PRESCRIBING INFORMATION

INFANRIX®

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

DESCRIPTION

INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is a noninfectious, sterile combination of diphtheria and tetanus toxoids and 3 pertussis antigens [inactivated pertussis toxin (PT) and formaldehyde-treated filamentous hemagglutinin (FHA) and pertactin (69 kiloDalton outer membrane protein)] adsorbed onto aluminum hydroxide. INFANRIX is intended for intramuscular injection only.

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 are at risk of bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The 3 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.

Each antigen is individually adsorbed onto aluminum hydroxide. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated PT, 25 mcg of FHA, and 8 mcg of pertactin.

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 components (inactivated PT and formaldehyde-treated FHA and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice.

Each 0.5-mL dose also contains 4.5 mg of NaCl, and aluminum adjuvant (not more than 0.625 mg aluminum by assay). Each dose also contains ≤100 mcg of residual formaldehyde and ≤100 mcg of polysorbate 80 (Tween 80). INFANRIX is formulated without preservatives.

The vaccine must be well shaken before administration to obtain a homogeneous, turbid, white suspension.

Diphtheria and Tetanus Toxoids Adsorbed Combined Bulk (For Further Manufacturing Use) is manufactured by Novartis Vaccines and Diagnostics GmbH & Co. KG, Marburg, Germany. The acellular pertussis antigens are manufactured by GlaxoSmithKline Biologicals,

Rixensart, Belgium. Formulation, filling, testing, packaging, and release of the vaccine are performed by GlaxoSmithKline Biologicals.

CLINICAL PHARMACOLOGY

Diphtheria: Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Diphtheria in the United States has been controlled through the use of diphtheria toxoid-containing vaccines. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. Following adequate immunization with diphtheria toxoid, protection persists for at least 10 years. 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.[1] Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nares or on the skin.[2]

Efficacy of diphtheria toxoid used in INFANRIX was determined on the basis of immunogenicity studies. A VERO cell toxin neutralizing test confirmed the ability of infant sera (N = 45), obtained one month after a 3-dose primary series, to neutralize diphtheria toxin. Levels of diphtheria antitoxin ≥0.01 IU/mL were achieved in 100% of the sera tested.

Tetanus: Tetanus is a condition manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C. tetani*. Spores of *C. tetani* are ubiquitous. Naturally acquired immunity to tetanus toxin does not occur. Thus, universal primary immunization and timed booster doses to maintain adequate tetanus antitoxin levels are necessary to protect all age groups.[2] 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 to 0.2 IU/mL has been considered as protective.[5] Following immunization, protection persists for at least 10 years.[2]

Efficacy of tetanus toxoid used in INFANRIX was determined on the basis of immunogenicity studies. An in vivo mouse neutralization assay confirmed the ability of infant sera (N = 45), obtained one month after a 3-dose primary series, to neutralize tetanus toxin. Levels of tetanus antitoxin ≥0.01 IU/mL were achieved in 100% of the sera tested.

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.

Efficacy of a 3-dose primary series of INFANRIX has been assessed in 2 clinical studies.[6,7]

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.[6] A total of 15,601 infants were immunized with 1 of 2 Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) vaccines, a US-licensed whole-cell Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTwP) vaccine, or with DT vaccine alone. The mean length of follow-up was 17 months (mean age 24 months), beginning 30 days after the third dose

of vaccine. 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% to 89%). When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was calculated to be 71% (95% CI: 60% to 78%) against >7 days of any cough and 73% (95% CI: 63% to 80%) against ≥14 days of any cough. Vaccine efficacy after 3 doses and with no booster dose in the second year of life was assessed in 2 subsequent follow-up periods. A follow-up period from 24 months to a mean age of 33 months was conducted in a partially unblinded cohort (children who received DT were offered pertussis vaccine and those who declined were retained in the study cohort). During this period, the efficacy of INFANRIX against WHO-defined pertussis was 78% (95% CI: 62% to 87%).[8] During the third follow-up period which was conducted in an unblinded manner among children from 3 to 6 years of age, the efficacy of INFANRIX against WHO-defined pertussis was 86% (95% CI: 79% to 91%). Thus, protection against pertussis in children administered 3 doses of INFANRIX in infancy was sustained to 6 years of age.[9]

A prospective efficacy trial was also conducted in Germany employing a household contact study design.[7] In preparation for this study, 3 doses of INFANRIX were administered at 3, 4, and 5 months of age to more than 22,000 children living in 6 areas of Germany in a safety and immunogenicity study. Infants who did not participate in the safety and immunogenicity study could have received a DTwP vaccine or DT vaccine. Index cases were identified by spontaneous presentation to a physician. Households with at least one other member (i.e., besides index case) aged 6 through 47 months were enrolled. Household contacts of index cases were monitored for incidence of pertussis by a physician who was blinded to the vaccination status of the household. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 household contacts who had not received a pertussis vaccine, 96 developed WHO-defined pertussis, as compared to 7 of 112 contacts vaccinated with INFANRIX. The protective efficacy of INFANRIX was calculated to be 89% (95% CI: 77% to 95%), with no indication of waning of protection up until the time of the booster vaccination. The average age of infants vaccinated with INFANRIX at the end of follow-up in this trial was 13 months (range 6 to 25 months). 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% to 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68% to 89%). The corresponding efficacy rates of INFANRIX against ≥14 days of any cough or paroxysmal cough were 73% (95% CI: 59% to 82%) and 84% (95% CI: 71% to 91%), respectively.

Immune Response to INFANRIX Administered as a 3-Dose Primary Series: The immune responses to each of the 3 pertussis antigens contained in INFANRIX were evaluated in sera obtained 1 month after the third dose of vaccine in each of 3 studies (schedule of

administration: 2, 4, and 6 months of age in the Italian efficacy study and one US study; 3, 4, and 5 months of age in the German efficacy study). One month after the third dose of INFANRIX, the response rates to each pertussis antigen were similar in all 3 studies. Thus, although a serologic correlate of protection for pertussis has not been established, the antibody responses to these 3 pertussis antigens (PT, FHA, and pertactin) in a US population were similar to those achieved in 2 populations in which efficacy of INFANRIX was demonstrated.

Immune Response to Concomitantly Administered Vaccines: In a clinical trial in the United States, INFANRIX was given concomitantly, at separate sites, with hepatitis B vaccine, *Haemophilus influenzae* type b vaccine (Hib), and poliovirus vaccine live oral (OPV), at 2, 4, and 6 months of age. One month after the third dose of hepatitis B vaccine given simultaneously with INFANRIX, 100% of infants demonstrated anti-HBs antibodies ≥10 mIU/mL (N = 64). Ninety percent of infants who received Hib simultaneously with INFANRIX achieved anti-PRP antibodies ≥1 mcg/mL (N = 72), and 96% to 100% of infants who received OPV simultaneously with INFANRIX showed protective neutralizing antibody to poliovirus Types 1, 2, and 3 (N = 60-61).[10]

In the Italian efficacy trial, 92% of infants received hepatitis B vaccine with the first and second dose of INFANRIX. Ninety-four percent of infants received OPV with the first and second dose of INFANRIX.[6]

No immunogenicity data are available for concurrent administration of INFANRIX with pneumococcal conjugate vaccine, inactivated poliovirus vaccine (IPV), measles, mumps, and rubella vaccine (MMR), or varicella vaccine.

INDICATIONS AND USAGE

INFANRIX is indicated for active immunization against diphtheria, tetanus, and pertussis (whooping cough) as a 5-dose series in infants and children 6 weeks to 7 years of age (prior to seventh birthday). Because of the substantial risks of complications from pertussis disease in infants, completion of the primary series of 3 doses of vaccine early in life is strongly recommended (see DOSAGE AND ADMINISTRATION).[2] INFANRIX should not be administered to any infant before the age of 6 weeks, or to individuals 7 years of age or older.

As with any vaccine, INFANRIX may not protect 100% of individuals receiving the vaccine, and is not recommended for treatment of actual infections.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine is a contraindication (see DESCRIPTION).

It is a contraindication to use this vaccine after a serious allergic reaction (e.g., anaphylaxis) temporally associated with a previous dose of this vaccine or with any components of this vaccine. Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, such individuals may be referred to an allergist for evaluation if immunizations are to be considered.[2]

In addition, the following events are contraindications to administration of any pertussis-containing vaccine, including INFANRIX:[5]

- 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;
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with these conditions until a treatment regimen has been established and the condition has stabilized.

In instances where the pertussis vaccine component is contraindicated, Diphtheria and Tetanus Toxoids Adsorbed (DT) For Pediatric Use should be administered.[2]

WARNINGS

The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper is latex-free.

If Guillain-Barré syndrome occurs within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give INFANRIX should be based on careful consideration of the potential benefits and possible risks.[5]

If any of the following events occur in temporal relation to receipt of DTwP or a vaccine containing an acellular pertussis component, the decision to give INFANRIX should be based on careful consideration of the potential benefits and possible risks:[11,12]

- 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.

When a decision is made to withhold pertussis vaccine, immunization with DT vaccine should be given.[2]

The decision to administer a pertussis-containing vaccine to individuals with stable CNS disorders must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. The Advisory Committee on Immunization Practices (ACIP) has issued guidelines for such individuals.[11] The parent or guardian should be advised of the potential increased risk involved (see PRECAUTIONS, Information for Vaccine Recipients and Parents or Guardians).

A family history of seizures or other CNS disorders is not a contraindication to pertussis vaccine.[11]

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 an acellular pertussis component (including INFANRIX) and for the ensuing 24 hours according to the

respective prescribing information recommended dosage to reduce the possibility of post-vaccination fever.[5,11]

The ACIP has published guidelines for vaccination of persons with recent or acute illness (www.cdc.gov).[5]

As with other intramuscular injections, INFANRIX should not be given to infants or children with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer INFANRIX to such persons, it should be given with caution with steps taken to avoid the risk of hematoma following the injection.[5]

PRECAUTIONS

Before the injection of any biological, the physician should take all reasonable precautions to prevent allergic or other adverse reactions, including understanding the use of the biological concerned, and the nature of the side effects and adverse reactions that may follow its use.

Prior to immunization, the patient's current health status and medical history should be reviewed. The physician should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions, and occurrence of any adverse-event-related symptoms and/or signs, in order to determine the existence of any contraindication to immunization with INFANRIX and to allow an assessment of benefits and risks. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

A separate sterile syringe and sterile disposable needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

Special care should be taken to prevent injection into a blood vessel.

As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.[13]

Information for Vaccine Recipients and Parents or Guardians: Parents or guardians should be informed by the healthcare provider of the potential benefits and risks of the vaccine, and of the importance of completing the immunization series. It is important that the parent or guardian be questioned concerning occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of a diphtheria, tetanus, and pertussis vaccine. The healthcare provider should inform the parents or guardians about the potential for adverse reactions that have been temporally associated with administration of INFANRIX or other vaccines containing similar components. The parent or guardian accompanying the recipient should be told to report severe or unusual adverse events to the physician or clinic where the vaccine was administered.

The parent or guardian should be 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 CDC website (www.cdc.gov/nip).

The United States Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[5] The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

Drug Interactions: For information regarding simultaneous administration with other vaccines, refer to DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY.

INFANRIX should not be mixed with any other vaccine in the same syringe or vial.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. The ACIP has published guidelines for vaccination of such persons and those with immunodeficiency disorders (www.cdc.gov).[13] If INFANRIX is administered to a person receiving immunosuppressive therapy, or who received a recent injection of immune globulin, or who has an immunodeficiency disorder, an adequate immunologic response may not be obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: INFANRIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

Pregnancy: Pregnancy Category C. INFANRIX is not indicated for women of child-bearing age. Animal reproduction studies have not been conducted with INFANRIX. It is not known whether INFANRIX can cause fetal harm when administered to a pregnant woman or if INFANRIX can affect reproductive capacity.

Geriatric Use: INFANRIX is not indicated for use in adult populations.

Pediatric Use: Safety and effectiveness of INFANRIX in infants younger than 6 weeks of age have not been evaluated. INFANRIX is not recommended for persons 7 years of age or older. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) should be used in individuals 7 years of age or older.

ADVERSE REACTIONS

Approximately 92,000 doses of INFANRIX have been administered in clinical studies. In these studies, 28,749 infants have received INFANRIX in primary series studies, 5,830 children have received INFANRIX as a fourth dose following 3 doses of INFANRIX, and 511 children have received INFANRIX as a fifth dose following 4 doses of INFANRIX. In addition, 439 children and 169 children have received INFANRIX as a fourth or fifth dose following 3 or 4 doses of whole-cell DTP vaccine, respectively. In comparative studies, the first 4 doses of INFANRIX have been shown to be followed by fewer of the local and systemic adverse reactions commonly associated with whole-cell DTP vaccination.[14] However, studies have

shown that the rate of local injection site reactions (erythema and swelling) and fever increased with successive doses of INFANRIX.

In the double-blind, randomized comparative trial in Italy, safety data in a 3-dose primary series are available for 4,696 infants who received at least one dose of INFANRIX and 4,678 infants who received at least one dose of US-licensed whole-cell DTP vaccine manufactured by Connaught Laboratories, Inc.[6,14] Data were actively collected by parents using standardized diaries for 8 consecutive evenings after each vaccine dose with follow-up telephone calls made by nurses after the eighth day. Table 1 lists adverse events reported during the 3 days after each dose. All common solicited adverse events were less frequent following vaccination with INFANRIX as compared to whole-cell DTP after each 1 of the 3 doses.

Table 1.[6] Adverse Events (%) Occurring Within the 3 Days Following Vaccination of Italian Infants With Either INFANRIX or Whole-Cell DTP at 2, 4, and 6 Months of Age

	INFANRIX			Whole-Cell DTP Vaccine		
	Dose 1	**Dose 2**	**Dose 3**	**Dose 1**	**Dose 2**	**Dose 3**
No. of infants	4,696	4,560	4,505	4,678	4,474	4,368
Local						
Redness	4.8	8.6	16.0	27.1	24.2	28.0
Redness ≥2.4 cm	1.0	1.3	3.5	12.4	7.3	7.7
Swelling	5.2	8.2	14.5	28.9	23.5	25.8
Swelling ≥2.4 cm	0.7	1.2	2.9	13.1	7.4	8.0
Tenderness	4.7	4.0	5.2	36.0	26.8	25.9
Systemic						
Fever (≥100.4°F)*	7.1	7.9	9.0	46.8	36.1	39.8
Irritability	36.3	34.9	28.8	57.2	50.1	47.2
Drowsiness	34.9	18.8	11.4	54.0	34.1	23.0
Loss of Appetite	16.5	13.9	11.5	31.2	22.8	19.1
Vomiting	5.8†	4.1†	3.3	6.7	4.7	4.8
Crying ≥1 Hour	3.9	3.3	2.2	17.3	11.1	8.2

* Rectal temperatures.

† For the comparison of INFANRIX and whole-cell DTP vaccine, all adverse events reached statistical significance ($p<0.001$) at all doses except vomiting at doses 1 and 2, which was not statistically significant at $p<0.05$.

A similar reduction in adverse events was seen in a randomized, double-blind, comparative trial conducted in the United States when INFANRIX was compared to 2 US-licensed whole-cell DTP vaccines. Adverse events were actively solicited using standardized diaries with follow-up telephone calls made at days 1, 4, and 8 by blinded study personnel. Table 2 summarizes the frequency of adverse events within 3 days of the three primary immunizing

doses. The incidence of redness, swelling, pain, fever (rectal temperature >101°F), fussiness, drowsiness, and poor appetite were lower following INFANRIX than following either whole-cell DTP vaccine.

Table 2.[15] Adverse Events (%) Occurring Within the 3 Days Following Vaccination of US Infants With Either INFANRIX or Whole-Cell DTP at 2, 4, and 6 Months of Age

	INFANRIX			Whole-Cell DTP Vaccine-Lederle			Whole-Cell DTP Vaccine-Connaught		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
No. of infants	407	402	395	74	73	73	76	75	74
Local									
Redness[*]	10.6	19.4	25.8	28.4	42.5	39.7	35.5	50.7	50.0
Swelling	7.4[†¶]	12.2[†¶]	17.5[¶]	23.0[†]	26.0[†]	27.4	30.3[¶]	37.3[¶]	31.1[¶]
Pain[*‡]	2.7	2.0	1.5	17.6	15.1	9.6	38.2	17.3	14.9
Systemic									
Fever (>101°F)[§]	0.5[†¶]	0.7[†¶]	5.1	12.2[†]	8.2[†]	6.8	14.5[¶]	18.7[¶]	8.1
Fussiness[**]	3.9[†¶]	3.5[†¶]	4.1	25.7[†]	13.7[†]	6.8	21.1[¶]	16.0[¶]	8.1
Drowsiness	26.3[†¶]	16.4[†¶]	12.9[†]	51.4[†]	34.2[†]	23.3[†]	52.6[¶]	28.0[¶]	18.9
Poor Appetite	8.1[†¶]	7.7	6.6	31.1[†]	15.1	9.6	19.7[¶]	14.7	9.5
Vomiting	6.6	3.7	3.8	8.1	4.1	2.7	7.9	2.7	2.7

‡ Moderate or severe = cried or protested to touch or cried when leg moved.

** Moderate or severe = prolonged crying and refusal to play or persistent crying that could not be comforted.

§ Rectal temperatures.

* $p<0.05$ for the comparison of INFANRIX and both whole-cell DTP vaccines.

† $p<0.05$ for the comparison of INFANRIX and whole-cell DTP vaccine-Lederle.

¶ $p<0.05$ for the comparison of INFANRIX and whole-cell DTP vaccine-Connaught.

The frequencies of adverse events following each dose in children who received INFANRIX at 2, 4, and 6 months of age in a US NIH-sponsored trial are shown in Table 3. Of the 120 infants who received the 3-dose primary series, a subset of 76 received a fourth dose of INFANRIX at 15 to 20 months of age and 22 of the 76 received a fifth dose of INFANRIX at 4 to 6 years of age. Adverse events were actively solicited using standardized diaries with follow-up telephone calls made at day 3 by blinded study personnel.

Table 3.[14,16,17,18] Adverse Events (%) Occurring Within the 3 Days Following Vaccination With INFANRIX in US Infants and Children in Which All Doses Were INFANRIX

	Primary			Booster	
	(N = 120 infants)			(N = 76 children)	(N = 22 children)
Event	Dose 1 (2 months)	Dose 2 (4 months)	Dose 3 (6 months)	Dose 4 (15 to 20 months)	Dose 5 (4 to 6 years)
Local					
Redness	16.6	15.4	26.3	39.5	59.1
Swelling	12.5	15.4	21.0	32.9	50.0
Pain*	5.0	5.1	0.9	10.5	27.3
Systemic					
Fever (≥101.1°F)†	0.0	0.9	3.5	6.6	4.6
Anorexia	7.5	6.0	9.6	11.8	NR
Vomiting	5.8	6.8	3.5	2.6	NR
Drowsiness	37.5	19.7	13.2	6.6	NR
Fussiness‡	3.3	7.7	8.8	9.2	0.0

* Moderate or severe = cried or protested to touch or cried when limb moved.

† Rectal temperatures for primary series and Dose 4; oral temperatures for Dose 5.

‡ Moderate or severe = prolonged crying and refusal to play or persistent crying that could not be comforted. For Dose 5, the solicited adverse event was irritability; however the definition for this term was the same as for fussiness.

NR = not reported in publication.

Of 22,505 children who had previously received 3 doses of INFANRIX at 3, 4, and 5 months of age in the German safety study, 5,361 received a fourth dose at 10 to 36 (mean 20) months of age. Standardized diaries were available on 2,457 children receiving the primary series and 1,809 children receiving the fourth dose. Rates of local and systemic adverse events within 3 days of vaccination for each dose are reported in Table 4. In this study, the rate of erythema, swelling, pain, and fever increased with successive doses of INFANRIX.

Table 4.[14] Adverse Events (%) Occurring Within the 3 Days Following Vaccination With INFANRIX in German Infants and Children in Which All Doses Were INFANRIX

Event	Primary (N = 2,457 infants)			Booster (N = 1,809 children)*
	Dose 1 (3 months)	Dose 2 (4 months)	Dose 3 (5 months)	Dose 4 (10 to 36 months†)
Local				
Redness	8.9	23.6	26.6	45.9
Redness >2 cm	0.0	0.5	1.3	13.8
Swelling	3.9	14.1	18.5	35.4
Swelling >2 cm	0.0	0.3	1.3	11.4
Pain	2.0	2.6	3.7	26.3
Systemic				
Fever (≥100.4°F)‡	6.3	8.3	13.3	26.4
Fever (>103.1°F)‡	0.0	0.1	0.1	1.1
Loss of Appetite	8.0	7.4	6.5	11.6
Vomiting	4.3	3.9	3.4	2.9
Restlessness	10.3	9.5	8.6	15.9
Unusual Crying	3.9	4.3	4.1	6.4
Diarrhea	6.0	4.9	4.0	11.0

* May not be same children as in primary series.

† Mean = 20 months.

‡ Rectal temperatures.

INFANRIX administered as a fifth dose in children 4 to 6 years of age previously vaccinated with 4 doses of INFANRIX was evaluated in 2 studies conducted in Germany.[14] Safety data are available for 93 children from Study A, a randomized and single (subject)-blinded trial and for 390 children from Study B, a non-randomized, open trial (see Table 5). Adverse events in both studies were actively solicited using standardized diary cards to record specific adverse events that occurred during the 15 days following vaccination. Note that most children who received a fifth dose of INFANRIX in these studies had received the fourth dose in the German study described earlier. However, the children included in Table 5 may not be the same children who are included in Table 4.

Rates of solicited local and systemic adverse events within 3 days of vaccination are reported in Table 5. Higher rates of local injection site reactions (redness, swelling, and pain) were observed following a fifth dose of INFANRIX compared with the fourth dose (see Table 4 and Table 5). The reported sizes of local redness and swelling tended to be greater following the fifth dose of INFANRIX compared with the fourth dose (see Table 4 and Table 5).

Table 5. Adverse Events (%) Occurring Within the 3 Days Following Vaccination[*] With INFANRIX Administered at 4 to 6 Years of Age in German Children Who Had Previously Received 4 Doses of INFANRIX

	Study A (N = 93)	Study B (N = 390)
Local		
Redness, any	51.6	52.1
Redness, ≥50 mm	23.7	29.2
Redness, ≥110 mm	4.3	6.4
Swelling, any	43.0	49.5
Swelling, ≥50 mm	15.1	20.0
Swelling, ≥110 mm	4.3	5.1
Pain, any	64.5	49.7
Pain, grade 2 or 3	20.4	13.8
Pain, grade 3	1.1	1.5
Systemic		
Fever[†], ≥99.5°F	12.9	11.3
Fever[†], ≥102.4°F	0.0	0.0
Loss of appetite	14.0	10.3
Vomiting	0.0	2.1
Irritability	18.3	14.1
Diarrhea	4.3	3.8

N = number of infants in a modified intent-to-treat (ITT) cohort (infants who received INFANRIX for their fifth dose of DTaP whose previous 4 doses of DTaP were all with INFANRIX, for whom at least one symptom sheet was completed; 2 subjects from Study B were excluded due to chronic illnesses that could have interfered with safety assessments).

Grade 2 pain defined as sufficiently discomforting to interfere with daily activities.

Grade 3 pain defined as preventing normal daily activities and needing medical advice.

[*] Within 3 days of vaccination defined as day of vaccination and the next 2 days.

[†] Axillary temperatures.

Cases of extensive swelling of the injected limb, involving an increase in limb circumference, and sometimes involving the entire injected thigh or upper arm, have been reported with INFANRIX.[14,19,20] These reactions have generally begun within 48 hours of vaccination and resolved over an average of 4 days (range 1 to 10 days) without sequelae.[14] In the German study in which 5,361 children received a fourth dose of INFANRIX after 3 doses of the same vaccine, swelling of the injected thigh was reported spontaneously in 62 vaccinees (1.2%).[14] This swelling was associated with pain upon digital pressure in 53% of cases, with rectal temperature ≥100.4°F in 45% of cases, and with injection site redness in 71% of cases (redness of the entire thigh was reported in 17% of such cases). The mean difference in the

circumference of the thighs in those subjects in whom this was measured (N = 17) was 2.2 cm (range: 0.5 to 5 cm). In 1,809 children for whom standardized diaries were available, extensive limb swelling was observed in 2.5% of vaccinees. In the two German studies in which subjects received a fifth consecutive dose of INFANRIX, the vaccine was administered in the deltoid muscle in most subjects, and in the thigh in a minority of subjects. In Study A, in which 93 children received a fifth dose of INFANRIX after 4 doses of the same vaccine, extensive swelling of the injected limb was reported spontaneously in 9 vaccinees (9.7%). This swelling was associated with pain and redness in all cases, and with fever in one case. The mean increase in the circumference of the injected limb compared with the opposite limb in those subjects in whom this was measured (N = 8) was 4.4 cm (range: 2 to 7 cm). In 3 cases, the investigators provided additional descriptive information – one case was described as involving the chest, and 2 cases were noted to involve the entire upper arm from the shoulder to the elbow. In Study B, in which 390 children received a fifth dose of INFANRIX after 4 doses of the same vaccine, extensive swelling of the injected limb was reported spontaneously in 25 vaccinees (6.4%). This swelling was associated with redness in all cases, with pain in 88%, and with fever in 12%. The mean increase in the circumference of the injected limb compared with the opposite limb in those subjects in whom this was measured (N = 22) was 3.8 cm (range: 1.2 to 16 cm).[14]

In postmarketing reports, extensive limb swelling also has been reported following administration of each of the first 3 doses of INFANRIX (see ADVERSE REACTIONS, Postmarketing Reports). Extensive limb swelling has also been reported following administration of other acellular DTP vaccines,[20,21] acellular pertussis vaccine alone (without DT),[22] whole-cell DTP vaccine,[23] and other vaccines.[24]

Table 6 lists the frequency of adverse events in US children who received INFANRIX (N = 110) or US-licensed whole-cell DTP vaccine (N = 55) manufactured by Lederle Laboratories at 15 to 20 months of age[25] and in US children who received INFANRIX (N = 115) or US-licensed whole-cell DTP vaccine (N = 57) manufactured by Lederle Laboratories at 4 to 6 years of age.[26] All children had previously received 3 or 4 doses of whole-cell DTP vaccine at approximately 2, 4, 6, and 15-18 months of age. Adverse events were actively solicited using standardized diaries with follow-up telephone calls made at days 1, 4, and 8 by blinded study personnel. Significantly fewer solicited local and general adverse events were reported following INFANRIX than following whole-cell DTP vaccine when administered as the fourth or fifth dose in those previously primed with 3 or 4 doses of whole-cell DTP vaccine.

Table 6.[25,26] Adverse Events (%) Occurring Within the 3 Days Following Vaccination With INFANRIX Administered at 15 to 20 Months and 4 to 6 Years of Age in US Children Who Had Previously Received 3 or 4 Doses of Whole-Cell DTP Vaccine

	15 to 20 months 3 Previous Doses of Whole-Cell DTP Vaccine		4 to 6 years 4 Previous Doses of Whole-Cell DTP Vaccine	
Event	**INFANRIX (N = 110)**	**Whole-Cell DTP Vaccine (N = 55)**	**INFANRIX (N = 115)**	**Whole-Cell DTP Vaccine (N = 57)**
Local				
Redness[*]	23	45	19	40
Redness[†] >10 mm	5	31	7	26
Swelling	14	24	15[*]	33[*]
Swelling >10 mm	7	15	8	18
Pain[†§]	5	38	12	40
Systemic				
Fever[*] (≥99.4°F)[‡]	25	42	23	47
Fever[†] (>100.5°F)[‡]	2	20	1	12
Fussiness	34[†]	69[†]	20	30
Drowsiness	9[*]	24[*]	11	18
Poor Appetite[*]	9	20	6	16
Vomiting	2	0	1	4

[*] $p<0.05$.

[†] $p<0.0001$.

[‡] Oral temperatures.

[§] Moderate or severe = cried or protested to touch or cried when arm moved.

Severe adverse events reported from the double-blind, randomized comparative Italian study involving 4,696 children administered INFANRIX or 4,678 children administered whole-cell DTP vaccine (manufactured by Connaught Laboratories, Inc.) as a 3-dose primary series are shown in Table 7. The incidence of rectal temperature ≥104°F, hypotonic-hyporesponsive episodes and persistent crying ≥3 hours following administration of INFANRIX was significantly less than that following administration of whole-cell DTP vaccine.[6] Hospitalization rates and death rates within 7 days of vaccination were similar between INFANRIX and DT vaccine recipients.[14]

Table 7.[6] Severe Adverse Events Occurring Within 48 Hours Following Vaccination With INFANRIX or Whole-Cell DTP in Italian Infants at 2, 4, or 6 Months of Age

Event	INFANRIX (N = 13,761 Doses)		Whole-Cell DTP Vaccine (N = 13,520 Doses)	
	Number	Rate/1,000 Doses	Number	Rate/1,000 Doses
Fever (≥104°F)[*†]	5	0.36	32	2.4
Hypotonic-hyporesponsive episode[‡]	0	0	9	0.67
Persistent crying ≥3 hours[*]	6	0.44	54	4.0
Seizures[**]	1[§]	0.07	3[¶]	0.22

[*] p<0.001.

[†] Rectal temperatures.

[‡] p = 0.002.

[§] Maximum rectal temperature within 72 hours of vaccination = 103.1°F.

[¶] Maximum rectal temperature within 72 hours of vaccination = 99.5°F, 101.3°F, and 102.2°F.

[**] Not statistically significant at p<0.05.

In the German safety study that enrolled 22,505 infants (66,867 doses of INFANRIX administered as a 3-dose primary series), all subjects were monitored for unsolicited adverse events that occurred within 28 days following vaccination using report cards. In a subset of subjects (N = 2,457), these cards were standardized diaries which solicited specific adverse events that occurred within 8 days of each vaccination in addition to unsolicited adverse events which occurred throughout the course of the entire trial (from study enrollment until approximately 30 days following the third vaccination). Cards from the whole cohort were returned at subsequent visits and were supplemented by spontaneous reporting by parents and a medical history after the first and second doses of vaccine. In the subset of 2,457, adverse events following the third dose of vaccine were reported via standardized diaries and spontaneous reporting at a follow-up visit. Adverse events in the remainder of the cohort were reported via report cards which were returned by mail approximately 28 days after the third dose of vaccine. Adverse events (rates per 1,000 doses) occurring within 7 days following any of the first 3 doses included: unusual crying (0.09), febrile seizure (0.0), afebrile seizure (0.13), and hypotonic-hyporesponsive episodes (0.01).

Rates of serious adverse events that are less common than those reported in this safety study are not known at this time.

In an ongoing US coadministration safety study, INFANRIX was administered concomitantly at separate sites with 7-valent pneumococcal and Hib conjugate vaccines (Lederle Laboratories), Hepatitis B Vaccine (Recombinant) (GlaxoSmithKline Biologicals), and inactivated poliovirus vaccine (IPV) (Sanofi Pasteur SA) at 2, 4, and 6 months of age. Following dose 1 at 2 months of age, fever ≥100.4°F, >101.3°F, >102.2°F, and >103.1°F occurring within 4 days (i.e., day of vaccination and the next 3 days) was reported in 19.8%, 4.5%, 0.3%, and

0.0%, respectively, of infants (N = 333). The frequency of irritability/fussiness, drowsiness, and loss of appetite was 61.5%, 54%, and 27.8%, respectively.

In clinical trials involving more than 29,000 infants and children, 14 deaths in INFANRIX recipients were reported. Causes of deaths included 9 cases of Sudden Infant Death Syndrome (SIDS) and one of each of the following: meal aspiration, hepatoblastoma, neuroblastoma, invasive bacterial infection, and sudden death in a child older than 1 year of age. None of these events was determined to be vaccine-related. The rate of SIDS observed in the German safety study that enrolled 22,505 infants was 0.3/1,000 vaccinated infants. The rate of SIDS in the Italian efficacy trial was 0.4/1,000 infants vaccinated with INFANRIX. The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births.[27] By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.[13]

As with any vaccine, there is the possibility that broad use of INFANRIX could reveal adverse events not observed in clinical trials.

Additional Adverse Reactions: Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[13] Arthus-type hypersensitivity reactions, characterized by severe local reactions, may follow receipt of tetanus toxoid. A review by the IOM found evidence for a causal relationship between receipt of tetanus toxoid and both brachial neuritis and Guillain-Barré Syndrome.[28] A few cases of demyelinating diseases of the CNS have been reported following some tetanus toxoid-containing vaccines or tetanus and diphtheria toxoid-containing vaccines, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.[28] A few cases of peripheral mononeuropathy and of cranial mononeuropathy have been reported following tetanus toxoid administration, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.

Postmarketing Reports: Worldwide voluntary reports of adverse events received for INFANRIX since market introduction are listed below. This list includes adverse events for which 20 or more reports were received with the exception of intussusception, idiopathic thrombocytopenic purpura, thrombocytopenia, anaphylactic reaction, encephalopathy, and hypotonic-hyporesponsive episode for which fewer than 20 reports were received. These latter events are included either because of the seriousness of the event or the strength of causal connection to components of this or other vaccines or drugs.

Body as a Whole: Fever, Sudden Infant Death Syndrome.

Cardiovascular System: Cyanosis.

Gastrointestinal System: Diarrhea, intussusception, vomiting.

Hematologic/lymphatic: Idiopathic thrombocytopenic purpura, lymphadenopathy, thrombocytopenia.

Hypersensitivity: Anaphylactic reaction, hypersensitivity.

Infections: Cellulitis.

Injection Site Reactions: Injection site reactions.

Musculoskeletal: Limb swelling.

Nervous System: Convulsions, encephalopathy, hypotonia, hypotonic-hyporesponsive episode, somnolence.

Psychiatric: Crying, irritability.

Respiratory System: Respiratory tract infection.

Skin and Appendages: Erythema, pruritus, rash, urticaria.

Special Senses: Ear pain.

These adverse events were reported voluntarily from a population of uncertain size; therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination.

Reporting Adverse Events: The National Childhood Vaccine Injury Act requires that the manufacturer and lot number of the vaccine administered be recorded by the healthcare provider in the vaccine recipient's permanent medical record, along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.[29] The Act further requires the healthcare provider to report to the US Department of Health and Human Services the occurrence following immunization of any event set forth in the Vaccine Injury Table including: Anaphylaxis or anaphylactic shock within 7 days, encephalopathy or encephalitis within 7 days, brachial neuritis within 28 days, or an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this prescribing information.[29,30] These events should be reported to VAERS. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

DOSAGE AND ADMINISTRATION

Preparation for Administration: INFANRIX is an adjuvanted vaccine; therefore shake vigorously to obtain a homogeneous, turbid, white suspension. DO NOT USE IF RESUSPENSION DOES NOT OCCUR WITH VIGOROUS SHAKING. Inspect visually for particulate matter or discoloration prior to administration. After removal of the dose, any vaccine remaining in the vial should be discarded.

Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide.

Recommended Schedule: A 0.5 mL dose of INFANRIX is approved for administration in infants and children 6 weeks to 7 years of age (prior to the seventh birthday) as a 5 dose series. INFANRIX should be administered by intramuscular injection. The series consists of a primary immunization course of 3 doses administered at 2, 4, and 6 months of age, followed by 2 booster doses, administered at 15 to 20 months of age and at 4 to 6 years of age. The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age. The recommended interval between the first three doses is 8 weeks, with a minimum interval of 4 weeks.[5,12] The recommended interval between the third and fourth dose is 6 to 12 months.[5,12] The fifth dose is recommended before entry into kindergarten or elementary school, and is not needed if the fourth dose was given after the fourth birthday.[12]

The preferred administration sites are the anterolateral aspects of the thigh or the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product subcutaneously or intravenously.

Use of INFANRIX with Other DTaP Vaccines: Interchanging INFANRIX and DTaP vaccines from different manufacturers for successive doses of the vaccination series is not recommended because data are limited regarding the safety and efficacy of such regimens.

INFANRIX may be used to complete a DTaP immunization series initiated with PEDIARIX™ [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, manufactured by GlaxoSmithKline Biologicals], because the diphtheria, tetanus, and pertussis components of INFANRIX are the same as those in PEDIARIX. However, the safety and efficacy of INFANRIX in such infants and children have not been evaluated.

Additional Dosing Information: If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with INFANRIX. There is no need to start the series over again, regardless of the time elapsed between doses.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.[5]

Preterm infants should be vaccinated according to their chronological age from birth.[5]

Concomitant Vaccine Administration: In clinical trials, INFANRIX was routinely administered, at separate sites, concomitantly with 1 or more of the following vaccines: poliovirus vaccine live oral (OPV), hepatitis B vaccine, and *Haemophilus influenzae* type b vaccine (Hib) (see CLINICAL PHARMACOLOGY). Safety data are available following the first dose of INFANRIX when administered concomitantly at separate sites with Hib and pneumococcal conjugate vaccines, hepatitis B vaccine, and IPV (see ADVERSE REACTIONS). No immunogenicity data are available on the simultaneous administration of INFANRIX with pneumococcal conjugate vaccine or IPV.

No immunogenicity or safety data are available on the simultaneous administration of INFANRIX with measles, mumps, and rubella vaccine (MMR) or varicella vaccine.

When concomitant administration of other vaccines is required, they should be given with separate syringes and at different injection sites.

STORAGE

Store INFANRIX refrigerated between 2° and 8°C (36° and 46°F). **Do not freeze.** Discard if the vaccine has been frozen. Do not use after expiration date shown on the label.

HOW SUPPLIED

INFANRIX is supplied as a turbid white suspension in single-dose (0.5 mL) vials and disposable prefilled TIP-LOK® syringes.

Single-Dose Vials and Prefilled Syringes (Preservative Free Formulation)
NDC 58160-810-11 Package of 10 Single-Dose Vials
NDC 58160-810-46 Package of 5 Single-Dose Prefilled Disposable TIP-LOK Syringes (packaged without needles)

REFERENCES

1. Wharton M and Vitek CR. Diphtheria Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 4th ed. Philadelphia, PA: Saunders Press; 2004:211-228. **2.** Centers for Disease Control. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures — Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991;40(RR-10):1-28. **3.** Wassilak SGF, Roper MH, Murphy TV and Orenstein WA. Tetanus Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 4th ed. Philadelphia, PA: Saunders Press; 2004:745-781. **4.** Department of Health and Human Services, Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Proposed rule. *Federal Register* December 13, 1985;50(240):51002-51117. **5.** Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51(RR-2):1-35. **6.** Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med* 1996;334(6):341-348. **7.** Schmitt H-J, von König CHW, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *JAMA* 1996;275(1):37-41. **8.** Salmaso S, Mastrantonio P, Wassilak SGF, et al. Persistence of protection through 33 months of age provided by immunization in infancy with two three-component acellular pertussis vaccines. *Vaccine* 1998;13(13):1270-1275. **9.** Salmaso S, Mastrantonio P, Tozzi AE, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: The Italian experience. *Pediatrics* 2001;108(5):E81. **10.** Blatter M, Reisinger K, Pichichero M, et al. Immunogenicity of diphtheria-tetanus-acellular pertussis (DT-tricomponent Pa), hepatitis B (HB) and *Haemophilus influenzae* type b (Hib) vaccines administered concomitantly at separate sites along with oral poliovirus vaccine (OPV) in infants. In: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 15-18, 1996; New Orleans, LA. Abstract G102. **11.** Centers for Disease Control and Prevention. Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children — Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-7):1-25. **12.** Centers for Disease Control and Prevention. Update: Vaccine side effects, adverse reactions, contraindications, and precautions — Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996;45(RR-12):1-35. **13.** Centers for Disease Control

and Prevention. Use of vaccines and immune globulins in persons with altered immunocompetence: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1993;42(RR-4):1-18. **14.** Data on File, GlaxoSmithKline. **15.** Bernstein HH, Rothstein EP, Pichichero ME, et al. Reactogenicity and immunogenicity of a three-component acellular pertussis vaccine administered as the primary series to 2, 4 and 6 month-old infants in the United States. *Vaccine* 1995;13(17):1631-1635. **16.** Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: Adverse reactions. *Pediatrics* 1995;96:557-566. **17.** Pichichero ME, Edwards KM, Anderson EL, et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four- to six-year-old children. *Pediatrics* 2000;105(1):e11. **18.** Pichichero ME, Deloria MA, Rennels MB, et al. A safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fourth dose in 15- to 20-month-old children. *Pediatrics* 1997;100(5):772-788. **19.** Schmitt H-J, Beutel K, Schuind A, et al. Reactogenicity and immunogenicity of a booster dose of a combined diphtheria, tetanus, and tricomponent acellular pertussis vaccine at fourteen to twenty-eight months of age. *J Pediatr* 1997;130:616-623. **20.** Rennels MB, Deloria MA, Pichichero ME, et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. *Pediatrics* 2000;105(1):E12. **21.** Noble GR, Bernier RH, Esber EC, et al. Acellular and whole-cell pertussis vaccines in Japan. Report of a visit by US scientists. *JAMA* 1987;257(10):1351-1356. **22.** Blennow M and Granström M. Adverse reactions and serologic response to a booster dose of acellular pertussis vaccine in children immunized with acellular or whole-cell vaccine as infants. *Pediatrics* 1989;84(1):62-67. **23.** Pim C and Farley J. Local reactions to kindergarten DPT boosters — Cranbrook. *Dis Surveill* 1988;9:230-239. **24.** Gold R, Scheifele D, Barreto L, et al. Safety and immunogenicity of *Haemophilus influenzae* vaccine (tetanus toxoid conjugate) administered concurrently or combined with diphtheria and tetanus toxoids, pertussis vaccine and inactivated poliomyelitis vaccine to healthy infants at two, four and six months of age. *Pediatr Infect Dis J* 1994;13:348-355. **25.** Bernstein HH, Rothstein EP, Reisinger KS, et al. Comparison of a three-component acellular pertussis vaccine with a whole-cell pertussis vaccine in 15- through 20-month-old infants. *Pediatrics* 1994;93(4):656-659. **26.** Annunziato PW, Rothstein EP, Bernstein HH, et al. Comparison of a three-component acellular pertussis vaccine with a whole-cell pertussis vaccine in 4- through 6-year-old children. *Arch Pediatr Adolesc Med* 1994;148:503-507. **27.** Centers for Disease Control and Prevention. Sudden Infant Death Syndrome — United States, 1983-94. *MMWR* 1996;45(40):859-863. **28.** Institute of Medicine (IOM). Stratton KR, Howe CJ, Johnston RB, eds. *Adverse events associated with childhood vaccines. Evidence bearing on causality.* Washington, DC: National Academy Press; 1994. **29.** Centers for Disease Control. National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 1988;37(13):197-200. **30.** National Vaccine Injury Compensation Program: Vaccine injury table. www.hrsa.gov/osp/vicp/table.htm. Accessed April 29, 2002.

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