

ADVISORY COMMISSION ON CHILDHOOD VACCINES
TABLE OF CONTENTS
December 2, 2016

	<u>TAB</u>
<ul style="list-style-type: none"> • ACCV Agenda • ACCV Charter • ACCV Roster • 2017 Meeting Dates 	1
<ul style="list-style-type: none"> • Meeting Minutes <ul style="list-style-type: none"> ○ Draft Minutes – September 20, 2016 	2
<ul style="list-style-type: none"> • Vaccine Injury Compensation Trust Fund Statement <ul style="list-style-type: none"> ○ Vaccine Injury Compensation Trust Fund Summary Sheet for the Period of 10/1/2015 – 9/31/2016 	3
<ul style="list-style-type: none"> • VICP Data and Statistics 	4
<ul style="list-style-type: none"> • Meeting Presentations & Updates <ul style="list-style-type: none"> ○ Report from the Division of Injury Compensation Programs ○ Report from the Department of Justice ○ Update on the Immunization Safety Office Vaccine Activities (CDC) ○ Update on the National Institute of Allergy and Infectious Diseases Vaccine Activities (NIH) ○ Update on the Center for Biologics, Evaluation and Research Vaccine Activities (FDA) ○ Update from the National Vaccine Program Office 	5.1 5.2 5.3 5.4 5.5 5.6
<ul style="list-style-type: none"> • Program-Related Articles/Publications <ul style="list-style-type: none"> ○ The Atlantic, “Cuba’s Innovative Cancer Vaccine Is Finally Coming to America” ○ The Blade, “Shot down: Many Adults Pass On Flu Vaccines” ○ National Public Radio, “Testing Begins On An Experimental Zika Vaccine With Inactivated Virus” ○ WSB TV Atlanta, “Federal program compensates vaccine victims after shots given incorrectly” ○ WSB TV Atlanta, “\$3B program to help vaccine victims falls short on promises” ○ Immunization Action Coalition, “It’s Federal Law! You must give your patients current Vaccine Information Statements (VISs)” 	6.1 6.2 6.3 6.4 6.5 6.6

***ADVISORY COMMISSION ON
CHILDHOOD VACCINES***

Agenda

November 14, 2016

ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV)

5600 Fishers Lane, Room 11SWH01

Rockville, MD 20857

Teleconference and Adobe Connect

December 2, 2016

(10:00 am – 2:30 pm Eastern Daylight Time)

Dial in: 1-800-779-3561

Passcode: 8164763

<https://hrsa.connectsolutions.com/accv/>

Time	Agenda Item	Presenter
10:00 AM	Welcome and Chair Report	Dr. Kristen Feemster, Chair
10:10 AM	Public Comment on Agenda Items	Dr. Kristen Feemster, Chair
10:15 AM	Approval of September 2016 Minutes	Dr. Kristen Feemster, Chair
10:20 AM	Report from the Division of Injury Compensation Programs	Dr. Narayan Nair Director, DICP
10:50 AM	Report from the Department of Justice	Ms. Catharine Reeves, Acting Deputy Director, Torts Branch, DOJ
11:20 AM	Update from ACCV Process Work Group	Ms. Martha Toomey ACCV
12:00 PM	Lunch	
1:00 PM	Update on the Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC) Vaccine Activities	Dr. Michael McNeil CDC
1:15 PM	Update on the National Institute of Allergy and Infectious diseases (NIAID), National Institutes of Health (NIH) Vaccine Activities	Dr. Barbara Mulach NIAID, NIH

Time	Agenda Item	Presenter
1:30 PM	Update on the Center for Biologics, Evaluation and Research (CBER), Food and Drug Administration (FDA) Vaccine Activities	LCDR Valerie Marshall CBER, FDA
1:45 PM	Update from the National Vaccine Program Office (NVPO)	Dr. Karin Bok NVPO
2:00 PM	Public Comment (follows the preceding topic and may commence earlier or later than 2:45 pm)	Dr. Kristen Feemster, Chair
2:15 PM	Future Agenda Items/New Business	Dr. Kristen Feemster, Chair
2:30 PM	Adjournment of the December ACCV Meeting	Dr. Kristen Feemster, 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 referred 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 forth 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 carry out the Program.

Agency or Official to Whom the Commission Reports

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

Support

Management and support services shall be provided by the Division of Injury 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 subcommittee meetings, adjourn any meeting when the DFO determines adjournment to be in the public interest, and chair meetings when directed to do so by the official to whom the Commission reports. The DFO or his/her designee shall be present at all meetings of the full Commission and subcommittees.

Estimated Number and Frequency of Meetings

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

Duration

Continuing.

Termination

Unless renewed by appropriate action prior to its expiration, this charter will expire 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) three members who are health professionals, who are not employees of the United States, and who have expertise in the health care of children, the epidemiology, etiology, and prevention of childhood diseases, and the adverse reactions associated with vaccines, of whom at least two shall be pediatricians;
 - (B) three members from the general public, of whom at least two shall be legal representatives of children who have suffered a vaccine-related injury or death; and
 - (C) three members who are attorneys, of whom at least one shall be an attorney whose specialty includes representation of persons who have suffered a vaccine-related injury or death and of whom one shall be an attorney whose specialty includes representation of vaccine manufacturers.
- (2) The Director of the National Institutes of Health, the Assistant Secretary for Health, the Director of the Centers for Disease Control and Prevention, and the Commissioner of the Food and Drug Administration (or the designees of such officials), each of whom shall be a non-voting ex officio member.

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

Subcommittees

Subcommittees may be established with the approval of the Secretary or designee. Subcommittee members may be members of the parent Commission. The subcommittee shall make recommendations to be deliberated by the parent Commission. The Department's Committee Management Officer will be notified upon the establishment of each subcommittee and will be provided information 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 of Information Act, 5 U.S.C. 552.


4 – ACCV Charter

Filing Date

July 21, 2016

Approved:

JUL 20 2016
Date



Jason E. Bennett
Director, Division of Executive Secretariat



Roster

**ADVISORY COMMISSION ON CHILDHOOD VACCINES (ACCV) ROSTER
DIVISION OF INJURY COMPENSATION PROGRAMS (DICP)**

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ADVISORY COMMISSION ON CHILDHOOD VACCINES

2016 MEETING DATES

March 3, 2016
June 3, 2016
September 20, 2016
December 2, 2016

2017 MEETING DATES

March 2 & 3, 2017
June 1 & 2, 2017
September 7 & 8, 2017
December 7 & 8, 2017

2

Advisory Commission on Childhood Vaccines

September 20, 2016

101st Meeting

Members Present

Kristen A. Feemster, M.D., Chair ('16)

Jason Smith, J.D., Vice Chair. ('16)

Charlene Douglas, Ph.D. ('16)

Edward Kraus, J.D., ('16)

Luisita dela Rosa, Ph.D. ('16)

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

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., Acting Director, DICP

Andrea Herzog, Principal Staff Liaison, ACCV

Welcome, Report of the Chair and Approval of Minutes, Kristen Feemster, ACCV Chair

Dr. Feemster called the meeting to order and completed a roll call to confirm those in attendance.

Public Comment on Agenda Items

Dr. Feemster invited public comment specifically related to the agenda. There was none.

Approval of June 2016 ACCV Meeting Minutes

Dr. Feemster invited approval of the minutes of the June 2016 meeting. On motion duly made and seconded, the minutes were unanimously approved.

Report from the Division of Injury Compensation Programs, Dr. Narayan Nair, Acting Director, DICP

Dr. Nair briefly reviewed the meeting agenda, which would include an update from the Department of Justice Vaccine Litigation Office, a report from the ACCV Process Workgroup, and the regular updates from the ex officio members representing the various Department of Health and Human Services (HHS) agencies. Noting that the DICP is on a fiscal year (FY) ending September 30, 2016, Dr. Nair reported that as of September 2, 2016, the division had received 986 petitions. The average number of petitions filed annually for the 5-year period beginning FY 2011 was 546. There has been an increase in petitions filed each fiscal year since then.

The number of compensable adjudications has increased annually from 266 in FY 2011 to 556 through September 2, 2016 of this fiscal year. The total number of adjudicated cases in FY 2011 was 1,637, of which 1,371 were dismissed. In FY 2016, there was a total of 718 adjudications through September 2, 2016, of which 162 cases were dismissed.

A 3-year snapshot of non-autism adjudications was presented to the commissioners. There were 581 compensable non-autism claims adjudicated in FY 2016 as of September 12. The 581 non-autism claims adjudicated were broken down into three categories: concession by the HHS, 171 (29%); court decisions, 41 (7%); and the majority by settlement, 369 (64%). There were 151 claims deemed not compensable, making a total of 732 non-autism adjudications in FY 2016 as of September 12, 2016.

Through September 1, 2016, the program awarded \$191 million to petitioners, and approximately \$20 million for attorneys for fees and costs. The Vaccine Injury Compensation Trust Fund stood at \$3.6 billion as of August 31, 2016. The sources of revenue were \$221 million from excise taxes and \$50 million from interest on investments, for a total of nearly \$272 million. Interest as a percentage of income was 19%.

Dr. Nair commented that the Notice of Proposed Rulemaking (NPRM) for revising the Vaccine Injury Table was published in the Federal Register on July 29, 2015. To obtain public comments, a public hearing was held on January 14, 2016 and a 180-day public comment period ended on January 25, 2016. The public comments were reviewed and a final rule has been developed which is being reviewed by the HHS. With regard to outreach, on August 9, 2016, Dr. Nair stated that he had provided an overview of the VICP to representatives of the Association of State and Territorial Health Officials (ASTHO).

Dr. Nair concluded his prepared remarks with instructions about obtaining ACCV meeting information and about how to contact ACCV support staff.

During the discussion, Dr. Nair was asked about the estimated release date of the Final Rule revising the Vaccine Injury Table, Dr. Nair said it is expected to be published by the end of the calendar year.

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

Ms. Reeves welcomed the commissioners. Ms. Reeves referenced the Department of Justice PowerPoint materials as part of her presentation for the 3-month period from May 15, 2016 to August 15, 2016. During this reporting period, 276 petitions were filed, which is an increase of 70 petitions compared to last period. Of those 276, 30 were filed on behalf of children (11%) and 246 were filed by adults (89%). (DOJ PP at 2).

With regard to total cases adjudicated, Ms. Reeves noted that 233 claims were adjudicated this quarter. (DOJ PP at 3). There were 180 cases compensated. Of those 180 cases, 67 were conceded cases by HHS. Of those 67 conceded cases, 65 were resolved by a decision adopting a proffer, and 2 were resolved by a decision adopting a settlement stipulation. Ms. Reeves noted that 17 more cases were adjudicated this period than last period. There were 113 cases compensated, but not conceded by HHS. Of those, all 113 cases were resolved by a decision adopting a settlement stipulation. (DOJ PP at 3). There were 53 cases dismissed. Of those, 51 non-OAP cases were resolved by decisions dismissing the petition, and 2 were

dismissed from the OAP. (DOJ PP at 3). There were 13 petitions voluntarily withdrawn, which Ms. Reeves remarked was an increase of 4 compared to last period. (DOJ PP at 4).

Turning to appeals, one case filed by petitioners was decided by the U.S. Court of Appeals for the Federal Circuit (CAFC). (DOJ PP at 5). In *Milik v. HHS*, the CAFC affirmed the dismissal of the case per curiam, and petitioner filed a combined petition for panel rehearing and en banc rehearing, which was denied. In addition to three appeals filed by petitioners that are pending, six new appeals were filed by petitioners in *Canuto v. HHS*, *R.V. v. HHS*, *Culligan v. HHS*, *Fishk is v. HHS*, *Meylor v. HHS*, and *Meylor v. HHS*. (DOJ PP at 6).

Ms. Reeves discussed appeals at the CFC, and noted that five appeals filed by petitioners were decided by the CFC. The CFC affirmed the denial of compensation in all five cases. (DOJ PP at 7). Ms. Reeves noted that petitioners filed eight new appeals to the CFC, most of which involve entitlement, but some of which involve attorneys' fees and costs. (DOJ PP at 8). Respondent filed appeals in two cases regarding attorneys' fees and costs, in *Allicock v. HHS* and *Garrison v. HHS*, and in one case involving a special master's award of interim damages. Six cases remain pending at the CFC. (DOJ PP 8).

No cases are scheduled for oral argument at the CAFC or CFC. (DOJ PP at 9).

Ms. Reeves noted the history of adjudicated settlements, which are listed in order of the time they took to resolve. (DOJ PP at 10-21).

Report from the ACCV Process Workgroup, Ms. Martha Toomey, ACCV Member and Workgroup Chair

Ms. Toomey summarized the recommendations proposed by the Workgroup that would address the existing inadequate funding and lack of staff support (both special masters and staff). The Workgroup felt that there were not enough special masters to properly handle the caseload, the result of increased petitions being filed (an increase of 80% in three years between 2013 and 2015, from 525 to 945). That has resulted in a backlog of cases that may eventually result in delayed compensation for vaccine-injured individuals who submit legitimate claims.

The Workgroup decided not to dilute the initial recommendation and to focus on the most important issues, lack of special masters and inadequate funding. The workgroup proposed a recommendation that would require a legislative amendment to the National Childhood Vaccine Injury Act of 1986, which contains the words the "office of special masters shall consist of not more than 8 special masters." The new wording would be: the "office of special masters shall consist of *at least* 8 special masters." A second recommendation proposed by the Workgroup was that the Secretary support an increase in the appropriations for the Office of Special Masters (OSM) to pay for additional special masters and VACP staff at HRSA, DOJ and OSM.

Ms. Toomey explained that the draft letter would be kept short and focused, but that supporting documentation, including statistics, would be attached. The final letter would be submitted to the Commission for review, revision, if deemed appropriate, and submission to the Secretary.

Ms. Jocelyn McIntosh, Senior Staff Attorney, OSM commented that Chief Special Master Dorsey had requested that a message be relayed to the Commission. Chief Special Master Dorsey, wanted the commission to know that she appreciated their interest in and consideration of her remarks when she participated in the March 2016 ACCV meeting. Ms. McIntosh, expressed the Chief Special Master's thanks for the Commission's diligent work in developing the recommendation. She added that the Chief Special Master was amenable to including her

endorsement as an attachment to the recommendation to the Secretary if the Commission felt it was appropriate.

Noting that the Commission had considered the recommendation, Dr. Feemster invited a motion to approve the submission of the recommendation to the Secretary of HHS.

On motion duly made and seconded, the Commission unanimously approved submitting the recommendation as written to the Secretary.

Ms. Toomey stated that the Workgroup had other items that were being discussed and recommendations related to those items (including a change in the statute of limitations and the inclusion of a vaccine-injured individual on the Commission) would be discussed by the Workgroup and included on a future meeting agenda.

Noting that the Commission had been especially efficient in conducting the first agenda items, Dr. Feemster re-ordered the agenda to accommodate those presenters who were scheduled after the lunch break. She invited LCDR Valerie Marshall to discuss FDA activities.

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

LCDR Marshall briefly reviewed her presentation, which would address recent vaccine approvals, the upcoming Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to be held on October 13, 2016, and the FDA emergency preparedness response to the Zika threat.

Regarding new approvals, LCDR Marshall discussed the approval in June 2016 of a cholera vaccine (live, oral) trade name Vaxchora. Cholera is caused by *Vibrio cholerae* serogroup 01. The vaccine is approved for adults 18 to 64 years of age who may be traveling to cholera-affected areas. Vaxchora is the only FDA-approved vaccine for cholera, and it is approved specifically for travelers to those high-risk areas. FDA granted this application fast track designation and priority review status.

In May 2016, the FDA approved a supplement to the biologics license application (BLA) for influenza vaccine, Flucelvax, manufactured by Seqirus, that adds a fourth strain to the mix, making it a quadrivalent formulation. Flucelvax quadrivalent is the first four-strain flu vaccine and it is indicated for persons four years of age and older.

In July 2016, the FDA approved a supplement to the BLA for Prevnar 13, expanding the indication to adults 18 through 49 years of age for the prevention of pneumonia. Prevnar is effective against 13 serotypes of *S. pneumoniae*. It was previously approved for children 6 through 17, and adults 50 and older. This change expanded the age indication for receipt of the vaccine.

Finally, in July 2016, the FDA approved a strain change supplements to the BLAs for licensed influenza vaccines to include the 2016-2017 seasonal influenza vaccine formulation. Flu vaccine lots released by the FDA are available for distribution by the manufacturers.

LCDR Marshall announced that one VRBPAC meeting is scheduled on October 13, 2016, to discuss the selection of strains to be included in an influenza virus vaccine for the 2017 Southern Hemisphere influenza season.

LCDR Marshall mentioned that investigational Zika virus vaccines are in the early stages of development. In June 2016, the FDA authorized the first clinical trial for an experimental Zika virus vaccine. The FDA will work with industry to clarify regulatory and data requirements necessary to move the product development forward as expeditiously as possible. During

discussion, LCDR Marshall clarified that the term “early stages of development” indicates that the new vaccines have not been tested in humans and have not undergone the standard FDA clinical trial reviews for new products. New drugs are tested in animals before beginning Phase I studies. There was a brief discussion of the potential of using existing drug development platforms for Zika virus vaccine.

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

Ms. Schuster described a large NIH-supported natural history study of Zika virus in pregnant women, which began in Puerto Rico and will expand to other countries including Brazil and Colombia. The study will enroll up to 10,000 pregnant women in their first trimester and observe them for the duration of their pregnancies with at least one-year of follow-up for their infants after birth. The National Institute of Allergy and Infectious Diseases (NIAID) began a study in August, enrolling up to 80 participants at three sites in the U.S., to evaluate a candidate Zika vaccine. The Phase I trial will assess efficacy and safety.

The journal, *Science*, reported on a study of three candidate Zika vaccines, an inactivated vaccine, a DNA-based vaccine, and an adenovirus vector-based vaccine. These vaccines protected against infection, induced immune responses, and showed no adverse side effects when tested in rhesus macaques. Another paper was published in *Nature*, that looked at two experimental Zika vaccines, a DNA-based vaccine and an inactivated virus vaccine. Both were tested in mice and a single dose of the vaccines protected against the Zika virus. Finally, the National Institute of Child Health and Development (NICHD) will sponsor a meeting in late September to look at how Zika virus affects child development.

In 2013, approximately 84,000 to 170,000 individuals worldwide were infected with yellow fever, with 29,000-60,000 deaths. The current yellow fever vaccine is in short supply and not recommended for certain populations, such as infants and pregnant women. An investigational vaccine developed by Bavarian Nordic is being evaluated in an NIAID-sponsored Phase I trial for its safety, tolerability, and potential ability to prevent yellow fever infection. The trial will enroll 90 healthy individuals who have never been infected by a flavivirus (the family of viruses that includes dengue, Zika, West Nile, among other viruses). The trial will assess the vaccine with and without an adjuvant.

NIAID continues to support influenza vaccine research, including a study that has led to the discovery of antibodies that can target multiple influenza strains. This study is discussed in a paper in the July 21 online edition of *Cell*. Additional publications of interest include a report in *Vaccine* (August 23, 2016) on a FDA/NIH workshop on respiratory syncytial virus (RSV) vaccines; and a summary of findings from an NIAID-sponsored workshop on gonorrhea vaccines in *Clinical and Vaccine Immunology* (August 5, 2016).

Although not specific to vaccines, Ms. Schuster mentioned the Cancer Moonshot initiative announced by President Obama in his State of the Union address in January. The Cancer Moonshot is led by Vice President Biden and seeks to broaden cancer diagnosis, prevention, and treatment in the U.S. Finally, on September 8, NIH announced the Antimicrobial Resistance Diagnostic Challenge which will award \$20 million in prizes for innovative point-of-care, in vitro, diagnostic tests to rapidly identify antibiotic-resistant

infections. The prize is offered by NIH and the HHS Office of the Assistant Secretary for Preparedness and Response.

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

Dr. McNeil announced that he would provide an update of the recent meeting of the Advisory Committee on Immunization Practices (ACIP); and discuss several recent publications that might be of interest to the Commission. In their session on cholera, the ACIP recommended Vaxcholora, previously mentioned in the FDA vaccine activities update, for travelers 18 to 64 years of age who are at increased risk of disease as described below. Although *Vibrio cholera* 01 infection can be effectively treated with timely rehydration, the disease can be fatal, if untreated. Individuals who are especially at risk include those with blood type O, pregnant women, those with immunocompromising conditions and those with cardiovascular and/or renal disease.

Dr. McNeil noted that the FDA had revised the dosing schedule for meningococcal B vaccine, Trumenba, as a 2-dose and a 3-dose schedule (the FDA noted a preference for the latter). For the meningococcal conjugate vaccine, ACIP voted unanimously to recommend meningococcal conjugate vaccine be administered routinely to HIV-infected people age two years and older. This was because it is now clear there is an increased risk in HIV-positive individuals.

Dr. McNeil commented that two new influenza vaccines are available. Flucelvax quadrivalent vaccine, licensed in May 2016, showed an immune response and evidence of safety and tolerability similar to the previous trivalent vaccine. FluLaval was licensed for persons three years and older, and the manufacturer (GSK) has submitted a supplemental BLA to revise the vaccine's age indication downward to include persons 6 month to 35 months. GSK presented safety and immunogenicity data that showed the vaccine compared favorably with Fluzone quadrivalent. An ISO report to the committee of end-of-season influenza safety monitoring revealed that analysis of the Vaccine Adverse Event Reporting System (VAERS) showed no new safety concerns regarding influenza vaccines. The CMS Medicare database did reveal an increased rate of Guillain-Barré Syndrome (GBS), 7.25 cases per million inoculations, up from 5.45 cases per million. The Vaccine Safety Datalink (VSD) identified a signal for GBS following inactivated influenza vaccine (IIV3) of 2.6 cases per million inoculations. These rates are similar to earlier surveillance figures. Asked about the discrepancy in the CMS data, Dr. McNeil explained that, historically, there has been low or no risk of GBS found in different studies and work is ongoing to better refine the risk estimate for this rare outcome.

An evaluation of vaccine effectiveness of IIV and live attenuated influenza vaccine (LAIV) against influenza A and B, revealed the latter was significantly less effective in children 2-17 years old. An AstraZeneca study released effectiveness percentages: LAIV4, 46%, and IIV, 65%. The third vote of the meeting was that ACIP recommends that the LAIV should not be used for the 2016-2017 flu season. A Vaccine for Children (VFC) program vote followed to remove LAIV from the VFC program for the 2016-2017 influenza season.

Dr. McNeil commented that there was a presentation on respiratory syncytial virus (RSV) infection that showed that children under two are most vulnerable, although there is also a significant disease burden in older adults. A formalin-activated vaccine failed in Phase I trials in the sixties, causing vaccine-enhanced disease syndrome in RSV-naïve infants. However, there

are currently Phase I clinical trials of a candidate vaccine for children, and Phase I-III trials for a vaccine in pregnant women.

The ISO presented a summary at ACIP of VAERS data for pregnant women, indicating no new unexpected vaccine safety concerns; and the VSD found that Tdap during pregnancy was not associated with an increased risk of birth defects among live offspring. The Clinical Immunization Safety Assessment (CISA) Project reported that Tdap was well tolerated in both pregnant and non-pregnant women. Moderate to severe injection site pain was more frequent among pregnant women, but did not lead to repeat medical visits for that issue. Half of the pregnant women had received a prior Tdap injection, but reactions were similar in all patients regardless of earlier Tdap injections. Both pregnant and non-pregnant women had significantly higher antibodies to all antigens after inoculation.

Finally, the human papillomavirus (HPV) vaccines show no evidence of waning protection after a 3-dose schedule, and antibody responses were maintained over time after the same vaccination schedule. Of 13 studies, 10 showed that 2 doses were not as effective as 3 doses. The ACIP is considering a proposed recommendation of two doses of HPV vaccine for children who begin inoculations before their 15th birthday (0 and 6-12 months); and a three dose schedule for those who have reached the age of 15 (0, 1-2, and 6 months).

Dr. McNeil briefly mentioned several publications that might be of interest to the Commission.

Duffy et al. looked at febrile seizure risk in children 6-23 months (*Pediatrics*. 2016; 138). Giving IIV3 and either pneumococcal conjugate vaccine or a DTaP-containing vaccine was associated with increased risk of febrile seizure.

Sawyer et al. quantified the risks associated with vaccines and febrile seizures (*Pediatrics*. 2016; 138). This review found that although the risk of febrile seizure is very small (estimated as ~1 episode in a 5-year period in pediatric office practice), the benefit of receiving the vaccine far outweighs the risk. It was noted that the study looked at febrile seizure and not later sequela.

Stockwell et al. assessed fever frequency after pediatric LAIV versus IIV vaccination. (*J Pediatric Infect Dis Soc*. 2016 Jun 14) Post vaccination fever frequency was low overall and did not differ with regard to vaccine type during the 2013-2014 flu season.

Moro et al. looked at post-marketing surveillance of human rabies diploid cell vaccine (Imovax) from 1990 to 2015 in VAERS. (*PLoS Negl Trop Dis*. 2016; 10(7)). The analysis did not identify any new or unexpected adverse events. The majority of adverse events reported were non-serious.

Lindsey et al. looked at VAERS reports following yellow fever vaccination from 2007-2013 (*J Travel Med* 2016 23(5)). The report substantiates the generally accepted safety profile of yellow fever vaccine, and encourages continued physician and traveler education.

Bardenheier et al. analyzed VAERS data on military and civilian personnel receiving the pandemic influenza A (H1N1) 2009 monovalent and seasonal flu vaccines during the 2009-2010 season (*Vaccine* 2016; 34(37)). Despite higher vaccination coverage in service personnel the rate of adverse events reported was about half that in civilians. The rate of GBS was higher in the military personnel.

Vazquez-Benitez et al. looked at the risk of small-for-gestational-age births after flu vaccination during pregnancy (*Am J Epidemiology* 2016 184(3)). Confounding factors include potential biases in outcomes that could be due to variable access to vaccines, and baseline differences between vaccinated and unvaccinated women.

Clogston et al. looked at unintentional administration of insulin instead of influenza vaccine (Drugs Ther Perspective Aug. 2016). The assessment revealed that deviations from recommended practices contributed to the adverse event, which would be preventable with proper training and controls.

Moro and Chen published a commentary in Vaccine 2016 Aug 20. The Global Alignment of Immunization Safety Assessment in pregnancy, and international collaboration associated with the Brighton Project, has developed 10 obstetric and neonatal definitions, along with tools to harmonize data collection, analysis and presentation. Vergnano et al. developed a case definition for neonatal infection immunization safety data (in Vaccine 2016 Aug. 1); and DeSilva et al. did the same for congenital anomalies (in Vaccine 2016 Jul. 16).

Dr. Feemster noting that the ex officio reports had been completed, suggested that the Commission continue to the Vaccine Information Statements.

Review of Vaccine Information Statements, Skip Wolfe, CDC

MMRV Vaccine (Measles, Mumps, Rubella and Varicella): What you need to know

Mr. Wolfe invited comment on the first section, “Why get vaccinated?” He noted that wording had been crafted to indicate that the four diseases covered by MMRV vaccine were not inherently serious diseases, and could have relatively mild symptoms, but those infected could experience serious consequences. It was noted that, per custom, words of four or more syllables are typically not used in the text of the VIS – specifically “consequences.” Mr. Wolfe felt the word should not be an obstacle to readers, but he would look for an appropriate synonym of three or fewer syllables. Mr. Wolfe also agreed that a suggestion that the words “especially among children” should be deleted. He added that there were separate VIS for MMR and varicella and the wording in those VIS had been harmonized with this MMRV version. There was a brief discussion about using the word “tiredness,” and Mr. Wolfe said that his staff would reconsider the wording. There was an observation that death could be a rare outcome of any of the four diseases, although only mentioned under measles and mumps. Mr. Wolfe agreed that death could be incorporated in the introductory sentence applying to all four (and deleted from measles and mumps).

Mr. Wolfe moved to the second section, for which there were no comments. In the third section, “Some people should not get this vaccine,” Mr. Wolfe noted that there had been some minor structural changes to the paragraphs. In the fourth section, concerning risks, Mr. Wolfe suggested that the wording of the second paragraph be revised to read, “Most children who get MMRV vaccine do not have any *serious* problems with it.” There was also a suggestion that the first sentence in that paragraph should address the fact that there is a risk of adverse reaction when being inoculated with any vaccine. The recommendation was to use a term like “less serious” rather than safer.

Mr. Wolfe commented that a sentence was added to the section entitled “Minor problems following MMRV vaccine include,” to explain that if a rash develops there is a possibility of contagion, albeit a rare event. In the paragraph on severe problems, the term “lowered consciousness” was deemed vague. There was a suggestion that it indicates a change in alertness or awareness. In the same section there was a comment that the sentence, “These reactions happen so rarely that it is difficult to tell whether they are caused by the vaccine,” might suggest

that the severe, rare problems are not caused by the vaccine. That might be misleading. There was a counter argument that it is, in fact, difficult to determine causation. Mr. Wolfe commented that the thoughts expressed would be useful in reconsidering the wording.

There was a comment that the Commission had previously agreed that the term “health care provider” should be used instead of “doctor.” Mr. Wolfe agreed that there had been a significant number of opinions offered concerning the two terms. After a brief discussion about the rationale for using the terms, Mr. Wolfe said that, if the term healthcare provider is clearly understood universally, he would be amenable to using the term rather than “doctor” throughout all VIS. Mr. Wolfe explained that the rest of the document contained wording that appears in all VIS. Since that wording had been reviewed a number of times, he suggested that the review was complete.

Dr. Feemster concluded the discussion of the VIS and moved to the public comment period.

Public Comment

Ms., Theresa Wrangham, representing the National Vaccine Information Center (NVIC), expressed appreciation to staff for the timely placement of the meeting book on the ACCV website. She emphasized the importance of having that prepared information available to supplement the meeting’s verbal discussions.

Ms. Wrangham recommended that, in addition to the Process Workgroup’s recommendation for the Secretary to increase the number of special masters and support staff for the special master’s office, that a recommendation be included to increase funding for research to fill the gaps in knowledge identified by the Institute of Medicine study. That research would support the expansion of the Vaccine Injury Table when appropriate quality research is available. The NVIC requested that the Commission support the premise that research must be funded outside the bounds of the Vaccine Injury Compensation Trust Fund. The NVIC recommended that the Commission establish a mechanism by which the satisfaction of petitioners, especially in light of experiences reported by petitioners who were dissatisfied with the awards made by the program. The Commission should review the comments in the 2009 Altarum report, the 2010 Banyan report and the 2014 GAO report.

Ms. Wrangham renewed her prior request that, since vaccines carry the risk of injury or death, the ACCV should support the right of every parent to make voluntary vaccine decisions for themselves and their children. They should be able to make those decisions without the threat of sanctions, such as being removed from a doctor’s practice.

Lastly, with regard to the MMRV VIS, it should be noted that these infections usually resolve without complication. Unfortunately, there is insufficient information about the diseases and the effects of vaccination to allow individuals to make informed decisions about the use of vaccines.

Future Agenda Items/New Business

Dr. Feemster invited suggestions for agenda items. She noted that the Process Workgroup would provide additional information about their recommendations beyond those approved at this meeting. She also suggested that there would be follow-up on the legislation that was in part a result of the ACCV Maternal Immunization Workgroup’s activities.

The format of the December meeting, teleconference or in person, will depend on a number of considerations, such as whether there will be new Commission member on board at that time.

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, 2016

\$3,687,636,528.98

Figures for October 1, 2016 to September 30, 2016

- Excise Tax Revenue: \$290,925,706.52
- Interest on Investments: \$98,971,102.35
- Total Income: \$389,896,808.87
- Interest as a Percentage of Total Income: 25%

*Source: U.S. Treasury, Bureau of Public Debt
November 14, 2016*

4



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:

- Over 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 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 U.S. Court of Federal Claims 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 CDC, from 2006 to 2014 over 2.5 billion doses of covered vaccines were distributed in the U.S. For petitions filed in this time period, 3,637 petitions were adjudicated by the Court, and of those 2,287 were compensated. This means for every 1 million doses of vaccine that were distributed, 1 individual was compensated.

Since 1988, over 17,554 petitions have been filed with the VICP. Over that 27 year time period, 15,150 petitions have been adjudicated, with 5,018 of those determined to be compensable, while 10,132 were dismissed. Total compensation paid over the life of the program is approximately \$3.4 billion.

This information reflects the current thinking of the United States Department of Health and Human Services on the topics addressed. This information is not legal advice and does not create or confer any rights for or on any person and does not operate to bind the Department or the public. The ultimate decision about the scope of the statutes authorizing the VICP is within the authority of the United States Court of Federal Petitions, which is responsible for resolving petitions for compensation under the VICP.

**VICP Adjudication Categories, by Alleged Vaccine,
 For Petitions Filed Since the Inclusion of Influenza as an Eligible Vaccine for Filings 01/01/2006
 Through 12/31/2014**

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 12/31/2014 (Source: CDC)	Compensable			Compensable Total	Dismissed/Non-Compensable Total	Grand Total
		Concession	Court Decision	Settlement			
DT	712,347	1		5	6	4	10
DTaP	83,052,184	14	19	91	124	89	213
DTaP-Hep B-IPV	51,305,397	4	8	23	35	40	75
DTaP-HIB	1,135,474			1	1	1	2
DTaP-IPV-HIB	46,401,211	1		7	8	17	25
DTap-IPV	15,490,820						
DTP	0	1	1	3	5	2	7
DTP-HIB	0			3	3	1	4
Hep A-Hep B	12,740,305			10	10	2	12
Hep B-HIB	4,787,457	1	1	1	3	1	4
Hepatitis A (Hep A)	136,935,713	6	3	27	36	23	59
Hepatitis B (Hep B)	143,946,953	2	11	53	66	48	114
HIB	93,160,376		1	4	5	5	10
HPV	77,506,945	13	4	87	104	119	223

National Vaccine Injury Compensation Program
 Monthly Statistics Report

Influenza	1,078,000,000	100	97	1,184	1,381	216	1,597
IPV	62,344,612			4	4	2	6
Measles	135,660			1	1		1
Meningococcal	64,004,175	1	4	27	32	5	37
MMR	80,115,475	19	14	68	101	84	185
Mumps	110,749						
MMR-Varicella	14,403,057	8		8	16	9	25
Nonqualified	N/A			3	3	23	26
OPV	0	1			1	3	4
Pneumococcal Conjugate	150,497,243		1	6	7	17	24
Rotavirus	79,636,437	4	4	17	25	7	32
Rubella	422,548		1	1	2		2
Td	57,940,972	7	6	55	68	19	87
Tdap	177,160,298	31	7	133	171	24	195
Tetanus	3,836,052	4		25	29	14	43
Unspecified	N/A	1	2	3	5	563	568
Varicella	96,646,081	4	7	24	35	12	47
Grand Total	2,532,428,541	222	190	1,874	2,287	1,350	3,637

Notes on the Adjudication Categories Table

The date range of 01/01/2006 through 12/31/2014 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, 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 11/01/2016

Vaccines	Filed			Compensated	Dismissed
	Injury	Death	Grand Total		
DTaP-IPV	6	0	6	1	1
DT	69	9	78	26	51
DTP	3,286	696	3,982	1,273	2,707
DTP-HIB	20	8	28	7	21
DTaP	415	80	495	208	218
DTaP-Hep B-IPV	67	30	97	35	38
DTaP-HIB	11	1	12	5	3
DTaP-IPV-HIB	38	18	56	8	17
Td	194	3	197	116	69
Tdap	402	2	404	219	32
Tetanus	116	2	118	56	42
Hepatitis A (Hep A)	89	6	95	39	24
Hepatitis B (Hep B)	639	56	695	261	380
Hep A-Hep B	25	0	25	13	2
Hep B-HIB	8	0	8	4	3
HIB	38	3	41	14	16
HPV	322	14	336	105	124
Influenza	2,928	114	3,042	1,766	240
IPV	264	14	278	8	267
OPV	282	28	310	158	151
Measles	143	19	162	55	107
Meningococcal	54	2	56	35	5
MMR	926	58	984	388	518
MMR-Varicella	37	1	38	16	9
MR	15	0	15	6	9
Mumps	10	0	10	1	9
Pertussis	4	3	7	2	5
Pneumococcal Conjugate	68	9	77	13	31
Rotavirus	76	1	77	45	19
Rubella	190	4	194	71	123
Varicella	88	9	97	56	23
Nonqualified1	96	9	105	3	95
Unspecified2	5,420	9	5,429	5	4,773
Grand Total	16,346	1,208	17,554	5,018	10,132

National Vaccine Injury Compensation Program
Monthly Statistics Report

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	115
Total	17,554

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	87	173
FY 2002	104	103	207
FY 2003	56	99	155
FY 2004	62	232	294
FY 2005	60	121	181
FY 2006	69	191	260
FY 2007	82	123	205
FY 2008	147	132	279
FY 2009	134	231	365
FY 2010	180	293	473
FY 2011	266	1,371	1,637
FY 2012	263	2,438	2,701
FY 2013	367	627	994
FY 2014	371	193	564
FY 2015	513	95	608
FY 2016	659	178	837
FY 2017	18	0	18
Total	5,018	10,132	15,150

National Vaccine Injury Compensation Program
 Monthly Statistics Report

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	73	\$2,511,313.26	2	\$117,265.31	\$83,536,901.46
FY 2009	131	\$74,142,490.58	\$5,404,711.98	36	\$1,557,139.53	28	\$4,241,362.55	\$85,345,704.64
FY 2010	173	\$179,387,341.30	\$5,961,744.40	56	\$1,886,239.95	22	\$1,978,803.88	\$189,214,129.53
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	\$9,104,488.60	1,017	\$8,621,182.32	37	\$5,420,257.99	\$186,637,927.73
FY 2013	375	\$254,666,326.70	\$13,333,179.53	703	\$6,970,278.84	50	\$1,454,851.74	\$276,424,636.81
FY 2014	365	\$202,084,196.12	\$11,990,035.82	504	\$6,784,885.79	38	\$2,493,460.73	\$223,352,578.46
FY 2015	508	\$204,137,880.22	\$14,380,254.90	113	\$3,384,950.95	50	\$3,089,497.68	\$224,992,583.75
FY 2016	688	\$228,494,104.01	\$15,817,788.17	82	\$2,280,350.70	59	\$3,502,709.91	\$250,094,952.79

National Vaccine Injury Compensation Program
 Monthly Statistics Report

FY 2017	58	\$17,288,007.88	\$1,852,493.43	12	\$349,783.52	4	\$371,113.93	\$19,861,398.76
Total	5,018	\$3,251,891,506.64	\$149,228,354.65	5,086	\$70,106,659.90	318	\$24,671,094.63	\$3,495,897,615.82

"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 2, 2016

CAPT Narayan Nair, MD

Director, Division of Injury Compensation Programs

Healthcare Systems Bureau (HSB)

Health Resources and Services Administration (HRSA)



ACCV Meeting Highlights

- Update on HRSA VICP Activities
- Update from the Department of Justice Vaccine Litigation Office
- Update on ACCV Process Workgroup Activities
- Updates from ACCV Ex Officio Members – FDA, CDC, NIH, NVPO

DICP Update

Number of Petitions Filed as of November 1, 2016

Average annual number of petitions filed during FY 2011-2015 = 546

Fiscal Year	Total
FY 2011	386
FY 2012	401
FY 2013	504
FY 2014	633
FY 2015	805
FY 2016	1,120
FY 2017	115



Number of Adjudications as of November 1, 2016

Fiscal Year	Compensable	Dismissed	Total
FY 2011	266	1,371	1,637
FY 2012	263	2,439	2,702
FY 2013	367	628	995
FY 2014	371	166	537
FY 2015	513	79	592
FY 2016	659	178	837
FY 2017	18	0	18



DICP Update

Adjudication Categories for Non-Autism Claims FY 2015– FY 2017 as of November 14, 2016

Adjudication Category	FY 2015	FY 2016	FY 2017
Compensable	513 (100%)	664 (100%)	42 (100%)
❖ Concession	90 (17%)	199 (29%)	10 (24%)
❖ Court Decision (includes proffers)	35 (7%)	36 (5%)	1 (2%)
❖ Settlement	388 (76%)	429 (65%)	31 (74%)
Not Compensable	65	168	0
Adjudication Total	578	832	42



DICP Update

Award Amounts Paid as of November 14, 2016

<u>Fiscal Year</u>	<u>Petitioners' Award</u>	<u>Attorneys' Fees & Costs</u>
FY 2011	\$216,319,428	\$17,163,231
FY 2012	\$163,491,999	\$23,145,929
FY 2013	\$254,666,327	\$21,758,310
FY 2014	\$202,084,196	\$21,268,382
FY 2015	\$204,137,880	\$20,811,802
FY 2016	\$228,494,104	\$21,600,848
FY 2017	\$17,288,007	2,573,390.88



Vaccine Injury Compensation Trust Fund

- **Balance as of September 30, 2016**
 - \$3,687,636,528.98
 - **Activity from October 1, 2015 to September 30, 2016**
 - Excise Tax Revenue: \$290,925,706.52
 - Interest on Investments: \$98,971,102.35
 - Net Income: \$389,896,808.87
 - Interest as a Percentage of Net Income: 25%
- Source: U.S. Treasury, Bureau of Public Debt (November 14, 2016)



Significant Activities

- Status of Revisions to Vaccine Injury Table Notice of Proposed Rulemaking (NPRM)
 - The final rule has been developed and is being reviewed by the U.S. Department Health and Human Services
- Highlights of Recent Outreach Activities
 - In August, presented to the Association of State and Territorial Health Officials (ASTHO)
 - Included information about the Program in its newsletter, and a link to the Program’s website on the ASTHO website
 - In September, provided an overview of the program to the US Public Health Service Physicians Professional Advisory Committee
 - In October, provided information about VICP during a webinar series entitled “Topics in Public Health”



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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Twitter: twitter.com/HRSAgov

Facebook: facebook.com/HHS.HRSA



5.2

5.3

5.4

Vaccine Activities Update

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

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

December 2016



National Institute of
Allergy and
Infectious Diseases

Zika Vaccine Research



National Institute of Allergy and
Infectious Diseases (NIAID)
<http://www.niaid.nih.gov>
Monday, November 7, 2016

Testing of Investigational Inactivated Zika Vaccine in Humans Begins

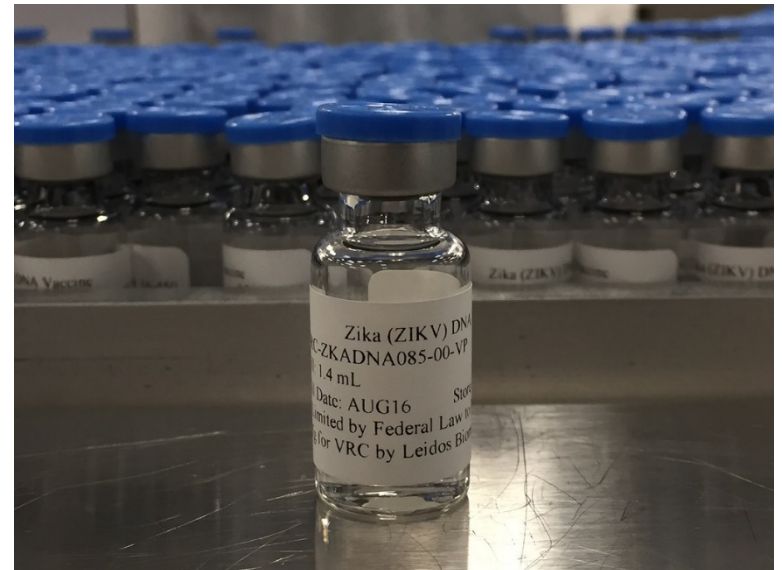
- Zika Purified Inactivated Virus (ZPIV) vaccine
 - Based on technology Walter Reed Army Institute of Research (WRAIR) used to develop Japanese encephalitis vaccine (2009)
- NIAID, WRAIR and HHS Biomedical Advanced Research and Development Authority (BARDA) are supporting development of this vaccine
- Phase 1 trials underway:
 - WRAIR Clinical Trial Center
 - NIAID-funded Vaccine and Treatment Evaluation Unit (Saint Louis University)

- 1 ■ Additional studies planned



Recent Publications

- KA Dowd, *et al.* Rapid Development of a DNA Vaccine for Zika Virus. *Science* (2016 Oct 14)
- HD Marston *et al.* Considerations for Developing a Zika Virus Vaccine. *The New England Journal of Medicine* (2016 Sep 29)

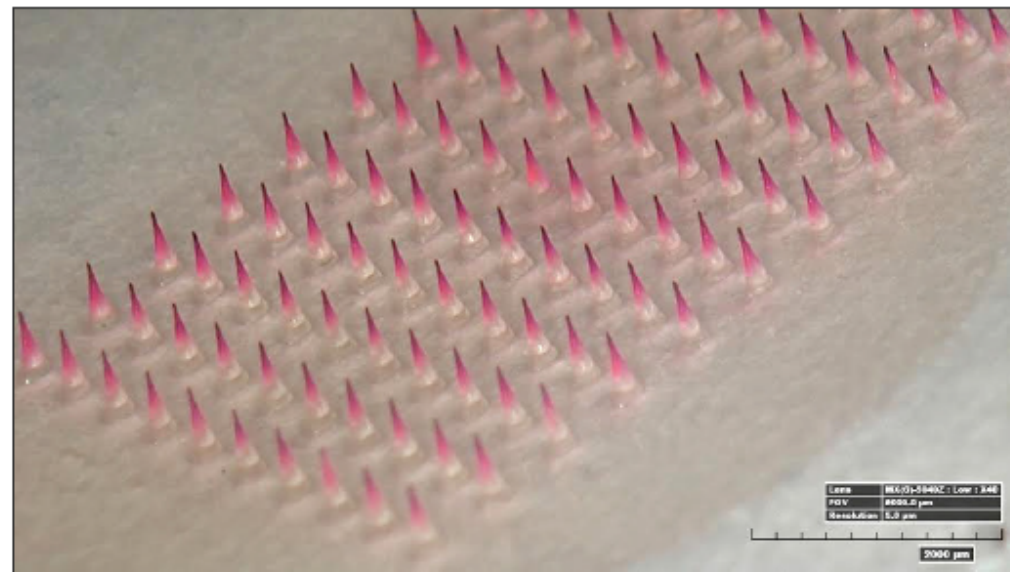


Credit: NIAID

NBIB Grantee Tests Efficacy, Appeal of Flu Vaccine Patch

BY RAYMOND MACDOUGALL

A dime-sized patch of tiny, dissolvable microneedles could be the biomedical advance that expands the reach of vaccines to remote parts of the world and overcomes feat that prevents many from getting a flu shot each year. Dr. Mark Prausnitz, Regents professor and J. Erskine Love chair in chemical and biomolecular engineering, Georgia Institute of Technology, presented the microneedle technology and results from his research leading up to a phase 1 clinical trial during a recent seminar at the National Institute of Biomedical Imaging and Bioengineering.



A dissolving microneedle patch encapsulating a model vaccine (colored pink). Each microneedle is 700 µm tall.

PHOTO: DEVIN MCALLISTER/GEORGIA TECH

Pediatric Allergy Research



National Institute of Allergy
and Infectious Diseases (NIAID)

<http://www.niaid.nih.gov>

Wednesday, October 26, 2016

Skin Patch to Treat Peanut Allergy Shows Benefit in Children

*NIH-Funded Study Suggests Patch Is Safe,
Convenient Mode of Treatment*



National Institute of Allergy
and Infectious Diseases (NIAID)

<http://www.niaid.nih.gov>

Monday, September 12, 2016

Infant Gut Microbiome Appears to Shape Allergy Risk by Altering Immune Responses

5.5

5.6

5.7

THE NATIONAL VACCINE PROGRAM OFFICE

**NATIONAL VACCINE PROGRAM OFFICE
UPDATE**

ACCV, DECEMBER 2, 2016

Dr. Karin Bok
Senior Vaccine Science Advisor



U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

NVPO'S COOPERATIVE AGREEMENT RATIONALE

- Seeks to strengthen vaccine safety research in areas/topics for which a national surveillance/monitoring system intervention or pre-clinical funding would not be suitable
- Funds exploratory research and early programmatic interventions that might influence scientific advancement and policy decisions
- Adapts specific objectives to support the ASH's specific priorities on Public Health
- Connects NVPO with the vaccine safety community to identify and address vaccine safety research hurdles and gaps

FY15 COOPERATIVE AGREEMENT

- **Research, Monitoring and Outcomes Definitions for Vaccine Safety**
- **Funding: 2 CA for \$250K**
 - Determining the safety profile of new vaccines during the early development stage,
 - Developing or modifying existing vaccines to improve their safety
 - Conducting applied research that will have a direct impact on the current vaccine safety monitoring system
 - Conducting research that will achieve consensus definitions of vaccine safety outcomes that could be utilized to collect consensus data in clinical research conducted globally.

FY15 COOPERATIVE AGREEMENT #1

1-"Creation and analysis of a maternal-neonatal vaccine safety database"

-Awarded to Kaiser in Oakland, CA





Vaccine

Volume 34, Issue 46, 4 November 2016, Pages 5519–5523



Kaiser Permanente Northern California pregnancy database:
Description and proof of concept study

Ousseny Zerbo, PhD^a,  , Berwick Chan^a, Kristin Goddard, MPH^a, Ned Lewis, MPH^a, Karin Bok, MS, PhD^b, Nicola P. Klein, MD, PhD^a, Roger Baxter, MD^a

 [Show more](#)

- Currently completing a second analysis on alternative benefits of influenza vaccination during pregnancy (SGA, etc)

FY15 COOPERATIVE AGREEMENT #2

2-"Prevention of injection site pain and syncope associated with preteen and teen vaccination"

-Awarded to Kaiser Foundation in Portland, OR



The image shows a brochure titled "VACCINATION Comfort Menu". On the left side, there is a photograph of a group of diverse preteens and teenagers smiling. The text on the right side of the brochure lists various comfort items and instructions. At the bottom right, the Kaiser Permanente logo is visible.

VACCINATION Comfort Menu

May We Offer You One of the Following Comfort Items?

- Water or juice**
Drinking fluids prior to vaccination may help reduce the risk of feeling faint or dizzy.
- Snack**
Eating a small snack prior to vaccination may help reduce the risk of feeling faint or dizzy. Soft snacks, such as crackers, may be especially helpful.
- Warm blanket**
For your comfort before or after vaccination.
- Squeeze ball**
Squeezing a ball can help keep your blood pressure up during vaccination. This action may help prevent faintness or dizziness and may also provide a good distraction.
- Headphones/earbuds**
You can use these with your own device to help distract you during vaccination.
- Pinwheel**
Blowing on the pinwheel encourages relaxing, deep breaths. Also a great distraction tool!
- "Shabliacker"®**
We will press a flexible plastic disk firmly against your skin at the injection site. This helps to block pain signals so you're at it less painful.
- Single-use cold pack**
Applying a cold pack to your injection site may help reduce pain and swelling after vaccination.
- Self-care info sheet**
Helpful tips for post-vaccination.

We Want You to be as Comfortable as Possible:

- Would you prefer to lie down or sit up while you receive your vaccination?
- Would you prefer your vaccination in your right or left arm?
- Please let us know if you feel dizzy or faint after your vaccination, so that we can allow you to rest for a few minutes before leaving.

KAISER PERMANENTE

-We are in the process of sharing study results with Region 10, to engage RHA in the implementation process

FY15 COOPERATIVE AGREEMENT

Research, Monitoring and Outcomes Definitions for Vaccine Safety

- Funding: Up to \$750K
- Conducting research that will improve the understanding of the safety profile of immunizations that are or may be recommended for adults over 65 years old;
- Predicting the safety profile of new vaccines during the early development stage;
- Developing new or modifying existing vaccines with improved safety profiles;
- Conducting research that will have a direct impact on current vaccine safety monitoring systems;
- Conducting research that will improve the safety profile of currently marketed vaccines; and
- Analyzing biospecimens to understand differences in the genetic or metabolic profile that may correlate with an individual's predisposition to adverse events following vaccination

NATIONAL VACCINE ADVISORY COMMITTEE

On September 20, 2016, NVAC voted on recommendations to the ASH entitled

“Overcoming Barriers and Identifying Opportunities for Developing Maternal Immunizations”

THANK YOU

Karin Bok

Karin.Bok@hhs.gov

202-690-1191

<http://www.hhs.gov/nvpo/>

<http://www.vaccines.gov/>

The National Vaccine Advisory Committee: Overcoming Barriers and Identifying Opportunities for Developing Maternal Immunizations

Executive Summary

Recognizing the importance and impact of maternal immunizations on public health, the Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) in June 2012 with reviewing the state of maternal immunizations and existing best practices to identify programmatic gaps and/or barriers to the implementation of current recommendations regarding maternal immunization.

The NVAC established the Maternal Immunization Working Group (MIWG) in August 2012 to conduct these assessments and provide recommendations for overcoming any identified barriers.

The report that follows reflects the work of the task group focused on identifying barriers to and opportunities for developing vaccines for pregnant women and make recommendations to overcome these barriers. The NVAC working group initially described four main focus areas on which to concentrate their efforts on. These included i) ethical issues; ii) policy issues; iii) pre-clinical and clinical research issues; and iv) provider education and support issues.

Focus Area 1: Ethical Issues

1.1 The ASH should work with the Office for Human Research Protections (OHRP) and other relevant stakeholders and agencies to revise the current exclusionary climate of research in pregnancy. Such areas of focus include but are not limited to:

1.1.1 Institutional Review Board (IRB) guidance on interpretation of minimal risk

1.1.2 Code of Federal Regulations language surrounding research in pregnancy

1.1.3 Collaboration with bioethics experts, regulatory agencies, and the scientific community to optimize the design of studies to minimize the risk of interventions for research in pregnancy

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1.1.4 Relevant regulations, statutes, and policies that should be modified to indicate that pregnant women are not a vulnerable population for the purposes of ethical review

1.2 The ASH should work with OHRP and the stakeholder community to develop policy and regulatory guidelines that would promote inclusion of pregnant women in clinical trials when scientifically appropriate

Focus Area 2: Policy Issues

2.1 The ASH should continue to support maternal immunization as an important public health strategy to encourage manufacturer investment in the development of new and currently licensed vaccines for additional indications for use specifically in pregnant women

2.2 The ASH should advocate to the Secretary of Health and Human Services to resolve the uncertainties around coverage under the Vaccine Injury Compensation Program (VICP) for vaccines administered to pregnant women that are not recommended for use in children by the CDC, and for liability protections for live-born infants born to mothers vaccinated during pregnancy

Focus Area 3: Pre-Clinical and Clinical Research Issues

3.1 The ASH should prioritize increased support for pre-clinical and early clinical research to understand the immune response during pregnancy and to develop vaccines for pregnant women:

3.1.1 The ASH should work with federal and non-federal stakeholders to create or promote mechanisms that support investigator-initiated and other types of research that fosters innovation and expands the field of vaccines for pregnant women

3.2 The ASH should emphasize the need for a better understanding of the public health burden of diseases preventable by maternal immunization

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3.3 The ASH should work with all relevant federal agencies and non-federal stakeholders to support evaluation of the maternal and neonatal outcomes of vaccines administered during pregnancy with respect to the (1) safety of vaccines and (2) effectiveness of vaccines to reduce maternal and infant morbidity and mortality caused by vaccine-preventable diseases, and (3) to better understand the potential risks and benefits of maternal immunization

3.4 The ASH should support continuing evaluation of vaccines in pregnant women and infants born to vaccinated mothers, while advocating for the adoption of standardized approaches to data collection, analysis, and safety evaluation

3.5 The ASH should support the adoption and utilization of standardized definitions of possible maternal and neonatal outcomes to evaluate the safety and effectiveness of vaccines administered during pregnancy

3.6 The ASH should convene stakeholders and other federal agencies to work on the expansion of pharmacovigilance systems that readily link maternal and infant electronic health records and safety surveillance systems

Focus Area 4: Provider Education and Support Issues

4.1 The ASH should encourage professional societies to continue to support the inclusion of pregnant women in clinical research

4.2 The ASH should work with relevant stakeholders to increase awareness among obstetric providers and pregnant women about the importance of vaccine research during pregnancy

4.3 The ASH should work with professional societies to educate obstetricians and other obstetric providers on vaccination and interpretation of new regulations regarding labelling (i.e., the Pregnancy and Lactation Labeling Rule) so they can make informed decisions and counsel their patients more effectively

Table of Contents

The National Vaccine Advisory Committee: Overcoming Barriers and Identifying Opportunities for Developing Maternal Immunizations.....	1
Executive Summary.....	1
Introduction	5
Charge to the National Vaccine Advisory Committee	8
NVAC Recommendations and Conclusions.....	9
Focus Area 1: Ethical Issues	9
Focus Area 2: Policy Issues.....	14
Focus Area 3: Pre-Clinical and Clinical Research Issues	17
Focus Area 4: Provider Education and Support Issues.....	22
Conclusion.....	25
References	26
Appendix I. National Vaccine Advisory Committee Members.....	32
Appendix II. National Vaccine Advisory Committee Maternal Immunizations Working Group (MIWG)33	
Appendix III. Table 1. Invited Speakers and Topic Presentations to the National Vaccine Advisory Committee Maternal Immunization Working Group, 2015-2016	36

Introduction

Infants are vulnerable to vaccine-preventable diseases during the first months of life due in part to the susceptibility gap that occurs when they are too young to be vaccinated but are still at a considerable risk of morbidity and mortality from those diseases. Early infancy, including the neonatal period or the first 28 days of life, is the most vulnerable time for childhood survival¹. For example, the risk of influenza hospitalizations in infants less than six months of age is higher than in older children or elderly populations^{2,3}. And although infants are at a significantly higher risk of influenza-related complications, the available influenza vaccines are not licensed for use in infants less than six months of age. The lack of existing measures to protect infants from complications related to acquiring a disease for which a vaccine is available for older children represents a considerable gap that needs to be addressed. Immunizing pregnant women to allow for transplacental transfer of maternal antibodies to the infant who will thus be born with existing antibodies against vaccine-preventable diseases (e.g. influenza, pertussis, and tetanus) is a strategy that has been successfully used to reduce the burden of these diseases in infants in the United States⁴. This has led to exploring the use of the same approach to shield infants from complications related to additional infectious diseases that could also be prevented by immunization (e.g. Respiratory Syncytial Virus and Group B Streptococcus)⁵⁻⁷.

Influenza. In the 1960s, the Advisory Committee on Immunization Practices (ACIP) managed by the Centers for Disease Control and Prevention (CDC) acknowledged the benefits of maternal influenza immunization both in preventing disease in the infant as well as in the mother. It was then that CDC first recommended that the influenza vaccine be administered to pregnant women who had high- risk medical conditions⁸. This recommendation was updated in 2004 for pregnant women to be vaccinated for influenza during any trimester and to vaccinate women who may become pregnant during the influenza season^{9,10}.

The coverage rate for the influenza vaccine administered during pregnancy since the recommendation was implemented has varied, but reached 47% after the H1N1 pandemic in 2009¹¹. More recently, the CDC reported an increase in coverage up to 52.2% for the seasonal influenza vaccination in pregnant women for the 2013-2014 season (17.6% women received the vaccine before pregnancy and 34.6% during pregnancy)¹², which has remained steady during the following seasons.

Maternal influenza vaccination has been an effective strategy used to protect infants less than six months of age from influenza-like illness and influenza-related hospitalizations. A retrospective study that included a cohort of 245,386 women and 249,387 infants demonstrated that infants who were born to vaccinated mothers had a reduced risk of 64% for influenza-like illness, 70% for laboratory-confirmed influenza, and 81% for influenza-related hospitalization within the first six months of life¹³. Similarly, other studies have also shown that maternal influenza vaccination is associated with an overall reduction in the incidence of hospitalization due to acute respiratory illness (regardless of etiology) among infants less than six months old¹⁴. Preventing maternal influenza infection might additionally reduce the risk of the mother being the source of infection to the infant, and could also result in transmission of antibodies to the infant through breast milk¹⁵. Furthermore, some studies have suggested that influenza vaccination during pregnancy may have other indirect benefits such as a decrease in the rate of infants born small for gestational age, a decrease in the rate of preterm birth, and improvement upon other birth outcomes in some populations, but these findings have not been consistent among recent randomized clinical trials and observational studies^{14,16-18}. In conclusion, these studies suggest that vaccinating pregnant women against influenza does not only protect the infant from influenza disease-like symptoms but may also provide additional health benefits for both the mother and the infant.

Pertussis. Infants are also exposed to other vaccine-preventable infectious diseases, such as pertussis (whooping cough). Infants have higher rates of pertussis infections than the rest of the population, and make up the largest burden of pertussis-related deaths, revealing the crucial need for providing protection against whooping cough during this stage¹⁹. CDC reported 3,159 cases of pertussis in infants less than six months of age between 2012 and 2013, compared to 892 cases of pertussis in infants 6-11 months of age²⁰. In 2014 the majority of pertussis-related deaths also occurred among infants less than three months of age²¹. Maternal immunization with the Tdap vaccine has been shown to effectively protect infants, through the passive transfer of antibodies from the mother to the baby. Thus in 2012, CDC recommended the routine administration of a Tdap booster dose for pregnant women²², and further recommended that women should be re-vaccinated between 27 and 36 weeks of gestation with each subsequent pregnancy²². Although this recommendation has been implemented for a few years, the coverage for Tdap vaccination in pregnant women remains low. A recent observational study that

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included a cohort of 438,487 live births found that only 14% of the mothers received Tdap during pregnancy²³. Recent efforts by CDC and professional societies have helped increase Tdap rates in pregnant women to 41.7% as of 2013, but efforts are needed to continue to increase these rates²³.

Maternal Tdap administration has been shown to be both safe and immunogenic, as no acute maternal safety events or increased risks to the infant or mother have been reported to date²³⁻²⁷. Infants in the United Kingdom born to mothers vaccinated with Tdap during pregnancy were less likely to have confirmed pertussis cases and more likely to have a reduction in pertussis-associated hospitalizations, demonstrating the effectiveness of Tdap immunization in decreasing infant disease²⁸. Tdap immunization during pregnancy is also associated with achieving higher levels of pertussis antibodies in the infant, which remain present at two months of age^{24,29}, and these high levels of pertussis antibodies in the cord blood have been correlated with protection against pertussis infection³⁰. These studies further validate the potential for maternal immunization as a strategy to protect infants from diseases such as pertussis.

Tetanus. The use of prenatal tetanus toxoid immunization is another example of how effective maternal immunization strategies have been in reducing the burden of infant disease⁴. The implementation of a tetanus immunization program during pregnancy in countries where neonatal tetanus is an issue has resulted in a reduction of 94% in neonatal mortality^{4,31,32}. Although neonatal tetanus is not a concern in the United States, the success of the implementation of maternal tetanus toxoid vaccination globally is another great example of how immunizing pregnant women against vaccine-preventable diseases is an effective strategy to reduce and prevent disease in infants^{4,31}.

Additional Targets for Maternal Immunization. There is also a great need for vaccines other than influenza and Tdap to be considered for administration to pregnant women to protect mothers and infants during the first months of life. The success of immunizing pregnant women against influenza has had such a positive outcome, that the same approach should certainly be attempted with immunizations against other diseases that put infants at risk. Relevant disease targets include vaccines against respiratory syncytial virus (RSV) and group B *Streptococcus* (GBS)^{33,34}, among others.

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RSV infection often leads to viral pneumonia in infants less than two years of age and is responsible for high infant morbidity and mortality globally³⁵. RSV vaccination during pregnancy would most likely provide temporary protection to vulnerable infants, for whom the burden of hospital admission and death remains the greatest³⁵. GBS infection, perinatally acquired during birth may be prevented by vaccinating pregnant women and thereby eliciting high GBS-specific antibody levels. This, in turn, could potentially prevent perinatal transmission of GBS (i.e., transmitted from mother to newborn during birth). High antibody concentrations in the pregnant mother may also provide protection in infants against late onset of GBS disease by passively transferring these protective antibodies transplacentally^{36,37}. These infectious diseases, which are still highly prevalent in infants, are just a few examples of why maternal immunization efforts need to continue to be supported as a strategy to protect infants.

Maternal immunizations have been an effective strategy to protect both the mother and the infant against vaccine-preventable diseases. However, significant barriers remain that prevent the development and licensing of additional vaccines for maternal immunization strategies. Some of those barriers include ethics and policy considerations about including pregnant women in research, the need for continued support of pre-clinical and clinical research on immunity, the impact and safety of immunizations during pregnancy, and educating obstetrical providers about the benefits of immunizations during pregnancy and the importance of including pregnant women in clinical research to provide the highest quality of health care. The Department of Health and Human Services recognized the need to address these barriers and subsequently charged the National Vaccine Advisory Committee with making recommendations that would address the problem.

Charge to the National Vaccine Advisory Committee

Recognizing the importance and impact of maternal immunizations on public health, the Assistant Secretary for Health (ASH) charged the National Vaccine Advisory Committee (NVAC) in June 2012 with reviewing the state of maternal immunizations and existing best practices to identify programmatic gaps and/or barriers to the implementation of current recommendations regarding maternal immunization.

The NVAC established the Maternal Immunization Working Group (MIWG) in August 2012 to conduct these assessments and provide recommendations for overcoming any identified barriers. The NVAC

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separated the task into two sections as it was first necessary to address and understand the demand for maternal immunizations in order to then address the challenges in developing maternal immunizations.

The MIWG first focused on understanding the demand for maternal immunization programs by identifying existing patient and provider barriers to maternal immunization, and then shifted its focus to addressing the second part of the charge, which was to identify barriers to and opportunities for developing vaccines for pregnant women and to make recommendations to overcome these barriers. These two objectives were studied, considered, and recommendations issued separately, mainly because they necessitated different subject matter expertise. The first report recommended that the use of vaccines during pregnancy (such as those against influenza and pertussis disease) should be incorporated as a standard of obstetrical care as well as a standard of practice among any and all health care providers who administered health care services to pregnant women³⁸. The report that follows reflects the work of the second task group. Specifically, it lists the barriers and states the recommendations NVAC issued to address the second part of the charge, which was to identify barriers to and opportunities for developing vaccines for pregnant women and make recommendations to overcome these barriers. The NVAC working group initially identified four main focus areas on which to concentrate their efforts on. These included i) ethical issues; ii) policy issues; iii) pre-clinical and clinical research issues; and iv) provider education and support issues.

NVAC Recommendations and Conclusions

Focus Area 1: Ethical Issues

1.1 The ASH should work with the Office for Human Research Protections (OHRP) and other relevant stakeholders and agencies to revise the current exclusionary climate of research in pregnancy. Such areas of focus include but are not limited to:

1.1.1 Institutional Review Board (IRB) guidance on interpretation of minimal risk

1.1.2 Code of Federal Regulations language surrounding research in pregnancy

FINAL version-Voted by NVAC on 9/20/16

1.1.3 Collaboration with bioethics experts, regulatory agencies, and the scientific community to optimize the design of studies to minimize the risk of interventions for research in pregnancy

1.1.4 Relevant regulations, statutes, and policies that should be modified to indicate that pregnant women are not a vulnerable population for the purposes of ethical review

1.2 The ASH should work with OHRP and the stakeholder community to develop policy and regulatory guidelines that would promote inclusion of pregnant women in clinical trials when scientifically appropriate

Exclusion of Pregnant Research Subjects. Participation in important areas of research continues to fall behind among women in general, and especially among the population of pregnant women, who are not frequently recruited to participate as vaccine research subjects. One could argue that the systematic exclusion of pregnant women from clinical research that might lead to significant benefits to the mother and the infant is harming, rather than protecting the woman and fetus from injuries, and that it is highly consequential. Although there is concern that including pregnant women in the study of new drugs and vaccines could potentially lead to fetal harm, it is critical to recognize that excluding pregnant women from research can also lead to harm ³⁹.

The majority of pregnant women are affected by illnesses that require treatment or immunizations during pregnancy, or require immunizations administered for the benefit of the infant. Nonetheless, very few drugs, and no immunizations, are currently approved or specifically indicated for use in pregnancy by the Food and Drug Administration (FDA). If the medical treatment of pregnant women is based on studies from which they were excluded as participants, a concern of generalizability must be raised, as pregnant women are at risk of not receiving the same level of care available to the rest of the population ³⁹.

Another challenge that contributes to the exclusionary climate toward pregnant subjects in clinical trials is that currently researchers must justify for the regulatory authorities the inclusion of pregnant women

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and specify what special protections will be in place during the test of the product³³. Interestingly, there is no requirement to justify their exclusion from a protocol. In an effort to modify this approach, the wording of Subpart B of the Code of Federal Regulations (C.F.R.) (the human research subject protection rules that deal specifically with pregnant subjects) was changed in 2001 (45 C.F.R. § 46 Subpart B). The new language states that pregnant women may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;(c) Any risk is the least possible for achieving the objectives of the research;(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;(g) For children as defined in § 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part; (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and (j) Individuals engaged in the research will have no part in determining the viability of a neonate.(45 C.F.R. § 46.204).

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Although this modification has relaxed the restrictions faced by Institutional Review Boards (IRBs) when evaluating protocols that propose the inclusion of pregnant women, it is still far from requiring a justification to exclude them from research. In the past, and in an attempt to address similar barriers, the Department of Health and Human Services (HHS) made successive modifications to the policies and statutes for inclusion of human research subjects, to eventually guarantee the inclusion of additional research subjects other than men (Public Law 108 – 155, Pediatric Research Equity Act of 2003)⁴⁰⁻⁴³. These included women, ethnic minorities, and children, leaving pregnant women to be one of the only major populations for which justification for exclusion does not need to be given (45 C.F.R. § 46.112(a)(3))⁴⁴. These historical precedents highlight the fact that pregnant women are not the only population to have faced challenges for the ethical testing of drugs. In 1963, the pediatric population was deemed an accidental “pharmaceutical orphan” due to their systematic exclusion from clinical trials in order to avoid perceived safety and liability concerns^{45,46}. Several directives, such as the Pediatric Research Equity Act (Public Law 108–55, 2003), and the Best Pharmaceuticals for Children Act (Title V of Public Law 110-85; FDA Amendment Act of 2007), were created in response to this claim, in order to deal with the discrimination against research on drugs that were being administered to children without including them in the pre-licensing testing. The result of these legislative efforts has been a marked increase in the number of clinical trials and studies that include pediatric subjects⁴⁷. A focused effort to encourage the inclusion of pregnant women in clinical trials might move the field towards a more balanced scientific consideration of issues.

Pregnant Women are Not a Vulnerable Population. One of the reasons that pregnant women have been systematically excluded from participating in clinical research, is that they are perceived as a vulnerable population. A vulnerable population is defined as one that has a compromised ability to protect its interests and provide informed consent⁴⁴. However, pregnant women have the same decision-making capacity, ability to judge risks and benefits, and ability to provide informed consent as their non-pregnant counterparts. Thus, in 2010, a workshop sponsored by the National Institutes of Health (NIH) Office of Research on Women’s Health, proposed that pregnant women in research trials should be defined as a “scientifically complex” rather than as a “vulnerable” population^{39,44}. This classification is intended to reflect a combination of both physiological and ethical complexities that should be considered when balancing the interests of pregnant women and the newborn³⁹. This proposal was

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later supported by the American College of Obstetricians and Gynecologists (ACOG) expert committee opinion and the American Academy of Pediatrics (AAP) as well.

IRB Interpretation of Minimal Risk. Another barrier that directly influences the inclusion of pregnant women in the design of clinical research is the inconsistency of the interpretation of regulations across IRBs. IRBs are tasked with reviewing and approving research protocols ensuring the protection of the rights and welfare of human subjects. One of the most problematic issues that IRBs face is the interpretation of minimal risk. Without clear standards that define a threshold of acceptable risk associated with research, IRBs are left to strike a delicate balance between what they consider to be “acceptably-low” harm or discomfort, and the benefit accrued from conducting said research. This has been a serious point of concern that was raised by both federal and non-federal stakeholders, and that currently affects clinical research in other populations as well, but that is especially sensitive when reviewing research that calls for the protection of both the mother and the infant. Indeed in 2008, the Secretary’s Advisory Committee on Human Subjects Research (SACHRP) issued recommendations advising on the interpretation of minimal risk related to all subjects involved in clinical research, but did not address the population of pregnant women specifically⁴⁸. Although this advisory committee gave its view and expanded on the definition of minimal risk as stated in the C.F.R. (45 C.F.R. part 46), it also clearly pointed out that “[i]n its estimate of research-related risk, the IRB should carefully consider the characteristics of subjects to be enrolled in research including an evaluation of subject susceptibility, vulnerability, resilience, and experience in relation to the anticipated harms and discomforts of research involvement”⁴⁸. In view of this, there might still be a role for the government, informed by the SACHRP and other specialized committees, to contribute to the education of IRB members regarding specific requirements, ethical standards, and regulations for research for scientifically complex populations such as pregnant women. Clear and standardized definitions of minimal risk interventions for both the mother and infant would ensure that all IRBs have access to shared guidance in order to decide i) whether to include pregnant women in clinical research and ii) the quantity and quality of interventions that could be approved in the protocol in order to maximize the benefit of said research.

Finally, in addition to the active development of vaccines for pregnant women and prevention of infections in the newborn period, and similar to the 2009 H1N1 influenza pandemic, the current Zika virus outbreak has once again raised awareness about the need for developing and articulating a

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pregnancy-specific ethical framework that can offer guidance to IRB and investigators for clinical trials to promote the inclusion of pregnant women⁴⁹. This highlights that the need for manufacturers, researchers, IRBs, providers, and the public to understand the benefits of creating a culture of inclusion of pregnant women in clinical research is paramount.

Focus Area 2: Policy Issues

2.1 The ASH should continue to support maternal immunization as an important public health strategy to encourage manufacturer investment in the development of new and currently licensed vaccines for additional indications for use specifically in pregnant women

2.2 The ASH should advocate to the Secretary of Health and Human Services to resolve the uncertainties around coverage under the Vaccine Injury Compensation Program (VICP) for vaccines administered to pregnant women that are not recommended for use in children by the CDC, and for liability protections for live-born infants born to mothers vaccinated during pregnancy

Maternal Immunization as a Public Health Strategy. Despite remarkable strides as a global community in combating mortality in children under the age of five, the rate of infant deaths due to infectious diseases remains unacceptably high^{1,50}. Maternal immunizations have emerged as a promising global strategy to protect infants against vaccine-preventable infectious diseases^{13,14,28,33,51,52}. Two types of vaccines, seasonal inactivated influenza and Tdap, are already routinely recommended by CDC to be administered during pregnancy^{8,19,22,53}, although there are currently no vaccines specifically indicated for use in pregnant women by the FDA. The lack of a specific indication for pregnancy for current vaccines, together with the fact that there are additional disease targets with significant morbidity and mortality affecting infants^{34,51,54}, motivates prioritizing the need for the development of new and improved vaccines for use by expectant mothers in order to successfully protect infants during the first months of life. Several immunizations that could be efficacious against infant disease are already being developed and include vaccines against RSV and GBS. The support of the public health community

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moving these prototypes through the pipeline is essential to ensure the success of the vaccines already in development and to promote the innovation of new vaccines that would address additional needs.

Liability Protection. Another significant hurdle preventing vaccine developers and manufacturers from fully committing to obtaining specific indications for use during pregnancy for new and developed vaccines is the uncertainty about the scope of coverage and liability protection for these vaccines under the Vaccine Injury Compensation Program (VICP) (42 U.S.C. § 300aa-10 to 300aa-15)⁵⁵. The VICP was created by the Childhood Vaccine Injury Act of 1986, as amended (Vaccine Act) (42 U.S.C. §§ 300aa-1 to 300aa-34), which also established the National Vaccine Program Office (NVPO) and the Health Resources and Services Administration's (HRSA) Advisory Commission on Childhood Vaccines (ACCV), which makes recommendations to the Secretary on issues related to the operation and implementation of the VICP. The VICP provides compensation to people (regardless of age) found to have been injured by, or to have died as a result of, the administration of certain covered vaccines. Even in cases in which such a finding is not made, petitioners may receive compensation through a settlement. Compensation may be available for vaccine injuries sustained by adults or children so long as the general category of vaccines is covered by the VICP. In order for a vaccine to be covered by the VICP, the category of vaccine must be (1) recommended by the CDC for routine administration to children (adults immunized with these vaccines may also submit a claim to VICP) and (2) subject to an excise tax by Federal law.

The CDC currently recommends two immunizations for routine use among pregnant women: seasonal inactivated influenza and Tdap vaccines. These vaccines are covered under the VICP as they are also recommended for routine administration to children and are subject to an excise tax. Because these vaccines are covered under the VICP, the manufacturers and administrators of such vaccines generally are afforded the Vaccine Act's liability protections⁵⁶. Although these two vaccines are currently covered under the provisions of the VICP, maternal immunizations in general still face several coverage gaps that endanger the current manufacturer's liability protection. Even as influenza and Tdap are covered under VICP, new categories of vaccines, that would potentially be only indicated for use during pregnancy and not routinely recommended for use in children, would not be covered under this program if they were not also recommended for use in children. Therefore, pregnant women receiving such vaccines would not be eligible to pursue claims related to such vaccines under the VICP. In order for such vaccines to be covered under current law (and absent a statutory amendment to cover other categories of vaccines),

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Congress would need to enact an excise tax with respect to such vaccines and the CDC would need to recommend this category of vaccines for routine administration to children (42 U.S.C. §§ 300aa-1 to 300aa-34).

Immunization Recipient. Even regarding vaccines currently covered under the VICP, a more detailed inspection of the Vaccine Act and VICP case law evidences another coverage gap with the potential to threaten liability protection. In the case of vaccines administered during pregnancy, uncertainty remains about whether a claim concerning an injury sustained *in utero* (after a pregnant woman's vaccination) can be pursued under the VICP on behalf of the child. This is in part because petitioners claiming a vaccine-related injury to the VICP must demonstrate that the person who suffered a vaccine-related injury or death "received a vaccine set forth in the Vaccine Injury Table [a covered vaccine]" (42 U.S.C. § 300aa-11(c)(1)(A)). In claims alleging that a child suffered an injury *in utero* as a result of a vaccine administered to the pregnant mother, the question is whether the child received a vaccine under the meaning of the statute. The question of whether a vaccine is received *in utero* has been a central issue explored in few VICP cases involving allegations of injuries sustained *in utero*⁵⁶. However, there is no binding case law resolving the issue, so it is one that remains unsettled.

The "One Petition Rule." The Vaccine Act also specifies that "[o]nly one petition may be filed with respect to each administration of a vaccine" (the "one petition rule") (42 U.S.C. § 300aa-11(b)(2)). To the extent that more than one VICP petition is filed with respect to a single vaccine administration, the second petition may be dismissed as barred by the Vaccine Act. In the event that two VICP petitions are filed with respect to a vaccine administration to a pregnant woman (i.e., one petition on behalf of an injured child *and* a separate petition on behalf of an injured mother), it would appear that the "one petition rule" would be violated. However, in this case, there is not a binding case law interpreting the provision either, so the issue is also unresolved.

Also administered by HRSA, the Countermeasures Injury Compensation Program (CICP) provides compensation for serious injuries and deaths directly caused by the administration or use of "covered countermeasures" identified by the Secretary in declarations issued under the Public Readiness and Emergency Preparedness (PREP) Act (42 U.S.C. § 247d-6d). The PREP Act provides the Secretary with authority to promulgate regulations to govern the procedures and requirements of the CICP. The

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regulation issued pursuant to that authority addresses the issue of injuries suffered by children born to women who were administered or used a covered countermeasure during pregnancy. The CFCP's regulation specifies that a child can qualify as an "injured countermeasure recipient" for purposes of the Program if the child survives birth, and is born with, or later sustains, a covered injury as the direct result of the mother's administration or use of a "covered countermeasure" during pregnancy (42 C.F.R. 110.3(n)(3); 75 FR 63660).

Recognizing the effect that certain changes to the VICP could have on such an important public health objective as the protection of vulnerable infants, two of the HHS' Advisory Committees ACCV and NVAC have already recommended the coverage of claims submitted to the VICP alleging injuries to the pregnant woman and/or her live-born infant for injuries sustained *in utero*, resulting from maternal immunization (which also may result in liability protections for the vaccines' manufacturers and administrators). This recommendation has also been supported by relevant stakeholders such as AAP and ACOG, members of Congress (including authors of the original legislation that established the VICP), and representatives of the pharmaceutical industry^{56,57}.

Unfortunately, uncertainties regarding maternal immunizations and liability protections under the VICP represent a barrier that discourages manufacturers and vaccine developers from i) investing in developing new vaccines for use in pregnancy and; ii) pursuing pregnancy-specific indications for vaccines already recommended by the CDC to be routinely administered to women during pregnancy. Modifications to the VICP program in order to resolve these uncertainties should be a priority to incentivize manufacturers to invest in safe and effective vaccinations specifically formulated for use during pregnancy.

Focus Area 3: Pre-Clinical and Clinical Research Issues

3.1 The ASH should prioritize increased support for pre-clinical and early clinical research to understand the immune response during pregnancy and to develop vaccines for pregnant women:

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3.1.1 The ASH should work with federal and non-federal stakeholders to create or promote mechanisms that support investigator-initiated and other types of research that fosters innovation and expands the field of vaccines for pregnant women

3.2 The ASH should emphasize the need for a better understanding of the public health burden of diseases preventable by maternal immunization

3.3 The ASH should work with all relevant federal agencies and non-federal stakeholders to support evaluation of the maternal and neonatal outcomes of vaccines administered during pregnancy with respect to the (1) safety of vaccines and (2) effectiveness of vaccines to reduce maternal and infant morbidity and mortality caused by vaccine-preventable diseases, and (3) to better understand the potential risks and benefits of maternal immunization

3.4 The ASH should support continuing evaluation of vaccines in pregnant women and infants born to vaccinated mothers, while advocating for the adoption of standardized approaches to data collection, analysis, and safety evaluation

3.5 The ASH should support the adoption and utilization of standardized definitions of possible maternal and neonatal outcomes to evaluate the safety and effectiveness of vaccines administered during pregnancy

3.6 The ASH should convene stakeholders and other federal agencies to work on the expansion of pharmacovigilance systems that readily link maternal and infant electronic health records and safety surveillance systems

Pre-clinical and Clinical Research Barriers to Advancing Vaccine Development for Pregnant Women.

Despite the scientific advances in understanding vaccines and human immune response to vaccines, there is still rather limited knowledge on maternal-fetal physiology and immunology, especially the immunological role of the placenta and the potential effects that maternal immunizations can have on the fetus, which remain poorly understood. A better understanding of topics such as: immunologic responses in women during pregnancy; antibody transfer from mother to fetus (transplacental transfer); antibody kinetics (the rate at which maternal antibodies are transferred to the fetus and the half-life of maternal antibodies, especially after transfer to the fetus); the optimal period for greater maternal

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immunization in relation to the period of disease and infectivity risk; the rate of antibody waning in the infant and its correlation with protection against infection or other outcomes of disease, and whether maternal antibodies persist during infancy; the potential effect of maternal antibodies on the infant's responses to primary immunization; and the role of breast milk antibodies, is still needed in order to fully understand the benefits and risks of maternal immunizations³³. The knowledge gap in the maternal immunization immunology field is partially due to the lack of available funding mechanisms to address these questions. Expanding federal funding to allow for investigator- initiated or exploratory research is a way to increase the studies that would address some of the areas mentioned above. Alternative pathways of funding would also promote research flexibility to explore the unknowns about the biology and immunology of maternal immunization and advance the maternal immunization field.

Furthermore, additional information on the safety and effectiveness of vaccines recommended for use during pregnancy could also improve implementation of maternal immunizations recommendations and, consequently, vaccination rates. The currently recommended maternal vaccines (influenza and Tdap) are not specifically indicated by FDA for use in pregnant women since pre-licensure trials did not include testing the safety and efficacy of the vaccine in the pregnant women population. The limited data available on pregnant women are usually obtained from non-randomized or observational clinical trials, which often exclude pregnant women from participating³³. Observational studies or retrospective studies present a problem since they are not designed to understand specific aspects of vaccine physiology, such as the effects and benefits of vaccines when administered in early pregnancy (first and second trimesters). Because of this lack in pre-licensure testing by the vaccine sponsor and the potential public health importance of maternal immunization against influenza and pertussis, ACIP/CDC gathered enough additional research data to support the wisdom of immunization recommendations for pregnant women, even though the vaccine sponsor had not sought a specific indication for use in pregnancy^{8,19,22,53}. However, the inconsistency between federal recommendations and specific indications leads obstetric providers to be unsure about making strong recommendations for maternal vaccinations as there is a limited understanding of the immunogenicity and safety of vaccine delivery during pregnancy⁴⁹. Finally, the exclusion of pregnant women from pre-licensure clinical trials has also influenced the availability of safety information, as vaccine safety data on maternal immunizations has been mostly obtained from retrospective population-based cohort studies and database reviews, which are not the ideal study design to determine the safety profile of a vaccine prior to or following licensure³³.

Understanding Disease Burden in Order to Better Inform Maternal Immunization Programs. A more thorough understanding of vaccine-preventable disease burden that affects infants in the first six months of life would also help with the accurate determination of the effectiveness of maternal immunizations on both the infant and the mother, and can help justify the importance of this intervention to policymakers and the general public as they prioritize health resources. Systems capable of tracking epidemiological data and disease burden for poorly surveyed diseases in both the United States and globally, would enhance evidence-based decision making for the recommendation and administration of vaccines during pregnancy, and support increased funding for research into maternal vaccine development. It is worth mentioning that two national efforts are already implementing some of the additional features needed to estimate disease burden. The National Notifiable Diseases Surveillance System (NNDSS, managed by the CDC) incorporated a new initiative called the NNDSS Modernization initiative (NMI), which has the main goal of “modernizing the systems and processes used to receive nationally notifiable disease data to provide more comprehensive, timely, and higher quality data than ever before for public health decision making”⁵⁸. NMI is an effort to strengthen and modernize the infrastructure supporting CDC’s system for notifiable disease as part of their existing surveillance system already in place and , but also to improve the system further to allow a more comprehensive, timely, and higher quality data for public health decisions⁵⁹. The Department of Defense (DoD) also employs the Global Emerging Infections Surveillance and Response System (DoD-GEIS), which focuses on surveying emerging infectious diseases that could affect the United States military⁶⁰, often used to make informed public health decisions⁶¹. Systems already in place could be used as infrastructure to collect disease burden data including and focusing on specific populations, such as pregnant women and infants, which are needed to better assess the justification and needs for vaccine development⁶²⁻⁶⁴.

Enhancing Safety Surveillance for Maternal Immunizations. Vaccine safety surveillance and research on pregnant women and their infants present unique challenges compared to immunization safety research conducted in other populations. Well established post-marketing vaccine adverse events reporting and surveillance systems allow for the study of vaccines currently in use, and to research diverse safety outcomes, even in the absence of reports of a specific adverse event. Implementing new or adapting existing surveillance systems can help facilitate maternal immunization research studies to improve the

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understanding of vaccine safety and immunogenicity in pregnant women and their infants, and can help identify very rare outcomes potentially associated to vaccine administration such as some types of congenital anomalies.

In the United States, the increased availability of nationwide electronic health records (EHs) and interconnected state-based immunization information systems (IIS) are potentially underutilized and invaluable resources to study the effects of vaccination in pregnant women and also follow their infants. There are currently two pharmacovigilance systems in place that employ EHRs to assess the safety of immunizations: the Vaccine Safety Datalink (VSD) managed by CDC⁶⁵⁻⁶⁷ and the Post-licensure Rapid Immunization Safety Monitoring (PRISM) system managed by FDA^{68,69}. These safety systems systematically analyze and link immunization registry and electronic health outcome data from several large integrated health plans to conduct near real time vaccine safety surveillance for pre-specified outcomes and targeted studies using automated data. Any potential safety signals identified from these automated studies can be further refined by accessing individual EHRs to validate cases. Adapting VSD and PRISM to surveying and assessing maternal immunizations safety outcomes has been somewhat challenging because it requires the modification of analytical algorithms to address hurdles such as the direct linking of the maternal and the infant clinical records. These existing surveillance systems utilize such prototype algorithms which could be further modified, expanded, and improved to allow for additional capabilities in areas such as direct mother and infant record-linking, and to enhance studies of very rare birth outcomes (e.g., some types of congenital anomalies).

Standardization of Data Collection, Analysis, Safety Evaluation, and Outcomes Definitions. To advance maternal immunization studies, it is important to recognize that clinical trials need to be conducted in a systematic manner in order to fully benefit from the results obtained. Several considerations make research including pregnant women uniquely challenging: IRBs lack proper guidance when approving protocols for research during pregnancy, pregnant women are notoriously harder to recruit for clinical trials, some clinical endpoints might be rare or difficult to define, and risks for safety outcomes that are usually found with extremely low prevalence in other populations, are harder to estimate given the background rate of common pregnancy complications⁴⁹. These considerations emphasize the need for

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standardized collection of data, analysis, and safety surveillance not only in the United States but globally in order to correlate results and issue findings that have been reproduced in multiple settings.

One of the critical aspects of reproducible data collection for surveying of maternal and infant safety outcomes, is the standardization of vaccine safety terminology and common case definitions, which may have surprisingly varied interpretations among obstetric and pediatrics practitioners. Standardizing vaccine obstetric, fetal, and neonatal safety terminology and case definitions would enable not only the United States, but other countries around the globe, to combine clinical study results when investigating vaccines during pregnancy, and to obtain significant risk determinations even for very rare maternal and infant birth outcomes. The Brighton Collaboration, a non-profit, scientifically independent global research network consisting mainly of volunteers, is one of the leaders in this effort, with the mission of advancing the science of immunization safety and defining globally acceptable common terminology for adverse events following immunization⁷⁰⁻⁷². The World Health Organization (WHO), along with the Brighton Collaboration, share the objective of (1) raising awareness of the availability of standardized case definitions and guidelines for data collection, analysis and presentation for global use, and (2) developing and implementing standard study protocols for evaluating case definitions⁷³. In collaboration, they provide independent, high-level, technical, and strategic advice focused on developing an interim set of key terms and concept definitions for the assessment of safety of vaccines given during pregnancy in the mother and the infant, which can be used to improve vaccine safety monitoring and evaluation. Obtaining a standardized definition that could be implemented globally is a complex process that requires thoroughness. The process involves recruiting international working groups who conduct systematic literature reviews to develop the case definitions; the definitions are then revised by a reference group, and then finalized to be distributed for global use⁷⁴. Examples of standardized safety outcomes definitions include 'Stillbirth' and 'Congenital Abnormalities' among others, which were recently released in order to aid collaborative immunization safety research studies⁷⁵⁻⁷⁷. Supporting these efforts will ensure that we are on the right path towards effective and reproducible surveillance of the safety of immunizations administered during pregnancy.

Focus Area 4: Provider Education and Support Issues

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4.1 The ASH should encourage professional societies to continue to support the inclusion of pregnant women in clinical research

4.2 The ASH should work with relevant stakeholders to increase awareness among obstetric providers and pregnant women about the importance of vaccine research during pregnancy

4.3 The ASH should work with professional societies to educate obstetricians and other obstetric providers on vaccination and interpretation of new regulations regarding labelling (i.e., the Pregnancy and Lactation Labeling Rule) so they can make informed decisions and counsel their patients more effectively

Support from Professional Societies. Maternal immunizations are an investment in better health outcomes for both pregnant women and their infants³³. Professional societies and maternal immunization stakeholders have a critical role in educating providers about the benefits of involving pregnant women in clinical research. Their community engagement efforts are essential to supporting a shift of the paradigm towards including pregnant women in order for the mother and infant to benefit from safe and effective vaccines that have been appropriately tested during the pre-licensure phase of clinical research. This will ensure that pregnant women have access to the same standard of care that other members of society have been afforded. However, even when the policy, regulatory, and ethical barriers to licensing safe and effective immunizations for use in pregnancy are addressed, pregnant women's recruitment and participation in research trials are the cornerstones for developing any vaccine with a specific indication for use during pregnancy. Pregnant women may be reluctant to enroll in clinical research due to a general lack of awareness about research in their community, which could lead them to express unease and distrust of the research⁷⁸. Pregnant women's hesitancy to participate could be altered by consulting with obstetrical providers, who are the most trusted advisors for a pregnant patient, and thus uniquely positioned to advocate for increased participation of pregnant women in clinical research^{79,80}. This is when the work of professional societies and other relevant stakeholders to influence healthcare professionals becomes invaluable, since the former have the ability to conduct outreach efforts to community providers, educate them, and encourage them to promote research studies to their patients. In many cases, a clinician's promotion of research will in turn increase a pregnant woman's willingness to participate in studies⁸¹. Increases in maternal immunization rates for

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influenza and Tdap have recently occurred following efforts by federal agencies and professional societies as detailed above.

The Pregnancy and Lactation Labeling Rule. Professional societies that have an interest in advocating for the safe use of medications and vaccines during pregnancy also should facilitate clinicians' transition into understanding of new and unique immunization product information. For example, professional societies should help clinicians understand FDA's new Pregnancy and Lactation Labeling Rule, also called PLLR (21 C.F.R 201.57 and 201.80; 79 FR 72963). In short, a critical step in the FDA's review process of a Biologics License Application (BLA) includes the evaluation of the product package insert⁸². Until recently, the FDA required that biologics' labels (for biologics, including vaccines), contained a letter code summarizing the determination of a risk category in for the biologic's letter coding (A, B, C, D, or X) for use in during pregnancy (A, B, C, D, or X). This was required for any biologic, including vaccines, without a specific indication for use during pregnancy (sometimes erroneously referred as "off-label" use), and was intended to provide the practitioner with a classification of the product according to the level of risk for pregnant women and infants, depending on the data available to the sponsor at the time of licensing. However, this system was difficult to interpret in practice, and cumbersome to convey to the patient when explaining the risk-benefit balance of administering a medication during pregnancy. In response to these challenges, the FDA recently amended the letter category rules with the PLLR (21 C.F.R. 201.57 and 201.80; 79 FR 72963). The PLLR eliminates the old classification and provides a new framework to describe more clearly the available data on the potential risks associated with use of drugs and biologics during pregnancy and lactation. This change not only allows for a consistent format for communicating risk and benefit information of a vaccine relevant to pregnant and lactating women, but it also enables the incorporation of exposure information from a variety of sources, including non-industry-sponsored epidemiological and interventional studies⁴⁹. As with any new regulation, the implementation of the rule will have challenges. Obstetric and other health care providers, who are unfamiliar with the new classification, will require guidance on how to best interpret the new package inserts. A clear understanding by both clinicians and patients of the labeling of vaccines administered during pregnancy will also promote confidence in the safety and efficacy of these products, which may lead to a more active participation of this population in clinical research during pregnancy.

Conclusion

Maternal immunization has been implemented as a successful national and global strategy to protect infants against vaccine-preventable diseases such as influenza, pertussis, and tetanus. Although CDC already recommends the use of vaccines during pregnancy, certain ethical, policy, education and research barriers remain to be addressed in order to improve uptake of currently recommended vaccines and promote the development of additional maternal immunizations. This NVAC report describes the barriers and opportunities for developing vaccines for pregnant women and makes recommendations to overcome those barriers. The NVAC submits these recommendations to the ASH for her consideration.

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Appendix I. National Vaccine Advisory Committee Members

Chair

Walt A. Orenstein, MD, Emory University, Atlanta, GA (Former NVAC Chair)

Kimberly M. Thompson, ScD, University of Central Florida College of Medicine, Orlando, FL (NVAC Chair as of June 2016)

Designated Federal Official

Bruce G. Gellin, MD, MPH, National Vaccine Program Office, U.S. Department of Health and Human Services, Washington, DC

Public Members

Richard H. Beigi, MD, MSc, Magee-Womens Hospital, Pittsburgh, PA

Sarah Despres, JD, Pew Charitable Trusts, Washington, DC

David Fleming, MD, PATH, Washington, DC

Ann Ginsberg, MD, PhD, Aeras, Rockville, MD

Ruth Lynfield, MD, Minnesota Department of Health, St. Paul, MN

Yvonne Maldonado, MD, Stanford University School of Medicine, Stanford, CA

Saad Omer, MBBS, MPH, PhD, Emory University, Atlanta, GA

Wayne Rawlins, MD, MBA, Aetna, Hartford, CT

Mitchel C. Rothholz, American Pharmacists Association, Washington, DC

Nathaniel Smith, MD, MPH, Arkansas Department of Health, Little Rock, AR

Representative Members

Philip Hosbach, Sanofi Pasteur, Swiftwater, PA

Tim Cooke, PhD, NovaDigm Therapeutics, Grand Forks, ND

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Appendix II. National Vaccine Advisory Committee Maternal Immunizations Working Group (MIWG)

Maternal Immunization Working Group Chairs

Richard H. Beigi, MD, MSc, Magee-Womens Hospital, Pittsburgh, PA

Saad Omer, MBBS, MPH, PhD, Emory University, Atlanta, GA

NVAC Members

Ruth Lynfield, MD, Minnesota Department of Health, St. Paul, MN

Seth Hetherington (former NVAC member), MD, Genocea Biosciences, Cambridge, MA

NVAC Liaison Representatives

Ajoke Sobanjo-ter Meulen, MD, MSc, Bill & Melinda Gates Foundation, Seattle, WA

Cynthia Pellegrini, March of Dimes, Washington, DC

Jan Bonhoeffer, MD, Brighton Collaboration, Switzerland

Danitza Tomianovic, PhD, Brighton Collaboration, Switzerland

Leonard Friedland, MD, Biotechnology Innovation Organization, Washington, DC

Debra Hawks, MPH, American College of Obstetricians and Gynecologists, Washington, DC

Jeanne Sheffield, MD, Society for Maternal-Fetal Medicine, Washington, DC

Niranjan Bhat, MD, MHS, PATH, Seattle, WA

Deborah Higgins, PATH, Seattle, WA

Gina Burns, BSN, The Group B Strep Association, Chapel Hill, NC

Sharon Humiston, MD, MPH, American Academy of Pediatrics, Vancouver, WA

Carol J. Baker, MD, Infectious Disease Society of America, Arlington, VA

NVAC Subject Matter Experts

Steven Black, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Catherine Mary Healy, MBBCh, Baylor College of Medicine, Houston, TX

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Flor M. Muñoz, MD, MSc, Baylor College of Medicine, Houston, TX

Geeta K. Swamy, MD, Duke University, Durham, NC

Kathryn M. Edwards, MD, Vanderbilt University, Nashville, TN

Fernando Polack, MD, Fundacion INFANT, Argentina

NVAC Ex-Officio Members

Karen R. Broder, MD, Centers for Disease Control and Prevention, Atlanta, GA

Jennifer Liang, DVM, MPVM, Centers for Disease Control and Prevention, Atlanta, GA

Stacey Martin, MSc, Centers for Disease Control and Prevention, Atlanta, GA

Pedro L. Moro, MD, MPH, Centers for Disease Control and Prevention, Atlanta, GA

Cheryl Broussard, PhD, Centers for Disease Control and Prevention, Atlanta, GA

Marion F. Gruber, PhD, Food and Drug Administration, Silver Spring, MD

Jeffrey Roberts, MD, Food and Drug Administration, Silver Spring, MD

Valerie Marshall, MPH, Food and Drug Administration, Silver Spring, MD

Avril Houston, MD, MPH, Health Resources and Services Administration

Emily Levine, JD, Office of the General Counsel, U.S. Department of Health and Human Services, Washington, DC

Barbara Mulach, PhD, National Institutes of Health, Bethesda, MD

Mirjana Nesin, MD, National Institutes of Health, Bethesda, MD

Jennifer S. Read, MD, MS, MPH, National Institutes of Health, Bethesda, MD

Amina White, MD, National Institutes of Health, Bethesda, MD

COL Margaret Yacovone, MD, Department of Defense, Washington, DC

Fran Cunningham, PharmD, U.S. Department of Veterans Affairs

Richard Martinello, MD, U.S. Department of Veterans Affairs

U.S. Department of Health and Human Services, National Vaccine Program Office Staff and Technical Advisors

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Cristina H. Messina, MS, PhD, National Vaccine Program Office, U.S. Department of Health and Human Services, Washington, DC

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Appendix III. Table 1. Invited Speakers and Topic Presentations to the National Vaccine Advisory Committee Maternal Immunization Working Group, 2015-2016

Title/ topic of presentation to the working group	Speaker(s) affiliation/ organization represented
Overview of the division of microbiology and infectious diseases' (DMID) consultative conference on enrolling pregnant women in clinical trials of antimicrobials and vaccines	Mirjana Negin, Senior Medical Officer NIH/DMID/NIAID
The changing landscape of respiratory syncytial virus (RSV)	Fernando P. Polack, Professor of Pediatrics Vanderbilt University, Fundacion INFANT
Group B streptococcus (GBS) epidemiology and potential impact of a GBS conjugated vaccine	Carol J. Baker, Professor of Pediatrics and Molecular Virology and Microbiology Texas Children's Hospital, Baylor College of Medicine
Barriers to research in pregnancy	Anne Zajicek, Chief Obstetrics and Pediatric Pharmacology and Therapeutic Branch NIH
The pregnancy and lactation labeling rule (PLLR) implications for vaccine labeling	Marion F. Gruber, Director Office of Vaccine Research and Review FDA/CBER
Ethical considerations for drug research in pregnancy	Amina White, Department of Bioethics NIH/Clinical Center
Maternal immunizations GSK's perspective: challenges and barriers, development of possible solutions	Leonard Friedland, Scientific Affairs and Public Health GSK Vaccines
Surveillance of adverse events in pregnancy in the vaccine adverse event reporting system (VAERS)	Pedro L. Moro, Immunization Safety Office CDC
Evaluating vaccine safety during pregnancy: the vaccine safety datalink experience	Allison Naleway, Center for Health Research Kaiser Permanente Northwest
Evaluating pregnancy outcomes using post-licensure rapid immunization monitoring system	David Martin, Director, Division of Epidemiology Office of Biostatistics and Epidemiology FDA/CBER
Clinical immunization safety assessment (CISA) project: maternal research overview	Karen Broader, Immunization Safety Office CDC
Maternal immunizations: perspective from NOVAVAX	Allison August, Lead Maternal Immunization Development Team NOVAVAX
Research challenges in development of influenza vaccines for use in pregnancy	Charles Altman, Head of U.S. Medical Affairs Jane Leong, Vice President Scientific Affairs bioSCL Christina Chambers, Professor Pediatrics University of California San Diego

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Title/ topic of presentation to the working group	Speaker(s) affiliation/ organization represented
Considerations and questions regarding new vaccine approaches to prevent fetal, neonate, and infant disease	Bill Gruber, Senior Vice President Vaccine Clinical Research and Development Pfizer Inc.
Clinical development and requirement licensure of vaccines intended for the use during pregnancy to prevent disease in the infant	Marion F. Gruber, Director Office of Vaccine Research and Review FDA/CBER

6.1

The Atlantic

Cuba's Innovative Cancer Vaccine Is Finally Coming to America

The country has a whole arsenal of unique drugs locked behind the U.S. embargo.



The Cuban flag flies at the Cuban Embassy in Washington

Jonathan Ernst / Reuters

SARAH ZHANG

NOV 7, 2016 | HEALTH

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Last week, in a historic first, a box of water made it from Havana to Buffalo, New York. It was roundabout journey, since you can't just FedEx a box from Cuba to the U.S. ([The embargo](#), no commercial cargo flights, etc.) The box flew first to Toronto. Customs brokers then escorted it across the U.S.-Canada border to its final destination at Roswell Park Cancer Institute.

Why such a production for a box of water? It was the test run for a promising lung-cancer vaccine called CIMAvax, which was developed in Cuba and soon will begin clinical trials in the U.S. But no one in America has ever run a clinical trial with Cuban drugs, and no one was even sure, logistically, how to ship fragile cargo between the two countries. (Again, the embargo, no commercial cargo flights.) So the researchers devised a roundabout route and tested it with this box of water. "We actually wanted them to ship a box of beer," joked Kelvin Lee, an immunologist at Roswell who helped forge the Cuban collaboration, "but it turned out to be too complicated."*

This shipment came, of course, at a time of [thawing relations](#) between U.S. and Cuba. The embargo is still in place—only Congress can vote to lift it—but the Obama administration has been issuing executive actions easing restrictions on trade and travel to the country. Last month, the administration made it easier to carry out joint U.S.-Cuban medical research, and the Food and Drug Administration promptly followed by approving clinical trials for the Cuban lung-cancer vaccine at Roswell.

CIMAvax is so interesting, scientifically speaking, because it belongs to a new class of cancer treatments called immunotherapy. Rather than using a scalpel, radiation, or chemicals to take cancerous cells out directly, immunotherapy stimulates the patient's own immune system to fight cancer. A few immunotherapies are already on the market, and pharmaceutical companies are racing to develop the next. For the past two decades, Cuba, a country with a tiny biomedical research budget, has been quietly sitting on CIMAvax. And this vaccine could be just the first of several Cuban drugs, currently locked behind the embargo, to make to the U.S.

* * *

The collaboration between Roswell and Cuba's Center for Molecular Immunology, which developed the vaccine, actually began in 2011, years before the Obama administration started easing restrictions on Cuba. Gisela Gonzalez, one of the Cuban researchers working on CIMAvax, was visiting family in Pittsburgh when she cold-called one of Lee's colleagues at Roswell.** She wanted to give a talk about the research they were doing in Cuba.

“We were not thinking about Cuba at all,” says Lee. “Our image of Cuba was from back in the *I Love Lucy* days. We didn't consider they had really advanced cancer treatments.” But Cuba manages to punch far above its weight in medicine. Although the country lacks access to advanced medical equipment due to the embargo, life expectancy in Cuba is even a bit higher than in the U.S. Its strength is a robust primary-care system that focuses on disease prevention.

That's how CIMAvax came along, too. In the 1980s, Cuba developed a vaccine to prevent meningitis, a bacterial infection of the membranes around the brain. The vaccine uses pieces of protein from meningitis bacteria, which signal “hey, I'm foreign” and switch the immune system into attack mode. One particular protein, they found, was especially good at activating the immune response.

So when researchers at the Center for Molecular Immunology turned their attention to lung cancer—then the number-two killer in Cuba—they didn't start from scratch. They took that unusually powerful meningitis protein and fused it to part of another protein called epidermal growth factor, or EGF. EGF is important for controlling cancer because, as its name implies, EGF makes cells grow, and cancer is essentially cells growing out of control. When injected, this fused hybrid protein kicks a patient's immune system into high gear (thanks to the meningitis) and targets cancer cells (thanks to the EGF). That's how CIMAvax is supposed to work. It's called a vaccine because like other vaccines, it stimulates the immune system, but it is actually used to treat rather than prevent lung cancer.

Lee recalls learning all this for the first time at Gonzalez's talk. “I'm just sitting in the audience and going, ‘That's really amazing,’” he says. CIMAvax had been approved in a handful of Latin American countries by then, and a handful of

desperate American patients [have since traveled abroad](#) to get CIMAvax. The vaccine doesn't necessarily kill cancer cells, but it slows their growth enough to prolong patients' lives by several months in trials. And its side effects are mild, especially compared to how chemotherapy can ravage the body.

Regardless of how well CIMAvax itself works, it will blaze a path for medical collaborations with Cuba.

So the Roswell and Center for Molecular Immunology started working together. It wasn't your typical collaboration though. Calling Cuba is expensive (something like a dollar a minute), and the country only has slow dial-up internet. And then there was all the complications from the embargo, which made moving materials or money between the countries pretty much impossible. "This has been a very challenging atmosphere for them to collaborate in," says Gail Reed, the founder of MEDICC, a nonprofit that promotes U.S.-Cuban partnerships in medicine. "It's really to their credit that they have been pursuing it."

As the Obama administration looked into restoring relations with Cuba, politicians, law firms, and nonprofits interested in Cuba started paying attention to CIMAvax. MEDICC was one of those nonprofits, and it wrote a [white paper](#) detailing policy changes that would make collaborations like the one over CIMAvax less challenging. The executive actions on medical research last month largely reflect those recommendations. And Lee himself has since made about a dozen trips to Havana.

Roswell is now recruiting patients to its clinical trial for CIMAvax in New York. This trial will be a rigorous test for how well the vaccine works. "There have been trials done outside of U.S., and when we test in U.S., they sometimes don't give us the same results, because the way we conduct clinical trials is very strict," says Erminia Massarelli, an oncologist specializing in lung, head and, throat cancer at City of Hope cancer treatment center. "We will have to see if this vaccine is truly successful. We hope so because we're hoping for better treatment."

Regardless of how well CIMAvax itself works, it will blaze a path for medical collaborations with Cuba. Behind CIMAvax, Roswell has prepared paperwork for clinical trials on a second cancer immunotherapy candidate from Cuba, and it's interested in several more. Cuba also has developed other cost-effective treatments that are currently unavailable in the U.S., such as injections for diabetes-related foot ulcers and the meningitis vaccine that predated CIMAvax. "This first trial really is the stone that we're throwing in the pond to see what happens," says Lee.

The collaboration has brought about all sorts of changes already, from explicitly allowing the FDA's policy to approve Cuban pharmaceuticals, to changes as mundane as getting Cuba's regulatory agency to follow the same drug application formats as the U.S. and other countries. Altogether, they could signal Cuba's slow reentry in the global community. And FedEx has announced plans for [commercial cargo service](#) between the U.S. and Cuba next year. Eventually, shipping a box of medicine from Havana to Buffalo may be no harder than shipping a box anywhere else in the world.

** This article originally stated that Lee is leading the CIMAvax clinical trial. We regret the error.*

*** This article originally stated that Gonzalez cold-called Lee at Roswell. We regret the error.*

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From The Web



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6.2

Shot down: Many adults pass on flu vaccines

11/7/2016

BY LAUREN LINDSTROM

BLADE STAFF WRITER



Alexandra Perez, a student in the University of Toledo's physician assistant program, gives a shot to UT junior Jada Woody.

The Blade/Amy E. Voigt

Much fretting occurs over the actions and opinions of Millennials, and whether or not they are buying houses, getting married, or saving for retirement.

Add another one to the list: Are they getting flu vaccines?

ADD ANOTHER ONE TO THE LIST. ARE THEY GETTING THE VACCINES?

CityMD, a network of urgent care centers, found that 52 percent of Millennials it recently surveyed aren't planning to get the vaccine, with one-quarter saying that cost was the driving factor in not getting it.

That prompted a recent New York Times headline, "Let's Talk a Millennial Into Getting a Flu Shot," which accompanied an interview with Dr. Joseph Bresee, chief of the epidemiology branch in the influenza division of the Centers for Disease Control and Prevention, who debunked concerns from a 27-year-old Times reporter who had yet to get the vaccine.

But in the 2015-2016 season, the CDC reports that 41.7 percent of all adults 18 to 64 received the flu vaccine, which means it is far more than just Millennials — or those between the ages of 19 and 35 in 2016 — who are apathetic, unable, or against getting vaccinated.

The medical journal *Vaccine* in 2011 published findings from a survey of college students following the outbreak of H1N1 on college campuses in 2009. The authors found that one-third of respondents believed they weren't "at risk of getting H1N1 flu because they were young" and only 15.8 percent of respondents planned on getting the vaccine. Participants questioned the vaccine's safety and effectiveness.

"We hear some [of those reasons]," said Susan Batten, an associate professor at the University of Toledo college of nursing. "We hear, 'My mom's not here, I'm not doing it.'"

"You want herd immunity, where a lot of people all get the vaccine," she said. "If you get the virus in a residence hall, it can spread like crazy."

While older adults, young children, and those with chronic conditions like asthma and weakened immune systems are at the greatest risk for serious health complications from influenza, recent flu strains like H1N1 or swine flu have younger populations — including college students — in their crosshairs.

"We encourage everybody to get the flu vaccine not only for themselves, but because in transmission it can be passed to somebody else," said Tara Barron, an infection preventionist at Mercy Health St. Vincent Medical Center.

Influenza is most often spread through respiratory droplets when people cough, sneeze, or talk, but can also be transmitted by touching commonly used items like phones and doorknobs, she said. Easy transmission — even before an infected person feels sick — is one of the biggest reasons medical professionals advise everyone 6 months and older get the shot.

"You can pass the flu virus one to two days before you show first symptoms and five to seven days after you get sick," Ms. Barron said. "Even if you're a healthy individual, it can go [from] mild to serious quickly."

Ms. Barron said common barriers to getting vaccinated include access, price, and education. Local universities are working to combat some of those barriers. The University of Toledo and Bowling Green State University offer flu shots on campus, either in walk-in clinics or during scheduled events.

BGSU spokesman Dave Kielmeyer said flu shots are available to students, staff, and the public at the Falcon Health Center and are billed through insurance, which is required for students and staff. The vaccination costs \$35 if not billed through insurance.

For those who do not face serious health complications, getting sick can still be costly.

Flu-related illness costs an estimated \$10.4 billion in direct medical expenses and \$16.2 billion

Flu-related illness costs an estimated \$10.4 billion in direct medical expenses and \$10.5 billion in lost earnings a year, according to the CDC.

The Toledo-Lucas County Health Department reported 233 influenza-related hospitalizations in the county last flu season. There have been no confirmed hospitalizations in the county so far this season. At this time last year, there was one hospitalization documented in the county.

Caitlin Ceglarek, 27, a second-year student in the physician assistant program at UT, said she has had conversations with peers about why they should get the shot. She joined several of her classmates last week giving out flu shots at Savage Arena on UT's main campus.

"There really is no reason not to get it," she said. "I think people are weird about getting injections in general, and some people think they get sick from getting the shot which is not true."

Ms. Barron said that she also hears patients who say they are waiting to get the shot after seeing if it's a particularly bad season. That doesn't work, she said, because it is difficult to predict any given season's seriousness, and flu vaccines typically take about two weeks to be effective.

Health experts recommend getting the flu shot by the end of October or early November, but they say it is still beneficial to get it even past the recommended time.

Flu shots are available at most doctors offices, the health department, and retail pharmacies. To find a location, visit flu.gov/resources/widgets and enter a ZIP code. To schedule an appointment with the health department, call 419-213-4163.

Contact Lauren Lindstrom at llindstrom@theblade.com, 419-724-6154, or on Twitter [@lelindstrom](https://twitter.com/lelindstrom).

6.3



shots

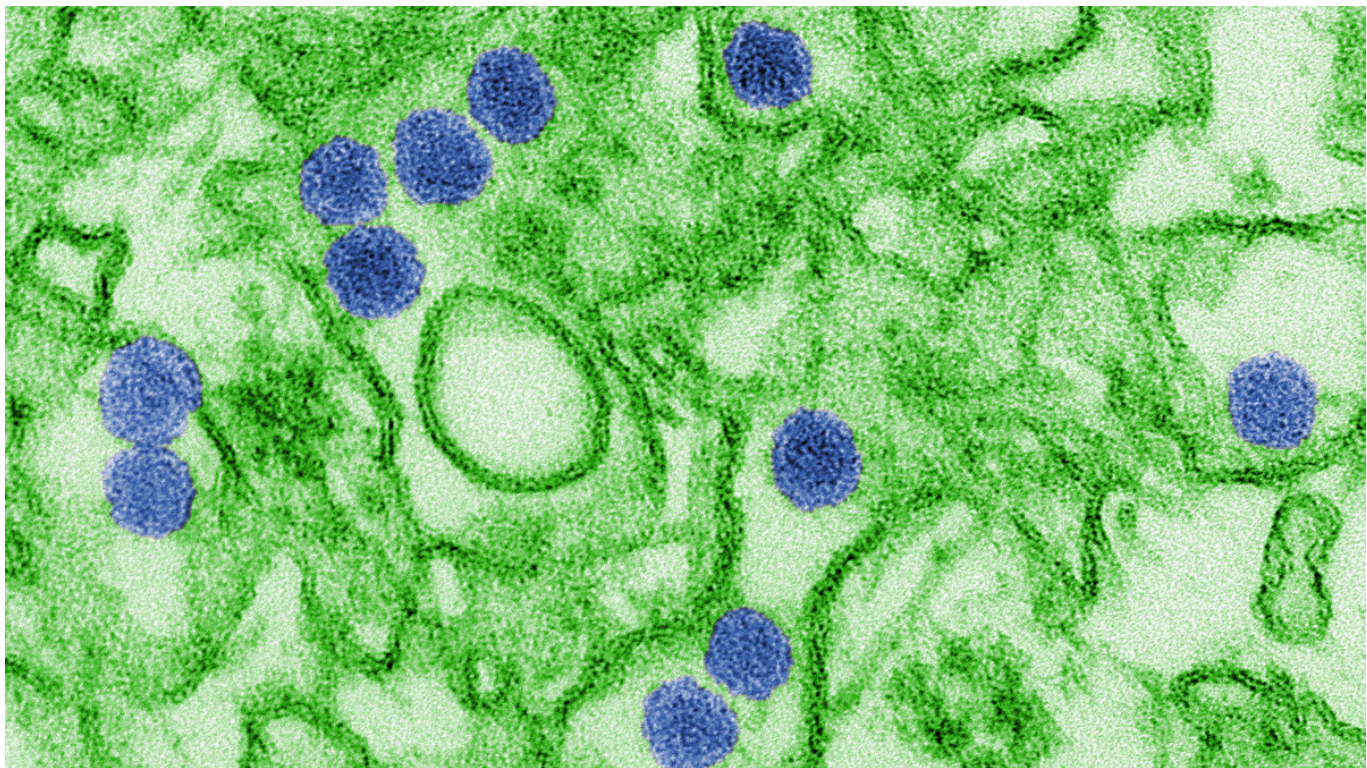
ZIKA VIRUS

Testing Begins On An Experimental Zika Vaccine With Inactivated Virus

November 7, 2016 · 12:15 PM ET



RICHARD HARRIS



A vaccine against the Zika virus could help prevent serious birth defects.

CDC

Federal scientists have launched another test in human volunteers of a Zika vaccine. This one uses a more traditional approach than an experiment that started in August.

Federal officials are eager to develop a vaccine as quickly as possible, which is why they are pursuing multiple approaches. This experimental vaccine, called ZPIV, has already proved effective when designed to target a virus similar to Zika, called Japanese encephalitis.

"We urgently need a safe and effective vaccine to protect people from Zika virus infection, as the virus continues to spread and cause serious public health consequences, particularly for pregnant women and their babies," Dr. Anthony Fauci said in a statement Monday. He heads the National Institute of Allergy and Infectious Diseases (NIAID), which is funding the research along with the Department of Defense.

Researchers at the Walter Reed Army Institute of Research in Silver Spring, Md., are recruiting 75 volunteers to test the vaccine. Researchers will monitor them to make sure the vaccine is safe. They want to find out whether people injected with the vaccine will produce antibodies that will protect them from the disease.

The vaccine has already been tested in monkeys, where it proved effective against Zika.

ZPIV uses a strategy that has worked in many other vaccines: scientists cripple the virus so it can't cause disease, but that inactivated form still triggers an immune reaction. Vaccines for polio and flu are two examples of inactivated vaccines.

In August, NIAID started testing a less traditional vaccine for Zika. That vaccine uses a small, circular piece of DNA that is injected into a person's arm. That DNA directs cells in the human body to produce Zika-like proteins, which in turn trigger an immune response. This technique was first used for developing a vaccine for the West Nile virus, but it's not yet on the market.



GOATS AND SODA

How An Electric Shock Could One Day Protect You From Zika

If that vaccine proves to be promising, federal researchers hope to expand trials of it in countries where Zika is prevalent in early 2017.

The World Health Organization says Zika has been identified in 73 nations as of Nov. 3. That includes the United States. The CDC reports about 4,000 cases in the continental United States and Hawaii, including 139 cases among people who acquired the disease domestically. More than 30,000 cases have been diagnosed in Puerto Rico.

Zika occasionally causes severe brain damage in children born to women who are infected with the virus while pregnant. Some people also experience a rare nervous system disorder called Guillian-Barre syndrome.

zika virus medical treatments vaccines

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6.4

• Federal program compensates vaccine victims after shots given incorrectly

by: Jodie Fleischer Updated: Nov 14, 2016 - 7:06 PM

- **ATLANTA** - Denise Procida wasn't scheduled to work on flu shot day at her office last year, but she went to work anyway to get the shot.

She immediately noticed something strange.

"The second she put the alcohol on my shoulder, I thought, 'Wow. That's really high.' And I didn't say anything," Procida told Channel 2 Investigative Reporter Jodie Fleischer.

Within a few days, she couldn't move her arm at all.

"The pain just continued to get worse. About a week in, it was just unbearable," said the mother of three, who was struggling to take care of her family, do simple chores, or even style her own hair.

When she told her boss about her injury, she found out a coworker who got the flu shot on the same day was having the same problem.

But Procida's primary care doctor and two orthopedists were stumped.

"When you tell someone, 'I can't move my arm because I got a flu shot four months ago,' they look at you like you're crazy," said Procida.

She wondered whether anyone else had the same severe shoulder pain weeks after getting a flu shot, and started researching on the Internet during her sleepless nights.

"It turned out, there are lots of people that had the same thing," she said. "It was reassuring that I wasn't the only one."

<http://www.wsbtv.com/news/2-investigates/federal-program-compensates-vaccine-victims-after-shots-given-incorrectly/466433922>

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6.5

\$3B program to help vaccine victims falls short on promises

by: Jodie Fleischer Updated: Nov 15, 2016 - 11:26 AM

- **ATLANTA** - A federal program designed to help victims suffering from life-altering reactions to vaccines is falling short on promises made when it started.

It's called the Vaccine Injury Compensation Program, a \$3.6 billion fund created to take care of victims with catastrophic reactions to vaccines.

But a Channel 2 Action News investigation found it also protects vaccine-makers from being subject to lawsuits.

And they don't pay for the program -- you do.

"I JUST HAD A BAD FEELING ABOUT IT"

Jessica Mura suffered a permanent reaction to a flu shot in 2006, a flu shot she never even wanted to get.

"I just had a bad feeling about it," she said. "I was healthy. I was 21. To me, I was on top of the world."

But the vaccine was required by her employer, a south Georgia ambulance company.

"That was my passion, helping people," said Mura. "EMTs don't make that much money, but I didn't care. I just loved what I did."

Within days of getting the shot, her co-workers noticed the symptoms.

She vividly remembers the very last time she walked. It was into an emergency room.

"It's hard to go from the person who cared for people, to be the one being cared for," said Mura.

She slipped into a coma for several months, endured 15 surgeries and had to learn to speak and eat again.

Now 31, she has a permanent brain injury and is confined to a wheelchair.

Channel 2 Investigative Reporter Jodie Fleischer asked Mura how sure she was that the flu shot caused her injuries.

"Two thousand percent," she said. "I was healthy, there was absolutely nothing wrong with me."

The federal government finally agreed, but not until seven years after she first got sick.

VACCINE-MAKERS IMMUNE FROM LAWSUITS

The program shields vaccine-makers from almost all litigation, to encourage them to remain in the risk-filled industry.

For consumers, it was supposed to be a less-complicated alternative to filing a lawsuit.

"I just knew what happened to me was wrong and I wanted to try to rectify it a little bit," Mura said.

It took her two years just to find an attorney who would stick with her case.

At the time, Diane Tiveron hadn't even heard of the Vaccine Injury Compensation Program.

"I think that there's not many attorneys that know how to handle this," Tiveron said. "It's kind of a well-kept secret in terms of what is available for people."

Even though those patients are the ones who pay for it.

Seventy-five cents of the fee from every shot given goes into that fund, which is now worth \$3.6 billion.

The vaccine makers don't pay anything toward the fund.

"Whoever came up with this idea, I have to congratulate them," Tiveron said. "I mean, the manufacturers are not bearing any responsibility."

She says that's also a problem because it takes away companies' incentive to make vaccines safer, since they know they can't be sued.

In a lawsuit, the victim would have to show negligence, not just that the shot caused the injury.

This program was supposed to be faster and easier.

"That's a joke, that's completely a joke. They don't want to give you anything," Mura said. "You have to jump through hoops, walk through fire; it's not easy."

When it was created in 1989, payouts were supposed to take roughly eight months.

But a federal audit in 2014 found more than half of the cases were taking longer than five years.

More patients are filing claims, without the staff to handle the claims.

TWO-THIRDS OF PATIENTS TURNED AWAY

"This is a drug company stockholder's dream, and a consumer's worst nightmare," said Barbara Loe Fisher, president of the National Vaccine Information Center, an advocacy group for families.

Fisher's son was a toddler when he had a reaction to a DPT vaccine.

She served as a congressional adviser when the fund was first created.

"It's completely in the hands of the Department of Health and Human Services and the Department of Justice to make this program work like we were promised it would work," Fisher said.

In the last 25 years, nearly 5,000 victims have received more than \$3 billion.

But another 10,000 patients who filed claims have been turned away.

"I can appreciate people standing guard and making sure there aren't frivolous claims, but those are pretty easy to take out of the equation," Tiveron said. "So I do think it should be easier."

In 2013, the advisory committee that oversees the program requested increasing the \$250,000 cap for pain and suffering, and a longer window to file a claim. Right now patients have three years.

The federal government has yet to do either.

That same advisory committee is now pushing for more judges to hear those cases.

They just voted this fall to file a formal request, but it will take congressional action to make it happen.

Tiveron says everyone who gets a shot should be told about the fund, which did ultimately give Jessica Mura more than \$1.6 million for her care.

But Mura says no amount of money is worth what she's been through.

"I would give everything back ten times over if I could just walk, if I could just have my life back."

6.6

It's Federal Law! You must give your patients current Vaccine Information Statements (VISs)

What are Vaccine Information Statements (VISs)?

Vaccine Information Statements (VISs) are documents produced by the Centers for Disease Control and Prevention (CDC), in consultation with panels of experts and parents, to properly inform vaccinees (or their parents/legal representatives) about the risks and benefits of each vaccine. VISs are not meant to replace interactions with health care providers, who should address any questions or concerns that the vaccinee (or parent/legal representative) may have.

Using VISs is legally required!

Federal law (under the National Childhood Vaccine Injury Act) requires a health care provider to give a copy of the current VIS to an adult patient or to a child's parent/legal representative before vaccinating an adult or child with a dose of the following vaccines: diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib), influenza, pneumococcal conjugate, meningococcal, rotavirus, human papillomavirus (HPV), or varicella (chickenpox).

Where to get VISs

All available VISs can be downloaded from the websites of the Immunization Action Coalition at www.immunize.org/vis or CDC at www.cdc.gov/vaccines/hcp/vis/index.html. Ready-to-copy versions may also be available from your state or local health department.

Translations: You can find VISs in more than 30 languages on the Immunization Action Coalition website at www.immunize.org/vis.

To obtain translations of VIS in languages other than English, go to www.immunize.org/vis.

According to CDC, the appropriate VIS must be given:

- Prior to the vaccination (and prior to each dose of a multi-dose series);
- Regardless of the age of the vaccinee;
- Regardless of whether the vaccine is given in a public or private health care setting.

Top 10 Facts About VISs

FACT 1 It's federal law! You must give current* VISs to all your patients before vaccinating them.

Federal law requires that VISs must be used for patients of **ALL** ages when administering these vaccines:

- DTaP (includes DT)
- Td and Tdap
- Hib
- hepatitis A
- hepatitis B
- HPV
- influenza (inactivated and live, intranasal)
- MMR and MMRV
- meningococcal
- pneumococcal conjugate
- polio
- rotavirus
- varicella (chickenpox)

For the vaccines not covered under the National Childhood Vaccine Injury Act (i.e., adenovirus, anthrax, Japanese encephalitis, pneumococcal polysaccharide, rabies, shingles, typhoid, and yellow fever), providers are not required by federal law to use VISs unless they have been purchased under CDC contract. However, CDC recommends that VISs be used whenever these vaccines are given.

*Federal law allows up to 6 months for a new VIS to be used.

FACT 2 VISs can be given to patients in a variety of ways.

In most medical settings, VISs are provided to patients (or their parents/legal representatives) in paper form. However, VISs also may be provided using electronic media. Regardless of the format used, the goal is to provide a current VIS just prior to vaccination.

CONTINUED ON NEXT PAGE ►

Most current versions of VISs (table)

As of August 9, 2016, the most recent versions of the VISs are as follows:

Adenovirus	6/11/14	MMR	4/20/12
Anthrax	3/10/10	MMRV	5/21/10
Chickenpox	3/13/08	Multi-vaccine	11/5/15
DTaP	5/17/07	PCV13	11/5/15
Hib	4/2/15	PPSV	4/24/15
Hepatitis A	7/20/16	Polio	7/20/16
Hepatitis B	7/20/16	Rabies	10/6/09
HPV-Cervarix	5/3/11	Rotavirus	4/15/15
HPV-Gardasil	5/17/13	Shingles	10/6/09
HPV-Gardasil 9	3/31/16	Td	2/24/15
Influenza	8/7/15	Tdap	2/24/15
Japanese enceph	1/24/14	Typhoid	5/29/12
MCV4/MPSV4	3/31/16	Yellow fever	3/30/11
MenB	8/9/16		

A handy list of current VIS dates is also available at www.immunize.org/catg.d/p2029.pdf.

(For information on special circumstances involving vaccination of a child when a parent/legal representative is not available at the time of vaccination, see CDC's *Frequently Asked Questions* at www.cdc.gov/vaccines/hcp/vis/about/vis-faqs.html.)

Prior to vaccination, VIS may be:

- Provided as a paper copy
- Offered on a permanent, laminated office copy
- Downloaded by the vaccinee (parent/legal representative) to a smartphone or other electronic device (VISs have been specially formatted for this purpose)
- Made available to be read before the office visit, e.g., by giving the patient or parent a copy to take home during a prior visit, or telling them how to download or view a copy from the Internet. These patients must still be offered a copy in one of the formats described previously to read during the immunization visit, as a reminder.

Regardless of the way the patient is given the VIS to read, providers must still offer a copy (which can be an electronic copy) of each appropriate VIS to take home following the vaccination. However, the vaccinee may decline.

FACT 3 VISs are required in both public and private sector health care settings.

Federal law requires the use of VISs in both public and private sector settings, regardless of the source of payment for the vaccinee.

FACT 4 You must provide a current VIS *before* a vaccine is administered to the patient.

A VIS provides information about the disease and the vaccine and must be given to the patient **before** a vaccine is administered. It is also acceptable to hand out the VIS well before administering vaccines (e.g., at a prenatal visit or at birth for vaccines an infant will receive during infancy), as long as you still provide a current VIS right before administering vaccines.

FACT 5 You must provide a current VIS for *each* dose of vaccine you administer.

The most current VIS must be provided before **each dose** of vaccine is given, including vaccines given as a series of doses. For example, if 5 doses of a single vaccine are required (e.g., DTaP), the patient (parent/legal representative) must have the opportunity to read the information on the VIS before each dose is given.

FACT 6 You must provide VISs whenever you administer combination vaccines.

If you administer a combination vaccine that does not have a stand-alone VIS (e.g., Kinrix, Quadracel, Pediarix, Pentacel, Twinrix) you should provide the patient with individual VISs for the component vaccines, or use the Multi-Vaccine VIS (see below).

The Multi-Vaccine VIS may be used in place of the individual VISs for DTaP, Hib, hepatitis B, polio, and pneumococcal when two or more of these vaccines are administered during the same visit. It may be used for infants as well as children through 6 years of age. The Multi-Vaccine VIS should not be used for adolescents or adults.

FACT 7 VISs should be given in a language /format that the recipient can understand, whenever possible.

For patients who don't read or speak English, the law requires that providers ensure all patients (parent/legal representatives) receive a VIS, regardless of their ability to read English. To obtain VISs in more than 30 languages, visit the Immunization Action Coalition website at www.immunize.org/vis. Providers can supplement VISs with visual presentations or oral explanations as needed.

FACT 8 Federal law does not require signed consent in order for a person to be vaccinated.

Signed consent is not required by federal law for vaccination (although some states may require it).

FACT 9 To verify that a VIS was given, providers must record in the patient's medical record (or permanent office log or file) the following information:

- The edition date of the VIS (found on the back at the right bottom corner)
- The date the VIS is provided (i.e., the date of the visit when the vaccine is administered)

In addition, providers must record:

- The office address and name and title of the person who administers the vaccine
- The date the vaccine is administered
- The vaccine manufacturer and lot number

FACT 10 VISs should not be altered before giving them to patients, but you can add some information.

Providers should not change a VIS or write their own VISs. However, it is permissible to add a practice's name, address, and contact information to an existing VIS.

Additional resources on VISs and their use are available from the following organizations:

Immunization Action Coalition

- VIS general information and translations in more than 30 languages: www.immunize.org/vis
- Current Dates of Vaccine Information Statements: www.immunize.org/catg.d/p2029.pdf

Centers for Disease Control and Prevention

- VIS website: www.cdc.gov/vaccines/hcp/vis
- VIS Facts: www.cdc.gov/vaccines/hcp/vis/about/facts-vis.html
- VIS FAQs: www.cdc.gov/vaccines/hcp/vis/about/vis-faqs.html