COLORADO
Department of Public Health & Environment

COLORADO
Department of Education

April 12, 2017

Regarding School Responsibility and Immunization Exemptions

In response to several requests from schools for support and clarity around the usage of immunization exemption forms, the Colorado Department of Public Health and Environment (CDPHE) and the Colorado Department of Education jointly issue this memo.

Schools are required to have an immunization record on file for every student enrolled. Immunization records are the official certificate of immunization, the official medical exemption form or a documented non-medical exemption. The certificate of immunization is located here: www.colorado.gov/pacific/cdphe/immunization-forms. Medical and nonmedical exemption forms are located here: www.colorado.gov/vaccineexemption.

We encourage the use of the CDPHE non-medical exemption form when possible. However, recognizing that some families may prefer not to use this form, a parent/guardian or emancipated student or student over the age of 18 may submit a signed non-medical statement of exemption per section 25-4-903(2)(b), C.R.S. Such a statement should include the following information: student's full name, age or date of birth, date the exemption was submitted, the vaccines declined, and which type of non-medical exemption is being taken (personal belief or religious).

Additionally, schools are not required to share immunization records with CDPHE but may do so if the parent has provided written consent, per the Family Educational Rights and Privacy Act (FERPA). Parents/guardians/students may choose to submit immunization and exemption forms directly to CDPHE for inclusion in the Colorado Immunization Information System (CIIS), the state's secure, confidential immunization registry. Once a record is in CIIS, schools can retrieve immunization or exemption records for their students at any time. All information contained in CIIS is kept confidential per section 25-4-2403, C.R.S. Parents/guardians/students can opt out of CIIS at any time by following the procedures here: www.colorado.gov/pacific/cdphe/ciis-opt-out-procedures.

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Vaccine Inserts

Pediarix

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PEDIARIX safely and effectively. See full prescribing information for PEDIARIX.

PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine]
Suspension for Intramuscular Injection
Initial U.S. Approval: 2002

---------- INDICATIONS AND USAGE----------
PEDIARIX is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a three-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday). (1)

----------DOSAGE AND ADMINISTRATION----------
Three doses (0.5-mL each) by intramuscular injection at 2, 4, and 6 months of age. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Single-dose prefilled syringes containing a 0.5-mL suspension for injection. (3)

---------- CONTRAINDICATIONS ----------
- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis-, hepatitis B-, or poliovirus-containing vaccine, or to any component of PEDIARIX. (4.1)
- Encephalopathy within 7 days of administration of a previous pertussis-containing vaccine. (4.2)
- Progressive neurologic disorders. (4.3)

---------- WARNINGS AND PRECAUTIONS----------
- In clinical trials, PEDIARIX was associated with higher rates of fever, relative to separately administered vaccines. (5.1)
- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give PEDIARIX should be based on potential benefits and risks. (5.2)
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.3)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.4)
- If specified adverse events (i.e., temperature ≥105°F, collapse or shock-like state, or inconsolable crying lasting ≥3 hours, within 48 hours after vaccination; seizures within 3 days after vaccination) have occurred following a pertussis-containing vaccine, the decision to give PEDIARIX should be based on potential benefits and risks. (5.5)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with PEDIARIX. (5.6)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.7)

---------- ADVERSE REACTIONS ----------
Common solicited adverse events following any dose (≥25%) included local injection site reactions (pain, redness, and swelling), fever (≥100.4°F), drowsiness, irritability/fussiness, and loss of appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---------- DRUG INTERACTIONS----------
Do not mix PEDIARIX with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PEDIARIX® is indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a three-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Attach a sterile needle and administer intramuscularly.

The preferred administration site is the anterolateral aspect of the thigh for children younger than 1 year. In older children, the deltoid muscle is usually large enough for an intramuscular injection. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response.

Do not administer this product intravenously, intradermally, or subcutaneously.

2.2 Recommended Dose and Schedule

Immunization with PEDIARIX consists of 3 doses of 0.5 mL each, by intramuscular injection, at 2, 4, and 6 months of age (at intervals of 6 to 8 weeks, preferably 8 weeks). The first dose may be given as early as 6 weeks of age. Three doses of PEDIARIX constitute a primary immunization course for diphtheria, tetanus, pertussis, and poliomyelitis and the complete vaccination course for hepatitis B.

2.3 Modified Schedules in Previously Vaccinated Children

Children Previously Vaccinated with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP)

PEDIARIX may be used to complete the first 3 doses of the DTaP series in children who have received 1 or 2 doses of INFANRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), manufactured by GlaxoSmithKline, identical to the DTaP component of PEDIARIX *[see Description (11)]* and are also scheduled to receive the other vaccine

components of PEDIARIX. Data are not available on the safety and effectiveness of using PEDIARIX following one or more doses of a DTaP vaccine from a different manufacturer.

Children Previously Vaccinated with Hepatitis B Vaccine

PEDIARIX may be used to complete the hepatitis B vaccination series following 1 or 2 doses of another hepatitis B vaccine (monovalent or as part of a combination vaccine), including vaccines from other manufacturers, in children born of HBsAg-negative mothers who are also scheduled to receive the other vaccine components of PEDIARIX.

A 3-dose series of PEDIARIX may be administered to infants born of HBsAg-negative mothers and who received a dose of hepatitis B vaccine at or shortly after birth. However, data are limited regarding the safety of PEDIARIX in such infants *[see Adverse Reactions (6.1)]*. There are no data to support the use of a 3-dose series of PEDIARIX in infants who have previously received more than one dose of hepatitis B vaccine.

Children Previously Vaccinated with Inactivated Poliovirus Vaccine (IPV)

PEDIARIX may be used to complete the first 3 doses of the IPV series in children who have received 1 or 2 doses of IPV from a different manufacturer and are also scheduled to receive the other vaccine components of PEDIARIX.

2.4 Booster Immunization following PEDIARIX

Children who have received a 3-dose series with PEDIARIX should complete the DTaP and IPV series according to the recommended schedule.[1] Because the pertussis antigens contained in INFANRIX and KINRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine), manufactured by GlaxoSmithKline, are the same as those in PEDIARIX, these children should receive INFANRIX as their fourth dose of DTaP and either INFANRIX or KINRIX as their fifth dose of DTaP, according to the respective prescribing information for these vaccines. KINRIX or another manufacturer's IPV may be used to complete the 4-dose IPV series according to the respective prescribing information.

3 DOSAGE FORMS AND STRENGTHS

PEDIARIX is a suspension for injection available in 0.5-mL single-dose prefilled TIP-LOK® syringes.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis antigen-, hepatitis B-, or poliovirus-containing vaccine or any component of this vaccine, including yeast, neomycin, and polymyxin B, is a contraindication to administration of PEDIARIX *[see Description (11)]*.

4.2 Encephalopathy

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX.

4.3 Progressive Neurologic Disorder

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX. PEDIARIX should not be administered to individuals with such conditions until the neurologic status is clarified and stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Fever

In clinical trials, administration of PEDIARIX in infants was associated with higher rates of fever, relative to separately administered vaccines *[see Adverse Reactions (6.1)]*.

5.2 Guillain-Barré Syndrome

If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give PEDIARIX or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

5.3 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.4 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.5 Adverse Events following Prior Pertussis Vaccination

If any of the following events occur in temporal relation to receipt of a vaccine containing a pertussis component, the decision to give any pertussis-containing vaccine, including PEDIARIX, should be based on careful consideration of the potential benefits and possible risks:

- Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

5.6 Children at Risk for Seizures

For children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at the time of vaccination with a vaccine containing a pertussis component, including PEDIARIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

5.7 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination.

5.8 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice.

A total of 23,849 doses of PEDIARIX have been administered to 8,088 infants who received one or more doses as part of the 3-dose series during 14 clinical studies. Common adverse events that occurred in ≥25% of subjects following any dose of PEDIARIX included local injection site reactions (pain, redness, and swelling), fever, drowsiness, irritability/fussiness, and loss of appetite. In comparative studies (including the German and U.S. studies described below), administration of PEDIARIX was associated with higher rates of fever relative to separately administered vaccines *[see Warnings and Precautions (5.1)]*. The prevalence of fever was highest on the day of vaccination and the day following vaccination. More than 96% of episodes of fever resolved within the 4-day period following vaccination (i.e., the period including the day of vaccination and the next 3 days).

In the largest of the 14 studies, conducted in Germany, safety data were available for 4,666 infants who received PEDIARIX administered concomitantly at separate sites with 1 of 4 *Haemophilus influenzae* type b (Hib) conjugate vaccines (GlaxoSmithKline [licensed in the U.S. only for booster immunization], Wyeth Pharmaceuticals Inc. [no longer licensed in the U.S.], Sanofi Pasteur SA [U.S.-licensed], or Merck & Co, Inc. [U.S.-licensed]) at 3, 4, and 5 months of

age and for 768 infants in the control group that received separate U.S.-licensed vaccines (INFANRIX, Hib conjugate vaccine [Sanofi Pasteur SA], and oral poliovirus vaccine [OPV] [Wyeth Pharmaceuticals, Inc.; no longer licensed in the U.S.]). In this study, information on adverse events that occurred within 30 days following vaccination was collected. More than 95% of study participants were white.

In a U.S. study, the safety of PEDIARIX administered to 673 infants was compared with the safety of separately administered INFANRIX, ENGERIX-B® [Hepatitis B Vaccine (Recombinant)], and IPV (Sanofi Pasteur SA) in 335 infants. In both groups, infants received Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.) and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were administered at 2, 4, and 6 months of age. Data on solicited local reactions and general adverse events were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days). Telephone follow-up was conducted 1 month and 6 months after the third vaccination to inquire about serious adverse events. At the 6-month follow-up, information also was collected on new onset of chronic illnesses. A total of 638 subjects who received PEDIARIX and 313 subjects who received INFANRIX, ENGERIX-B, and IPV completed the 6-month follow-up. Among subjects in both study groups combined, 69% were white, 18% were Hispanic, 7% were black, 3% were Oriental, and 3% were of other racial/ethnic groups.

Solicited Adverse Events

Data on solicited local reactions and general adverse events from the U.S. safety study are presented in Table 1. This study was powered to evaluate fever >101.3°F following Dose 1. The rate of fever ≥100.4°F following each dose was significantly higher in the group that received PEDIARIX compared with separately administered vaccines. Other statistically significant differences between groups in rates of fever, as well as other solicited adverse events, are noted in Table 1. Medical attention (a visit to or from medical personnel) for fever within 4 days following vaccination was sought in the group who received PEDIARIX for 8 infants after the first dose (1.2%), 1 infant following the second dose (0.2%), and 5 infants following the third dose (0.8%) (Table 1). Following Dose 2, medical attention for fever was sought for 2 infants (0.6%) who received separately administered vaccines (Table 1). Among infants who had a medical visit for fever within 4 days following vaccination, 9 of 14 who received PEDIARIX and 1 of 2 who received separately administered vaccines, had one or more diagnostic studies performed to evaluate the cause of fever.

Table 1. Percentage of Infants with Solicited Local Reactions or General Adverse Events within 4 Days of Vaccination[a] at 2, 4, and 6 Months of Age with PEDIARIX Administered Concomitantly with Hib Conjugate Vaccine and 7-Valent Pneumococcal Conjugate Vaccine (PCV7) or with Separate Concomitant Administration of INFANRIX, ENGERIX-B, IPV, Hib Conjugate Vaccine, and PCV7 (Modified Intent-to-Treat Cohort)

	PEDIARIX, Hib Vaccine, & PCV7			INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
Local[b]						
N	**671**	**653**	**648**	**335**	**323**	**315**
Pain, any	36.1	36.1	31.2	31.9	30.0	29.8
Pain, Grade 2 or 3	11.5	10.9	10.6	9.0	8.7	8.9
Pain, Grade 3	2.4	2.5	1.7	2.7	1.5	1.3
Redness, any	24.9[c]	37.2	40.1	18.2	32.8	39.0
Redness, >5 mm	6.0[c]	9.6[c]	12.7[c]	1.8	5.9	7.3
Redness, >20 mm	0.9	1.2[c]	2.8	0.3	0.0	1.9
Swelling, any	17.3[c]	26.5[c]	28.7	9.6	20.4	24.8
Swelling, >5 mm	5.8[c]	9.6[c]	9.3[c]	1.8	5.0	4.1
Swelling, >20 mm	1.9	2.5[c]	3.1	0.6	0.0	1.3
General						
N	**667**	**644**	**645**	**333**	**321**	**311**
Fever[d], ≥100.4°F	27.9[c]	38.8[c]	33.5[c]	19.8	30.2	23.8
Fever[d], >101.3°F	7.0	14.1[c]	8.8	4.5	9.7	5.8
Fever[d], >102.2°F	2.2[c]	3.6	3.4	0.3	3.1	2.3
Fever[d], >103.1°F	0.4	1.4	1.1	0.0	0.3	0.3
Fever[d], M.A.	1.2[c]	0.2	0.8	0.0	0.6	0.0
N	**671**	**653**	**648**	**335**	**323**	**315**
Drowsiness, any	57.2	51.6	40.9	54.0	48.3	38.4
Drowsiness, Grade 2 or 3	15.8	13.8	11.4	17.6	12.4	11.1
Drowsiness, Grade 3	2.5	1.2	0.9	3.6	0.6	1.9
Irritability/Fussiness, any	60.5	64.9	61.1	61.5	61.6	56.5
Irritability/Fussiness, Grade 2 or 3	19.8	27.9[c]	25.2[c]	19.4	21.1	19.4
Irritability/Fussiness, Grade 3	3.4	4.4	3.5	3.9	3.4	3.2
Loss of appetite, any	30.4	30.6	26.2	27.8	26.6	23.8
Loss of appetite, Grade 2 or 3	6.6	7.8[c]	5.9	5.1	3.4	5.4
Loss of appetite, Grade 3	0.7	0.3	0.2	0.6	0.3	0.0

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Modified intent-to-treat cohort = All vaccinated subjects for whom safety data were available.

N = Number of infants for whom at least one symptom sheet was completed; for fever, numbers exclude missing temperature recordings or tympanic measurements.

M.A. = Medically attended (a visit to or from medical personnel).
Grade 2 defined as sufficiently discomforting to interfere with daily activities.
Grade 3 defined as preventing normal daily activities.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] Local reactions at the injection site for PEDIARIX or INFANRIX.

[c] Rate significantly higher in the group that received PEDIARIX compared with separately administered vaccines (*P* value <0.05 [2-sided Fisher Exact test] or the 95% CI on the difference between groups [Separate minus PEDIARIX] does not include 0).

[d] Axillary temperatures increased by 1°C and oral temperatures increased by 0.5°C to derive equivalent rectal temperature.

Serious Adverse Events

Within 30 days following any dose of vaccine in the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 7 serious adverse events were reported in 7 subjects (1% [7/673]) who received PEDIARIX (1 case each of pyrexia, gastroenteritis, and culture-negative clinical sepsis and 4 cases of bronchiolitis) and 5 serious adverse events were reported in 4 subjects (1% [4/335]) who received INFANRIX, ENGERIX-B, and IPV (uteropelvic junction obstruction and testicular atrophy in one subject and 3 cases of bronchiolitis).

Deaths

In 14 clinical trials, 5 deaths were reported among 8,088 (0.06%) recipients of PEDIARIX and 1 death was reported among 2,287 (0.04%) recipients of comparator vaccines. Causes of death in the group that received PEDIARIX included 2 cases of Sudden Infant Death Syndrome (SIDS) and one case of each of the following: convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma. One case of SIDS was reported in the comparator group. The rate of SIDS among all recipients of PEDIARIX across the 14 trials was 0.25/1,000. The rate of SIDS observed for recipients of PEDIARIX in the German safety study was 0.2/1,000 infants (reported rate of SIDS in Germany in the latter part of the 1990s was 0.7/1,000 newborns). The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births. By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.

Onset of Chronic Illnesses

In the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 21 subjects (3%) who received PEDIARIX and 14 subjects (4%) who received INFANRIX, ENGERIX-B, and IPV reported new onset of a chronic illness during the period from 1 to 6 months following the last dose of study vaccines. Among the chronic illnesses reported in the subjects who received PEDIARIX, there were 4 cases of asthma and 1 case each of diabetes mellitus and chronic neutropenia. There were 4 cases of asthma in subjects who received INFANRIX, ENGERIX-B, and IPV.

Seizures

In the German safety study over the entire study period, 6 subjects in the group that received PEDIARIX (N = 4,666) reported seizures. Two of these subjects had a febrile seizure, 1 of whom also developed afebrile seizures. The remaining 4 subjects had afebrile seizures, including 2 with infantile spasms. Two subjects reported seizures within 7 days following vaccination (1 subject had both febrile and afebrile seizures, and 1 subject had afebrile seizures), corresponding to a rate of 0.22 seizures per 1,000 doses (febrile seizures 0.07 per 1,000 doses, afebrile seizures 0.14 per 1,000 doses). No subject who received concomitant INFANRIX, Hib vaccine, and OPV (N = 768) reported seizures. In a separate German study that evaluated the safety of INFANRIX in 22,505 infants who received 66,867 doses of INFANRIX administered as a 3-dose primary series, the rate of seizures within 7 days of vaccination with INFANRIX was 0.13 per 1,000 doses (febrile seizures 0.0 per 1,000 doses, afebrile seizures 0.13 per 1,000 doses).

Over the entire study period in the U.S. safety study in which all subjects received concomitant Hib and pneumococcal conjugate vaccines, 4 subjects in the group that received PEDIARIX (N = 673) reported seizures. Three of these subjects had a febrile seizure and 1 had an afebrile seizure. Over the entire study period, 2 subjects in the group that received INFANRIX, ENGERIX-B, and IPV (N = 335) reported febrile seizures. There were no afebrile seizures in this group. No subject in either study group had seizures within 7 days following vaccination.

Other Neurological Events of Interest

No cases of hypotonic-hyporesponsiveness or encephalopathy were reported in either the German or U.S. safety studies.

Safety of PEDIARIX after a Previous Dose of Hepatitis B Vaccine

Limited data are available on the safety of administering PEDIARIX after a previous dose of hepatitis B vaccine. In 2 separate studies, 160 Moldovan infants and 96 U.S. infants, respectively, received 3 doses of PEDIARIX following 1 previous dose of hepatitis B vaccine. Neither study was designed to detect significant differences in rates of adverse events associated with PEDIARIX administered after a previous dose of hepatitis B vaccine compared with PEDIARIX administered without a previous dose of hepatitis B vaccine.

6.2 Postmarketing Safety Surveillance Study

In a safety surveillance study conducted at a health maintenance organization in the U.S., infants who received one or more doses of PEDIARIX from approximately mid-2003 through mid-2005 were compared with age-, gender-, and area-matched historical controls who received one or more doses of separately administered U.S.-licensed DTaP vaccine from 2002 through approximately mid-2003. Only infants who received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with PEDIARIX or DTaP vaccine were included in the cohorts. Other U.S.-licensed vaccines were administered according to routine practices at the study sites, but concomitant administration with PEDIARIX or DTaP was not a criterion for

inclusion in the cohorts. A birth dose of hepatitis B vaccine had been administered routinely to infants in the historical DTaP control cohort, but not to infants who received PEDIARIX. For each of Doses 1-3, a random sample of 40,000 infants who received PEDIARIX was compared with the historical DTaP control cohort for the incidence of seizures (with or without fever) during the 8-day period following vaccination. For each dose, random samples of 7,500 infants in each cohort were also compared for the incidence of medically-attended fever (fever ≥100.4°F that resulted in hospitalization, an emergency department visit, or an outpatient visit) during the 4-day period following vaccination. Possible seizures and medical visits plausibly related to fever were identified by searching automated inpatient and outpatient data files. Medical record reviews of identified events were conducted to verify the occurrence of seizures or medically-attended fever. The incidence of verified seizures and medically-attended fever from this study are presented in Table 2.

Table 2. Percentage of Infants with Seizures (with or without Fever) within 8 Days of Vaccination and Medically-attended Fever within 4 Days of Vaccination with PEDIARIX Compared with Historical Controls

	PEDIARIX			Historical DTaP Controls			Difference (PEDIARIX–DTaP Controls)
	N	n	% (95% CI)	N	n	% (95% CI)	% (95% CI)
All Seizures (with or without fever)							
Dose 1, Days 0-7	40,000	7	0.02 (0.01, 0.04)	39,232	6	0.02 (0.01, 0.03)	0.00 (-0.02, 0.02)
Dose 2, Days 0-7	40,000	3	0.01 (0.00, 0.02)	37,405	4	0.01 (0.00, 0.03)	0.00 (-0.02, 0.01)
Dose 3, Days 0-7	40,000	6	0.02 (0.01, 0.03)	40,000	5	0.01 (0.00, 0.03)	0.00 (-0.01, 0.02)
Total doses	120,000	16	0.01 (0.01, 0.02)	116,637	15	0.01 (0.01, 0.02)	0.00 (-0.01, 0.01)
Medically-attended Fever[a]							
Dose 1, Days 0-3	7,500	14	0.19 (0.11, 0.30)	7,500	14	0.19 (0.11, 0.30)	0.00 (-0.14, 0.14)
Dose 2, Days 0-3	7,500	25	0.33 (0.22, 0.48)	7,500	15	0.20 (0.11, 0.33)	0.13 (-0.03, 0.30)
Dose 3, Days 0-3	7,500	21	0.28 (0.17, 0.43)	7,500	19	0.25 (0.15, 0.39)	0.03 (-0.14, 0.19)
Total doses	22,500	60	0.27 (0.20, 0.34)	22,500	48	0.21 (0.16, 0.28)	0.05 (-0.01, 0.14)

DTaP – any U.S.-licensed DTaP vaccine. Infants received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with each dose of PEDIARIX or DTaP. Other U.S.-licensed vaccines were administered according to routine practices at the study sites.
N = Number of subjects in the given cohort.
n = Number of subjects with events reported in the given cohort.
[a] Medically-attended fever defined as fever ≥100.4°F that resulted in hospitalization, an

emergency department visit, or an outpatient visit.

6.3 Postmarketing Spontaneous Reports for PEDIARIX

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for PEDIARIX since market introduction of this vaccine are listed below. This list includes serious adverse events or events that have a suspected causal connection to components of PEDIARIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders

Cyanosis.

Gastrointestinal Disorders

Diarrhea, vomiting.

General Disorders and Administration Site Conditions

Fatigue, injection site cellulitis, injection site induration, injection site itching, injection site nodule/lump, injection site reaction, injection site vesicles, injection site warmth, limb pain, limb swelling.

Immune System Disorders

Anaphylactic reaction, anaphylactoid reaction, hypersensitivity.

Infections and Infestations

Upper respiratory tract infection.

Investigations

Abnormal liver function tests.

Nervous System Disorders

Bulging fontanelle, depressed level of consciousness, encephalitis, hypotonia, hypotonic-hyporesponsive episode, lethargy, somnolence, syncope.

Psychiatric Disorders

Crying, insomnia, nervousness, restlessness, screaming, unusual crying.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, cough, dyspnea.

Skin and Subcutaneous Tissue Disorders

Angioedema, erythema, rash, urticaria.

Vascular Disorders

Pallor, petechiae.

6.4 Postmarketing Spontaneous Reports for INFANRIX and/or ENGERIX-B

Worldwide voluntary reports of adverse events received for INFANRIX and/or ENGERIX-B in children younger than 7 years of age but not already reported for PEDIARIX are listed below. This list includes serious adverse events or events that have a suspected causal connection to components of INFANRIX and/or ENGERIX-B. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic System Disorders

Idiopathic thrombocytopenic purpura,[a,b] lymphadenopathy,[a] thrombocytopenia.[a,b]

Gastrointestinal Disorders

Abdominal pain,[b] intussusception,[a,b] nausea.[b]

General Disorders and Administration Site Conditions

Asthenia,[b] malaise.[b]

Hepatobiliary Disorders

Jaundice.[b]

Immune System Disorders

Anaphylactic shock,[a] serum sickness–like disease.[b]

Musculoskeletal and Connective Tissue Disorders

Arthralgia,[b] arthritis,[b] muscular weakness,[b] myalgia.[b]

Nervous System Disorders

Encephalopathy,[a] headache,[a] meningitis,[b] neuritis,[b] neuropathy,[b] paralysis.[b]

Skin and Subcutaneous Tissue Disorders

Alopecia,[b] erythema multiforme,[b] lichen planus,[b] pruritus,[a,b] Stevens Johnson syndrome.[a]

Vascular Disorders

Vasculitis.[b]

[a] Following INFANRIX (licensed in the United States in 1997).

[b] Following ENGERIX-B (licensed in the United States in 1989).

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

Immune responses following concomitant administration of PEDIARIX, Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.), and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) were evaluated in a clinical trial *[see Clinical Studies (14.3)]*.

When PEDIARIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes and at different injection sites. PEDIARIX should not be mixed with any other vaccine in the same syringe or vial.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to PEDIARIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with PEDIARIX. It is not known whether PEDIARIX can cause fetal harm when administered to a pregnant woman or if PEDIARIX can affect reproduction capacity.

8.4 Pediatric Use

Safety and effectiveness of PEDIARIX were established in the age group 6 weeks through 6 months on the basis of clinical studies *[see Adverse Reactions (6.1), Clinical Studies (14.1, 14.2)]*. Safety and effectiveness of PEDIARIX in the age group 7 months through 6 years are supported by evidence in infants 6 weeks through 6 months of age. Safety and effectiveness of PEDIARIX in infants younger than 6 weeks of age and children 7 to 16 years of age have not been evaluated.

11 DESCRIPTION

PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] is a noninfectious, sterile vaccine for intramuscular administration. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated pertussis toxin (PT), 25 mcg of filamentous hemagglutinin (FHA), 8 mcg of pertactin (69 kiloDalton outer membrane protein), 10 mcg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The diphtheria, tetanus, and

pertussis components are the same as those in INFANRIX and KINRIX. The hepatitis B surface antigen is the same as that in ENGERIX-B.

The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium derived from bovine casein. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor present an undue risk for bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

The hepatitis B surface antigen is obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus, in synthetic medium. The surface antigen expressed in the *S. cerevisiae* cells is purified by several physiochemical steps, which include precipitation, ion exchange chromatography, and ultrafiltration.

The inactivated poliovirus component is an enhanced potency component. Each of the 3 strains of poliovirus is individually grown in VERO cells, a continuous line of monkey kidney cells, cultivated on microcarriers. Calf serum and lactalbumin hydrolysate are used during VERO cell culture and/or virus culture. Calf serum is sourced from countries the USDA has determined neither have nor present an undue risk for BSE. After clarification, each viral suspension is purified by ultrafiltration, diafiltration, and successive chromatographic steps, and inactivated with formaldehyde. The 3 purified viral strains are then pooled to form a trivalent concentrate.

Diphtheria and tetanus toxoids and pertussis antigens (inactivated PT, FHA, and pertactin) are individually adsorbed onto aluminum hydroxide. The hepatitis B component is adsorbed onto aluminum phosphate.

Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis component (inactivated PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice. Potency of the hepatitis B component is established by HBsAg ELISA. The potency of the inactivated poliovirus component is determined by using the D-antigen ELISA and by a poliovirus neutralizing cell culture assay on sera from previously immunized rats.

Each 0.5-mL dose contains aluminum salts as adjuvant (not more than 0.85 mg aluminum by

assay) and 4.5 mg of sodium chloride. Each dose also contains ≤100 mcg of residual formaldehyde and ≤100 mcg of polysorbate 80 (Tween 80). Neomycin sulfate and polymyxin B are used in the poliovirus vaccine manufacturing process and may be present in the final vaccine at ≤0.05 ng neomycin and ≤0.01 ng polymyxin B per dose. The procedures used to manufacture the HBsAg antigen result in a product that contains ≤5% yeast protein.

The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex.

PEDIARIX is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection; a level of 0.1 IU/mL is regarded as protective.[2]

Tetanus

Tetanus is an acute toxin-mediated disease caused by a potent exotoxin released by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.[3,4] A level ≥0.1 IU/mL is considered protective.[5]

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood. There is no established serological correlate of protection for pertussis.

Hepatitis B

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.[6]

Poliomyelitis

Poliovirus is an enterovirus that belongs to the picornavirus family. Three serotypes of poliovirus have been identified (Types 1, 2, and 3). Poliovirus neutralizing antibodies confer protection

against poliomyelitis disease.[7]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PEDIARIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

The efficacy of PEDIARIX is based on the immunogenicity of the individual antigens compared with licensed vaccines. Serological correlates of protection exist for the diphtheria, tetanus, hepatitis B, and poliovirus components. The efficacy of the pertussis component, which does not have a well established correlate of protection, was determined in clinical trials of INFANRIX.

14.1 Efficacy of INFANRIX

Efficacy of a 3-dose primary series of INFANRIX has been assessed in 2 clinical studies.

A double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial conducted in Italy, sponsored by the National Institutes of Health (NIH), assessed the absolute protective efficacy of INFANRIX when administered at 2, 4, and 6 months of age. The population used in the primary analysis of the efficacy of INFANRIX included 4,481 infants vaccinated with INFANRIX and 1,470 DT vaccinees. After 3 doses, the absolute protective efficacy of INFANRIX against WHO-defined typical pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76%, 89%). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was 71% (95% CI: 60%, 78%) against >7 days of any cough and 73% (95% CI: 63%, 80%) against ≥14 days of any cough. A longer unblinded follow-up period showed that after 3 doses and with no booster dose in the second year of life, the efficacy of INFANRIX against WHO-defined pertussis was 86% (95% CI: 79%, 91%) among children followed to 6 years of age. For details see INFANRIX prescribing information.

A prospective efficacy trial was also conducted in Germany employing a household contact study design. In this study, the protective efficacy of INFANRIX administered to infants at 3, 4, and 5 months of age, against WHO-defined pertussis was 89% (95% CI: 77%, 95%). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against ≥7 days of any cough was 67% (95% CI: 52%, 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68%, 89%). For details see INFANRIX prescribing information.

14.2 Immunological Evaluation of PEDIARIX

In a U.S. multicenter study, infants were randomized to 1 of 3 groups: (1) a combination vaccine

group that received PEDIARIX concomitantly with Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.) and U.S.-licensed 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.); (2) a separate vaccine group that received U.S.-licensed INFANRIX, ENGERIX-B, and IPV (Sanofi Pasteur SA) concomitantly with the same Hib and pneumococcal conjugate vaccines; and (3) a staggered vaccine group that received PEDIARIX concomitantly with the same Hib conjugate vaccine but with the same pneumococcal conjugate vaccine administered 2 weeks later. The schedule of administration was 2, 4, and 6 months of age. Infants either did not receive a dose of hepatitis B vaccine prior to enrollment or were permitted to receive one dose of hepatitis B vaccine administered at least 30 days prior to enrollment. For the separate vaccine group, ENGERIX-B was not administered at 4 months of age to subjects who received a dose of hepatitis B vaccine prior to enrollment. Among subjects in all 3 vaccine groups combined, 84% were white, 7% were Hispanic, 6% were black, 0.7% were Oriental, and 2.4% were of other racial/ethnic groups.

The immune responses to the pertussis (PT, FHA, and pertactin), diphtheria, tetanus, poliovirus, and hepatitis B antigens were evaluated in sera obtained one month (range: 20 to 60 days) after the third dose of PEDIARIX or INFANRIX. Geometric mean antibody concentrations (GMCs) adjusted for pre-vaccination values for PT, FHA, and pertactin and the seroprotection rates for diphtheria, tetanus, and the polioviruses among subjects who received PEDIARIX in the combination vaccine group were shown to be non-inferior to those achieved following separately administered vaccines (Table 3).

Because of differences in the hepatitis B vaccination schedule among subjects in the study, no clinical limit for non-inferiority was pre-defined for the hepatitis B immune response. However, in a previous U.S. study, non-inferiority of PEDIARIX relative to separately administered INFANRIX, ENGERIX-B, and an oral poliovirus vaccine, with respect to the hepatitis B immune response was demonstrated.

Table 3. Antibody Responses following PEDIARIX as Compared with Separate Concomitant Administration of INFANRIX, ENGERIX-B, and IPV (One Month[a] after Administration of Dose 3) in Infants Vaccinated at 2, 4, and 6 Months of Age When Administered Concomitantly with Hib Conjugate Vaccine and Pneumococcal Conjugate Vaccine (PCV7)

	PEDIARIX, Hib Vaccine, & PCV7	INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7
	(N = 154-168)	**(N = 141-155)**
Anti-diphtheria Toxoid % ≥0.1 IU/mL[b]	99.4	98.7
Anti-tetanus Toxoid % ≥0.1 IU/mL[b]	100	98.1
Anti-PT % VR[c] GMC[b]	98.7 48.1	95.1 28.6
Anti-FHA % VR[c] GMC[b]	98.7 111.9	96.5 97.6
Anti-pertactin % VR[c] GMC[b]	91.7 95.3	95.1 80.6
Anti-polio 1 % ≥1:8[b,d]	100	100
Anti-polio 2 % ≥1:8[b,d]	100	100
Anti-polio 3 % ≥1:8[b,d]	100	100
	(N = 114-128)	**(N = 111-121)**
Anti-HBsAg[e] % ≥10 mIU/mL[f] GMC (mIU/mL)[f]	97.7 1032.1	99.2 614.5

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Assay methods used: ELISA for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-pertactin, and anti-HBsAg; micro-neutralization for anti-polio (1, 2, and 3).

VR = Vaccine response: In initially seronegative infants, appearance of antibodies (concentration ≥5 EL.U./mL); in initially seropositive infants, at least maintenance of pre-vaccination concentration.

GMC = Geometric mean antibody concentration. GMCs are adjusted for pre-vaccination levels.

[a] One month blood sampling, range: 20 to 60 days.

[b] Seroprotection rate or GMC for PEDIARIX not inferior to separately administered vaccines (upper limit of 90% CI on GMC ratio [separate vaccine group/combination vaccine group] <1.5 for anti-PT, anti-FHA, and anti-pertactin, and upper limit of 95% CI for the difference in

seroprotection rates [separate vaccine group minus combination vaccine group] <10% for diphtheria and tetanus and <5% for the 3 polioviruses). GMCs are adjusted for pre-vaccination levels.

[c] The upper limit of 95% CI for differences in vaccine response rates (separate vaccine group minus combination group) was 0.31, 1.52, and 9.46 for PT, FHA, and pertactin, respectively. No clinical limit defined for non-inferiority.

[d] Poliovirus neutralizing antibody titer.

[e] Subjects who received a previous dose of hepatitis B vaccine were excluded from the analysis of hepatitis B seroprotection rates and GMCs presented in the table.

[f] No clinical limit defined for non-inferiority.

14.3 Concomitant Vaccine Administration

In a U.S. multicenter study *[see Clinical Studies (14.2)]*, there was no evidence for interference with the immune responses to PEDIARIX when administered concomitantly with 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) relative to 2 weeks prior.

Anti-PRP (Hib polyribosyl-ribitol-phosphate) seroprotection rates and GMCs of pneumococcal antibodies one month (range: 20 to 60 days) after the third dose of vaccines for the combination vaccine group and the separate vaccine group from the U.S. multicenter study *[see Clinical Studies (14.2)]*, are presented in Table 4.

Table 4. Anti-PRP Seroprotection Rates and GMCs (mcg/mL) of Pneumococcal Antibodies One Month[a] following the Third Dose of Hib Conjugate Vaccine and Pneumococcal Conjugate Vaccine (PCV7) Administered Concomitantly with PEDIARIX or with INFANRIX, ENGERIX-B, and IPV

	PEDIARIX, Hib Vaccine, & PCV7	INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7
	(N = 161-168)	(N = 146-156)
	% (95% CI)	% (95% CI)
Anti-PRP ≥0.15 mcg/mL	100 (97.8, 100)	99.4 (96.5, 100)
Anti-PRP ≥1.0 mcg/mL	95.8 (91.6, 98.3)	91.0 (85.3, 95.0)
	GMC (95% CI)	GMC (95% CI)
Pneumococcal Serotype		
4	1.7 (1.5, 2.0)	2.1 (1.8, 2.4)
6B	0.8 (0.7, 1.0)	0.7 (0.5, 0.9)
9V	1.6 (1.4, 1.8)	1.6 (1.4, 1.9)
14	4.7 (4.0, 5.4)	6.3 (5.4, 7.4)
18C	2.6 (2.3, 3.0)	3.0 (2.5, 3.5)
19F	1.1 (1.0, 1.3)	1.1 (0.9, 1.2)
23F	1.5 (1.2, 1.8)	1.8 (1.5, 2.3)

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Assay method used: ELISA for anti-PRP and 7 pneumococcal serotypes.

GMC = Geometric mean antibody concentration.

[a] One month blood sampling, range: 20 to 60 days.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

PEDIARIX is available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes (packaged without needles):

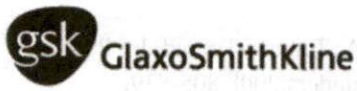
NDC 58160-811-43 Syringe in Package of 10: NDC 58160-811-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

The parent or guardian should be:

- informed of the potential benefits and risks of immunization with PEDIARIX, and of the importance of completing the immunization series.
- informed about the potential for adverse reactions that have been temporally associated with administration of PEDIARIX or other vaccines containing similar components.
- instructed to report any adverse events to their healthcare provider.
- given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/nip).



Manufactured by **GlaxoSmithKline Biologicals**

Rixensart, Belgium, U.S. License 1617, and

GSK Vaccines GmbH

Marburg, Germany, U.S. License 1617

Distributed by **GlaxoSmithKline**

Research Triangle Park, NC 27709

PDX:24PI

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

INFORMED CONSENT ACTION NETWORK,

Plaintiff,

-against-

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES

Defendant.

STIPULATION

18-cv-03215 (JMF)

WHEREAS, 42 U.S.C. § 300aa-27, entitled "Mandate for safer childhood vaccines," provides as follows:

> (a) General rule
>
> In the administration of this part and other pertinent laws under the jurisdiction of the Secretary [of the Department of Health and Human Services], the Secretary shall—
>
> > (1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on December 22, 1987, and promote the refinement of such vaccines, and
> >
> > (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.
>
> . . .
>
> (c) Report
>
> Within 2 years after December 22, 1987, and periodically thereafter, the Secretary shall prepare and transmit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the

> actions taken pursuant to subsection (a) of this section during the preceding 2-year period.

WHEREAS, on August 25, 2017, Informed Consent Action Network ("ICAN") submitted a Freedom of Information Act request (the "FOIA Request") to the Department of Health and Human Services ("HHS" or the "Department"), which was assigned control number 2017-01119-FOIA-OS, that sought the following records:

> **Any and all reports transmitted to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate by the Secretary of HHS pursuant to 42 U.S.C. §300aa-27(c).**

WHEREAS, on April 12, 2018, ICAN filed a Complaint for Declaratory and Injunctive Relief in the United States District Court, Southern District of New York against HHS seeking records, if any, responsive to the FOIA Request;

WHEREAS, the HHS Immediate Office of the Secretary ("IOS") maintains the official correspondence file of the Secretary of HHS, including reports to Congress by the Secretary of HHS, and therefore those files were most likely to contain records responsive to the FOIA Request;

WHEREAS, on June 27, 2018, HHS sent ICAN the following response to the FOIA Request:

> The [Department]'s searches for records did not locate any records responsive to your request. The Department of Health and Human Services (HHS) Immediate Office of the Secretary (IOS) conducted a thorough search of its document tracking systems. The Department also conducted a comprehensive review of all relevant indexes of HHS Secretarial Correspondence records maintained at Federal Records Centers that remain in the custody of HHS. These searches did not locate records responsive to your request, or indications that records responsive to your request and in the custody of HHS are located at Federal Records Centers.

WHEREAS, ICAN believes the foregoing response from HHS now resolves all claims asserted in this action;

IT IS HEREBY STIPULATED AND AGREED, by and between the parties by and through their respective counsel:

1. That the above-captioned action is voluntarily dismissed, with prejudice, pursuant to Federal Rule of Civil Procedure 41(a)(1)(A)(ii), each side to bear its own costs, attorney fees, and expenses; and

2. That this stipulation may be signed in counterparts, and that electronic (PDF) signatures may be deemed originals for all purposes.

Dated: July 6, 2018
New York, New York

KENNEDY & MODONNA LLP
Attorney for Plaintiff

By: _____
Robert F. Kennedy, Jr.
48 Dewitt Mills Road
Hurley, NY 12443
(845) 481-2622

Dated: July 6, 2018
New York, New York

GEOFFREY S. BERMAN
United States Attorney
Attorney for Defendant

By: _____
ANTHONY J. SUN
Assistant United States Attorney
86 Chambers Street, Third Floor
New York, New York 10007
(212) 637-2810
anthony.sun@usdoj.gov

SO ORDERED:

_____
HON. JESSE M. FURMAN, U.S.D.J.

Dated: New York, New York
July 6, 2018

Any pending motions are moot. All conferences are vacated. The Clerk of Court is directed to close the case.

ICAN

Informed Consent Action Network

For Immediate Release: July 13, 2018

US District Court Judge signs order granting Plaintiff, Informed Consent Action Network (ICAN) and counsel, Robert F. Kennedy, Jr., the relief sought in a lawsuit against the US Department of Health and Human Services (HHS)

On Monday, June 9th, the United States District Court for the Southern District of New York signed an order granting Plaintiff, the nonprofit Informed Consent Action Network (ICAN), the relief it sought against the Defendant, the United States Department of Health and Human Services, HHS. ICAN was represented by Robert F. Kennedy, Jr.

In May 2017, ICAN Founder, Del Bigtree, Robert F. Kennedy, Jr.. and a handful of other individuals concerned about vaccine safety were selected by the White House to participate in a seminal meeting with the Counselor to the Secretary of HHS, the heads of the National Institute of Health, NIH, the Center for Disease Control, CDC, and Food and the Drug Administration, FDA. Del Bigtree and Robert F. Kennedy, Jr. suspected that HHS was not fulfilling its critical vaccine safety obligations as required by Congress in The National Childhood Vaccine Injury Act of 1986.

The 1986 Act granted unprecedented, economic immunity to pharmaceutical companies for injuries caused by their products and eviscerated economic incentive for them to manufacture safe vaccine products or improve the safety of existing vaccine products. Congress therefore charged the Secretary of HHS with the explicit responsibility to assure vaccine safety.

Hence, since 1986, HHS has had the primary and virtually sole responsibility to make and assure improvements in the licensing, manufacturing, adverse reaction reporting, research, safety and efficacy testing of vaccines in order to reduce the risk of adverse vaccine reactions. In order to assure HHS meets its vaccine safety obligations, Congress required as part of the 1986 Act that the Secretary of HHS submit a biennial reports to Congress detailing the improvements in vaccine safety made by HHS in the preceding two years.

ICAN therefore filed a Freedom of Information Act, FOIA, request on August 25th, 2017 to HHS seeking copies of the biennial reports that HHS was supposed to submit to Congress, starting in 1988, detailing the improvements it made every two years to vaccine safety. HHS stonewalled ICAN for eight months refusing to provide any substantive response to this request.

ICAN
Informed Consent Action Network

ICAN was therefore forced to file a lawsuit to force HHS to either provide copies of its biennial vaccine safety reports to Congress or admit it never filed these reports. The result of the lawsuit is that HHS had to finally and shockingly admit that it never, not even once, submitted a single biennial report to Congress detailing the improvements in vaccine safety. This speaks volumes to the seriousness by which vaccine safety is treated at HHS and heightens the concern that HHS doesn't have a clue as to the actual safety profile of the now 29 doses, and growing, of vaccines given by one year of age.

In contrast, HHS takes the other portions of the 1986 Act, which require promoting vaccine uptake, very seriously, spending billions annually and generating a steady stream of reports on how to improve vaccine uptake. Regrettably, HHS has chosen to focus on its obligation to increase vaccine uptake and defend against any claim vaccines cause harm in the National Injury Vaccine Compensation Program (aka, the Vaccine Court) to such a degree that it has abandoned its vaccine safety responsibilities. If HHS is not, as confirmed in Court this week, even fulfilling the simple task of filing a biennial report on vaccine safety improvements, there is little hope that HHS is actually tackling the much harder job of actually improving vaccine safety.

For additional information or interviews please contact:
Catharine Layton, COO, ICAN
cat@icandecide.org (512) 522-8739

CDC CONTRAINDICATIONS

- Anaphylaxis
  (life-threatening allergy)
- Encephalopathy
  (coma, reduced consciousness)
- Anaphylactic allergy to egg/yeast
- Severe immunodeficiency
  (ex. cancer, organ transplant)
- Intussusception
  (only for Rotavirus vaccine)

IMMUNITY EDUCATION group.org

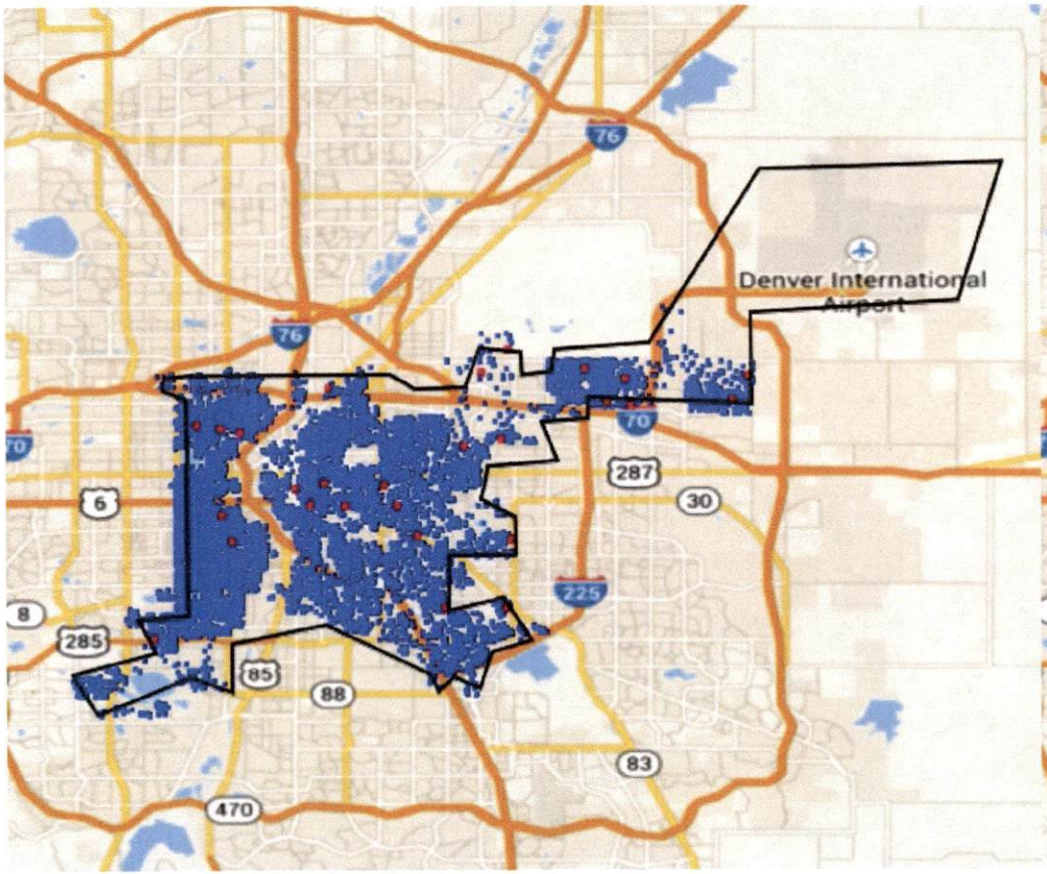
VACCINE REACTIONS (according to FDA package inserts) NOT INCLUDED in CDC CONTRAINDICATIONS

- Encephalitis
- Guillain-Barré syndrome
- Seizures
- Brachial neuritis
- Fever over 105 degrees
- Stevens-Johnson syndrome
- Stroke
- Hypotonic, unresponsive episodes
- Severe nerve dysfunction
- Vasculitis (blood vessel inflammation)
- Spinal cord paralysis
- Coma
- Pulmonary Embolism
- Systemic Lupus Erythematosus
- Severe nerve paralysis
- Moderate to severe allergic reactions
- Angioneurotic edema
- Limb paralysis
- Apnea
- Cyanosis
- Swollen lymph nodes
- Cellulitis
- Hypotonia
- Spinal cord inflammation
- Pneumonia
- Thrombocytopenia purpura
- Worsening of multiple sclerosis symptoms
- Rapid heart rate or palpitations
- Wheezing or asthma attacks
- Eczema
- Hair loss
- Vasovagal syncopy
- Vertigo
- Chronic tinnitus
- Facial nerve paralysis
- Inflammatory bowel disease
- Inflammation of the pancreas
- Permanent arthritis
- Acute disseminated encephalomyelitis (brain and spinal cord inflammation)
- Optic nerve inflammation
- Kawasaki disease
- Multiple nerve inflammation and dysfunction
- Onset of multiple sclerosis
- Henoch-Schönlein purpura (a very severe immune reaction that involves the skin and kidneys)
- Bloody stools
- Panniculitis
- Nerve deafness in the ear
- Severe eye inflammation that can permanently affect vision
- Abscess at the injection site
- Testicular pain and swelling
- Subacute sclerosing panencephalitis
- Ataxia (balance problems with difficulty walking)
- Pneumonitis (a severe inflammatory reaction in the lungs)
- Extensive swelling of the injected limb and nearby joints
- Bacterial skin and tissue infections
- Difficulty swallowing
- Tremors
- Autoimmune arthritis
- Thyroiditis
- Blood clots in the limbs

***All above adverse reactions are listed on FDA Vaccine Package Inserts for Childhood Vaccines on the CDC Recommended Schedule including:** *Hep B, Hib, PCV, Rotavirus, DTaP, Polio, Flu, MMR, VZ, Hep A, Meningococcal, HPV.* Source: https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm

HB-19-1312
SB-07-097
Justin Kerr

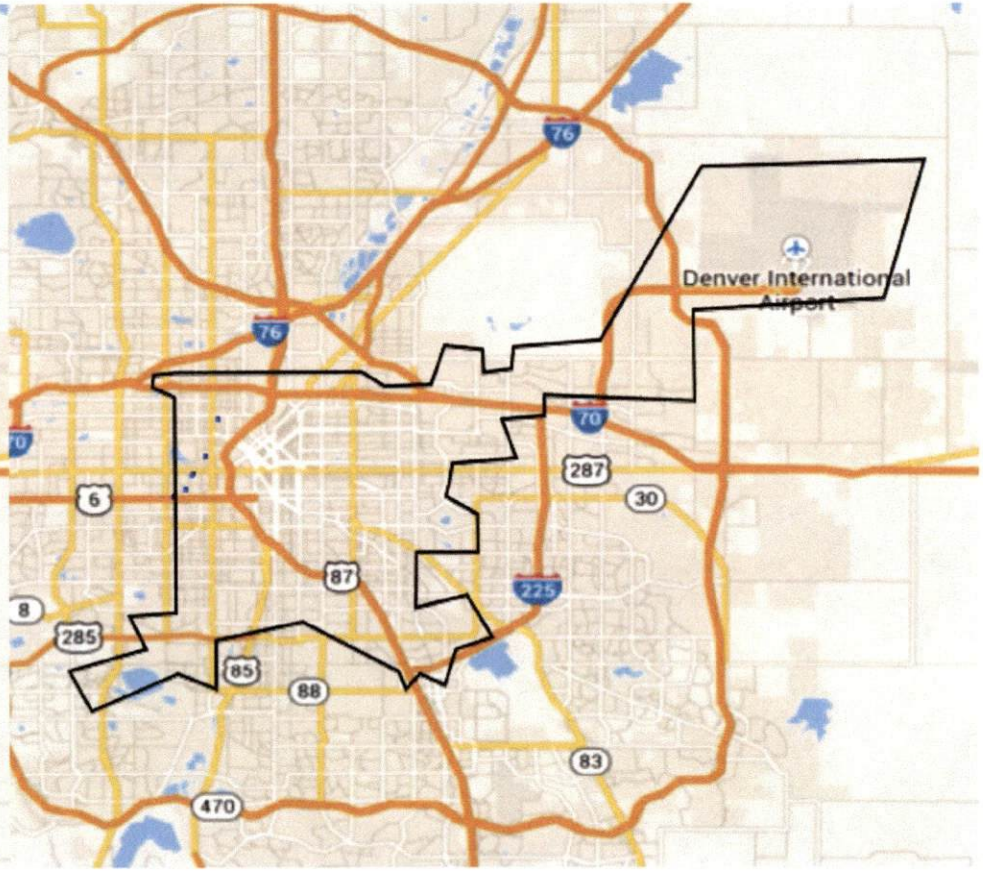
Measles in Denver County, CO
Coverage = 80%
Day 238



Red Dot = Infectious Case

Blue Dot = Recovered Case

Measles in Denver County, CO
Coverage = 95%
Day 238



Red Dot = Infectious Case

Blue Dot = Recovered Case

Appendix

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Vaccine Recommendations and Guidelines

Pam Long

ACIP Recs Home

Vaccine-Specific Recommend

Advisory Committee on Immunization Practices (ACIP)

Vaccine-Specific ACIP Recommendations

- Anthrax
- BCG
- Cholera
- DTaP/Tdap/Td
- Hepatitis A **UPDATED Feb 2019**
- Hepatitis B
- Hib
- HPV
- Influenza
- Japanese Encephalitis
- Measles, Mumps and Rubella
- MMRV
- Meningococcal
- Pneumococcal
- Polio
- Rabies
- Rotavirus
- Smallpox (Vaccinia)
- Typhoid
- Varicella (Chickenpox)
- Yellow Fever
- Zoster (Shingles)

Page last reviewed: July 16, 2013
Content source: National Center for Immunization and Respiratory Diseases

TABLE 3-1. Recommended and minimum ages and intervals between vaccine doses[a],[b],[c],[d]				
Vaccine and dose number	**Recommended age for this dose**	**Minimum age for this dose**	**Recommended interval to next dose**	**Minimum interval to next dose**
DTaP-1[e]	2 months	6 weeks	8 weeks	4 weeks
DTaP-2	4 months	10 weeks	8 weeks	4 weeks
DTaP-3	6 months	14 weeks	6-12 months[f]	6 months[f]
DTaP-4	15-18 months	15 months[f]	3 years	6 months
DTaP-5[g]	4-6 years	4 years	—	—
HepA-1[e]	12-23 months	12 months	6-18 months	6 months
HepA-2	≥18 months	18 months	—	—
HepB-1[h]	Birth	Birth	4 weeks-4 months	4 weeks
HepB-2	1-2 months	4 weeks	8 weeks-17 months	8 weeks
HepB-3[i]	6-18 months	24 weeks	—	—
Hib-1[j]	2 months	6 weeks	8 weeks	4 weeks
Hib-2	4 months	10 weeks	8 weeks	4 weeks
Hib-3[k]	6 months	14 weeks	6-9 months	8 weeks
Hib-4	12-15 months	12 months	—	—
HPV-1[l]	11-12 years	9 years	8 weeks	4 weeks
HPV-2	11-12 years (+2 months)	9 years (+4 weeks)	4 months	12 weeks[l]
HPV-3[l], [m]	11-12 years (+6 months)	9 years (+5 months)	—	—
Influenza, inactivated[n]	≥6 months	6 months[o]	4 weeks	4 weeks
IPV-1[e]	2 months	6 weeks	8 weeks	4 weeks
IPV-2	4 months	10 weeks	8 weeks-14 months	4 weeks
IPV-3	6-18 months	14 weeks	3-5 years	6 months

IPV-4[p]	4-6 years	4 years	—	—
LAIV[n]	2-49 years	2 years	4 weeks	4 weeks
MenACWY-1[q]	11-12 years	2 months [r]	4-5 years	8 weeks
MenACWY-2	16 years	11 years (+8 weeks)[s]	—	—
MenB-1	Healthy adolescents: 16-23 years	16 years	Bexsero: 4 weeks Trumenba: 6 months[c]	Bexsero: 4 weeks Trumenba: 6 months[c]
	Persons at increased risk: ≥10 years	10 years	Bexsero: 4 weeks Trumenba: 1-2 months[c]	Bexsero: 4 weeks Trumenba: 1 month
MenB-2	Healthy adolescents: 16-23 years (+1 month)	16 years (+1 month)	—	—
	Persons at increased risk: ≥10 years (+1 month)	10 years (+1 month)	Bexsero: — Trumenba: 4-5 months[c]	Bexsero: — Trumenba: 4 months[c]
MenB-3[t]	Persons at increased risk: ≥ 10 years (+ 6 months[c])	10 years (+ 6 months[c])	—	—
MMR-1[u]	12-15 months	12 months	3-5 years	4 weeks
MMR-2[u]	4-6 years	13 months	—	—
PCV13-1[j]	2 months	6 weeks	8 weeks	4 weeks
PCV13-2	4 months	10 weeks	8 weeks	4 weeks
PCV13-3	6 months	14 weeks	6 months	8 weeks
PCV13-4	12-15 months	12 months	—	—
PPSV-1	—	2 years	5 years	5 years
PPSV-2[v]	—	7 years	—	—
Rotavirus-1[w]	2 months	6 weeks	8 weeks	4 weeks

Rotavirus-2	4 months	10 weeks	8 weeks	4 weeks
Rotavirus-3[w]	6 months	14 weeks	—	—
Td	11-12 years	7 years	10 years	5 years
Tdap[x]	≥11 years	7 years	—	—
Varicella-1[u]	12-15 months	12 months	3-5 years	12 weeks[y]
Varicella-2[u]	4-6 years	15 months[z]	—	—
ZVL[aa]	≥60 years	60 years[bb]	—	—
RZV - 1	≥50 years	50 years[cc]	2-6 months	4 weeks
RZV - 2	≥50 years (+ 2-6 months)	50 years	—	—

Abbreviations: DTaP = diphtheria and tetanus toxoids and acellular pertussis; HepA = hepatitis A; HepB = hepatitis B; Hib = Haemophilus influenzae type b; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MenACWY = quadrivalent meningococcal conjugate vaccine; MenB = serogroup B meningococcal vaccine; MenB-4C = Bexsero; MenB-FHbp = Trumenba; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV13 = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; PRP-OMP = polyribosylribitol phosphate-meningococcal outer membrane protein conjugate; RZV = recombinant zoster vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; ZVL = zoster vaccine live.

[a] Combination vaccines are available. Use of licensed combination vaccines is generally preferred to separate injections of their equivalent component vaccines. When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components. The minimum interval between doses is equal to the greatest interval of any of the individual components.

[b] Information on travel vaccines, including typhoid, Japanese encephalitis, and yellow fever, is available at https://www.cdc.gov/travel. Information on other vaccines that are licensed in the United States but not distributed, including anthrax and smallpox, is available at http://emergency.cdc.gov/bioterrorism/ .

[c] "Months" refers to calendar months.

[d] Within a number range, a hyphen (-) should be read as "through."

[e] Combination vaccines containing the hepatitis B component are available (see Table 3-2). These vaccines should not be administered to infants aged <6 weeks because of the other vaccine components (i.e., Hib, DTaP, HepA, and IPV).

[f] The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3. This is a special grace period of 2 months which can be used if evaluating records retrospectively. An additional 4 days should not be added to this grace period prospectively, but can be added retrospectively.

[g] If a fourth dose of DTaP is given on or after the fourth birthday, a fifth dose is not needed

[h] Adjuvanted Hepatitis B vaccine (HepB-CgG) can be administered to adults 18 years old and older on a two dose schedule, the first and second dose separated by 4 weeks.

[i] HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1 and should not be administered before age 24 weeks.

[j] For Hib and PCV13, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series.

[k] If PRP-OMP (Pedvax-Hib, Merck Vaccine Division) was administered at ages 2 and 4 months, a dose at age 6 months is not necessary. The final dose has a minimum age of 12 months.

[l] Quadrivalent and nine-valent HPV vaccines are approved for males and females aged 9-26 years. The minimum age for HPV-3 is based on the baseline minimum age for the first dose (i.e., 9 years) and the minimum interval of 5 months between the first and third dose. Dose 3 need not be repeated if it is administered at least 5 months after the first dose and the intervals between dose 1 and dose 2, and dose 2 and dose 3, are maintained at 4 weeks and 12 weeks, respectively.

[m] A two-dose schedule of HPV vaccine is recommended for most persons beginning the series between 9 through 14 years of age. See HPV vaccine-specific recommendations for details.
www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf

[n] One dose of influenza vaccine per season is recommended for most persons. To determine which children younger than 9 years should receive 2 doses in a single season, please see influenza vaccine-specific recommendations (*81*).

[o] The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. See package insert for vaccine-specific minimum ages.

[p] A fourth dose is not needed if the third dose was administered at ≥4 years and at least 6 months after the previous dose.

[q] Revaccination with meningococcal vaccine is recommended for previously vaccinated persons who remain at high risk for meningococcal disease (*46*).

[r] MenACWY-D (Menactra) can be given as young as 9 months for high-risk persons. MenACWY-CRM (Menveo) can be given as young as 2 months for high-risk persons. Hib-MenCY can be given as young as 6 weeks for high-risk persons. Hib-MenCY is given as a 4-dose series at 2 months, 4 months, 6 months and 12-18 months.

[s] For routine non-high risk adolescent vaccination, the minimum age for the booster dose is 16 years.

[t] This dose is not necessary if Bexsero is correctly administered, or if Trumenba is correctly administered to healthy adolescents.

[u] Combination MMRV vaccine can be used for children aged 12 months-12 years. See text for details.

[v] A second dose of PPSV23 5 years after the first dose is recommended for persons aged ≤65 years at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration (*60*).

[w] The first dose of rotavirus must be administered at age 6 weeks through 14 weeks and 6 days. The vaccine series should not be started for infants aged ≥15 weeks, 0 days. Rotavirus should not be administered to children older than 8 months, 0 days of age regardless of the number of doses received between 6 weeks and 8 months, 0 days of age. If 2 doses of Rotarix (GlaxoSmithKline) are administered as age appropriate, a third dose is not necessary.

[x] Only 1 dose of Tdap is recommended. Subsequent doses should be given as Td. For management of a tetanus-prone wound in persons who have received a primary series of tetanus-toxoid–containing vaccine, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.

[y] A special grace period of 2 months, based on expert opinion, can be applied to the minimum interval of 3 months, when evaluating records retrospectively, which results in an acceptable minimum interval of 4 weeks. An additional 4 days should not be added on to this grace period.

[z] A special grace period of 2 months, based on expert opinion, can be applied to the minimum age of 15 months when evaluating records retrospectively, which results in an acceptable minimum age of 13 months. An additional 4 days should not be added on to this grace period.

[aa] Zoster vaccine live is recommended as a single dose for persons aged ≥60 years.

[bba]If a dose of zoster vaccine live is administered to some one 50-59 years of age, the dose does not need to be repeated. A 4 day grace period can be added to the absolute minimum age of 50 years when evaluating records retrospectively.

[cc]If a 1st dose of recombinant zoster vaccine is administered to someone 18 – 49 years of age, the dose does not need to be repeated. A 4 day grace period can be added to the absolute minimum age of 18 years when evaluating records retrospectively.

TABLE 3-2. FDA-licensed combination vaccines[a]

Vaccine[b]	Trade name (year licensed)	Age range	Routinely recommended ages
HepA-HepB	Twinrix (2001)	≥18 years	Three doses on a schedule of 0, 1, and 6 months
DTaP-HepB-IPV	Pediarix (2002)	6 weeks-6 years	Three-dose series at 2, 4, and 6 months of age
MMRV	ProQuad (2005)	12 months-12 years	Two doses, the first at 12-15 months, the second at 4-6 years
DTaP-IPV	Kinrix (2008)	4-6 years	Fifth dose of DTaP and fourth dose of IPV
DTaP-IPV/Hib	Pentacel (2008)	6 weeks-4 years	Four-dose schedule at 2, 4, 6, and 15-18 months of age
Hib-MenCY	MenHibrix (2012)	6 weeks-18 months	Four-dose schedule at 2, 4, 6, and 12-15 months of age[c]
DTaP-IPV	Quadracel (2015)	4-6 years	Fifth dose of DTaP and fourth or fifth dose of IPV

Abbreviations: DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; FDA = Food and Drug Administration; HepA = hepatitis A; HepB = hepatitis B; Hib = Haemophilus influenzae type b; IPV = inactivated poliovirus; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

Source: (*82*).

[a] Although MMR, DTaP, DT, Td, and Tdap are combination vaccines, they are not included on this list because they are not available in the United States as single-antigen products.

[b] In descriptions of combination vaccines, dash (-) indicates products in which the active components are supplied in their final (combined) form by the manufacturer; slash (/) indicates products in which active components must be mixed by the user.

[c] Hib-MenCY can be used for routine dosing of Hib vaccine but is recommended only for meningococcal vaccination in persons at high-risk of meningococcal disease.

TABLE 3-3. Guidelines for spacing of live and inactivated antigens	
Antigen combination	**Recommended minimum interval between doses**
Two or more inactivated[a],[b]	May be administered simultaneously or at any interval between doses
Inactivated and live[c]	May be administered simultaneously or at any interval between doses
Two or more live injectable[c]	28 days minimum interval, if not administered simultaneously

Source: (*82*).

[a] Certain experts suggest a 28-day interval between tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine and tetravalent meningococcal conjugate vaccine if they are not administered simultaneously.

[b] In persons with functional or anatomic asplenia, MCV-D and PCV13 should not be administered simultaneously and should be spaced by 4 weeks. Likewise for persons with immunosuppressive high-risk conditions indicated for PCV13 and PPSV23, PCV13 should be administered first, and PPSV23 should be administered no earlier than 8 weeks later. For persons 65 years old or older indicated for PCV13 and PPSV23, PCV13 should be administered first and PPSV23 should be administered 6-12 months later.

[c] The live oral vaccines Ty21a typhoid vaccine and rotavirus vaccine may be administered simultaneously with or at any interval before or after inactivated or live injectable vaccines.

TABLE 3-4. Guidelines for administering antibody-containing products[a] and vaccines			
Type of administration	**Products administered**		**Recommended minimum interval between doses**
Simultaneous (during the same clinic day)	Antibody-containing products and inactivated antigen		Can be administered simultaneously at different anatomic sites or at any time interval between doses
	Antibody-containing products and live antigen		Should not be administered simultaneously.[b] If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval (see Table 3-5)
Nonsimultaneous	**Administered first**	**Administered second**	
	Antibody-containing products	Inactivated antigen	No interval necessary
	Inactivated antigen	Antibody-containing products	No interval necessary
	Antibody-containing products	measles, mumps, rubella vaccine, varicella vaccine, and combined measles, mumps, rubella, varicella vaccine antigens	Dose related[b],[c]

	MMR vaccine, varicella vaccine, and combined measles, mumps, rubella, varicella vaccine antigens	Antibody-containing products	2 weeks[b]

[a] Blood products containing substantial amounts of immune globulin include intramuscular, subcutaneous, and intravenous immune globulin, specific hyperimmune globulin (e.g., hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, and rabies immune globulin), whole blood, packed red blood cells, plasma, and platelet products.

[b] Yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; live, attenuated influenza vaccine; and zoster vaccine are exceptions to these recommendations. These live, attenuated vaccines can be administered at any time before or after or simultaneously with an antibody-containing product.

[c] The duration of interference of antibody-containing products with the immune response to the measles component of measles-containing vaccine, and possibly varicella vaccine, is dose related (see Table 3-5).

Please vote "YES" on HB 1213!

(Modernization of Immunization Requirements to Improve Vaccination Rates)

James K. Todd, MD 10 April 2019

1. **Vaccines have been shown to be safe and highly effective in Colorado, saving tens of thousands of hospitalizations and hundreds of millions of dollars annually.[1] [2]**

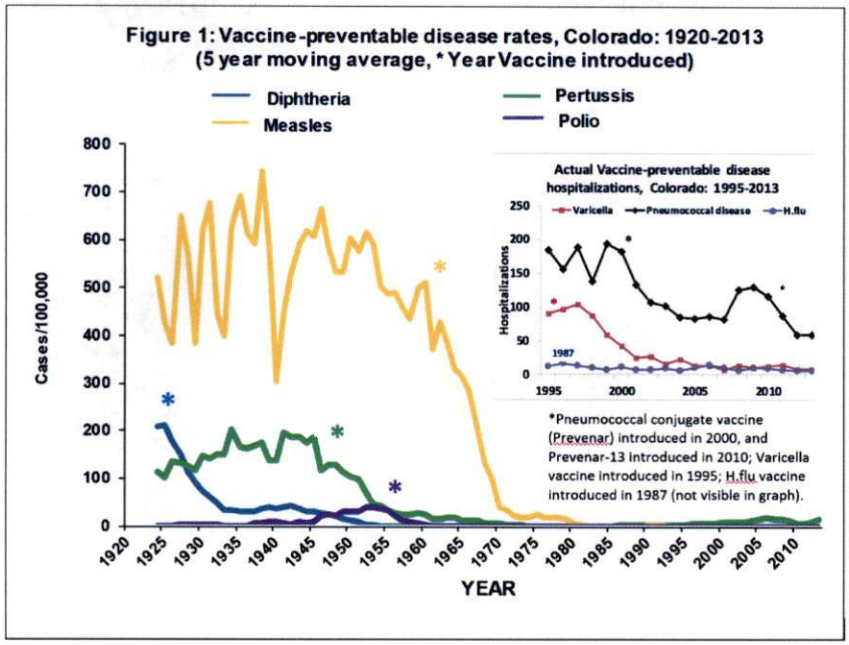


Table 2: Hospital cases and charges prevented among Colorado children due to vaccination, 2014

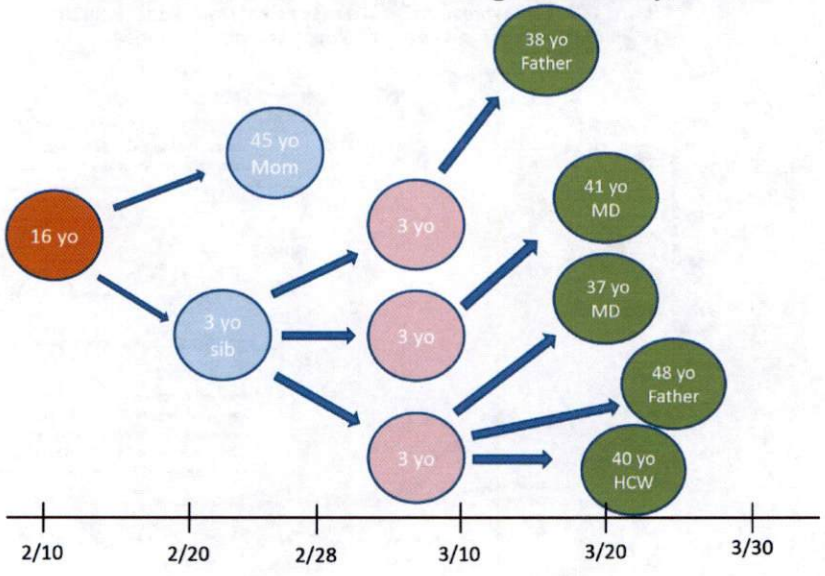
Disease	Index years[a]	Statewide pre-vaccination rate per 100,000[b]	Statewide rate per 100,000 2014[b]	Statewide reportable cases prevented: 2014[c]	Actual hospitalized cases: 2014[d]	Estimated hospitalized cases prevented: 2014[e]	Estimated hospital charges prevented: 2014[f]
Diphtheria	1920-1922	461	0.0	6,471	0	1,760	$75,359,651
H. influenzae	1984-1986	12.4	1.0	173	1	47	$2,051,743
Measles	1960-1962	784	0.0	11,004	2	2,993	$128,153,488
Mumps	1964-1966	408	0.0	5,736	0	1,560	$66,800,189
Pertussis	1945-1947	328	66.4	4,577	35	1,245	$68,223,045
Pneumococcal disease	1997-1999	14.8	2.6	159	48	148	$21,045,008
Polio	1952-1954	68	0.0	948	0	258	$11,040,083
Rubella	1966-1968	124	0.0	1,743	0	474	$20,301,335
Tetanus	1927-1929	1.1	0.0	15	0	4	$174,691
Varicella	1995-1997	8.7	22.6	113	9	114	$7,289,274
Total		**2,210**	**92.6**	**30,939**	**95**	**8,603**	**$400,438,507**

[1] https://www.childrenscolorado.org/globalassets/healthcare-professionals/vaccine-preventable-disease-2014.pdf

[2] https://www.childrenscolorado.org/globalassets/healthcare-professionals/vaccine-preventable-disease-2015.pdf

2. **Unvaccinated individuals put many others at risk at great cost to the community[3]**
   a. **Sick, unvaccinated individuals are highly contagious.**
   b. **Vaccinated individuals may still be at risk if heavily exposed.**
   c. **Immune compromised individuals are at special risk.**
   d. **Individual decisions impose public health costs on the community (tax payers).**

Measles Cluster 1, Orange County, 2014



Healthcare Workers with Measles Clinical and Epidemiologic Features, 2014

Age (y)	Measles Immunity Prior to Exposure	Exposure	Illness Onset	Fever	Cough	Coryza	Rash	Days Considered infectious while asymptomatic	Days working during active symptoms	Number of patients exposed
32	IgG+	3/3/2014	3/17/2014	Y	Y	N	3/18/14	3	0	0
36	IgG+	3/3/2014	3/14/2014	Y	N	N	3/18/14	0	4	850
41	2 MMR	3/7/2014	3/18/2014	Y	N	N	3/20/14	2	2	26
37	4 MMR IgG+	3/7/2014	3/16/2014	N	Y	N	3/20/14	0	4	72
40	Unknown vaccine history, IgG equivocal	3/7/2014	3/19/2014	Y	Y	Y	3/21/14	2	0	0

Cost of Washington's Measles Outbreak Tops $1 Million

The Seattle Times reports that a state health official expects that number to climb.

By **Megan Trimble**, Digital News Editor Feb. 21, 2019

[3] Matt Zahn, MD; Medical Director Epidemiology and Assessment, Orange County Health Care Agency

DAVID COLE
970.214.7814
REPRESENTING: MYSELF

ACIP

Conflicts of Interest

Presented to the Health and Insurance Committee

4/15/2019

i. Written Statement

1) "Conflicts of Interest and Vaccine Development" Hearing before the Committee on Government Reform, June 15th 2000, pp.7-10
2) "Advisors on Vaccines Often Have Conflicts, Report Says" New York Times, Dec 17th 2009
3) "CDC's Ethics Program..." Office of Inspector General, HHS, Dec 17th 2009, pp.i-iii
4) Krahling and Wlochowski V. Merck & Co., filed 2012, case active 7 years
5) "Candidate to Lead FDA Has Close Ties to Big Pharma," Time, Feb 19th 2015
6) CDC Director quits over financial conflicts, NPR, Jan 31st 2018

i. Written Statement

Thank you, members of the committee for this opportunity to speak.

I am in firm opposition to HB 1312.

This Bill forces our State Board of Health to blindly enforce recommendations by ACIP (Advisory Committee on Immunization Practices), it behooves the committee to take a very close look at ACIP.

Submitted for your review are Six references spanning 18 years. In Ref. 1, a Hearing before the Committee on Government reform; to quote from Committee Chair Dan Burton:

> *"Families need to have confidence that the vaccines... their children take are safe, effective and very necessary... Has that trust been violated? How confident... would doctors and parents be if they learned the following:*
>
> *One, that members, including the chair of the FDA and CDC advisory committees... own stock in drug companies that make the vaccines.*
>
> *Two, that individuals on both advisory committees own patents for vaccines under consideration...*
>
> *Three, that three out of the five of the members of the FDA's advisory committee... for the rotavirus vaccine had conflicts of interest that were waived.*
>
> *Four, that 7 individuals... were not present at the meeting. Two others were excluded from the vote, and the remaining five were joined by five temporary voting members who all voted [YES] to license the product.* [Rotashield]
>
> *Five, that the CDC grants conflict of interest waivers to every member of their advisory committee a year at a time, and allows full participation in the discussions leading up to a vote by every member, whether they have a financial stake in the decision or not. So they're discussing it, influencing other members possibly, whether they have a financial stake or not.*
>
> *Sixth, that [ACIP] has no public members, no parents have a vote in whether or not a vaccine belongs on the childhood immunization schedule. The FDA's committee only has one public member.*
>
> *These are just a few of the problems we found."*

I implore the Committee to abandon party lines and responsibly OPPOSE this Bill. Thank you.

[House Hearing, 106 Congress]
[From the U.S. Government Printing Office]

FACA: CONFLICTS OF INTEREST AND VACCINE DEVELOPMENT--PRESERVING THE INTEGRITY OF THE PROCESS

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HEARING

before the

COMMITTEE ON
GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

SECOND SESSION

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COMMITTEE ON GOVERNMENT REFORM

DAN BURTON, Indiana, Chairman

two important advisory committees. The Food and Drug Administration and the Centers for Disease Control and Prevention rely on these advisory committees to help them make vaccine policies that affect every child in America. We've looked very carefully at conflicts of interest. We've taken a good, hard look at whether the pharmaceutical industry has too much influence over these committees.

From the evidence we've found, we believe that they do. The first committee is the Food and Drug Administration's Vaccine and Related Biological Products Advisory Committee. This committee makes recommendations on whether new vaccines should be licensed.

The second committee is the CDC's Advisory Committee on Immunization Practices. This committee recommends which vaccines should be included in the childhood immunization schedule.

To make these issues easier to understand, we're going to focus on one issue handled by these two committees, the rotavirus vaccine. There are other vaccines that we may get into later, but today we're going to use this as the primary example.

It was approved for use by the FDA in August 1998. It was recommended for universal use by the CDC in March 1999. Serious problems cropped shortly after it was introduced. Children started developing serious bowel obstructions. The vaccine was pulled from the U.S. market in October 1999.

So the question is, was there evidence to indicate that the vaccine was not safe, and if so, why was it licensed in the first place? How good a job did the advisory committees do?

We reviewed the minutes of the meetings. At the FDA's committee, there were discussions about adverse events. They were aware of potential problems. Five children out of 10,000 developed bowel obstructions. There were also concerns about children failing to thrive and developing high fevers, which as we know from other vaccine hearings, can lead to brain injury. Even with all of these concerns, the committee voted unanimously to approve it.

At the CDC's committee, there was a lot of discussion about whether the benefits of the vaccine really justified the cost. Even though the cost benefit ratio was questioned, the committee voted unanimously to approve it.

Were they vigilant enough? Were they influenced by the pharmaceutical industry? Was there appropriate balance of expertise and perspective on vaccine issues?

We've been reviewing their financial disclosure statements. We've interviewed staff from the FDA and the CDC. The staff has prepared a staff report summarizing what we found. At the end of this statement, while I won't ask unanimous consent to enter this report in the record today, I've already agreed not to do that, we've identified a number of problems that need to be brought to light, and we will be discussing those.

Families need to have confidence that the vaccines that their children take are safe, effective and very necessary. Doctors need to feel confident that when the FDA licenses a drug, that it's really safe and that the pharmaceutical industry has not influenced the decisionmaking process. Doctors place trust in the FDA and assume that if the FDA has licensed

a drug, it's safe for use.

Has that trust been violated? How confident in the safety and need of specific vaccines would doctors and parents be if they learned the following: One, that members, including the chair of the FDA and CDC advisory committees who make these decisions own stock in drug companies that make the vaccines. Two, that individuals on both advisory committees own patents for vaccines under consideration, or affected by the decisions of the committees.

Three, that three out of the five of the members of the FDA's advisory committee who voted for the rotavirus vaccine had conflicts of interest that were waived. Four, that 7 individuals of the 15 member FDA advisory committee were not present at the meeting. Two others were excluded from the vote, and the remaining five were joined by five temporary voting members who all voted to license the product.

Five, that the CDC grants conflict of interest waivers to every member of their advisory committee a year at a time, and allows full participation in the discussions leading up to a vote by every member, whether they have a financial stake in the decision or not. So they're discussing it, influencing other members possibly, whether they have a financial stake or not.

Sixth, that the CDC's advisory committee has no public members, no parents have a vote in whether or not a vaccine belongs on the childhood immunization schedule. The FDA's committee only has one public member.

These are just a few of the problems we found. Specific examples of this include Dr. John Modlin. He served for 4 years on the CDC advisory committee and became the chair in February 1998. He participated in the FDA's committee as well. He owns stock in Merck, one of the largest manufacturers of the vaccine, valued at $26,000. He also serves on Merck's immunization advisory board.

Dr. Modlin was the chairman of the rotavirus working group. He voted yes on eight different matters pertaining to the ACIP's rotavirus statement, including recommending for routine use and for inclusions in the Vaccines for Children program. It was not until this past year that Dr. Modlin decided to divest himself of his vaccine manufacturer stock.

At our April 6th autism hearing, Dr. Paul Offit disclosed that he holds a patent on a rotavirus vaccine and receives grant money from Merck to develop this vaccine. He also disclosed that he is paid by the pharmaceutical industry to travel around the country and teach doctors that vaccines are safe. Dr. Offit is a member of the CDC's advisory committee and voted on three rotavirus issues, including making the recommendation of adding the rotavirus vaccine to the Vaccines for Children program.

Dr. Patricia Ferrieri, during her tenure as chair of the FDA's advisory committee, owned stock in Merck valued at about $20,000 and was granted a full waiver.

Dr. Neal Halsey, who serves as a liaison member to the CDC committee on behalf of the American Association of Pediatrics, and is a consultant to the FDA's committee, has extensive ties to the pharmaceutical industry, including having solicited and received startup funds from industry for his Vaccine Center. As

a liaison member to the CDC committee, Dr. Halsey is there to represent the opinions of the organizations he represents, but was found in the transcripts to be offering his personal opinion.

Dr. Harry Greenberg, who serves as chair of the FDA committee, owns $120,000 of stock in Aviron, a vaccine manufacturer. He also is a paid member of the board of advisors of Chiron, another vaccine manufacturer, and owns $40,000 of stock. This stock ownership was deemed not to be a conflict, and a waiver was granted. To the FDA's credit, he was excluded from the rotavirus discussion, because he holds the patent on the Rotashield vaccine.

How confident can we be in the process when we learned that most of the work of the CDC advisory committee is done in ``working groups'' that meet behind closed doors, out of the public eye? Members who can't vote in the full committee because of conflicts of interest are allowed to work on the same issues in working groups, and there is no public scrutiny. I was appalled to learn that at least 6 of the 10 individuals who participated in the working group for the rotavirus vaccine had financial ties to pharmaceutical companies developing rotavirus vaccines.

How confident can we be in the recommendations for the Food and Drug Administration when the chairman and other individuals on their advisory committee own stock in major manufacturers of vaccines?

How confident can we be in a system when the agency seems to feel that the number of experts is so few around the country that everyone has a conflict and thus waivers must be granted? It almost appears that there is an ``old boys network'' of vaccine advisors that rotate between the CDC and FDA, at times serving simultaneously. Some of these individuals served for more than 4 years. We found one instance where an individual served for 16 years continuously on the CDC committee. With over 700,000 physicians in this country, how can one person be so indispensable that they stay on a committee for 16 years?

It's important to determine if the Department of Health and Human Services has become complacent in their implementation of the legal requirements on conflicts of interest and committee management. If the law is too loose, we need to change it. if the agencies aren't doing their job, they need to be held accountable. That's the purpose of this hearing, to try to determine what needs to be done.

Why is this review necessary? Vaccines are the only substances that a government mandates a U.S. citizen receive. State governments have the authority to mandate vaccines be given to children prior to admission to day care centers and schools. State governments rely on the recommendations of the CDC and the FDA to determine the type and schedule of vaccines.

I am not alone in my concern about the increasing influence of industry on medicine. Last year, the New England Journal of Medicine learned that 18 individuals who wrote drug therapy review articles had financial ties to the manufacturer of the drugs they were discussing. The Journal, which has the most stringent conflict of interest disclosures of medical journals, had a recent editorial discussing the increasing level of academic research funded by the industry. The editor stated,

``What is at issue is not whether researchers can be `bought' in the sense of a quid pro quo, is that close and remunerative collaboration with a company naturally creates goodwill on the part of the researchers and the hope that the largesse will continue. This attitude can subtly influence scientific judgment.''

Can the FDA and the CDC really believe that scientists are more immune to self-interest than anybody else?

Maintaining the highest level of integrity over the entire spectrum of vaccine development and implementation is essential. The American people have to have trust in the system. The Department of Health and Human Services has a responsibility to the American public to ensure the integrity of this process by working diligently to appoint individuals that are totally without financial ties to the vaccine industry to serve on these and all vaccine-related panels.

No individual who stands to gain financially from the decisions regarding vaccines that may be mandated for use should be participating in the discussion or policymaking for vaccines. We have repeatedly heard in our hearings that vaccines are safe and needed to be protecting the public. If the panels that have made the decisions on all vaccines on the childhood immunization schedule had as many conflicts as we have found with rotavirus, then the entire process has been polluted and the public trust has been violated. I intend to find out if the individuals who have made these recommendations that affect every child in this country and around the world stood to gain financially and professionally from the decisions of the committees on which they served.

The hearing record will remain open until June 28th for those who would like to submit a statement for the record.

I now recognize the ranking minority member, Mr. Waxman, for his opening statement.

[The prepared statement of Hon. Dan Burton follows:]

[GRAPHIC] [TIFF OMITTED] T3042.001

[GRAPHIC] [TIFF OMITTED] T3042.002

[GRAPHIC] [TIFF OMITTED] T3042.003

[GRAPHIC] [TIFF OMITTED] T3042.004

[GRAPHIC] [TIFF OMITTED] T3042.005

[GRAPHIC] [TIFF OMITTED] T3042.006

Mr. Waxman. Thank you very much, Mr. Chairman.

This hearing is about conflicts of interest and vaccine decisionmaking. This is an issue I take very seriously. I have probably done more than any other member of this committee to identify and oppose genuine conflicts of interest in Federal decisionmaking.

In 1991, I held a hearing on conflicts of interest in Vice President Quayle's Council on Competitiveness. These hearings revealed that the executive director of the council owned 50 percent of a chemical plant subject to regulation under the Clean Air Act at the same time that he was chairing biweekly

Advisers on Vaccines Often Have Conflicts, Report Says

By GARDINER HARRIS

Published: December 17, 2009

WASHINGTON — A new report finds that the Centers for Disease Control and Prevention did a poor job of screening medical experts for financial conflicts when it hired them to advise the agency on vaccine safety, officials said Thursday.

Most of the experts who served on advisory panels in 2007 to evaluate vaccines for flu and cervical cancer had potential conflicts that were never resolved, the report said. Some were legally barred from considering the issues but did so anyway.

Related

Document: CDC's Ethics Program for Special Government Employees on Federal Advisory Committees (pdf)

In the report, expected to be released Friday, Daniel R. Levinson, the inspector general of the Department of Health and Human Services, found that the centers failed nearly every time to ensure that the experts adequately filled out forms confirming they were not being paid by companies with an interest in their decisions.

The report found that 64 percent of the advisers had potential conflicts of interest that were never identified or were left unresolved by the centers. Thirteen percent failed to have an appropriate conflicts form on file at the agency at all, which should have barred their participation in the meetings entirely, Mr. Levinson found. And 3 percent voted on matters that ethics officers had already barred them from considering.

The inspector general recommended that the centers do a far better job of screening. In a reply, the agency's new director, Dr. Thomas R. Frieden, agreed.

"Since the period covered in this review, C.D.C. has strengthened the financial disclosures and conflict-of-interest process by instituting improved business processes and realigning responsibilities and oversight," Dr. Frieden wrote.

As numerous medicines have been pulled from the market in recent years, worries have grown that experts may be recommending medical products — even ones they know to be unsafe — in part because manufacturers are paying them.

As a result, government agencies, medical societies and medical journals have become increasingly insistent that experts disclose potential conflicts. And while the experts invariably insist that they have done so, government audits routinely find large gaps between these disclosures and the experts' actual income from consulting.

Congress tightened the rules on outside consulting after similar conflicts were found among members of advisory panels to the Food and Drug Administration. But little attention has been paid to the potential conflicts of advisers to the C.D.C., even though that agency's committees have significant influence over what vaccines are sold in the United States, what tests are performed to detect cancer and how coal miners are protected.

Most of the advisers identified by Mr. Levinson had either a job or a grant from a company or other entity whose interests were affected by the committees' discussions, and a considerable number also owned stock in such companies, the report said.

Representative Rosa DeLauro, a Connecticut Democrat who said she had long been a supporter of the C.D.C., said: "That is why I am so concerned about this report issued by the inspector general exposing serious ethics violations within the C.D.C. All members of the federal advisory committees, whose recommendations direct federal policy, should be without conflict of interest."

A version of this article appeared in print on December 18, 2009, on page A28 of the New York edition.

Washington, D.C. 20201

DEC 17 2009

TO: Thomas R. Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention

FROM: Daniel R. Levinson
Inspector General

SUBJECT: OIG Final Report: *CDC's Ethics Program for Special Government Employees on Federal Advisory Committees*, OEI-04-07-00260

Attached is our final report entitled *CDC's Ethics Program for Special Government Employees on Federal Advisory Committees*.

Please send us your final management decision, including any action plan, as appropriate, within 60 days. If you have any questions about this report, please do not hesitate to call me or one of your staff may contact Linda Abbott, Deputy Director, Evaluation Planning and Support Division, at (410) 786-4662 or through email [Linda.Abbott@oig.hhs.gov]. To facilitate identification, please refer to report number OEI-04-07-00260 in all correspondence.

Attachment

cc: Edgar Swindell
Designated Agency Ethics Official
Office of the General Counsel

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

CDC'S ETHICS PROGRAM FOR SPECIAL GOVERNMENT EMPLOYEES ON FEDERAL ADVISORY COMMITTEES

Daniel R. Levinson
Inspector General

December 2009
OEI-04-07-00260

Office of Inspector General

http://oig.hhs.gov

The mission of the Office of Inspector General (OIG), as mandated by Public Law 95-452, as amended, is to protect the integrity of the Department of Health and Human Services (HHS) programs, as well as the health and welfare of beneficiaries served by those programs. This statutory mission is carried out through a nationwide network of audits, investigations, and inspections conducted by the following operating components:

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The Office of Audit Services (OAS) provides auditing services for HHS, either by conducting audits with its own audit resources or by overseeing audit work done by others. Audits examine the performance of HHS programs and/or its grantees and contractors in carrying out their respective responsibilities and are intended to provide independent assessments of HHS programs and operations. These assessments help reduce waste, abuse, and mismanagement and promote economy and efficiency throughout HHS.

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The Office of Counsel to the Inspector General (OCIG) provides general legal services to OIG, rendering advice and opinions on HHS programs and operations and providing all legal support for OIG's internal operations. OCIG represents OIG in all civil and administrative fraud and abuse cases involving HHS programs, including False Claims Act, program exclusion, and civil monetary penalty cases. In connection with these cases, OCIG also negotiates and monitors corporate integrity agreements. OCIG renders advisory opinions, issues compliance program guidance, publishes fraud alerts, and provides other guidance to the health care industry concerning the anti-kickback statute and other OIG enforcement authorities.

EXECUTIVE SUMMARY

OBJECTIVE

To determine the extent to which the Centers for Disease Control and Prevention (CDC) and its special Government employees (SGE) on Federal advisory committees (committees) complied with ethics requirements.

BACKGROUND

Committees play an influential role in decisionmaking for the Federal Government. Committee members (i.e., SGEs) are typically involved in work outside the Federal Government in the same areas as their committees' work. To protect the committees' integrity and credibility, agencies must not permit SGEs with conflicts of interest to inappropriately influence their committees' work.

At CDC, committees address important public health topics. For example, in 2007, one committee recommended the routine vaccination of young females in the United States to prevent cervical cancer. In 2009, this same committee recommended that H1N1 influenza vaccination efforts focus on five target groups in the United States.

CDC must obtain from SGEs Confidential Financial Disclosure Reports, Office of Government Ethics (OGE) Forms 450, containing information such as the SGEs' assets, sources of income, and non-income-earning activities. Before permitting SGEs to participate in committee meetings, CDC must review these forms and certify them to indicate that they are complete and that it has identified and resolved all conflicts of interest. CDC must create ethics agreements (e.g., waivers) to resolve SGEs' conflicts of interest. CDC collaborates with the Department of Health and Human Services' (HHS) Office of the General Counsel to identify and resolve conflicts of interest.

CDC must also provide initial and annual ethics training to SGEs within required timeframes and obtain ethics training certificates from SGEs to document that they received the training. Finally, CDC must monitor SGEs' compliance with ethics requirements during committee meetings. That is, SGEs must not participate in committee work during committee meetings without current, certified OGE Forms 450 or participate in committee work related to particular matters if their waivers prohibit such participation.

We reviewed financial disclosure files (e.g., current, certified OGE Forms 450 and ethics agreements) for 246 SGEs on 17 CDC committees in

2007. We determined whether SGEs' OGE Forms 450 were complete after CDC certified them. Then, we determined whether CDC identified potential conflicts of interest that we identified. We also determined the extent to which CDC created ethics agreements and adequately documented them to resolve potential conflicts of interest. Further, we determined whether CDC ensured that SGEs' financial disclosure files contained ethics training certificates to document that SGEs received ethics training within required timeframes. Finally, we determined whether SGEs complied with ethics requirements during committee meetings.

FINDINGS

For almost all special Government employees, CDC did not ensure that financial disclosure forms were complete in 2007. CDC certified OGE Forms 450 with at least one omission in 2007 for 97 percent of SGEs. Most of the forms had more than one type of omission.

CDC did not identify or resolve potential conflicts of interest for 64 percent of special Government employees in 2007. Sixty-four percent of SGEs had potential conflicts of interest in 2007 that CDC did not identify and/or resolve before it certified their OGE Forms 450. Specifically, 58 percent of SGEs had potential conflicts of interest that CDC did not identify. In addition, 32 percent of SGEs had potential conflicts of interest that CDC identified but did not resolve. Twenty-six percent of SGEs had both CDC-unidentified and unresolved potential conflicts of interest.

CDC did not ensure that 41 percent of special Government employees received required ethics training in 2007. CDC did not ensure that 41 percent of SGEs had ethics training certificates on file to document that SGEs received initial or annual ethics training within required timeframes in 2007.

Fifteen percent of special Government employees did not comply with ethics requirements during committee meetings in 2007. Fifteen percent of SGEs did not comply with ethics requirements during committee meetings in 2007. Specifically, 13 percent of SGEs participated in committee meetings in 2007 without having current, certified OGE Forms 450 on file. In addition, 3 percent of SGEs voted on particular matters when their waivers prohibited such participation. Four SGEs both participated in committee meetings without current, certified OGE Forms 450 on file and voted on particular matters when their waivers prohibited such participation.

RECOMMENDATIONS

We found that CDC had a systemic lack of oversight of the ethics program for SGEs. That is, CDC and its SGEs did not comply with ethics requirements in 2007.

To address our findings, we recommend that CDC:

Ensure that special Government employees' Confidential Financial Disclosure Reports are complete before certifying them.

Require special Government employees to disclose their involvement in grants and other relevant interests that could pose conflicts but that are not disclosed on the Confidential Financial Disclosure Report.

Identify and resolve all conflicts of interest for special Government employees before permitting them to participate in committee meetings.

Increase collaboration among CDC officials and with the HHS Office of the General Counsel.

Ensure that special Government employees and CDC employees receive ethics training.

Monitor special Government employee compliance with ethics requirements during committee meetings.

Track special Government employee compliance with ethics requirements.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

CDC concurred with all seven of our recommendations. Since the time of our review, CDC indicated that it has begun or plans to implement improvements that coincide with our recommendations.

We made technical changes to the report based on CDC's comments.

(CDJ)

(12)

UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

United States of America *ex rel.*,	Civil Action No. 10-4374 (CDJ)
Stephen A. Krahling and Joan A. Wlochowski,	
Plaintiffs,	**AMENDED COMPLAINT FOR VIOLATIONS OF THE FEDERAL FALSE CLAIMS ACT**
v.	
Merck & Co., Inc.	**JURY TRIAL DEMANDED**
Defendant.	

Stephen Krahling and Joan Wlochowski bring this *qui tam* action as Relators on behalf of the United States against their former employer, Merck & Co., Inc. ("Merck"), under the False Claims Act, 31 U.S.C. §§ 3729-3733, and allege -- upon knowledge with respect to their own acts and those they personally witnessed, and upon information and belief with respect to all other matters -- as follows:

INTRODUCTION

1. This case is about Merck's efforts for more than a decade to defraud the United States through Merck's ongoing scheme to sell the government a mumps vaccine that is mislabeled, misbranded, adulterated and falsely certified as having an efficacy rate that is significantly higher than it actually is.

2. Specifically, in an effort to maintain its exclusive license to sell the vaccine and its monopoly of the U.S. market for mumps vaccine, Merck has fraudulently represented and continues to falsely represent in its labeling and elsewhere that its mumps vaccine has an

efficacy rate of 95 percent or higher. This is the efficacy rate on which Merck's original government approval for the vaccine was based more than forty years ago. In truth, Merck knows and has taken affirmative steps to conceal -- such as by using improper testing techniques, falsifying test data in a clinical trial, and violating multiple duties of government disclosure -- that the efficacy rate of Merck's mumps vaccine is, and has been since at least 1999, significantly lower than this 95 percent rate.

3. Relators Krahling and Wlochowski were employed as virologists in the Merck lab that performed this fraudulent efficacy testing. They witnessed firsthand the improper testing and data falsification in which Merck engaged to conceal what Merck knew about the vaccine's diminished efficacy. In fact, their Merck superiors and senior Merck management pressured them to participate in the fraud and subsequent cover-up when Relators objected to and tried to stop it.

4. As a result of Merck's fraudulent scheme, the United States has over the last decade paid Merck hundreds of millions of dollars for a vaccine that does not provide the efficacy Merck claims it provides and does not provide the public with adequate immunization. Had Merck complied with its multiple duties of disclosure and reported what it knew of the vaccine's diminished efficacy -- rather than engage in fraud and concealment -- that information would have affected (or surely had the potential to affect, which is all the law requires) the government's decision to purchase the vaccine. However, since the government was not fully informed, it did not have the opportunity to consider its options, including not purchasing the vaccine from Merck, paying less, requiring a labeling change, requiring additional testing, or prioritizing development and approval of a new vaccine from Merck or another manufacturer.

5. Merck's failure to disclose what it knew about the diminished efficacy of its mumps vaccine has caused the government to purchase mislabeled, misbranded, adulterated and falsely certified vaccines in violation of Merck's contract with the Centers for Disease Control ("CDC") and in violation of the law.

6. As the single largest purchaser of childhood vaccines (accounting for more than 50 percent of all vaccine purchases), the United States is by far the largest financial victim of Merck's fraud. But the ultimate victims here are the millions of children who every year are being injected with a mumps vaccine that is not providing them with an adequate level of protection against mumps. And while this is a disease the CDC targeted to eradicate by now, the failure in Merck's vaccine has allowed this disease to linger with significant outbreaks continuing to occur.

7. Relators bring this case on behalf of the United States to recover the funds that the government spent for this fraudulently mislabeled, misbranded, adulterated and falsely certified vaccine, and for all associated penalties. They also bring this case to stop Merck from continuing with its scheme to misrepresent the true efficacy of its mumps vaccine and require Merck to comply with its reporting, labeling and testing obligations under its contract with the CDC and under this country's vaccine regulatory regime.

PARTIES

8. Relator Stephen A. Krahling is a citizen of the United States and a resident of Pennsylvania. He was employed by Merck from 1999 to 2001 as a virologist in Merck's vaccine division located in West Point, Pennsylvania. During his employment at Merck, Krahling witnessed firsthand, and was asked to directly participate in, fraud in a clinical trial relating to

the efficacy of Merck's mumps vaccine.

9. Relator Joan Wlochowski is a citizen of the United States and a resident of Connecticut. She was employed by Merck from January 2001 to August 2002 as a virologist in Merck's vaccine division in West Point, Pennsylvania. During her employment there, Wlochowski also witnessed firsthand, and was asked to directly participate in, fraud in a clinical trial relating to the efficacy of Merck's mumps vaccine.

10. Defendant Merck is headquartered in New Jersey with its vaccine division based in West Point, Pennsylvania. Merck is one of the largest pharmaceutical companies in the world with annual revenues exceeding $20 billion. Merck is also a leading seller of childhood vaccines and currently markets in the U.S. vaccines for 12 of the 17 diseases for which the CDC currently recommends vaccination.

11. Merck is the sole manufacturer licensed by the Food and Drug Administration ("FDA") to sell mumps vaccine in the United States. Merck's mumps vaccine, together with Merck's vaccines against measles and rubella are sold as MMRII. Merck annually sells more than 7.6 million doses of the vaccine in the U.S. for which it derives hundreds of millions of dollars of revenue. The U.S. purchases approximately 4 million of these doses annually. Merck also has a license in the U.S. to sell ProQuad, a quadravalent vaccine containing MMRII vaccine and chickenpox vaccine. Under a license from the European Medicines Agency ("EMA"), Merck also sells mumps vaccine in Europe as a part of the trivalent MMRVaxpro and the quadravelent ProQuad through Sanofi Pasteur MSD, a joint venture with the vaccine division of the Sanofi Aventis Group. ProQuad has been sold intermittently in the U.S. and Europe from its approval in 2005 until 2010.