ADVISORY COMMISSION ON CHILDHOOD VACCINES
TABLE OF CONTENTS
December 8, 2017

ADVISORY COMMISSION ON CHILDHOOD VACCINES

Agenda

ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV)

5600 Fishers Lane, Room 5N54
Rockville, MD 20857
Teleconference and Adobe Connect
Friday, December 8, 2017
(9:00 am Eastern Daylight Time)

Dial in:1-800-369-1833
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Time	Agenda Item	Presenter
9:00 AM	Welcome and Chair Report	Ms. Beth Luthy, Interim Chair
9:10 AM	Public Comment on Agenda Items	Ms. Beth Luthy, Interim Chair
9:15 AM	Approval of September 2017 Minutes	Ms. Beth Luthy, Interim Chair
9:20 AM	Report from the Division of Injury Compensation Programs	Dr. Narayan Nair Director, DICP
9:50 AM	Report from the Department of Justice	Ms. Catharine Reeves, Deputy Director, Torts Branch, DOJ
10:20 AM	Petitions to Add Injuries to Vaccine Injury Table Introduction	Dr. Narayan Nair Director, DICP
10:30 AM	Petition to Add Tics as an Injury to the Vaccine Injury Table	Dr. Mary Rubin DICP Medical Officer
	Petition to Add Asthma as an Injury to the Vaccine Injury Table	Dr. Stacy Stryer DICP Medical Officer

Time	Agenda Item	Presenter
12:00 PM	Lunch	
1:00 PM	Petition to Add Pediatric Autoimmune Neuropsychiatric Syndrome (PANS), Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorders (PITANDS), and Pediatric Autoimmune Neuropsychiatric Disorders (PANDAS) as Injuries to the Vaccine Injury Table	Dr. Mark Ditmar DICP Medical Officer
1:40 PM	Petition to Add Experimental Autoimmune Encephalomyelitis (EAE) and/or Acute Demyelinating Encephalomyelitis (ADEM) as Injuries to the Vaccine Injury Table	Dr. Terry Dalle-Tezze DICP Pediatric Team Lead and Medical Officer
2:20 PM	Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities	Dr. Tom Shimbakuro CDC
2:35 PM	Update on the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) Vaccine Activities	Dr. Barbara Mulach NIAID, NIH
2:50 PM	Update on the Center for Biologics, Evaluation and Research (CBER), Food and Drug Administration (FDA) Vaccine Activities	LCDR Valerie Marshall CBER, FDA
3:05 PM	Update from the National Vaccine Program Office (NVPO)	Dr. Karin Bok NVPO
3:20 PM	Public Comment (follows the preceding topic and may commence earlier or later than 3:20 pm)	
3:35 PM	Future Agenda Items/New Business	Ms. Beth Luthy, Interim Chair
3:50 PM	Adjournment of the December 8, 2017 ACCV Meeting	Ms. Beth Luthy, Interim Chair

Charter

CHARTER

ADVISORY COMMISSION ON CHILDHOOD VACCINES

Authority

42 U.S.C. 300aa-19, Section 2119 of the Public Health Service (PHS) Act. The Advisory Commission on Childhood Vaccines (hereinafter refen-ed to as the "Commission") is governed by the provisions of the Federal Advisory Committee Act, Public Law 92-463 (5 U.S.C. App. 2), which sets f01ih standards for the formation of advisory committees.

Objectives and Scope of Activities

The Secretary of Health and Human Services (Secretary) is mandated under Section 2119 of the 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 cmTy out the Program.

Agency or Official to Whom the Commission Reports

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

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Management and support services shall be provided by the Division ofinjury Compensation Programs, Healthcare Systems Bureau, Health Resources and Services Administration (HRSA).

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 $34,545. The estimate of annual person-years of staff support required is 1.5 at an estimated annual cost of $233,015.

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, call all of the Commission or subconnnittee meetings, adjourn any meeting when the DFO determines adjournnient to be in the public interest, and chair meetings when directed to do so by the official to whom the Connnission 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, with the approval of the DFO. Meetings shall be open to the public except as determined otherwise by the Secretary or designee in accordance with the Govefllllent 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 2 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) tlnee 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) tlnee 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 Drng 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 Govermnent Employees. The ex officio members 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 Depmtment's Committee Management Officer will be notified upon the establishment of each subcommittee and will be provided infmmation on the subcommittee's name, membership, function, and estimated frequency of meetings.

Recordkeeping

Meetings of the Committee and its subcommittees will be conducted according to the Federal Advisory Committee Act, other applicable laws and Departmental policies. Committee and subcommittee records will be handled in accordance with General Records Schedule 6.2, Federal Advisory Committee Records or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom oflnformation Act, 5 U.S.C. 552.

4 -ACCV Charter

Filing Date

July 21, 2016

Approved:

JUL 20 2016

Date

Roster

ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV) ROSTER
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2017 & 2018
Meeting Dates

ADVISORY COMMISSION ON CHILDHOOD VACCINES

2017 MEETING DATES

December 8, 2017

2018 MEETING DATES

March 8 & 9, 2018
June 14 & 15, 2018
September 6 & 7, 2018
December 6 & 7, 2018

2

Advisory Commission on Childhood Vaccines

September 8, 2017

103rd Meeting

Members Present

Karlen E. Luthy, D.N.P., Interim Chair, (’18)
Kathleen F. Gaffney, PhD, RN (’19)
H. Cody Meissner, MD, (’19)
Tina Tan, MD, (’19)
Alexandra Stewart, J.D., (‘18)
Martha Toomey (’18)

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

Narayan Nair, M.D., Director, DICP
Andrea Herzog, Principal Staff Liaison, ACCV

Welcome and Report of the Interim Chair
Beth Luthy, ACCV Interim Chair

Ms. Luthy called the meeting to order and introduced the Commission members present (reflected above), ex-officio members, DICP staff and a representative from the Office of the General Counsel. She invited public comment on the meeting agenda,

Public Comment on Agenda Items

There were no requests to comment on agenda items.

Approval of December 2016 ACCV Meeting Minutes

Ms. Luthy requested approval of the December 2016 ACCV meeting minutes. The Commission unanimously approved the minutes.

Report from the DICP, Dr. Narayan Nair, Director

Dr. Nair stated that the agenda would include an update on HRSA VICP activities; a presentation on the 21st Century Cures Act (enacted in December 2016); a presentation on proposed changes to the Vaccine Injury Table (Table); an update from the Department of Justice (DOJ) Vaccine Litigation Office; and updates from ACCV ex-officio members representing the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and National Vaccine Program Office (NVPO).

Looking at the data for claims filed with the VICP during fiscal year (FY) 2017, October 1, 2016 to September 30, 2017, Dr. Nair noted that average number of petitions filed from FY 2011 to FY 2015 was 546 per year. The number of petitions began to increase significantly in 2014 (633), reaching a high in FY 2016 of 1,120. The pace of claims filed in FY 2017 is consistent with the previous fiscal year. As of August 1, 2017, 987 claims were filed. The number of claims filed in FY 2017 should exceed FY 2016.

Dr. Nair presented data for adjudicated cases by category for FYs 2015, 2016 and 2017. For FY 2017, as of August 19, 2017, 730 cases were adjudicated. Of those 730 cases -- 135 were not compensable and 595 were compensable. The compensable cases were decided as follows: 156 by concession, 40 were court decisions, and 399 by settlement. Awards have increased from $216 million in FY 2011 to $230 million in FY 2016. As of August 1, 2017, the VICP has paid $259 million in compensation with attorneys' fees accounting for $26 million of that total compensation payment.

Dr. Nair discussed the balance of the Vaccine Injury Compensation Trust Fund (Trust Fund). The Trust Fund balance was $3.6 billion as of July 31, 2017. At the end of June, which was the end of the third quarter of FY 2017, the Trust Fund had collected $181 million from excise tax payments and earned $47 million in interest, for a total income of $228 million. Interest was 20.5% of total income.

In other activities, Dr. Nair reported that Revisions to the Vaccine Injury Table Final Rule went into effect on March 21, 2017, and the implementation of maternal immunization provisions were updated on the VICP website. The ACCV will discuss additional revisions to the Table, related to maternal immunizations, as part of this meeting's agenda. Finally, with regard to outreach, the maternal immunization provisions were presented to the National Vaccine Advisory Committee (NVAC) at their February meeting, and as an informational presentation at Johns Hopkins University. Dr. Nair noted that further information can be found on the Web at: www.hsa.gov/advisorycommittees/childhoodvaccines/index.html.

During discussion, he was asked for clarification about the VICP. Dr. Nair explained that the VICP is the federal program that oversees the vaccine injury compensation authorized by the National Childhood *Vaccine Injury Act* of 1986 (Vaccine Act). Agencies involved include HRSA, DOJ and the U.S. Court of Federal Claims (Court). When the Act established the compensation program, the Advisory Commission on Childhood Vaccines was also established to advise the VICP.

Report on the 21st Century Cures Act, Dr. Narayan Nair

Dr. Nair explained that the 21st Century Cures Act (Cures Act) amends the Vaccine Act. He stated that the Cures Act was passed in December 2016, and one provision in the Act applies specifically to the VICP – adding vaccines recommended by the CDC for routine administration to pregnant women to the Table. New vaccines would also be covered as they are recommended for use in pregnant womenand subject to an excise tax. . Currently, the two vaccines recommended for pregnant women are seasonal influenza and diphtheria, tetanus and pertussis (DTaP) vaccines which are currently covered by the VICP because they are recommend for routine administration to children.

The Act clarified several issues that were previously unresolved when a claim was made under the Vaccine Act, including the fact that a single administration of a vaccine to a mother would constitute a concomitant administration to the in utero child. The Act will cover the

pregnant woman who receives the vaccine and any child in utero when the vaccine was administered, and who was born alive.

Dr. Nair clarified an issue raised by a Commission member; if a child is stillborn or the mother miscarries, although the child is not eligible for compensation under the Act, the mother could still file a claim if she could prove a vaccine-related cause. He also clarified that if a vaccine is administered in error (e.g., a vaccine not routinely recommended) it would be covered and a claim could be filed.

Presentation on Proposed Changes to the Vaccine Injury Table to Add Vaccines Recommended for Routine Administration by the CDC to Pregnant Women, Dr. Narayan Nair

Dr. Nair explained that the Cures Act amended the Vaccine Act, requiring revisions to the Table to add vaccines recommended for routine administration by the CDC to pregnant women. Since DTaP and seasonal influenza vaccines are currently recommended for routine administration by the CDC to children, they are already on the Table and covered by the VICP, but for new vaccines the Table must be changed. The process is to develop a Notice of Proposed Rulemaking (NPRM) after consultation with the ACCV. The VICP provided three options for ACCV consideration. Ultimately, the ACCV will select one and formalize the recommendation with a vote.

- Option 1 – Revise Category XVII on the Table to reflect addition of the italicized words: Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children *and/or pregnant women* after publication by the Secretary of a notice of coverage.

- Option 2 – Create a Category XVIII on the Table and adding a new paragraph: Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to pregnant women, after publication by the Secretary of a notice of coverage.

- Option 3 -- Present Options 1 and 2 in an NPRM to get public comment on the issue: During discussion, it was noted that there is a filing deadline that permits retroactive claims to be filed for aspect to newly covered vaccines. An individual would have two years to file a claim for injuries incurred within eight years prior to effective date of coverage of the new vaccine on the Table. To add a vaccine to the Table, it would have to be subject to excise tax and recommended by CDC for routine administration in pregnant women.

Dr. Nair indicated that the Commission should settle on one of the three options and formalize the recommendation with a vote. He observed that Option 1 and 2 accomplish the same thing; neither has an advantage over the other. Ms. Stewart commented that the third option, involving the Notice of Proposed Rulemaking, would afford the public an opportunity to provide input. It would be the most equitable option. There was agreement that the additional input would be helpful. Ms. Luthy invited a motion.

On motion duly made and seconded, the Commission unanimously approved the third option, to publish a Notice of Proposed Rulemaking regarding the revisions to the Injury Table.

There was a comment from a Commission member about the history of the rubella vaccine, which at the outset, created significant concern among women who were pregnant and who had received the rubella vaccine before becoming aware of their pregnancy. During that period, some women chose to terminate the pregnancy because of that concern, which later proved to be unfounded. There was an observation that the anecdote might serve as a deterrent to any similar response to new vaccines (e.g., the Zika virus vaccine) when they become available.

Dr. Bok observed that one aspect of the Cures Act was encouragement to expand the participation of pregnant and lactating women in research trials, to expand the scientific knowledge concerning the risks and benefits of various prevention programs. Dr. Shimabukuro commented that essentially the two options represent the same outcome through different approaches – one, the addition of the "either/or" wording (lumping); the other creation of a separate category (splitting). Dr. Shimabukuro observed, option 3 is not an option, just a mechanism to gather more input. The Commission briefly discussed the earlier vote and agreed, by consensus; to recommend Option 1 instead of Option 3.

Report from the Department of Justice, Ms. Sarah Duncan, Trial Attorney

Ms. Duncan welcomed the commissioners and explained that she would be presenting the report from the Department of Justice (DOJ) on behalf of Catharine Reeves, Deputy Director, Torts Branch. Ms. Duncan noted that the reporting period for DOJ is different from that of the Division of Injury Compensation Programs. Ms. Duncan referenced the DOJ Power Point materials as part of her presentation for the nine-month period from November 16, 2016 to August 15, 2017. During this reporting period, 856 petitions were filed. Of those 856, 103 were filed on behalf of children (12%) and 753 were filed by adults (88%). (DOJ PP at 2).

With regard to total cases adjudicated, Ms. Duncan noted that 593 claims were adjudicated this period. (DOJ PP at 3). There were 485 cases compensated. Of those 485 cases, 153 were conceded by HHS. Of those 153 conceded cases, all 153 were resolved by a decision adopting a proffer. There were 332 cases compensated but not conceded by HHS. Of those, all 332 cases were resolved by a decision adopting a settlement stipulation. (DOJ PP at 3). There were 108 cases dismissed. Of those, 103 non-OAP cases were resolved by decisions dismissing the petition, and 5 were dismissed from the OAP. (DOJ PP at 3). There were 45 petitions voluntarily withdrawn. (DOJ PP at 4).

Turning to appeals, eight cases were decided by the U.S. Court of Appeals for the Federal Circuit (CAFC) during the reporting period. (DOJ PP at 5). Seven of these appeals were filed by petitioners and all seven concerned entitlement. Of these seven, one was affirmed per curiam (*R.K. v. HHS*), one was affirmed (*Lasnetski v. HHS*), two were remanded (*Contreras v. HHS* and *Moriarty v. HHS*), one was voluntarily dismissed by petitioner (*Murphy v. HHS*), and two were dismissed by the Court (*G.G.M. v. HHS* and *Osele v. HHS*). The eighth case concerned attorneys' fees and costs and was filed by respondent but voluntarily dismissed (*Allicock v. HHS*). In addition to one appeal filed by petitioners that is pending, three new appeals were filed by petitioners in *Simmons v. HHS, D'Tiole v. HHS*, and *Anderson v. HHS.* (DOJ PP at 6).

Ms. Duncan discussed appeals at the Court of Federal Claims (CFC), and noted that twenty-six appeals filed by petitioners were decided by the CFC. (DOJ PP at 7-9). Eighteen of the twenty-six appeals concerned entitlement and eight concerned attorneys' fees and costs. Of the twenty-six cases, twenty were affirmed, two were affirmed in part, two were remanded, one

was dismissed as untimely, and one was voluntarily dismissed by petitioner. Ms. Duncan reported that the CFC also decided one appeal filed by respondent. (DOJ PP at 9). In *Day v. HHS*, the special master's award of interim damages to petitioner was affirmed. Ms. Duncan noted that petitioners filed five new appeals to the CFC, three of which involve entitlement, and two of which involve attorneys' fees and costs. (DOJ PP at 10). Six total cases remain pending at the CFC. (DOJ PP 10).

Two oral arguments are scheduled at the CAFC in *H.L. v. HHS* and *Simmons v. HHS*. (DOJ PP at 11). No oral arguments are scheduled at the CFC.

Ms. Duncan noted the history of adjudicated settlements, which are listed in order of the time they took to resolve. (DOJ PP at 12-42). Most of the cases involved injuries related to Guillain-Barré Syndrome and shoulder injury related to vaccine administration (SIRVA).

There was a brief discussion regarding the distinction between settlement and concession. Ms. Duncan explained that a concession by HHS requires evidence that the alleged injury was caused by a covered vaccine, whereas a settlement may occur for a variety of reasons, including litigative risk on both sides.

Ms. Toomey asked how often a petitioner passes away during the pendency of a case. Ms. Duncan indicated that she did not believe DOJ tracked that information but that DOJ would confirm.

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

Vaccine Adverse Event Reporting System (VAERS) Transition to VAERS-2.0

Dr. Shimabukuro stated that he would focus the CDC agency update on the transition to the Vaccine Adverse Event Reporting System (VAERS) version 2.0 reporting process. VAERS is a passive reporting system for monitoring the safety of U.S.-licensed vaccines. CDC and FDA co-manage VAERS. Since 1990, data have been collected using the VAERS-1 form, a printable form that had to be manually filled out and submitted by mail or fax. On June 30, 2017, CDC and FDA implemented VAERS 2.0, which consists of an updated electronic VAERS reporting form with revised and expanded data elements and an updated VAERS online reporting tool. The VAERS 2.0 reporting process offers two options, an updated version of the online reporting tool; and a "writable" PDF that can be filled out using a computer, saved for later revision if need be, and submitted when completed through an electronic document upload feature on the VAERS website. The VAERS 2.0 online reporting tool still has a time out feature for security reasons.

Dr. Shimabukuro reviewed the development of the VAERS-2.0 form, which began in 2014, underwent extensive user testing, and was completed in 2016. After information technology upgrades to the VAERS website in 2017, VAERS 2.0 was ready for release. Beginning with the release and continuing through the end of 2017, CDC and FDA are implementing VAERS-2.0 and phasing out the VAERS-1 paper forms.

Dr. Shimabukuro noted that VAERS 2.0 applies to public reporters, which includes healthcare professionals, patients, caregivers, guardians and other non-manufacturer reporters. Vaccine manufacturers report through a different process using electronic data transfer. Dr. Shimbakuro illustrated the reporting process through a screenshot of the new forms. He noted that commissioners and the public can access instructions on submitting reports on the Web

(https://vaers.hhs.gov/reportevent.html) or by e-mail (info@vaers.org) or phone (1-800-822-7967).

Selected Vaccine Safety Publications

Dr. Shimabukuro discussed several recent vaccine safety-related publications:

- Stockwell et al. Feasibility of Text Message Influenza Vaccine Safety Monitoring During Pregnancy in American Journal of Preventive Medicine. This study demonstrated the feasibility of text messaging for influenza vaccine safety surveillance sustained throughout pregnancy. In these women receiving inactivated influenza vaccination during pregnancy, post-vaccination fever was infrequent and a typical pattern of maternal and neonatal health outcomes was observed. Compliance on the part of participants was high.
- Moro et al. Major Birth Defects after Vaccination Reported to the Vaccine Adverse Event Reporting System (VAERS), 1990 to 2014, in Birth Defects Research. This review of the VAERS database found that major birth defects were infrequently reported, with no particular condition reported disproportionally. Birth defects after routine maternal vaccination will continue to be monitored in VAERS for signals to prompt future studies.
- Lipkind et al. Maternal and Infant Outcomes after Human Papillomavirus Vaccination in the Periconceptional Period or During Pregnancy, a Vaccine Safety Datalink study, in Obstetrics & Gynecology. Quadrivalent HPV vaccine inadvertently administered in pregnancy or during the periconceptional period was not associated with adverse pregnancy or birth outcomes.

Dr. Shimabukuro ended his report. During the discussion after his presentation, Dr. Shimabukuro explained that the VAERS is smartphone-capable. One of the aspects of the development of the system was to ensure that the website was compatible with mobile devices or notebooks and tablets. Although it is slightly more difficult to use a mobile device for reporting, the Internet connection is designed to be compatible with mobile devices – it is not just a condensed version of the web site.

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

Ms. Schuster discussed respiratory syncytial virus (RSV), a common respiratory virus that can have serious effects on infants and older adults. Although there is no vaccine currently licensed for the illness, a monoclonal antibody is licensed for limited use in children to prevent respiratory disease. The monoclonal antibody is not available to the general population. In February 2017, NIAID announced a Phase 1 clinical trial on an investigational vaccine, developed by researchers at NIAID. Phase 1 trials evaluate safety and tolerability of new drugs and vaccines. The study is being conducted at NIH. Ms. Schuster invited commissioners to visit the ClinicalTrials.gov web site for more information on this and other trials at NIH.

NIAID is also focused on Zika infection, looking at studies that are broadly directed at the natural history of the disease, and specific research into vaccines, diagnostics, therapeutics

and vector control. In June 2017, a study in several Latin American countries was launched looking at Zika disease in infants and pregnant women.

NIAID is sponsoring a large natural history study in Guatemala. This study of infants and children will focus on those infected after birth. The study will enroll about 1,200 children, including those with dengue and/or Zika infection, and a cohort who are not infected with Zika virus. NIAID has also launched a Phase 2 Zika vaccine trial using an experimental DNA vaccine developed by scientists at NIAID. A similar vaccine was developed for West Nile virus. The trial aims to enroll 2,490 healthy participants in areas of confirmed mosquito-transmitted Zika infection. A Phase 2 trial seeks to validate efficacy and further evaluate safety.

In September 2016, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development convened a workshop to develop a research agenda to improve the evaluation, monitoring and management of neonates, infants and children affected by Zika virus. The agenda included consideration of the effects of Zika exposure on child development. Finally, in February 2017, NIAID announced the launch of a Phase 1 trial to develop a vaccine to provide broad protection against mosquito-transmitted diseases – Zika, dengue fever, malaria, and West Nile virus. The research will specifically look at triggering an immune response to the mosquito's saliva, rather than a virus or parasite carried by the mosquito.

Ms. Schuster explained that NIAID is involved in a collaborative longitudinal (5-year) study, with international partners, investigating three vaccination strategies for Ebola. More than 5,000 participants in the high-risk areas of Africa will be involved in the study. In addition, results of a study of one of the three regimens was published in the Journal of the American Medical Association. The study showed that the regimen induced a persistent immune response to Ebola that lasted one year in healthy adult volunteers.

Ms. Schuster recommended the following recently published publications:

- NG Rouphael, et al. The Safety, Immunogenicity, and Acceptability of Inactivated Influenza Vaccine Delivered by Microneedle Patch --A Randomized, Partly Blinded, Placebo-controlled, Phase 1 Trial. Lancet (2017 Aug 12). The study, sponsored by NIH, found that the use of a single, dissolvable microneedle patch was well-tolerated, resulted in robust antibody responses, and was preferred by participants over the conventional flu vaccine using syringe and needle. The vaccine was reliably selfadministered, and was stable for at least a year at 40 degrees Celsius.
- Poland GA, et al. Personalized Vaccinology: A Review. Vaccine (2017 Jul 31). Personalized vaccinology suggests the development of specific vaccines based on factors that relate to overcoming the potential for poor immunogenicity or immune response, and the potential for adverse events.
- XX Gu, et al. Waning Immunity and Microbial Vaccines Workshop of the National Institute of Allergy and Infectious Diseases. Journal of Clinical Vaccine Immunology (2017 Jul 5). This was a report on a workshop.

Finally, Ms. Schuster mentioned the *All of Us* Research Program, a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health. *All of Us* will serve as a national research resource to inform thousands of studies, covering a wide variety of health conditions. By taking into account individual

differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine. Additional information is available at: https://allofus.nih.gov/

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

CDR Marshall stated that no new vaccine approvals have occurred since the last ACCV meeting. She focused the update on meetings of the Vaccines and Related Biological Products Advisory Committee (VRBPAC).

On March 9, 2017, VRBPAC met in an open session to discuss and make recommendations on the selection of strains to be included in the influenza virus vaccines for the 2017-2018 influenza season. The update includes information on world surveillance and U.S. surveillance.

On May 17, 2017, the committee met to discuss considerations for evaluation of RSV vaccine candidates in seronegative infants. The committee discussed approaches to evaluate new RSV vaccines.

On July 28, 2017, the committee met to discuss and make recommendations on the safety and efficacy of a Hepatitis B Vaccine manufactured by Dynavax. The committee voted 12 to one, with three abstentions, to support the approval of that vaccine.

CDR Marshall stated that the next committee meeting would be held on September 13, 2017 to discuss and make recommendations on the safety and effectiveness of Zoster Vaccine Recombinant (Adjuvanted) [Shingrix], manufactured by GlaxoSmithKline Biologicals.

CDR Marshall concluded her report.

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

Dr. Bok announced a new round of Cooperative Agreements. Three were awarded:

- The first was to Cincinnati Children's Hospital, which involved validation of the Global Alignment of Immunization Safety Assessment in pregnancy (GAIA) maternal and neonatal outcome definitions to standardize the evaluation of the safety of vaccines. The study is also supported by the Bill and Melinda Gates Foundation.
- The second was to the Kaiser Foundation Hospitals, which focuses on adversomics. It aims to identify inherited, immunologic, and clinical factors that may predict the occurrence of febrile seizures after measles vaccination. Tissue samples will be collected from children who had both measles and a febrile event to look at clinical indications, genetic (familial) associations.
- The third was to Rockefeller University, to look at the role of precision medicine. NIH is a co-funder. It aims to analyze the genetic determinants of the immune response following yellow fever vaccination among individuals who experience serious adverse events.

Dr. Bok stated that the 21st Century Cures Act asked NVPO, on behalf of the Secretary, to develop a report to congress about which vaccines will be beneficial to public health and how information on recommended vaccines is disseminated to key stakeholders. NVPO was also tasked to examine and identify whether obstacles exist that inhibit the development of beneficial

vaccines. Finally, the request asked for recommendations about how best to remove any obstacles in order to promote and incentivize vaccine innovation and development. The report is expected to be sent to congress before the end of the year.

The Act also establishes a task force on research specific to pregnant women and lactating women. The task force is charged with:

1. Developing a plan to identify and address gaps in knowledge and research regarding pregnant women;
2. Considering ethical issues surrounding the inclusion of pregnant women in clinical research; develop
3. Developing effective communication strategies with health care providers and the public;
4. Identifying federal activities, including existing federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities; and
5. Provide recommendations to improve the development of safe and effective therapies for pregnant women and lactating women.

Dr. Bok announced the first Vaccine Confidence Meeting, at Emory University in Atlanta, GA. It was a gathering of researchers, government agencies and health care organizations to discuss ways to increase vaccine confidence in the U.S.

Finally, Dr. Bok announced the recipient of the Vaccine Safety Award. It was presented posthumously to Dr. Roger Baxter, who was director of the Kaiser Permanente Vaccine Study Center, for his prolific contributions to vaccine safety research**.**

Public Comment

Ms. Luthy invited public comment.

Ms. Theresa Wrangham, executive director, National Vaccine Information Center, expressed appreciation for the opportunity to comment. She noted that the meeting book was posted, as had been requested in the past, but that it did not contain the complete presentations of the DOJ or the DICP. She added that speakers often make last minute changes which should be reflected in the material on the website. The National Vaccine Information Center supports the intent of the DVIC to include public comment, such as the use of the NPRM regarding coverage of maternal vaccines, as discussed during the meeting. Ms. Wranghram concurred with what Ms. Toomey mentioned: parents are most concerned about adverse vaccine events related to their own children, vaccine injury cannot be predicted before vaccination, which relates to the informed consent ethic. The National Vaccine Information Center renews its request that the ACCV issue a statement that affirms that the use of vaccines carries with it the risk of injury or death, and because of that risk, the ACCV supports the individual's right to exercise informed consent and the right to make voluntary vaccine decisions for themselves.

Concerning the VAERS-2.0 online reporting system, Ms. Wrangham commented that, according to a CDC presentation in December 2015, VAERS received about 30,000 reports annually, 70% of which are hand-prepared, 30% are submitted in an online format. It was also

estimated at that meeting that only 1% to 10% of adverse events reported to VAERS are captured. Underreporting is widely acknowledged as a weakness of VAERS. The proposed online reporting system is likely to result in even greater underreporting. It penalizes those who are not computer literate or who have limited access to Internet services. NVIC encourages the ISO to provide information to the ACCV regarding the potential negative effects of the system will be monitored and negated.

Finally Ms. Wrangham commented, National Vaccine Injury Center renews its request for the Commission to consider recommendations for a mechanism that would gauge ongoing petitioner satisfaction with the VICP. This requested is based, in part, on a report that a petitioner was dissatisfied with the amount of award. Given the number of awards and the potential for awards to be insufficient, NVIC requests that ongoing petitioner satisfaction be revisited, and that the Commission review the findings of the Altarum Report (2009) and the Banyon Report (2010), and the 2014 GAO Report.

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

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

Ms. Luthy noted that the next meeting will take place on December 7-8, 2017. She invited suggestions for agenda items for that meeting.

Ms. Toomey suggested reviewing the work that the previous working groups were involved in to see if any of those discussions should be revisited. She also indicated it would be helpful to define the current relationship between the ACCV and the new administration. Ms. Stewart agreed that it would be helpful if the subcommittees met before the December meeting to update the individual agendas. It was noted that none of the current members were involved with the workgroup activities, so it would be worthwhile considering how to restructure the working groups to fit the current situation. Ms. Tamara Overby, Deputy Director, DICP, suggested reviewing the recommendations made by the previous workgroups, with the expectation that the new workgroup or workgroups would have to be redefined.

Dr. Nair commented that he anticipated agenda item for the December meeting would be consideration of new petitions for additions to the Vaccine Injury Table. There was also a suggestion that a discussion of RSV and Zika vaccine clinical trials be an agenda item.

Adjournment

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

3

Vaccine Injury Compensation Trust Fund

Balance as of September 30, 2017

$3,710,215,677

Figures for October 1, 2016 to September 30, 2017

- Excise Tax Revenue: $269,526,013
- Interest on Investments: $56,921,530
- Refund from Prior Year: $5,012,757
- Total Income: $331,460,300
- Interest as a Percentage of Total Income: 17%

Source: U.S. Treasury, Bureau of Public Debt
October 22, 2017

4

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

Data & Statistics

The United States has the safest, most effective vaccine supply in history. In the majority of cases, vaccines cause no side effects, however they can occur, as with any medication—but most are mild. Very rarely, people experience more serious side effects, like allergic reactions.

In those instances, the National Vaccine Injury Compensation Program (VICP) allows individuals to file a petition for compensation.

What does it mean to be awarded compensation?
Being awarded compensation for a petition does not necessarily mean that the vaccine caused the alleged injury. In fact:

- Almost 80 percent of all compensation awarded by the VICP comes as result of a negotiated settlement between the parties in which HHS has not concluded, based upon review of the evidence, that the alleged vaccine(s) caused the alleged injury.
- Attorneys are eligible for reasonable attorneys' fees, whether or not the petitioner is awarded compensation by the U.S. Court of Federal Claims (Court), if certain minimal requirements are met. In those circumstances, attorneys are paid by the VICP directly. By statute, attorneys may not charge any other fee, including a contingency fee, for his or her services in representing a petitioner in the VICP.

What reasons might a petition result in a negotiated settlement?

- Consideration of prior Court decisions, both parties decide to minimize risk of loss through settlement
- A desire to minimize the time and expense of litigating a case
- The desire to resolve a petition quickly

How many petitions have been awarded compensation?
According to the Centers for Disease Control and Prevention, from 2006 to 2015 over 2.8 billion doses of covered vaccines were distributed in the U.S. For petitions filed in this time period, 4,606 petitions were adjudicated by the Court, and of those 2,997 were compensated. This means for every 1 million doses of vaccine that were distributed, 1 individual was compensated.

Since 1988, over 18,823 petitions have been filed with the VICP. Over that 29-year time period, 16,793 petitions have been adjudicated, with 5,722 of those determined to be compensable, while 11,071 were dismissed. Total compensation paid over the life of the program is approximately $3.8 billion.

VICP Adjudication Categories, by Alleged Vaccine, For Petitions Filed Since the Inclusion of Influenza as an Eligible Vaccine for Filings 01/01/2006 Through 12/31/2015

Name of Vaccine Listed First in a Petition (other vaccines may be alleged or basis for compensation)	Number of Doses Distributed in the U.S., 01/01/2006 through 12/31/2015 (Source: CDC)	Compensable			Compensable Total	Dismissed/Non-Compensable Total	Grand Total
		Concession	Court Decision	Settlement			
DT	756,377	1		5	6	4	10
DTaP	88,814,104	15	23	98	136	101	237
DTaP-Hep B-IPV	56,700,877	5	8	24	37	43	80
DTaP-HIB	1,135,474		1	2	3	2	5
DTaP-IPV	18,613,490			2	2	1	3
DTap-IPV-HIB	52,242,336	2	2	7	11	26	37
DTP	0	1	1	3	5	2	7
DTP-HIB	0			3	3	1	4
Hep A-Hep B	13,767,345			15	15	4	19
Hep B-HIB	4,787,457	1	1	2	4	1	5
Hepatitis A (Hep A)	150,276,481	5	4	33	42	28	70
Hepatitis B (Hep B)	158,988,970	4	11	57	72	60	132
HIB	101,459,227	1	1	5	7	8	15
HPV	89,696,704	15	13	95	123	142	265

Name of Vaccine Listed First in a Petition (other vaccines may be alleged or basis for compensation)	Number of Doses Distributed in the U.S., 01/01/2006 through 12/31/2015 (Source: CDC)	Compensable			Compensable Total	Dismissed/Non-Compensable Total	Grand Total
		Concession	Court Decision	Settlement			
Influenza	1,226,400,000	236	140	1,545	1,921	307	2,228
IPV	65,399,472			4	4	3	7
Measles	135,660			1	1		1
Meningococcal	70,797,701	1	5	34	40	7	47
MMR	87,990,038	20	16	77	113	104	217
Mumps	110,749						
MMR-Varicella	18,023,247	8	1	9	18	12	30
Nonqualified	N/A			3	3	30	33
OPV	0	1			1	5	6
Pneumococcal Conjugate	180,357,916		1	7	8	21	29
Rotavirus	89,501,227	8	5	17	30	10	40
Rubella	422,548		1	1	2		2
Td	60,068,722	8	7	55	70	23	93
Tdap	202,021,173	50	13	178	241	44	285
Tetanus	3,836,052	6	1	29	36	18	54
Unspecified	N/A	1	1	4	6	584	590
Varicella	103,643,469	4	8	25	37	18	55
Grand Total	**2,845,946,816**	**393**	**264**	**2,340**	**2,997**	**1,609**	**4,606**

Notes on the Adjudication Categories Table

The date range of 01/01/2006 through 12/31/2015 was selected to reflect petitions filed since the inclusion of influenza vaccine in July 2005. Influenza vaccine now is named in the majority of all VICP petitions.

In addition to the first vaccine alleged by a petitioner, which is the vaccine listed in this table, a VICP petition may allege other vaccines, which may form the basis of compensation.

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. 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.
"Unspecified" means insufficient information was submitted to make an initial determination. The conceded "unspecified" petition was for multiple unidentified vaccines that caused abscess formation at the vaccination site(s), and the "unspecified" settlements were for multiple vaccines later identified in the Special Masters' decisions

Definitions

Compensable – The injured person who filed a petition was paid money by the VICP. Compensation can be achieved through a concession by the U.S. Department of Health and Human Services (HHS), a decision on the merits of the petition by a special master or a judge of the U.S. 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 petitions, compensable court decisions are based in part on one of the following determinations by the court:
  1. The evidence is legally sufficient to show that the vaccine more likely than not caused (or significantly aggravated) the injury; or
  2. The injury is listed on, and meets all of the requirements of, the Vaccine Injury Table (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. Petitions 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 petition was ultimately not paid money. Non-compensable Court decisions include the following:
  1. The Court determines that the person who filed the petition 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).
  2. The petition 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).
  3. The injured person voluntarily withdrew his or her petition.

Petitions Filed, Compensated and Dismissed, by Alleged Vaccine, Since the Beginning of VICP, 10/01/1988 through 11/01/2017

Vaccines	Filed			Compensated	Dismissed
	Injury	Death	Grand Total		
DTaP-IPV	9	0	9	2	1
DT	69	9	78	26	52
DTP	3,286	696	3,982	1,273	2,709
DTP-HIB	20	8	28	7	21
DTaP	430	81	511	217	241
DTaP-Hep B-IPV	73	32	105	39	44
DTaP-HIB	11	1	12	7	4
DTaP-IPV-HIB	40	19	59	11	25
Td	201	3	204	120	73
Tdap	514	3	517	290	48
Tetanus	125	2	127	65	46
Hepatitis A (Hep A)	96	7	103	43	27
Hepatitis B (Hep B)	666	57	723	267	407
Hep A-Hep B	27	0	27	16	5
Hep B-HIB	8	0	8	5	3
HIB	42	3	45	16	19
HPV	356	14	370	118	140
Influenza	3,830	131	3,961	2,297	359
IPV	267	14	281	8	269
OPV	282	28	310	158	151
Measles	143	19	162	55	107
Meningococcal	59	2	61	40	7
MMR	953	61	1,014	396	570
MMR-Varicella	39	1	40	19	12
MR	15	0	15	6	9
Mumps	10	0	10	1	9
Pertussis	4	3	7	2	5
Pneumococcal Conjugate	122	11	133	25	40
Rotavirus	82	4	86	51	21
Rubella	190	4	194	71	123
Varicella	93	9	102	60	30
Nonqualified1	97	9	106	3	99
Unspecified2	5,424	9	5,433	8	5,395
Grand Total	**17,583**	**1,240**	**18,823**	**5,722**	**11,071**

[1] Nonqualified petitions are those filed for vaccines not covered under the VICP.

[2] Unspecified petitions are those submitted with insufficient information to make a determination.

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	215
FY 2002	958
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	448
FY 2011	386
FY 2012	401
FY 2013	504
FY 2014	633
FY 2015	803
FY 2016	1,120
FY 2017	1,243
FY 2018	141
Total	**18,823**

Adjudications

Generally, petitions are not adjudicated in the same fiscal year as filed.
On average, it takes 2 to 3 years to adjudicate a petition after it is filed.

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	88	174
FY 2002	104	104	208
FY 2003	56	100	156
FY 2004	62	247	309
FY 2005	60	229	289
FY 2006	69	193	262
FY 2007	82	136	218
FY 2008	147	151	298
FY 2009	134	257	391
FY 2010	180	329	509
FY 2011	266	1,740	2,006
FY 2012	265	2,533	2,798
FY 2013	369	649	1,018
FY 2014	371	193	564
FY 2015	517	139	656
FY 2016	697	179	876
FY 2017	663	153	816
FY 2018	13	33	46
Total	**5,722**	**11,071**	**16,793**

Awards Paid

Fiscal Year	Number of Compensated Awards	Petitioners' Award Amount	Attorneys' Fees/Costs Payments	Number of Payments to Attorneys (Dismissed Cases)	Attorneys' Fees/Costs Payments (Dismissed Cases)	Number of Payments to Interim Attorneys'	Interim Attorneys' Fees/Costs Payments	Total Outlays
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	$87,509,650.06
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	74	$2,531,394.20	2	$117,265.31	$83,556,982.40
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	59	$1,933,550.09	22	$1,978,803.88	$189,261,439.67
FY 2011	251	$216,319,428.47	$9,572,042.87	403	$5,589,417.19	28	$2,001,770.91	$233,482,659.44
FY 2012	249	$163,491,998.82	$9,241,427.33	1,020	$8,649,676.56	37	$5,420,257.99	$186,803,360.70
FY 2013	375	$254,666,326.70	$13,543,099.70	704	$7,012,615.42	50	$1,454,851.74	$276,676,893.56
FY 2014	365	$202,084,196.12	$12,161,422.64	508	$6,824,566.68	38	$2,493,460.73	$223,563,646.17
FY 2015	508	$204,137,880.22	$14,507,692.27	117	$3,484,869.16	50	$3,089,497.68	$225,219,939.33
FY 2016	689	$230,140,251.20	$16,225,881.12	99	$2,741,830.10	59	$3,502,709.91	$252,610,672.33

Fiscal Year	Number of Compensated Awards	Petitioners' Award Amount	Attorneys' Fees/Costs Payments	Number of Payments to Attorneys (Dismissed Cases)	Attorneys' Fees/Costs Payments (Dismissed Cases)	Number of Payments to Interim Attorneys'	Interim Attorneys' Fees/Costs Payments	Total Outlays
FY 2017	706	$252,245,932.78	$22,063,861.36	128	$4,337,592.83	52	$3,363,464.24	$282,010,851.21
FY 2018	46	$9,982,629.05	$1,861,506.05	15	$574,103.65	13	$1,081,492.14	$13,499,730.89
Total	**5,713**	**$3,498,478,207.78**	**$172,355,004.67**	**5,250**	**$75,407,873.26**	**379**	**$28,744,937.08**	**$3,774,986,022.79**

NOTE: Some previous fiscal year data has been updated as a result of the receipt and entry of data from documents issued by the Court and system updates which included petitioners' costs reimbursements in outlay totals,

"Compensated" are petitions 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/petitions are determined compensable. "Dismissed" includes 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 petition, whether or not the petition/petition 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.

Since influenza vaccines (vaccines administered to large numbers of adults each year) were added to the VICP in 2005, many adult petitions related to that vaccine have been filed, thus changing the proportion of children to adults receiving compensation.

5.1

The National Vaccine Injury Compensation Program (VICP)

Division of Injury Compensation Programs Update

Advisory Commission on Childhood Vaccines

December 8, 2017

CAPT Narayan Nair, MD
Director, Division of Injury Compensation Programs
Healthcare Systems Bureau (HSB)
Health Resources and Services Administration (HRSA)

HRSA Healthcare Systems

DICP Update
ACCV Meeting Highlights

- **Update on HRSA VICP Activities**
- **Presentations on Petitions to Add Injuries to the Vaccine Injury Table**
  - Tics (vaccine not specified)
  - Food Allergies, Autism and Asthma (vaccine not specified)
  - PITANDS/PANS/PANDAS for pertussis, pneumococcal conjugate and *Haemophilus* influenza type b (Hib) vaccines
  - Experimental Autoimmune Encephalomyelitis for pertussis vaccines
- **Update from the Department of Justice Vaccine Litigation Office**
- **Updates from ACCV Ex Officio Members – FDA, CDC, NIH, NVPO**

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DICP Update

Number of Petitions Filed as of October 26, 2017

Average annual number of petitions filed during FY 2012-2015 = 585

Fiscal Year	Total
FY 2012	401
FY 2013	504
FY 2014	633
FY 2015	803
FY 2016	1,120
FY 2017	1,243
FY 2018	125

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DICP Update

Award Amounts Paid as of October 26, 2017

Fiscal Year	Petitioners' Award	Attorneys' Fees & Costs
FY 2012	$163,491,999	$23,311,362
FY 2013	$254,666,327	$22,010,567
FY 2014	$202,084,196	$21,479,450
FY 2015	$204,137,880	$21,082,059
FY 2016	$230,140,251	$22,470,421
FY 2017	$252,245,933	$29,764,918
FY 2018	$7,862,771	$2,897,815

DICP Update

Number of Adjudications as of October 26, 2017

Fiscal Year	Compensable	Dismissed	Total
FY 2012	265	2,533	2,798
FY 2013	369	649	1,018
FY 2014	371	193	564
FY 2015	517	139	656
FY 2016	697	179	876
FY 2017	662	153	815
FY 2018	11	30	41

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DICP Update

Adjudication Categories for Non-Autism Claims FY 2015– FY 2017 as of October 26, 2017

Adjudication Category	FY 2016	FY 2017	FY 2018
Compensable ❖Concession ❖Court Decision (includes proffers) ❖Settlement	697 (100%) 204 (29%) 44 (6%) 449 (65%)	662 (100%) 174 (26%) 41 (6%) 447 (68%)	11 (100%) 2 (18%) 0 (0%) 9 (82%)
Not Compensable	168	147	8
Adjudication Total	865	809	19

DICP Update
Vaccine Injury Compensation Trust Fund

- **Balance as of September 30, 2017**
  - $3,710,215,677
- **Activity from October 1, 2016 to September 30, 2017**
  - Excise Tax Revenue: $269,526,013
  - Interest on Investments: $56,921,530
  - Refund from Prior Year: $5,012,757
  - Total Income: $331,460,300
  - Interest as a Percentage of Total Income: 17%

Source: U.S. Treasury, Bureau of the Fiscal Service (October 22, 2017)

DICP Update
Significant Activities

- **Implementation of Maternal Immunization Provisions**
  - The ACCV voted on language to revise the Vaccine Injury Table (Table) at the September 8, 2017 ACCV meeting.
  - The Notice of Proposed Rulemaking announcing proposed revisions to the Table is in development.

- **Highlights of Recent Outreach Activities**
  - Presented information on SIRVA at the Advisory Committee on Immunization Practices on October 25, 2017

DICP Update
ACCV Meeting Information

- Information on ACCV meetings, presentations and minutes can be found at:

http://www.hrsa.gov/advisorycommittees/childhoodvaccines/index.html

DICP Update
Contact Information
Public Comment/Participation in Commission Meetings

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5.2

5.3

The National Vaccine Injury Compensation Program (VICP): Discussion of Petitions to Add Injuries to the Vaccine Injury Table

Narayan Nair, M.D., Director
Division of Injury Compensation Programs (DICP)
Healthcare Systems Bureau (HSB)
Health Resources and Services Administration (HRSA)

HRSA Healthcare Systems

Overview

- Background on the Vaccine Injury Table
- Discuss ACCV Guiding Principles for Recommending Changes to the Vaccine Injury Table
- Discuss Petition to Add Food Allergies and Autism to Vaccine Injury Table

Vaccine Injury Table

- The National Childhood Vaccine Injury Act of 1986 (Act), as amended, authorizes the Secretary to create and modify a list of injuries, disabilities, illnesses, conditions, and deaths (and their associated time frames) associated with each category of vaccines included on the Table.
- Lists specific injuries and the time frames in which they must occur
- Provides legal mechanism for defining complex medical conditions
- Allows legal “presumption of causation”
- Provides compensation unless alternative cause unrelated to vaccine

Claims Can Be Filed for Injuries Not on the Vaccine Injury Table

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

Petitions to Add Injuries to the Table

- The statute states: "Any person (including the Advisory Commission on Childhood Vaccines) may petition the Secretary to propose regulations to amend the Vaccine Injury Table. Unless clearly frivolous, or initiated by the Commission, any such petition shall be referred to the Commission for its recommendations. Following –

  (A) Receipt of any recommendation of the Commission or

  (B) 180 days after the date of the referral to the Commission,

  whichever occurs first, the Secretary shall conduct a rulemaking proceeding on the matters proposed in the petition or publish in the Federal Register a statement of reasons for not conducting such proceeding." 42 U.S.C. § 300aa-14(c)(2).

ACCV Guiding Principles

- ACCV established “Guiding Principles for Recommending Changes to the Vaccine Injury Table” (Guiding Principles).
- These consist of two overarching principles:
  - The Table should be scientifically and medically credible; and
  - Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

ACCV Guiding Principles

- To the extent that the National Academy of Medicine (NAM) has studied the possible association between a vaccine and an adverse effect, the conclusions of the NAM should be considered by the ACCV and deemed credible but those conclusions should not limit the deliberations of the ACCV.

ACCV Guiding Principles

- ACCV members should acknowledge that differing sources of data should be afforded different weight and should do so by adopting the following hierarchy (listed from strongest to weakest sources of data):
  - Clinical laboratory data (such as PCR confirmation of vaccine strain virus following immunization against varicella)
  - Challenge/re-challenge/de-challenge data involving non-relapsing symptoms or diseases (particularly when documented in multiple individuals)
  - Controlled clinical trials (including, but not limited to, double-blind, placebo controlled clinical trials)
  - Controlled observational studies such as cohort and case control studies, including but not limited to studies based upon data from the Vaccine Safety Datalink (VSD) database
  - Uncontrolled observational studies such as ecological studies
  - Case series
  - Data from passive surveillance systems, including but not limited to the Vaccine Adverse Event Reporting System
  - Case reports
  - Editorial articles on scientific presentations
  - Non-peer reviewed publications

Petitions to Add Injuries to the VIT

- Asthma (Food Allergies/Autism will be addressed separately) (vaccines not specified) - Dr. Stacy Stryer
- Pediatric Infection-Triggered, Autoimmune, Neuropsychiatric Disorders (PITANDS) and/or Pediatric Autoimmune and Neuropsychiatric Syndrome (PANS), and Pediatric Autoimmune Neuropsychiatric Disorder Associated with group A Streptococcus (PANDAS) for pertussis, pneumococcal conjugate and Haemophilus influenza type b (Hib) vaccines – Dr. Mark Ditmar
- Experimental Autoimmune Encephalomyelitis for pertussis vaccines – Dr. Terry Dalle-Tezze
- Tics (vaccines not specified) – Dr. Mary Rubin

Petitions to Add Food Allergy to the Table

- On September 19, 2015, a private citizen submitted an email to HHS and the Commission requesting that food allergies be added to the Table.
- DICP conducted a review of the evidence presented in the petition and conducted an additional review of the medical literature.
- This petition was presented to the ACCV on December 3, 2015.
- The ACCV voted unanimously not to add food allergies to the Table.

Petition to Add Food Allergy, Asthma and Autism to the Table

- On April 3, 2017 another petition was submitted by the same individual asking to add food allergies, asthma and autism to the Table.
- At this time there is no new data addressing whether vaccines cause food allergies.

Petition to Add Autism to the Table

- Omnibus Autism Proceeding
  - Ordered in July 2002 by Court
  - >5,600 claims
  - 2-phase process
  - Discovery: 2002-2006
  - >200,000 pages of documents submitted
  - Entitlement hearings (2007 & 2008)

Petition to Add Autism to the Table

- In decisions released in 2009 and 2010, and affirmed without exception on appeal, the Court found there is no credible evidence that measles-mumps-rubella vaccine in combination with thimerosal-containing vaccines, or thimerosal-containing vaccines alone, can cause autism.
- These decisions mirror the current body of scientific evidence.

Petition to Add Autism to the Table

- In 2011, the National Academy of Medicine reviewed the medical and scientific evidence on vaccines and adverse events in order to update the Table.
- A review of the evidence favored rejection of a causal relationship between MMR vaccine and autism.
- These findings were presented to the ACCV on September 1, 2011 and March 8, 2012.

Petition to Add Autism to the Table

- DICP also reviewed evidence whether vaccines other than MMR caused autism.
- DICP was unable to identify any medical literature in peer reviewed publications that concluded that vaccines cause autism.

Petition to Add Autism to the Table

- Several studies have also found that vaccines other than MMR are not associated with autism:
  - DeStefano F., Price C. S., Weintraub E. S. (2013). Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. J. Pediatr. 163, 561–567.
  - Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. Vaccine. 2014 Jun 17;32(29):3623-9.
  - Iqbal S, Barile JP, Thompson WW, DeStefano F. Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7-10 years. Pharmacoepidemiol Drug Saf. 2013 Dec;22(12):1263-70.

Petition to Add Autism to the Table

- A number of professional and international organizations have reviewed the evidence and concluded that there is no association between vaccines and autism.
- These include the American Academy of Pediatrics, American Medical Association, American Academy of Family Physicians, Children's Hospital of Philadelphia, the Canadian National Advisory Committee on Immunization, and the Department of Health of the United Kingdom.

Petition to Add Autism to the Table

- A request regarding adding autism to the Table was recently considered and rejected by HHS with respect to the Final Rule amending the Table.
- HHS' response to the comment can be found in the preamble to the Final Rule amending the Table. (See 82 FR 6294, 6298.)

ACCV Guiding Principles

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- These consist of two overarching principles:
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  - Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

Options

Option 1: Add autism as an injury to the Vaccine Injury Table.

Option 2: Do not add autism as an injury to Vaccine Injury Table.

Contact Information

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5.4

The National Vaccine Injury Compensation Program (VICP): Discussion of Petition to Add Tic Disorders to the Vaccine Injury Table

December 8, 2017

Mary Nythel Rubin, M.D.
Medical Officer, Division of Injury Compensation Programs (DICP)
Healthcare Systems Bureau (HSB)
Health Resources and Services Administration (HRSA)

HRSA Healthcare Systems

Overview

- Discuss petition that tics be added to the Vaccine Injury Table (Table)
- Review background on tics/tic disorders
- Review medical evidence regarding vaccines and tics/tic disorders

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Background
Petition

- **On March 16, 2017 a private citizen submitted a letter to HHS and the ACCV requesting that tics be added to the Table.**
  - Petitioner claims that two CDC employees have been quoted as believing there is evidence that vaccines can cause tics.
  - Petitioner mentions a study by Barile in support of his request.

Background
Tic: Definition and Features

- Sudden, rapid, recurrent, non-rhythmic, stereotyped motor movement or vocalization (DSM-V)
- Experienced as involuntary but can be suppressed for varying lengths of time
- Markedly diminished during sleep
- Simple vs. complex tics

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Background
Tic Disorder

- **Epidemiology**
  - Onset almost always occur in childhood
  - Multiple tics and complex vocal sounds can develop over time, peaking in severity by age 10 – 12 years
- **Etiology**
  - Possibly due to abnormalities in dopamine, serotonin and norepinephrine neurotransmitter systems
- **Risk and prognostic factors**
  - Influenced by temperamental, environmental, genetic and physiological factors

Background
Tic Disorders: Diagnostic Categories

- Tourette's disorder
- Persistent (chronic) motor or vocal tic disorder
- Provisional tic disorder
- Other specified and unspecified tic disorders

Tic disorders are hierarchical in order, such that once a tic disorder at one level of the hierarchy is diagnosed, a lower hierarchy diagnosis cannot be made

Background

Tourette's Disorder	Persistent (Chronic) Motor or Vocal Tic Disorder	Provisional Tic Disorder
A. Both multiple motor and one or more vocal tics have been present at some time during the illness.	A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.	A. Single or multiple motor and/or vocal tics.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.	B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.	B. The tics have been present for less than 1 year since first tic onset.
C. Onset is before age 18 years.	C. Onset is before age 18 years.	C. Onset is before age 18 years.

Background

Tourette's Disorder	Persistent (Chronic) Motor or Vocal Tic Disorder	Provisional Tic Disorder
D. The disturbance is not attributable to the physiological effects of a substance or another medical condition.	D. The disturbance is not attributable to the physiological effects of a substance or another medical condition. E. Criteria have never been met for Tourette's disorder.	D. The disturbance is not attributable to the physiological effects of a substance or another medical condition E. Criteria have never been met for Tourette's disorder or persistent (chronic) motor or vocal tic disorder.

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Background

- **Other specified or unspecified tic disorder**
  - Symptoms characteristic of a tic disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for a tic disorder or any of the disorders in the neurodevelopmental disorders diagnostic class.
- **Other movements or disorders similar to tics:**
  - Abnormal movements
  - Substance-induced and paroxysmal dyskinesias
  - Myoclonus
  - Obsessive-compulsive and related disorders

Background
Tic Disorder: Treatment

- **Multilevel approach**
  - Cognitive-behavioral therapy
  - Medications

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ACCV Guiding Principles

- **ACCV established "Guiding Principles for Recommending Changes to the Vaccine Injury Table" (Guiding Principles).**
- **These consist of two overarching principles:**
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Claims Can Be Filed for Injuries Not on the Vaccine Injury Table

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

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Review of Evidence: Barile Article

Barile, J. P., G. P. Kuperminc, et al. (2012). "Thimerosal exposure in early life and neuropsychological outcomes7-10 years later." J Pediatr Psychol 37(1): 106-18.

Objective: To investigate associations between thimerosal-containing vaccines and immunoglobulins early in life and neuropsychological outcomes assessed at 7 – 10 years

Sample: 1,047 children ages 7-10, born between January 1993 and March 1997

Methods: Trained evaluators measured seven neuropsychological outcomes during a 3-hour testing period with the child: intellectual functioning, speech and language, verbal memory, executive functioning, fine motor coordination, tics and behavior regulation.

Results: The authors found no statistically significant associations between thimerosal exposure from vaccines early in life in six of the seven outcomes. There was a small, statistically significant association between early thimerosal exposure and the presence of tics in boys.

Conclusion: This finding should be interpreted with caution due to limitations in the measurement of tics and the limited biological plausibility regarding a causal relationship. Additional studies are needed to examine these associations using more reliable and valid measure of tics.

Review of Evidence
Limitations of the Barile Study

- **The likelihood of diagnostic misclassification is unknown, and may be high.**
  - The training that the evaluators received for tic assessment was based on a 30-minute video on the diagnosis of Tourette Syndrome.
- **Tics run in families. Although less prevalent in girls than boys, there is no reason to think that external etiological factors would differ for boys and girls. In this study, the purported relationship between thimerosal exposure and tics was not identified in girls, only in boys.**
- **The response rate was low – only 30% of participants invited agreed to participate. Some degree of self-selection which could bias the results in either direction cannot be excluded.**

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Thimerosal

- **Thimerosal is a mercury-based preservative.**
- **There is no evidence of harm caused by low doses of thimerosal in vaccines except for minor reactions like redness and swelling at the injection site.**
- **Thimerosal was removed from childhood vaccines in the United States in 2001, as a precautionary measure.**
  - Measles, mumps, and rubella (MMR) vaccines do not and never did contain thimerosal. Varicella (chickenpox), inactivated polio (IPV), and pneumococcal conjugate vaccines have also never contained thimerosal.
  - Influenza (flu) vaccines are currently available in both thimerosal-containing (for multi-dose vaccine vials) and thimerosal-free versions.

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Thimerosal

Studies and Assessments Regarding Safety

- Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association by Nick Andrews et al. Pediatrics. September 2004. Vol 114: pages 584–591. http://pediatrics.aappublications.org/cgi/content/ full/114/3/584
- Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links with Immunizations by Eric Frombonne et al. Pediatrics. July 2006. Vol 118: e139-e150. http://pediatrics.aappublications.org/cgi/content/full/118/ 1/e139
- Association between Thimerosal-Containing Vaccine and Autism by Anders Hviid et al. Journal of the American Medical Association. October 2003. Vol 290: pages 1763–1766. http://jama.ama-assn.org/cgi/content/full/290/13/1763

Thimerosal

Studies and Assessments Regarding Safety (Cont'd)

- Immunization Safety Review: Vaccines and Autism. Institute of Medicine. The National Academies Press: 2004. http://www.iom.edu/Reports/2004/Immunization-SafetyReview-Vaccines-and-Autism.aspx
- Prenatal and Infant Exposure to Thimerosal from Vaccines and Immunoglobulins and Risk of Autism by Cristofer Price et al. Pediatrics. September 2010. Vol 126: pages 656-664. http://pediatrics.aappublications.org/cgi/reprint/peds.2010 0309v1
- Continuing Increases in Autism Reported to California's Developmental Services System by Robert Schechter et al. Archives of General Psychiatry. January 2008. Vol 65: pages 19-24. http://archpsyc.ama-assn.org/cgi/content/ full/65/1/19
- Early Thimerosal Exposure and Neuropsychological Outcomes at 7 to 10 Years by William Thompson et al. The New England Journal of Medicine. September 2007. Vol 357: pages 1281 1292. http://www.nejm.org/doi/pdf/10.1056/NEJMoa071434

Thimerosal

More Studies and Assessments Regarding Safety

- World Health Organization, Global Advisory Committee on Vaccine Safety. (2006). Statement on Thiomersal.
- Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for mercury. Atlanta, GA: 1999.
- American Academy of Pediatrics. Vaccine Safety: Examine the Evidence. April 2013
- Magos L. (2001) Review on the toxicity of ethylmercury, including its presence as a preservative in biological and pharmaceutical products. J Appl Toxicol 21(1):1-5. Review on the toxicity of ethylmercury, including its presence as a preservative in biological and pharmaceutical products.
- Mitkus RJ, King DB, Walderhaug MO, Forshee RA. A comparative pharmacokinetic estimate of mercury in U.S. Infants following yearly exposures to inactivated influenza vaccines containing thimerosal. Risk Anal 2014; 34:735.

Thimerosal

More Studies and Assessments Regarding Safety (Cont'd)

- Olczak M, Duszczyk M, Mierzejewski P, Wierzba-Bobrowicz T, Majewska MD (2010) Lasting neuropathological changes in rat brain after intermittent neonatal administration of thimerosal. Folia Neuropathol. 48(4): 258-69.
- Pichichero, ME, E Cernichari, J Lopreiato, and J Treanor. (2002) Mercury Concentrations and Metabolism in Infants Receiving Vaccines Containing Thiomersal: A Descriptive Study. The Lancet 360:1737-41.
- Pichichero ME, Gentile A, Giglio N, Umido V, Clarkson T, Cernichiari E, Zareba G, Gotelli C, Gotelli M, Yan L, and Treanor J. (2008) Mercury Levels in Newborns and Infants After Receipt of Thimerosal-Containing Vaccines. Pediatrics. 121(2):e208 14.

https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-thimerosal-color-office.pdf

https://www.fda.gov/biologicsbloodvaccines/safetyavailability/vaccinesafety/ucm096228.htm#bib

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Review of Evidence
Other Studies on Tics by Dr. William Thompson

- Iqbal S., Barile J.P., Thompson W.W., DeStefano F. (2013). "Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7-10 years." Pharmacoepidemiol Drug Saf 22(12): 1263-70.
- Thompson, W. W., C. Price, et al. (2007). "Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years." New England Journal of Medicine 357(13): 1281-1292.

Review of Evidence
Iqbal Article

Objective: To evaluate the association between antibody-stimulating proteins and polysaccharides from early childhood vaccines and neuropsychological outcomes at age 7-10 years.

Sample: 1,047 children from a public data set

Methods: Children took standardized tests for domain-specific neuropsychological outcomes: general intellectual function, speech and language, verbal memory, attention and executive function, tics, achievement, visual spatial ability and behavioral regulation.

Results: There were no adverse associations between antigens through vaccines in the first 2 years of life and neuropsychological outcomes in later childhood.

Review of Evidence
Limitations of Iqbal Study

- The analysis assumed that the levels of immune response were similar for all antigens, which is an over simplification.
- Enrollment was less than 30% which could have resulted in selection bias. There are also recall issues due to self-reporting.
- The level of antigenic exposure from vaccines received by children in the study was greater than the current vaccination schedule.

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Review of Evidence
Additional Literature

- **A comprehensive literature review of the major medical databases was conducted to search for articles linking tics/tic disorders to vaccinations.**
  - Collaboration with the National Institutes of Health Library, Office of Research Services
- **There was very little literature on tics/tic disorders as a result of vaccinations. The publications on this topic are predominantly from two researchers (Geier and Dorea) and focused on thimerosal-containing vaccines and neurodevelopmental disorders including tics and Tourette Syndrome.**
- **There was only one other publication on vaccinations and neuropsychiatric disorders, including tics that did not focus on thimerosal.**

HRSA Healthcare Systems

Review of Evidence: Leslie Article

Leslie, D. L., R. A. Kobre, et al. (2017). "Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination of Children and Adolescents: A Pilot Case-Control Study." Front Psychiatry 8: 3.

Objective: To examine whether antecedent vaccinations are associated with increased incidence of OCD, AN, anxiety disorder, chronic tic disorder, ADHD, major depressive disorder and bipolar disorder.

Sample: Children aged 6-15 with a diagnosis of one of the specified conditions.

Methods: Using claims data, the investigators compared the prior year's occurrence of vaccinations in children and adolescents with the above neuropsychiatric disorders that were newly diagnosed between 1/2002 and 12/2002, as well as two control conditions, broken bones and open wounds.

Results: Children with OCD, AN, anxiety disorder, and tic disorder were more likely to have received influenza vaccine during the preceding 1-year period (for OCD in the preceding 3-, 6-, and 12-month periods; for AN in the preceding 3- and 6-month periods; for anxiety disorder in the preceding 6- and 12-month periods; for tic disorder in the preceding 6- and 12-month periods).

Conclusion: The onset of some neuropsychiatric disorders may be temporally related to prior vaccinations. This warrants further investigation but does not prove a causal role of vaccinations in the etiology of these conditions.

Review of Evidence
Limitations of Leslie Study

- Providers may designate ICD-9 insurance/billing codes for vaccines without specifying the particular vaccine.
- The study used administrative retrospective data rather than systematically obtained clinical data. Therefore, diagnostic misclassification may have occurred.
- Diagnosis dates do not indicate disease onset dates.
- Control groups may not be similar enough to the disease groups.
- The influenza vaccine is given annually and is the most frequently administered vaccine. By chance, there may be many diagnoses made within a year of flu vaccination.
- This case-control study provides no more than a temporal association and does not give an absolute risk.

Review of Evidence
Summary

- There is limited literature on tics/tic disorders and vaccinations.
- Childhood vaccines do not contain thimerosal. Influenza vaccines have thimerosal-free formulations.
- Current scientific evidence does not support a causal association between thimerosal-containing and thimerosal-free vaccinations and tics/tic disorders.

ACCV Guiding Principles

- The Table should be scientifically and medically credible; and

- Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

ACCV Recommendation

Options

Option 1: Add tics/tic disorders to the Vaccine Injury Table.

Option 2: Do not add tics/tic disorders to Vaccine Injury Table.

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

Contact Information

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Petition

MAR 17 2017

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VIA FEDEX

March 16, 2017

U.S. Department of Health & Human Services
HHS Office of the Secretary
Dr. Thomas E. Price, M.D.
Secretary of Health & Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Re: *Notice Pursuant to 42 U.S.C. § 300aa-31*

Dear Secretary Price:

Congratulations on your recent appointment and confirmation as the Secretary of Health and Human Services (the "**Secretary**").

We represent several individuals that developed tics shortly after vaccination. A senior scientist at the Center for Disease Control (the "**CDC**") recently confirmed that "vaccines cause tics" and expressly stated that tics should have been added to the Vaccine Injury Table. It is therefore respectfully requested that the Department of Health and Human Services ("**HHS**") confirm that it intends to add tics to the Vaccine Injury Table and Vaccine Information Statements.

In the 1980s many pharmaceutical companies announced they would cease producing vaccines due to their liability from the injuries their vaccines were causing. In response, Congress passed the National Childhood Vaccine Injury Act of 1986 ("**NCVIA**"), codified at 42 U.S.C. §§ 300aa-1 - 300aa-34, to shield pharmaceutical companies from financial liability for injuries caused by vaccines they manufacture. In recognition that Congress had eliminated the market incentives to create safer vaccines, Congress placed the responsibility to "coordinate and provide direction for safety...testing for vaccines" in the hands of the Secretary of the Department of Health and Human Services. 42 U.S.C. § 300aa-2. This responsibility includes, *inter alia*, that the "Secretary shall...promote the development of childhood vaccines that result in fewer and less serious adverse reactions...and make or assure improvements in...the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, ... adverse reaction reporting, ...and research on vaccines in order to reduce the risks of adverse reactions to vaccines." 42 U.S.C. § 300aa-27(a).

In recognition that Congress had put the Secretary of the Department of Health and Human Services in the shoes of the pharmaceutical companies with regard to vaccine safety by transferring the responsibility of vaccine safety and liability to the Secretary, 42 U.S.C. 300aa-

31(a), entitled "Citizen's actions", provides that "any person may commence in a district court of the United States a civil action on such person's own behalf against the Secretary where there is alleged a failure of the Secretary to perform any act or duty under this part." One of the Secretary's specific duties in that regard is to amend the Vaccine Injury Table (the "**Table**") to include any injuries, disabilities, illnesses, conditions and deaths associated with each vaccine on the Table. In relevant part, 42 U.S.C. § 300aa-14(d)(e)(2) provides that:

> When...the Center for Disease Control and Prevention recommends a vaccine to the Secretary for routine administration to children, the Secretary shall, within 2 years of such recommendation, amend the Vaccine Injury Table...to include...(A) vaccines which were recommended for routine administration to children, (B) the injuries, disabilities, illnesses, conditions, and deaths *associated* with such vaccines, and (C) the time period in which the first symptoms...associated with such vaccines may occur.

(emphasis added.) The Secretary also has the separate and distinct obligation to disclose the risks "associated" with each vaccine on the Vaccine Information Statement developed by the Secretary for each vaccine on the Vaccine Injury Table. 42 U.S.C. § 300aa-26 ("the Secretary shall develop and disseminate vaccine information materials for distribution by health care providers to the legal representatives of any child or to any other individual receiving a vaccine set forth in the Vaccine Injury Table" and the "information in such materials shall be based on available data and information...and shall include...a concise description of the risks *associated* with the vaccine.") (emphasis added.)

Dr. William Thompson is a senior scientist at the CDC, including over a decade in the CDC's Immunization Safety Branch. Dr. Thompson was the lead scientist and author of many of the seminal peer reviewed papers produced by the CDC to support its public claim that vaccines are safe. Dr. Thompson was also the lead scientist and author on most of the peer reviewed papers produced by the CDC regarding vaccination and tics.

In a recorded conversation, Dr. Thompson recently confirmed that patients developing tics is one of the injuries, disabilities, illnesses, and conditions resulting from vaccines. As stated by Dr. Thompson, "vaccines cause tics." The full quote in which Dr. Thompson made this assertion follows:

> The only thing I know for sure, is that I can say that pretty confidently, vaccines cause tics. We replicated that. The Barile article replicated that and showed that once you took into account the number of tests and reduced them down to constructs, the one thing you couldn't get to go away was the tic effect.

In this recorded conversation, Dr. Thompson went on to express his exasperation and disbelief that tics had not been added to the Vaccine Injury Table. As stated by Dr. Thompson: "And this is what blows my mind. What blows my mind is somehow, tics has not been added to the vaccine...adverse events schedule."

Dr. Thompson is not alone at the CDC in believing that the correlation between tics and

vaccines has been confirmed. Another senior CDC scientist, Dr. Marshalyn Yeargin-Allsop, stated essentially the same thing in an email on February 12, 2007 regarding a study that looked at, *inter alia*, vaccines and tics. That email was obtained under the Freedom of Information Act and in it Dr. Yeargin-Allsop stated: "I think it is interesting that where there were negative effects, they are with the (sic) some of the same outcomes as from the other analyses (tics, articulation, suggesting overall speech and language disorders). Seems almost confirmatory."

In his recorded conversation, Dr. Thompson also discussed efforts by the CDC to hide the association between vaccines and tics, explaining one instance in which the CDC systematically, purposely and improperly watered down this association:

> Well, I would say every study that has ever come out on immunization safety, the people above know.... If there's a significant finding, they know months in advance of it going into clearance. So, my paper I put into clearance without them knowing anything about it, and it caught people off guard, and then we went through the process we went through which was a slow, laborious. But I kept pounding away; they kept watering it down. They watered it down. Then we sent it out to the journals. And the journals were just like, "What the fuck?"

Based on the foregoing, it is clear that Dr. Thompson, the senior CDC scientist that spearheaded the research into whether vaccines are associated with tics, has concluded that "vaccines cause tics." In fact, Dr. Thompson's conclusion of a causal relationship between vaccines and tics far exceeds the standard of merely showing an "association" between vaccines and tics. Thus, as required pursuant to the above referenced sections of the U.S. Code, tics must be added to the Vaccine Injury Table and Vaccine Information Statements.

We look forward to a timely response to this request and to your prompt addition of tics to the Vaccine Injury Table and Vaccine Information Statements. If you choose not to take this action, our clients have authorized us to initiate an action in court to enforce the NCVIA.

This letter constitutes the notice required by 42 U.S.C. § 300aa-31(b) which provides that "No action may be commenced under subsection (a) [42 U.S.C. 300aa-31(a), entitled "Citizen's actions"] before the date which is 60 days after the person bringing the action has given written notice of intent to commence such action to the Secretary."

Very truly yours,

Aaron Siri, Esq.

5.5

Discussion of Petition to Add Asthma to the Vaccine Injury Table

December 8, 2017

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Healthcare Systems Bureau (HSB)
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HRSA Healthcare Systems

Overview

- Define asthma
- Discuss email and petition requesting that asthma be added to the Vaccine Injury Table (VIT)
- Review medical evidence regarding vaccines and asthma
- Present options for voting on adding asthma to the Table

Petition to Add Asthma to VIT

On April 3, 2017, a private citizen submitted an email to HHS and the Commission petitioning asthma to be added to the VIT.

This individual asserts that:

- The injection of food allergen-contaminated vaccines causes sensitization and subsequently asthma.

Asthma Definition

- Asthma is a chronic inflammatory disorder contributing to hyperresponsive airways, decreased airflow, breathing difficulties (such as wheezing and shortness of breath), and disease chronicity.

- Asthma is thought to develop in individuals who have a combination of certain host and environmental factors.

- Individuals with asthma vary in terms of onset age, presentation, severity, exacerbating factors, and response to treatment.

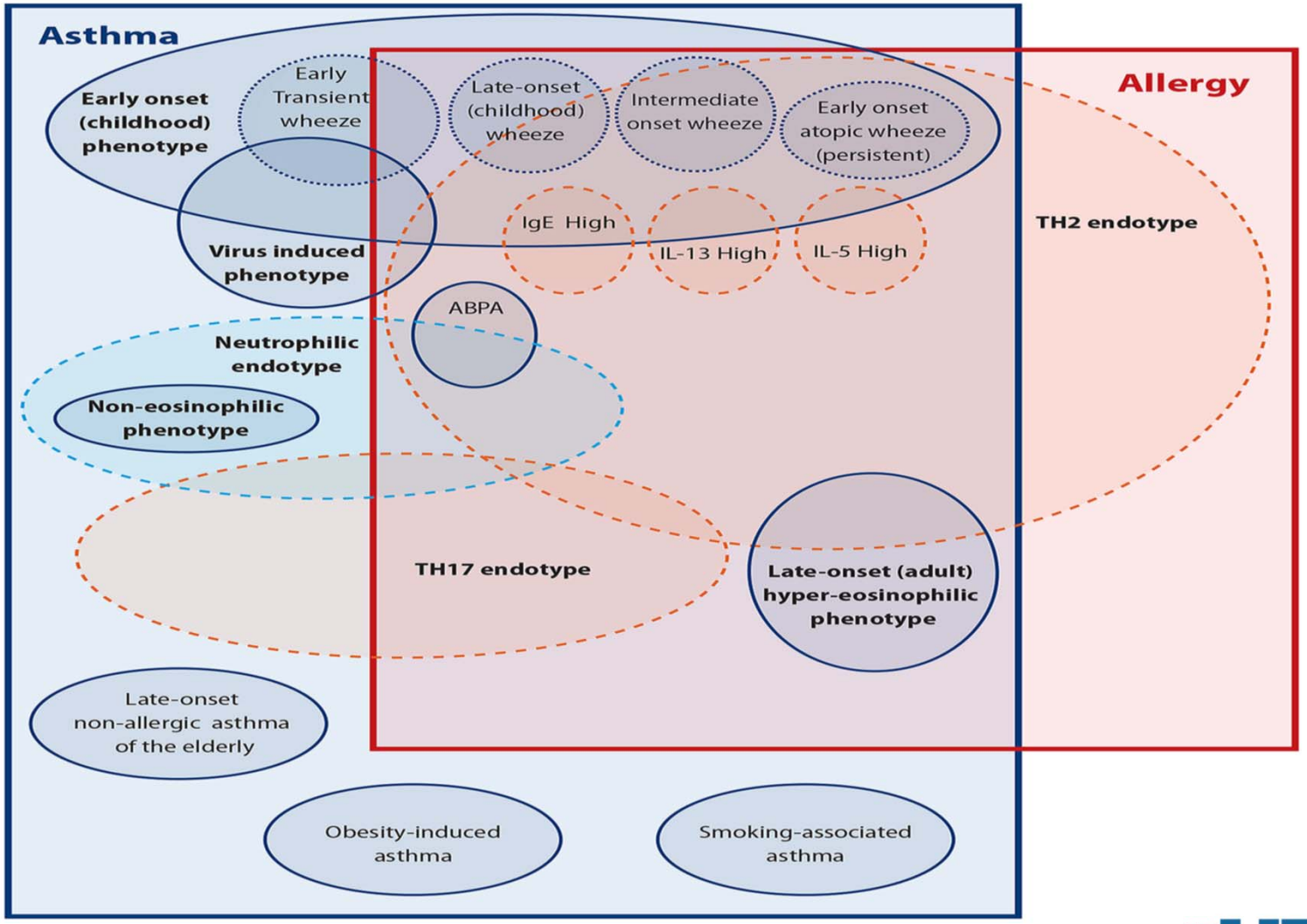
Asthma Definition

- Comorbid features commonly exist, such as gastroesophageal reflux and aspirin intolerance.

- There are several risk factors for developing asthma, including genetic and prenatal factors, lung size in infancy, exposure to environmental factors (i.e., microbial organisms, smoke, and pollution), viral infections, obesity and atopy (tendency to produce immunoglobulin E(IgE) antibodies).

- It is difficult to attribute a single mechanism to a syndrome with such a wide range of clinical manifestations. Asthma has several different causes that result in similar clinical features.

Diagram of potential allergic and non-allergic causes of asthma



Taken from: Relationship of Allergy with Asthma: There are More Than the Allergy "Eggs" in the Asthma Basket. Guibas G. et al. Front Pediatr. 2017 Apr 28;5:92.

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Etiology of Asthma

- Individuals who develop allergic-type asthma are usually sensitized, or first develop IgE (Immunoglobulin E) antibodies when they come into contact with an allergen through the respiratory route.
- When they are re-exposed to the sensitized allergen in their airways, IgE antibodies will hyper react and bind to the specific allergen, causing an allergic reaction.
- It does this by stimulating the release of many pro-inflammatory mediators such as histamine, tryptase, leukotrienes, and prostaglandins, which are responsible for asthma exacerbation.
- There may also be permanent changes in the bronchial airways.

Etiology of Asthma

- Viral infections, likely mediated by IgE, trigger up to 85 percent of asthma exacerbations in school-aged children and up to 50 percent of exacerbations in adults and may also contribute to asthma onset.

- Factors such as exercise, intense emotions and cold air, among others, can cause an exacerbation through a non-allergic pathway.

- Atopy, the genetic predisposition for developing an IgE-mediated response to common allergens, is the strongest identifiable predisposing factor for developing asthma.

Review of Evidence

- ACCV established “Guiding Principles for Recommending Changes to the Vaccine Injury Table” (Guiding Principles).
- These consist of two overarching principles:
  - The Table should be scientifically and medically credible; and
  - Where there is credible scientific and medical evidence both to support and/or to reject a proposed change (i.e., addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

Claims Can Be Filed for Injuries Not on the Vaccine Injury Table

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

Review of Evidence in Petition

To support the claim that asthma is caused by vaccines, the individual references a non peer-reviewed article that he wrote and published online, citing 15 references.

- Medical Muddles that Maim our Children with Allergies, Asthma and Autism

(https://www.researchgate.net/publication/313918596_Medical_muddles_that_maim_our_children_with_allergies_asthma_and_autism)

Review of Evidence in Petition

- The individual also provided an additional four articles, two of which he wrote and published online without peer review:

➢ Strong protein sequence alignment between autoantigens involved in maternal autoantibody related autism and vaccine antigens

(https://www.researchgate.net/profile/Vinu_Arumugham/publication/316785758_Strong_protein_sequence_alignment_between_autoantigens_involved_in_maternal_autoantibody_related_autism_and_vaccine_antigens/links/59115a620f7e9bfa06d43d5e/Strong-protein-sequence-alignment-between-autoantigens-involved-in-maternal-autoantibody-related-autism-and-vaccine-antigens.pdf?origin=publication_list)

Review of Evidence in Petition

- Significant protein sequence alignment between Saccharomyces Cerevisiae Proteins (a Vaccine Contaminant) and Systemic Lupus Erythematosus Associated Epitopes

(https://www.google.com/search?q=Significant+protein+sequence+alignment+between+Saccharomyces+Cerevisiae+Proteins+%28a+Vaccine+Contaminant%29+and+Systemic+Lupus+Erythematosus+Associated+Epitopes&ie=utf-8&oe=utf-8)

Review of Evidence in Petition

The other two articles are:

- Fox-Edmiston, E. and Judy Van de Water. Maternal anti-fetal brain IgG autoantibodies and autism spectrum disorders: current knowledge and its implications for potential therapeutics. CNS Drugs. 2015 Sep;29(9):715-724.

- Fresquet M., Jowitt T., Gummadova J. et al. Identification of a Major Epitope Recognized by PLA2R Autoantibodies in Primary membranous Nephropathy. J Am Soc Nephrol. 2015 Feb;26(2):302-13.

None of these four articles are related to asthma and, therefore, will not be discussed.

Petition to Add Asthma to VIT

In this individual's article, "Medical Muddles that Maim our Children with Allergies, Asthma and Autism," he asserts that vaccines cause allergy-induced asthma by at least 2 mechanisms.

- Individuals can develop IgE-mediated sensitization by injection of food proteins in vaccines, and then when they inhale the sensitized food particles they can suffer asthma symptoms.

- Individuals can also become sensitized to "pathogen associated vaccine antigens" via IgE. Upon inhalation of these particles, such as influenza viral particles, pertussis bacterial particles, etc., they will develop asthma symptoms.

Review of Evidence in Petition

He cites 15 articles to support his claim:

- References 1-6 discuss general immunology or examine food allergies and anaphylaxis rather than asthma.
- Reference 7 is written by the individual filing this claim. He theorizes that food proteins in vaccines cause food allergies. There is no discussion of asthma.
- Reference 8, by Nakayama et al., examines increased IgE antibodies and anaphylaxis after receipt of the 2011/12 split influenza vaccine which contained a certain preservative. They found high levels of IgE antibodies against influenza vaccine components. Asthma wasn't mentioned.

Review of Evidence in Petition

- In reference 9, Davidsson et al. discuss a study where they immunized mice with influenza vaccine and found an IgE response in the blood but without evidence of allergy. They concluded that the "study supports the view that influenza vaccination is a safe procedure and the involvement of IgE probably does not have a direct adverse effect … There may even be a beneficial role for IgE by initiating a rapid local inflammatory response quickly recruiting lymphocytes and by modulating the immune response." There was no mention of asthma.

Review of Evidence in Petition

- In reference 10, Ryan et al. found children had IgE anti pertussis antigens after immunization, but no generalized further increase in IgE to food or inhalant antigens to which they were already sensitive. There was no suggestion that IgE to food or bacterial antigens would be a trigger for asthma and the authors concluded that “modifications of vaccine formulation aimed at preventing IgE production do not seem warranted.”

Review of Evidence in Petition

- In reference 11, Holt et al. found increases in IgE in patients immunized with acellular pertussis containing vaccines to a greater degree than those immunized with whole cell pertussis containing vaccines. They suggested that the IgE antibody against those viruses could contribute to the respiratory symptoms during acute infection, but did not discuss a role for the development of chronic asthma.

- In reference 12, Smith-Morowitz et al. found persistence of IgE anti-influenza antibody for 2 years after immunization and concluded that their results “suggest that IgE is associated with anti-influenza immunity and their [sic] memory responses.”

Review of Evidence in Petition

- Reference 13 examines atopic dermatitis.

- Reference 14 is the 2012 Institute of Medicine report, Adverse Effects of Vaccines: Evidence and Causality.

- Reference 15, Kuno-Sakai et al,, evaluated whether gelatin in MMR vaccine was a cause of an acute allergic reaction. MMR, varicella and some influenza vaccines continue to contain hydrolyzed gelatin, but acute reactions are rare as is the incidence of gelatin allergy in the general population, suggesting that vaccines are not a likely cause of widespread allergy to gelatin. No evidence was provided that inhalation of gelatin causes asthma.

Summary of Petition

In summary, the individual's proposition that vaccine-induced IgE leads to asthma relies on a series of observations that are implied to be a cause of childhood asthma.

- No evidence that vaccination leads to IgE antibody against the most common causes of wheezing in childhood, namely respiratory syncytial virus and human rhinovirus.

- No evidence that individuals develop IgE sensitization by injection of food proteins in vaccines and that subsequent inhalation of these particles causes symptoms of asthma.

- No evidence that inhalation of vaccine antigens triggers asthma symptoms via an IgE mechanism.

Review of Evidence: IOM Report

The 2012 IOM report, “Adverse Effects of Vaccines: Evidence and Causality”, reviewed asthma exacerbation or reactive airway disease episodes in children and adults after inactivated influenza vaccine, and asthma exacerbation/reactive airway disease episodes in both children younger than 5 years of age and in persons 5 years of age or older after live attenuated influenza vaccine (LAIV). They concluded that:

- The evidence favors a rejection of a causal relationship between inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults (the IOM only favored rejection in 5 out of 158 causality conclusions).

Review of Evidence: IOM Report

- The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age.

- The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older.

Review of Evidence: IOM Report

- The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age.

- The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older.

IOM Asthma Summary

- The IOM did not evaluate evidence regarding a causal association between other vaccines and asthma.
- Aside from influenza vaccines, the IOM does not comment on the strength of the epidemiologic or mechanistic evidence regarding asthma and vaccination.
- Therefore, the IOM report does not support the petitioner's position for adding asthma to the Table with regards to influenza vaccine.

Review of Evidence: Expert Reviews

In 2007, the National Heart, Lung, and Blood Institute (NHLBI) published, "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma: *Clinical Practice Guidelines.* National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Bethesda (MD): 2007 Aug."

- Developed by a panel consisting of 18 experts from around the country, commissioned by the National Asthma Education and Prevention Program Coordinating Committee, coordinated by the NHLBI of the National Institutes of Health.
- Discusses development/causes of asthma in detail, but vaccines are not considered as a potential cause.

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Review of Evidence: Expert Reviews

Additional expert reviews on the etiology of asthma published in the literature do not mention vaccines as a risk factor or potential risk factor.

- Litonjua A. and S. Weiss. Risk Factors for Asthma. UptoDate. Last updated 4/29/2016.

- Guibas G. et al. Contributing factors to the development of childhood asthma: working toward risk minimization. Expert Rev Clin Immunol. 2015 Jun;11(6):721-35.

- Guibas G. et al. Relationship of Allergy with Asthma: There Are More Than the Allergy "Eggs" in the Asthma "Basket". Front Pediatr. 2017 Apr 28;5:92.

- Subbarao et al. Epidemiology of asthma: risk factors for development. Expert Rev Clin Immunol. 2009 Jan:5(1):77-95.

Review of Evidence: Additional Data

- VICP gathered additional data from evidence submitted in the petition and existing medical literature (studies on influenza vaccine were not evaluated as this was already done by the IOM).
- A literature search was conducted of the major medical databases for any articles linking vaccination and the development of asthma. VICP used studies published in 2000 or later.
- An extensive search identified numerous studies that directly or tangentially evaluated the development of asthma after vaccination. The overwhelming majority found no potential causality between vaccinations covered by the VICP and the development of asthma.
- VICP collaborated with the National Institutes of Health Library, Office of Research Services.

Review of Evidence: Additional Data

- The search did not identify any peer-reviewed articles that evaluated or discussed the possible role of food allergen contaminated vaccines or “pathogen associated vaccine antigens” in the development or exacerbation of asthma.
- Vaccines studied in the published articles include DPT, MMR, measles, OPV, Prevnar 13, HIB, and Hepatitis B.
- While most (15) studies found no association between vaccinations and asthma, a few actually found a protective effect.
- Three studies had mixed results, although 2 had possible confounding variables. One showed a decreased risk of asthma with delay of vaccination receipt.

Results of the numerous studies will be provided in chart format.

Review of Evidence: Articles Showing No Association between Vaccines and Asthma

Lead Author, Year	Patients/Vaccine(s)	Main results
Anderson, 2001	>400,000/DTwP, BCG, Measles; subjects from ISAAC (Int'l Study of Asthma and Allergies in Children)	Study found moderate negative association between DPT and measles vaccines and symptoms indicative of atopic disease
Wickens, 2001	Random selection of children with asthma (233) and without asthma (241); ages 7-9 from New Zealand/ISAAC	No association between polio or HepB vaccination and asthma; No statistically significant increase in risk in development of asthma for any vaccine when accounting for confounding variables.
Destefano, 2002	167,240 children enrolled in HMOs '91-'97, up to 6 year follow-up/multiple vaccines	No association between asthma and DTwP, OPV, MMR. Weak association between HIB and hepB partially accounted for by informational bias/healthcare utilization
Roost, 2004	1,537 children, 13-15 years of age; Switzerland/MMR	No association with RAD; inverse association between risk of asthma and measles vaccination
Maher, 2004	1,778 infants born into HMOs '91-'94/data from 0-18 months/multiple vaccines	HepB, DTwP, HIB, OPV, MMR not associated with asthma, even with combined or increase # of vaccines; age of vaccination didn't matter
Mommers, 2004	510 Dutch and German 7 to 8 year olds with symptoms and equal controls participating in long term study/multiple vaccines	Pertussis, MMR, and HIB vaccines weren't associated with respiratory symptoms or allergic sensitization (specific IgE levels)
Mullooly, 2006	1,074 6-16 year old new allergy clinic patients/multiple vaccines; non-atopic controls	Atopy (including asthma) not associated with number of vaccines, antigen doses, or number of different antigens in 1st 2 years of life

Review of Evidence: Articles Showing No Association between Vaccines and Asthma

Lead Author/Year	Patients/Vaccine(s)	Main results
Ballicer, 2007	186,663 comparing vaccinated vs unvaccinated with asthma status from publications 1966-3/2006 /BCG and DTwP vaccines	No association between BCG or DTwP and incidence of asthma during childhood or adolescence
Spycher, 2009	6,811 children born between 1993-1997/DTP	No increased risk of wheezing or asthma after DPT vaccines compared to non-vaccinated children ("eliminated bias from previous studies")
Mullooly, 2011	18,628 premature infants from Vaccine Safety Datalink (VSD)/multiple vaccines	No increased wheezing lower respiratory disease for any vaccine type among non-fragile or fragile premature infants. Live attenuated vaccines may have a temporary protective effect.
Mullooly, 2011	1,366 (case controlled study) infants born 1991-1994/multiple vaccines	DTwP, hepB, HIB, OPV, MMR not associated with wheezing in infancy
Nagel, 2012	54,943 randomly selected 8-12 year olds with 31,759 skin prick tested to common allergens; from 29 centers in 21 countries/ISAAC study, 1995-2005/pertussis and measles vaccines	Pertussis and measles vaccination were not significantly associated with any allergy outcomes or skin test positivity
Tseng, 2013	599,229 doses of Prevnar 13, VSD study; post-licensing; compared to Prevnar 7	No signals for wheezing at any age or vaccine dose
Timmermann, 2015	640 children followed from birth in Faroe Islands, ages birth-13 years/MMR vaccine	Early MMR resulted in 2/3 decrease of asthma and hypersensitivity at age 5 and 13; serum total IgE was decreased in vaccinated children by 62%
DeMicheli, 2012	14,700,000; evaluated all online studies in children up to 15 years of age/MMR vaccine	No association between MMR vaccine and wheezing or asthma

Review of Evidence: Articles Showing Mixed (Mostly Negative) Results between Vaccines and Asthma

Lead Author, Year	Patients/Vaccine(s)	Main results
Laubereau, 2000	1,943 children ages 4-14 years in '98-'99; Parental/doctor reporting and IgE testing/HIB in 1676 children	HIB-vaccinated children had a slightly higher risk for asthma, wheezing, hay fever and sensitization but only significant for asthma. *Authors state "results have to be interpreted with caution. Biological evidence to support a causal association is not available." They pose questions of validity of parental reports, recall bias, self selected group who did/did not get vaccinated, age and atopic outcomes.*
Benke, 2004	3,200 22-44 year olds in Australia	No difference in DTP, HepB, measles MMR, and OPV except those who had all vaccines (MMR, OPV and DTP) had an increased risk of asthma. *Authors state "relatively weak support … vaccinations may lead to increased risk of asthma, but caution is advised due to possible recall bias." They later write that typically studies of young adults who self report vaccination histories may be subject to significant recall bias. In this study, childhood vaccination was based entirely on subject recall. Also, as noted by the authors, associations for atopy and vaccinations appeared consistently weak for all vaccines investigated, which is important since atopic asthma would need a strong association with atopy.*
Thomson, 2010	610 infants up to age 6 years at increased risk of asthma due to 1st degree relatives with allergic diseases (488 infants by age 6 years due to loss to follow-up). Less than 5% or 30 subjects received at least 1 DT vaccine)	OPV and MMR vaccines decreased risk of asthma at age 2 years; OPV decreased risk of asthma at age 6; DT in 1st year increased asthma at 6 years. *Some problems include: 21% were lost to follow-up (self-selected group?), DT was only given to children with a previous reaction to DPT vaccine (maximum of 30 subjects) questioning whether this was an at-risk group and noting the small sample size, and there was no control group.*

Review of Evidence

One study demonstrated an association between timing of DPT receipt and risk of asthma, although it did not compare this to an unvaccinated group.

Lead author, year	Patients/Vaccine(s)	Main results
McDonald, 2008	11,531 children born in Manitoba in 1995 receiving 4+ DPT doses – looked at timing of vaccine receipt/DTP – mostly whole cell (Chart review)	Association between timing of DPT and RAD; delaying of 1st dose by > 2 months decreased risk of asthma by 50%. *One potential confounding factor is the fact that the reason for the delay in immunization was unknown and this group may have been self-selected. Per the authors, asthma may be less prevalent in unvaccinated children with a low frequency of physician visits, families who consult their doctor less frequently may be late in receiving vaccines and not come in for asthma symptoms, those who come in late may be from larger families which protects against asthma, etc.*

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- Roost H. et al. Influence of MMR-vaccinations and diseases on atopic sensitization and allergic symptoms in Swiss schoolchildren. Pediatr Allergy Immunol.. 2004 Oct;15(5):401-7.

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Review of Evidence

- ACCV established “Guiding Principles for Recommending Changes to the Vaccine Injury Table” (Guiding Principles).
- These consist of two overarching principles:
  - The Table should be scientifically and medically credible; and
  - Where there is credible scientific and medical evidence both to support and/or to reject a proposed change (i.e., addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

Options

Option 1: Add asthma as an injury to the Vaccine Injury Table.

Option 2: Do not add asthma as an injury to Vaccine Injury Table.

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

Contact Information

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Petition

From:	Vinu Arumugham
To:	Nair, Narayan (HRSA); Advisory Committee on Immunization Practices (CDC); nipinfo@cdc.gov; feemster@email.chop.edu; michelle.williams@alston.com; aljjp@aol.com; jason.smith@pfizer.com; opus@taospeds.org; louiedrosa@gmail.com; ekraus@kentlaw.edu; bgellin@osophs.dhhs.gov; ch25v@nih.gov; marion.gruber@hda.hhs.gov; tshimabukuro@cdc.gov; Houston, Avril (HRSA); Herzog, Andrea (HRSA); Davey, Andrea (HHS/OGC); Overby, Tamara (HRSA); Vaccine Compensation; feemster@email.chop.edu; aljjp@aol.com; dking@salesmotion.com; louiedrosa@gmail.com; opus@taospeds.org; jason.smith@pfizer.com; michelle.williams@alston.com; ekraus@kentlaw.edu; CBER OCOD Consumer Account; cdphe.information@state.co.us; Trefren - CDPHE, Lynnsay; cdphe DCEEDRequests - CDPHE; Karen.Smith@cdph.ca.gov; IZBranch; kathleen.harriman@cdph.ca.gov; jennifer.zipprich@cdph.ca.gov; Fauci, Anthony (NIH/NIAID) [E]; tfrieden2@cdc.gov; anne.schuchat@cdc.hhs.gov; Rotrosen, Daniel (NIH/NIAID) [E]; Secretary@HHS.gov
Cc:	Gina@
Subject:	Please add food allergy, asthma and autism to the vaccine injury table
Date:	Monday, April 03, 2017 11:36:24 PM

Secretary Price,

The new vaccine injury table lists anaphylaxis as an injury for nearly every vaccine.
Anyone with basic knowledge of immunology taught to every doctor in medical school, knows that anaphylaxis occurs after the SECOND injection of allergens. The first injection is asymptomatic and causes the development of allergy (sensitization), in a few weeks time. So any vaccine that can cause anaphylaxis can also cause the development of allergies. The Institute of Medicine (IOM) has made it absolutely clear in its report on vaccine adverse events, that allergens in vaccines cause SENSITIZATION AND SUBSEQUENTLY, ANAPHYLAXIS. Yet, HRSA doctors and scientists continue to ignore the scientific evidence and have refused to add allergies to the vaccine injury table.

I request that food allergies, asthma and autism be added to the vaccine injury table.

My article below with numerous peer-reviewed published scientific references shows the evidence of food allergen contaminated vaccines causing food allergies, asthma and autism.

Medical muddles that maim our children with allergies, asthma and autism

https://www.researchgate.net/publication/313918596_Medical_muddles_that_maim_our_children_with_allergies_asthma_and_autism

Thanks,
Vinu

5.6

The National Vaccine Injury Compensation Program (VICP)

Discussion of Petitions to Add PANS/PITAND/PANDAS to the Vaccine Injury Table

December 8, 2017

Mark Ditmar, MD
Medical Officer, Division of Injury Compensation Programs (DICP)
Healthcare Systems Bureau (HSB)
Health Resources and Services Administration (HRSA)

HRSA Healthcare Systems

Overview

- Discuss petitions requesting that PANS/PITAND/PANDAS be added to the Vaccine Injury Table (Table)
- Background on PANS/PITAND/PANDAS
- Review medical evidence regarding vaccines and PANS/PITAND/PANDAS

ACCV Guiding Principles

- The Table should be scientifically and medically credible; and

- Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

Claims Can Be Filed for Injuries Not on the Vaccine Injury Table

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

Background: Petition

- **On February 20, 2017 and March 20, 2017, a private citizen submitted written petitions to HHS requesting that PANS and/or PITAND and/or PANDAS be added to the Table.**
  - The petitions assert that components of pertussis present in vaccines cause the development of PANS and/or PITAND and that components of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) present in vaccines cause or enable the development of PANS and/or PANDAS.

Background: Definitions

- **PANS: P**ediatric **A**utoimmune and **N**europsychiatric **S**yndrome
- **PITAND: P**ediatric **I**nfection-**T**riggered **A**utoimmune **N**europsychiatric **D**isorder
- **PANDAS: P**ediatric **A**utoimmune **N**europsychiatric **D**isorder **A**ssociated with group A **S**treptococcus
- **Concept:** an immune basis may underlie and may trigger disorders associated with movement abnormalities (neuro) and behavioral abnormalities (psychiatric).
- **Hypothesis:** "neuropsychiatric syndromes may result from various etiologies, including hereditary, environmental and inflammatory causes".

  Ref: Williams KA, Swedo SE (2015). "Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond." *Brain Res* 1617 (Aug 18), 145.

Background: Acute Rheumatic Fever

- Historical Model: Acute rheumatic fever (ARF)
- Sequelae of group A streptococcal (GAS) infections
- *Concept:* Immune activation by GAS antigens→antibodies

  Heart → Carditis

  Joints → Arthritis

  Skin → Erythema marginatum (characteristic rash)

  Brain → Sydenham chorea (involuntary movements)
- Psychiatric co-morbidities are reported in increased frequency in ARF, including obsessive-compulsive disorder (OCD)
- Theory: antibodies against GAS cross-react with brain antigens by molecular mimicry resulting in autoantibody-mediated neuronal cell signaling in susceptible hosts

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Background: PITAND

Allen AJ, Leonard HL, Swedo SE. (1995). "Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome". *J Am Acad Child Adolesc Psychiatry* 34(3): 307-311

- Hypothesized→ process similar to chorea in ARF; infections with group A strep and others→ may trigger autoimmune responses→ cause or exacerbate childhood-onset OCD or tic disorder (including Tourette syndrome)
- 4 cases: 2 GAS, 2 viral→ treated with plasmapheresis, IVIG or prednisone→ improved "immediately"
- Coined the term "**PITAND"**

Background: PANDAS

Swedo SE, Leonard HL, et al. (1998). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 155(2): 264-271.

- Described 50 patients with similar features:
  - *1) Presence of OCD or tic disorder*
  - *2) Prepubertal symptom onset*
  - *3) Acute symptom onset and episodic (relapsing-remitting course)*
  - *4) Temporal association between group A strep infection and symptom onset/exacerbation*
  - *5) Associated with neurologic abnormalities (particularly hyperactivity and choreiform movements)*
- Coined the term **"PANDAS"**

Background: PANS

Swedo SE, Leckman JF, Rose NR (2012). "From research subgroup to clinic syndrome: modifying the PANDAS criteria to describe PANS." *Pediatr Therapeut* 2:113. doi:10.4172/2161-0065.100113.

- Expanded PANDAS to a broader **"PANS"** category
- Authors listed problems with a PANDAS diagnosis
  1) "impediments to establishing GAS as the etiologic agent in PANDAS"
  2) "lack of clear separation between PANDAS cases and non-PANDAS cases"
  3) Desire to improve effort "to determine which microorganisms produce sequelae that include acute-onset neuropsychiatric symptoms and to investigate the variety of etiologies and pathogenic mechanisms"

Background: PANS Criteria

Swedo SE, Leckman JF, Rose NR (2012). *Pediatr Therapeut* 2:113. doi:10.4172/2161-0065.100113.

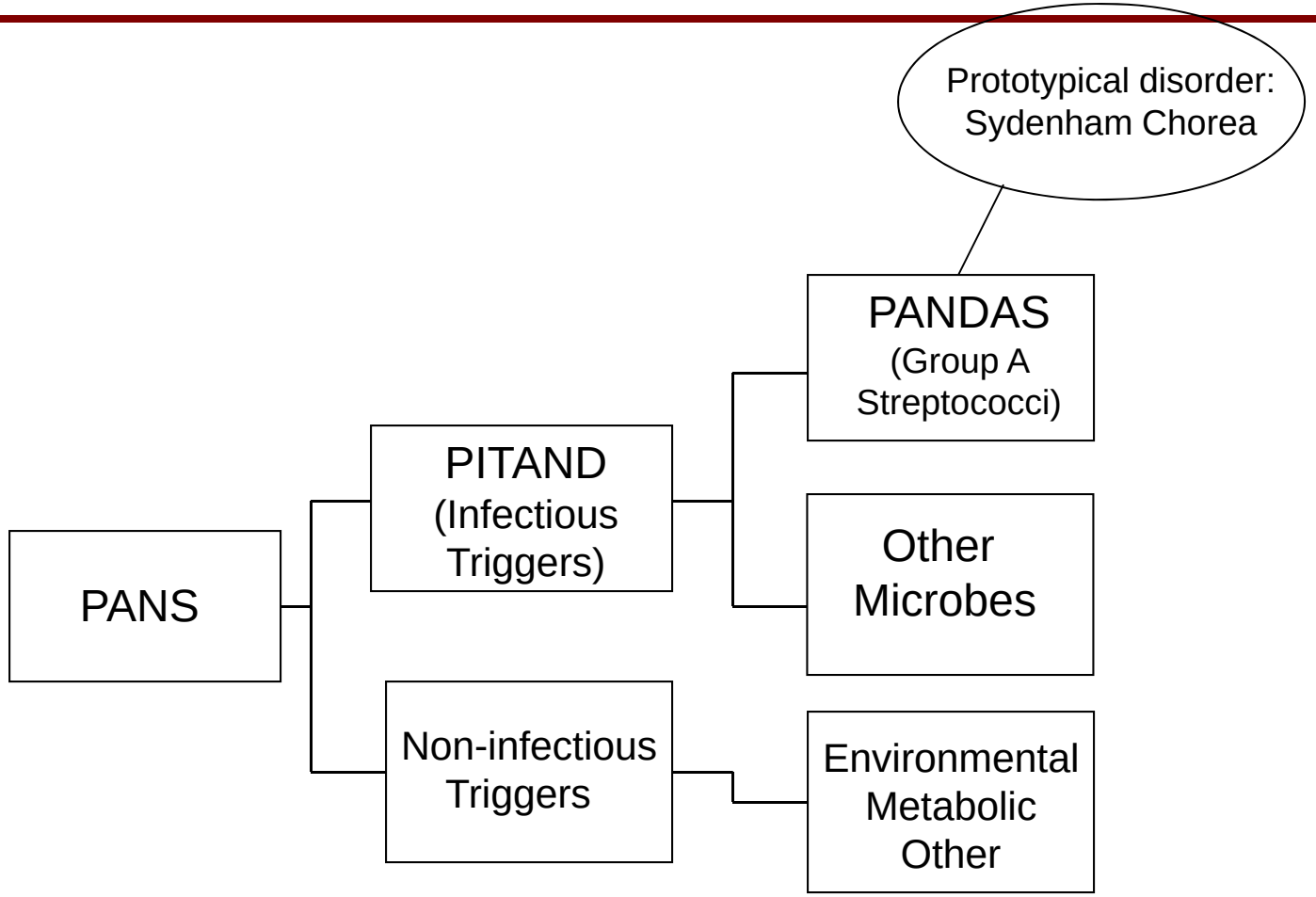
PANS Criteria:

- Abrupt onset of symptoms of OCD or food restriction (anorexia) plus 2 of the following:

  -anxiety, emotional lability and/or depression, irritability, aggression and/or severely oppositional behaviors, behavioral (developmental) regression, deterioration in school performance, sensory or motor abnormalities, somatic signs and symptoms (e.g., sleep disturbances, enuresis, urinary frequency)

- Symptoms not better explained by a known neurologic or medical disorder

Background: Theoretic Framework



Adapted from Swedo SE, et al. (2012): From research group to clinical syndrome: Modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). *Pediatr Therapeut* 2:113. doi:10.4172/2161-0665.100113.

Review of Evidence - Pertussis

- To support the claim that PANS and/or PITAND are caused by pertussis-containing vaccines, the petition outlines a mechanism of molecular mimicry and autoantibody-mediated neuronal cell-signaling as follows:

Vaccination with pertussis toxin →

MOG/Tubulin molecular mimicry →*

*Activation of CaMK II** →*

Neuronal excitation →

Symptoms characteristic of PANS/PITAND

*myelin oligodendrocyte glycoprotein [a CNS protein]

**calcium/calmodulin-dependent protein kinase II [a CNS enzyme]

Review of Evidence – Pneumococcal/Hib vaccines

- To support the claim that PANS and/or PANDAS are caused or enabled by pneumococcal and Hib vaccines, the petition outlines a mechanism of injury as follows:

  Vaccination with pneumococcal/Hib vaccines →

  Results in disruption of the blood-brain barrier in susceptible child which allows circulating GAS antibodies to enter CNS →

  Results in a cross-reactivity between GAS antibodies and CNS structures →

  Results in symptoms of PANS/PANDAS

ACCV Guiding Principles

- ACCV established "Guiding Principles for Recommending Changes to the Vaccine Injury Table" (Guiding Principles).
- These consist of two overarching principles:
  - The Table should be scientifically and medically credible; and
  - Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

Claims Can Be Filed for Injuries Not on the Vaccine Injury Table

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

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Review of Evidence – IOM Report

The 2012 IOM Report did not review:

- any possible association between pertussis-containing vaccines or any vaccine and PANS and/or PITAND.
- any possible association between pneumococcal conjugate vaccines and *Haemophilus influenzae* type b (Hib) vaccines or any vaccine and PANS and/or PANDAS.

Review of Evidence

- DICP gathered data from the existing medical literature in addition to the evidence submitted in the petition.
- A literature search was conducted of the major medical databases searching for any articles linking the development of PANS and/or PITAND and/or PANDAS to vaccinations, including pertussis-component vaccine, pneumococcal conjugate vaccines and Hib vaccines.
  - Collaboration with the National Institutes of Health Library, Office of Research Services
- Despite an extensive search, no published research was found that addressed any linkages or potential causality or enablement between vaccinations covered by the VICP, including pertussis-containing, pneumococcal conjugate and Hib vaccinations, and the development of PANS and/or PITAND and/or PANDAS in any population.

Submitted Petitions Prompt the Following Questions – I

1. Is PANS and/or PITAND and/or PANDAS mechanistically established as an autoimmune process via molecular mimicry and autoantibody-mediated neuronal cell signaling?
2. Is PANS and/or PANDAS mechanistically established as a result of blood-brain barrier disruption which allows an influx of GAS antibodies with a subsequent autoimmune process via molecular mimicry and autoantibody-mediated neuronal cell signaling in a susceptible individual?
3. Do pertussis-containing vaccines or pertussis infections generate antibodies that could result in acute neuropsychiatric symptoms via a mechanism of molecular mimicry and autoantibody-mediated neuronal cell signaling?
4. Do pneumococcal vaccines or pneumococcal infections and Hib vaccines or Hib infections cause or enable the development of acute neuropsychiatric symptoms via a mechanism of blood-brain barrier disruption with GAS antibody-mediated neuronal cell signaling in a susceptible individual?

Submitted Petitions Prompt the Following Questions – II

5. Does natural pertussis infection trigger PANS and/or PITAND?
6. Do pertussis-containing vaccines trigger PANS and/or PITAND?
7. Does natural pneumococcal infection or Hib infection trigger PANS and/or PANDAS?
8. Do conjugate pneumococcal vaccines and Hib vaccines trigger PANS and/or PANDAS?
9. Are PANS and/or PITAND and/or PANDAS generally accepted as independent disease entities?

Review of Evidence – Question 1

Question 1. Is PANS and/or PITAND and/or PANDAS mechanistically established as an autoimmune process via molecular mimicry and autoantibody-mediated neuronal cell-signaling?

- There are no published data on PANS and PITAND regarding possible specific infectious or non-infectious triggers and autoimmune mechanisms. Data on the more well-studied PANDAS are unclear and conflicting.
- "The PANDAS hypothesis remains controversial, and most prior studies are small and have methodological shortcomings. Furthermore, not all studies confirmed the findings of autoantibodies against the basal ganglia in children with PANDAS, and several other studies did not support the PANDAS hypothesis."

  Ref: Orlovska S, Vestergaard CH, et al. (2017). "Association of streptococcal throat infection with mental disorders: Testing key aspects of the PANDAS hypothesis in a nationwide study." *JAMA Psychiatry* 74(7): 741.

Review of Evidence: Question 1 (continued)

Question 1. Is PANS and/or PITAND and/or PANDAS mechanistically established as an autoimmune process via molecular mimicry and autoantibody-mediated neuronal cell-signaling?

- Theory is based heavily on **proposed diagnostic biomarkers**: autoantibodies to dopamine receptors D1 and D2, β-tubulin, lysoganglioside-GM1 (lyso-GM1)and calcium modulin dependent kinase II activity (CaMKII-activity)
- Available commercially "as an aid to the physician in their diagnosis of PANDAS or PAN" as the Cunningham Panel at Moleculera Labs in Oklahoma City. [www.moleculeralabs.com. Accessed on 09/30/2017.]
- Diagnostic accuracy of these potential biomarkers has been unclear.

Review of Evidence: Question 1 (continued)

Hesselmark E, Bejerot S, (2017). "Biomarkers for diagnosis of Pediatric Acute Neuropsychiatric Syndrome (PANS) – Sensitivity and specificity of the Cunningham Panel." *J Neuroimmunol* 312:31-37, 2017.

- Assessed diagnostic accuracy of the Cunningham Panel in patients with suspected PANS or PANDAS
- 154 patients with previous panel results; 53 participated in the study with old and new panel results and classified based on comprehensive psychiatric assessment; 21 healthy patients served as controls.
- Sensitivity: 15-60%; Specificity: 28-92%; Positive predictive value: 17-40%
- "A majority of the healthy controls had pathological Cunningham Panel Results"
- **Conclusion**: Use of the Cunningham Panel in diagnosing PANS or PANDAS is not supported by this study.

Review of Evidence: Question 1 (continued)

- Multiple prospective studies have found no relationship between symptom exacerbation and changes in biomarker levels.

  Morris-Berry CM, Pollard M, et al, (2013). "Anti-streptococcal, tubulin, and dopamine receptor 2 antibodies in children with pandas and tourette syndrome: single-point and longitudinal assessment. *J Neuroimmunol* 264, 106-113.

  Singer HS, Gause C, et al, (2008). "Serial immune markers do not correlate with clinical exacerbations in pediatric auto-immune neuropsychiatric disorders associated with streptococcal infections". *Pediatrics* 121, 1198-1205.

Review of Evidence: Question 1 (continued)

- "It should be noted that no specific autoimmune antibody is agreed upon as a pathogenic mechanism for SC [Sydenham chorea] or PANDAS symptomology, and that multiple studies have failed to find differences between PANDAS serum and control serum in autoimmune antibody binding to neuronal proteins. Further research is needed to address these discrepancies."

  Ref: Williams KA, Swedo SE. (2015). "Post-infectious autoimmune disorders: Sydenham's chorea, PANDAS and beyond." *Brain Res* 1617 (Aug 18), 145.

Review of Evidence: Question 1 (continued)

Williams KA, Swedo SE, et al. (2016). "Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections." *J Am Acad Child Adolesc Psychiatry 55* (10): 860-867.

- -35 children with criteria for PANDAS and moderate to severe OCD
- -Given IVIG or placebo with follow-up at 12 to 24 weeks
- *Results*: "Double-blind comparison failed to demonstrate superiority of IVIG over placebo."
- The study called into question proposed immune mechanisms and value of immunomodulatory therapy.

Review of Evidence: Question 2

Question 2: Is PANS and/or PANDAS mechanistically established as a result of blood-brain barrier disruption which allows an influx of GAS antibodies with a subsequent autoimmune process via molecular mimicry and autoantibody-mediated neuronal cell-signaling?

- After an extensive literature search, we were unable to locate any published study that has examined this relationship.
- "An association between GAS infection and sudden onset of obsessive-compulsive behaviors, prepubertal anorexia nervosa, or tic disorders—pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), also known as pediatric acute-onset neuropsychiatric syndrome (PANS)—has been proposed, but **carefully performed prospective studies have not shown that there is a specific relationship between these disorders and GAS infections."**

Ref: American Academy of Pediatrics. Group A Streptococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015, p 732.

Review of Evidence: Question 3

Question 3: Do pertussis-containing vaccines or does pertussis infection generate antibodies that could result in acute neuropsychiatric symptoms via a mechanism of molecular mimicry and auto-antibody neuronal cell signaling?

- After an extensive literature search, we were unable to locate any published study that examines anti-neuronal antibodies including anti-dopamine receptor 1 (DR1), anti-dopamine receptor 2 (DR2), anti-tubulin, anti-lysoganglioside –GM1 or antibody-mediated activation of calcium calmodulin dependent protein kinase II (CaMKII) in children suspected of PANS and/or PITAND following pertussis infection or following pertussis immunization.

Review of Evidence: Question 4

Question 4: Do conjugate pneumococcal vaccines or pneumococcal infections and Hib vaccines or Hib infections cause or enable the development of acute neuropsychiatric symptoms via a mechanism of blood-brain barrier disruption with GAS antibody-mediated CNS cross-reaction in a susceptible child?

- After an extensive literature search, we were unable to locate any published study that has examined this relationship.
- Again, per the AAP *Red Book*, 30th edition (2015), "**carefully performed prospective studies have not shown that there is a specific relationship between these disorders [PANS, PANDAS] and GAS infections.**"

Review of Evidence: Question 5

Question 5: Does natural pertussis infection trigger PANS and/or PITAND and/or PANDAS?

- "Infections are postulated to be a trigger for PANS. Except for GAS [group A strep], no infections have been definitively linked to PANS".

  Ref: Frankovich J, Thienemann M, et al. (2015). "Multidisciplinary clinic dedicated to treating youth with pediatric acute-onset neuropsychiatric syndrome: presenting characteristics of the first 47 patients." *J Child Adolesc Psychopharmacol* 25(1): 44.

- After an extensive literature search, we were unable to locate any published case report of PANS and/or PITAND and/or PANDAS during or following pertussis infection.

Review of Evidence – Question 5 (continued)

- "Although many parents report a possible association between infections and onset or flare of psychiatric symptoms, it is difficult to know if these infections are coincidental or are in the causal pathway."
- "Well-designed prospective studies are needed to better explore connections between infections and psychiatric deterioration."

Ref: Frankovich J, Thienemann M, et al. (2015). "Multidisciplinary clinic dedicated to treating youth with pediatric acute-onset neuropsychiatric syndrome: presenting characteristics of the first 47 patients." *J Child Adolesc Psychopharmacol* 25(1): 44.

Review of Evidence: Question 6

Question 6: Do pertussis-containing vaccines trigger PANS, PITAND and/or PANDAS?

- After an extensive literature search, we were unable to locate any published case report of PANS and/or PITAND and/or PANDAS following pertussis vaccination.

Review of Evidence: Question 7

Question 7: Does natural pneumococcal infection or Hib infection trigger PANS, PITAND and/or PANDAS?

- After an extensive literature search, we were unable to locate any published case report of PANS and/or PITAND and/or PANDAS during or following pneumococcal or *Haemophilus influenzae* type b infection.

Review of Evidence: Question 8

Question 8: Do pneumococcal conjugate vaccines and Hib vaccines trigger PANS, PITAND and/or PANDAS?

- After an extensive literature search, we were unable to locate any published case report of PANS and/or PITAND and/or PANDAS following either pneumococcal conjugate vaccination or *Haemophilus influenzae* type b vaccination.

Review of Evidence: Question 9

Question 9: Are PANS and/or PITAND and/or PANDAS generally accepted as independent disease entities?

- Neither PITAND or PANS or PANDAS has been validated as an officially-recognized disease entity.
- There are no diagnostic codes for any of the three in either:

  a) International Statistical Classification of Diseases and Related Health Problems (ICD-10, most recent revision, 2010); or

  b) Diagnostic and Statistical Manual of Mental Disorders (DSM-V; most recent revision, 2013)

Review of Evidence – Question 9 (continued)

- In the paper (2012) proposing PANS criteria, the authors wrote:

  "Research investigations are required to evaluate the validity, reliability and utility of the draft criteria, as well as to evaluate potential etiologic factors and mechanisms of disease that might be common to the disorders subsumed under the PANS clinical description."

  "To achieve those objectives, a number of immediate and longer term research studies are required."

  Ref: **Swedo SE, Leckman JF, Rose NR. (2012). "From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)." *Pediatr Therapeut* 2:113. doi:10.4172/2161-0665.100113.**

- PANS, PITAND and PANDAS remain investigational diagnoses.

Review of Evidence – Question 9 (continued)

- The more well-studied PANDAS concept remains controversial as a diagnosis.
- "Despite the specificity in concept, the existence of PANDAS has been difficult to prove. Whether PANDAS is indeed a specific clinical entity, whether it is rare or more common, and whether the symptoms can be treated or prevented with antimicrobial or immunomodulatory therapy continue to be investigated."
- ***Ref*: Mink JW. (2016). "Intravenous immunoglobulin is not an effective treatment for pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection obsessive-compulsive disorder." *J Am Acad Child Adolesc Psychiatry* 55(10): 837.**

Review of Evidence: Summary

- There is some theoretic basis for an acute onset of neuropsychiatric symptoms via a mechanism of autoimmunity and molecular mimicry with this theory based primarily on research involving group A streptococcal bacteria and acute rheumatic fever.
- This theory, particularly applied to other clinical settings, remains debated and speculative, is currently subject to continued research, has not been applied to other microbes and should be considered investigational and preliminary.
- We could find no published evidence that natural pertussis infection triggers PANS and/or PITAND.
- We could find no published evidence that pertussis-containing vaccines trigger PANS and/or PITAND.

Review of Evidence: Summary (continued)

- We could find no published evidence that natural pneumococcal infection and/or natural *Haemophilus influenzae* type b infection trigger or enable the development of PANS and/or PANDAS.
- We could find no published evidence that pneumococcal conjugate vaccines and *Haemophilus influenzae* type b (Hib) vaccines trigger or enable the development of PANS and/or PANDAS.
- The diagnoses of PANS and/or PITAND and/or PANDAS are controversial and none is generally accepted currently as an independent disease entity.

ACCV Guiding Principles

- ACCV established "Guiding Principles for Recommending Changes to the Vaccine Injury Table" (Guiding Principles).
- These consist of two overarching principles:
  - The Table should be scientifically and medically credible; and
  - Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

ACCV Recommendation Options: Petition 1

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

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

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

ACCV Recommendation Options: Petition 2

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

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

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

Contact Information

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Petition

Janet Ferguson, Ph.D.
122 Forked Pine Ct.
Chapel Hill, NC 27517

Secretary Thomas Price, M.D.
The U.S. Department of Health & Human Services

Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Price,

I am writing to exercise my right as a United States citizen to petition for the addition of the injury of pediatric infection-triggered, autoimmune, neuropsychiatric disorders (PITANDS) and/or Pediatric Autoimmune and Neuropsychiatric Syndrome (PANS) to the 42 U.S. Code § 300aa–14 - Vaccine Injury Table following administration of Pertussis containing vaccines. I also petition for the addition of Experimental Autoimmune Encephalomyelitis, a separate but related disorder, and provide a scientific review in support of my petition.

In the case of PITANDS/PANS, the fimbriae in the Pertussis portion of the DTaP vaccine is a molecular mimic of myelin oligodendrocyte glycoprotein (MOG). Tubulin, found in large concentrations in the brain, are made of MOG. In some, the immune system mistakenly attacks MOG (tubulin), identifying it as Pertussis, resulting in a cluster of symptoms identified as PITANDS/PANS. In this disorder, laboratory findings document anti-tubulin antibodies using enzyme-linked immunosorbent assay (ELISA). Coincident elevation of CaM Kinase II is typical and indicative of an autoimmune attack on the neuronal tissues found specifically in the brain. Activation of CaMK II leads to neuronal excitation. An MRI may, or may not, reveal evidence of the disorder.

While this mechanism is closely related to encephalopathy or encephalitis, the Vaccine Injury Table associated timeframe does not align with the science surrounding PITANDS/PANS, which can manifest suddenly and strongly or slowly over the course of weeks or even several months, pointing to a unique condition with symptoms that can range from suddenly alarming to slowly insidious.

An examination of the Vaccine Adverse Event Reporting System reveals that these two disorders are not within the query menu of the CDC's Vaccine Adverse Event Reporting System (VAERS) through the Wonder menus, however a query of the past decade of VAERS reports reveals at least a dozen descriptions of adverse reactions by children following DTaP administration that meet the criteria defined in the literature.

Experimental Autoimmune Encephalomyelitis, sometimes called Acute Disseminated Encephalomyelitis, is a similar but separate disorder that can be triggered by Pertussis containing vaccines. On January 19, 2017, the Secretary at the time clarified that this disorder and excluded it from the Injury Table because it involves demyelination. With this petition I am requesting that the Secretary list Experimental Autoimmune Encephalomyelitis as an adverse event following Pertussis vaccination because it is a

widely recognized disorder routinely initiated in laboratories using Pertussis vaccine, is documented to have occurred with pertussis vaccination in a case-control study, and a review of the VAERS database reveals seven reports within the last decade, six of which are children.

In Pertussis triggered Experimental Autoimmune Encephalomyelitis, the combination of Pertussis vaccine and amyloid beta open the blood brain barrier allowing entry of anti-MOG antibodies resulting in monophasic inflammatory disease with sparse perivenous demyelination. Unlike PITANDS/PANS, MRI findings in this disorder show evidence of acute demyelination.

The following literature review outlines the mechanistic science behind the initiation of PITANDS/PANS and Experimental Autoimmune Encephalomyelitis, detailing their connection to the Pertussis vaccine and the mechanisms involved. This review should enable you to distinguish the difference between each and establish appropriate timing for the Vaccine Injury Table.

It is in the interest of the citizens of the United States that each of these disorders are added to the table with appropriate timing to ease the extremely disproportionate burden and costs a few bear so that the public can benefit from vaccination. With prompt identification and treatment, the disabling symptoms of PITANDS/PANS and Experimental Autoimmune Encephalomyelitis can be prevented or even reversed. Inclusion in the Vaccine Injury Compensation Program table will increase awareness of these adverse events within the medical community, and reduce litigation costs to the National Vaccine Injury Compensation Program.

Unfortunately PITAND/PANS associated with Pertussis containing vaccines was not considered in the 2012 report *Adverse Effects of Vaccines: Evidence and Causality* making that effort useless in providing guidance to the Advisory Committee on Childhood Vaccines concerning this disorder. Additionally, the review of ADEM (aka Experimental Autoimmune Encephalomyelitis) only looked at five articles associated with DTaP, is less than half of a page, failed to explore the publications provided in this petition, and was inadequate to make a credible determination of its appropriateness for inclusion in the Vaccine Injury Table for Pertussis containing vaccines. In all, the report writers missed an entire body of work that has received funding by HHS in the National Institute of Mental Health for more than a decade, and missed almost sixty peer-reviewed publications concerning these.

It is my belief that the science surrounding PITANDS/PANS and Experimental Autoimmune Encephalomyelitis supports a causal relationship. The 2012 IOM Report, on pages 17-18 explains that strong mechanistic evidence "always carries sufficient weight for the committee to conclude the evidence convincingly supports a causal relationship. . . In 2006, the Advisory Committee on Childhood Vaccines (ACCV) established "Guiding Principles for Recommending Changes to the Vaccine Injury Table" (Guiding Principles) to assist the ACCV in evaluating proposed Table revisions and determining whether to recommend changes to the Table to the Secretary. The Guiding Principles consist of two overarching principles: (1) The Table should be scientifically and medically credible; and (2) where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners. The attached literature review shows there is credible scientific and medical evidence to support a causal relationship

between pertussis containing vaccines and PITANDS/PANS and Experimental Autoimmune Encephalomyelitis and I am requesting that the Vaccine Injury Table be changed to include these disorders with timing consistent with the literature provided in the attached review.

While it is customary to request the opinion of Advisory Committees in regards to Vaccine Injury Table amendment requests, such a review is not required for the Secretary to take the requested regulatory action. It is also customary for amendment to the Table to take effect for petitions submitted to the National Vaccine Injury Compensation Program after the rulemaking, however due to the disservice done to the American people by the 2012 report published by HHS under a prior Secretary entitled *Adverse Effects of Vaccines: Evidence and Causality*, I ask that the rulemaking apply to petitions received from January 1, 2012 to present. I also ask that when notification of receipt of my petition is posted in the Federal Register, please do so in its entirety, including this letter and the complete literature review, 22 pages in total.

Thank you,
Janet Ferguson, Ph.D.

2/20/17

Carolyn M. Robertson Long
Notary Public
Durham County
North Carolina
My Commission Expires 8-17-2019

Literature Review

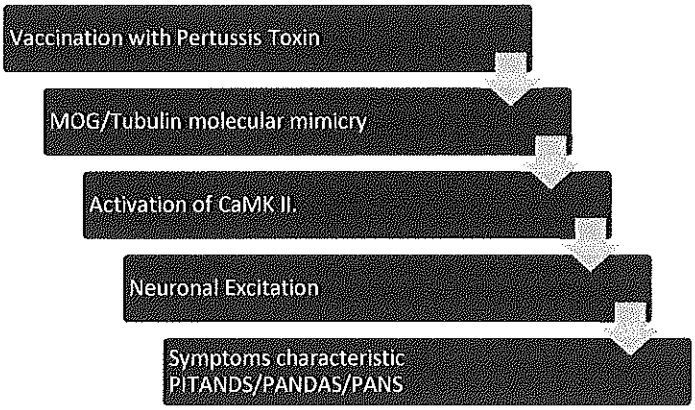
Immunity and Autoimmunity

The establishment of immunity in vaccines

An antigen is a triggering substance in vaccinations. The antigen activates Lymphocytes B-cells and T-cells to divide and secrete compounds. B-cells make and secrete antibody. Some T-cells secrete cytokines, some T-cells seek out and kill target cells on contact. The cell surface receptors on B-cells and T-cells are highly specific in terms of what they bind to, or recognize . The B-cell receptor (BCR) is called an antibody. The T-cell receptor is usually abbreviated as the TCR. A more general or non-specific set of cell surface receptors called major histocompatibility complex (MHC) molecules are found on the surface of antigen presenting cells. The B-cell or the T-cell receptor latches onto a small part or epitope of the antigen molecule. Triggering cells to divide and proliferate. Clones of cells arise from each cell that initially interacted with antigen. Some of these cells will be effector cells that secrete substances, B-cells secrete antibody, and T-cells secrete cytokines (TH cells) and perforin (TC cells). Some of the cells will be memory cells. The cell surface receptors on B-cells and T-cells are highly specific in terms of what they bind or recognize. The B-cell receptor (BCR) is called an antibody. The T-cell receptor is usually abbreviated as the TCR. A more general or non-specific set of cell surface receptors called major histocompatibility complex (MHC) molecules are found on the surface of antigen presenting cells. A repertoire of lymphocytes with a myriad of specificities exists before antigen ever enters the system. When and how antigen encounters the system is important under certain circumstances it may actually turn off the response. This is called tolerance. In general, a bodies' immune system is tolerant of its self-antigens (or its own cells), if this property disintegrates, autoimmunity results. (Berestecky 2016)

Mechanisms of Autoimmunity in PITANDS/PANS

The following flow chart illustrates the mechanism through which PITANDS/PANS can be triggered by vaccination with the DTaP vaccine.



Cunningham, 2009, describes molecular mimicry as structural, functional or immunological similarities shared between macromolecules found on infectious pathogens and in host tissues. Molecular mimicry plays an important role in immune responses to infection and in autoimmune diseases. Infection may induce autoimmune responses which attack and destroy body tissues or organs. Normally, the body is tolerant to self-antigens which are present in individual tissues. In autoimmune disease, tolerance is abrogated to self-antigens, and tissues or organs are destroyed by the immune system, with irreversible effects. Molecular mimicry of a self-antigen by an infectious pathogen, such as bacteria and viruses, may trigger autoimmune disease due to a cross-reactive immune response against the infection. Cross-reactive antigen–antibody and T cell–antigen reactions are used to identify the mimicking macromolecules on the pathogen and in tissues or organs. These parameters define the concept of molecular mimicry.

Pertussis

Pertussis Toxin and Vaccines

Locht et al. (2011) say that pertussis toxin binds to ATP. Interestingly, binding of ATP to PTX destabilizes the S1–B oligomer interactions and results in the release of S1 from the holotoxin. This was proposed to occur in the endoplasmic reticulum, which is the only subcellular compartment in addition to the cytosol that contains ATP. This compartment also contains protein disulphide isomerases that may reduce the intramolecular disulphide bond of S1, thereby further helping to release this subunit from the holotoxin. Taken together, these observations suggest that, upon receptor-mediated endocytosis, the holotoxin traffics via the endosomal pathway and Golgi apparatus to the endoplasmic reticulum, where it encounters ATP and disulphide isomerases, which results in release of the S1 subunit from the B oligomer. S1 then translocates directly, and without further help from the B pentamer, through the endoplasmic reticulum membrane into the cytosol. Translocation is assumed to involve unfolding of S1 and escape from the endoplasmic reticulum-associated degradation as a result of a lack of lysine residues, which are the usual substrates of ubiquitination and subsequent degradation by the 26S

proteasome. Nevertheless, isolated S1 is thermally unstable and can be degraded by the ubiquitin-independent S20 proteasome. However, the interaction with NAD is able to stabilize the S1 structure.

Locht et al. (2011) note that extensive studies have been undertaken on protective *B. pertussis* antigens (with pertussis toxin being one of the most studied), with the aim of developing acellular vaccines with improved safety compared to the available cellular pertussis vaccines. Clinical trials undertaken in Sweden have shown that a monocomponent pertussis toxoid vaccine is protective in children. However, the efficacy monocomponent pertussis toxin vaccines remains controversial and most commercially available acellular pertussis vaccines currently contain at least FHA in addition to detoxified pertussis toxin. Given the importance of pertussis toxin as a protective antigen, many studies were undertaken attempting to optimize its production and purification. Because it is also a major virulence factor of *B. pertussis*, pertussis toxin has to be detoxified at the same time as maintaining its immunogenicity. This can be achieved through chemical means or through genetic inactivation. Formaldehyde-detoxified pertussis toxin has been included, together with FHA, in the first acellular pertussis vaccine developed in Japan in the 1970s.

According to Locht et al. (2011), pertussis toxin, produced and secreted by the whooping cough agent Bordetella pertussis, is one of the most complex soluble bacterial proteins. It is actively secreted through the B. pertussis cell envelope by the Ptl secretion system, a member of the widespread type IV secretion systems. The toxin is composed of five subunits (named S1 to S5 according to their decreasing molecular weights) arranged in an A-B structure. The A protomer is composed of the enzymatically active S1 subunit, which catalyzes ADP-ribosylation of the α subunit of trimeric G proteins, thereby disturbing the metabolic functions of the target cells, leading to a variety of biological activities. The B oligomer is composed of 1S2:1S3:2S4:1S5 and is responsible for binding of the toxin to the target cell receptors and for intracellular trafficking via receptor-mediated endocytosis and retrograde transport. The toxin is one of the most important virulence factors of B. pertussis and is a component of all current vaccines against whooping cough.

Poolman and Hallander (2007) note that the Diphtheria-tetanus-acellular pertussis (DTPa) vaccines have ensured continued high level disease protection in these countries following the shift from Pw- to Pa-containing vaccines, and allowed pertussis booster programs to be implemented. Vaccines containing between one and five components have been licensed and implemented. Those with three or more components consisting of filamentous hemagglutinin (FHA), pertussis toxin (PT) and pertactin (PRN) are considered to be more effective than one/two-component Pa vaccines that contain only PT or both PT and FHA. Changes in circulating Bordetella pertussis strains may impact vaccine efficacy and, thus, incidence and transmission of pertussis and deserve to be followed carefully. To date, vaccine-induced shifts among fimbriae (FIM) are reported and this could impact the efficacy of FIM-containing vaccines. Currently, FIM3 appears to be dominant in most European countries, Canada and Australia. Data obtained from a DTPa5 vaccine containing FIM2 and FIM3 have indicated a shift towards an increase in FIM3-expressing B. pertussis clinical breakthrough cases when compared with control vaccine. By contrast, relatively minor PT and PRN sequence polymorphisms have been identified without demonstrable association with vaccination programs. Adsorption of PRN to aluminum salt appears

critical for optimal protective capacity in murine pertussis lung challenge. In addition, clinical studies have shown anti-PRN antibody levels to be higher when PRN is adsorbed at a 8-microg dosage versus non-adsorbed PRN at a 3-microg dosage.

Gorringe and Vaughan (2014) explain that Bordetella pertussis produces two serologically distinct fimbriae, Fim2 and Fim3. Expression of these antigens is governed by the BvgA/S system and by the length of a poly(C) tract in the promoter of each gene. Fim2 and Fim3 are important antigens for whole cell pertussis vaccines as clinical trials have shown an association of anti-fimbriae antibody-mediated agglutination and protection. The current five component acellular pertussis vaccine contains co-purified Fim2/3 and provided good efficacy in clinical trials with the anti-Fim antibody response correlating with protection when pre and post exposure antibody levels were analyzed. The predominant serotype of B. pertussis isolates has changed over time in most countries but it is not understood whether this is vaccine-driven or whether serotype is linked to the prevailing predominant genotype. Recent studies have shown that both Fim2 and Fim3 are expressed during infection and that Fim2 is more immunogenic than Fim3 in the acellular vaccine.

Pertussis Vaccine and Timing of Immunity

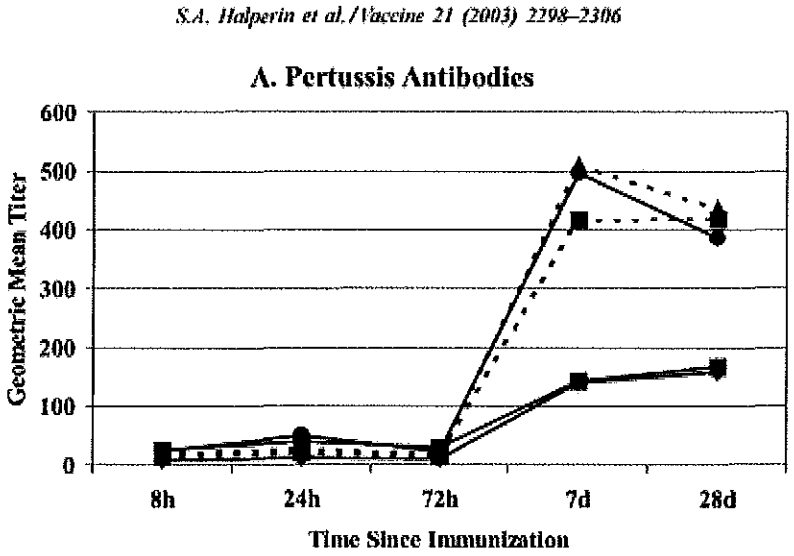


Fig. 1. Time course of antibody increase after a fifth consecutive dose of a five-component acellular pertussis vaccine. Panel A depicts pertussis antibodies including anti-pertussis toxoid (solid line with diamonds), anti-filamentous hemagglutinin (solid line with squares), anti-pertactin (solid line with circles), anti-fimbriae 2 and 3 (dashed line with squares), and agglutinins (dashed line with triangles) (Halperin et al. 2003)

Halperin notes uniformity in antibody response across subjects. Also noted is the reduced antibody response with the fifth DTaP following four previous acellular vaccinations compared with 4 previous whole cell vaccinations.

The Vaccines conference in 2007 poster indicates most people experience a four-fold rise in antibodies within two weeks of vaccination. (see percentages of subjects across time)
https://idsa.confex.com/idsa/2007/webprogram/Paper23586.html

Pertussis Toxin and Autoimmunity to myelin oligodendrocyte glycoprotein

Pertussis toxin has the ability to increase predisposition to autoimmune diseases, possibly inhibiting tolerance mechanisms that normally operate within secondary lymphoid tissues (Furlan et al. 2003, Cyster *et al.*, 1995) Vojdani summarizes autoimmunity in brain diseases in the International Journal of Immunopathology and Pharmacology in 2008. According to Vojdani, the understanding of autoimmune disease, including neuroautoimmune disorders, has expanded considerably in recent years. Autoimmune neurological disorders occur when immunological tolerance to antigens of Schwann cells, axons, motor neurons, receptors and synapses is lost. The resulting demyelinating diseases share pathological features characterized by destruction of myelin and other neural cell antigens accompanied by neural inflammation in the brain, spinal cord or optic nerve (1-2). It is commonly accepted that the early steps of neuroimmune disorders such as multiple sclerosis (MS) are mediated by T cells, in particular the TH17 phenotype, followed by the production of antibodies against different neural antigens. Disruption of the blood-brain barrier (BBB) is the key factor in lymphocyte transmigration and the entry of unwanted molecules across BBB endothelial cells (BBB-ECs). Different environmental factors, such as xenobiotics, infections, dietary peptides, toll-like receptors, adhesion molecules, cytokines and antibodies also play a significant role in BBB dysfunction. TH17 transmigration across the BBB-ECs highly expresses granzyme-B, kills human Key words: predictive antibodies, neuroimmune disorders, autoimmune diseases, cancer, environmental triggers, polyreactive antibodies, ELISA Introduction 554513 Int. J. Immunopathol. Pharmacol. neurons, and promotes central nervous system (CNS) inflammation through microglia CD4+ lymphocyte recruitment. Granzyme-B, the killing of neurons, and possibly astrocytes and microglia, can induce the release of neural cell antigens such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), myelin associated glycoprotein (MAG), PLP, alpha-B-crystallin, tubulin, neurofilaments, glutamate receptors and other antigens. Immune response against these neural antigens and their cross-reactive epitopes can result in different neuroautoimmune disorders such as MS, peripheral neuropathy, Guillain-Barre syndrome (GBS), amyotropic lateral sclerosis (ALS), Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS/OCD), and neural tube defect (NTD).

The fimbriae found in the Bordetela pertussis vaccine can serve as a molecular mimic in Autoimmunity. Bordetella pertussis fimbriae are composed of major and minor subunits, and recently it was shown that the minor fimbrial subunit binds to Vla-5, a receptor located on monocytes (W. Hazenbos et al., 1995). Geuijen's 1998 work shows that the major subunits bind to sulfated sugars, which are ubiquitous in the respiratory tract. Binding was observed to chondroitin sulfate, heparan sulfate, and dextran sulfate but not to dextran. Removal of the minor subunit from fimbriae did not significantly affect binding to sulfated sugars, indicating that the major subunit alone is sufficient for this binding. Fimbriae were also

able to bind HEp-2 cells, which are known to display glycoconjugates on their surface. This binding was not dependent on the presence of the minor subunit. However, binding was dependent on the sulfation state of the glycoconjugates, since inhibition of the sulfation resulted in a significant reduction of fimbria binding. The specificity of fimbria binding was further characterized by using heparan sulfate-derived disaccharides in inhibition assays. Two disaccharides were highly effective inhibitors, and it was observed that both the degree of sulfation and the arrangement of the sulfate groups on the disaccharides were important for binding to fimbriae. B. pertussis bacteria also bound to sulfated sugars and HEp-2 cells, and analysis of B. pertussis mutants indicated that both filamentous hemagglutinin and fimbriae were required for this binding. A host protein present in the extracellular matrix, fibronectin, has binding activities similar to those of B. pertussis fimbriae, binding to both Vla-5 and sulfated sugars. Two regions in the major fimbrial subunit were identified which showed similarity with fibronectin peptides which bind to sulfated sugars. Thus, B. pertussis fimbriae exemplify molecular mimicry and may co-opt host processes by mimicking natural ligand-receptor interactions, such as by fibronectin.

The development of many autoimmune diseases has been etiologically linked to exposure to infectious agents (Rose 1998). For example, a subset of patients with a history of Salmonella infection develop reactive arthritis (Maki-Ikola 1990, Granfors, K. et al.,1990, Yu, D. & Inman, R.1991, Taggart, A.J. & Bell, A.L.1989, Kondowe, G.B. et al. 1989). The persistence of bacterial antigen in arthritic tissue and the isolation of Salmonella or Yersinia reactive CD8+ T cells from the joints of patients with reactive arthritis support the etiological link between Gram-negative bacterial infection and autoimmune disease (Hermann 1993, Sieper, J. et al,1995). Models proposed to account for the link between infection and autoimmunity include inflammation- induced presentation of cryptic self-epitopes, antigen persistence and molecular mimicry (Rose 1998). Several studies support molecular mimicry as a mechanism for the involvement of class II epitopes in infectious disease-induced self-reactivity (Hemmer, B. et al., 1997; Wucherpfennig, K.W. & Strominger 1995; Gross, D.M., et al., 1998; Zhao, Z.S. et al., 1998). Wei-Feng Lo et al., 2000, identified an immunodominant epitope derived from the S. typhimurium GroEL molecule. This epitope is presented by the mouse H2-T23-encoded class Ib molecule Qa-1 and was recognized by CD8+ cytotoxic T lymphocytes induced after natural infection. S. typhimurium-stimulated cytotoxic T lymphocytes recognizing the GroEL epitope cross-reacted with a peptide derived from mouse heat shock protein 60 and recognized stressed macrophages, indicating involvement of MHC class Ib molecules in infection-induced autoimmune recognition and indicate a mechanism for the etiological link between Gram-negative bacterial infection and autoimmunity.

Tubulin are made of Small Myelin-Associated Glycoprotein

Kursula et al. 2001 link tubulin and myelin-associated glycoprotein (gl). The myelin-associated glycoprotein (MAG) exists as two isoforms, differing only by their respective cytoplasmic domains, that have been suggested to function in the formation and maintenance of myelin. In the present study, a 50 kDa protein binding directly to the small MAG (S-MAG) cytoplasmic domain was detected and identified

as tubulin, the core component of the microtubular cytoskeleton. In vitro, the S-MAG cytoplasmic domain slowed the polymerization rate of tubulin and co-purified with assembled microtubules. A significant sequence homology was found between the tau family tubulin-binding repeats and the carboxy-terminus of S-MAG. Results indicate that S-MAG is the first member of the Ig superfamily that can be classified as a microtubule-associated protein, and place S-MAG in a dynamic structural complex that could participate in linking the axonal surface and the myelinating Schwann cell cytoskeleton.

PITANDS/PANDAS/PANS

As early as 1998, the National Institute of Mental Health identified cross-reactive antineuronal antibodies as a neurological disorder called Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders (PITANDS) (Kirvan et al., 2003). Swedo (2012) documents that as early as 1998 it was observed that onset of symptoms was preceded by bacterial or viral infection such as influenza, varicella, and group A streptococcal pharyngitis (Swedo et al. 2012). Molecular mimicry and autoantibody-mediated neuronal cell signaling has been identified and is well established in Sydenham chorea (C. A. Kirvan et al., 2003). Kirvan et al. describe chorea producing antibodies that target the surface of human neuronal cells, with specific induction of calcium/calmodulin-dependent protein (CaM) Kinase II activity by monoclonal antibodies and sera from active chorea patients. M.W. Cunningham (2012) notes that pathogenic mechanisms of cross-reactive autoantibodies which target the valve in rheumatic heart disease and the neuronal cell in Sydenham chorea share a common streptococcal epitope GlcNAc and target intracellular biomarkers of disease including cardiac myosin in the myocardium and tubulin, a protein abundant in the brain. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) was coined, but it required a temporal association with streptococcus, creating diagnostic difficulties for clinicians (Gabbay et al. 2008). Swedo (2012) describes a process through which six clinicians develop a new subcategory of PANDAS, called Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

Swedo's 2012 document describes PANS as a broader category including disorders associated with a preceding infection and without. In PANS, symptom onset is an "Abrupt, dramatic onset of OCD" which is the first diagnostic criterion for PANS. The acuity of onset and initial severity of the OC symptoms are hallmarks of the diagnosis. The obsessive-compulsive symptoms must be sufficiently frequent and intense to meet DSM-IV criteria for OCD and must cause significant distress and interference in the child's activities at home, at school and with peers. Although an acute and dramatic onset of OCD is required for a PANS diagnosis, a prior history of mild, non-impairing obsessions or compulsions does not rule out the syndrome, as children may have had subclinical symptoms present for an extended period prior to the sudden onset of the full disorder. Abrupt onset of obsessions or compulsions or severely restricted food intake, concurrent with at least two of seven neuropsychiatric symptoms: anxiety, emotional lability and/or depression, irritability, aggression and/or severely oppositional behaviors, behavioral (developmental) regression, deterioration in school performance, sensory or motor abnormalities, and somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.

Most recently, in 2015, Singer et al. argue that in sydenham's chorea, it is suspected that dopamine (D1 and D2) receptors are the primary antibody target, although cross reactive antibodies are also generated which bind to CNS lysogangliside-GM 1, and the cytoskeletal protein tubulin. Despite the lack of a definitive specific epitope on neuronal cells, the mechanism causing neurological symptomatology is believed to involve the alteration of neuronal cell signal transduction via calcium calmodulin dependent protein kinase II (CaMKII) activation. This study documented anto-antibodies in Sydenham Chorea patients and PANDAS patients including a longitudinal analysis of case and control subjects. They were able to identify two groups of PANDAS, a cohort lacking choreiform movements and elevated antibodies against D2R; and a group with choreiform movements and elevated anti-D2R antibodies similar to Sydenham's chorea.

Frankovich et al. (2015) reported the onset and suspected trigger of the first 47 patients attending a multidisciplinary clinic dedicated to treating youth with PANS. Among this group of patients, symptoms started acutely (<= 3 days) in 40%, subacutely (3 days-8 weeks) in 31% of patients, and insidiously (>8 weeks) in 29% of patients. The mean age of the subacute and insidious-onset groups was about 2 years younger than the acute group. Most patients in the cohort were male (77%). Preexisting but low-level neuropsychiatric symptoms were common in all groups. In the cohort, only 17% had a documented GAS infection within 12 weeks prior to or during presentation and/or elevated streptococcal titers at presentation as well as having acute-onset of symptoms. All patients met the required secondary symptom criteria, but only 40% has an abrupt onset. There was a high rate of somatic symptoms (sleep disturbances, urinary frequency and enuresis, gastrointestinal symptoms) and sensory amplification (hyperacusis, photophobia, generalized pain). Patients also had high rates of suicidality, aggressive ideation, violent behavior, and psychosis. Illness in the three weeks prior to or during presentation included such conditions as otitis media, sinusitis, urinary tract infection, anaphylactic reaction, mononucleosis, pheumonia, impetigo, arthritis/inflammatory disease flare, and vaccine. Below is the

hierarchy categorization of PAN triggers, which includes non-infectious environmental triggers.

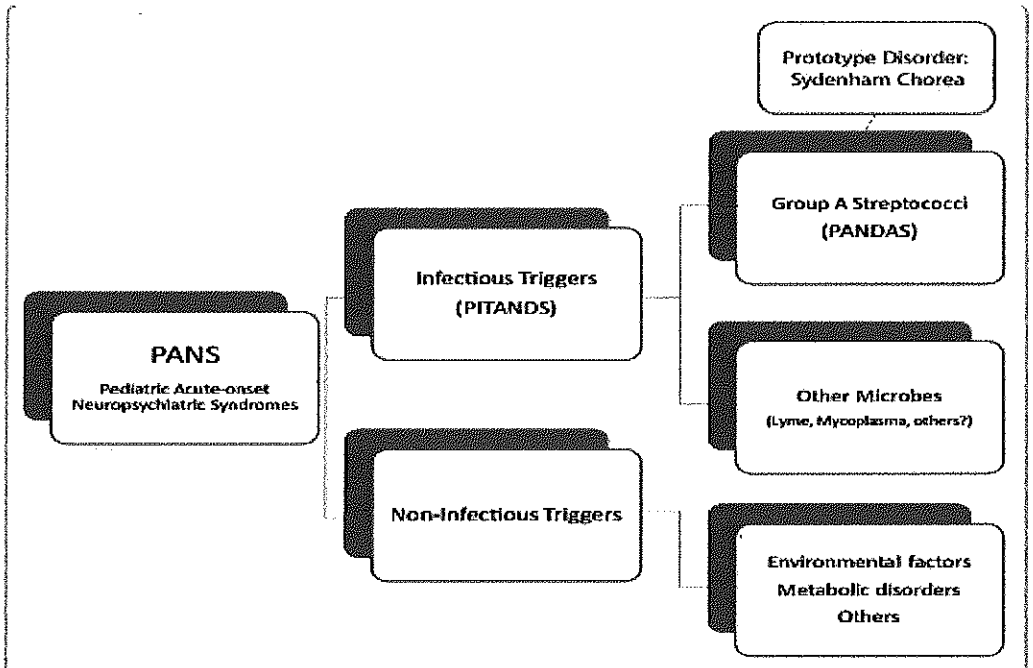
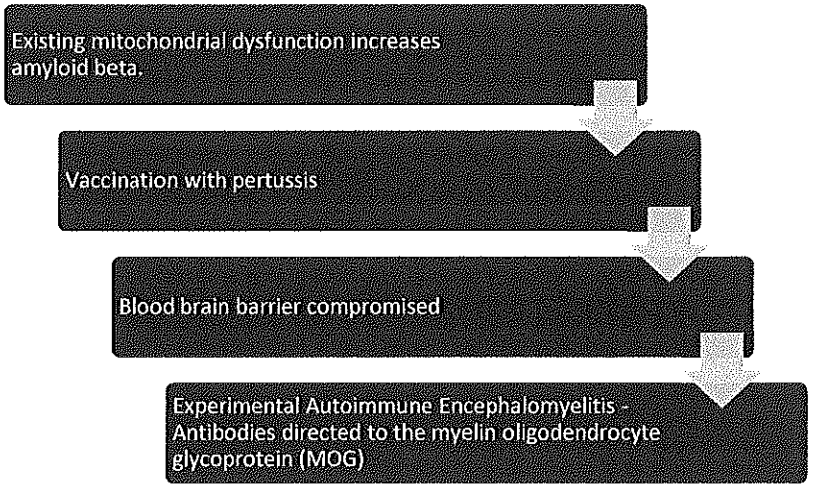


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

Experimental Autoimmune Encephalomyelitis (EAE)

The following flow chart illustrates the potential mechanism through which Experimental Autoimmune Encephalomyelitis (EAE) can be triggered by vaccination with the DTaP vaccine.



Experimental autoimmune encephalomyelitis (EAE) is a model of the neuroimmune system responding to priming with central nervous system (CNS)-restricted antigens. It is an excellent model of post-vaccinal encephalitis and a useful model of many aspects of multiple sclerosis (Baxter 2007). In as early as 2002, Hofstetter et al. connect pertussis toxin with autoimmunity. Pertussis toxin (PT) has been widely used to facilitate the induction of experimental autoimmune encephalomyelitis (EAE) in rodents. It has been suggested that this microbial product promotes EAE by opening up the blood-brain barrier and thereby facilitates the migration of pathogenic T cells to the CNS. However, PT has other biological effects that could contribute to its activity in EAE, such as enhancing the cytokine production by T cells and induction of lymphocytosis. In Hofstetter's work, the effects of PT on the pathogenicity, cytokine differentiation, and clonal sizes of neuroantigen-reactive T cells in EAE in mice are investigated. Results show that PT prevented the protection from EAE conferred by injection of PLPp139–151 in IFA and induced high frequencies of peptide-specific Th1 cells and disease. Interestingly, the mice developed EAE despite the simultaneous vigorous clonal expansion of PLPp139–151-specific Th2 cells. The data indicate that the Th2 cells in this model neither were protective against EAE nor promoted the disease. Furthermore, the results suggested that the effects of the toxin on neuroantigen-reactive T cells were promoted by the PT-induced activation of APCs in lymphoid tissues and the CNS. Together, the results suggest that microbial products, such as PT, could contribute to the initiation of autoimmune disease by modulating the interaction between the innate and adaptive immune system in the response to self Ags. Though the pertussis vaccine is a toxoid, which is an inactivated or attenuated toxin, it is still as immunogenic as the toxin itself (Berestecky 2016)

In reference to an animal model for multiple sclerosis (MS), Diamond, 2013, describes how activated leukocytes, notably monocytes and autoreactive T cells, can transmigrate into the CNS during autoimmune pathology, as has been well described for EAE. EAE is typically induced by immunization with myelin components and adjuvant (freunds adjuvant or pertussis toxin) or by adoptive transfer of encephalitogenic CD4+ T cells. Antibodies directed to the myelin oligodendrocyte glycoprotein (MOG) can augment demyelination. Anti-MOG antibodies display pathogenic effects in vitro (135). Few studies have described the presence of such antibodies in active MS brain lesions (136, 137). Interestingly, MOG antibodies can be detected in serum of healthy individuals by ELISA and Western blot but not by cell-based assays. Whether access of antibody to brain tissue or antibody fine specificity distinguishes patients from healthy individuals is not known.

Surprisingly, Diamond says that using MOG-transfected cells for antibody screening revealed MOG as a target antigen in approximately 40% of pediatric patients with acute disseminated encephalomyelitis (ADEM). High-titer antibodies to MOG are largely absent in adult MS patients but are detected in some patients with AQP4 IgG–seronegative NMO, pediatric MS, and optic neuritis using a cell-based immunofluorescence assay. ELISA and Western blot assays largely failed to detect these antibodies. These data illustrate the absence of a uniform assay for all brain-reactive antibodies.

Furlan et al. (2003) accidentally discovered that the combination of amyloid beta and pertussis toxin led to autoimmune encephalitis. Experimental evidence shows that vaccination with amyloid-beta of

transgenic mouse models of Alzheimer's disease protects from the pathological accumulation of amyloid within the CNS. Phase I/II clinical trials of amyloid beta vaccination in mild to moderate Alzheimer's disease have been undertaken. Unexpectedly, one of these trials has been suspended because 15 patients showed clinical signs consistent with CNS inflammation. In a recent mouse model C57BL/6 mice immunized with amyloid beta 1-42 peptide develop an inflammatory disease of the CNS characterized by the presence both in the brain and spinal cord of perivenular inflammatory foci containing macrophages, T and B cells, and immunoglobulins. The experimental disease was observed only when pertussis toxin, an agent known to favor autoimmune processes, was co-administered intravenously. Mice injected with amyloid beta alone did not show any abnormalities. The immune-mediated CNS reaction was associated to amyloid-beta-induced CD4(+) cells showing a Th1-type cytokine expression profile and to elevated levels of circulating anti-amyloid-beta immunoglobulins. Results indicate that vaccination with amyloid-beta could determine, under certain circumstances, an aberrant autoimmune-type reaction to amyloid-beta resulting in a perivenular inflammatory encephalomyelitis. http://www.ncbi.nlm.nih.gov/pubmed/12538398

Linker and Lee (2009) state that in mouse models, to initiate EAE, amyloid-beta peptides are combined with an adjuvant (freunds adjuvant or pertussis) to establish experimental autoimmune encephalitis and experimental allergic encephalomyelitis.

Cliffort et al. (2007) investigated the possibility that disruption of the integrity of the BBB can lead to a chronic influx of plasma components, including soluble Aβ peptides, into the brain. They also examined the fate of key soluble exogenous Aβ peptides, Aβ42 and Aβ40, within the brain parenchyma. To accomplish this, they tracked the fate of fluorescein isothiocyanate (FITC)-labeled Aβ peptides introduced via tail vein injection into mice in which the BBB had been compromised by prior exposure to pertussis. Results show that blood-borne FITC-labeled Aβ peptides can indeed traverse a defective BBB, enter into the brain parenchyma, bind selectively to the surfaces of certain neurons and, in the case of Aβ42, accumulate selectively within the same subtype of neurons that are known to exhibit prominent Aβ42-immunopositive deposits in AD brains. In view of the high incidence of BBB compromise in nearly all patients with AD, as supported here by direct detection of extravasated plasma components in AD brains, we propose that the blood represents a major and chronic source of exogenous, soluble Aβ42 that eventually deposits within neurons in AD brains. These findings provide a possible link between BBB compromise and the development of AD pathology and highlight the potential effectiveness of therapies aimed at maintaining and/or reinforcing the integrity of the BBB, lowering plasma levels of Aβ peptides and blocking the interactions of soluble exogenous Aβ peptides with neurons. The results showed that Aβ42 readily leaks through the defective blood–brain barrier (BBB) of arterioles into the parenchyma of AD brains, but only rarely in age-matched control brains.

Clifford et al (2007) applied immunohistochemistry to post-mortem human brains to determine if Aβ42 leaks from blood vessels through a defective BBB into the parenchyma of AD brains. If so, it might be possible to detect significant amounts of Aβ42 as well as other extravasated plasma components in these brains (Figs. 1A–D). Results showed that, in addition to the well-documented localization of Aβ42

within neurons, plaques and the walls of blood vessels, Aβ42 was also often localized to diffuse "perivascular leak clouds" occupying the region immediately surrounding arterioles (Fig. 1A). The gradual diminution in the intensity of Aβ42-positive immunostaining with increasing distance from arterioles is consistent with the notion that these blood vessels are the main source of the Aβ42 within the leak cloud. In most AD brains, leak clouds were not associated with capillaries or venules and thus appeared to be selective for arterioles (Figs. 1A–D). An exception to this selectivity was occasionally observed in regions of AD brains exhibiting particularly severe pathology, as noted by widespread neuronal loss, numerous amyloid plaques and signs of local inflammation. In this case, smaller and more numerous leak clouds were also found in association with capillaries and venules.
It is now generally accepted that a progressive accumulation of amyloid beta aggregates eventually triggers a cascade of cellular changes, including mitochondrial oxidative damage, the hyperphosporylation of tau, synaptic failure, and inflammation. However, initial triggers of mutant amyloid precursor protein and/or intracellular amyloid beta were not clearly understood in 2006 (Manczak et al. 2006). It is now known that amyloid beta can both lead to, and be a result of mitochondrial dysfunction. In 2011, Pagani and Ekert sate that Aβ triggers mitochondrial dysfunction through a number of pathways such as impairment of oxidative phosphorylation, elevation of reactive oxygen species (ROS) production, alteration of mitochondrial dynamics, and interaction with mitochondrial proteins. Mitochondria were found to be the target both for amyloid precursor protein (APP) that accumulates in the mitochondrial import channels and for Aβ that interacts with several proteins inside mitochondria and leads to mitochondrial dysfunction. In a more recent study, Leuner et al. (2012) induced complex I and III dysfunction in a cell model using the respiratory inhibitors rotenone and antimycin, resulting in mitochondrial dysfunction and enhanced ROS levels and elevated levels of Amyloid beta. Leuner also found that dysfunction in complex I alone increased amyloid beta.

Glycoprotein can serve as a Pertussis Antigen

In Lassman's 2010 work attempting to differentiate between acute disseminated encephalomyelitis, he/she refers to a classical post-infectious or post-vaccinal acute disseminated encephalomyelitis as a monophasic inflammatory disease with sparse perivenous demyelination resembles, in many respects, experimental autoimmune encephalomyelitis (Alvord 1985). However, considering the multiplicity of different agents that can trigger this condition, it is not clear whether post-infectious acute disseminated encephalomyelitis can be subsumed under a single disease entity. Furthermore, experimental autoimmune encephalomyelitis can present pathologically, not only with perivenous but also with confluent demyelination, depending upon the immunological mechanisms of disease (Lassmann, 1983).

Hans Lassmann (2010) notes that A substantial number of children with inflammatory demyelinating disease present with very high antibody titres against a conformational epitope of myelin oligodendrocyte glycoprotein, which is the target of demyelinating antibodies (O'Connor *et al.*, 2007; Brillot *et al.*, 2009). Such antibodies are particularly prevalent in children who develop inflammatory demyelinating disease under the age of 10 years; and the incidence of patients with such autoantibodies decreases with age. These patients present with an acute disseminated encephalomyelitis or multiple

sclerosis-like clinical disease. However, the pathology shows widespread primary demyelination, as seen in multiple sclerosis, and experimental studies indicate that such antibodies can indeed induce demyelination *in vitro* and *in vivo* (Zhou et al., 2006; Brillot et al.,2009).

Timing and Initiation of Experimental Autoimmune Encephalomyelitis

For obvious reasons, there are no human experiments to induce Autoimmune Encephalitis, Allergic Encephalitis, or Autoimmune Encephalomyelitis. In order to establish a range of probable timing between introduction of a triggering agent (bacterial, viral, toxic, or other), a review of animal models and human case studies are presented.

Experimental Animal Models

The pathogenesis and pathology of EAE varies considerably depending on the model animal and the source, chemical nature and anatomical distribution of the antigenic immunogen (Baxter 2007, Gold et al. 2006), or genetic factors and the specific immunogen/adjuvant used (Linkler and Lee 2009). In Furlan et al. (2003) autoimmune encephalomyelitis in all five mice injected with both amyloid beta and intravenous administration of pertussis toxin developed symptoms and signs evocative of a neurological disorder affecting the CNS between 13 and 20 days post-immunization. Symptoms and signs lasted for up to 75 days, with a caudo-cranial progression and a chronic course, making them indistinguishable from those observed in chronic forms of mouse EAE.

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MAR 2 3 2017

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Secretary Thomas Price, M.D.
The U.S. Department of Health & Human Services

Hubert H. Humphrey Building
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Washington, D.C. 20201

Dear Secretary Price,

I am writing to exercise my right as a United States citizen to petition for the addition of the injury of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci (PANDAS) and/or Pediatric Autoimmune and Neuropsychiatric Syndrome (PANS) to the 42 U.S. Code § 300aa–14 - Vaccine Injury Table following administration of Streptococcus pneumoniae, and Hameophilius influenza serogroup B (HIB) vaccines.

PANDAS/PANS is an autoimmune disorder that can be triggered by several pathogens including Group A Streptococcus. For PANDAS/PANS to develop, circulating antibodies must have access to the central nervous system. PCV13, Pneumovax23, and Hib vaccination can open the door (blood brain barrier) to neuronal tissue enabling the characteristic cross-reactivity between Group A Streptococcus antibodies and central nervous system structures, leading to behavioral dysregulation and malfunction of brain circuits involved in memory, learning and cognition.

Anywhere from 2 to 40% of children show no signs of having an infection, but have circulating antibodies to Group A Streptococcus with the potential to cross-react. Since no symptoms are present, the infection goes un-noticed and medical professionals proceed with vaccination, risking compromise of the blood brain barrier. The synergistic effect of mild blood-brain barrier breakdown suddenly worsened by vaccination with multiple LPS antigens could enable a flood of existing GABHS antibodies to cross-react with the CNS resulting in PANDAS/PANS, a poorly understood condition that has been documented to be preceded by vaccination.

Children may have had subclinical neurological symptoms present for an extended period prior to the sudden onset of the full disorder; however, they may appear to their parents and peers as having suddenly regressed in skills, or changed from an upward progression in development to a downward course that slowly unfolds over months. The timing of symptom onset may depend on the amount of circulating antibodies, number of polysaccharide vaccinations administered, and individual susceptibility to disruption of the blood brain barrier and/or the presence of other synergistic factors like exposure to fine particle air pollution, elevated core body temperature, light mitochondrial dysfunction, and pain; all of which are known to contribute to blood brain barrier permeability. The autoimmune disorder can be reversed if identified and treated quickly with an antibiotic, steroid and IV immunoglobulin. Once the immune response is reversed, risk factors can be avoided and long term outcomes can be improved. Failure to treat can result in IQ loss, disability, and poor long term outcomes.

Vaccination with polysaccharide is only one scenario under which PANDAS/PANS can be enabled. It's possible that PANDAS/PANS can be the result of a number of different scenarios, but among them, only vaccination is a choice based on an understood risk/benefit framework. The National Vaccine Injury

Compensation Program was established in 1983 to protect drug company profitability, but also to compensate the public for adverse unintended consequences of vaccination, regardless of how rare. Children injured by vaccine-enabled PANDAS/PANS are failing to receive compensation within the program because their symptoms are usually confused with Autism. Family members of the injured then become vocal opponents to vaccination and the program itself.

An examination of the Vaccine Adverse Event Reporting System reveals more than 50 reports of adverse reactions displaying PANDAS/PANS symptoms following PCV7, PCV13, or PPV, and more than 30 reports of similar adverse reactions following Hib vaccination. It is in the interest of the citizens of the United States that each of these disorders are added to the table with appropriate timing to ease the extremely disproportionate burden and costs a few bear so that the public can benefit from vaccination.

With prompt identification and treatment, the disabling symptoms of PANDAS/PANS can be improved or even reversed with a steroid and intravenous immunoglobulin for a cost of under $20,000, however, delays increase treatment costs dramatically to as much as $500,000, and reduce likelihood of effectiveness of treatment. Inclusion in the Vaccine Injury Compensation Program table will increase awareness of these adverse events within the medical community, reduce the expense of treatment, and reduce litigation costs to the National Vaccine Injury Compensation Program. In fact, once awareness is improved and treatment routinely and quickly available, costs to the program would simply shift from litigation to treatment with no net loss to the funding pool. This would provide merciful relief to so many for whom the treatment is inaccessible due to insurance company medical policy documents already in place defining it as "not medically necessary".

Unfortunately PANDAS/PANS associated with PCV13, Pneumovax23, and Hib containing vaccines was not considered in the 2012 Institute of Medicine (IOM) report *Adverse Effects of Vaccines: Evidence and Causality* making that effort useless in providing guidance to the Advisory Committee on Childhood Vaccines concerning this disorder. The report writers missed an entire body of work that has received funding by HHS in the National Institute of Mental Health for more than a decade, and missed almost forty peer-reviewed publications that clearly detail the mechanism behind vaccine-enabled PANDAS/PANS.

The science surrounding PANDAS/PANS supports a causal relationship. The 2012 IOM Report, on pages 17-18 explains that strong mechanistic evidence "always carries sufficient weight for the committee to conclude the evidence convincingly supports a causal relationship. . . In 2006, the Advisory Committee on Childhood Vaccines (ACCV) established "Guiding Principles for Recommending Changes to the Vaccine Injury Table" (Guiding Principles) to assist the ACCV in evaluating proposed Table revisions and determining whether to recommend changes to the Table to the Secretary. The Guiding Principles consist of two overarching principles: (1) The Table should be scientifically and medically credible; and (2) where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners. The attached literature review shows there is credible scientific and medical evidence to support a causal relationship between PCV13, Pneumovax23, and Hib for PANDAS/PANS and I am requesting that the Vaccine Injury Table be changed to include these disorders with timing consistent with the literature provided in the attached review.

While it is customary to request the opinion of Advisory Committees in regards to Vaccine Injury Table amendment requests, waiting for such a review is not required for the Secretary to take the requested regulatory action. I respectfully request that you, Secretary Price, swiftly add PANDAS/PANS to the

Vaccine Injury Table amendment that is currently on hold at the request of the President for pneumococcal and Hib vaccines.

When you publish notification of receipt of my petition in the Federal Register, please do so in its entirety, including this letter and the complete literature review, 17 pages in total.

Thank you,
Janet Ferguson, Ph.D.

CATHERINE L DAVIS
NOTARY PUBLIC
ALAMANCE COUNTY, NC
My Commission Expires 9-11-2019

State of NC
County of Chatham
Signed before me this
20th day of March 2017

Notary Public

Vaccines

Vaccines are considered by many to be one of most successful medical interventions against infectious disease. In designing effective vaccines, several key elements are required. First, an antigen is required, against which a memory immune response is targeted. Second, the innate immune system must be stimulated to elicit an adaptive immune response, often accomplished through the inclusion of immune potentiators (also termed adjuvants), which trigger early innate immune responses to aid in the generation of robust and long-lasting adaptive immune responses, a crucial step in ensuring vaccine effectiveness. Finally, delivery systems must target the vaccine (both antigen and immune potentiators) to appropriate cells of the immune system (Pashine et al. 2005).

The innate immune system constitutes the first line of defense against invading microbial pathogens and relies on a large family of pattern recognition receptors (PRRs), which detect distinct evolutionarily conserved structures on pathogens, termed pathogen-associated molecular patterns (PAMPs). Among the PRRs, the Toll-like receptors have been studied most extensively. Upon PAMP engagement, PRRs trigger intracellular signaling cascades ultimately culminating in the expression of a variety of proinflammatory molecules, which together orchestrate the early host response to infection, and also is a prerequisite for the subsequent activation and shaping of adaptive immunity (Mogensen 2009).

The immune system has two main functions: to react quickly (within minutes) to molecular patterns found in pathogens, and to develop slowly (over days to weeks), precisely targeted specific adaptive immune responses. The faster-acting innate immune responses provide a necessary first line of defense because of the relatively slow nature of adaptive immunity. In contrast, adaptive immunity uses selection and clonal expansion of immune cells harboring made-to-order somatically rearranged receptor genes (T- and B-cell receptors) recognizing antigens from the pathogen, thereby providing specificity and long-lasting immunological memory (Pashine et al. 2005).

Polysaccharide Vaccines

Polysaccharides are major components on the surface of bacteria. They are heterogeneous, T-lymphocyte independent antigens and in some cases poor immunogens. Carbohydrates in the form of capsular polysaccharides and/or lipopolysaccharides are the major components on the surface of bacteria. These molecules are important virulence factors in many bacteria isolated from infected persons. Immunity against these components confers protection against the disease. However, developing vaccines based on polysaccharides is difficult. First of all, most of the bacterial polysaccharides are T-lymphocyte independent antigens and anti-polysaccharide immune response is characterized by lack of T-lymphocyte memory, isotype restriction and delayed ontogeny. Children below 2 years of age and the elderly respond poorly to polysaccharide antigens. Secondly, the wide structural heterogeneity among the polysaccharides within and between species is a problem. Thirdly, some bacterial polysaccharides are poor immunogens in humans due to their structural similarities with glycolipids and glycoproteins present in man. The T-lymphocyte independent nature of a polysaccharide may be overcome by conjugating the native or depolymerised polysaccharide to a protein carrier. Such neoglycoconjugates have been proven to be efficient in inducing T-lymphocyte dependent immunity and to protect both infants and the elderly from disease. (Weintraub 2003)

Encapsulated bacteria such as streptococcus pneumoniae, and Hameophilius influenza serogroup B (HIB) are a major cause of disease worldwide. Vaccine development for these diseases has targeted their capsular polysaccharides (CPS) because anti-capsular antibodies often protect against disease. The capsular polysaccharide vaccines were not protective for children and the immunocompromised, so conjugate vaccines were developed. By conjugating capsular polysaccharides to carrier proteins, a T-dependent immune response can be induced against the antigens (Lesinski 2001).

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein), Prevnar , is a sterile solution of saccharides of the capsular antigens of Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM197 protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides which are directly conjugated to the protein carrier CRM197 to form the glycoconjugate. This is effected by reductive amination. CRM197 is a nontoxic variant of diphtheria toxin isolated from cultures of Corynebacterium diphtheriae strain C7 (β197) grown in a casamino acids and yeast extract-based medium. CRM197 is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and are analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein. The individual glycoconjugates are compounded to formulate the vaccine, Prevnar®. Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens, and by the saccharide to protein ratios in the individual glycoconjugates. Prevnar® is manufactured as a liquid preparation. Each 0.5 mL dose is formulated to contain: 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of serotype 6B per dose (16 µg total saccharide); approximately 20 µg of CRM197 carrier protein; and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant (RxList 2017).

The 13-valent pneumococcal CRM 197 conjugate vaccine (PCV13) was licensed in the United States in February 2010 and replaces PCV7 for the prevention of invasive pneumococcal disease and otitis media. This vaccine contains serotypes 1, 3, 5, 6A, 7F, and 19A in addition to the serotypes found in PCV7. PCV13 elicited significantly higher enzyme-linked immunosorbent assay (ELISA) IgG-binding antibody responses than did PCV7 for the additional PCV13 serotypes (serotypes 1, 3, 5, 6A, 7F, and 19A), and for the common serotype 19F, with similar or lower responses for the remaining common

serotypes (Liang et al. 2015). Pneumovax 23 is based on the polysaccharide antigens and is not conjugated to a protein, it does not elicit a lasting immune response in children under 2 (CDC 2017, RxList 2017).

Induction of Autoimmunity to the Central Nervous System (CNS)

According to Wucherpfennig (1995), activation of autoreactive T cells is a critical event in the induction of autoimmunity to the central nervous system (CNS). In animal models of T cell mediated autoimmunity, disease can be transferred only with activated but not with resting T cells specific for a central nervous system (CNS)-specific autoantigen. Resting autoreactive T cells are part of the normal immune repertoire and do not induce disease as the blood-brain barrier only allows activated T cells to gain access to the CNS. This protective mechanism makes circulating self-reactive T cells "ignorant" of the complex set of tissue-specific self-antigens hidden behind the blood-brain barrier. Invasion of the CNS requires autoreactive T cells to be activated in the peripheral immune system. This activation occurs in the absence of their nominal self-antigen, which is sequestered in the CNS. Two mechanisms could account for the activation and clonal expansion of autoreactive T cells in the periphery: activation by bacterial or viral superantigens (Sags) that cause non-specific activation of T-cells resulting in polyclonal T cell activation and massive cytokine release or trigger T cells bearing particular T cell receptor Vβ segments, or activation by viral or bacterial peptides that have sufficient sequence similarity with an immunodominant self-peptide (molecular mimicry).

According to Liang (2015), the mechanisms of autoimmune phenomena after vaccination may be analogous to those following natural infections, so that biological plausibility may be based on factors that include: epitope spreading (the activation and expansion of T cells with additional specificities); molecular mimicry (peptides from microbial proteins that have sufficient structural similarity with self-peptides can activate autoreactive T cells); bystander activation (expansion of previously activated T cells at an inflammatory site); activation of superantigens (infectious particles may cross-link the T cell receptor and major histocompatibility complex molecule independent of specific antigen recognition); direct inflammatory damage; the vascular deposition of circulating immune-complexes (CIC) and complement.

Structural homology between mammalian tissues and pathogens has been demonstrated for over 50 years, and knowledge of molecular mimicry has increased greatly with the application of newer immunochemical and molecular biological techniques. Cross-reacting antibodies occur where there is an interaction between the antigen and an antibody which differs from its proper immunogen (Froude et al. 1989).

Wucherpfennig and Strominger (1995) identified streptococcus pneumoniae as having the ability to activate human myelin basic protein-specific (85-99) T cell clones, though their experiment did not initiate clonal expansion, which is the explosive increase in the number of lymphocytes, both B cells and T cells, from just a few, to millions in the presence of an infection. When lymphocytes multiply during clonal expansion, some of them are destined to live on as memory T and B cells. These clones are a subset of the expanded number of T and B cells that develop from your first exposure to a germ, and they protect you against subsequent attacks by the same germ. Because of this new population of

memory cells, the responses to subsequent attacks are faster and greater than the first. This is why once you've had an infectious illness, you don't get sick when you're exposed to it the next time around.

Streptococcus pneumonia Induced Autoimmunity

According to Rice et al. (2005), a critical feature of the adaptive immune response is antigenic specificity, yet it is becoming increasingly clear that the specificity of lymphocyte receptors admits of some laxity. Cross-reactivity may, in fact, be necessary for lymphocyte survival as antigen receptor signaling maintains cellular viability in the absence of antigen activation. Studies of molecular mimicry have revealed many instances in which antibodies to microbial antigens bind also to self-antigens; in some cases, this cross-reactivity has pathogenic potential. For example, antibodies with specificity for DNA in patients with splenic lupus may cause central nervous system damage by virtue of binding also to neuronal receptors (Kowal et al., 1999). Cross-reactivity may exist among self-antigens as well as between foreign and self-antigens. Anti-DNA antibodies can cross-react with NMDA receptors expressed on neurons (DeGiorgio et al., 2001). This binding causes neuronal death, leading to altered behavior and impaired cognition (Kowal et al., 2004). This observation represents an example of molecular mimicry, with autoantibodies recognizing multiple self-antigens, and perhaps mediating damage through multiple mechanisms.

Typically, a normal immune system must have the ability to respond to foreign challenges and leave untargeted, self molecules. This is accomplished through negative selection regulatory networks and immune privilege. In molecular mimicry, microbial antigens might induce the production of anti-DNA antibodies in hosts with poor regulation of autoreactivity. Diamond and Scharff (1984) showed that phosphoryl-choline, an epitope on pneumococcal cell wall polysaccharide, could acquire a single amino acid substitution and gain specificity for dsDNA, and when protein conjugated, elicit B cells that cross-react with dsDNA. In individuals with poor immune system regulation, some B cells that acquire autospecificity after antigen activation may mature into plasma cells and memory B cells and lead to elevated serum anti-DNA reactivity. Further immunization with a phage peptide display library with a murine anti-DNA antibody, R4A, a peptide present in pneumococcal choline kinase, elicited high titers of anti-DNA antibodies in mice. This peptide motif is also present in the extracellular, ligand-binding domain of both mouse and human N-methyl-D-aspartate (NMDA) receptor subunits NR2a and NR2b. These receptors are widely expressed by neurons in the forebrains, and bind the neurotransmitter glutamate. Ultimately western blot analysis confirmed that anti-dsDNA antibodies bound NR2-containing receptors (DeGiorgio et al., 2001).

As early 1962, Fessel proposed that the immune system contributes to the development and pathogenesis of neuropsychiatric disorders. In some situations, there is evidence that infection triggers the generation of autoantibodies through the mechanism of molecular mimicry. It has also been argued that autoreactivity occurs secondary to brain injury and the ensuing autoimmune response reflects a novel exposure of mature lymphocytes to brain antigens. Autoimmunity may cause inflammation and compromise the blood-brain barrier (BBB), which may result in neurological side-effects that are not directly related to a new loss of self-tolerance, but instead the exposure of brain tissue to antibodies in systemic circulation. Neuropathology often develops slowly and may not be identified until after the instigating pathogen has been cleared.

The BBB shields the CNS from potentially pathogenic infectious or inflammatory agents. The brain is isolated because loss of even a few neuronal cells may be devastating, and the skull constrains the tissues and does not allow for expansion. The BBB plays a central role in controlling the movement of cells and small molecules into and out of the central nervous system. Infection, stress, epinephrine, and lipopolysaccharide can open the BBB. This is especially important because the antibody R4A is found on both the glutamate receptor and in Streptococcus pneumonia.

One week after immunization, Xaio et al. (2001) observed intense immunoglobulin deposition in the hippocampal neurons and neuronal loss in the absence of inflammation, especially of pyramidal neurons in the CA1 region of the hippocampus resulting in cognitive dysfunction in mice. A repeat test performed on mice pre-treated with memantine, an NR2 inhibitor, protected mice from neuronal apoptosis and hippocampal injury confirming that autoantibody-mediated cell signaling by NR2-containing receptors was responsible for the observed neuronal damage. Xaio concludes that it is possible that foreign antigens and vaccines can elicit unanticipated cross-reactivities.

GABHS infection

Group A beta-hemolytic streptococcal (GABHS) or Group A Streptococcus (GAS) infection is the most common bacterial cause of tonsillopharyngitis, but this organism also produces acute otitis media; pneumonia; skin and soft-tissue infections; cardiovascular, musculoskeletal, and lymphatic infections; bacteremia; and meningitis (Pichichero 1998). GAS, or GABHS infections can be present with no symptoms in children, which makes identification and management of GAS carriers difficult and often causes frustration for the clinician, the patient, parents, and researchers (DeMuri and Wald 2014). Studies have shown that, at any given time, the percentage of asymptomatic children who carry GAS without symptoms can range from 2% to 40% of a population. Overall, asymptomatic carriage of GAS is common, especially among school-aged children. The rate of carriage depends highly on the methods of the study and how carriers are defined. In surveys of asymptomatic children, the rate is approximately 2%–5%, whereas in children who experience microbiological treatment failure, the rate is 5%–25%. Lastly, in school surveys, the carriage rates are between 8% and 40% (DeMuri and Wald 2014).

Studies have shown that all rheumatogenic streptococci produce the superantigen SPE C, including all M18 strains. Additionally, it has been shown that SPE C has the ability to penetrate the blood-brain barrier, with possible central nervous system effects resembling Sydenham's chorea. Although not definitively established, it has been suggested that SPE C and other M18-associated superantigens may enhance immune cross-reactivity to M proteins and in this way be associated with the autoimmune disease and even other illnesses such as pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS) (Spaulding et al. 2013).

It's well established that group A Streptococcus can produce postinfectious non-supperative, often called "autoimmune" conditions that may affect the heart, kidney, joints, and central nervous system (Cunningham, 2000, 2003; Stollerman, 2001, 2002) and can exacerbate pediatric autoimmune neuropsychiatric disorders (PANDAS) (Snider and Swedo, 2003). The natural and adaptive antibody-mediated reaction to streptococcus has been proposed to potentially turn into a pathological autoimmune response in vulnerable individuals. Specifically, in conditions of increased permeability of the blood brain barrier (BBB), streptococcus-induced antibodies have been proposed to: (i) reach

neuronal targets located in brain areas responsible for motion control; and (ii) contribute to the exhibition of symptoms.

As early as 1998, the National Institute of Mental Health identified cross-reactive antineuronal antibodies as a neurological disorder called Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders (PITANDS) (Kirvan et al., 2003). Swedo (2012) documents that it was observed that onset of symptoms was preceded by bacterial or viral infection such as influenza, varicella, and group A streptococcal pharyngitis (Swedo et al. 2012). Molecular mimicry and autoantibody-mediated neuronal cell signaling has been identified and is well established in Sydenham chorea (C. A. Kirvan et al., 2003). Kirvan et al. describe chorea producing antibodies that target the surface of human neuronal cells, with specific induction of calcium/calmodulin-dependent protein (CaM) Kinase II activity by monoclonal antibodies and sera from active chorea patients. M.W. Cunningham (2012) notes that pathogenic mechanisms of cross-reactive autoantibodies which target the valve in rheumatic heart disease and the neuronal cell in Sydenham chorea share a common streptococcal epitope GlcNAc, and target intracellular biomarkers of disease including cardiac myosin in the myocardium and tubulin, a protein abundant in the brain. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) was coined, but it required a temporal association with streptococcus, creating diagnostic difficulties for clinicians (Gabbay et al. 2008). Swedo (2012) describes a process through which six clinicians develop a new subcategory of PANDAS, called Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

It is possible for a child to have GAS antibodies from an asymptomatic infection, receive multiple lipopolysaccharide vaccinations, or otherwise suffer an exposure which compromises the BBB and floods the CNS with cross-reacting antibodies that swiftly become pathogenic, and present as Pediatric Autoimmune Neuropsychiatric Syndrome (PANS). Swedo's 2012 document describes PANS as a broader category including disorders associated with a preceding infection and without. In PANS, symptom onset is an abrupt, dramatic onset of OCD or restricted food intake, which is the first diagnostic criterion for PANS. The acuity of onset and initial severity of the symptoms are hallmarks of the diagnosis. Although an acute and dramatic onset of symptoms is required for a PANS diagnosis, a prior history of mild, non-impairing obsessions or compulsions does not rule out the syndrome, as children may have had subclinical symptoms present for an extended period prior to the sudden onset of the full disorder or diagnosis. The complete PANS criteria includes an abrupt onset of obsessions or compulsions (OCD) or severely restricted food intake (Anorexia Nervosa), concurrent with at least two of seven neuropsychiatric symptoms: anxiety, emotional lability and/or depression, irritability, aggression and/or severely oppositional behaviors, behavioral (developmental) regression, deterioration in school performance, sensory or motor abnormalities, and somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.

Most recently, in 2015, Singer et al. argue that in sydenham's chorea, it is suspected that dopamine (D1 and D2) receptors are the primary antibody target, although cross reactive antibodies are also generated which bind to CNS lysogangliside-GM 1, and the cytoskeletal protein tubulin. Despite the lack of a definitive specific epitope on neuronal cells, the mechanism causing neurological symptomatology is believed to involve the alteration of neuronal cell signal transduction via calcium calmodulin dependent protein kinase II (CaMKII) activation. This study documented anto-antibodies in Sydenham Chorea patients and PANDAS patients including a longitudinal analysis of case and control subjects. They were able to identify two groups of PANDAS, a cohort lacking both choreiform movements and elevated antibodies against D2R; and a group with both choreiform movements and elevated anti-D2R antibodies similar to Sydenham's chorea.

Frankovich et al. (2015a) reported the onset and suspected trigger of the first 47 patients attending a multidisciplinary clinic dedicated to treating youth with PANS. Among this group of patients, symptoms started acutely (<= 3 days) in 40%, subacutely (3 days-8 weeks) in 31% of patients, and insidiously (>8 weeks) in 29% of patients. The mean age of the subacute and insidious-onset groups was about 2 years younger than the acute group. Most patients in the cohort were male (77%). Preexisting but low-level neuropsychiatric symptoms were common in all groups. In the cohort, only 17% had a documented GAS infection within 12 weeks prior to or during presentation and/or elevated streptococcal titers at presentation as well as having acute-onset of symptoms. All patients met the required secondary symptom criteria, but only 40% has an abrupt onset. There was a high rate of somatic symptoms (sleep disturbances, urinary frequency and enuresis, gastrointestinal symptoms) and sensory amplification (hyperacusis, photophobia, generalized pain). Patients also had high rates of suicidality, aggressive ideation, violent behavior, and psychosis. Illness in the three weeks prior to or during presentation included such conditions as otitis media, sinusitis, urinary tract infection, anaphylactic reaction, mononucleosis, pneumonia, impetigo, arthritis/inflammatory disease flare, and vaccine. More recently, Leslie (2017) found in a case-control study a statistically significant association between Streptococcus pneumoniae vaccination and the onset of the two primary symptoms of PANDAS/PANS (OCD, Anorexia Nervosa).

Below is the hierarchy categorization of PAN triggers, which includes non-infectious environmental triggers.

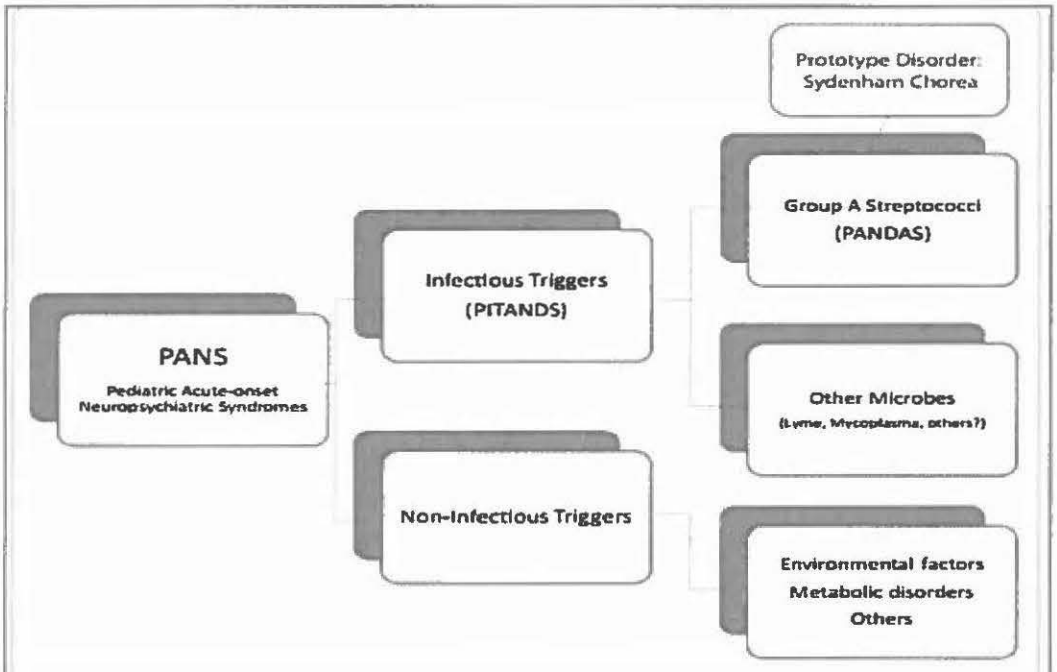

Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

Opening the BBB enabling PANDAS/PANS

According to Banks and Erickson (2010), many factors can increase the permeability of the blood brain barrier allowing for antigens to cross-react with the central nervous system. Intracisternal inoculation of Haemophilus influenza type b(Hib) lipopolysaccharide (LPS) resulted in a dose-dependent increase in blood brain barrier permeability by damaging vascular endothelium and is used in labs to induce experimental meningitis. BBB permeability can also be altered by increased absorptive endocytosis, a process that depends on interactions of glycoproteins on the surface of the cell composing the BBB with glycoproteins of the transported moiety (Banks et al., 1999). Tunkel et al. (1991) examined the effects of purified Haemophilus influenzae type b lipopolysaccharide (LPS) and found that it increased permeability in their in vitro model. Immune cell adhesion and trafficking are enhanced by LPS. In fact, LPS has been shown to enhance the transport of human immunodeficiency virus and its surface coat glycoprotein gp120 across the BBB to enter the brain (Dohgu and Banks, 2008).

The bacterial protein lipopolysaccharide affects the permeability of BBB tight junctions. This is mediated by the production of free radicals, IL-6 and IL-1β154 (Abbott et al., 2006). The blood–brain barrier (BBB) is the monocellular interface that divides the peripheral circulation from direct contact with the central nervous system (CNS). This interface consists of several parallel barriers that include most notably the capillary bed of the CNS and the choroid plexus. These barriers at one level create the dichotomy between the circulating factors of the immune system and the components of the CNS only to regulate interactions between the immune and central nervous systems at other levels. The BBB is thus an integral part of the neuroimmune axis (Banks and Erickson 2010).

Abbott et al. (2006) explain that the BBB is a selective barrier formed by the endothelial cells that line cerebral microvessels. It acts as a 'physical barrier' because complex tight junctions between adjacent endothelial cells force most molecular traffic to take a transcellular route across the BBB, rather than moving paracellularly through the junctions, as in most endothelia. Small gaseous molecules such as O2 and CO2 can diffuse freely through the lipid membranes, and this is also a route of entry for small lipophilic agents, including drugs such as barbiturates and ethanol. The presence of specific transport systems on the luminal and abluminal membranes regulates the transcellular traffic of small hydrophilic molecules, which provides selective 'transport barrier', permitting or facilitating the entry of required nutrients, and excluding or effluxing potentially harmful compounds. Finally, a combination of intracellular and extracellular enzymes provides a 'metabolic barrier': ecto-enzymes such as peptidases and nucleotidases are capable of metabolizing peptides and ATP, respectively, whereas intracellular enzymes such as monoamine oxidase and cytochrome P450 (1A and 2B) can inactivate many neuroactive and toxic compounds. Large hydrophilic molecules such as peptides and proteins are generally excluded, unless they can be transferred by specific receptor-mediated transcytosis, or by the less specific adsorptive-mediated transcytosis. However, the brain endothelium has a much lower degree of endocytosis/transcytosis activity than does peripheral endothelium, which contributes to the transport-barrier property of the BBB. Hence, the term 'blood–brain barrier' covers a range of passive and active features of the brain endothelium. Most studies of the BBB have concentrated on the brain capillary endothelium, the largest surface area for blood–brain exchange. Similar properties are found in the endothelium of brain arterioles and venules, although these segments of the microvasculature may be more leaky and subject to greater modulation.

Pathological disruption of the BBB by LPS and cytokines was the first clear interaction between the neuroimmune system and the BBB. Other interactions include immune cell trafficking, transport of cytokines, modulation of BBB saturable transport systems and other mechanisms of permeation, and secretion of neuroimmune substances by the BBB. Additionally, children exposed to air pollution show

an early brain imbalance in oxidative stress, inflammation, innate and adaptive immune response-associated genes, and blood-brain barrier breakdown (Calderón-Garcidueñas, Lilian, et al. 2015, 2013).

amyloid beta can both lead to, and be a result of mitochondrial dysfunction. In 2011, Pagani and Ekert sate that Aβ triggers mitochondrial dysfunction through a number of pathways such as impairment of oxidative phosphorylation, elevation of reactive oxygen species (ROS) production, alteration of mitochondrial dynamics, and interaction with mitochondrial proteins. Mitochondria were found to be the target both for amyloid precursor protein (APP) that accumulates in the mitochondrial import channels and for Aβ that interacts with several proteins inside mitochondria and leads to mitochondrial dysfunction. In a more recent study, Leuner et al. (2012) induced complex I and III dysfunction in a cell model using the respiratory inhibitors rotenone and antimycin, resulting in mitochondrial dysfunction and enhanced ROS levels and elevated levels of Amyloid beta. Leuner also found that dysfunction in complex I alone increased amyloid beta. In animal models of Alzheimer's disease, amyloid-β (Aβ) accumulation is often first seen in the neighborhood of blood vessels, with toxicity on endothelium and astrocytes observed before significant neuronal loss. Furlan et al. (2003) accidentally discovered that the combination of amyloid beta and pertussis toxin led to autoimmune encephalitis. Experimental evidence shows that vaccination with amyloid-beta of transgenic mouse models of Alzheimer's disease protects from the pathological accumulation of amyloid within the CNS. Phase I/II clinical trials of amyloid beta vaccination in mild to moderate Alzheimer's disease have been undertaken. Unexpectedly, one of these trials has been suspended because 15 patients showed clinical signs consistent with CNS inflammation.

In rats, whole-body hyperthermia induced by prolonged exposure to passive heat stress has been demonstrated to result in impaired BBB integrity (Sharma and Dey 1987, Wijsman and Shivers 1993). Signs of impaired BBB integrity were also measured in humans when subject core temperatures were, on average, elevated above 102.2 F. (Watson et al., 2005).

The synergistic effect of mild blood-brain barrier breakdown suddenly worsened by vaccination with multiple LPS antigens could enable a flood of existing GABHS antibodies to cross-react with the CNS resulting in Pediatric Autoimmune Neuropsychiatric Syndrome, a poorly understood condition that has even been documented by Frankovich et al., (2015a) to be preceded by vaccination.

Finally, there could be positive feedback loops in PANDAS/PANS through the initiating of pain. It has recently been proposed that activated astrocytes and microglial cells could maintain neuropathic pain. As astrocytes have extensive gap junctional connectivity and form glial networks, it has been suggested that glia may be involved in the spreading of pain sensation. In injury, several substances are released from central and peripheral neurons, connective tissue cells and blood cells. Many of these substances, such as substance P, calcitonin gene-related peptide (CGRP), serotonin, histamine and ATP, can affect the BBB from both the blood and the nervous tissue sides. For example, the release of IL-1β leads to a decreased concentration or altered localization of the tight junction protein occludin, and increased BBB permeability. TNFα, histamine and interferon-γ released in inflammatory pain can also cause changes in brain endothelial permeability) (Abbott et al., 2006).

The involvement of microglia in signalling within the pathological neurovascular unit has been mentioned above. It is possible that damage to the endothelium and basal lamina allows expression of endothelial receptors that are normally downregulated (for example, receptors for nucleotides such as ATP), opening new communication loops between endothelium, pericytes, astrocytes and microglia that are important in barrier repair (Abbott et al., 2006).

Labs to Identify PANDAS/PANS

Serum samples from acutely ill children with SC or PANDAS show elevated titers of antibodies against lysoganglioside (Kirvan et al. 2006a), tubulin (Kirvan et al. 2007), dopamine D2 receptor (Brimberg et al. 2012; Ben-Pazi et al. 2013; Cox et al. 2013), and dopamine D1 receptor (Ben-Pazi et al. 2013). More importantly, in both SC and PANDAS, the antibodies produced activation of calcium calmodulin protein kinase II (CaMK II) in the SK-N-SH human neuronal cell line (Kirvan et al. 2003, 2006b). Activation of CaMK II results in neuronal excitation and increased dopamine transmission (Kirvan et al. 2006b), which may be at least partially responsible for PANS symptoms. Recent studies have shown that IgG in youth with SC and PANDAS reacts with and signals the dopamine D2 receptor expressed in transfected cell lines (Cox et al. 2013). Similar results have also been shown for the D1 receptor expressed in transfected cell lines. Currently, Moleculera Labs (www.moleculera.com) is the only Clinical Laboratory Improvement Amendments (CLIA)-certified/Commission on Office Laboratory Accreditation (COLA)-accredited laboratory that provides testing for antitubulin, antilysoganglioside and antidopamine receptor antineuronal antibody titers by enzyme-linked immunosorbent assay (ELISA), as well as assays to measure CaMKII signaling.

Treatment with IV Immunoglobulin can help

Anti-tubulin and anti-lysoganglioside GM1 antibodies disrupt the function of the CamKinase II enzyme, a multifunctional enzyme highly concentrated in the brain that functions to control in neurotransmission and neuronal excitability (Greengard et al., 1993) and is closely associated with regulation of catecholamine (Griffith and Schulman, 1988) and glutamate (Chakrabarty et al., 2005) neurotransmission. In addition, abnormalities in the function of CamKinase II have been associated with neuropsychiatric disorders (Chakrabarty et al., 2005) and studies have linked autoantibodies to Cam Kinase II to movement disorders and neuropsychiatric disorders in children (Kirvan et al., 2003; 2006b). Up-regulation of CamKinase II can increase dopamine output and function of the N-methyl-D-aspartate receptor, resulting in behavioral dysregulation and malfunction of brain circuits involved in memory, learning and cognition. In addition, anti-dopamine and anti-NMDA autoantibodies can directly block or activate ion channels on cell membranes and alter the function of the cell by directly influencing electrical membrane potential and excitability of cells including neurons. Psychiatric and cognitive manifestations associated with these autoantibodies have been documented to be successfully treated with intravenous immunoglobulin (IVIG) in placebo control studies (Perlmutter et al., 1999), case reports (Perlmutter et al., 1998) and case series (Kovacevic et al., 2015).

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5.7

National Vaccine Injury Compensation Program (VICP)

Discussion of Petition to Add Experimental Autoimmune Encephalomyelitis (EAE) and/or Acute Demyelinating Encephalomyelitis (ADEM) as injuries to the Vaccine Injury Table

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Overview of Presentation

- ACCV Guiding Principles
- Review of Petition
- EAE Background
- Review articles provided by petition
- Background on Encephalopathy and Vaccine Injury Table (Table)
- History of whole cell pertussis vaccination and encephalopathy
- History of acellular pertussis vaccination and encephalopathy
- ADEM overview
- Similarities/Differences between ADEM and other forms of encephalopathy
- Discussion of literature as it pertains to vaccinations/pertussis vaccinations and ADEM
- Conclusion

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ACCV Guiding Principles

- The Table should be scientifically and medically credible; and

- Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

Claims Can Be Filed for Injuries Not on the Vaccine Injury Table

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

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Review of Petition

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

Petitioner's Evidence

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

EAE Background

- EAE (experimental autoimmune encephalitis) is an **ANIMAL MODEL** of autoimmune disease of the central nervous system (CNS) 1 (Lindsey – Experimental Models of Multiple Sclerosis; 2005. p. 1-9)
- EAE is not a disease/illness/injury in humans
- It is an inflammatory demyelinating disease of the CNS that is induced **in the laboratory** by the generation of an immune response against myelin epitopes 2 (Rao- Autoimmunity 2004; p. 363-375)
- In simplest form, antigens are introduced into the test subject (animal) that mimic some component of myelin sheath proteins in the CNS. The test subject forms antibodies which cross the blood brain barrier and find and attach to myelin sheath proteins in the CNS which leads to a pro-inflammatory cascade and subsequent myelin sheath destruction (demyelination)

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EAE Background

- Pertussis toxin (NOT PERTUSSIS VACCINE) has been commonly used as an adjuvant (substance that is added to increase body's immune response) in EAE due to it's immunogenic properties
  - Pertussis toxin is an exotoxin/virulence factor that is secreted by the B. Pertussis bacteria (Future Microbiol. 2010 Mar; 5: 455–469).
  - Exact mechanism of action unclear for pertussis toxin
    - Opens up blood brain barrier, facilitating migration of pathogenic T cells into the CNS (Hofstetter; J Immuno July 1, 2002, 169(1) 117-125)
    - Enhancing the cytokine production by T cells and induction of lymphocytosis (Hofstetter; J Immuno July 1, 2002, 169(1) 117-125)
    - Priming or reactivation of autoreactive T cells may be facilitated by structurally unrelated microorganisms that have in common the activation of APC's (antigen presenting cells) (Hofstetter; J Immuno July 1, 2002, 169(1) 117-125)

EAE Summary

- EAE is an experimental model in which autoimmunity can be studied
  - Animals are injected with antigens that have similar epitopes to CNS neural tissue. Antibodies are formed which attack the CNS and cause demyelination.

- EAE discovered accidentally when rabies vaccine inoculated into humans in the 1930's (J Exp Med. 2005 Jul 4; 202(1).
  - CNS neural tissues (from rabbit brains) were used in production of vaccine
  - CNS neural tissue antigens were unknowingly injected along with the vaccine
  - Vaccines with lower concentrations were less effective
  - When increasing concentration of vaccines used, meningoencephalomyelitis occurred.

EAE Summary

- Pertussis antigen (particles from pertussis bacteria) have been used in EAE studies due to its immunogenicity (ability to evoke an immune response)
- Acellular pertussis vaccinations DO NOT contain pertussis antigen
- EAE has been critical to understanding CNS demyelinating conditions including ADEM and MS
- EAE is NOT A CLINICAL CONDITION
- EAE IS NOT ADEM

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Review of Articles Submitted by Petitioner

- 12 articles were reviewed that were submitted by the petitioner in support of adding ADEM/EAE to the Table

Review of Articles Submitted by Petitioner

- **Hofstetter et al. J Immuno July 1, 2002, 169(1) 117-125 (animal model)**
  - Study examines role that Pertussis Toxin (PT) has in facilitating the induction of EAE
    - Suggested an "alternative mechanism by which microbial products, such as PT, could contribute to the initiation of human autoimmune disease in the absence of molecular mimicry"
      - Priming/reactivation of autoreactive T cells may be facilitated by structurally unrelated microorganisms that have in common the activation of APC's (antigen presenting cells).

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Review of Articles Submitted by Petitioner

- **Diamond et al. (Annu Rev Immunol. 2013; 31; 345-385. Brain-Reactive Antibodies and Disease)**
  - This review article (not a study) concludes that "brain-reactive antibodies are found in humans with autoimmune disease, with exposure to microbes or other exogenous antigens that induce cross-reactivity, and with tumors expressing brain antigens.
  - Importantly, these mechanisms may not be mutually exclusive. Both autoimmune predisposition and exposure to cross-reactive antigens are responsible for disease-specific autoantibodies that bind CNS antigens"

Review of Articles Submitted by Petitioner

- **Lassman et al. (Brain 2010: 133; 317-319. ADEM and MS)**
  - Review article on the difficulty distinguishing ADEM from MS, both CNS demyelinating conditions
  - Much overlap with early symptoms
  - Treatments of ADEM - anti-inflammatories; usually monophasic and brief
  - Treatment of MS - immunomodulators; lifelong condition
  - Key may be to understand pathology, pathophysiology

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Review of Articles Submitted by Petitioner

- **Leuner et al. (Antioxidants and Redox Signaling: volume 16, #12, 2012. 1421-143)/animal study)**

  - Mitochondrion derived reactive oxygen species (ROS) results in enhanced amyllidogenic amyloid precursor protein procession

  - Intracellular-amyloid beta leads to mitochondrial dysfunction and increased ROS levels

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Review of Articles Submitted by Petitioner

- **Zhou et al. (PNAS 12/12/06; vol. 103. No. 50. 19057-19062)**

  - Serum from MS patients with high anti-MOG (myelin oligodendrocyte glycoprotein) antibody titers stained white matter myelin in rat brain and enhanced dissemination and axonal damage when transferred to autoimmune encephalomyelitis animals

  - Suggests a pathogenic antibody response to native MOG in a subgroup of MS patients

Review of Articles Submitted by Petitioner

- **Clifford et al. (Brain Research 1142 (2007) 223-236/animal study)**
  - Study to evaluate the possibility that soluble blood borne amyloid beta peptides can cross a defective BBB (blood brain barrier) and interact with neurons in the brain
  - Concluded that blood may serve as a major chronic source of soluble exogenous antibody peptides that can bind selectively to certain subtypes of neurons and accumulate within these cells

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Review of Articles Submitted by Petitioner

- **Linker (Experimental & Translational Stroke Medicine 2009. 1:5)**
  - Review article on MS/EAE
  - Concluded that EAE models continue to play an important role in neuroimmunology thereby also stimulating research in other fields of the neurosciences and immunobiology

Review of Articles Submitted by Petitioner

- **O'Connor et al. (Nat Med. 2007 February; 13 (2): 211-217 – in vitro)**
  - MOG is a more prominent target antigen in ADEM than MS

Review of Articles Submitted by Petitioner

- **Brilot et al. (Ann Neurol 2009;66:833-842/human study)**
  - MOG is a candidate target antigen in demyelinating disease of the CNS
  - MOG is a major target of the humoral immune response in a subgroup of children affected by inflammatory demyelinating disease of the CNS

Review of Articles Submitted by Petitioner

- **Baxter et al.(review) (Nature. November 2007. volume 7. p. 904-910)**
  - EAE is a model of the neuroimmune system responding to priming with CNS restricted antigens

Review of Articles Submitted by Petitioner

- **Furlan et al. (Brain 2003, 126, p. 285-291)**
  - Furlan noted that a recent amyloid – B peptide vaccination trial suspended due to CNS inflammation
    - Furlan induced mice with amyloid-B peptide with and without PT
      - Only immunization with amyloid peptide and PT produced inflammatory encephalomyelitis
      - Concluded that “vaccination with amyloid B peptide may trigger an aberrant autoimmune reaction”

Summary of Articles Submitted by Petitioner

- **Summary of Articles**
  - Very strong experimental research on EAE
  - EAE is an instrumental tool in the study of demyelinating CNS conditions, including MS and ADEM
  - Pertussis antigen (NOT PERTUSSIS VACCINE) and it's use as an immunologically-reactive adjuvant has been critical in EAE studies
  - These are experimental EAE studies with no relevance to pertussis vaccinations and/or ADEM
  - These studies do not provide any evidence or support to the allegations that pertussis vaccinations cause ADEM
  - These studies on EAE do not provide any support that ADEM should be added to the Vaccine Injury Table

Background on Encephalopathy and the Table

- **The Table for the acellular pertussis vaccination and encephalopathy/encephalitis**
  - Onset within 72 hours
  - Evidence of acute encephalopathy
  - Evidence of chronic encephalopathy
  - No evidence of an alternate cause and/or other conditions as set forth in the Qualifications and Aids to Interpretation (QAI)

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Background on Encephalopathy and the Table

Definition of a Table encephalopathy (Current Table Definition)

- *Encephalopathy.* A vaccine recipient shall be considered to have suffered an encephalopathy if an injury meeting the description below of an acute encephalopathy occurs within the applicable time period and results in a chronic encephalopathy, as described in paragraph (d) of this section.
- (i) *Acute encephalopathy*

  (A) For children less than 18 months of age who present:

  - (*1*) Without a seizure, an acute encephalopathy is indicated by a significantly decreased level of consciousness that lasts at least 24 hours.
  - (*2*) Following a seizure, an acute encephalopathy is demonstrated by a significantly decreased level of consciousness that lasts at least 24 hours and cannot be attributed to a postictal state—from a seizure or a medication.

Background on Encephalopathy and the Table

(B) For adults and children 18 months of age or older, an acute encephalopathy is one that persists at least 24 hours and is characterized by at least two of the following:

- (*1*) A significant change in mental status that is not medication related (such as a confusional state, delirium, or psychosis);
- (*2*) A significantly decreased level of consciousness which is independent of a seizure and cannot be attributed to the effects of medication; and
- (*3*) A seizure associated with loss of consciousness.

Background on Encephalopathy and the Table

Table Encephalopathy QAI (pre-March 2017)

An encephalopathy shall not be considered to be a condition set forth in the Table if in a proceeding on a petition, it is shown by a preponderance of the evidence that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known). If at the time a decision is made on a petition filed under section 2111(b) of the Act for a vaccine-related injury or death, it is not possible to determine the cause by a preponderance of the evidence of an encephalopathy, the encephalopathy shall be considered to be a condition set forth in the Table.

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Background on Encephalopathy and the Table

Table Encephalopathy QAI (post- March 2017)

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

> **Acute disseminated encephalomyelitis (ADEM). Although early ADEM may have laboratory and clinical characteristics similar to acute encephalitis, findings on MRI are distinct with ADEM displaying evidence of acute demyelination (scattered, focal, or multifocal areas of inflammation and demyelination within cerebral subcortical and deep cortical white matter; gray matter involvement may also be seen but is a minor component);**

Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

Initial Table QAI 1986 reflected Congress' initial legislative determinations on injuries for the DTwP (whole cell) vaccine (Federal Register/ Vol. 80, No. 135 - 7/29/15)

- Dudgeon Panel
- The Meade Panel
- Northwest Thames Study
- NCES (National Childhood Encephalopathy Study)

Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

Initial Table QAI 1986 reflected Congress' initial legislative determinations on injuries for the DTwP (whole cell) vaccine (Federal Register/ Vol. 80, No. 135 - 7/29/15)

- Dudgeon Panel (Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunization, Department of Health and Social Security. *Whooping Cough.* HMSO, London, 1981, pp. 1-184)
  - Case histories of 50 children between 1956-1976 who received DTP and suffered from serious neurologic illness
  - Panel unable to draw conclusions from case studies and recommended more rigid studies

Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

Initial Table QAI 1986 reflected Congress' initial legislative determinations on injuries for the DTwP (whole cell) vaccine (Federal Register/ Vol. 80, No. 135 - 7/29/15)

- The Meade Panel (Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation, Department of Health and Social Security. *Whooping Cough.* HMSO, London, 1981, pp. 1-184)
  - 125/229 cases between 1970-1974 classified as suspected cases where "more likely than unlikely" that the neurologic condition was associated with DTP (Vaccine, Vol. 7, June 1989. P. 199-210).

Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

Initial Table QAI 1986 reflected Congress' initial legislative determinations on injuries for the DTwP (whole cell) vaccine (Federal Register/ Vol. 80, No. 135 - 7/29/15)

- Northwest Thames Study (Pollock, T.M and Morris, J. A 7-year survey of disorders attributed to vaccination in North West Thames region. *Lancet* 1983, i, 753)
  - 15 cases of febrile convulsions in **first 48** hours after vaccination
  - No convincing evidence that DTP caused major neurological damage (Vaccine, Vol. 7, June 1989 . P. 199-210).

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Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

Initial Table QAI 1986 reflected Congress' initial legislative determinations on injuries for the DTwP (whole cell) vaccine (Federal Register/ Vol. 80, No. 135 - 7/29/15)

- NCES (National Childhood Encephalopathy Study), a case control study in the UK (1976-1979)
  - Examined 1182 cases, 1167 cases with immunization data available
  - 263 cases with infantile spasms excluded, as authors concluded that infantile spasms were not related to immunizations.
  - 904 remaining cases; concluded increased risk of seizures/ encephalopathy within 7 days (Vaccine, Vol. 11, Issue 14, 1993;pp. 1371-1379) , "particularly within 72 hours of the DTP vaccination" (Vaccine, Vol. 7, June 1989 . P. 199-210).

Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

- NCES (National Childhood Encephalopathy Study), a case control study in the UK (1976-1979)
  - A 10-year NCES follow-up study showed evidence of chronic nervous system complaints
  - 1991 IOM concluded that “evidence is consistent with a causal relationship between DPT vaccine and acute encephalopathy

Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

Studies raising questions in regards to a relationship between whole cell pertussis vaccinations and encephalopathy/encephalitis

- Range of excess risk consistent with NCES study 0-10.5 per 1 million immunizations (1991 IOM)
- Case reports/case series offer no consistent evidence for a clinically distinctive pertussis vaccine induced encephalopathy (Vaccine, Vol. 11, Issue 14, 1993;pp. 1371-1379)
- Animal models of pertussis vaccine-induced encephalopathy do not appear to be pertinent to human disease (Vaccine, Vol. 11, Issue 14, 1993;pp. 1371-1379)
- NCES study only 1 of 4 epidemiologic studies to show a statistically significant relationship between pertussis vaccination/encephalopathy (Vaccine, Vol. 11, Issue 14, 1993;pp. 1371-1379)

Pertussis/ADEM
History of Pertussis/Encephalopathy/Vaccines

Studies raising questions in regards to a relationship between whole cell pertussis vaccinations and encephalopathy/encephalitis

- The potential for error and bias in the NCES study has been examined by many authors (Griffith, 1989; MacRae, 1988; Marcuse and Wentz, 1990; Miller et al., 1989; Stuart-Smith, 1988; Wentz and Marcuse, 1991). Major criticisms have involved potential bias and error in (1) case ascertainment, (2) determination of onset of illness, and (3) lack of control for potential confounding factors. (1991 IOM. Pertussis and Rubella vaccines)
- The 1991 Institute of Medicine (IOM) concluded that evidence is insufficient to indicate either the presence or absence of a causal relationship between the DTwP and permanent neurologic damage (Vaccine, Vol. 11, Issue 14, 1993;pp. 1371-1379)
- Recent epidemiologic study (Ray et al) did not show a relationship with DTwP and encephalopathy (Pediatric Inf. Disease Jrnl 2006 Sep;25(9):768-73.)

Background on Encephalopathy and Table

- The Secretary/ACCV decided to keep encephalopathy on the VIT despite the mixed findings:
  - "The IOM conclusions in 1991 and 1994 were mixed regarding the statistically significant findings of encephalopathy in both the original NCES and its 10 year follow-up. [IOM, Adverse Effects of Pertussis and Rubella Vaccines, 1991. IOM, Adverse Events Associated with Childhood Vaccines, 1994.] In the end, the Secretary, with unanimous support of the ACCV, retained encephalopathy on the Table, but clarified the definition of encephalopathy in the QAI to make it more clinically precise" (Federal Register / Vol. 80, No. 145 / Wednesday, July 29, 2015).

Background on Encephalopathy and Table

Acellular pertussis vaccination (DTaP) approved by the FDA on July 31, 1996

- **Safety of acellular pertussis vaccination**
  - In 2011 the IOM found that evidence was inadequate to accept or reject a causal relationship between acellular pertussis vaccinations and encephalopathy/encephalitis
    - 9 studies reviewed epidemiologic evidence
    - 5 studies looked at mechanistic evidence
  - Chang et al. (US post licensure safety surveillance for adolescent and adult tetanus diphtheria and acelluar pertussis vaccines: 2005-2007. Vaccine 31 (2013) 1447-1452)
    - No statistically significant adverse events including ADEM, TM and encephalopathy/encephalitis

Background on Encephalopathy and the Table

The Secretary/ACCV decision in 2015 with acellular pertussis and encephalopathy/encephalitis (Federal Register, Volume 80, No. 145; July 29 2015; pp. 45132-45138)

Despite the lack of literature to support vaccine causation with acellular pertussis and encephalopathy/encephalitis, Secretary made decision to keep encephalopathy/encephalitis on Table for acellular pertussis

- "there is **no credible evidence of a causal relationship between acellular pertussis vaccines and encephalopathy/encephalitis**…." (p. 45138)
- "In view of the limited epidemiological data, and as influenced by the Guiding Principles, **the Secretary does not propose to make any changes to the Table, leaving intact the Table injury of encephalopathy/encephalitis for vaccines containing pertussis antigens, with an onset less than 72 hours from vaccination.** However, the Secretary proposes to re-organize, clarify, and update the QAI for acute and chronic encephalopathy, and to include a new definition for acute encephalitis based on the Brighton Collaboration criteria" (p. 45138)

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Background on Encephalopathy and the Table

Summary of pertussis vaccinations and encephalopathy

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

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

ADEM (Autoimmune Demyelinating Encephalomyelitis)

- Pathologic auto-immune condition of the Central Nervous System with hallmark symptoms of **encephalopathy** and **demyelination in the CNS**

- Etiology unclear- infectious etiology suspected; majority of cases have occurred after a preceding illness
  - Chang et al. (Neurology 68(suppl 2) April 17, 2007; S24 – S36) reviewed 10 studies between 2000-2004 and between 46-100% of patients had prodromal (infectious) symptoms

Background on ADEM

Non-Table Definition of Encephalopathy

- "any diffuse disease of the brain that alters brain function or structure"

(www.ninds.nih.gov)

- Very generic term that is a symptom and not a cause
  - Almost any type of insult to the brain can result in encephalopathy
- May be caused by:
  - Infectious agents, metabolic, brain tumor, increased pressure in the skull, toxins, trauma, poor nutrition, lack of oxygen or blood flow to the brain (www.ninds.nih.gov)
    - Many of these are listed in the QAI

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Background on ADEM

Similarities/Differences with other forms of encephalopathy

- **Similarities**
  - ADEM can have encephalopathy as a symptom

- **Differences**
  - Autoimmune etiology specific for ADEM
  - Literature supports onset between primary exposure and development of primary antibody response of 7-10 days (2011 IOM Report Adverse Effects of Vaccines - Evidence and Causality)
    - Time frame for autoimmune conditions is well outside 0-72 hour time frame of Table for acellular pertussis and encephalopathy/encephalitis
  - Characteristic demyelination in CNS
  - Strong association with prodromal (infectious) illness
  - Enough differences that IOM 2011 Report considered ADEM separate from encephalopathy/encephalitis

Pertussis/ADEM
Pertussis/ADEM and Findings of 2012 IOM Report

- **Pertussis containing vaccinations and ADEM**
  - Epidemiologic evidence
    - No studies were identified to evaluate risk of ADEM with diphtheria toxoid, tetanus toxoid or acellular pertussis antigens alone or in combination
    - Epidemiologic evidence insufficient or absent to assess an association between ADEM with diphtheria toxoid, tetanus toxoid or acellular pertussis antigens alone or in combination
  - Mechanistic evidence
    - 5 publications reviewed
      - 4 did not produce evidence beyond temporality
      - 5th study (whole cell pertussis) did not present sufficient clinical evidence to conclude that the vaccines may have been a contributing cause to ADEM (Lopez et al. Revista de Neurologia 38(5): 405-410)

Pertussis/ADEM
Pertussis/ADEM and Findings of 2012 IOM Report

- **Pertussis containing vaccinations and ADEM**
  - Causality conclusion
    - Evidence is inadequate to accept or reject a causal relationship between pertussis-containing vaccines and ADEM

Review of Data on ADEM

- **Baxter et al. CID 2016/63 (1 December): p. 1456-1462. Acute Demyelinating Events Following Vaccines: A Case Centered Analysis**
  - Identified all cases of ADEM in the Vaccine Safety Datalink population
  - Calculated risk difference (excess risk) of TM and ADEM for each vaccine
  - 64 million doses
  - 7 cases of TM 5-28 days after vaccination
    - No statistical significant increased risk of immunization
  - 8 cases of ADEM
    - Statistically significant increased risk found after Tdap vaccination
    - Based on 2 exposed cases, estimated excess risk was 0.385 cases per million doses

Review of Data on ADEM

- **Baxter et al. CID 2016/63 (1 December): p. 1456-1462. Acute Demyelinating Events Following Vaccines: A Case Centered Analysis**
  - Possible association of ADEM with Tdap
    - Limitations
      - Number of exposed cases (2) very small
      - "Authors not surprised by 1 exposed case and the 2nd case gives statistical significance"
      - In the 2nd case, patient also received a meningococcal vaccine that was not recommended for the age group
      - Did not adjust for multiple testing
        - Multiple testing refers to any instance that involves the simultaneous testing of several hypotheses (Romano et al. University of Chicago)
        - If one does not take the multiplicity of tests into account, then the probability that some of the true null hypotheses are rejected by chance alone may be unduly large.
      - Result could be due to chance alone

Pertussis/ADEM
Pertussis/ADEM and Medical Literature

- **Chang et al. (US post licensure safety surveillance for adolescent and adult tetanus diphtheria and acelluar pertussis vaccines: 2005-2007. Vaccine 31 (2013), 1447-1452)**
    - No statistically significant adverse events including ADEM, TM and encephalopathy/encephalitis

Pertussis/ADEM
Pertussis/ADEM and Medical Literature

- **Pelligrino, et al. (ADEM Onset: Evaluation Based on Vaccine Adverse Event Reporting Systems (VAERS). PLoS One 8(10): October 2013, e77766, 1-7**
  - Reviewed VAERS/EudraVigilance[A centralized European database of suspected adverse reactions to medicines that are authorized or being studied in clinical trials in the European Economic Area (EEA)] post-authorization module (EVPM)
  - 2005-2012; 1 billion cases
  - First epidemiologic data regarding ADEM following vaccination
  - **Diminishing trend in post vaccine ADEM <u>reporting</u>** related to DTaP–IPV- Hib vaccine group

Pertussis/ADEM
Pertussis/ADEM and Medical Literature

Huynh et al. (Post-Vaccination encephalomyelitis: Literature Review and Illustrative Case. Journal of Clinical Neuroscience 15 (2008) 1315–1322)

- Post-vaccination ADEM accounts for <5% of ADEM cases
- "It should be emphasized to parents, patients, health care providers, and all others concerned with immunization safety, that encephalomyelitis or **ADEM – or any other adverse event – that follows administration of an inactivated component or live vaccine may be temporally associated with, but is not necessarily the result of, administration of a vaccine"**

Pertussis/ADEM
Conclusions

- Most current literature does not support relationship between **whole cell pertussis** and encephalopathy/encephalitis.
- Most current literature does not support relationship between **acellular pertussis vaccination** and encephalopathy/encephalitis.
- ADEM is a very distinct condition from other forms of encephalopathy/ encephalitis.
  - Distinct autoimmune etiology
  - Onset of 72 hours is not supported by the medical literature
  - Strongly associated with prodromal symptoms
  - Characteristic CNS demyelination
  - The distinction was large enough that the IOM 2011 Report considered ADEM separately from encephalopathy/encephalitis.
- 2012 IOM Report does not support vaccine causation.
- Literature provided in the petition does not support vaccine causation.
- Current medical literature does not support vaccine causation.

HRSA Healthcare Systems

ACCV Guiding Principles

- The Table should be scientifically and medically credible; and

- Where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners.

ACCV Recommendation Options

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

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

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

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Petition

Janet Ferguson, Ph.D.
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Chapel Hill, NC 27517

Secretary Thomas Price, M.D.
The U.S. Department of Health & Human Services

Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Price,

I am writing to exercise my right as a United States citizen to petition for the addition of the injury of pediatric infection-triggered, autoimmune, neuropsychiatric disorders (PITANDS) and/or Pediatric Autoimmune and Neuropsychiatric Syndrome (PANS) to the 42 U.S. Code § 300aa–14 - Vaccine Injury Table following administration of Pertussis containing vaccines. I also petition for the addition of Experimental Autoimmune Encephalomyelitis, a separate but related disorder, and provide a scientific review in support of my petition.

In the case of PITANDS/PANS, the fimbriae in the Pertussis portion of the DTaP vaccine is a molecular mimic of myelin oligodendrocyte glycoprotein (MOG). Tubulin, found in large concentrations in the brain, are made of MOG. In some, the immune system mistakenly attacks MOG (tubulin), identifying it as Pertussis, resulting in a cluster of symptoms identified as PITANDS/PANS. In this disorder, laboratory findings document anti-tubulin antibodies using enzyme-linked immunosorbent assay (ELISA). Coincident elevation of CaM Kinase II is typical and indicative of an autoimmune attack on the neuronal tissues found specifically in the brain. Activation of CaMK II leads to neuronal excitation. An MRI may, or may not, reveal evidence of the disorder.

While this mechanism is closely related to encephalopathy or encephalitis, the Vaccine Injury Table associated timeframe does not align with the science surrounding PITANDS/PANS, which can manifest suddenly and strongly or slowly over the course of weeks or even several months, pointing to a unique condition with symptoms that can range from suddenly alarming to slowly insidious.

An examination of the Vaccine Adverse Event Reporting System reveals that these two disorders are not within the query menu of the CDC's Vaccine Adverse Event Reporting System (VAERS) through the Wonder menus, however a query of the past decade of VAERS reports reveals at least a dozen descriptions of adverse reactions by children following DTaP administration that meet the criteria defined in the literature.

Experimental Autoimmune Encephalomyelitis, sometimes called Acute Disseminated Encephalomyelitis, is a similar but separate disorder that can be triggered by Pertussis containing vaccines. On January 19, 2017, the Secretary at the time clarified that this disorder and excluded it from the Injury Table because it involves demyelination. With this petition I am requesting that the Secretary list Experimental Autoimmune Encephalomyelitis as an adverse event following Pertussis vaccination because it is a

widely recognized disorder routinely initiated in laboratories using Pertussis vaccine, is documented to have occurred with pertussis vaccination in a case-control study, and a review of the VAERS database reveals seven reports within the last decade, six of which are children.

In Pertussis triggered Experimental Autoimmune Encephalomyelitis, the combination of Pertussis vaccine and amyloid beta open the blood brain barrier allowing entry of anti-MOG antibodies resulting in monophasic inflammatory disease with sparse perivenous demyelination. Unlike PITANDS/PANS, MRI findings in this disorder show evidence of acute demyelination.

The following literature review outlines the mechanistic science behind the initiation of PITANDS/PANS and Experimental Autoimmune Encephalomyelitis, detailing their connection to the Pertussis vaccine and the mechanisms involved. This review should enable you to distinguish the difference between each and establish appropriate timing for the Vaccine Injury Table.

It is in the interest of the citizens of the United States that each of these disorders are added to the table with appropriate timing to ease the extremely disproportionate burden and costs a few bear so that the public can benefit from vaccination. With prompt identification and treatment, the disabling symptoms of PITANDS/PANS and Experimental Autoimmune Encephalomyelitis can be prevented or even reversed. Inclusion in the Vaccine Injury Compensation Program table will increase awareness of these adverse events within the medical community, and reduce litigation costs to the National Vaccine Injury Compensation Program.

Unfortunately PITAND/PANS associated with Pertussis containing vaccines was not considered in the 2012 report *Adverse Effects of Vaccines: Evidence and Causality* making that effort useless in providing guidance to the Advisory Committee on Childhood Vaccines concerning this disorder. Additionally, the review of ADEM (aka Experimental Autoimmune Encephalomyelitis) only looked at five articles associated with DTaP, is less than half of a page, failed to explore the publications provided in this petition, and was inadequate to make a credible determination of its appropriateness for inclusion in the Vaccine Injury Table for Pertussis containing vaccines. In all, the report writers missed an entire body of work that has received funding by HHS in the National Institute of Mental Health for more than a decade, and missed almost sixty peer-reviewed publications concerning these.

It is my belief that the science surrounding PITANDS/PANS and Experimental Autoimmune Encephalomyelitis supports a causal relationship. The 2012 IOM Report, on pages 17-18 explains that strong mechanistic evidence "always carries sufficient weight for the committee to conclude the evidence convincingly supports a causal relationship. . . In 2006, the Advisory Committee on Childhood Vaccines (ACCV) established "Guiding Principles for Recommending Changes to the Vaccine Injury Table" (Guiding Principles) to assist the ACCV in evaluating proposed Table revisions and determining whether to recommend changes to the Table to the Secretary. The Guiding Principles consist of two overarching principles: (1) The Table should be scientifically and medically credible; and (2) where there is credible scientific and medical evidence both to support and to reject a proposed change (addition or deletion) to the Table, the change should, whenever possible, be made to the benefit of petitioners. The attached literature review shows there is credible scientific and medical evidence to support a causal relationship

between pertussis containing vaccines and PITANDS/PANS and Experimental Autoimmune Encephalomyelitis and I am requesting that the Vaccine Injury Table be changed to include these disorders with timing consistent with the literature provided in the attached review.

While it is customary to request the opinion of Advisory Committees in regards to Vaccine Injury Table amendment requests, such a review is not required for the Secretary to take the requested regulatory action. It is also customary for amendment to the Table to take effect for petitions submitted to the National Vaccine Injury Compensation Program after the rulemaking, however due to the disservice done to the American people by the 2012 report published by HHS under a prior Secretary entitled *Adverse Effects of Vaccines: Evidence and Causality*, I ask that the rulemaking apply to petitions received from January 1, 2012 to present. I also ask that when notification of receipt of my petition is posted in the Federal Register, please do so in its entirety, including this letter and the complete literature review, 22 pages in total.

Thank you,
Janet Ferguson, Ph.D.

2/20/17

Carolyn M. Robertson Long
Notary Public
Durham County
North Carolina
My Commission Expires 8-17-2019

Literature Review

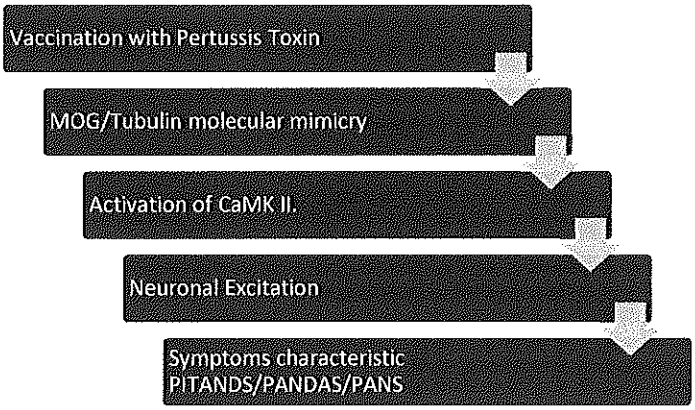
Immunity and Autoimmunity

The establishment of immunity in vaccines

An antigen is a triggering substance in vaccinations. The antigen activates Lymphocytes B-cells and T-cells to divide and secrete compounds. B-cells make and secrete antibody. Some T-cells secrete cytokines, some T-cells seek out and kill target cells on contact. The cell surface receptors on B-cells and T-cells are highly specific in terms of what they bind to, or recognize . The B-cell receptor (BCR) is called an antibody. The T-cell receptor is usually abbreviated as the TCR. A more general or non-specific set of cell surface receptors called major histocompatibility complex (MHC) molecules are found on the surface of antigen presenting cells. The B-cell or the T-cell receptor latches onto a small part or epitope of the antigen molecule. Triggering cells to divide and proliferate. Clones of cells arise from each cell that initially interacted with antigen. Some of these cells will be effector cells that secrete substances, B-cells secrete antibody, and T-cells secrete cytokines (TH cells) and perforin (TC cells). Some of the cells will be memory cells. The cell surface receptors on B-cells and T-cells are highly specific in terms of what they bind or recognize. The B-cell receptor (BCR) is called an antibody. The T-cell receptor is usually abbreviated as the TCR. A more general or non-specific set of cell surface receptors called major histocompatibility complex (MHC) molecules are found on the surface of antigen presenting cells. A repertoire of lymphocytes with a myriad of specificities exists before antigen ever enters the system. When and how antigen encounters the system is important under certain circumstances it may actually turn off the response. This is called tolerance. In general, a bodies' immune system is tolerant of its self-antigens (or its own cells), if this property disintegrates, autoimmunity results. (Berestecky 2016)

Mechanisms of Autoimmunity in PITANDS/PANS

The following flow chart illustrates the mechanism through which PITANDS/PANS can be triggered by vaccination with the DTaP vaccine.



Cunningham, 2009, describes molecular mimicry as structural, functional or immunological similarities shared between macromolecules found on infectious pathogens and in host tissues. Molecular mimicry plays an important role in immune responses to infection and in autoimmune diseases. Infection may induce autoimmune responses which attack and destroy body tissues or organs. Normally, the body is tolerant to self-antigens which are present in individual tissues. In autoimmune disease, tolerance is abrogated to self-antigens, and tissues or organs are destroyed by the immune system, with irreversible effects. Molecular mimicry of a self-antigen by an infectious pathogen, such as bacteria and viruses, may trigger autoimmune disease due to a cross-reactive immune response against the infection. Cross-reactive antigen–antibody and T cell–antigen reactions are used to identify the mimicking macromolecules on the pathogen and in tissues or organs. These parameters define the concept of molecular mimicry.

Pertussis

Pertussis Toxin and Vaccines

Locht et al. (2011) say that pertussis toxin binds to ATP. Interestingly, binding of ATP to PTX destabilizes the S1–B oligomer interactions and results in the release of S1 from the holotoxin. This was proposed to occur in the endoplasmic reticulum, which is the only subcellular compartment in addition to the cytosol that contains ATP. This compartment also contains protein disulphide isomerases that may reduce the intramolecular disulphide bond of S1, thereby further helping to release this subunit from the holotoxin. Taken together, these observations suggest that, upon receptor-mediated endocytosis, the holotoxin traffics via the endosomal pathway and Golgi apparatus to the endoplasmic reticulum, where it encounters ATP and disulphide isomerases, which results in release of the S1 subunit from the B oligomer. S1 then translocates directly, and without further help from the B pentamer, through the endoplasmic reticulum membrane into the cytosol. Translocation is assumed to involve unfolding of S1 and escape from the endoplasmic reticulum-associated degradation as a result of a lack of lysine residues, which are the usual substrates of ubiquitination and subsequent degradation by the 26S

proteasome. Nevertheless, isolated S1 is thermally unstable and can be degraded by the ubiquitin-independent S20 proteasome. However, the interaction with NAD is able to stabilize the S1 structure.

Locht et al. (2011) note that extensive studies have been undertaken on protective *B. pertussis* antigens (with pertussis toxin being one of the most studied), with the aim of developing acellular vaccines with improved safety compared to the available cellular pertussis vaccines. Clinical trials undertaken in Sweden have shown that a monocomponent pertussis toxoid vaccine is protective in children. However, the efficacy monocomponent pertussis toxin vaccines remains controversial and most commercially available acellular pertussis vaccines currently contain at least FHA in addition to detoxified pertussis toxin. Given the importance of pertussis toxin as a protective antigen, many studies were undertaken attempting to optimize its production and purification. Because it is also a major virulence factor of *B. pertussis*, pertussis toxin has to be detoxified at the same time as maintaining its immunogenicity. This can be achieved through chemical means or through genetic inactivation. Formaldehyde-detoxified pertussis toxin has been included, together with FHA, in the first acellular pertussis vaccine developed in Japan in the 1970s.

According to Locht et al. (2011), pertussis toxin, produced and secreted by the whooping cough agent Bordetella pertussis, is one of the most complex soluble bacterial proteins. It is actively secreted through the B. pertussis cell envelope by the Ptl secretion system, a member of the widespread type IV secretion systems. The toxin is composed of five subunits (named S1 to S5 according to their decreasing molecular weights) arranged in an A-B structure. The A protomer is composed of the enzymatically active S1 subunit, which catalyzes ADP-ribosylation of the α subunit of trimeric G proteins, thereby disturbing the metabolic functions of the target cells, leading to a variety of biological activities. The B oligomer is composed of 1S2:1S3:2S4:1S5 and is responsible for binding of the toxin to the target cell receptors and for intracellular trafficking via receptor-mediated endocytosis and retrograde transport. The toxin is one of the most important virulence factors of B. pertussis and is a component of all current vaccines against whooping cough.

Poolman and Hallander (2007) note that the Diphtheria-tetanus-acellular pertussis (DTPa) vaccines have ensured continued high level disease protection in these countries following the shift from Pw- to Pa-containing vaccines, and allowed pertussis booster programs to be implemented. Vaccines containing between one and five components have been licensed and implemented. Those with three or more components consisting of filamentous hemagglutinin (FHA), pertussis toxin (PT) and pertactin (PRN) are considered to be more effective than one/two-component Pa vaccines that contain only PT or both PT and FHA. Changes in circulating Bordetella pertussis strains may impact vaccine efficacy and, thus, incidence and transmission of pertussis and deserve to be followed carefully. To date, vaccine-induced shifts among fimbriae (FIM) are reported and this could impact the efficacy of FIM-containing vaccines. Currently, FIM3 appears to be dominant in most European countries, Canada and Australia. Data obtained from a DTPa5 vaccine containing FIM2 and FIM3 have indicated a shift towards an increase in FIM3-expressing B. pertussis clinical breakthrough cases when compared with control vaccine. By contrast, relatively minor PT and PRN sequence polymorphisms have been identified without demonstrable association with vaccination programs. Adsorption of PRN to aluminum salt appears

critical for optimal protective capacity in murine pertussis lung challenge. In addition, clinical studies have shown anti-PRN antibody levels to be higher when PRN is adsorbed at a 8-microg dosage versus non-adsorbed PRN at a 3-microg dosage.

Gorringe and Vaughan (2014) explain that Bordetella pertussis produces two serologically distinct fimbriae, Fim2 and Fim3. Expression of these antigens is governed by the BvgA/S system and by the length of a poly(C) tract in the promoter of each gene. Fim2 and Fim3 are important antigens for whole cell pertussis vaccines as clinical trials have shown an association of anti-fimbriae antibody-mediated agglutination and protection. The current five component acellular pertussis vaccine contains co-purified Fim2/3 and provided good efficacy in clinical trials with the anti-Fim antibody response correlating with protection when pre and post exposure antibody levels were analyzed. The predominant serotype of B. pertussis isolates has changed over time in most countries but it is not understood whether this is vaccine-driven or whether serotype is linked to the prevailing predominant genotype. Recent studies have shown that both Fim2 and Fim3 are expressed during infection and that Fim2 is more immunogenic than Fim3 in the acellular vaccine.

Pertussis Vaccine and Timing of Immunity

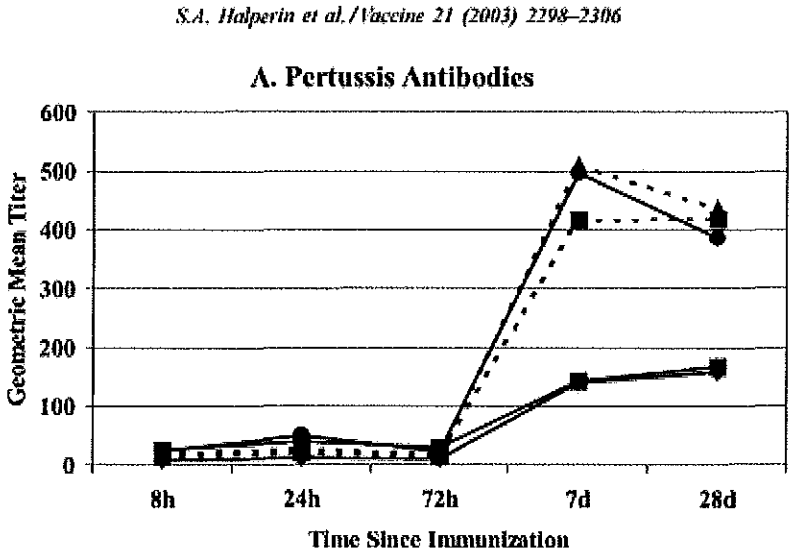


Fig. 1. Time course of antibody increase after a fifth consecutive dose of a five-component acellular pertussis vaccine. Panel A depicts pertussis antibodies including anti-pertussis toxoid (solid line with diamonds), anti-filamentous hemagglutinin (solid line with squares), anti-pertactin (solid line with circles), anti-fimbriae 2 and 3 (dashed line with squares), and agglutinins (dashed line with triangles) (Halperin et al. 2003)

Halperin notes uniformity in antibody response across subjects. Also noted is the reduced antibody response with the fifth DTaP following four previous acellular vaccinations compared with 4 previous whole cell vaccinations.

The Vaccines conference in 2007 poster indicates most people experience a four-fold rise in antibodies within two weeks of vaccination. (see percentages of subjects across time)
https://idsa.confex.com/idsa/2007/webprogram/Paper23586.html

Pertussis Toxin and Autoimmunity to myelin oligodendrocyte glycoprotein

Pertussis toxin has the ability to increase predisposition to autoimmune diseases, possibly inhibiting tolerance mechanisms that normally operate within secondary lymphoid tissues (Furlan et al. 2003, Cyster *et al.*, 1995) Vojdani summarizes autoimmunity in brain diseases in the International Journal of Immunopathology and Pharmacology in 2008. According to Vojdani, the understanding of autoimmune disease, including neuroautoimmune disorders, has expanded considerably in recent years. Autoimmune neurological disorders occur when immunological tolerance to antigens of Schwann cells, axons, motor neurons, receptors and synapses is lost. The resulting demyelinating diseases share pathological features characterized by destruction of myelin and other neural cell antigens accompanied by neural inflammation in the brain, spinal cord or optic nerve (1-2). It is commonly accepted that the early steps of neuroimmune disorders such as multiple sclerosis (MS) are mediated by T cells, in particular the TH17 phenotype, followed by the production of antibodies against different neural antigens. Disruption of the blood-brain barrier (BBB) is the key factor in lymphocyte transmigration and the entry of unwanted molecules across BBB endothelial cells (BBB-ECs). Different environmental factors, such as xenobiotics, infections, dietary peptides, toll-like receptors, adhesion molecules, cytokines and antibodies also play a significant role in BBB dysfunction. TH17 transmigration across the BBB-ECs highly expresses granzyme-B, kills human Key words: predictive antibodies, neuroimmune disorders, autoimmune diseases, cancer, environmental triggers, polyreactive antibodies, ELISA Introduction 554513 Int. J. Immunopathol. Pharmacol. neurons, and promotes central nervous system (CNS) inflammation through microglia CD4+ lymphocyte recruitment. Granzyme-B, the killing of neurons, and possibly astrocytes and microglia, can induce the release of neural cell antigens such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), myelin associated glycoprotein (MAG), PLP, alpha-B-crystallin, tubulin, neurofilaments, glutamate receptors and other antigens. Immune response against these neural antigens and their cross-reactive epitopes can result in different neuroautoimmune disorders such as MS, peripheral neuropathy, Guillain-Barre syndrome (GBS), amyotropic lateral sclerosis (ALS), Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS/OCD), and neural tube defect (NTD).

The fimbriae found in the Bordetela pertussis vaccine can serve as a molecular mimic in Autoimmunity. Bordetella pertussis fimbriae are composed of major and minor subunits, and recently it was shown that the minor fimbrial subunit binds to Vla-5, a receptor located on monocytes (W. Hazenbos et al., 1995). Geuijen's 1998 work shows that the major subunits bind to sulfated sugars, which are ubiquitous in the respiratory tract. Binding was observed to chondroitin sulfate, heparan sulfate, and dextran sulfate but not to dextran. Removal of the minor subunit from fimbriae did not significantly affect binding to sulfated sugars, indicating that the major subunit alone is sufficient for this binding. Fimbriae were also

able to bind HEp-2 cells, which are known to display glycoconjugates on their surface. This binding was not dependent on the presence of the minor subunit. However, binding was dependent on the sulfation state of the glycoconjugates, since inhibition of the sulfation resulted in a significant reduction of fimbria binding. The specificity of fimbria binding was further characterized by using heparan sulfate-derived disaccharides in inhibition assays. Two disaccharides were highly effective inhibitors, and it was observed that both the degree of sulfation and the arrangement of the sulfate groups on the disaccharides were important for binding to fimbriae. B. pertussis bacteria also bound to sulfated sugars and HEp-2 cells, and analysis of B. pertussis mutants indicated that both filamentous hemagglutinin and fimbriae were required for this binding. A host protein present in the extracellular matrix, fibronectin, has binding activities similar to those of B. pertussis fimbriae, binding to both Vla-5 and sulfated sugars. Two regions in the major fimbrial subunit were identified which showed similarity with fibronectin peptides which bind to sulfated sugars. Thus, B. pertussis fimbriae exemplify molecular mimicry and may co-opt host processes by mimicking natural ligand-receptor interactions, such as by fibronectin.

The development of many autoimmune diseases has been etiologically linked to exposure to infectious agents (Rose 1998). For example, a subset of patients with a history of Salmonella infection develop reactive arthritis (Maki-Ikola 1990, Granfors, K. et al.,1990, Yu, D. & Inman, R.1991, Taggart, A.J. & Bell, A.L.1989, Kondowe, G.B. et al. 1989). The persistence of bacterial antigen in arthritic tissue and the isolation of Salmonella or Yersinia reactive CD8+ T cells from the joints of patients with reactive arthritis support the etiological link between Gram-negative bacterial infection and autoimmune disease (Hermann 1993, Sieper, J. et al,1995). Models proposed to account for the link between infection and autoimmunity include inflammation- induced presentation of cryptic self-epitopes, antigen persistence and molecular mimicry (Rose 1998). Several studies support molecular mimicry as a mechanism for the involvement of class II epitopes in infectious disease-induced self-reactivity (Hemmer, B. et al., 1997; Wucherpfennig, K.W. & Strominger 1995; Gross, D.M., et al., 1998; Zhao, Z.S. et al., 1998). Wei-Feng Lo et al., 2000, identified an immunodominant epitope derived from the S. typhimurium GroEL molecule. This epitope is presented by the mouse H2-T23-encoded class Ib molecule Qa-1 and was recognized by CD8+ cytotoxic T lymphocytes induced after natural infection. S. typhimurium-stimulated cytotoxic T lymphocytes recognizing the GroEL epitope cross-reacted with a peptide derived from mouse heat shock protein 60 and recognized stressed macrophages, indicating involvement of MHC class Ib molecules in infection-induced autoimmune recognition and indicate a mechanism for the etiological link between Gram-negative bacterial infection and autoimmunity.

Tubulin are made of Small Myelin-Associated Glycoprotein

Kursula et al. 2001 link tubulin and myelin-associated glycoprotein (gl). The myelin-associated glycoprotein (MAG) exists as two isoforms, differing only by their respective cytoplasmic domains, that have been suggested to function in the formation and maintenance of myelin. In the present study, a 50 kDa protein binding directly to the small MAG (S-MAG) cytoplasmic domain was detected and identified

as tubulin, the core component of the microtubular cytoskeleton. In vitro, the S-MAG cytoplasmic domain slowed the polymerization rate of tubulin and co-purified with assembled microtubules. A significant sequence homology was found between the tau family tubulin-binding repeats and the carboxy-terminus of S-MAG. Results indicate that S-MAG is the first member of the Ig superfamily that can be classified as a microtubule-associated protein, and place S-MAG in a dynamic structural complex that could participate in linking the axonal surface and the myelinating Schwann cell cytoskeleton.

PITANDS/PANDAS/PANS

As early as 1998, the National Institute of Mental Health identified cross-reactive antineuronal antibodies as a neurological disorder called Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders (PITANDS) (Kirvan et al., 2003). Swedo (2012) documents that as early as 1998 it was observed that onset of symptoms was preceded by bacterial or viral infection such as influenza, varicella, and group A streptococcal pharyngitis (Swedo et al. 2012). Molecular mimicry and autoantibody-mediated neuronal cell signaling has been identified and is well established in Sydenham chorea (C. A. Kirvan et al., 2003). Kirvan et al. describe chorea producing antibodies that target the surface of human neuronal cells, with specific induction of calcium/calmodulin-dependent protein (CaM) Kinase II activity by monoclonal antibodies and sera from active chorea patients. M.W. Cunningham (2012) notes that pathogenic mechanisms of cross-reactive autoantibodies which target the valve in rheumatic heart disease and the neuronal cell in Sydenham chorea share a common streptococcal epitope GlcNAc and target intracellular biomarkers of disease including cardiac myosin in the myocardium and tubulin, a protein abundant in the brain. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) was coined, but it required a temporal association with streptococcus, creating diagnostic difficulties for clinicians (Gabbay et al. 2008). Swedo (2012) describes a process through which six clinicians develop a new subcategory of PANDAS, called Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

Swedo's 2012 document describes PANS as a broader category including disorders associated with a preceding infection and without. In PANS, symptom onset is an "Abrupt, dramatic onset of OCD" which is the first diagnostic criterion for PANS. The acuity of onset and initial severity of the OC symptoms are hallmarks of the diagnosis. The obsessive-compulsive symptoms must be sufficiently frequent and intense to meet DSM-IV criteria for OCD and must cause significant distress and interference in the child's activities at home, at school and with peers. Although an acute and dramatic onset of OCD is required for a PANS diagnosis, a prior history of mild, non-impairing obsessions or compulsions does not rule out the syndrome, as children may have had subclinical symptoms present for an extended period prior to the sudden onset of the full disorder. Abrupt onset of obsessions or compulsions or severely restricted food intake, concurrent with at least two of seven neuropsychiatric symptoms: anxiety, emotional lability and/or depression, irritability, aggression and/or severely oppositional behaviors, behavioral (developmental) regression, deterioration in school performance, sensory or motor abnormalities, and somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency.

Most recently, in 2015, Singer et al. argue that in sydenham's chorea, it is suspected that dopamine (D1 and D2) receptors are the primary antibody target, although cross reactive antibodies are also generated which bind to CNS lysogangliside-GM 1, and the cytoskeletal protein tubulin. Despite the lack of a definitive specific epitope on neuronal cells, the mechanism causing neurological symptomatology is believed to involve the alteration of neuronal cell signal transduction via calcium calmodulin dependent protein kinase II (CaMKII) activation. This study documented anto-antibodies in Sydenham Chorea patients and PANDAS patients including a longitudinal analysis of case and control subjects. They were able to identify two groups of PANDAS, a cohort lacking choreiform movements and elevated antibodies against D2R; and a group with choreiform movements and elevated anti-D2R antibodies similar to Sydenham's chorea.

Frankovich et al. (2015) reported the onset and suspected trigger of the first 47 patients attending a multidisciplinary clinic dedicated to treating youth with PANS. Among this group of patients, symptoms started acutely (<= 3 days) in 40%, subacutely (3 days-8 weeks) in 31% of patients, and insidiously (>8 weeks) in 29% of patients. The mean age of the subacute and insidious-onset groups was about 2 years younger than the acute group. Most patients in the cohort were male (77%). Preexisting but low-level neuropsychiatric symptoms were common in all groups. In the cohort, only 17% had a documented GAS infection within 12 weeks prior to or during presentation and/or elevated streptococcal titers at presentation as well as having acute-onset of symptoms. All patients met the required secondary symptom criteria, but only 40% has an abrupt onset. There was a high rate of somatic symptoms (sleep disturbances, urinary frequency and enuresis, gastrointestinal symptoms) and sensory amplification (hyperacusis, photophobia, generalized pain). Patients also had high rates of suicidality, aggressive ideation, violent behavior, and psychosis. Illness in the three weeks prior to or during presentation included such conditions as otitis media, sinusitis, urinary tract infection, anaphylactic reaction, mononucleosis, pheumonia, impetigo, arthritis/inflammatory disease flare, and vaccine. Below is the

hierarchy categorization of PAN triggers, which includes non-infectious environmental triggers.

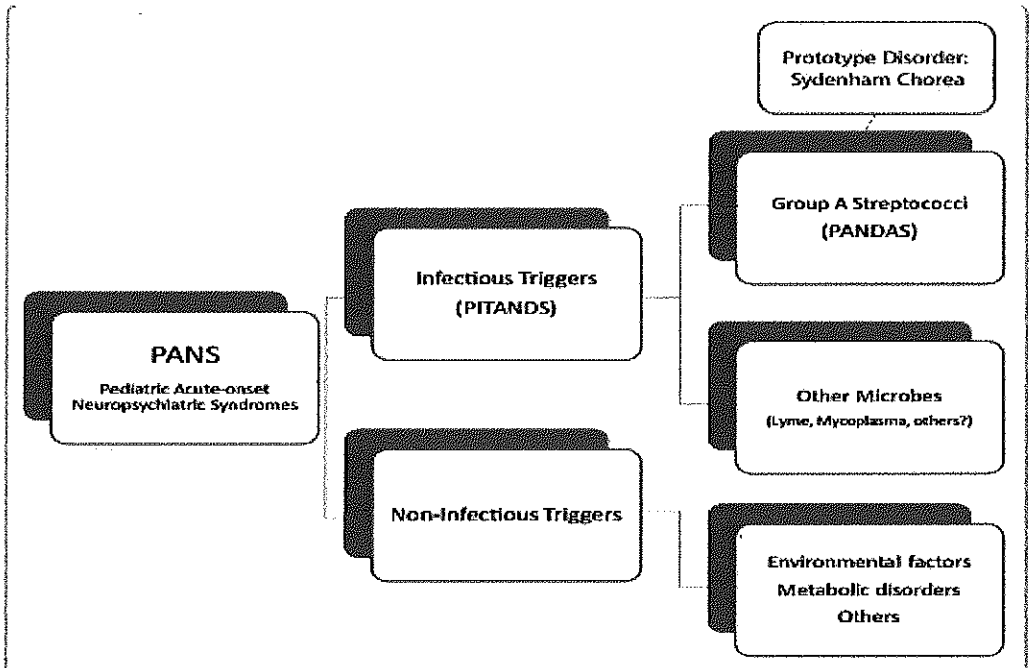
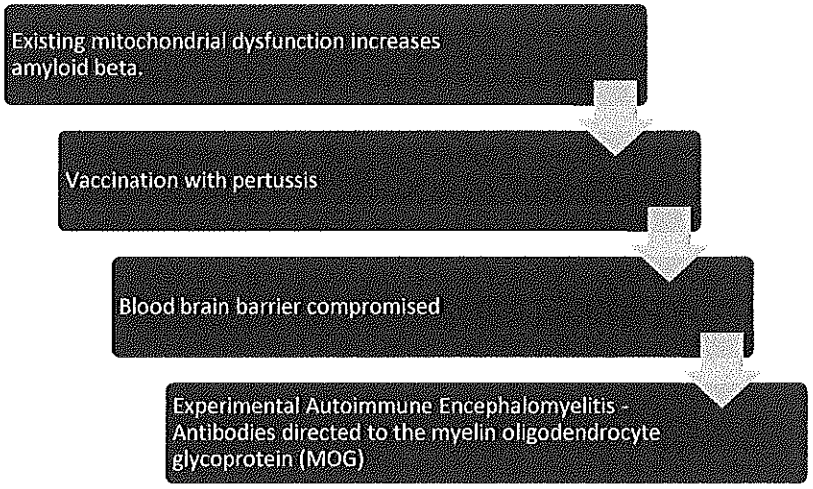


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

Experimental Autoimmune Encephalomyelitis (EAE)

The following flow chart illustrates the potential mechanism through which Experimental Autoimmune Encephalomyelitis (EAE) can be triggered by vaccination with the DTaP vaccine.



Experimental autoimmune encephalomyelitis (EAE) is a model of the neuroimmune system responding to priming with central nervous system (CNS)-restricted antigens. It is an excellent model of post-vaccinal encephalitis and a useful model of many aspects of multiple sclerosis (Baxter 2007). In as early as 2002, Hofstetter et al. connect pertussis toxin with autoimmunity. Pertussis toxin (PT) has been widely used to facilitate the induction of experimental autoimmune encephalomyelitis (EAE) in rodents. It has been suggested that this microbial product promotes EAE by opening up the blood-brain barrier and thereby facilitates the migration of pathogenic T cells to the CNS. However, PT has other biological effects that could contribute to its activity in EAE, such as enhancing the cytokine production by T cells and induction of lymphocytosis. In Hofstetter's work, the effects of PT on the pathogenicity, cytokine differentiation, and clonal sizes of neuroantigen-reactive T cells in EAE in mice are investigated. Results show that PT prevented the protection from EAE conferred by injection of PLPp139–151 in IFA and induced high frequencies of peptide-specific Th1 cells and disease. Interestingly, the mice developed EAE despite the simultaneous vigorous clonal expansion of PLPp139–151-specific Th2 cells. The data indicate that the Th2 cells in this model neither were protective against EAE nor promoted the disease. Furthermore, the results suggested that the effects of the toxin on neuroantigen-reactive T cells were promoted by the PT-induced activation of APCs in lymphoid tissues and the CNS. Together, the results suggest that microbial products, such as PT, could contribute to the initiation of autoimmune disease by modulating the interaction between the innate and adaptive immune system in the response to self Ags. Though the pertussis vaccine is a toxoid, which is an inactivated or attenuated toxin, it is still as immunogenic as the toxin itself (Berestecky 2016)

In reference to an animal model for multiple sclerosis (MS), Diamond, 2013, describes how activated leukocytes, notably monocytes and autoreactive T cells, can transmigrate into the CNS during autoimmune pathology, as has been well described for EAE. EAE is typically induced by immunization with myelin components and adjuvant (freunds adjuvant or pertussis toxin) or by adoptive transfer of encephalitogenic CD4+ T cells. Antibodies directed to the myelin oligodendrocyte glycoprotein (MOG) can augment demyelination. Anti-MOG antibodies display pathogenic effects in vitro (135). Few studies have described the presence of such antibodies in active MS brain lesions (136, 137). Interestingly, MOG antibodies can be detected in serum of healthy individuals by ELISA and Western blot but not by cell-based assays. Whether access of antibody to brain tissue or antibody fine specificity distinguishes patients from healthy individuals is not known.

Surprisingly, Diamond says that using MOG-transfected cells for antibody screening revealed MOG as a target antigen in approximately 40% of pediatric patients with acute disseminated encephalomyelitis (ADEM). High-titer antibodies to MOG are largely absent in adult MS patients but are detected in some patients with AQP4 IgG–seronegative NMO, pediatric MS, and optic neuritis using a cell-based immunofluorescence assay. ELISA and Western blot assays largely failed to detect these antibodies. These data illustrate the absence of a uniform assay for all brain-reactive antibodies.

Furlan et al. (2003) accidentally discovered that the combination of amyloid beta and pertussis toxin led to autoimmune encephalitis. Experimental evidence shows that vaccination with amyloid-beta of

transgenic mouse models of Alzheimer's disease protects from the pathological accumulation of amyloid within the CNS. Phase I/II clinical trials of amyloid beta vaccination in mild to moderate Alzheimer's disease have been undertaken. Unexpectedly, one of these trials has been suspended because 15 patients showed clinical signs consistent with CNS inflammation. In a recent mouse model C57BL/6 mice immunized with amyloid beta 1-42 peptide develop an inflammatory disease of the CNS characterized by the presence both in the brain and spinal cord of perivenular inflammatory foci containing macrophages, T and B cells, and immunoglobulins. The experimental disease was observed only when pertussis toxin, an agent known to favor autoimmune processes, was co-administered intravenously. Mice injected with amyloid beta alone did not show any abnormalities. The immune-mediated CNS reaction was associated to amyloid-beta-induced CD4(+) cells showing a Th1-type cytokine expression profile and to elevated levels of circulating anti-amyloid-beta immunoglobulins. Results indicate that vaccination with amyloid-beta could determine, under certain circumstances, an aberrant autoimmune-type reaction to amyloid-beta resulting in a perivenular inflammatory encephalomyelitis. http://www.ncbi.nlm.nih.gov/pubmed/12538398

Linker and Lee (2009) state that in mouse models, to initiate EAE, amyloid-beta peptides are combined with an adjuvant (freunds adjuvant or pertussis) to establish experimental autoimmune encephalitis and experimental allergic encephalomyelitis.

Cliffort et al. (2007) investigated the possibility that disruption of the integrity of the BBB can lead to a chronic influx of plasma components, including soluble Aβ peptides, into the brain. They also examined the fate of key soluble exogenous Aβ peptides, Aβ42 and Aβ40, within the brain parenchyma. To accomplish this, they tracked the fate of fluorescein isothiocyanate (FITC)-labeled Aβ peptides introduced via tail vein injection into mice in which the BBB had been compromised by prior exposure to pertussis. Results show that blood-borne FITC-labeled Aβ peptides can indeed traverse a defective BBB, enter into the brain parenchyma, bind selectively to the surfaces of certain neurons and, in the case of Aβ42, accumulate selectively within the same subtype of neurons that are known to exhibit prominent Aβ42-immunopositive deposits in AD brains. In view of the high incidence of BBB compromise in nearly all patients with AD, as supported here by direct detection of extravasated plasma components in AD brains, we propose that the blood represents a major and chronic source of exogenous, soluble Aβ42 that eventually deposits within neurons in AD brains. These findings provide a possible link between BBB compromise and the development of AD pathology and highlight the potential effectiveness of therapies aimed at maintaining and/or reinforcing the integrity of the BBB, lowering plasma levels of Aβ peptides and blocking the interactions of soluble exogenous Aβ peptides with neurons. The results showed that Aβ42 readily leaks through the defective blood–brain barrier (BBB) of arterioles into the parenchyma of AD brains, but only rarely in age-matched control brains.

Clifford et al (2007) applied immunohistochemistry to post-mortem human brains to determine if Aβ42 leaks from blood vessels through a defective BBB into the parenchyma of AD brains. If so, it might be possible to detect significant amounts of Aβ42 as well as other extravasated plasma components in these brains (Figs. 1A–D). Results showed that, in addition to the well-documented localization of Aβ42

within neurons, plaques and the walls of blood vessels, Aβ42 was also often localized to diffuse "perivascular leak clouds" occupying the region immediately surrounding arterioles (Fig. 1A). The gradual diminution in the intensity of Aβ42-positive immunostaining with increasing distance from arterioles is consistent with the notion that these blood vessels are the main source of the Aβ42 within the leak cloud. In most AD brains, leak clouds were not associated with capillaries or venules and thus appeared to be selective for arterioles (Figs. 1A–D). An exception to this selectivity was occasionally observed in regions of AD brains exhibiting particularly severe pathology, as noted by widespread neuronal loss, numerous amyloid plaques and signs of local inflammation. In this case, smaller and more numerous leak clouds were also found in association with capillaries and venules.
It is now generally accepted that a progressive accumulation of amyloid beta aggregates eventually triggers a cascade of cellular changes, including mitochondrial oxidative damage, the hyperphosporylation of tau, synaptic failure, and inflammation. However, initial triggers of mutant amyloid precursor protein and/or intracellular amyloid beta were not clearly understood in 2006 (Manczak et al. 2006). It is now known that amyloid beta can both lead to, and be a result of mitochondrial dysfunction. In 2011, Pagani and Ekert sate that Aβ triggers mitochondrial dysfunction through a number of pathways such as impairment of oxidative phosphorylation, elevation of reactive oxygen species (ROS) production, alteration of mitochondrial dynamics, and interaction with mitochondrial proteins. Mitochondria were found to be the target both for amyloid precursor protein (APP) that accumulates in the mitochondrial import channels and for Aβ that interacts with several proteins inside mitochondria and leads to mitochondrial dysfunction. In a more recent study, Leuner et al. (2012) induced complex I and III dysfunction in a cell model using the respiratory inhibitors rotenone and antimycin, resulting in mitochondrial dysfunction and enhanced ROS levels and elevated levels of Amyloid beta. Leuner also found that dysfunction in complex I alone increased amyloid beta.

Glycoprotein can serve as a Pertussis Antigen

In Lassman's 2010 work attempting to differentiate between acute disseminated encephalomyelitis, he/she refers to a classical post-infectious or post-vaccinal acute disseminated encephalomyelitis as a monophasic inflammatory disease with sparse perivenous demyelination resembles, in many respects, experimental autoimmune encephalomyelitis (Alvord 1985). However, considering the multiplicity of different agents that can trigger this condition, it is not clear whether post-infectious acute disseminated encephalomyelitis can be subsumed under a single disease entity. Furthermore, experimental autoimmune encephalomyelitis can present pathologically, not only with perivenous but also with confluent demyelination, depending upon the immunological mechanisms of disease (Lassmann, 1983).

Hans Lassmann (2010) notes that A substantial number of children with inflammatory demyelinating disease present with very high antibody titres against a conformational epitope of myelin oligodendrocyte glycoprotein, which is the target of demyelinating antibodies (O'Connor *et al.*, 2007; Brillot *et al.*, 2009). Such antibodies are particularly prevalent in children who develop inflammatory demyelinating disease under the age of 10 years; and the incidence of patients with such autoantibodies decreases with age. These patients present with an acute disseminated encephalomyelitis or multiple

sclerosis-like clinical disease. However, the pathology shows widespread primary demyelination, as seen in multiple sclerosis, and experimental studies indicate that such antibodies can indeed induce demyelination *in vitro* and *in vivo* (Zhou et al., 2006; Brillot et al.,2009).

Timing and Initiation of Experimental Autoimmune Encephalomyelitis

For obvious reasons, there are no human experiments to induce Autoimmune Encephalitis, Allergic Encephalitis, or Autoimmune Encephalomyelitis. In order to establish a range of probable timing between introduction of a triggering agent (bacterial, viral, toxic, or other), a review of animal models and human case studies are presented.

Experimental Animal Models

The pathogenesis and pathology of EAE varies considerably depending on the model animal and the source, chemical nature and anatomical distribution of the antigenic immunogen (Baxter 2007, Gold et al. 2006), or genetic factors and the specific immunogen/adjuvant used (Linkler and Lee 2009). In Furlan et al. (2003) autoimmune encephalomyelitis in all five mice injected with both amyloid beta and intravenous administration of pertussis toxin developed symptoms and signs evocative of a neurological disorder affecting the CNS between 13 and 20 days post-immunization. Symptoms and signs lasted for up to 75 days, with a caudo-cranial progression and a chronic course, making them indistinguishable from those observed in chronic forms of mouse EAE.

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5.8

Centers for Disease Control and Prevention Immunization Safety Office Updates

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Advisory Commission on Childhood Vaccines (ACCV)
December 8, 2017

Disclaimer

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

Topics

- Updates from the October 2017 meeting of the Advisory Committee on Immunization Practices (ACIP)
- Selected publications

Updates from the October 2017 meeting of the Advisory Committee on Immunization Practices (ACIP)

https://www.cdc.gov/vaccines/acip/meetings/downloads/agenda-archive/agenda-2017-10.pdf

ACIP update – herpes zoster vaccine

- Herpes zoster adjuvanted subunit (HZ/su) vaccine
  - Strong evidence that HZ/su is efficacious and durable
  - Minimal waning in 1st 4 years post-vaccination
  - Acceptable safety profile, but locally reactogenic (contains AS01 adjuvant)
  - 21% of herpes zoster episodes occur in age group 50-59 years each year
  - Cost effectiveness similar to or more favorable than other adult vaccines

ACIP update – herpes zoster vaccine

- HZ/su vaccine and zoster vaccine live (ZVL)
  - HZ/su and ZVL have not been studied in head-to-head efficacy trial
  - However, HZ/su estimates of efficacy are significantly higher than ZVL across all age groups
    - 60-69 years, 97% vs. 64%
    - 70-79 years, 91% vs. 41%
    - ≥80 years, 91% vs. 18%
  - Hz/su vaccine effectiveness (VE) >91% in 1st year and ≥85% during 1st 4 years for all ages
  - Significant waning of protection from ZVL: by 6 years post-vaccination, VE <35%, with negligible protection by 10 years

ACIP update – herpes zoster vaccine

- HZ/su vaccine and zoster vaccine live (ZVL), continued
  - Vaccination with HZ/su 5 years following ZVL did not alter the safety or immunogenicity of HZ/su
  - Neither vaccine associated with serious adverse events in immunocompetent persons, although HZ/su is more reactogenic than ZVL
  - HZ/su leads to more disease prevention and decreased overall costs

ACIP update – herpes zoster vaccine

Votes

- Should ACIP recommend HZ/su for vaccination of immunocompetent adults aged ≥50 years?
  - Yes: unanimous
- Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL? (minimum interval of 8 weeks)
  - Yes: 12 to 3
- Should ACIP recommend HZ/su be preferred over ZLV?
  - Yes: 8 to 7

*Language regarding votes is provisional until published in the MMWR

HZ/su vaccine safety

- Limited safety data exists on AS01 adjuvant and on the safety of vaccination with HZ/su in persons that have previously received ZVL
  - Safety monitoring for HZ/su will be important during the uptake period
  - Safety monitoring will include enhanced VAERS surveillance, rapid cycle analysis in CDC's Vaccine Safety Datalink, and manufacturer post-marketing commitment studies

ACIP update – hepatitis vaccine

- HEPLISAV-B vaccine (Dynavax); not yet licensed at time of October 2017 ACIP meeting
  - Contains yeast-derived recombinant hep B surface antigen (20 ug HBsAg) and Adjuvant-Toll-like receptor 9 (TLR9) agonist 1018 (3 mg)
  - Administered 2 doses over 1 month vs. 3 doses over 6 months for other hep B vaccines
  - Induces high rate of protection in all adults including those with reduced responses to current vaccines
  - Similar safety profile to the Engerix-B hep B vaccine except imbalances in:
    - Prostate cancer for Engerix-B
    - Acute myocardial infarction for HEPLISAV-B

ACIP update – influenza

- Influenza surveillance
  - Influenza A (H3N2) viruses have predominated in the United States since July 2017
  - Low activity into October 2017
  - Majority of circulating viruses similar to those in 2017-18 vaccine

ACIP update – influenza

- Update on live attenuated influenza vaccine (LAIV) effectiveness*
  - In five clinical studies, LAIV effectiveness for H3N2 strains show an estimate of 45% which is comparable to inactivated influenza vaccine
  - In vitro investigations identified reduced replicative fitness of post-pandemic H1N1 strains as likely root cause of reduced effectiveness
  - Additional data on LAIV effectiveness will be available in December 2017
  - Improvements in strain selection will help inform ACIP recommendation on future use of LAIV in next few months

*LAIV not recommended for the 2017-2018 influenza season

ACIP update – influenza

- Donahue et al. (2017). Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12
  - In the Vaccine Safety Datalink (VSD), miscarriage significantly associated with IIV receipt in the 28 day exposure window
    - Similar VSD study before 2009 pandemic and other studies have not found an association between IIV and miscarriage
  - Association between IIV and miscarriage significant in 2010-11, but not 2011-12
  - In both seasons, association was elevated only in the 28-day window and only in women who received pH1N1-containing vaccine in the prior season
- Follow-up case-control study in VSD is underway
- No policy change proposed

ACIP update – mumps

- Numerous mumps outbreaks since 2015, majority in university settings
- Workgroup had discussed evidence on MMR vaccination in outbreak settings that a 3rd dose of MMR would improve protection for those at increased risk due to outbreak

Vote

- Persons previously vaccinated with 2 doses of MMR and who are at increased risk of mumps due to outbreak should receive a 3rd dose
  - Vote passed unanimously*

*Language regarding votes is provisional until published in the MMWR

ACIP update – shoulder dysfunction following immunization

- VAERS reports from 2010-16 of shoulder dysfunction following IIV
  - Ranged from 128-223 reports per season during six influenza seasons
  - Higher % of reports among females vs. non-shoulder dysfunction reports
  - 70% of reports in 19-59 year age group, <1% in 0-18 year age group
  - Most commonly reported possible contributing factor was vaccine given too high on the arm
  - Most commonly reported places of vaccination were pharmacies and doctor's offices/hospitals
  - Does not appear to be an increase in shoulder dysfunction reports to VAERS following IIV in recent influenza seasons
    - Around 2% of all IIV reports from 2010-11 season to 2015-16 season

ACIP update – other sessions

- Human papillomavirus vaccine
- Adult and child/adolescent immunization schedule vote
- Japanese encephalitis vaccine
- Pneumococcal vaccines

Selected publications

Selected publications

- Duffy et al. Febrile Seizure Risk after Vaccination in Children One to Five Months. Pediatr Neurol. 2017;76:72-78.
  - Vaccination in children aged 3 through 5 months was associated with a large relative risk of febrile seizure on the day of and day after vaccination, but the risk was small in absolute terms.
  - Post-vaccination febrile seizure should not be a concern for the vast majority of children receiving vaccines, but clinicians might take this risk into consideration when evaluating and treating children susceptible to seizures precipitated by fever.

Selected publications

- Arana et al. Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System. J Adolesc Health. 2017;61(5):577-582.
  - Postural orthostatic tachycardia syndrome (POTS) is rarely reported following HPV vaccination.
  - This VAERS review did not detect any unusual or unexpected reporting patterns that would suggest a safety problem.

Selected publications

- McCarthy et al. Patterns of childhood immunization and all-cause mortality. Vaccine. 2017. pii: S0264-410X(17)31442-1.
  - Although there were few deaths, the results do not indicate a difference in risk of all-cause mortality among fully vaccinated versus undervaccinated children.
  - Findings support the safety of the currently recommended immunization schedule with regard to all-cause mortality.

Selected publications

- Myers TR, McNeil MM. Current safety issues with quadrivalent meningococcal conjugate vaccines. Hum Vaccin Immunother. 2017 Sep 21:1-4.
  - Commentary describes the current state of knowledge with respect to the safety of quadrivalent meningococcal conjugate vaccines and identifies potential areas for safety research for these vaccines.

Selected publications

- Donahue et al. Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12. Vaccine. 2017 Sep 25;35(40):5314-5322.
  - Miscarriage was associated with influenza vaccination in the preceding 28 days.
  - The association was significant only among women vaccinated in the previous influenza season with pH1N1-containing vaccine.
  - This study does not and cannot establish a causal relationship between repeated influenza vaccination and miscarriage, but further research is warranted.

Selected publications

- Vickers et al. Risk of venous thromboembolism following influenza vaccination in adults aged 50 years and older in the Vaccine Safety Datalink. Vaccine. 2017 Oct 13;35(43):5872-5877.
  - Overall, there was no evidence that inactivated influenza vaccine was associated with VTE in adults ≥50years old. An increased risk was found among current smokers in a post hoc analysis.
  - These findings are consistent with previous research and support the safety of annual vaccination in this population.

Selected publications

- Woo et al. Postmarketing safety surveillance of trivalent recombinant influenza vaccine: Reports to the Vaccine Adverse Event Reporting System. Vaccine. 2017; 35(42): 5618-5621.
  - Allergic reactions following recombinant influenza vaccine were reported.
  - Occurrence of anaphylaxis and other allergic reactions in some individuals may reflect an underlying predisposition to atopy that may manifest itself after an exposure to any drug or vaccine, and it does not necessarily suggest a causal relationship with the constituents specific to the vaccine product administered.

Selected publications

- Gee et al. Risk of Guillain-Barré Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety Datalink. Vaccine. 2017 Oct 13;35(43):5756-5758.
  - No evidence of an increased risk of GBS following 4vHPV. With an upper 95% confidence limit, if an increased risk exists, would expect at most 1.08 additional cases of GBS per million people vaccinated with 4vHPV.

Selected publications

- Eaton et al. Birth outcomes following immunization of pregnant women with pandemic H1N1 influenza vaccine 2009-2010. Vaccine. 2017 Sep 13. pii: S0264-410X(17)31180-5.
  - Although constrained by small sample size, complex vaccine groups, and differential vaccine availability during 2009-2010, study found no difference in adverse birth outcomes between H1N1 vaccine and trivalent inactivated influenza vaccine.

Selected publications

- Kemper et al. Drinking Water to Prevent Postvaccination Presyncope in Adolescents: A Randomized Trial. Pediatrics. 2017 Nov;140(5). pii: e20170508.
  - Drinking water before vaccination did not prevent postvaccination presyncope.
  - Predictors of postvaccination presyncope suggest opportunities for presyncope and syncope prevention interventions.

Selected publications

- Walter et al. The effect of antipyretics on immune response and fever following receipt of inactivated influenza vaccine in young children. Vaccine. 2017 Oct 19. pii: S0264-410X(17)31416-0.
  - Significant blunting of the immune response was not observed when antipyretics were administered to young children receiving IIV.
  - Studies with larger sample sizes are needed to definitively establish the effect of antipyretics on IIV immunogenicity.

Selected publications

- Stockwell et al. A multi-site feasibility study to assess fever and wheezing in children after influenza vaccines using text messaging. Vaccine. 2017 Oct 28. pii: S0264-410X(17)31481-0.
  - Text messaging can provide information about pediatric post-vaccination fever and wheezing and was viewed positively by parents.
  - It could be a helpful tool for rapid vaccine safety monitoring during a pandemic or other emergency vaccination program.

Selected publications

- VanWormer et al. Association between parent attitudes and receipt of human papillomavirus vaccine in adolescents. BMC Public Health. 2017; 17(1):766.
  - Reductions in parents' uncertainties appeared to result in greater likelihood of their children receiving the HPV vaccine.
  - Only baseline concerns about vaccine harms were associated with lower series completion rate.
  - Education for parents should emphasize the HPV vaccine's safety profile.

Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

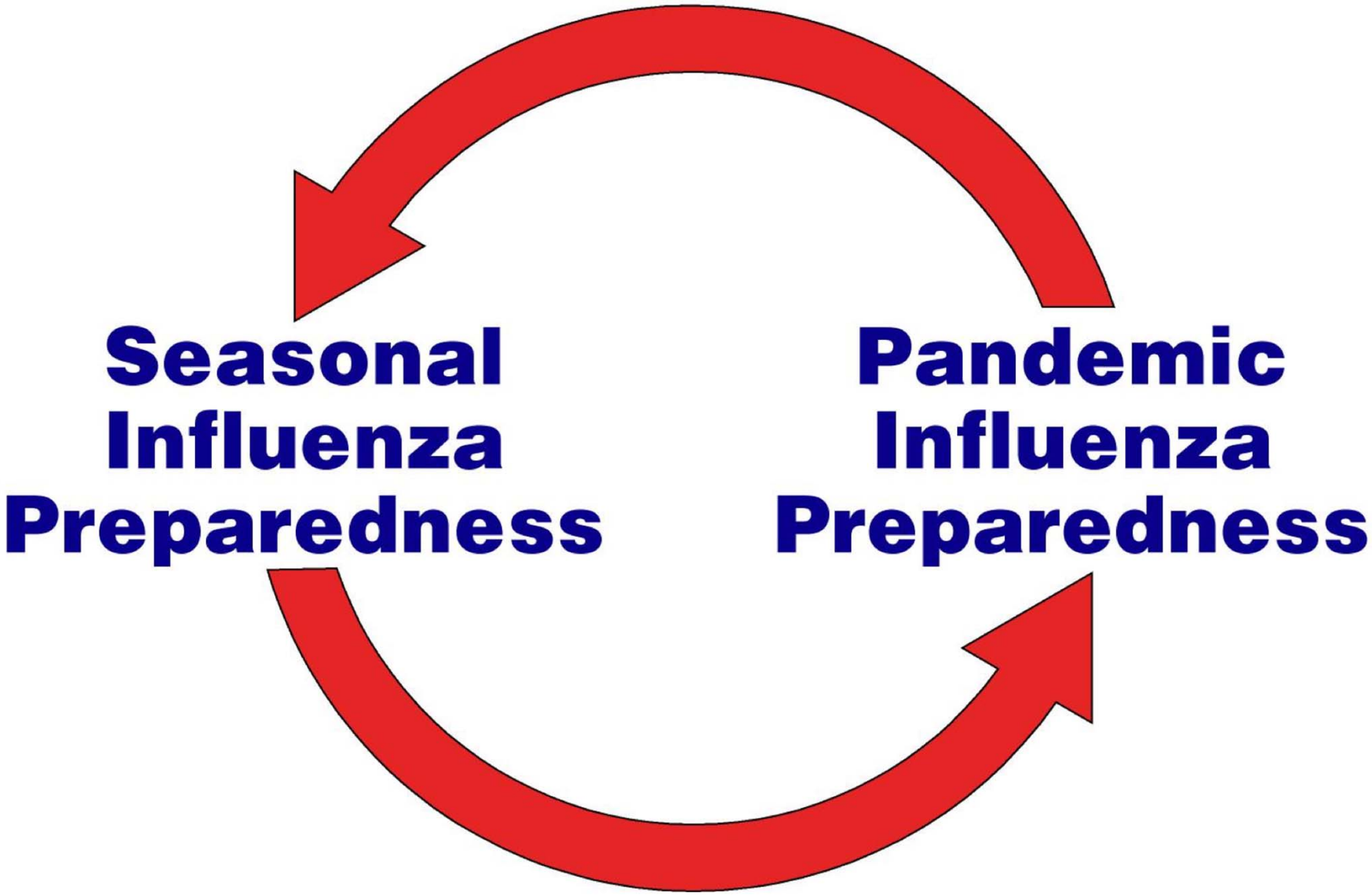
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

5.9

National Institutes of Health Update

Claire Schuster, MPH
National Institute of Allergy and Infectious Diseases
National Institutes of Health

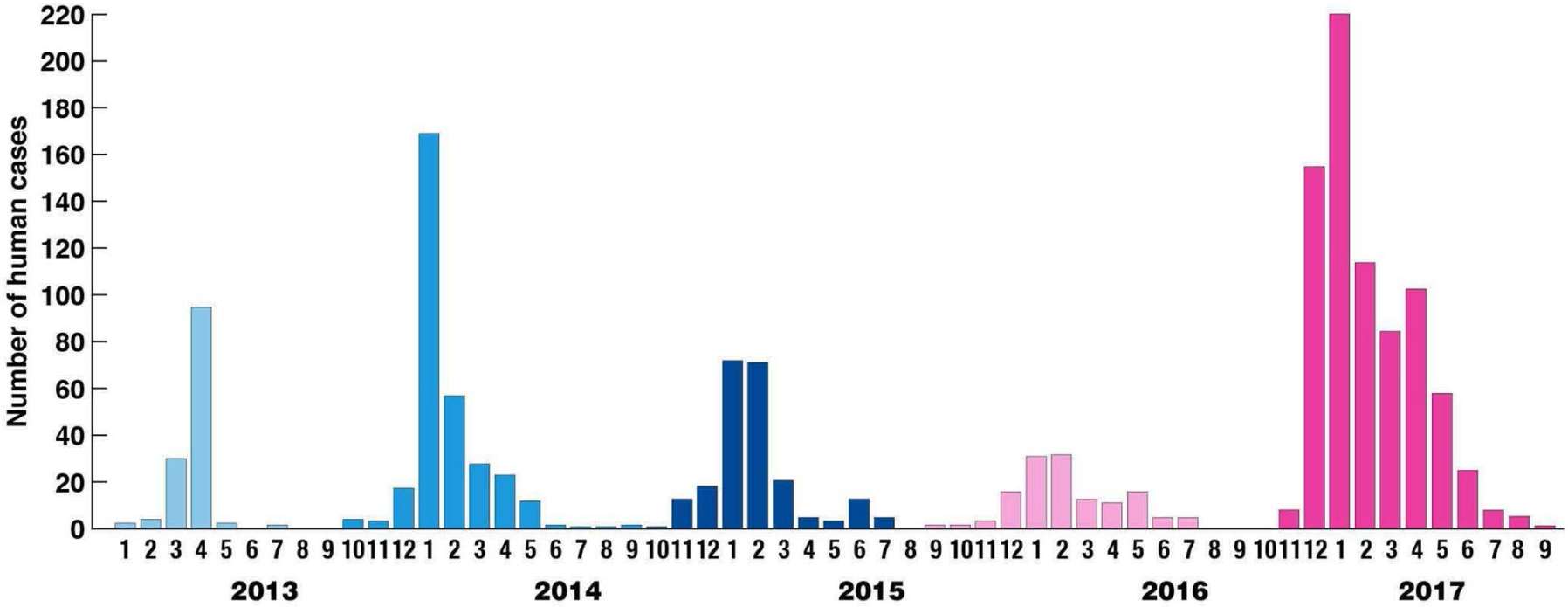
December 2017



AS Fauci/NIAID

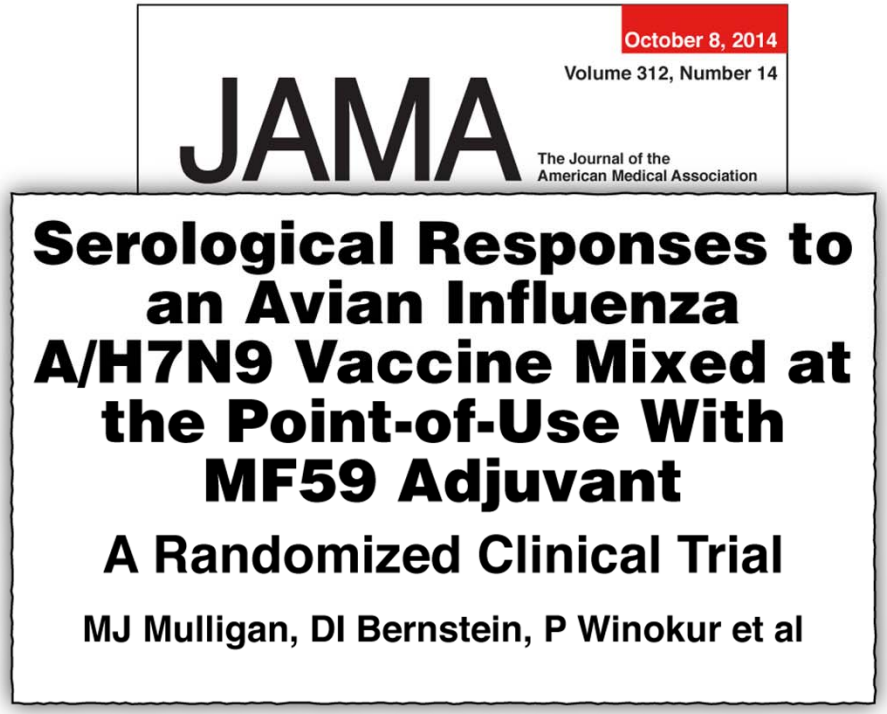
Five Waves of Human H7N9 Influenza Infections in China, February 2013-present

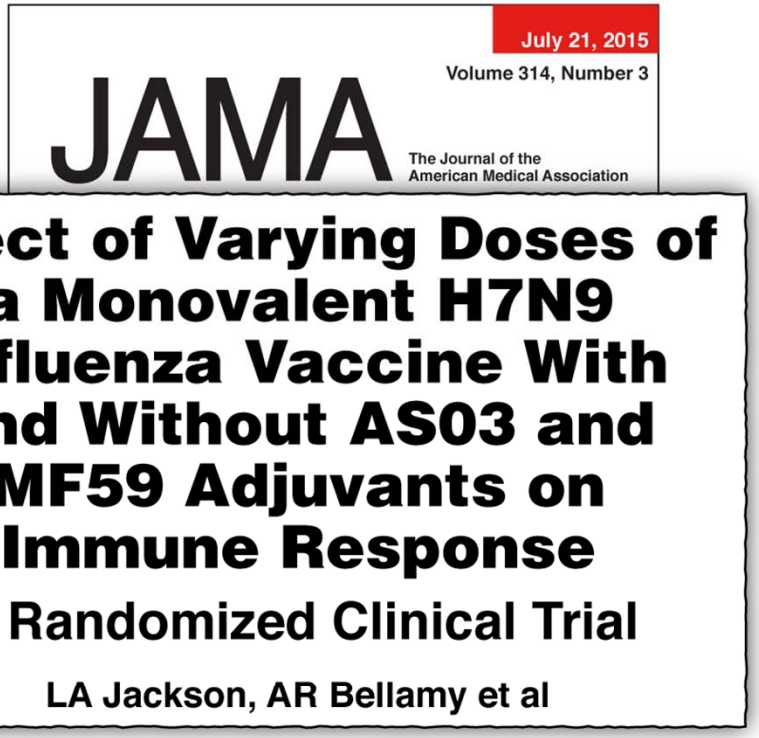
- **1,622** confirmed human cases, **619** deaths
- 5th wave: >50% of cumulative cases



Source: FAO, 10/25/17

Phase 2 Trials of 2013 H7N9 Vaccine in Healthy Adults



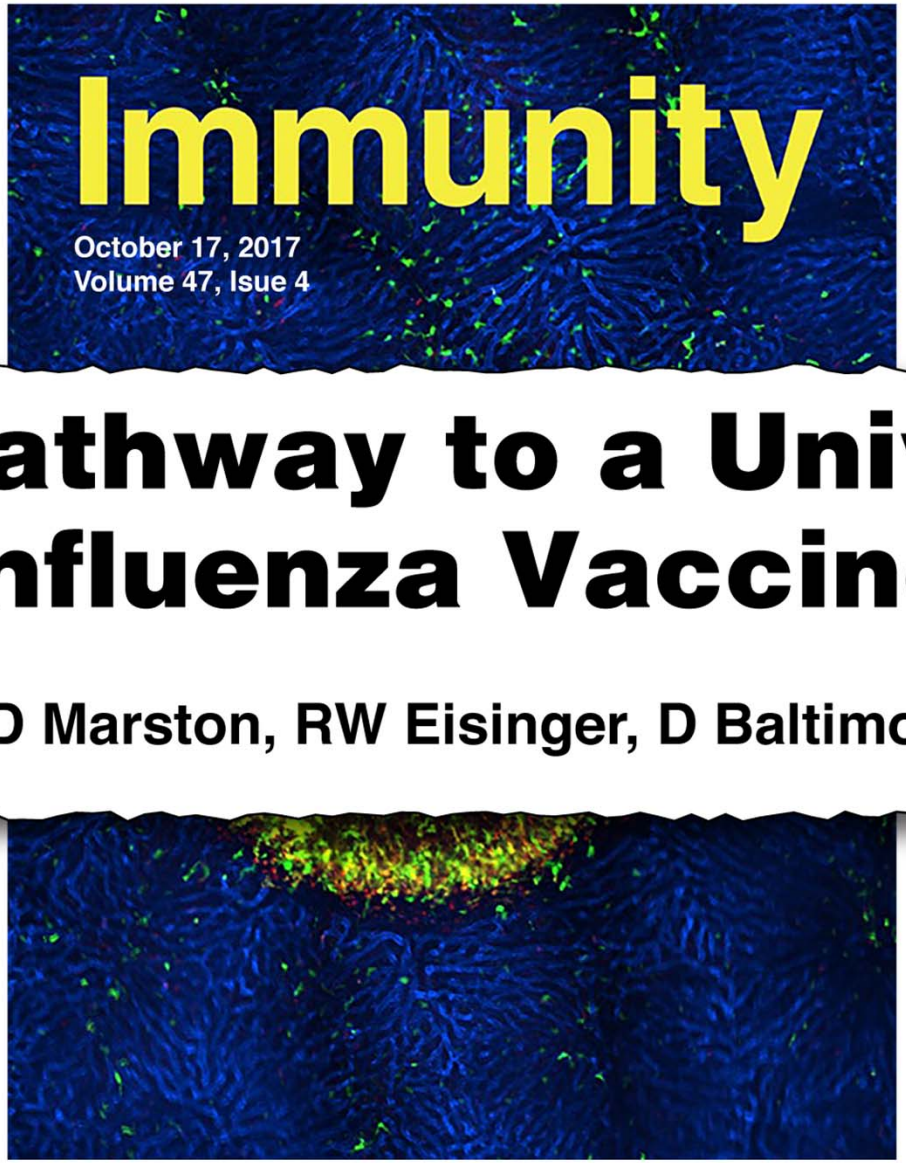


- ***Acceptable safety profile; two adjuvanted doses needed to induce adequate immune response***

STAT

May 1, 2017

As Bird Flu Spreads, US Concludes Its Vaccine Doesn't Provide Adequate Protection



The Pathway to a Universal Influenza Vaccine

CI Paules, HD Marston, RW Eisinger, D Baltimore, AS Fauci

Ebola Vaccine Research

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
October 11, 2017

Experimental Ebola vaccines elicit year-long immune response

NIH reports final data from large clinical trial in West Africa.

- NIAID-sponsored Phase 2 clinical trial
- Conducted by U.S.-Liberia Partnership for Research on Ebola Virus in Liberia (PREVAIL)
- Two candidate Ebola vaccines elicit immune responses by one month after initial vaccination that last for at least one year

SB Kennedy *et al*. Phase 2 Placebo Controlled Trial of Two Vaccines to Prevent Ebola in Liberia. *N Engl J Med*. (2017 Oct 12)

NIH National Institute of Allergy and Infectious Diseases

Environmental influences on Child Health Outcomes (ECHO) Program

- New seven-year NIH initiative to investigate environmental exposures on child health and development
- Will support multiple, synergistic, longitudinal studies using existing study populations
- Launched study focusing on newborns affected by opioids
  - Funded by ECHO and NIH's *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
  - ACT NOW (Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome)

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

NIAID Now Blog

https://www.niaid.nih.gov/news-events/blog

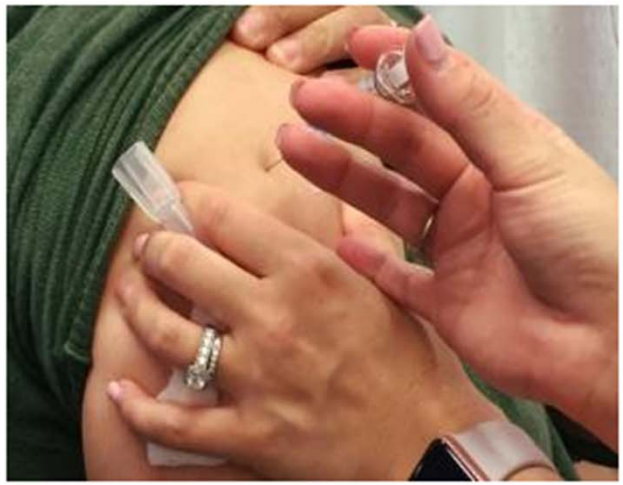
National Institute of Allergy and Infectious Diseases

NIAID Now Blog

Can Your Immune Profile Predict How You'll Respond to Flu Vaccination?

August 25, 2017

In a new study, researchers describe immune profiles measured prior to vaccination that may predict a person's antibody response to the seasonal flu vaccine. Their findings also indicate that immune states that predict good vaccine responses in young adults may be associated with poorer responses in older people.



NIH National Institute of Allergy and Infectious Diseases

5.10

Advisory Commission on Childhood Vaccines (ACCV)

Food and Drug Administration Update

December 8, 2017

CDR Valerie Marshall, MPH
Immediate Office of the Director
Office of Vaccines Research and Review (OVRR)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

Outline

- **Vaccine Approvals**
- **Advisory Committee Meeting**

Vaccine Approvals

Zoster Vaccine Recombinant, Adjuvanted (Shingrix)

- Approved by FDA in October 2017
- Manufactured by GSK
- For prevention of herpes zoster (shingles) in adults aged 50 years and older.
  - After the age of 50, a person's risk for shingles increases.
  - Shingles typically presents as a painful, itchy rash that develops on one side of the body and can last for two to four weeks.
  - Even once the rash is gone, a person can experience postherpetic neuralgia (PHN), pain lasting from at least three months up to several years.
- Shingrix is a non-live, recombinant adjuvanted subunit vaccine given intramuscularly in two doses.

Hepatitis B Vaccine, Recombinant, Adjuvanted (Heplisav)

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

Advisory Committee Meeting

Advisory Committee Meeting

- **The Vaccines and Related Biological Products Advisory Committee** met on November 7 to
  - Discuss the clinical development plan of Pfizer's investigational Staphylococcus aureus vaccine (SA4Ag) vaccine intended for pre-surgical prophylaxis in elective orthopedic surgical populations.
- Invasive *Staphylococcus aureus* infections (SSIs) are a serious complication after elective surgeries and result in significant morbidity and mortality.
- Based on data reported to CDC's National Healthcare Safety Network for healthcare-associated infections (HAIs) that occurred in 2011-2014, SSIs accounted for 36.4% of HAIs reported.
- Overall, *S. aureus* was the most prevalent pathogen isolated from SSIs (20.7%).

Advisory Committee Meeting (continued)

- To address this unmet medical need, Pfizer has proposed a clinical development plan to support traditional approval of their investigational SA4Ag vaccine for use in adults undergoing elective orthopedic surgery.
- The purpose of this VRBPAC meeting was to seek input regarding the clinical data needed to support an indication for use in adults undergoing elective orthopedic surgery, with a focus on the extent to which safety and efficacy data accrued in a spinal surgery population can be generalized to other elective orthopedic surgical populations.

Advisory Committee Meeting (continued)

- Briefing Materials and Other Information
  - https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm538209.htm

Thank you!


FDA
U.S. FOOD & DRUG
ADMINISTRATION

5.11

THE VACCINE CONFIDENCE MEETING

Collaborating to Advance Vaccine Confidence

Meeting Report
August 15–16, 2017
Atlanta, Georgia

NVPO

EMORY

THE VACCINE CONFIDENCE MEETING

Collaborating to Advance Vaccine Confidence

Table of Contents

Introduction

As vaccine-preventable diseases become increasingly less visible, and new vaccines become available to address new and emerging disease threats, health care providers, parents, and individuals need to have confidence in vaccines and their decisions to receive recommended vaccinations. Critical steps towards achieving those ends include facilitating partnerships and sharing knowledge on research and practice.

What is vaccine confidence?

The trust that parents, patients, or providers have in:

- Recommended vaccines
- Providers who administer vaccines
- Processes and policies that lead to vaccine development, licensure, and recommendations for use

The Vaccine Confidence Meeting, cohosted by the National Vaccine Program Office (NVPO) and Emory University, brought together stakeholders from academic research groups, government agencies, and health care provider organizations, along with members of the broader vaccination enterprise to examine the latest insights from research and practice on increasing vaccine confidence in the United States and around the world.

Recommendations from the National Vaccine Advisory Committee (NVAC) and feedback from stakeholders informed the meeting's structure and content (see Appendix A for the meeting agenda). Held August 15–16, 2017 in Atlanta, Georgia, the meeting placed particular emphasis on identifying and examining the practical implications of the presentations. Meeting objectives for attendees included:

- Learning more about the work being done to address vaccine confidence, hesitancy, and acceptance
- Sharing new research and identifying research gaps
- Strengthening the community of professionals working to increase vaccine confidence
- Meeting and speaking with leaders in related fields

This report summarizes perspectives and comments made during the Vaccine Confidence Meeting (see list of sessions and speakers below; speaker and moderator bios are in Appendix B). Judy Mendel of NVPO and Saad Omer of Emory University planned and facilitated the meeting. Representatives from government agencies, academia, health care agencies, nonprofit organizations, and the private sector gave presentations while attendees provided input, recommendations, and queries as necessary. The meeting was organized into 4 thematic sessions:

- Measuring and monitoring vaccine confidence
- Building and fostering confidence using public communication approaches, which included an interactive session on using advertising concepts to promote influenza vaccination
- Values, confidence, and vaccine acceptance
- System approaches to building confidence

Sectors Represented at the Meeting 76 individuals attended the meeting:

- 55% (*n* = 42) from academia
- 17% (*n* = 13) from the federal government
- 16% (*n* = 12) from nonprofit, advocacy, and membership organizations
- 4% (*n* = 3) from state or local health departments
- 8% (*n* = 6) from other sectors such as health care systems and advertising

Opening Plenary

- Judy Mendel, MPH, NVPO (cohost)
- Saad Omer, MBBS, MPH, PhD, Emory University (cohost)
- Brendan Nyhan, PhD, Dartmouth College (keynote speaker)

Measurement and Monitoring: Research Insights into the Vaccine Confidence Landscape

- Glen Nowak, PhD, University of Georgia (moderator)
- Gaëlle Vallée-Tourangeau, MSc, PhD, Kingston University
- Allison Kennedy Fisher, MPH, Centers for Disease Control and Prevention (CDC)
- Paula Frew, PhD, MA, MPH, Emory University
- Sandra Quinn, PhD, University of Maryland School of Public Health

Building and Fostering Confidence Using Public Communication Approaches

- Ann Aikin, MA, NVPO (moderator)
- Alisa Johnson Athen, MA, Hennepin County, Minnesota, Public Health Department
- Amelia Burke-Garcia, MA, Westat
- Leslie Schrader, MA, Ketchum
- David Rauch, Creative Director and Health Care Consultant
- Norma Birnbaum, Publicis LifeBrands

Values, Confidence, and Vaccine Acceptance

- LJ Tan, MS, PhD, Immunization Action Coalition (moderator)
- Robert Bednarczyk, PhD, Emory University
- Amanda Dempsey, MD, PhD, MPH, University of Colorado at Denver
- Melissa Gilkey, PhD, University of North Carolina at Chapel Hill
- Noni MacDonald, MD, MSc, FRCPC, FCAHS, Dalhousie University

Systems Approaches to Building Confidence

- Allison Kennedy Fisher, MPH, CDC (moderator)
- Saad Omer, MBBS, MPH, PhD, Emory University
- Jason Schwartz, PhD, Yale University
- Sean O'Leary, MD, MPH, University of Colorado at Denver
- Dan Salmon, PhD, MPH, Johns Hopkins University
- Catherine Flores Martin, California Immunization Coalition
- Mimi Kiser, DMin, MPH, Emory University

Closing Plenary

- Judy Mendel, MPH, NVPO (cohost)
- Saad Omer, MBBS, MPH, PhD, Emory University (cohost)
- Walt Orenstein, MD, DSc (Hon), Emory University (closing speaker)

Meeting Summary

Opening Plenary

Judy Mendel of NVPO and Saad Omer of Emory welcomed attendees to the Vaccine Confidence Meeting. Ms. Mendel provided an overview of the meeting objectives, structure, and content. She also reviewed the development of the NVPO's Vaccine Confidence Strategy. Dr. Omer thanked the audience for participating in this first-of-its-kind meeting and then introduced the keynote speaker, Brendan Nyhan.

Keynote presentation. Dr. Nyhan of Dartmouth College presented a talk entitled "Echo Chambers and the Challenges of Communicating in the 21st Century." The purpose of his presentation was to "prime the pump" and encourage dialogue among the attendees regarding approaches to overcoming communication challenges in vaccine promotion.

Even when providing factual information and proven science, 2 barriers to communication exist:

- *Selective exposure*, where individuals only pursue information that is consistent with their attitude and beliefs. Selective exposure runs the risk of developing an "echo chamber," where particular ideas, beliefs or even data are reinforced through replication within a closed system that forbids unrestricted movement of alternative or competing ideas or concepts. In this case, certain notions or

Facts are not enough.
Selective exposure and selective acceptance create barriers to effective communication about vaccines.

conclusions are adopted because of an inherent unfairness in how information was gathered.

- *Selective acceptance*, where individuals deny information that is inconsistent to their attitude and beliefs. The foundation of selective acceptance is *directionally motivated reasoning*, which causes individuals to validate their beliefs while ignoring contrary facts, and develop reasoning to defend their logic.

With the increase of fake news and myths regarding vaccines, more research on overcoming selective exposure and selective acceptance is needed to combat vaccine hesitancy. To this end, Dartmouth College, in collaboration with the Vermont Department of Health, will conduct a field experiment through the National Academy of Sciences (Building Capacity for Science Communication Partnership Award). This study will examine the effects of messages sent to parents regarding vaccines. There will be registry outcomes to test effectiveness in changing behavior.

What works best for messaging is an unresolved area. While no magic bullet or a one-size-fits-all message exists, Dr. Nyhan recommended some strategies to counteract the communication barriers relating to vaccines:

- Work within communities to determine the most effective approaches
- Quickly stop myths before they spread widely
- Minimize controversy and value conflict, which enhance directionally motivated reasoning
- Promote social norms and defaults
- Find effective points of intervention, like trusted intermediaries
- Avoid conflicts in the media
- Maintain, when possible, consensus across the political and ecological spectrum in favor of vaccines

He also noted areas needing more investigation to improve the science of vaccine promotion:

1. Better early warning systems
2. More experiments
3. More behavioral measures
4. More systematic training of providers
5. Better estimates of regulatory effects

Discussion. One attendee raised a concern about the growing wellness industry, whose claims of effectiveness are rarely confirmed by science and research. How can messages effectively contradict claims from the wellness arena? Dr. Nyhan suggested working with the public where they are and meshing vaccine messages into the wellness concept. Another attendee warned

against overselling vaccine safety in messaging. Honest dialogue, she expressed, could lend more credibility. She also suggested meeting parents where they are to decrease resistance. Another recommendation was to engage parents before beliefs are internalized, using opportunities for obstetricians to educate them before their babies arrive. Dr. Nyhan agreed but noted that obstetricians may not prioritize this education in their work.

Measuring and Monitoring: Research Insights into the Vaccine Confidence Landscape

Glen Nowak of the University of Georgia moderated this panel discussion. Topics in this session included conceptualizing the determinants of vaccine uptake, surveying vaccine confidence, and measuring vaccine confidence.

Conceptualizing the determinants of vaccine uptake. Gaëlle Vallée-Tourangeau of Kingston University presented a talk entitled "The 5 A's: A Practical Taxonomy for the Determinants of Vaccine Uptake." The development of this taxonomy arose from an attempt to answer a practical question: How can research diagnose the likely root causes of the vaccination coverage gap? A gap exists between what public health officials deem as suitable coverage rates for vaccination and the actual coverage rates. Research shows the influences of values, experiences, context, and culture ultimately shape individuals' behaviors with regards to vaccinations.

From this research were derived these root causes of vaccine-related behavior:

1. *Access:* the ability of individuals to be reached by, or to reach, recommended vaccines
2. *Affordability:* the ability of individuals to afford vaccination, both in terms of financial and nonfinancial costs (e.g., time)
3. *Awareness:* the degree to which individuals know of the need for, and availability of, recommended vaccines and their objective benefits and risks
4. *Acceptance:* the degree to which individuals accept, question, or refuse vaccination
5. *Activation:* the degree to which individuals are nudged towards vaccination uptake

Dr. Vallée-Tourangeau described the 5 A's as "levers." The optimal adjustment and pulling of these levers will ultimately increase vaccine uptake.

One approach used to test the validity of the 5 A's was to review articles on vaccination and immunization acceptance to uncover factors that lead to uptake. Those factors were then

Finding and Using Levers of Change
The optimal adjustment and pulling of these levers — root causes of the vaccination coverage gap — will ultimately increase vaccine uptake.

classified in the taxonomy of the 5 A's. Another strategy employed was to review studies that used a variety of methods (e.g., surveys, interviews) across populations (e.g., parents of infants, the elderly), which found that meaningful categorization of the "levers" identified in study findings could be made using the 5-A taxonomy. Dr. Vallée-Tourangeau stressed that the 5 A's are not a solution but instead a tool or a roadmap that can help create strategies to address any gaps in a contextualized setting using questions to identify which levers to tweak to increase vaccine uptake.

Surveying vaccine confidence. Allison Kennedy Fisher of CDC presented a talk entitled "CDC National Center for Immunization and Respiratory Diseases Efforts around Surveillance of Vaccine Confidence." CDC has completed research regarding parents', patients', and health care providers' knowledge and attitudes regarding vaccines that were used to inform education and outreach efforts to be used across an individual's lifespan. Ms. Fisher's presentation focused on 3 recent projects completed by CDC: the 2016 National Poll of Parents, the Longitudinal Mothers Survey, and several cognitive interviews with vaccine-hesitant parents.

<u>2016 National Polls of Parents</u>
The goal of this study was to assist CDC in better understanding the behaviors, questions and concerns surrounding childhood immunization, and to develop messages, communication products, and recommendations to help improve national immunization rates.

The specific objectives were to:

1. Assess vaccine knowledge attitudes and beliefs
2. Determine self-reported vaccination behaviors and vaccination plans
3. Explore parental perceptions of health care professional communication

CDC collected data via GfK KnowledgePanel®, an online survey of 2,510 parents of children under the age of 7 years old. Key findings of the study included the following:

- Most parents surveyed stated that they consented to vaccines for their children as suggested
- Irrespective of vaccination beliefs, most parents considered their child's doctor a trusted source of vaccine knowledge
- The number of vaccines, vaccine ingredients, and potential side effects were common apprehensions

Longitudinal Mothers Survey

The goal of this study was to examine mothers' knowledge, attitudes, beliefs, behaviors, and information needs throughout the vaccination process, from the second trimester of pregnancy to their child's 19th month of life.

The specific objectives were to:

1. Understand how mothers' needs, expectations, and attitudes change over time
2. Identify how best to meet those needs and expectations
3. Identify any critical decision points in the vaccination process

CDC collected data through a series of 7 online surveys conducted for a panel of 200 pregnant women or first-time moms beginning in their second trimester of pregnancy and ending when their child was 19 months old. Key findings of the study included the following:

- Maternal choices on vaccine acceptance were almost always made before a child was born and stayed relatively unchanged over time
- Confidence in vaccines was relatively high and stable, but did rise with time and experience
- Participants most commonly spoke with their child's doctor about their vaccine questions and concerns — these conversations were most common at the 2-month well visit
- There is room for improvement in mothers' perceived satisfaction with vaccine discussions during office visits

Interviews with Vaccine-Hesitant Parents

The goal of this study was to test messages and materials with vaccine-hesitant parents. The specific objectives were to:

1. Explore thoughts and perceptions on messages and materials designed for parents about childhood vaccination
2. Examine whether existing messages and materials address vaccine-hesitant parents' questions and concerns
3. Identify possible improvements in how CDC communicates with this audience
4. Identify whether additional informational opportunities or outstanding informational needs exist

CDC collected data via interviews with 24 parents or caregivers of children ages 0 through 23 months with an expressed hesitancy toward childhood vaccinations. Key findings of the study included the following:

- Interview participants wanted to know more about the potential short-term and long-term side effects of vaccines, as well as the potential consequences of not vaccinating

- Parents did discuss vaccines with their child's doctor, but trust in the doctor's information and advice varied
- Materials were well-received by parents

Ms. Fisher concluded her talk by describing CDC's future directions regarding surveillance of vaccine confidence:

- Continuing to perform lifespan exploration on vaccine knowledge, attitudes, and practices
- Continuing to aid parents and health care professionals in their conversations about vaccines
- Discovering new ways to involve parents and prenatal health care professionals earlier in the decision-making process
- Strengthening collaborations and capacity to address vaccine confidence locally

Measuring vaccine confidence among parents. Paula Frew of Emory presented a talk entitled "Development of an Index for Measurement of Parents' Vaccine Confidence and Linkage to Pediatric Immunization Acceptance." This index is a proof-of-concept psychometric endeavor to gauge changes in parents' confidence at national, state, and community levels; and to measure vaccine confidence over time among parents in health systems. Data were collected via a national survey of 893 parents, guardians, and caregivers over the age of 18 in the U.S. who have children 7 years old or younger, and are able to read and comprehend English. Surveys included questions about the child's vaccination history and sociodemographic characteristics. Factor analysis was used to cluster 30 survey items into broader classes for the Vaccine Confidence Index (VCI): vaccine attitudes and beliefs, vaccine information, trust in government and experts, and social norms. The research team then created a summation scoring rubric for the VCI, calculated correlation between the VCI and immunization status, and ran logistic regression models for each vaccine.

Key findings from the development phase of the study included the following:

- There was a robust correlation between reported vaccine receipt and VCI score
- Increasing VCI score is parallel to increased odds of vaccine receipt
- Confidence, as measured by the VCI, appears to act autonomously of sociodemographic characteristics, which suggests scale robustness

Dr. Frew and her colleagues then fashioned an 8-item version of the VCI with strong internal reliability. To validate the results of the survey, 2 subsequent rounds of psychometric testing were added. The first occurred in July 2017, and the other is planned for December 2017. In the first validation sample, 831 respondents were matched to the 700 in the final dataset on criteria such as gender, age, race, education, and region using the 2013 American Community Survey

as a frame. The first-round validation results found very similar trends in robustness and recorded confidence values.

Dr. Frew concluded her talk by describing the next steps for the Index development process:

- A tool to identify populations, not topics
- Second validation test in December 2017
- Validation of the index using the vaccine confidence IIS surveillance system
- VCI extension testing for other populations
- Testing in clinical, research, and surveillance settings

Measuring vaccine confidence among African American and white adults. Sandra Quinn of the University of Maryland School of Public Health then presented a talk entitled "Exploring the Continuum: Measuring Vaccine Confidence and Hesitancy among African American and White Adults." This study was part of a larger line of research about cultural beliefs behind racial disparities in vaccines, in particular the influenza immunization. During flu season, hesitancy can contribute to increased morbidity, mortality and costs from flu.

The conceptual foundation of this study is the "3-C model" developed by the SAGE Working Group on Vaccine Hesitancy in 2015. According to this model barriers to vaccination fall into the following categories:

- *Complacency:* perceived risk of vaccine-preventable diseases is low, so individuals do not feel under enough threat to engage in protective behavior
- *Confidence:* strong negative attitudes toward vaccination, misinformed understanding about risks of vaccination, and/or conscious reactance against complying with vaccination norm or perceived coercion
- *Convenience:* when impediments to vaccination such as lack of access, cost, or travel time are stronger than the intention to vaccinate

The purpose of this study was to identify relationships and meaningful measures of general and flu vaccine specific hesitancy and confidence. Specifically, the research team sought to determine:

- The relationship between vaccine hesitancy and the 3 C's (complacency, convenience, and confidence)
- The relationship between vaccine hesitancy, vaccine confidence, and trust

Data were collected via the GfK online panel of U.S. adults: 63.1% whites and 51.2% African Americans (total sample size of 1,643). Overall, African Americans had a lower level of education and income compared to whites. Fewer African Americans got the flu vaccine

compared to whites but neither group was close to the Healthy People goal of 70%. Only data from those who had received a recommendation from their health care provider for an adult vaccine (flu, Tdap booster, Hep A and Hep B, shingles, or pneumococcal) were analyzed. The outcomes of interest were having had the flu vaccine this year and consistent acceptance of flu vaccine over 5 years.

Measures for the General Vaccine Hesitancy Model addressed the:

- Likelihood of acceptance if a doctor recommends a vaccine
- Acceptance of recommended vaccines
- General hesitancy about being vaccinated
- Trust in vaccines in general
- Necessity, importance, safety, effectiveness, convenience, and affordability of vaccines in general

Guided by the literature, the research team used confirmatory factor analysis to compare models that indicated different relations of the 3 C's and hesitancy. The final model defined the 3 C's (complacency, confidence, and convenience) and the hesitancy factor with shared indicator variables in a bifactor configuration (that is, the variances of the items that are not explained by one factor are further explained by the other factor). The indicators for the hesitancy factor included:

- The likelihood of accepting a doctor's recommendations for vaccines
- General hesitancy about vaccines
- Actual behavior on a set of recommended adult vaccines

These indicators for hesitancy were shared with the complacency, confidence, and convenience factors. Key findings based on measures for the General Vaccine Hesitancy Model included the following:

- Trust in vaccines was positively associated with confidence and convenience but negatively associated with complacency and hesitancy
- Adults with higher confidence in the flu vaccine were *less likely* to get the flu vaccine this season and in the past 5 years
- Those with greater vaccine hesitancy were less likely to get the flu vaccine this season and in the past 5 years

Regarding the unexpected finding that higher confidence in the flu vaccine was associated with lower likelihood to have been vaccinated, qualitative research conducted by Dr. Quinn and colleagues suggests that having confidence in the vaccine is not sufficient under conditions of high complacency and low perceived risk, as there is such significant complacency and a sense that the vaccine is not necessary.

The Flu Vaccine Hesitancy Model was created by adding 2 flu vaccine specific hesitancy items. Confirmatory factor analysis also found a good fit for a 4-factor model with confidence, convenience, and complacency as separate factors, now all specific to the flu vaccine, and shared with hesitancy, which is a separate factor. Key findings based on measures for the Flu Vaccine Hesitancy Model include:

- Trust in the flu vaccine was positively associated with confidence and convenience but negatively associated with complacency and hesitancy
- Adults with higher confidence in the flu vaccine are more likely to get the flu vaccine this season and in the past 5 years
- People with higher flu vaccine hesitancy are less likely to get the flu vaccine this season and in the past 5 years

Dr. Quinn noted that the 3 C's are similar to the 5 A's (discussed by Dr. Vallée-Tourangeau earlier) in that convenience is similar to access, and that affordability and complacency may contain similar items from awareness, including identifying need and benefits of the vaccine. Furthermore, hesitancy and confidence seem to echo acceptance, and convenience may have a part in activation and can assist in weakening complacency. From the findings of this study, she concluded that:

- We can most effectively measure hesitancy and confidence with the flu vaccine specific model
- Vaccine hesitancy and confidence are important concepts in flu vaccine uptake among adults
- Trust remains a key component associated with the 3 C's
- Complacency may be a more significant challenge than confidence

This research illustrates that monitoring and addressing complacency, for example through social media, is as important as addressing confidence and trust. It also demonstrates that the most effective communication messages are likely to be those that combine verbatim information with bottom-line meaning.

Discussion. One audience member noted the importance of separating awareness and compliance in adults versus children. For children, there is a mandate to vaccinate, which is not the case for adults. Mortality and morbidity burden of disease in adults is an important part of the discussion of vaccination compliance. The audience member stated that there was a danger in thinking too much about confidence in vaccine versus confidence in awareness of the disease burden itself. Dr. Quinn agreed with these sentiments but stated that while the perceived risk of the disease is important, it will not drive behavior. Particularly for African Americans, perceived risk of side effects from vaccines can trump disease risk.

Another audience member wondered if the VCI presented by Dr. Frew would help in studying, maybe over the course of 6 months or a year, the messages impacting vaccine confidence. Dr. Frew said the hope is to enable the VCI to be embedded in polls or surveillance systems to gauge the impact and to use the VCI to monitor over time whether sentiments change. A second validation test will be needed to identify any trends that have developed.

One audience member suggested that there may be a parallel to some vaccines in the past that caused concerns, as well as to lessons learned about how public health stakeholders listen to the public's concerns regarding safety and make changes. This could help to increase vaccine confidence and acceptance.

Finally, audience and panel members discussed the importance of proper conceptualization of the determinants of vaccine uptake to making progress in vaccine confidence. Dr. Vallée-Tourangeau suggested use of the 5-A taxonomy to help desegregate and unpack the problems and highlight where resources should be focused. One attendee observed that the 3-C model does not include religious context, which is a component that cannot be ignored.

Building and Fostering Confidence Using Public Communication Approaches

The second panel was moderated by Ann Aikin from NVPO. Topics in this session included communicating during an outbreak, promoting vaccine confidence using social media, and viewing vaccine confidence through the lens of advertising.

Communicating during an outbreak. Alisa Johnson Athen of the Hennepin County, Minnesota Public Health Department presented a talk entitled "Communications Planning and Implementation during an Outbreak." The unfounded claims of measles vaccinations being linked to autism caused a growing problem for Hennepin County, Minnesota. The county has approximately 1.2 million residents and of those residents, 13% are foreign born, mainly Somali-Minnesotan immigrants and refugees. It is not certain how the measles outbreak began, but the first confirmed case was in April 2017. Ultimately, 70 cases of measles showed up in Hennepin, with the majority of cases occurring in unvaccinated Somali-Minnesotan children. Approximately 9,000 individuals were exposed, and 22 cases resulted in hospitalization. Measles, mumps, and rubella (MMR) vaccination rates for the entire state remain at a good level of 89%, but the rates are only 42% for Somali Americans.

The county has effectively executed surveillance efforts due to its coordination with public health partners like state and county health departments and the Health Alert Network System. Responses were coordinated through an incident command structure. To support increased immunization, the state health department issued an accelerated MMR dosing schedule.

Clinicians were advised to assess MMR status among every patient they saw — and to recall children and adolescents whose records showed a gap in getting MMR.

Community outreach efforts proved to be the turning point in getting the outbreak under control. Community leaders trusted among Somali Americans made more than 150 visits to apartment buildings, businesses, community centers, and mosques to expose myths, provide education, and encourage immunization. Families excluded due to cases of exposure and individuals unreachable by phone received home visits. These visits particularly helped with reluctant individuals and provided a comfortable setting for candid discussions about their reluctance. This community outreach approach and messaging increased the number of vaccinations of Somali-Minnesotans in Hennepin County from about 200 to 1,600, a stunning 8-fold increase. During the 13-week period of the campaign (4/2/17 to 7/1/17), over 25,000 vaccines were given to Hennepin County residents compared with about 8,000 during the preceding 13-week period, an over 3-fold increase.

Ms. Athen ended her presentation with the following recommendations for mass communications and media relations:

- Seize the opportunity when the media is interested
- Anticipate and guide the "life cycle" of coverage
- Issue only facts and correct all misinformation
- Own your messages, stick to them, and shed the rest
- Let others own their parts
- Let the media do some work
- Trust the uncontrollable

Promoting vaccine confidence using social media. Amelia Burke-Garcia of Westat presented a talk entitled "The New Normal: Using Digital and Social Media in Support of Vaccine Communication." Ms. Burke-Garcia began by defining social norm marketing as the "[delivery of] normative information as a primary tool for changing socially significant behaviors." This type of marketing uses a non-confrontational tone and positive, reassuring messages, which may engender less resistance than policies that control behavior. She expressed her belief that social media can be used to help normalize health behaviors.

Approximately 70% of Americans use social media connect with others, explore news outlets, and disseminate information. In addition, social media is widely used among sociodemographic groups (e.g., members of racial and ethnic minority groups, older

Social media users are not a niche population.
Almost 3 in 4 Americans use social media. This diverse group includes members of racial/ethnic minority groups and older adults.

adults). Ms. Burke-Garcia highlighted a few success stories using social media. CDC's Flu Vaccination Program is a digital ambassador initiative to increase flu vaccine uptake. The effort employed 13 ambassadors, who shared more than 800 posts and garnered over 127 million impressions related to flu vaccination promotion. Another successful effort, blog relays, has generated 7 blog posts, 124 social media posts from collaborating partners, and 21.6 million total impressions emphasizing the importance of flu vaccinations. The #VaxWithMe hashtag campaign showcases famous athletes and entertainers receiving flu vaccinations. The effort has 575 participants, who assisted in generating 866 posts and 19 million impressions.

Ms. Burke-Garcia recommended thinking about people's social networks when considering social marketing. For the CDC influenza campaign, Meetup.com was used as a vehicle for social marketing. For this effort, 75 groups were selected and 17 recruited, with more than 300 people receiving vaccinations together. The messages reached more than 10,000 people. She ended the presentation with the following takeaway messages:

- All audiences are involved in social media
- Influencers can help spread the message in positive, appropriate ways
- Think about virtual and real life as being connected

Creating a social media strategy to reach millennials. Leslie Schrader of Ketchum presented a talk entitled "Promoting Flu Vaccination and Disease Prevention to Young Millennials." Most millennials think that the flu will not happen to them or that they are immune to it, so they are unlikely to internalize prevention messages. However, millennials are very moved when disease prevention is paralleled with aversion of pain and not missing out on personal activities. Clorox's hashtag education campaign, #FluFOMO, used the fear of missing out (FOMO) as part of its campaign strategy.

Clorox partnered with Sickweather, an online social health network with sickness forecasting and mapping features, to use trends in social media discussions about the flu to accomplish flu prevention education. By scanning social media platforms, Sickweather can predict where large outbreaks may occur. Clorox integrated this information into its website along with the tag #FluFOMO. Clorox also used these data to create public service announcements (PSAs), where individuals shared their FOMO. Celebrities also promoted the #FluFOMO PSA with their personal stories, and influencers started the conversation with blogs and social posts about their flu encounters and prevention tips. Experts also participated in interviews about flu prevention with leading media outlets providing medical advice.

Sickweather data were also used to create engaging content and infographics at key moments during the flu season to remind the public about flu prevention. One product was a transportation hub infographic listing of the 10 "sickest" travel hubs for Thanksgiving travelers. In

January 2017, Clorox used these data points to illustrate the impact of flu on absenteeism in schools and workplaces. Then, during March Madness, Clorox again employed the data points to promote flu vaccinations, using the top basketball rivals, with their risk for cold, flu, and other illnesses.

Several spinoffs were created as a result of the #FluFOMO Campaign. One was the Do Over Sweepstakes, which asked consumers what they missed out on due to #FluFOMO. The Sympathy Button allowed people to share get-well messages and receive coupon codes for Clorox disinfection products for family, friends, and coworkers who use the Sickweather app. Clorox also used social media listening to search out sick celebrities and influencers, and the company sent them "Survival Kit" care packages.

The ultimate results of all the programs included:

- 3,800 #FluFOMO social posts
- 700,000 organic social impressions
- 2,200 sweepstakes entries
- 3 million influencer impressions
- 3,000 media placements
- 21 million media impressions
- 5.4 million Pandora users reached

Ms. Schrader concluded with key learnings from these campaigns about health promotion for young millennials:

- *Tone is key:* not all doom and gloom — draw people in by being relatable and bringing some humor
- *Start a conversation:* people aren't naturally talking about vaccination (unless something goes wrong), so start the conversation with what they are already talking about and what's relevant to them — when it's flu, it's about what you miss out on
- *Evolve the message:* depending on prevention vs. control and severity of flu season
- *Reach people where they already are:* if it takes an extra step, they won't engage, so reach them with social media channels, apps, influencers, and celebrities that they are already engaging with
- *Make their life easier:* go beyond being informative — no one wants to be lectured, so if you make their life easier in some way they will be more likely to engage, participate, and take action
- *Real time = Relevant:* repeating the same message over and over gets stale, so the message needs to be tied to real-time conversations and topics to be relevant and fresh

Vaccine confidence through the lens of advertising. David Rauch, freelance Creative Director, presented a talk entitled "From Strategy to Implementation: Insights from HPV and Zoster Campaigns." Insight, he said, is the key to opening the mind. Several companies have used insight to inspire people to think differently about their products.

The HPV "What will you say?" campaign, focused on facts, the target audience, and supporting CDC's recommendation to vaccinate adolescents. To succeed in this effort, it was decided that the message should be shifted from being about preventing a sexually transmitted infection (STI) to being about preventing devastating cancer. This tactic was employed in recent HPV PSAs, which chronicle the lives of 2 adults, a man and a woman, who have cancers that would have been prevented by HPV vaccination when they were children and who had the option to accept the HPV vaccine that would have protected them. The short videos end with the children asking their parents if they knew that the vaccine would prevent them from having cancer as adults. In the case of HPV, parents often have a hard time envisioning their child having sex and, therefore, tend to reject the idea of their child getting the HPV vaccine. The PSA helped tie the adult suffering from cancer back to the young child who needs protection, thereby making it easier for parents to embrace the idea of vaccinating their children.

Similarly, the shingles campaign also required a new message approach. Oftentimes, older adults think shingles will not affect them. The only ones motivated to be vaccinated for shingles are those who have had the disease or those who know someone who had the disease. Therefore, the PSA sought to help the public understand that the shingles virus may already be living inside of them if they previously had chickenpox.

Mr. Rauch emphasized the importance of testing messages with the intended audience and the importance of tone. He ended his presentation by suggesting that with intensive study of the target audience when developing advertising, the audience will provide the insight of how to convey the message effectively.

Gaining Insight

Human truth is what resonates.

- Focus on the target audience
- Try different ideas
- Use simple statements

Discussion. One audience member requested recommendations for evaluating effectiveness of communication initiatives. One speaker suggested monitoring impact by assessing increases in website traffic. Another speaker stated that surveys can be used to capture comments and feedback from the initiative.

Another audience member asked for ideas on developing insights for target audiences. Mr. Rauch said more than 50% of conceptualizing is focusing on the target. He noted that once one

becomes knowledgeable about the target, insights become intuitive. He suggested that people keep trying different ideas until the right insight is achieved. The next step is execution. Ms. Schrader added that insight is based on research and grasping the target audience. Insight will never be a compound sentence and is the simplest statement possible. She suggested looking at other campaigns targeting similar audiences or issues and noticing how they arrive at human truth or insight — human truth is what resonates.

Another audience question concerned how to strengthen immunization outreach through social media. Ms. Burke-Garcia said that from a social media perspective, the answer was to determine the right channel for the population. Community organizers and influencers can provide direction to the right areas; it is all about relationships. She recommended empowering people to work with the target audience and convey consistent messages throughout the year. Doctors and health care providers also have to be ready to provide information to support the messages, so they should be equipped and prepared to have these discussions. Ms. Athen also suggested being mindful of how the message is translated to avoid fueling the vaccination opponent's message.

Another audience member was under the impression that vaccination opponents do not challenge messages from Clorox but will go after drug manufactures like Merck. Ms. Schrader countered that Clorox is not immune to attacks from vaccination opponents but said one must be willing to stand one's ground. Ms. Burke-Garcia added that opposition is coming and people have to be ready for it. She suggested thinking of some online advocates, who can help convey the message — but no matter what, stick to the message. Mr. Rauch suggested incorporating both the pro-vaccination and anti-vaccination audiences into the discussion.

Participants then asked questions about which specific points should be pressed and in what combination to sustain behavior and how to incorporate multiple messages into a single, simple message. Ms. Schrader said human experience is always evolving and insight is never going to last forever. If one creates an issue, one must also create a solution. Ms. Athen suggested confronting fear by having the conversation. She has found conversation empowers the population to balance the message. Regarding messaging, Mr. Rauch said to personalize the communication to maintain it over time.

Another participant asked for ideas for communication techniques that help build trust. Ms. Schrader recommended examining how health care is delivered and then link it to something actionable and relatable. Building trust requires ongoing relationships, which need to be maintained online and offline.

Another audience member expressed that activities happening outside of the country may help provide some perspectives. Efforts to combat vaccine hesitancy in some countries outside of the

U.S. are in their infancy. People need more awareness of how the World Health Organization (WHO) is dealing with hesitancy. Moreover, slow vaccination uptake might not be caused by lack of understanding but instead by how the message is delivered.

Changes in how doctors address their community can help build trust. Tailoring the messages to the population can aid as well. Ms. Athen said her health department is working with the University of Minnesota to conduct studies to determine better ways to talk to the community. Allowing conversations about the fears of vaccinations has helped. These conversations also help with structuring responses that combat inaccurate information.

Applying the advertising lens to influenza vaccine uptake. Advertising can be a great force in aiding vaccine acceptance, but a clear goal and an appropriate strategy are needed. For her interactive session, Norma Birnbaum of Publicis LifeBrands reviewed a few examples of advertising to illustrate her points on clear goals and strategies and invited audience members to share their thoughts and feelings about each advertisement, including if they felt the advertisement had achieved its goal.

Get the tone and feeling right.
People will remember how they were made to feel long after they forget what was said to feel.

She began the session by describing the concepts that should be considered when constructing an effective advertisement. The *communication goal* is about creating a change or shift in behavior. The communication goal needs to be single-minded. *Target audience and insight* identifies who is at the core of the message. Being single-minded regarding the target is important as well, along with understanding what makes the core target tick or what brings them closer to the advertised product or service. Knowledge of the target can come from quantitative research or qualitative research, which is needed "to put meat on the bones." Use of values, hopes, dreams, and ambitions come from this type of research and can be acquired from deep listening and dialogue with the target. *Core message* is the key product truth and should be framed to appeal to the target. Advertisers should talk about the desired outcome in a way that makes it a priority for the target audience. It is best to say as little as possible but as often as possible. All of these aforementioned concepts lead to determining *tone and feeling*. Long after a person forgets what was said, they will remember how the ad or message made them feel.

Ms. Birnbaum then presented a few examples of flu advertising and had the audience deconstruct them based on the core concepts that she had laid out earlier. She concluded the session with the following takeaway messages:

- Be ruthlessly focused in goals — and in the core message, "say as little as you can, as often as you can"
- Know your target intimately and how to speak in their terms

- Invoking strong emotions can be motivating — but the emotion has to be exactly right and one must consider whether to leverage fear or encouragement
- Leverage others' learnings

Wrap-Up and Closing of Day 1

Dr. Omer ended by briefly summarizing each presentation. After receiving some housekeeping reminders, attendees were thanked for their participation, and Day 1 of the meeting was adjourned.

Values, Confidence, and Vaccine Acceptance

LJ Tan moderated this panel. Topics included in this session included putting values in service of vaccine uptake, providing support to health care providers, and building vaccine confidence from the ground up.

Putting values in service of vaccine uptake. Robert Bednarczyk of Emory presented a talk entitled "Making a Values-Based Argument for Vaccines." Nonmedical exemptions for school vaccine requirements have increased over the years, which may indicate a larger issue — vaccine hesitancy. Should the strategy to address vaccine hesitancy come in the form of vaccination reminders, educational materials, or value-based appeals? Dr. Bednarczyk and colleagues adopted the Moral Foundations Theory to answer this question. This framework defines 6 areas of moral concern that influence how individuals develop and change their mindsets on certain subjects:

1. Harm/Care
2. Fairness/Cheating
3. Loyalty/Betrayal
4. Authority/Subversion
5. Purity/Degradation
6. Liberty/Oppression

The research team conducted 2 studies to test this framework in relation to vaccination.

Study 1

The goal of this study was to determine

Dimensions of Moral Concern

Harm/Care: virtues of kindness, gentleness, and nurturance

Fairness/Cheating: ideas of justice, rights, and autonomy

Loyalty/Betrayal: virtues of patriotism and self-sacrifice for the group

Authority/Subversion: virtues of leadership and followership, including deference to legitimate authority and respect for traditions

Purity/Degradation: religious notions of striving to live in an elevated, less carnal, more noble way

Liberty/Oppression: reactance and resentment people feel toward those who dominate them and restrict their liberty

whether vaccine-hesitant and vaccine-acceptant individuals emphasized different moral foundations. The researchers analyzed survey data via 1,007 parents who were between 18 and 50 years old, residents of the United States, and whose youngest child was less than 13 years old. The survey consisted of the Parent Attitudes about Childhood Vaccines (PACV) short scale, Moral Foundations Questionnaire, Liberty Foundation Questionnaire, and sociodemographic items (number of children, gender, education, age). Key findings included the following:

- Medium hesitancy parents were more likely than low hesitancy parents to endorse purity concerns and, among those above the age of 40, less likely to endorse liberty concerns.
- High hesitancy parents were less likely to endorse authority concerns and more likely to endorse purity concerns and, among those age 40 and below, liberty concerns.
- Endorsement of harm and fairness concerns did not discriminate between vaccine-hesitant and vaccine-acceptant parents.

Dr. Bednarczyk noted that these studies provide empirical evidence that values are associated with vaccine hesitancy and suggested that herd immunity (i.e., fairness) and harm-based arguments may not be effective in combatting vaccine hesitancy. When engaging with hesitant individuals, he suggested assessing which values might be important and responding accordingly. These findings could also help with designing interventions and messaging campaigns, e.g., targeting different sets of moral foundations depending on the audience to persuade.

Identifying the values that underlie pro-vaccine attitudes, vaccine hesitancy, and late vaccination. Amanda Dempsey of the University of Colorado at Denver presented a talk entitled "Motivational Interviewing to Promote Vaccine Uptake." Dr. Dempsey began by defining values as personal priorities and beliefs that influence attitudes and behaviors. Values are the criteria for evaluating actions and decisions, as well as the underlying attitudes and beliefs. In other behavior domains, aligning messages with an individual's values improves acceptance of those messages, as is the case in self-affirmation and motivational interviewing interventions.

Values should inform pro-vaccination messaging. People's attitudes and beliefs regarding vaccination, as well as their degree of vaccine hesitancy, are informed by their values. Aligning messages informed by specific sets of values may improve acceptance of those methods by the targeted population.

Dr. Dempsey and her colleagues created and validated a value scale to determine which values have the most impact on vaccine decision-making. The research team first reviewed the literature for immunization-related values and examined existing values scales. The Schwartz

Portraits Values Questionnaire (PVQ) domains (universalism, benevolence, conformity, tradition, security, and self-direction) were used for the scale because they could be applied to vaccinations. The researchers conducted exploratory and confirmatory factor analysis on data from 295 individuals (Kaiser Permanente Colorado data) to determine the factor structure of the measure. The analysis suggested a new 6-factor structure, where "security" factor was split into 2 (disease prevention and vaccine risk), and the "universalism" and "benevolence" factors collapsed into 1. Four items were dropped as they did not fit into any factor.

The following are key findings to date regarding the associations between values, vaccine hesitation, and vaccination behavior:

- Conformity is associated with decreased vaccine hesitancy
- Universalism is associated with increased vaccine hesitancy
- Self-direction is associated with late vaccination
- All of the above associations were explained by attitudes

These findings regarding the association of specific values with pro-vaccine attitudes, vaccine hesitancy, and late vaccination may help with developing interventions. Specifically, values are a good target for interventions because they can explain vaccination behaviors better than vaccination-related attitudes.

Dr. Dempsey and her colleagues then conducted a 3-year, CDC-funded, pragmatic, cluster-randomized trial (PCOM) to determine the impact of the values on vaccination behavior. Participants were recruited from 12 pediatric clinics and 4 family medicine clinics to assess the influence of an HPV vaccine provider toolkit on adolescent HPV vaccination rates. The trial involved more than 30,000 adolescents.

The toolkit contained the following:

- Website tailored by the International Vaccine Access Center (IVAC)
- Fact sheet
- Disease images
- Decision aid

Health care providers were also provided with training in both the presumptive and motivational interviewing communication approaches. The presumptive ("blanket") approach requires introducing the vaccine to the patient and family member as no different than any other recommended vaccine and to "tell" the patient, rather than "ask," that the vaccine needs to be administered. The motivational interviewing approach is a way of being with the client and not just a set of counseling techniques. The provider becomes a "helper" in the change process and works to reinforce a person's inherent motivation for a behavior. The focus is on making

behavior harmonious with values rather than changing attitudes. Motivational interviewing trainings focused specifically on the HPV vaccine conversation and emphasized using particular motivational interview techniques. Key findings of the PCOM trial included the following:

- Improved provider self-efficacy for addressing HPV vaccine hesitancy
- No increase in time spent discussing the vaccine with hesitant parents
- Decreased time spent discussing the vaccine with non-hesitant parents

The communication training and fact sheets were the most used components of the toolkit, with health care providers finding the communication training particularly valuable to their work. Use of those elements continued over a 12-month period.

Dr. Dempsey concluded her talk by noting that motivational interviewing, which capitalizes on parents' intrinsic values, is one of few interventions specifically shown to address vaccine hesitancy. Future research should explore use of this approach more broadly. Dr. Dempsey provided the following take away messages:

- Values are a relatively unstudied domain, and this work and others' suggest it may be an important leverage point for increasing vaccine confidence
- The immunization values scale begins to define what the values are
- The motivational interview result suggests values can be used to influence vaccine decision-making

Dr. Dempsey also mentioned that an ongoing trial is looking more explicitly at the role of values in influencing parents' vaccination behaviors.

Providing support to health care providers. Melissa Gilkey of the University of North Carolina Gillings School of Global Public Health presented a talk entitled "Improving Health Care Providers' Communication about HPV Vaccine." She reviewed 3 studies that examined HPV vaccine recommendations and messages. HPV vaccination in the U.S. is routinely administered to adolescents between the ages of 11 and 12. Thus far, the statistics show poor results in vaccination rates. By age 13, only 56% of girls have been vaccinated and 49% of boys. Parents' confidence or lack of confidence in HPV is directly related to the vaccination rates. It is believed that providers advocating in favor of the HPV vaccine can increase the numbers because, according to parents, the providers are the most influential and trusted sources.

<u>Study 1: HPV Vaccine Recommendation Quality</u>

The purpose of this study was to determine the extent to which physicians' HPV vaccine recommendations are consistent with national guidelines. Specific aims of the study were to:

1. Assess physicians' HPV vaccine recommendation practices on 5 quality indicators
2. Identify correlates of overall recommendation quality

Data were collected via the 2014 Physician Communication Study, a cross-sectional, online survey of pediatric or family medicine specialty providers of preventive care to patients ages 11 to 17. The national sample (*n* = 776) was 53% pediatrics specialty, 68% male, and 55% in practice 20 years or more. A "strong" recommendation to vaccinate included the following quality indicators:

- *Timeliness*: Recommended by target age
- *Strength of endorsement*: Provider says vaccine is very important
- *Consistency:* Provider delivers routine vs. risk-based recommendations
- *Urgency*: Provider recommends same-day vaccination

The majority of survey respondents reported high-quality practices:

- 74% recommended vaccination for HPV by target age for girls and 61% for boys
- 73% told patients and family members that the HPV vaccine is very important
- 61% delivered routine vs. risk-based recommendations for the HPV vaccine
- 60% recommended same-day vaccination

Overall recommendation quality was high (4 or 5 from a range of 0–5; timeliness for girls and boys assessed separately) for 46% of physicians surveyed. Dr. Gilkey and her colleagues then examined potential correlates of high recommendation quality:

- Physician characteristics (specialty, sex, years in practice)
- Clinic characteristics (practice type [private vs. other], size, national region)
- Physician perceptions (talking about a sexually transmitted infection [STI] is uncomfortable; parents feel that HPV vaccination is not important)

Key findings included the following:

- Only physician perceptions were significantly associated with recommendation quality. Respondents who did not strongly or somewhat disagree that talking about an STI was uncomfortable were less likely to have high recommendation quality scores (35% vs. 57%). Those who believed that parents feel that the HPV vaccine is not important or slightly important were less likely to have high recommendation quality scores (41% vs. 51%).
- Half of physicians reported 2 or more recommendation practices that likely compromise guideline-consistent delivery of HPV vaccine.
- Recommendation quality was lower among physicians with negative perceptions of HPV vaccine discussions.

Dr. Gilkey provided an example of a model effective recommendation: “Now that Michael is 11 [timeliness], he’s due for 3 shots that are really important [endorsement] for all kids his age [consistency]: meningitis, HPV, and Tdap. We’ll give these at the end of the visit [urgency].”

Study 2: Physicians’ Perspectives on Persuasive HPV Vaccine Messages

The purpose of this study was to determine which kinds of messages physicians find effective for persuading parents to vaccinate. Data were collected via an open-ended survey item in the Physician Communication Study: “What is the most effective thing to say to parents to persuade them to get HPV vaccine for their 11 to 12 year olds?" The team examined responses to this question for themes of experience, risk behavior, and comparisons. Exhibit 1 illustrates some of the messages.

Key findings included the following:

- Physicians’ messages for inspiring HPV vaccination were varied
- Some messages aimed to heighten perceived risk
- Other messages framed HPV vaccination as an unremarkable part of routine care

Exhibit 1: Themes of HPV Vaccine Messages from Physicians

Experience	***Personal:*** “My own children, both my daughters and son, have gotten the vaccine, and I recommend it for yours.”	***Professional:*** “I have seen this infection repeatedly. HPV vaccine will help protect them.”
Risk behavior	***Patient’s:*** “Kids usually don’t share their thoughts on sex or their level of curiosity, which can lead to action. Don’t want to judge, but best to be safe.”	***Partner’s:*** “I advise them that while their child may never have sex with anyone but their spouse on their wedding night, their spouse may have had a one-time occurrence in the past (college) and put their child at risk.”
Comparisons	***Novel:*** “HPV vaccine is one of the first vaccines to prevent cancer. It’s an amazing scientific breakthrough.”	***Similar:*** “Like all vaccines, HPV vaccine prevents serious diseases.”

Study 3: Parents’ Perspective on Persuasive HPV Vaccine Messages

The purpose of this study was to determine which messages that parents find persuasive. Data were collected via a cross-sectional, online survey in September 2016 of parents of adolescents

aged 11 to 17. The national sample (*n* = 1,223) was 51% male, 72% non-Hispanic white, and 35% who had a high school degree or less. This survey was scored on a best to worst scale, where parents were given 5 out of a pool of 11 messages to rate.

The study found that parents were most persuaded by messages about vaccination effectiveness (in order of persuasiveness):

- It can prevent cancer
- It can prevent a common infection
- It has lasting benefits
- It is a safe vaccine
- It works best at this age

The least persuasive messages relied on physician authority and experience or scientific justifications (in reverse order of persuasiveness):

- Your child is due for it
- I got it for my own child
- It is a scientific breakthrough
- Getting it on time will mean fewer shots
- I think it is important
- It should be given before sexual contact

Dr. Gilkey concluded by saying that providers have a great deal of influence on parents' decision-making about HPV vaccination but that raising coverage rates requires more frequent and effective recommendations by providers. HPV vaccination affords an opportunity to think conceptually about what makes recommendations for vaccination effective.

Building vaccine confidence from the ground up. Noni MacDonald of Dalhousie University presented a talk entitled "Building Resilient Pro-Vaccine Communities." Vaccine decisions are complex for several reasons. Risk perceptions are intuitive, involuntary and often instinctive. Emotions play a part in how people come to their determinations. Lastly, decisions are deeply affected by what others do and their expectations of others. Dr. MacDonald introduced a different way of dealing with vaccine decisions by focusing on vaccine acceptance. What makes a person a proponent of vaccinations?

She first defined pro-vaccine resilience. Among immunization programs, resilience is "programs that can withstand major shocks and disruptions, to quickly adapt to changing circumstances and to maintain high vaccine uptake and acceptance over time." Resilience is a relatively new term to the vaccine arena but is used readily in other areas of public health when developing strategies for overcoming emergencies or disasters. It is a complex concept, so strategies must

be fluid and able to change to fit the community's need. Dr. MacDonald proposed 5 strategies that could be used:

1. *Involve the whole community:* This involves bringing together a spectrum of groups like academics, private and civic organizations, public health, and government to promote vaccine acceptance as a social norm. Norms, behavioral intention, and behavior affect vaccine resilience. She recommended using pro-vaccine stories and reaching out to vaccine-accepting groups like HPV-immunized teens or flu-immunized pregnant women. These influencers can help readjust social norms.

2. *Develop effective communication strategies:* Dr. MacDonald suggesting employing existing information channels and taking note of concerns from both sides of the vaccine spectrum. Communities that are hesitant hear pro-vaccine messages differently. Dr. MacDonald also recommended tailoring both communications and interventions to the specific communities where they are being presented.

3. *Nurture trust:* Immunization programs and health care workers should be transparent. Being open to discussing issues such as vaccine manufacturing processes, safety, and risk can increase the trust in the relationship between patients and parents and also demonstrates care.

4. *Give positive reinforcement to vaccine acceptant and value acceptors individuals:* Very rarely are vaccine acceptors celebrated for protecting themselves and the public. Be sure to appeal to their social identity and seek out individuals or groups who can be champions.

5. *Nurture resilience in children, adolescents, and adults:* Dr. MacDonald suggested using civil service organizations, businesses, religious events and programs, as well as adult education as avenues for nurturing resilience in adults. For children or adolescents, she suggested using school vaccine education to:
   - Demonstrate that the community values immunization
   - Underscore vaccine acceptance as the norm
   - "Inoculate" against misinformation and anti-vaccine tactics

She concluded by recommending that vaccine proponents and programs continuously survey the landscape for misinformation. She emphasized the need to research changes in beliefs, to determine a plan of action to address fabrications, to correct distorted information quickly, and to unmask the tactics utilized.

Discussion. One participant asked for ideas on ways to award people for being vaccine acceptant. She also asked for curriculum suggestions. Dr. MacDonald said more research is needed on what positive reinforcements have the most impact. Denmark will have a curriculum next year to address current vaccine perceptions, and Ontario, Canada, has curriculum development as part of its 2020 plan. In the state of New York, vaccines are part of the education. Many schools are having a problem fitting it into the curriculum due to other demands, limited time, and testing restrictions. Curriculum alone may not be sufficient, and vaccine education will have to be built into other areas.

Another participant wondered if a survey could be given on motivators to find out what stops people from being promoters of change in their community or among their social community and what toolkit they need to make that transition. Dr. MacDonald agreed. She expressed that good listening skills are necessary, so that examiners can tease out the blocker. She added that self-beliefs are a main contributor but suggested the need for communication guidance.

Another attendee suggested using social media to draw in parents and train them to do vaccine advocacy. Parents have been very successful at blocking legislation. This could be an encouraging model of activating people to become promoters and provide concrete examples of actions they can take. A recommendation was made to start on a small scale with parents and friends and encourage them to pass it along to their social circle.

Another audience member asked Dr. MacDonald about the differences she sees in other countries versus the U.S. in her work. The suggestion also was made to involve children in advocacy efforts and messaging. Dr. MacDonald responded that all the ideas she put forward can be translated to any country. The only difference is how to translate the ideas to partners.

Ideas were solicited on how to work with providers, get them onboard, and shift the way they hold vaccination conversations. Dr. Dempsey suggested offering certification credits. Another motivator is reviewing their vaccination rates, which may move them to be more mindful of vaccination conversations. Dr. Gilkey felt that nurses could also be instrumental in vaccination education.

A question arose regarding the characteristics of the ideal person for conducting motivational interviewing and what should be offered to that individual to make this effort sustainable. Dr. Dempsey said anyone can do motivational interviewing and it normally takes 2 to 3 minutes at a clinic visit. Once providers become comfortable, it becomes a routine part of their discussions. Obstetrician-gynecologists (OB-GYNs), however, are different. An immunization champion may be needed for those physicians.

A recommendation was made to bring risk communication, risk of immunizing, and not immunizing back into the conversation. This audience member stated that numbers are not a good way of communicating; therefore, some tools should be developed to help in those discussions. Another attendee highlighted the importance of shifting anti-vaccine messages to a pro-parent choice or parent empowerment frame. Dr. Bednarczyk expressed that some of the ideas of liberty and authority could help develop messages that speak to that component.

Systems Approaches to Building Confidence

Ms. Fisher of CDC moderated the last panel discussion. Topics in this session included the power of policy, capacity building in medicine and public health around vaccine confidence, and partnerships and collaborations.

The power of policy. Dr. Omer of Emory presented a talk entitled "Vaccine Laws as Behavioral Interventions." School immunization requirements in the U.S. are state-regulated and help aid in the low rates of vaccine-avoidable diseases. However, people can avoid immunization requirements by acquiring an exemption through the state. Most states accept exemptions for the following reasons: medical considerations, religious convictions, and personal or philosophical beliefs. A 2016 article in the *Journal of the American Medical Association* presented data showing that between 2000 and 2015, 69% of nonvaccination was due to nonmedical exemptions. School vaccine exceptions vary by states. Most exemptions are due to nonmedical reasons and only 3 states have no vaccine exemptions.

Another way of looking at exemptions is the ease of obtaining them by state. In some states, acquiring a nonmedical exemption is as easy as printing and filing an exception form. Expectedly, the states with easy exemption requirements had the most increases in exemptions.

So why not eliminate exemptions all together, as in California? To support the argument of elimination of exemptions aiding in decreasing disease burden, Dr. Omer suggested an assessment study to evaluate the correlation over a 5,10, and 15-year timeframe. From 2009 to 2012, no laws to expand exemptions have passed; therefore, another model has been proposed. SB 5005 is a law in Washington State that makes educational counseling a requirement for parents desiring an exemption for their child, as well a signed form from a state-licensed health care provider, in order to obtain a nonmedical exemption. The law went into effect on July 22, 2011 and since then, exemption rates went down by 42% (returning to rates seen a decade ago) and clustering of measles cases also decreased.

Several approaches have been suggested to deal with vaccine skeptics:

- Requiring signature on a form that discusses the risks of nonvaccination

- Requiring a letter elaborating on the reason that their child should be exempt
- Conducting in-person counseling
- Providing the exemption form only by specific request from a state or local health department instead of making it available online
- Establishing procedures to review each request for exemption
- Having an annual renewal requirement

Dr. Omer concluded his talk by providing a list of policy documents that have cited his and colleagues' work, which can aid in making an argument to states of the consequences of exemptions, disease management, and impact on vaccination rates.

Understanding the influence of policy on vaccine confidence. Jason Schwartz of the Yale School of Public Health presented a talk entitled "Policy as Intervention for Fostering Vaccine Confidence." Dr. Schwartz began by asking the audience the following question: How do issues related to vaccine confidence shape the deliberative processes that lead to vaccine policies and recommendations (and vice versa)? Attention to potential consequences of policy options regarding vaccine confidence, he stated, has been a part of decision-making, alongside assessments of risks and benefits, safety, effectiveness, and related evidence. The existing structures and processes for developing evidence-based vaccine recommendations are significant assets in promoting confidence in vaccines, vaccine policies, and vaccine policymakers, as well as additional opportunities to highlight them to providers and parents.

Dr. Schwartz then discussed the history of the Advisory Committee on Immunization Practices (ACIP) and the RotaShield vaccine, which was used from 1998 to 1999. This vaccine caused severe, and in some cases fatal, intestinal intussusception. In the summer of 1999, a research study revealed that 429 infants from a control group of 1,763 had been hospitalized with intussusception in 19 states. The vaccine heightened the risk of intussusception 3 to 14 days after the first dose of the vaccine. The ultimate finding was that 1 case of intussusception was attributable to the vaccine for every 4,670 to 9,474 infants vaccinated. However, the vaccine's considerable benefits were not discussed at that time, due to ACIP's recommendation of withdrawal in October 1999. Dr. Schwartz wondered if there could have been a possible way to move forward with the vaccine because of its effectiveness. This issue is an example of the politics of acceptable risk.

The ACIP can be an aid in these cases, as the ACIP is an interdisciplinary group of outside experts that includes a consumer representative as a voting member. ACIP meetings and deliberations were open to the public, who therefore had access to meeting presentations, minutes, transcripts, and the committee recommendations (and supporting evidence and rationale). The meetings also allowed the public to provide remarks during the public comments

time. This session is an important part of the meetings to engage the public and make them a part of the process.

Dr. Schwartz closed his talk by sharing some implications and opportunities for using the ACIP:

- Potential value of more explicit consideration to role of vaccine confidence in ACIP discussions and commendations (and vice versa)
    - Are new kinds of evidence needed (before and after new recommendations approved)?
    - Are new kinds of expertise needed (as members or consultants)?
- Potential value of improved endeavors aimed at emphasizing, demystifying (and, at times, humanizing) the activities and people that develop evidence-based vaccination recommendations

Building capacity in the public health system. Daniel Salmon of Johns Hopkins University presented a talk entitled "Building Vaccine Confidence in Public Health Settings." In his remarks, he shared some personal reflections on the 2009 H1N1 epidemic. The decision to vaccinate for H1N1 became a very controversial issue. Over 77% of parents reported vaccine concerns for a variety of reasons, such as: it was painful for their child to receive so many shots, too many vaccines in the first 2 years of life, the vaccine may cause fever, and ingredients being unsafe. People perceived the risk from taking the vaccine to avoid having the virus as being greater than catching the virus. He paralleled this incident to the 1976 swine flu, where vaccinations were ceased when the risk of Guillain-Barre syndrome (GBS) was identified. This episode was considered a public health and political disaster.

In the end, H1N1 vaccine production took longer than expected. CDC led an enormous national effort to vaccinate everyone as rapidly as possible, which created substantial pressure on states and localities. Many in the vaccine safety community recognized challenges for safety monitoring and the potential for factual or perceived problems to destabilize the program. Additionally, on a political level, failure to implement this process correctly could have undermined health care reform legislation.

The National Vaccine Advisory Committee (NVAC) recommended the following steps for H1N1 safety monitoring:

1. Assembling background rates of adverse events that occur in the general population
2. Developing and disseminating a federal plan
3. Enhancing active surveillance for signal detection, assessment, and confirmation of possible associations between vaccines and adverse events
4. Establishing a transparent and independent review of vaccine safety data as they accumulate

5. Developing and, where possible, testing in advance a strong and organized response to scientific and public concerns about vaccine safety

A published paper also provided estimates of coincident, temporally associated events. The lesson learned was that science has to rapidly separate coincident from causality.

In an effort to prepare the media, 3 tabletop exercises were convened with Health and Human Services (HHS) leadership and the media. These drills were used to examine scenarios and stress possible events. Participating in the drills showed the science and government communities what questions might arise, how the media would report on the issues, and how the media would respond to the science and government communities' responses. The drills also helped to prepare the media for what was to come.

The Vaccine Safety Datalink (VSD) limitations caused problems with active surveillance during the 2009 H1N1 epidemic. People then recognized the need for a new system to address surveillance needs. Therefore, the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) was developed.

The aims of PRISM are to:

- Link health plan data and state immunization registry data in new H1N1 vaccine safety surveillance network
- Conduct continuous active surveillance for pre-specified outcomes
- Provide timely information on unanticipated potential adverse events

PRISM identified GBS as the only outcome associated with vaccination for the H1N1 virus. Data from a chart review done for GBS contributed to a U.S. meta-analysis and an international study. The Food and Drug Administration (FDA) later picked up PRISM as vaccine component of a mini-sentinel project.

Dr. Salmon concluded his presentation with some policy questions that if answered can be useful in future policy efforts on vaccinations:

- Did vaccine safety efforts make a difference?
- What is worth keeping?
- How did 2009 H1N1 impact vaccine confidence?
- What was learned from H1N1 that could be useful in the U.S. and internationally?

Training physicians to communicate about vaccinations. Sean O'Leary of the University of Colorado at Denver presented a talk entitled "Training Providers: Beyond Vaccine Administration." Dr. O'Leary began by asking the audience to think about how many times

provider recommendations have been cited as being most effective in helping parents make decisions about vaccinating their children. However, in his formal education, he was not trained on vaccinations or how to have vaccination discussions.

The American Board of Pediatrics has the assigned task of making requirements for board certification. They provide a content outline that serves as the blueprint for initial certification and maintenance of certification. Immunizations are included under preventive pediatrics and well-child care and are 8% of the "exam weight." However, the outline only says "current recommendations" and "special circumstances" (e.g., contraindications, lapsed immunizations). In the past, the outline did provide more detail regarding individual vaccines and included the phrase "plan an appropriate approach to addressing the needs of the vaccine-hesitant family."

The Accreditation Council for Graduate Medical Education (ACGME) accredits residency and fellowship programs and sets the standards for each of the programs including explaining "milestones" and directing curriculum development. The words *vaccine*, *vaccination*, *immunization*, and *immunize* are not found in the 32 pages of competencies for pediatric training, however. Moreover, program requirements only state that the pediatric resident must be able to give immunizations.

NVAC gives clear recommendations for both safety training and communication training in regard to vaccines, but they have not been translated into the training requirements for the Board or the Council. To determine the extent to which medical training addressed vaccine safety, a survey was conducted of 199 U.S. pediatric training program directors (46% response rate). Of those surveyed, 59% reported no formal vaccine safety training.

Medical education about immunization is lacking.
NVAC recommendations regarding provider training about vaccines have not been translated into requirements by the American Board of Pediatrics or the Accreditation Council for Graduate Medical Education.

Of those who had received vaccine safety training:

- 37% received training through a continuity clinic didactic session
- 29% attended a standard in-person lecture
- 13% completed an online module
- 21% received training through other means (e.g., standardized patients, videos, Red Book, journal club, specific rotation)

Training topics included the following:

- Common adverse events following vaccines (100%)

- How vaccines are created, licensed, and recommended in the U.S. and who is responsible for making these decisions (44.7%)
- What resources are available for physicians who believe a patient may have experienced an adverse event (76.3%)
- How to talk with vaccine-hesitant parents about vaccine safety concerns (94.7%)

Among those without training, 82% showed an interest in participating in training, with a majority preferring online training as the form of delivery.

There are some existing online learning modules such as TIME (Teaching Immunization for Medical Education) sponsored by the Association for Prevention Teaching and Research, TIDE (Teaching Immunization Delivery Evaluation) sponsored by the Ambulatory Pediatric Association and CDC, as well as continuing education courses from the American Academy of Pediatrics (AAP). There are even smartphone apps like Shots Immunization and The Vaccine Handbook.

Dr. O'Leary also noted some existing curricula for individual residency programs like the University of California, San Diego; Children's Hospital of Orange County; and Children's Hospital Colorado. The MedEd portal also publishes curricula for training residents and medical students online, and Yale and Johns Hopkins have comprehensive primary care curricula designed to be delivered in continuity clinics. Most of the curricula content is regarding basic and vaccine-specific immunology, vaccine basics, vaccine-preventable diseases, vaccine safety, and communication. The first 4 elements address what is known about vaccines, but the area of communication (the "how") is lacking.

Collaboration for Vaccine Education and Research for Residents (CoVER), is an industry-funded randomized trial to develop and evaluate a vaccine curriculum for pediatric and family medicine residents. This trial was performed at 28 sites using 4 one-hour online modules. The modules covered vaccine fundamentals, vaccine-preventable diseases, vaccine safety, and communication and vaccine confidence. The curriculum uses a "flipped learning" approach where activities traditionally done in the classroom (e.g., lectures, discussions, research) are conducted online and activities traditionally completed individually are done in a group setting, usually with guidance from a mentor.

He then outlined some challenges that he has observed regarding vaccination training for health care providers:

- Little, if any, evaluation of most curricula
    - No current curricula have been shown to increase vaccination uptake
    - How can we teach trainees when we know little about what works?

- Lack of uniformity
- Dependent on “champions” within individual programs
- Not enough “seat time”
- Vaccine-hesitant trainees

He also presented data from 2 other studies he and colleagues conducted on physician’s confidence in vaccine safety. The first was a nationally representative study of pediatricians and family medicine practitioners (response rate of 81%). When queried regarding confidence in pre- and post-licensure vaccine safety studies, less than 10% of pediatricians and 35% of family physicians reported little or no confidence in pre-licensure vaccine safety studies. Less than 5% of pediatricians and 10% of family physicians reported little or no confidence in post-licensure vaccine safety studies. In a study of residents conducted in October 2016, 101 pediatric and family medicine providers were asked, “Overall, how hesitant about childhood vaccines would you consider yourself to be?” and 78% said “not at all.” Then the providers were asked, “How concerned are you that one of the childhood vaccines may not be safe?” and 81% responded “not at all.”

Dr. O’Leary concluded with the following takeaway messages:

- No real requirements exist for residents to be trained about vaccines
- Many curricula have been developed, but these have taken a piecemeal approach
- Vaccine hesitancy appears to be a problem among trainees

Partnering to promote vaccine confidence. Catherine Flores Martin of the California Immunization Coalition presented a talk entitled “The California Immunization Coalition’s Work to Foster Vaccine Confidence.” Ms. Martin began by reviewing lessons learned about engaging parents and advocates from collaborative work with Vaccinate California. The mission of the California Immunization Coalition is to achieve and maintain full immunization protection for all Californians and to promote health and prevent serious illness. The collaboration is about the facts and science. Vaccinate California, a grassroots parent advocacy group, is part of this statewide coalition. They communicate messages focused on the human factor of vaccination through avenues such as billboards and ads. The California Immunization Coalition also spends a great deal of effort getting through to the “dark side” of vaccination issues. One of their activities is the “I Heart Immunity Campaign” to promote vaccine acceptance. Several major organizations came on board and provided a letter of support to the state legislature on behalf of the California Immunization Coalition. The Coalition also obtained a great deal of press coverage of their efforts.

There was also backlash. One anti-vaccination organization co-opted images and messages of the “I Heart Immunity” campaign and presented personal, medical, and religious freedom as

antithetical to SB 277, the bill about mandatory vaccinations for children. Unhappy parents demonstrated against the proposed legislation. Vaccine conspiracy events were held in Los Angeles to encourage the questioning of vaccines within communities of color. Advertising on billboards and social media stoked vaccination fears.

SB 277 passed, however, and Ms. Martin feels that the I Heart Immunity campaign contributed to this big win. She shared important lessons learned from collaborating with Vaccinate California:

- Know your goals — protecting vulnerable children and creating safer schools
- Control the message — no matter how the opposition responds
- Find supporters — you are not changing minds
- Recognize that it takes a huge team — it's not just about the numbers, but having the right people at the table

Challenges for leadership, in her experience, included:

- Inspiring supporters to believe that this is what is needed
- Trusting the team
- Keeping people productive and happy

Other lessons from the collaboration with Vaccinate California on the I Heart Immunity campaign included the following:

- Conveying how intensely controversial this issue is for some people is challenging
- Stay positive to bolster each other
- Working with thoughtful, professional leaders is very empowering for parents

Ms. Martin emphasized that the majority of Americans vaccinate their children and believe that vaccines in schools should be mandatory. They do not normally use social media as a platform to lash out at public health officials or doctors, or to criticize legislators. However, these parents are powerful and can act as advocates for vaccine acceptance just in their conversations with vaccine-hesitant people. They also find it inspiring to engage and work in collaboration with thoughtful and professional leaders.

The Coalition uses social media to educate parents through:

- Facilitate online discussions, providing evidence-based perspectives
- Active dismantling of medical (vaccine) myths and misinformation
- Educational videos on vaccine safety in advance of scheduled appointments

She concluded her presentation with the following lessons learned:

- Stay above the fray and stay on message

- Messengers matter
- Focus and timing
- Work together and trust each other

Collaborating with faith communities. Mimi Kiser of Emory then presented a talk entitled "Collaborating with Faith Communities to Promote Influenza Immunization." The goal of the Interfaith Health Project is to build and mobilize capacity within networks of faith-based organizations and community organizations linked with public health to extend their reach to vulnerable, at-risk, and minority populations for improving influenza vaccination outreach and uptake. Emory University and CDC have trained 78 teams of religious and public health leaders in 24 states to work together on eliminating health disparities.

The HHS Center for Faith-Based and Neighborhood Partnerships worked with Emory University's Interfaith Health Program (IHP) and 9 sites during the 2009 H1N1 epidemic. For that project, 10 sites with multi-sector partnerships:

- Modified evidence-based educational tools for hard to reach populations
- Incorporated participatory research findings about the meaning of trust into educational and outreach tools
- Led community leader trainings on emergency communication
- Employed trusted networks with different channels for information distribution, such as e-newsletters to congregations, radio, and family nurses
- Connected with low-income, uninsured, and minority populations

The project team employed a practice-based, discovery process using a modified Delphi technique to classify and combine distinctive elements from across the 10 sites. Other methods of data collection included:

- Document review and thematic analysis
- In-person inductive identification of key elements of practice (4 of 10 sites)
- Online survey to validate key elements and characteristics (16 respondents across 10 sites)
- Multisite, in-person meeting to define and describe operational components of the practices

The following are the outcomes from the project for 2 sites.

<u>Buddhist Tzu Chi Medical Foundation: Compassion-Driven Flexibility</u>
There is an unwavering commitment to find a way to serve the community that may risk or go beyond self-interest. How does one recognize and build this? An enduring and imaginative creative ability to see new resources, push the boundaries of convention, and think outside the

box is evident. There is a willingness to let go, reframe objectives, and find different solutions to new issues that arise in the face of changing policy or structural barriers. To address the needs of hard-to-reach populations, Buddhist Tzu Chi Medical Foundation has built itself to be agile in order to work when and wherever people are best served.

Lowell Community Health Center: Build and Maintain Trust

Trust is primarily relational. It is built over time when respect for differences, commitment to the good of the community, integrity, and transparency are experienced consistently in the face of challenging collaborative endeavors. The Lowell Community Health Center (LCHC) has a long history of responding to the needs of immigrant communities and making institutional adjustments to respond effectively to their needs with:

- Metta Health Center: a meditation room in the LCHC created in partnership with a local Buddhist center
- A strong outreach relationship to a network of African churches
- Staff who represent the ethnicities and cultures of those they serve
- A community health worker program adapted to different ethnic populations

Ms. Kiser emphasized that trusted and accessible messages outside of the health care system are often transmitted through:

- Trusted networks and relationships
- Partners who have flexible, adaptive organizational capacity
- Those who deliver messages in an appropriate language and with relevant cultural meaning

She concluded by saying that most communities have leaders with relationships and the kinds of commitments that can leverage connections and social capital resources for the well-being and health of all.

Discussion. During the brief question and answer session, an attendee asked Dr. O'Leary if he has examined the adult medicine training program for vaccination curriculum. Dr. O'Leary said there is no curriculum currently related to adult vaccinations. He also felt all providers regardless of specialty should be taught about vaccinations because they are important to wellness. Furthermore, specialists who take care of immune-compromised individuals are also not getting adequate training, so many gaps need to be addressed.

Closing Plenary

Ms. Mendel of NVPO began by thanking attendees for sharing their ideas and engaging in important discussions about the best ways to promote vaccine confidence. Dr. Omer of Emory also expressed his appreciation and then introduced the closing speaker, Walter Orenstein.

Closing presentation. Dr. Orenstein of Emory presented a talk entitled "The Effects of Vaccine Confidence on the Immunization System: A Retrospective." A major outbreak of measles in the 1970s underscored the need for better prevention strategies. The significant component of those strategies was the requiring of vaccinations in order for children to enter school. A major measles outbreak in 1977 led health officials to prohibit unvaccinated children from entry into schools, which resulted in a decrease in measles cases. This practice soon became standard throughout the U.S. and led to the Childhood Immunization Initiative of 1977 that inaugurated a perpetual system to vaccine the children born each year.

The beginning of modern-day vaccine hesitancy came with the 1974–1976 pertussis vaccine controversy in the United Kingdom. In January 1974, a newspaper article told the story of 36 children believed to have suffered severe neurological complications after receiving the diphtheria, pertussis, and tetanus (DPT) vaccine. Due to this occurrence, parents formed vaccination opponent groups to bring attention to the public of the risks of DPT. By 1977, coverage against pertussis (whooping cough) had declined from 77% to 33%. The decrease in vaccinations caused 3 major epidemics of whooping cough. A research study of the vaccine found that although the vaccine could be linked to an escalated risk of acute illness, the risk was very low.

As a result of the United Kingdom incident and the litigation pursued afterwards, the National Childhood Vaccine Injury Act of 1986 created the national Vaccine Injury Compensation Program (VICP) in the United States on October 1, 1988. This program allowed financial reimbursement to individuals who filed a petition and were found to have been injured by a VICP-covered vaccine. Even in cases where a finding was not made, petitioners could receive compensation through a settlement. The VICP covered both recipient and contact cases.

Dr. Orenstein's experience with polio came in 1988 with an outbreak in Israel. There were 15 cases of paralytic poliomyelitis caused by type 1 vaccines, but Hadera, Israel, had been using an inactivated polio vaccine (IPV) schedule only since 1982. The investigators were divided in their reading of the findings. The pro-oral polio vaccine (OPV) investigators believed that IPV-vaccinated individuals silently transmitted wild polio virus (WPV) to older persons, while the pro-IPV investigators believed that WPV was transmitted through OPV vaccine failure. This was all theoretical and the groups submitted their findings to the *Lancet*. Data presented at the ACIP meeting held June 19–20, 1996, showed that OPV caused an average of 8 to 10 cases of

vaccine-derived polio per year. Among OPV recipients, the risk was higher with first doses, compared to subsequent doses. In the absence of wild-type disease, the public and authorities began to deem the risk from the vaccine unacceptable. The following statement was thus added to the ACIP recommendations: “ACIP recommends a transition policy that will increase use of IPV and decrease use of OPV during the next 3 to 5 years.”

Dr. Orenstein also discussed a retracted study that linked MMR vaccinations to autism. Wakefield and his colleagues conducted this study of 12 children in 1998. It suggested that MMR vaccination led to intestinal abnormalities and behavioral disorders. The findings were found to be false and were retracted, but unfortunately the damage had been done. Measles vaccinations decreased, and the measles resurfaced in the United Kingdom.

Then the thimerosal controversy occurred in 1999. Thimerosal is a preservative used in inactivated vaccines that contains ethyl mercury. Studies showed that a 6-month-old infant could be exposed to 187.5 micrograms of mercury if he or she received the recommended doses of vaccines. This exceeds EPA’s safety limits for *methyl* mercury, but not the limits set by Agency for Toxic Substances and Disease Registry (ATSDR), FDA, and WHO. Questions arose concerning obligations to make parents aware, the time it would take to test for validity, and moving to single dosages for safety. On July 7, 1999, after 2 weeks of deliberation, it was decided to delay the birth dosage of Hepatitis B vaccine. Manufactures were urged to remove thimerosal from vaccines as soon as possible, and the AAP released a statement to the public. The outcome from this event was that autism groups began alleging that the mercury led to autism.

The last incident reviewed was the RotaShield vaccine and its relationship to intussusception. Removal of the vaccine triggered the need for large clinical trials of future rotavirus vaccines to rule out the risk of intussusception. NVAC issued recommendations to aid in increasing vaccine confidence, which included:

- Measuring and tracking vaccine confidence
- Communication and community strategies
- Health care provider strategies
- Policy strategies
- Continued support and monitoring

The 2015 NVAC report on vaccine confidence was triggered by the following factors:

- Pockets of low coverage
- Increasing school law exemptions, especially in states with personal belief exemptions
- Geographic clustering of individuals with exemptions

- Increase in parents stating they delayed at least 1 vaccine (from 21.8% in 2003 to 25.8% in 2009)
- 2010 survey that found 87% of pediatricians had parents who requested an alternative schedule
- 2012 physician survey that found that 93% of parents in a typical month requested spreading out of vaccines

Discussion. One audience member asked about the current administration's position on vaccination. Dr. Orenstein reported that Secretary Tom Price and HHS are supportive of vaccine efforts, although conversations coming from the Executive Branch are concerning. A suggestion has been posed to form an Autism Commission. Decreased disease burden illustrates the success of the immunization community, but is often overlooked.

Another attendee noted that terms like "vaccine-hesitant" are problematic and expressed that a simple change in the nomenclature may make parents feel more at ease. Dr. Orenstein agreed and said this is why "vaccine confidence" is being used instead.

The last question regarded the use of an alternate ACIP schedule as a harm reduction strategy. Dr. Orenstein disagreed and stated the need for a continued focus on using the ACIP schedule as is. If necessary, providers should point out risks in using an alternate schedule and identify who could be harmed by its use.

Concluding thoughts. Dr. Omer ended the meeting first with a brief summary of each of the presentations from Day 2. He expressed that the conversations held at the meeting symbolized the maturing of the immunization discussions. He then recommended the following steps for moving forward the important work in building vaccine confidence:

- Develop evidence-based strategies on effective way to persuade physicians
- Think of the next advances in science that would modify assumptions
- Continuously absorb the science that is generated

Dr. Omer thanked the "giants of immunization," including Barry Bloom, Kathy Edwards, Noni MacDonald, and Walt Orenstein, upon whose shoulders the vaccine community stands. He also thanked all the staff and contractors for making the meeting a success. Dr. Omer concluded by encouraging all attendees to share their thoughts via the evaluation sheets and to propose strategies for advancing vaccine acceptance via the ideas board.

Ideas Board

Participants were encouraged to share new ideas generated as the meeting progressed by writing thoughts on index cards, which were displayed on an idea board.

Below are participants' thoughts in their own words:

- Embrace the anti-vaxxer as a part of the conversation. Bring their voice into the same platform that pro-vaccine has. Would be powerful to watch an anti-vaxxer do a 180˚ and change course. Powerful transformation actions.
- Vaccine science curricula in schools
- Battery of all confidence/hesitancy measures
- More research/practice collaborations and interdisciplinary approaches
- Need for open data sharing
- Vaccine confidence reflects larger socioecologic landscape
- Please compile list of scales/indices and in what context they were developed/applied
- Begin to reframe vaccination as a complete maintenance program throughout one's life as a way to optimize health over a lifetime.
- Improve our ability to recognize vaccine confidence issues before they bubble up.
- Create ICD code so providers can be reimbursed for motivational interviewing or education towards vaccine acceptance.
- Trace trust in the system regularly (more than yearly). Maybe work up the trust parameter?
- Create a large social norming campaign (using positive reinforcement) to reinforce the norms of childhood vaccination with more tailored approaches for pockets with higher hesitancy.
- Develop some form of virtual committee to work on proactive "inoculation" of pro-vaccine communities with TPs, tips on unmasking fake news, new updates on fake news, etc.
- Create a tested message bank for use/customization during outbreaks that include vaccine confidence issues.
- How can we circumvent knee-jerk reactions against expert authorities?

Meeting Assessment

A total of 33 of the 76 attendees completed the meeting assessment (43.4% response rate). The majority of respondents worked in academic settings (see Exhibit 2).

Exhibit 2. Professional Sector of Assessment Respondents

Sector	% (*n*)
Academia	64% (21)
State or local health department	0% (0)
Health care system	3% (1)
Federal government	15% (5)
Nonprofit/advocacy/membership	18% (6)
Other	0% (0)
Total	**33**

Respondents felt that the meeting met its intended objectives and was a satisfying experience. Approximately 75% of respondents strongly agreed that they learned about important work being done to address vaccine confidence, hesitancy, and acceptance (see Exhibit 3). Over 50% strongly agreed that they were able to speak with leaders in the field and identify relevant research and intervention gaps. Respondents also strongly agreed the meeting strengthened the community of professionals working to increase vaccine confidence. Respondents reflected these positive views in their perceptions of the meeting as a whole. For example, over 50% strongly agreed that the meeting agenda met their expectations (see Exhibit 4).

Exhibit 3. Achievement of Meeting Objectives

	Strongly disagree % (*n*)	Disagree % (*n*)	Agree % (*n*)	Strongly agree % (*n*)	Total
a. I learned about the important work being done to address vaccine confidence, hesitancy, and acceptance.	3% (1)	0% (0)	21% (7)	76% (25)	33
b. I identified relevant gaps in research and interventions that address vaccine confidence, hesitancy, and acceptance.	3% (1)	9% (3)	33% (11)	55% (18)	33
c. I was able to share new ideas with colleagues.	3% (1)	9% (3)	47% (15)	41% (13)	32
d. The meeting strengthened the community of professionals working to increase vaccine confidence.	3% (1)	3% (1)	36% (12)	58% (19)	33
e. I was able to meet and speak with leaders in vaccine confidence-related fields.	3% (1)	3% (1)	33% (11)	61% (20)	33

Exhibit 4. Perceptions of the Meeting Experience

	Strongly disagree % (*n*)	Disagree % (*n*)	Agree % (*n*)	Strongly agree % (*n*)	Total
a. Overall, the agenda met my expectations.	0% (0)	0% (0)	41% (13)	59% (19)	32
b. I am satisfied with the amount of participation I had in the sessions.	0% (0)	6% (2)	47% (15)	47% (15)	32
c. I was given adequate opportunity to get answers to my questions.	0% (0)	9% (3)	44% (14)	47% (15)	32
d. I was able to clearly understand and follow the presentations.	0% (0)	0% (0)	34% (11)	66% (21)	32
e. The conference facilities were comfortable and appropriate for the meeting goals.	0% (0)	0% (0)	25% (8)	75% (24)	32

The meeting assessment form included 3 open-ended questions. Participants were asked what they liked best about the session content and the way sessions were delivered, what they would change about session content and the way the sessions were delivered, and what other suggestions they had for the meeting. A summary of their responses is included below.

The majority of the responses focused on the high quality of the speakers (perceived as leaders in the field of vaccine confidence) and the content of their presentations. Specifically, respondents valued the variety of speakers from different disciplines, including research, practice, and policy issues, as well as the diversity and mix of new and seasoned researchers. Participants also liked the overall organization of the panel discussions, which offered a good mix of topics of relevance in the field of vaccine confidence. Participants found it useful to hear expert opinions not only of important concepts but also high-level ideas or the "big picture." Participants also enjoyed the pace of the sessions and the opportunity to ask questions following each panel. A couple of participants also noted having enjoyed the opportunity to interact with colleagues, including speaking with experts that they would "typically not have access to" in their day-to-day work.

Participants recommended changing aspects of the content delivery — specifically, making the meeting more interactive. For instance, some participants noted that the flow and pace of the meeting could be improved by including activities between presentations such as group work, showing videos, extending the question and answer periods, or facilitating discussions that will make participants engage with each other in a meaningful way. Another suggestion was to have exercises that make participants engage in solving problems as a group. Related to adding interactive activities to the agenda, meeting participants noted that some sessions were too long and some panels could benefit from limiting the number of speakers. These concerns could be addressed by adding some of the suggestions noted above regarding interactive activities.

Respondents expressed a need for the Vaccine Confidence Meeting to continue in the future. A few respondents indicated wanting to make the meeting focus more on applied work, to show how programs are disseminating best practices and highlight possible solutions to key challenges that frontline staff face. One respondent recommended designing a panel that includes providers (e.g., obstetricians and pediatricians) who have experience engaging with vaccine-hesitant parents, as well as social media thought leaders who support vaccination to discuss challenges and share messages or strategies that work. Another respondent suggested engaging a keynote speaker from a different, but related, field to bring different ways of thinking to the vaccine confidence field. Finally, respondents cautioned not to let the meeting get too large in the future. The total number of participants was the right size according to some respondents.

The meeting requires follow up so momentum is not lost. Respondents noted the need for follow up from the meeting so that the momentum gained is not lost. One respondent recommended that the meeting summary serve as a basis for a call to action and that the presentations be shared and available to a wide audience. Another respondent realized the need for a vaccine confidence network to serve as a forum for discussion and collaboration on interventions that work. Another participant added that a forum could keep everyone informed of new publications, news about conference funding opportunities, and other relevant news on vaccine confidence. This forum could also include developing a "research sandpit" for individuals to discuss research that is needed on a particular topic.

A number of improvements to the meeting were recommended. Respondents recommended producing a document that summarizes research gaps in vaccine confidence and make it available to participants. Also, the presentation slides should be available during the meeting. A participant recommended that the presentations flow more quickly in a "rapid-fire talk" format to keep the conversation moving. Finally, the idea board that produced about 12 entries could have worked better by having someone read the ideas aloud so those ideas could spark other ideas during the meeting.

Meeting participants offered kudos and accolades to meeting hosts and planners. The majority of respondents expressed gratitude to NVPO and Emory for bringing together a diverse group of experts in vaccine confidence. The participants also mentioned how well the meeting was executed.

Appendix A: Meeting Agenda

THE VACCINE CONFIDENCE MEETING

Collaborating to Advance Vaccine Confidence

Agenda

The Vaccine Confidence Meeting, co-hosted by the National Vaccine Program Office (NVPO) and Emory University, is being held on August 15-16, 2017, on Emory University's campus.

Meeting Location
Emory Conference Center and Hotel
Silverbell Pavilion
1615 Clifton Road NE
Atlanta, Georgia 30329

Background

Achieving high acceptance of recommended vaccinations requires that healthcare providers, parents, and people for whom vaccines are recommended have confidence in their safety, effectiveness, value, and need. Research and practice have seen much growth in recent years as healthcare providers, government agencies, and social/behavior scientists seek to better understand vaccine-related confidence and the factors that foster it. As such, it is increasingly important to facilitate partnerships and share knowledge around research and practice.

As vaccine preventable diseases become increasingly less visible, and new vaccines become available to address new and emerging disease threats, it is essential that healthcare providers, parents, and individuals have confidence in vaccines and their decisions to receive recommended vaccination. The Vaccine Confidence Meeting brings together researchers, government agencies, healthcare, and professional organizations to discuss the latest insights from research and practice for increasing vaccine confidence in the United States.

Objectives

The meeting will help attendees:

1. Learn more about the work being done to address vaccine confidence, hesitancy, and acceptance;
2. Share new research and identify gaps;
3. Strengthen the community of professionals working to increase vaccine confidence; and
4. Meet and speak with leaders in related fields.

Tuesday, August 15, 2017

Registration (8:00am – 9:00am)

I. Opening Plenary (9:00am – 10:00am)

- Judy Mendel, National Vaccine Program Office and Saad Omer, Emory University
  Welcome and meeting overview

- Keynote speaker: Brendan Nyhan, Dartmouth College
  Echo chambers and the challenges of communicating in the 21st century

II. Measurement and Monitoring: Research Insights into the Vaccine Confidence Landscape (10:00am – 11:45am)

- Moderator: Glen Nowak, University of Georgia

- Gaëlle Vallée-Tourangeau, Kingston University
  The 5 A's: a practical taxonomy for the determinants of vaccine uptake

- Allison Kennedy Fisher, Centers for Disease Control and Prevention
  CDC/NCIRD efforts around surveillance of vaccine confidence

- Paula Frew, Emory University
  Development of an index for measurement of parents' vaccine confidence and linkage to pediatric immunization acceptance

- Sandra Quinn, University of Maryland School of Public Health
  Exploring the continuum: measuring vaccine confidence and hesitancy among African American and White adults

Group Picture (11:45am – 12:00pm)

Lunch (12:00pm – 1:15pm)

III. Building and Fostering Confidence Using Public Communication Approaches (1:15pm – 3:00pm)

- Moderator: Ann Aikin, National Vaccine Program Office

- Alisa Johnson Athen, Hennepin County (MN) Public Health Department
  Communications planning and implementation during an outbreak

- Amelia Burke-Garcia, Westat
  The new normal: using digital and social media in support of vaccine communication

- Leslie Schrader, Ketchum
  Promoting flu vaccination and disease prevention to young millennials

- David Rauch, Creative Director/Healthcare Consultant
  From strategy to implementation: insights from HPV and Zoster campaigns

Break (3:00pm – 3:15pm)

IV. Interactive Activity (3:15pm – 4:00pm)

- Ann Aikin, National Vaccine Program Office
  Introduction

- Norma Birnbaum, Publicis LifeBrands
  Workshopping the influenza vaccine advertising landscape

V. Wrap Up and Closing of Day One (4:00pm – 4:15pm)

- Saad Omer, Emory University

Emory-sponsored Dinner (6:00pm)

Wednesday, August 16, 2017

VI. Welcome (9:00am – 9:05am)

- Judy Mendel, National Vaccine Program Office and Saad Omer, Emory University

VII. Values, Confidence, and Vaccine Acceptance (9:05am – 10:45am)

- Moderator: LJ Tan, Immunization Action Coalition

- Robert Bednarczyk, Emory University
  Making a values-based argument for vaccines

- Amanda Dempsey, University of Colorado at Denver
  Motivational interviewing to promote vaccine uptake

- Melissa Gilkey, University of North Carolina at Chapel Hill
  Improving healthcare providers' communication about HPV vaccine

- Noni MacDonald, Dalhousie University
  Building resilient pro-vaccine communities

Break (10:45am – 11:00am)

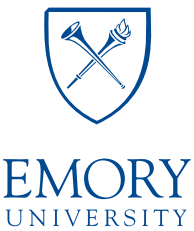
VIII. Systems Approaches to Building Confidence (11:00am – 1:00pm)

- Moderator: Allison Kennedy Fisher, Centers for Disease Control and Prevention
- Saad Omer, Emory University
  Vaccine laws as behavioral interventions
- Jason Schwartz, Yale University
  Policy as intervention for fostering vaccine confidence
- Dan Salmon, Johns Hopkins University
  Building vaccine confidence in public health settings
- Sean O'Leary, University of Colorado at Denver
  Training providers: beyond vaccine administration
- Catherine Flores-Martin, California Immunization Coalition
  The California Immunization Coalition's work to foster vaccine confidence
- Mimi Kiser, Emory University
  Collaborating with faith communities to promote influenza immunization

Break (1:00pm – 1:10pm)

IX. Closing Plenary (1:10pm – 2:00pm)

- Saad Omer, Emory University
  Introduction
- Closing speaker: Walt Orenstein, Emory University
  The effects of vaccine confidence on the immunization system: a retrospective
- Judy Mendel, National Vaccine Program Office and Saad Omer, Emory University
  Concluding thoughts



THE VACCINE CONFIDENCE MEETING

Collaborating to Advance Vaccine Confidence

Appendix B: Speaker & Moderator Bios

NVPO

EMORY

Ann Aikin
National Vaccine Program Office

Ann Aikin, MA is the Director of Communications at the National Vaccine Program Office (NVPO) and has spent her career advocating for smart and strategic use of media to meet communication and behavior change goals. At NVPO, Ann directs communications activities to inform vaccine decision-making, nurtures public support for vaccines across the lifespan, and increases compliance with immunization recommendations. She is responsible for the Vaccines.gov website and developing communication materials and tools targeting a variety of audiences. She is a frequent collaborator in advancing research on a number of vaccine-related communication issues, and works to ensure coordination among the many federal agencies and non-federal entities involved in vaccine and immunization activities. Ann was also the primary author of the first *Health Communicator's Social Media Toolkit* and a number of other efforts to advance health communication practice.

Before joining NVPO, Ann worked at the U.S. Food and Drug Administration's Center for Tobacco Products, where she used health communication and behavior change theory and practice to develop campaigns and communication efforts aimed at reducing the burden of tobacco use in the United States. Prior to this, Ann worked at the Centers for Disease Control and Prevention on the Social Media Team. While at CDC, Ann developed integrated social media strategies and innovative communication products for use in a variety of health communication campaigns and health marketing efforts. She also led the social media efforts for a number of award-winning emergency responses, including the novel H1N1 pandemic (2009-2010), the Haiti Earthquake (2010), and the Peanut Butter and Peanut Containing Product Recalls (2008-2009). Additionally, Ann collaborated in the development of Text4Baby, a free text messaging service designed to promote maternal and infant health. This successful program won an HHSinnovates award in 2010. Ann has also worked on a variety of other mHealth projects and won the Golden Phone Award in 2009. Before working for CDC, Ann spent two years in the U.S. Peace Corps, working for the Jamaican Ministry of Health and the Kingston and St. Andrew Health Department. Additionally, Ann holds Bachelor of Arts degrees in journalism and political science and a Master of Arts in communications all from the University of Iowa.

Alisa Johnson Athen
Hennepin County (MN) Public Health Department

Alisa Johnson Athen is a dedicated public health professional with 24 years in public health service. She currently serves the Hennepin County, Minnesota community as the manager of Public Health Protection and Promotion, an area comprised of the following public health programs: Maternal and Child Health, WIC, EPSDT, Health Promotion, Better Together Hennepin Teen Pregnancy Prevention, Environmental Health, Epidemiology, ImmuLink regional immunization registry, Data Assessment/Evaluation, and Emergency Preparedness. She is in her fourth year of membership in the National

Association of County and City Health Officials (NAACHO) Immunization Workgroup. As part of her leadership role, she had led public health responses, including two measles outbreaks and H1N1 influenza. She previously led the Hennepin County Immunization Services programs which included ImmuLink as well as Perinatal Hepatitis B, Baby Tracks immunization support program, walk-in immunization clinics and Immunization Practice Improvement. She joined Hennepin County to assist in coordinating and growing ImmuLink in its infancy stages. She has a Bachelor's Degree in Child Psychology and a Master's Degree in Health and Human Services Administration. She also has a certificate in Organizational Development. Her areas of interest include policymaking, leadership development, operations and organizational change. While she loves the beautiful summers and falls in Minnesota, she spends winters eager to get to her condo on the gulf coast of Florida!

Robert Bednarczyk
Emory University Rollins School of Public Health

Dr. Robert A. Bednarczyk is an Assistant Professor of Global Health and Epidemiology in the Emory University Rollins School of Public Health. He is also a faculty member of the Emory Vaccine Center and the Winship Cancer Institute Cancer Prevention and Control Program. He received his PhD in Epidemiology from the University at Albany (SUNY) School of Public Health in 2010, and has been at Emory since 2011. Prior to coming to Emory University, he was the Assistant to Chair for the National Vaccine Advisory Committee. Dr. Bednarczyk's research interests are focused on adolescent and adult vaccination uptake, including identification of barriers and methods to address these barriers. He is currently the Principal Investigator of an NIH Career Development Award through which he is evaluating a practice-, provider-, and parent-level intervention to improve HPV vaccination in primary care pediatric practices.

Norma Birnbaum
Publicis LifeBrands

Norma Birnbaum is Senior Vice President and Director of Strategic Planning at Publicis LifeBrands (PLBM). Norma has had a life-long curiosity about people and what makes them tick. It's perhaps no surprise, then, that Norma has dedicated her career to understanding people as customers and what motivates them to choose the products and services that they do *and* don't. Norma has an uncanny knack for pushing past the rational and rationalized — to uncover important insights even for the most challenging categories. During her tenure at PLBM, Norma has had the opportunity to apply her strategic craft to numerous healthcare categories as far ranging as baby nutrition to breast cancer. Prior to PLBM, she had enjoyed a long-standing stint as a consumer marketer and insights specialist at Young & Rubicam. Norma holds a degree in anthropology from Princeton University.

Amelia Burke-Garcia
Westat

Amelia Burke-Garcia is Westat's Senior Director of Digital Media and Director of Westat's Center for Digital Strategy & Research. With nearly 15 years of experience in digital, social, and mobile media, she is an innovator in the digital space for the public sector. She currently acts as the Project Director for the Centers for Disease Control and Prevention's National Center on Birth Defects and Developmental Disabilities Communication Support Program where she is leading the development of an evaluation framework for social media and building an influencer platform for the broad dissemination of their messages. Prior to this work, she served as Campaign Director for CDC's National Influenza Vaccination campaign and Principal Investigator for the National Institutes of Health's National Children's Study looking at using social media to retain study participants in longitudinal research. Before joining Westat, she has served as the Social Media Group Supervisor for indie agency Horizon Media in New York City. In this role, she spearheaded first-to-market digital and social media campaigns for clients such as Cadbury Confections, GEICO insurance, Sobieski vodka, and A&E television. She also has led digital media initiatives for international non-profits, Academy for Educational Development and Management Sciences for Health. She is the author of the published S.O.C.I.A.L. framework for planning and evaluating digital campaigns, the author of the Socialibriumm Experiment blog, a member of the editorial board for *Social Marketing Quarterly journal*, and has been published in numerous books and journals. She holds a Master's degree from Georgetown University, a Bachelor's degree from McGill University, and is a PhD candidate at George Mason University, where her dissertation research is focused on online influencers as opinion leaders for health.

Amanda Dempsey
University of Colorado Denver

Amanda Dempsey is Associate Professor of Pediatrics at the University of Colorado Denver and a practicing general pediatrician. She has studied pediatric immunization delivery for the last 15 years, with a focus on adolescent vaccination, HPV vaccination and vaccine hesitancy. She has been involved in several large, pragmatic, randomized, controlled trials related to improving HPV vaccination in the primary care setting and is a practicing general pediatrician. She serves as a standing member of the American Cancer Society's HPV Vaccination Roundtable Provider Intervention workgroup and serves on the board of the Colorado Children's Immunization Coalition.

Allison Kennedy Fisher
Centers for Disease Control and Prevention

Allison Kennedy Fisher is a health communications specialist with CDC's National Center for Immunization and Respiratory Diseases. She has been at CDC since 2002, first in the Immunization Safety Office before joining the Immunization Services Division

in 2006 and the Health Communication Science Office in 2013. Her areas of research interest include: adolescent vaccines, health and risk communication, health care decision-making behavior, and vaccine acceptance and hesitancy. Allison's experience includes conducting communication and epidemiologic research; writing scientific manuscripts; and writing health education and health communication materials. She has authored or co-authored articles on parent and health care provider immunization attitudes and behaviors, and has presented at national conferences and meetings on various aspects of childhood and pre-teen immunization and communication research. Allison earned her undergraduate degree in anthropology from the University of Notre Dame in 1999. In 2002, she earned a Master's of Public Health degree with a concentration in behavioral science and community health education from Saint Louis University.

Catherine Flores Martin
California Immunization Coalition

Catherine Flores Martin is the Executive Director for the California Immunization Coalition based in Sacramento, California and works in partnership with coalitions and professional organizations that support their mission of ensuring that everyone has access to lifesaving vaccines.

Ms. Martin has over twenty five years of healthcare experience involving health care systems, private medical practices, public health departments, nonprofit organizations and numerous volunteer activities. She has worked in the immunization arena for nineteen years in health promotion, coalition development, registry recruitment and program management.

She coordinates and facilitates professional and community education programs, conferences and media events including webinars, on-line and in person trainings, provider updates, regional immunization events and statewide immunization coalition conferences. She earned her Bachelors of Science degree in Health Administration and Communication at California State University, Fresno.

Catherine works with public health leaders around the country to support coalition development and create effective advocacy and education campaigns; identifying resources, developing collaborative partnerships, and utilizing social media and other technologies to promote immunizations to local, state and national stakeholders. She is a board member of Every Child By Two and works closely with the National Public Health Information Coalition to coordinate the VICNetwork webinars and promotions such as National Immunization Awareness Month.

Paula Frew
Emory University School of Medicine

Dr. Paula Frew is currently Assistant Professor of Medicine within the Division of Infectious Diseases at Emory University School of Medicine and she holds a secondary appointment at the same rank within the Departments of Global Health and Behavioral Sciences and Health Education at the Emory Rollins School of Public Health. Her research interests focus on addressing health disparities and developing interventions with community-based organizations, clinics, state/territorial, and federal, global/international entities to promote immunization acceptance and uptake strategies. She is the Principal Investigator on projects on behalf of the U.S. Centers for Disease Control and Prevention, the National Institutes of Health, and foundations that address an array of vaccine issues from participation in vaccine clinical trials to evaluating strategies for improving vaccine uptake.

Melissa Gilkey
University of North Carolina Gillings School of Global Public Health

Melissa B. Gilkey, PhD, is Assistant Professor of Health Behavior in the University of North Carolina Gillings School of Global Public Health. With research interests in adolescent health, cancer prevention, and health services research, Dr. Gilkey studies individual and organizational approaches to improving the delivery of adolescent vaccines, including human papillomavirus (HPV) vaccine. Her work includes survey research to understand barriers to vaccination, such as provider and parental hesitancy, as well as intervention research aimed at improving vaccine delivery systems. Dr. Gilkey is co-PI of a study funded by the Robert Wood Johnson Foundation to evaluate the CDC's AFIX (Assessment, Feedback, Incentives, and eXchange) model for improving HPV vaccine coverage in primary care settings. She has also received a Transition Career Development Award (K22) from the National Cancer Institute to develop a brief communication training program aimed at supporting healthcare providers in delivering effective recommendations for HPV vaccine. Dr. Gilkey holds a PhD in the social and behavioral sciences from Johns Hopkins Bloomberg School of Public Health.

Mimi Kiser
Emory University Rollins School of Public Health

Mimi Kiser, DMin, MPH is an Assistant Professor in the Department of Global Health, Rollins School of Public Health, Emory University. Ms. Kiser joined the Interfaith Health Program in 1993 during its first seven years at The Carter Center and continues that work now at the school of public health. She teaches interdisciplinary courses at Emory in faith and health, religion and development, and social justice. Ms. Kiser has led the Academic Programs Working Group for Emory's Religion and Public Health Collaborative and work with Emory colleagues in teaching and community mobilization activities supported by the CDC and HHS throughout the US and in Africa. She directed

IHP's "Institute for Public Health and Faith Collaborations," funded by the CDC to provide multi-sector leadership development for the elimination of health disparities. Recently, she has worked with partners in Kenya to adapt this model for mobilization of social resources to support community members in long term HIV/AIDS care. For over 20 years, she has been working to facilitate faith community and public health partnerships that can successfully address the challenges of health disparities. Her roles in these activities have been network and interdisciplinary convener, project director, trainer, curriculum designer (leadership development), and manager of program evaluation operational activities. Ms. Kiser has conducted this kind of work in different contexts and scales – national in the U.S., state level in the U.S., and with multi-local networks in both the U.S. and Africa.

Noni MacDonald
Dalhousie University and the IWK Health Centre in Halifax, Canada

Dr. Noni MacDonald is a Professor of Pediatrics (Infectious Diseases) at Dalhousie University and the IWK Health Centre in Halifax, Canada. She is a former Dean of Medicine at Dalhousie University. Her two current major areas of interest are (1) vaccines including vaccine safety, hesitancy, demand, pain mitigation, education and policy, especially through her work with the World Health Organization, recently appointment to SAGE (the Strategic Advisory Group of Experts on immunization that provides advice to WHO on all aspect of vaccinology), and with the Canadian Centre for Vaccinology Health Policy and Translation Group; and (2) MicroResearch, building capacity in community focused research in developing countries and now also in Canada (www.microresearch-international.ca) to help interdisciplinary health professionals find local solutions for local maternal child health problems that fit the context, culture, and resources. She is a founder and co-director of the Centre for MicroResearch International. Dr. MacDonald has published over 380 papers; was the founding Editor-in-Chief of *Pediatrics & Child Health* and Editor-in-Chief for 20 years; and a former Editor-in-Chief of *CMAJ (Canadian Medical Association Journal)*. She has recently been appointed Editor for Child Health for a new Oxford University Press publication called the *Oxford Research Encyclopedia of Global Public Health*. Dr. MacDonald has long been recognized in Canada and internationally as an advocate for children and youth health and as a leader in pediatric infectious disease and global health.

Judith (Judy) Mendel
National Vaccine Program Office

Judith (Judy) Mendel, MPH is a Health Communications Specialist at the National Vaccine Program Office within the Office of the Assistant Secretary for Health at the U.S. Department of Health & Human Services. Judy joined NVPO in 2014 and leads or supports a number of NVPO's strategic communications efforts, manages NVPO's vaccine confidence portfolio, and serves as the communication research lead for the office.

Judy came to NVPO from George Washington University Milken Institute School of Public Department of Prevention and Community Health. There she worked on the development, management, and evaluation of mHealth programs targeting smoking cessation (Text2quit, Quit4Baby, SmokefreeMOM) and an eHealth program to aid in opioid relapse prevention (Recovery Warrior). Judy holds a Masters of Public Health degree from GW where she won a faculty-nominated Excellence in Culminating Experience award for her thesis.

Prior to graduate school, Judy worked at large advertising agencies (Deutsch, Ogilvy) in New York City where she managed complex client accounts in beauty care (Avon), OTC pharmaceutical (Tylenol, Imodium) and retail (Ikea) sectors. It was there that she discovered her passion for public health communications through work for Avon on breast cancer awareness and with the Ad Council on underage drinking prevention. As an undergraduate, Judy studied advertising at the Newhouse School of Public Communications and political science at the Maxwell School of Citizenship and Public Affairs at Syracuse University, where she was a Chancellor's Scholar.

Glen Nowak
University of Georgia Grady College of Journalism and Mass Communication

Glen Nowak, Ph.D., is director of the Center for Health and Risk Communication in the Grady College of Journalism and Mass Communication at the University of Georgia. He is also a professor of advertising and public relations in the Grady College. He is also currently serving as a visiting senior communications specialist with the National Vaccine Program Office in Washington, D.C.

Prior to re-joining the University of Georgia faculty in January 2013, Dr. Nowak worked 14 years at the Centers for Disease Control and Prevention. He joined CDC in 1999 as the Associate Director for Communications for the National Immunization Program. In 2004, he became CDC's Chief of Media Relations, including serving as Director of CDC's Division of News and Electronic Media. After six years as Chief of Media Relations, Dr. Nowak became a senior advisor to the director of CDC's National Center for Immunization and Respiratory Diseases. While at CDC, Dr. Nowak was extensively involved in efforts to communicate science and public health information and recommendations to the public and the media. He was also extensively involved in vaccine and immunization-related communication efforts, including vaccination promotion and vaccine safety. He has a Ph.D. in mass communication and an M.A. in journalism from the University of Wisconsin. Over the course of his career, he has authored or co-authored 30 peer-reviewed journal articles on communication practices, vaccine communications, social marketing, and health communications. A recently published study examined parents' confidence in childhood vaccines, including compared to childhood antibiotics, over-the-counter medicines, and vitamins.

Brendan J. Nyhan
Dartmouth College

Brendan Nyhan is a professor in the Department of Government at Dartmouth College. His research, which focuses on misperceptions about politics and health care, has been published in journals including the *American Journal of Political Science*, *British Journal of Political Science*, *Journal of Politics*, *Medical Care*, *Pediatrics*, *Political Analysis*, *Political Behavior*, *Political Psychology*, *Social Networks*, and *Vaccine*. Before coming to Dartmouth, he was a Robert Wood Johnson Scholar in Health Policy Research at the University of Michigan. Nyhan has also been a contributor to the *New York Times* website The Upshot since its launch in 2014. He previously served a media critic for *Columbia Journalism Review*; co-edited *Spinsanity*, a non-partisan watchdog of political spin that was syndicated in *Salon* and the *Philadelphia Inquirer*; and co-authored *All the President's Spin*, a *New York Times* bestseller that Amazon.com named one of the ten best political books of the year in 2004.

Sean O'Leary
University of Colorado School of Medicine and Children's Hospital Colorado

Sean O'Leary, MD, MPH, is an Associate Professor of Pediatrics at the University of Colorado School of Medicine and Children's Hospital Colorado, a pediatric infectious diseases specialist, and an investigator at the Adult and Child Consortium for Health Outcomes Research and Delivery Science (ACCORDS). Dr. O'Leary's research focuses on identifying barriers to vaccination and developing and testing interventions to address those barriers, with numerous publications in the areas of vaccine safety, vaccine hesitancy and refusal, immunization policy, vaccination in OB/GYN settings, and influenza vaccine. He is also the director of Colorado's pediatric practice-based research network, the Colorado Children's Outcomes Network. Dr. O'Leary is a member of the American Academy of Pediatrics' Committee on Infectious Diseases (aka the Red Book Committee) and is the liaison to the Advisory Committee on Immunization Practices for the Pediatric Infectious Diseases Society.

Saad Omer
Emory University Schools of Public Health and Medicine

Saad B. Omer is the William H. Foege Professor of Global Health and Professor of Epidemiology & Pediatrics at Emory University, Schools of Public Health and Medicine. He is also a faculty member at the Emory Vaccine Center. Dr. Omer has conducted multiple studies – including vaccine trials – in Guatemala, Kenya, Uganda, Ethiopia, India, Pakistan, Bangladesh, South Africa, and the United States. His research portfolio includes clinical and field trials to estimate efficacy and immunogenicity of maternal and/or infant influenza, pertussis, polio, measles and pneumococcal vaccines; studies on the impact of spatial clustering of vaccine refusers; and clinical trials to evaluate drug regimens to reduce mother-to-child transmission of HIV in Africa. He has conducted several studies to evaluate the roles of schools, parents, health care providers, and

state-level legislation in relation to immunization coverage and disease incidence. Dr. Omer has published widely in peer-reviewed journals including the *New England Journal of Medicine*, *JAMA*, the *Lancet*, *British Medical Journal*, *Pediatrics*, *American Journal of Public Health*, and *American Journal of Epidemiology*. Moreover, he has written op-eds for publications such as the *New York Times*, the *Washington Post*, and *Politico*.

In 2009, Dr. Omer was awarded the Maurice Hilleman Award in Vaccinology by the National Foundation of Infectious Diseases on his work on impact of maternal influenza immunization on respiratory illness in infants younger than 6 months – for whom there is no vaccine. He is currently a member of the National Vaccine Advisory Committee.

Walter A. Orenstein
Emory University

Walter A. Orenstein, MD, DSc (Hon) is Associate Director of the Emory Vaccine Center and Professor of Medicine, Pediatrics, and Global Health at Emory University. Dr. Orenstein has had a long and distinguished career at Centers for Disease Control and Prevention, Emory University, and the Bill & Melinda Gates Foundation (BMGF). Dr. Orenstein began his career in the Epidemic Intelligence Service of the CDC, focusing on immunization, particularly on smallpox eradication and measles elimination. Between 1988 and 2004, he was Director of the United States Immunization Program rising to become an Assistant Surgeon General of the United States Public Health Service. During Dr. Orenstein's tenure at the CDC, record high levels of immunization coverage among children were reached and indigenous transmission of measles and rubella was eliminated. Multiple new vaccines were introduced into the childhood immunization schedule. From 2004-2008, Dr. Orenstein was Associate Director of the Emory Vaccine Program with a major focus on policy issues related to influenza vaccination in the United States. In 2008, he left Emory University to become the Deputy Director for Immunization Programs at the BMGF, in charge of a large portfolio ranging from implementation of polio eradication activities to basic research on improved vaccines and diagnostics. Polio eradication was the number one priority of the BMGF.

Sandra Crouse Quinn
University of Maryland School of Public Health

Sandra Crouse Quinn, PhD, is a Professor in the Department of Family Science, Director of the doctoral program in Maternal and Child Health, and Senior Associate Director of the Maryland Center for Health Equity at the School of Public Health, University of Maryland. She is currently Principal Investigator (joint with Stephen Thomas) for the Center of Excellence in Race, Ethnicity and Health Disparities Research (P20 MD006737, National Institute of Minority Health and Health Disparities). Within the Center of Excellence, she is also the PI on a 5-year study, "Uncovering and Addressing Cultural Beliefs behind Vaccine Racial Disparities." She is joint PI (with

David Broniatowski, George Washington University) on a National Institute of General Medical Sciences grant, “Supplementing Survey-Based Analyses of Group Vaccination Narratives and Behaviors Using Social Media.” She was the PI on a recently-completed pilot study of “Public Attitudes toward Medical Countermeasures,” funded through the FDA’s MD Center for Regulatory Science and Innovation. Additionally, she was the PI on a grant from the U.S. Food and Drug Administration entitled “Investigating Factors Associated with Participation of Racial & Ethnic Minority Populations in FDA Regulated Research.” Dr. Quinn was PI (with Stephen Thomas) of a prestigious Grand Opportunity (“GO”) grant sponsored by the Office of the Director, NIH, NIMHD, and the American Recovery and Reinvestment Act titled “Bioethics Research Infrastructure Initiative: Building Trust between Minorities and Researchers” (7RC2MD004766; 2009-2012). As the PI of a CDC funded study, “Public Attitudes toward H1N1 Influenza,” she worked successfully on two national surveys on attitudes and behaviors during the H1N1 influenza pandemic, including the first study to examine public attitudes toward emergency use authorizations for drugs and vaccines. Her research interests include factors associated with vaccine acceptance in routine and emergency situations; racial disparities in vaccine uptake; crisis and emergency risk communication with a specific focus on minority populations; and engagement of minority and marginalized communities in research.

David Rauch
Creative Director/Healthcare Consultant

David is an award-winning creative director with 30 years of design and creative leadership experience on some of the world’s leading brands. While studying advertising at Syracuse University, he found that the majority of the advertising he loved was coming from an agency called Doyle Dane Bernbach. Armed with a student portfolio, he set out to the School of Visual arts to hone his craft and learn from the best in the business. In 1984, he was hired by his SVA teacher to be his assistant at DDB surrounded by the most creative minds of the era. The team concept of writer and art director working together was the formula for pushing creative thinking that would lead to not just awards but undeniable consumer action. Later in his career, David took this mindset to work in the healthcare arena. In 2003, he worked on the launch of Prilosec OTC, helping it to become a billion dollar brand for P&G. His campaign for Plavix landed on Adweek's best healthcare list in 2008. In 2014, he became the creative lead at Publicis NY overseeing Merck vaccines and creating the “What will you say” campaign urging parents to protect their children from HPV related cancer. David is currently working as a freelance consultant for multiple healthcare agencies.

Daniel Salmon
Johns Hopkins Bloomberg School of Public Health

Dr. Salmon’s primary research and practice interest is optimizing the prevention of childhood infectious diseases through the use of vaccines. He is broadly trained in vaccinology, with an emphasis in epidemiology, behavioral epidemiology, and health

policy. Dr. Salmon's focus has been on determining the individual and community risks of vaccine refusal, understanding factors that impact vaccine acceptance, evaluating and improving state laws providing exemptions to school immunization requirements, developing systems and science in vaccine safety, and effective vaccine risk communication. Dr. Salmon has considerable experience developing surveillance systems, using surveillance data for epidemiological studies, and measuring immunization coverage through a variety of approaches. Dr. Salmon has worked with state and federal public health agencies to strengthen immunization programs and pandemic planning.

Leslie Schrader
Ketchum

Leslie personifies leadership in the PR industry, bringing more than 20 years of public relations agency experience and hands-on leadership of award-winning campaigns. Leslie led campaigns for America's most recognizable consumer packaged goods brands that target such key audiences including women, millennials and parents. She creates and brings her clients' biggest ideas to life, making her a key player on any team's roster. Leslie directs programming on behalf of The Clorox Company, Mattel, The Hershey Company and the Truth Initiative, as well as provides client counsel across the Ketchum network.

Several years ago, Leslie created Well-Connected, a dedicated specialty practice that takes the best in Ketchum's expertise and influencer relationships in the food and nutrition, healthcare and brand marketing spaces and helps companies develop high-impact campaigns that drive consumer behavior change. While heading up Well-Connected, she established an impressive client roster of pharmaceutical, over-the-counter and household-name brands. Leslie currently serves as the senior strategic counselor for the Truth Initiative client, focusing on campaigns to stop teen smoking. She worked with nonprofit Families Fighting Flu, which successfully encouraged CDC to expend its flu immunization recommendations to include children six months to eight years. Leslie also managed the successful "Say 'Boo!' to the Flu" on behalf of The Clorox Company, which encourages parents to have their children immunized against the flu.

Communications campaigns that Leslie has led have earned industry recognition including Cannes PR Bronze Lion, multiple Silver Anvils from the Public Relations Society of America, IRIS Awards from the International Association of Business Communicators and a Diamond SABRE Award for Superior Achievement in Measurement and Evaluation.

Leslie received her Master of Arts in Public Communications from American University and a Bachelor of Arts in English, with minors in political science and women's studies, from Gettysburg College.

Jason L. Schwartz
Yale School of Public Health

Jason L. Schwartz is an Assistant Professor of Health Policy and the History of Medicine at the Yale School of Public Health and Yale School of Medicine. He has written widely on vaccines and vaccination programs, decision-making in public health policy, and the structure and function of scientific expert advice to government. His general research interest is in the ways in which evidence is interpreted, evaluated, and translated into regulation and policy in medicine and public health.

Schwartz's publications on topics in public health policy and history have appeared in *The New England Journal of Medicine*, *JAMA*, *The American Journal of Public Health*, *Health Affairs*, and elsewhere. He is also an author of the chapter titled “Ethics” in *Plotkin’s Vaccines*, the leading textbook of vaccine science and policy, and editor of *Vaccination Ethics and Policy: An Introduction with Readings* (MIT Press, 2017). He is currently working on a book manuscript, *Medicine by Committee: Expert Advice and Health Care in Modern America*, which examines the emergence, evolution, and continuing influence of expert advisory committees in American medicine and public health from the 1960s to the present, particularly regarding pharmaceuticals, vaccines, and screening technologies. His research and perspectives have appeared in *The New York Times, Washington Post, NPR, Time, Associated Press,* and elsewhere.

Prior to arriving at Yale, Schwartz taught at the Princeton University Center for Human Values and the Department of Medical Ethics and Health Policy at the University of Pennsylvania Perelman School of Medicine. He was also a staff member for President Barack Obama’s Presidential Commission for the Study of Bioethical Issues.

Schwartz is a graduate of Princeton University, where he received an A.B. in classics, and the University of Pennsylvania, where he received a Ph.D. in the history and sociology of science and a master's degree (MBE) in bioethics.

Litjen (LJ) Tan
Immunization Action Coalition

Litjen (LJ) Tan, MS, PhD, is chief strategy officer of the Immunization Action Coalition, co-chair and co-founder of the National Adult and Influenza Immunization Summit, and former president of the Board of the Adult Vaccine Access Coalition. He is an associate editor of *Vaccine*, *BMC Infectious Diseases*, *Medscape Infectious Diseases*, and a member of the ESCMID Vaccine Study Group.

Dr. Tan received his Master of Science degree in biology at New York University and earned his Doctorate of Philosophy in microbiology/immunology from Northwestern University Feinberg School of Medicine in Chicago.

Dr. Tan's current appointments include serving as a special consultant for the European Union Influenza Summit and the Asia-Pacific Influenza Summit, and serving as a member of the Advisory Board for Unity (United for Adolescent Vaccination) Consortium, the 317 Coalition, and the AMGA's Adult Immunization Collaborative, to name a few. He was a voting member of the National Vaccine Advisory Committee from 2009 to 2013 and a liaison member of the Advisory Committee for Immunization Practices, Centers for Disease Control and Prevention (CDC), from 2002 to 2012.

Dr. Tan has also served on numerous national and international expert advisory committees on issues ranging from vaccine hesitancy, to adult immunizations, to immunization access and delivery.

His many recognitions include the 2011 CDC National Center for Immunization and Respiratory Diseases Honor Awards: Excellence in Partnering, and an American Pharmacists Association 2009 National Immunization Champion Award.

Throughout his career, Dr. Tan has been deeply involved with projects and publications on vaccine-related issues, including scientific and policy reports from the American Medical Association, where he was their director of Medicine and Public Health for 15 years. He is the proud father of three fully-immunized children.

Gaëlle Vallée-Tourangeau
Kingston University Business School

I am a professor of organisational behaviour, director of research for the department of management at Kingston University Business School and head of the Decision, Attitudes, Risk and Thinking research group. I studied at Paris Ouest University (1998, MSc Social Psychology) and the University of Hertfordshire (2004, PhD) then was a lecturer at the Leeds University Business School (2001-2004) and the University of Toulouse (2004-2009) before joining Kingston University in 2009. My expertise lies in behavioural sciences and my research focuses on the role played by social, physical and/or mental processes in decision-making, reasoning and uncertainty judgements, both in the lab and in applied settings. Current projects include a study of the role of intuition in judgements, a study of the role of autonomous drive in healthcare workers' vaccination decisions and vaccination advocacy, and a study of systemic thinking in work productivity. My work has been published in leading psychology journals such as the *Journal of Experimental Psychology - General*, *Psychological Science*, *Cognition*, *Memory & Cognition*, and *Acta Psychologica* among others. My research has been funded by the Fyssen Foundation (2004), the French National Research Agency (2008), the Leverhulme Trust (2011), and Sanofi-Pasteur (2013).

6.1

Why are we so bad at producing the right flu vaccines?

And how can we improve?

Because of this constant change, the World Health Organization has to wait to make the call on what vaccine should be available until the February before the Northern Hemisphere's flu season. This gives pharmaceutical companies enough time to manufacture the shot, but is hopefully close enough to the season's start to get the prediction right. But six or so months is a lot of time for the virus to evolve, so sometimes the vaccine ends up being a poor protector. If we could manufacture shots instantaneously—or know what the virus would look like each winter—we'd get it right more often. But we don't.

We're finally developing forecasting tools

In recent years, there's been something of an uptick in the tools available to predict the flu. The Epidemic Prediction Initiative, run by the Centers for Disease Control, takes predictions from 28 different models and monitors how well each is able to predict the flu season. EPI also combines those models into one uber-model, which is generally more accurate than any individual estimate.

Each model takes different factors into account and predicts specific variables. Some focus on the timing of outbreaks, others on which strains will dominate. One system from Carnegie Mellon University took weekly polls from volunteers and attempted to predict outbreaks based on the wisdom of the crowds. That model did almost as well as their other system, which used machine learning to analyze data from the CDC. Both outperformed the combined model.

Other universities have also joined the forecasting fray, but so far none of the systems are solid enough to base real decisions on.

Taking virus evolution into account could improve forecasts

In June 2016, unbeknownst to the public, researchers at the University of Chicago were predicting how many flu cases would turn up in the upcoming season. Their system uses standard epidemiological data, but it also includes information about how much the virus is evolving. That extra component allowed them to accurately predict the severity of outbreaks during the 2016-17 season. They published their results in *Science Translational Medicine* on Wednesday.

A quick note of caution: this particular analysis only focused on one region of the U.S., and it didn't look at outbreak timing at all. That being said, it did outpace all of our current forecasting methods. Right now, we're reliant on data as it comes in during the flu season, whereas this model was able to make a prediction the summer before. That's not early enough to affect the vaccine choice, but it could be early enough to allow health care systems time to prepare better. If particular areas were known to be high risk, we could provide more vaccines and other supplies.

This is all preliminary—we're not going to be forecasting next year's flu with any especially high degree of accuracy—but it's all important progress in fighting an annual battle that we too often lose. People don't tend to take influenza very seriously, even though it kills TK people a year in the U.S. alone. If we had better predictions, we might motivate more people to get vaccinated—and maybe save a few lives in the process.

Latest News

6.2

I Never Get The Flu, So Why Do I Need A Flu Shot?

11/21/2017 10:18 am ET | **Updated** 20 hours ago

Brian S. Koll, MD

Recently retired as Executive Medical Director for Infection Prevention and Control, Mount Sinai Health System

The seasonal flu is a contagious illness caused by influenza viruses that infect the respiratory tract. When people have the flu, some are only mildly affected, yet others may miss work, be hospitalized, or even die due to complications. Influenza vaccine, though not perfect, is the best way to prevent flu. But if you have always avoided vaccination and

have never had the flu, you may wonder, “Why do I need a flu shot?” Here are five good reasons, along with answers to some common questions about flu vaccine.

1. Your luck may run out. People who have never had the flu are very fortunate. But flu viruses mutate every year, so even if you did not get last season’s virus, you may still succumb to this season’s.

2. The symptoms feel awful. After you are exposed to an influenza virus, it takes about two days to develop symptoms, which, unlike those of a cold, come on suddenly. Flu symptoms include high fever, cough, and severe muscle aches and pains, which usually last three to five days. After these symptoms resolve, you may still feel extremely weak, and it usually takes another week or two to build up your strength.

The vaccine is not always effective, but if you do get the flu despite being vaccinated, it will still offer some protection, making your disease less severe.

3. Even healthy, young people can die from complications of flu. Complications can be mild, like a painful ear infection, or severe, like bacterial pneumonia or encephalitis. Having severe influenza increases your risk of hospitalization and death. I once took care of a healthy 18-year-old high school senior who had not had a flu shot. Sadly, he came down with influenza, and died of flu-related pneumonia. The risk of complications drastically increases for older people, even those in their 50s and 60s.

4. You can have the flu and not know it. Only half of people infected will actually have symptoms. You can be completely asymptomatic and unaware you are infected, but still have the virus in your body and still be capable of transmitting it to others.

5. Do it for your loved ones. In addition to protecting you, getting a flu shot also protects your family—especially vulnerable children and grandparents—as well as your friends, coworkers, and everyone else with whom you come into contact.

Who should be vaccinated?

Anyone who is 6 months of age or older should be vaccinated, especially those at high risk of complications from flu, such as young children, older people, pregnant women, people with a chronic illness like diabetes or heart disease, and those with weakened immune systems due to disease or medication like chemotherapy. A study published recently in the journal *Pediatrics* showed that vaccination significantly reduces children’s risk of dying from influenza.

People with emphysema, asthma, cystic fibrosis, or other lung diseases are especially susceptible to flu-related pneumonia. Those with heart disease are at risk of developing congestive heart failure. Pregnant women exposed to flu are at increased risk for miscarriage or having a baby with a low birth weight, often requiring neonatal intensive care for a few days.

Who should not be vaccinated?

The only people who should definitely not have a flu shot are those who have had a severe reaction to it in the past. If you have ever had Guillain-Barré syndrome, you should discuss vaccination with your primary care physician.

When should I be vaccinated?

You need to get a flu shot every flu season, because the vaccine is updated each year. It is best to be vaccinated before the winter holidays, when you come into close contact with people through travel and indoor gatherings.

The Centers for Disease Control and Prevention recommends vaccination by the end of October, but even if you haven't been vaccinated by wintertime, it is not too late. Flu season can start in September and last through May, so even if you are not vaccinated until December, you will still be protected for the rest of the season.

What if I have an egg allergy?

Unless you have a history of severe reaction (anaphylaxis) to egg, you can get any type of vaccine. Close to a dozen influenza vaccines are now available—many of them no longer egg-based—so if you are concerned about it, you can request an egg-free vaccine.

Can a flu shot actually give you the flu?

No. It is impossible to catch the flu from a flu shot because vaccines are made either from dead influenza virus or are cell-based, meaning they just contain some genetic material, not the whole virus. A flu shot does not offer protection immediately; it takes up to three weeks for your body to make the antibodies that protect you against influenza. So when people say they got the flu right after having the shot, it means they were exposed to the virus before they developed immunity.

Are side effects possible?

After flu shot, you might have a sore arm, feel a little achy, or develop a fever. These side effects are usually mild and will go away within a couple of days.

I'm concerned about preservatives. What are my options?

Despite the lack of scientific evidence that preservatives cause any harm, manufacturers have listened to patients' concerns, and the majority of vaccines are now preservative-free.

Is there a special flu shot for older people?

Yes. People 65 or older should get a high-dose flu vaccine. As we age, our bodies need more stimulation to make antibodies, so with a stronger dose, you have a better chance of responding to the vaccine. The down side is that you may be more likely to have a sore arm after getting the shot.

Are there any options for people who hate needles?

For kids, unfortunately not. But for adults age 18 to 64 who want to avoid needles, flu vaccine administered by jet injection, which uses high pressure, is available. The nasal spray vaccine, though still available, is not recommended because it does not provide immunity.

OK, I'm convinced. Where can I get a flu shot?

You can be vaccinated at your doctor's office or one of the many pharmacies, grocery stores, and walk-in clinics that offer flu shots. To find a convenient location, just plug your ZIP code into the "Flu Vaccine Finder" at Flu.gov.

If you haven't been vaccinated this season, do it now—for yourself and your loved ones.

6.3

ANTI-VACCINE MOVEMENT: RELIGIOUS OBJECTIONS, ONCE RAMPANT ACROSS THE COUNTRY, SUDDENLY PLATEAU

BY **KASTALIA MEDRANO** ON 11/21/17 AT 4:34 PM

TECH & SCIENCE ANTI-VACCINATION MOVEMENT VACCINES AUTISM

Is the anti-vaccination movement nearly over?

Vaccinations are in most cases required for children to enroll in school, but the laws exist at the state level. Doctors at Emory University in Atlanta analyzed the country's kindergarten-entry vaccination records from the school years between 2011 and 2016. They factored in data on the number of nonmedical exemptions and the level of difficulty associated with getting those

exemptions in different states. That data showed that while nonmedical exemptions were on the rise up until 2013, by 2016 they had leveled off. A paper explaining the findings was published in the journal *Open Forum Infectious Diseases*.

According to the Centers for Disease Control and Prevention, all states offer medical exemptions. Nonmedical exemptions,

vaccines will cause their children to develop autism or other medical complications.

A nurse holds out a tray of immunizations at the city of Newark's School Bus Express free immunization program for Newark youth, in Newark, New Jersey, on August 28, 2013. Nonmedical vaccine exemptions were on the rise up through 2013. Now they appear to have leveled off.

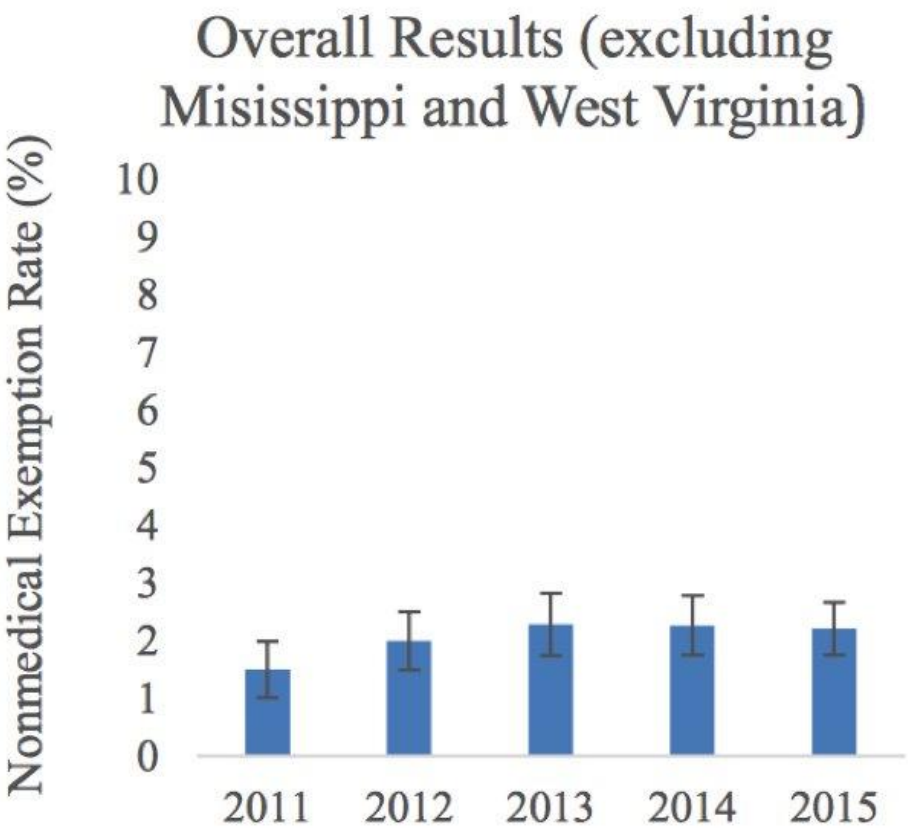
SPENCER PLATT/GETTY IMAGES

Anti-vaxxers are responsible for, among other things, the nation-wide surge in measles, as outlets like ScienceAlert reported earlier this year. More than 100 cases broke out in Disneyland in one 2015 incident alone. The number of nonmedical exemptions has plateaued overall, but in some states the movement appears to be persisting. Rates of nonmedical exemptions in Texas, for example, have not only failed to plateau but are now 19 times what they were in the early 2000s.

"We are still seeing an aggressive increase in nonmedical exemptions [here in Texas]," Peter Hotez, a pediatrician at Baylor College of Medicine, told *Vox,* "with at least 52,000 last year, up from 45,000 the year before."

Philosophical exemptions are a bit less common, but nearly every state offers religious ones. (The paper says that 48 states and the District of Columbia offer nonmedical exemptions; since the study was conducted, California has joined Mississippi and West Virginia to become the third state to exclude nonmedical exemptions of any kind.)

"Some people with an M.D. are perfectly willing to write or sign a note, for a price," Jesse Hackell, a pediatrician and researcher who co-authored a 2016 report on vaccine hesitancy, told *STAT News* earlier this year.



Nonmedical exemptions have recently leveled off.

OPEN FORUM INFECTIOUS DISEASES/OMER ET AL

The researchers wrote that the data represents “an important shift in trend” toward fewer nonmedical exemptions. Lead author Saad Omer, a professor in global health, epidemiology, and pediatrics at Emory, told *Vox* that the results left him “cautiously optimistic,” and that he expects the trend to carry forward.