and their last dose of polio vaccine was administered >12 months before the date they will be departing that country, an additional dose of IPV should be given.
- If, before departure from the United States, the time residing in the polio-exporting or polio-infected country is anticipated to be >12 months, available polio vaccine (IPV or OPV) may be

administered while in the affected country and 4 weeks to 12 months before departing that country.
- Clinicians performing overseas evaluations of immigrants and refugees migrating to the United States from polio-exporting or polio-infected countries should consult the 2014 Addendum to Technical Instructions for Panel Physicians for Vaccinations: Technical Instructions for Polio Vaccination for Applicants for U.S. Immigration for specific instructions.¶

Vaccine Safety, Contraindications, and Precautions

Minor local reactions (pain and redness) can occur after IPV administration. No serious adverse reactions to IPV have been documented; however, experience with administration of multiple additional doses is limited. IPV should not be administered to persons who have experienced a severe allergic reaction (such as anaphylaxis) after a previous dose of IPV or after receiving streptomycin, polymyxin B, or neomycin, which IPV contains in trace amounts. Hypersensitivity reactions can occur after IPV administration among persons sensitive to these three antibiotics. If a pregnant woman is unvaccinated or incompletely vaccinated and requires immediate protection against polio because of planned travel to a country or area where polio cases are occurring, IPV can be administered as recommended for adults. Breastfeeding is not a contraindication to administration of polio vaccine to an infant or mother (*10*,*12*).**

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* Full information on ACIP recommendations for poliomyelitis vaccination is available at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/polio.html. Additional information is available at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/poliomyelitis. Vaccine recommendation information for specific countries is available at http://wwwnc.cdc.gov/travel/destinations/list.

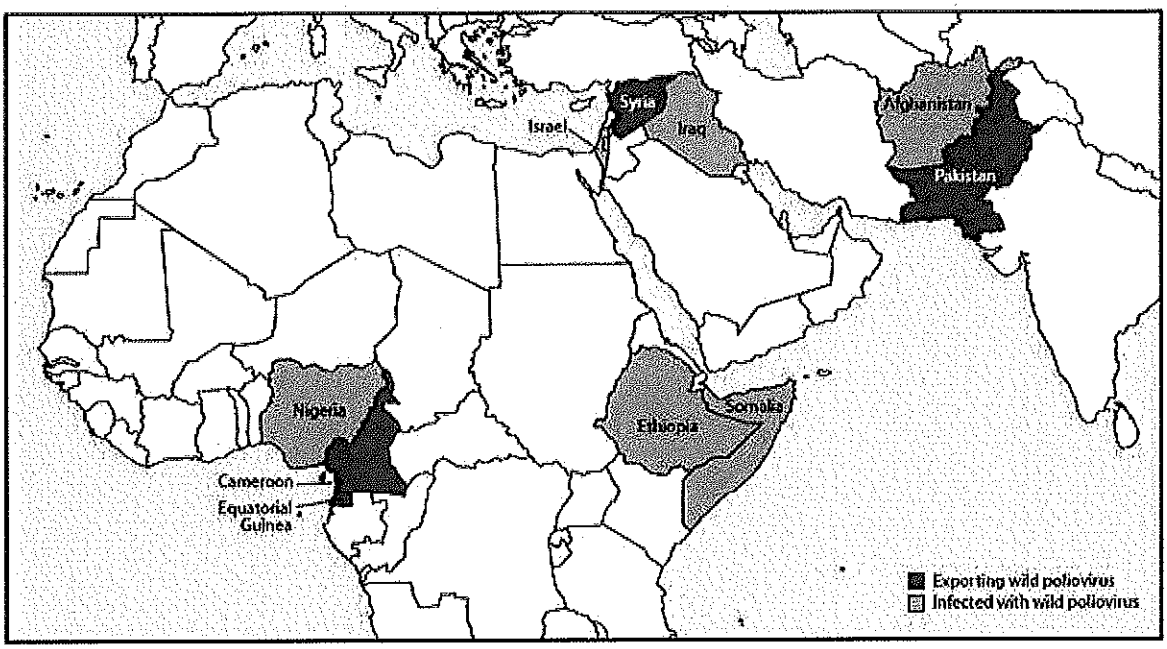
† Updates will be available at http://wwwnc.cdc.gov/travel/page/clinician-updates.

§ Additional information on the International Certificate of Vaccination or Prophylaxis is available at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/yellow-fever#2849.

¶ Available at http://www.cdc.gov/immigrantrefugeehealth/exams/ti/panel/technical-instructions-panel-physicians.html.

** Additional information on precautions, contraindications, and immunization of persons with immunosuppression and their household contacts is available at http://www.cdc.gov/vaccines/vpd-vac/polio.

FIGURE. Countries identified by the World Health Organization as exporting wild poliovirus and those currently wild poliovirus–infected — worldwide, 2014*



* As of June 30, 2014.

Iternate Text The figure above shows countries identified by the World Health Organization (WHO) as exporting wild poliovirus and those currently wild poliovirus-infected worldwide during 2014. U.S. clinicians should be aware of possible new vaccination requirements for patients planning travel for more than four weeks to the 10 countries identified by WHO as polio-infected.

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US flu vaccine supply expected to top 150 million doses

Robert Roos | News Editor | CIDRAP News | Jul 29, 2014

Influenza vaccine producers recently began shipping the first doses of a US supply that's expected to top 150 million doses for the coming season, with more quadrivalent (four-strain) products in the mix this year.

The three biggest suppliers for the US market, Sanofi Pasteur, GSK, and Novartis, announced the start of vaccine shipments this month. Three others—MedImmune, bioCSL, and Protein Sciences—expect to start shipping their products soon. Most of the doses are given in the late summer and fall, though health officials stress that immunizations later in the season can still be beneficial.

Recent estimates from the companies suggest that they will produce a total of somewhere between 154 million and 160 million doses for the US market this season. That compares with 134.9 million doses distributed last season, according to Centers for Disease Control and Prevention (CDC) figures presented recently to the Advisory Committee on Immunization Practices (ACIP).

One new wrinkle this year is that the ACIP, which develops federal immunization advice, expressed a preference for use of the intranasal vaccine (FluMist, made by MedImmune) in children from 2 through 8 years old, because of evidence of higher efficacy in that age-group.

Quadrivalent doses expected to rise

Several of the producers are providing quadrivalent vaccines, which contain two influenza B strains along with the standard two A strains (H1N1 and H3N2). The aim of including two B strains is to provide protection against both of the type B lineages, which circulate in varying and unpredictable proportions. Quadrivalent vaccines made their debut on the US market last year.

The ACIP has not stated a preference for quadrivalent over trivalent vaccines, and few randomized trials of the four-strain vaccines have been completed. One such trial, published last December, found that a quadrivalent vaccine showed about 55% efficacy in children 3 to 8 years old, which was similar to some previous findings for trivalent vaccines.

This year, the CDC expects that about half of the doses made for the US market will be quadrivalent, which is well above the share last year.

"Based on manufacturer projections for the upcoming season, we anticipate that approximately 50% of the vaccine produced will be quadrivalent vaccine," said Jeanne Santoli, MD, MPH, chief of the Vaccine Supply and Assurance Branch (VSAB) at the CDC's National Center for Immunization and Respiratory Diseases (NCIRD). She said quadrivalent vaccines generally cost more than trivalent ones.

This year the vast majority of flu vaccine doses the CDC ordered for the Vaccines for Children (VFC) and Section 317 programs are quadrivalent, Santoli reported. She said the agency ordered 19.1 million doses of quadrivalent vaccine and close to 600,000 doses of trivalent vaccine. About 5.3 million doses are FluMist, the nasal spray product.

The VFC and Section 317 programs provide vaccines mainly for low-income, uninsured, and underinsured children.

Novartis and GSK first to ship

Novartis was the first producer to announce the start of vaccine shipments this year, which occurred Jul 2. In a press release, the company said it planned to ship 30 million doses of two flu vaccines—Flucelvax and Fluvirin—before the peak of the flu season.

Both vaccines are trivalent inactivated products. Flucelvax, for adults 18 and older, is manufactured in cell culture and was the first cell-based flu vaccine to be approved in the United States, in 2012. Fluvirin, made with traditional egg-based technology, is approved for everyone from age 4 on up.

GSK announced the start of its flu vaccine shipments on Jul 16, predicting that it would supply between 28 million and 33 million doses for the US market. The company makes trivalent and quadrivalent vaccines: Fluarix, Fluarix Quadrivalent, Flulaval, and Flulaval Quadrivalent, all of which are approved for ages 3 and older.

The first shipments were Fluarix Quadrivalent, GSK said in a press release. Shipments of the other three vaccines are expected to begin in early August.

The company's estimate of total production is somewhat lower than the 35 million doses it estimated in a presentation at the annual National Adult and Influenza Immunization Summitin May. Since then, US and Canadian regulators have raised some concerns about GSK's vaccine facility in Ste. Foy, Quebec, which makes Flulaval and Flulaval Quadrivalent.

The US Food and Drug Administration (FDA) told the company in a Jun 21 warning letter that 21% of the upcoming season's production had unacceptable bacterial counts and could not be used, according to previous reports. The Ste. Foy plant was scheduled to make about 23 million doses for the US market for 2014-15.

GSK said in its summit presentation that about two thirds of the doses produced this year would be quadrivalent.

Up to 65 million doses from Sanofi

Sanofi Pasteur, the biggest contributor to the US flu vaccine supply, reported in a statement last week that its first shipments went out on Jul 21. The company said it expects to supply at least 65 million doses, with shipments continuing through October.

Sanofi makes four flu vaccine formulations: Fluzone, Fluzone Quadrivalent, Fluzone High-Dose, and Fluzone Intradermal. The high-dose version is for people 65 and older, who have a weaker immune response than younger people. The company did not specify how many doses of each product are expected.

Another 16.5 million doses of vaccine are expected from bioCSL (formerly CSL Biotherapies), with shipping starting in August, according to company spokeswoman Natalie de Vane.

The company makes the trivalent inactivated vaccine Afluria. It is approved for ages 5 and older, but the ACIP currently recommends it for ages 9 and older, because of increased febrile reactions reported in Australia in 2010 in younger children who received an associated vaccine, Fluvax.

MedImmune and Protein Sciences

MedImmune, maker of FluMist, expects to distribute between 14 million and 15 million doses of the nasal-spray vaccine in the United States this season, according to company spokeswoman Melissa Garcia. That compares with about 13 million doses distributed last year.

Garcia said last week that the first shipments of the vaccine were expected to begin before the end of this month. Since last year, MedImmune has produced only a quadrivalent formulation of FluMist. The vaccine is approved for ages 2 through 49.

How the new ACIP recommendation on use of FluMist in 2- to 8-year-old children will affect demand for the vaccine is difficult to predict, said Santoli of the CDC. "Clinician recommendations play a big role in patients' vaccination decisions. It will depend on how that recommendation is put into practice at the level of patient care," she commented.

A smaller portion of the US flu vaccine supply comes from Protein Sciences Corp., maker of the recombinant egg-free vaccine FluBlok. The company announced in June that it expected to make up to 500,000 doses for this season, about twice as many as last year, with doses available from a broader distribution network. The first doses are expected to be available in September.

FluBlok, approved for ages 18 to 49, is made by using a baculovirus to infect insect cells, prompting them to produce the influenza hemagglutinin protein. Last year was the product's first full season on the market.

Because FluBlok is made without using eggs, last year the ACIP recommended it for use in people ages 18 to 49 who have an egg allergy of any severity.

Note: *Staff writer Lisa Schnirring contributed to this story.*

See also:

Jul 2 Novartis press release

Jul 16 GSK press release

Jul 22 Sanofi press release

bioCSL presentation from National Adult & Influenza Immunization Summit in May

MedImmune presentation from flu immunization summit

Jun 10 Protein Sciences press release

Jul 23 CIDRAP News item on GSK's Ste. Foy plant

Jun 25 CIDRAP News story on ACIP advisory on FluMist

Dec 13, 2013, CIDRAP News story on randomized trial of a quadrivalent flu vaccine in children

Aug 5, 2013, CIDRAP News story on last year's vaccine production forecast

Information on the 2015 National Adult and Influenza Immunization Summit