

**Pertussis Vaccination:  
Use of Acellular Pertussis Vaccines  
Among Infants and Young Children**

**Recommendations of the Advisory Committee on  
Immunization Practices (ACIP)**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
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# **Pertussis Vaccination: Use of Acellular Pertussis Vaccines Among Infants and Young Children**

## **Recommendations of the Advisory Committee on Immunization Practices (ACIP)**

### **Summary**

*Concerns about the safety of whole-cell pertussis vaccines prompted development of acellular vaccines that are less likely to provoke adverse events because they contain purified antigenic components of Bordetella pertussis. Two diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines—ACEL-IMUNE<sup>®\*</sup> and Tripedia<sup>®†</sup>—have been licensed for several years, but (until recently) only for administration of the fourth and fifth doses in the series to children aged 15 months–6 years who previously had received three or more doses of diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine. Published reports indicate that, when administered to infants aged 2, 4, and 6 months, acellular pertussis vaccines are effective in preventing pertussis disease and associated with fewer local, systemic, and certain more serious adverse events than whole-cell pertussis vaccines. On the basis of these data, the Food and Drug Administration (FDA) has licensed three DTaP vaccines for use among children aged 6 weeks–6 years. Tripedia<sup>®</sup> is now licensed for the initial four doses, and ACEL-IMUNE<sup>®</sup> for all five doses of the diphtheria, tetanus and pertussis vaccination series. A third DTaP vaccine (Infanrix<sup>™</sup>)<sup>‡</sup> was licensed in January 1997 for the initial four doses of the series. Tripedia<sup>®</sup>, ACEL-IMUNE<sup>®</sup>, and Infanrix<sup>™</sup> are now recommended for routine vaccination of infants and young children, although whole-cell pertussis vaccines remain acceptable alternatives. Tripedia<sup>®</sup>, ACEL-IMUNE<sup>®</sup>, and Infanrix<sup>™</sup> are recommended for all remaining doses in the schedule for children who have started the vaccination series with one, two, three, or four doses of whole-cell pertussis vaccines. In September 1996, FDA licensed the use of TriHIBit<sup>™</sup> (ActHIB<sup>®</sup> reconstituted with Tripedia<sup>®</sup>)<sup>¶</sup> for the fourth dose in the series of vaccinations against diphtheria, tetanus, pertussis, and Haemophilus influenzae type b disease.*

\*Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, ACEL-IMUNE<sup>®</sup>, prepared by Lederle Laboratories and distributed by Wyeth-Lederle Vaccines and Pediatrics (Pearl River, New York) was licensed on December 30, 1996 for use in infants. The acellular pertussis vaccine component is produced by Takeda Chemical Industries, Ltd. (Osaka, Japan), and is combined with diphtheria and tetanus toxoids manufactured by Lederle Laboratories.

†Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, prepared and distributed as Tripedia<sup>®</sup> by Connaught Laboratories, Inc. (Swiftwater, Pennsylvania), was licensed July 31, 1996 for use in infants. The acellular pertussis vaccine component is produced by BIKEN/Tanabe Corporation (Osaka, Japan), and is combined with diphtheria and tetanus toxoids manufactured by Connaught Laboratories, Inc.

‡Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, prepared and distributed as Infanrix<sup>™</sup> was licensed January 29, 1997. The diphtheria and tetanus toxoids are produced by Chiron Behring GmbH & Co. (Marburg, Germany). The acellular pertussis component is manufactured by SmithKline Beecham Biologicals S. A. (Rixensart, Belgium).

¶Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) is manufactured by Pasteur Mérieux Sérums & Vaccins S.A. ActHIB<sup>®</sup> is identical to Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)—OmniHIB<sup>®</sup> (distributed by SmithKline Beecham Pharmaceuticals) and is manufactured by Pasteur Mérieux Sérums & Vaccins S.A.

*This statement a) provides general information regarding whole-cell pertussis vaccines currently licensed in the United States; b) summarizes results of recent studies of the immunogenicity, efficacy, and safety of acellular pertussis vaccines administered to infants and young children; c) presents recommendations for the use of Tripedia<sup>®</sup>, TriHIBit<sup>™</sup>, ACEL-IMUNE<sup>®</sup>, and Infanrix<sup>™</sup> vaccines; and d) supplements previous recommendations on pertussis vaccination.*

## INTRODUCTION

### Whole-Cell Pertussis Vaccines

Four diphtheria and tetanus toxoids combined with whole-cell pertussis (DTP) vaccines are presently licensed for use in the United States.\* Vaccines of this type, prepared from suspensions of inactivated *Bordetella pertussis* bacterial cells, have been licensed for routine vaccination of infants since the mid-1940s. Based on controlled efficacy trials conducted in the 1940s and on subsequent observational efficacy studies, a primary series comprising four doses of whole-cell DTP vaccine is considered 70%–90% effective in preventing serious pertussis disease (1–4).

Whole-cell DTP vaccines are commonly associated with several local adverse events (e.g., erythema, swelling, and pain at the injection site), fever, and other mild systemic events (e.g., drowsiness, fretfulness, and anorexia) (5,6). More severe systemic events (e.g., convulsions [with or without fever] and hypotonic hyporesponsive episodes) occur less frequently (ratio of one case to 1,750 doses administered) among children who receive whole-cell DTP vaccine (5). Acute encephalopathy occurs even more rarely (ratio of 0–10.5 cases to one million doses administered) (7). Experts disagree on whether whole-cell pertussis vaccine causes lasting brain damage, but agree that if the vaccine causes such damage it does so only rarely (7). Concerns about safety prompted the development of more purified (acellular) pertussis vaccines that are associated with a lower frequency of adverse events and are effective in preventing pertussis disease.

### Trends in Pertussis Disease in the United States

In the United States, the highest recorded annual incidence of pertussis occurred in 1934 when >260,000 cases were reported. The incidence of reported pertussis disease declined substantially as use of whole-cell DTP vaccines became widespread. By 1970, the reported incidence had declined >99%; the fewest cases (1,010) were reported in 1976. However, since the early 1980s reported pertussis incidence has increased steadily. Cyclical peaks in incidence occurred in 1983, 1986, 1990, and in 1993 when 6,586 cases were reported—more than in any year since 1976 (8). The number of reported cases has increased in all age groups, but the increase is greatest among persons aged  $\geq 5$  years (9). Nevertheless, infants and young children continue to have the highest risk for pertussis and its complications (4,8,10).

\*Whole-cell DTP vaccines are manufactured by Connaught Laboratories Inc., Lederle Laboratories, Massachusetts Public Health Biologic Laboratories, and Michigan Biologic Products Institute; those produced by Connaught Laboratories and Lederle Laboratories are distributed nationally.



The increase in reported pertussis cases has occurred despite pertussis vaccination coverage levels that are higher than at any time in the past. The proportion of children aged 19–35 months who had received three or more doses of whole-cell DTP or diphtheria and tetanus toxoids vaccine (DT) reached 93% in 1994 (11). (Of those vaccinated, <2% are estimated to have received DT [CDC, unpublished data].) Possible explanations of this increase in disease include a) decreased vaccine efficacy, b) waning immunity among adolescents and adults vaccinated during childhood, c) increased diagnosis and reporting of pertussis because of greater awareness among physicians about the disease, and d) enhanced surveillance and more complete reporting in some states (12,13).

Recent randomized controlled trials in Sweden and in Italy with one of the whole-cell DTP vaccines presently licensed in the United States (manufactured by Connaught Laboratories, Inc.) yielded estimates of low clinical efficacy—60% in the 6 months immediately following administration of the third dose. Estimates of vaccine efficacy for the total followup period were even lower—48% in Sweden and 36% in Italy (14,15). These estimates were substantially lower than expected on the basis of estimates obtained from observational studies in the United States. One possible explanation for the disparity is the number of doses administered—three in the trials in Sweden and Italy versus five in the United States (doses at ages 2, 4, 6, and 12–18 months and 4–6 years). A recent study in Germany with another whole-cell DTP vaccine currently in use in the United States (distributed by Wyeth-Lederle Vaccines and Pediatrics) demonstrated 83% protective efficacy after the third dose and before administration of the fourth dose and 94% efficacy after four doses (Wyeth-Lederle Vaccines and Pediatrics, ACCEL-IMUNE® package insert). The effectiveness of the current pertussis vaccination program in the United States, which has relied on four different whole-cell DTP vaccines for primary vaccination, remains high (3,4).

## **Acellular Pertussis Vaccines**

Acellular pertussis vaccines contain inactivated pertussis toxin (PT) and may contain one or more other bacterial components (e.g., filamentous hemagglutinin [FHA], a 69-kilodalton outer-membrane protein—pertactin [Pn], and fimbriae [Fim] types 2 and 3). PT is detoxified either by treatment with a chemical (e.g., hydrogen peroxide, formalin and/or glutaraldehyde) or by using molecular genetic techniques. Acellular pertussis vaccines contain substantially less endotoxin than whole-cell pertussis vaccines.

Since 1991, two acellular pertussis vaccines (Tripedia® and ACCEL-IMUNE®) have been licensed for use in the United States. Until recently, both vaccines were licensed for use only as the fourth and fifth doses of the diphtheria, tetanus, and pertussis vaccination series among children aged 15 months–6 years who had received three primary doses of whole-cell DTP (16,17). This licensure was based on findings of studies conducted in Sweden and Japan. These studies did not evaluate the efficacy of acellular pertussis vaccines administered to infants on a schedule similar to the one used in the United States and did not directly compare the efficacy of DTaP vaccines with that of whole-cell DTP vaccines (18–22).

## Studies of the Efficacy of DTaP Vaccines in Infants

Since 1991, seven studies conducted in Europe and Africa have evaluated the efficacy of eight DTaP vaccines administered to infants. The vaccines, produced by different manufacturers, contained a varying number and quantity of antigens. The derivation and formulation of the individual antigens also varied among vaccines (Table 1). Four doses of vaccine were administered in one study (Wyeth-Lederle Vaccines and Pediatrics, ACCEL-IMUNE<sup>®</sup> package insert); the other six studies involved three doses (14, 15, 23–25). These studies also differed in other ways (Table 2):

- Design. Three studies were randomized placebo-controlled clinical trials; such studies usually provide the most accurate measure of a treatment effect and are less subject to biases than observational studies.
- Case definition. Estimates of vaccine efficacy tend to be higher when the case definition excludes mild clinical cases.
- Laboratory method used to confirm the diagnosis of pertussis.

Because of these differences, comparisons among studies should be made with caution. Within individual studies, however, the efficacy of acellular pertussis vaccines can be compared directly with that of whole-cell DTP.

The efficacy of three doses of acellular pertussis vaccines in preventing moderate to severe pertussis disease was within the range expected for most whole-cell DTP vaccines. Point estimates of efficacy ranged from 59% to 89%. Mild local and systemic adverse events occurred less frequently among infants vaccinated with acellular pertussis vaccines for the first three or four doses than among those vaccinated with whole-cell DTP. More serious adverse events (e.g., fever  $\geq 105$  F [ $\geq 40.5$  C], persistent crying of  $\geq 3$  hours duration, hypotonic hyporesponsive episodes, and seizures) generally occurred less frequently among infants who received acellular pertussis vaccines than among those vaccinated with whole-cell DTP. The number of subjects included in these studies was insufficient to estimate the risk for rare severe reactions (i.e., encephalopathy or anaphylactic shock). Surveillance for these rare adverse events will be needed as acellular pertussis vaccines are used more widely.

## Interpretation of Immunogenicity Data

The findings of efficacy studies have not demonstrated a direct correlation between antibody responses and protection against pertussis disease. However, antibody studies are useful to compare immune responses elicited by a single vaccine under different conditions or in different studies. Thus, efficacy studies are required to measure clinical protection conferred by each pertussis vaccine.

## TRIPEDIA<sup>®</sup>

On July 31, 1996, the Food and Drug Administration (FDA) licensed Tripedia<sup>®</sup> for use as the initial four doses of the recommended diphtheria, tetanus, and pertussis vaccination series among children aged 6 weeks–6 years. The acellular pertussis vaccine components are purified from *B. pertussis* by salt precipitation, ultracentrifugation, and ultrafiltration. After purification, fractions containing PT and FHA are

**TABLE 1. Vaccines containing acellular pertussis antigens combined with diphtheria and tetanus toxoids (DTaP) tested in recent studies of efficacy among infants, by manufacturer and characteristics\***

Manufacturers/ DTaP vaccines	Abbreviation	PT <sup>†</sup> ( $\mu$ g/dose)	FHA <sup>†</sup> ( $\mu$ g/dose)	Pn <sup>†</sup> ( $\mu$ g/dose)	Fim <sup>†</sup> ( $\mu$ g/dose)	Aluminum (mg/dose)	Preservative	Diphtheria toxoid <sup>§</sup>	Tetanus toxoid <sup>§</sup>	Inactivation of PT
North American Vaccine	NAV-1	40.0				0.50	Thimerosal	25.0	7.0	Chemical
Connaught(US)/ BIKEN (Tripedia <sup>®</sup> )	CB-2	23.4		23.4		0.17	Thimerosal	6.7	5.0	Chemical
Pasteur Mérieux	PM-2	25.0	25.0			0.50	Thimerosal	15.0	5.0	Chemical
SmithKline Beecham Biologicals	SKB-2	25.0	25.0			0.50	Phenoxyethanol	17.0	10.0	Chemical
Biocine	BSc-3P	5.0	2.5	2.5		0.35	Thimerosal	25.0	10.0	Genetic <sup>¶</sup>
SmithKline Beecham Biologicals (Infanrix <sup>™</sup> )	SKB-3P	25.0	25.0	8.0		0.625	Phenoxyethanol	25.0	10.0	Chemical
Connaught Laboratories (Canada)	CLL-4F <sub>2</sub>	10.0	5.0	3.0	5.0**	0.33	Phenoxyethanol	15.0	5.0	Chemical
Lederle Praxis/Takeda (ACEL-IMUNE <sup>®</sup> )	LPT-4F <sub>1</sub>	3.2	34.4	1.6	0.8 <sup>††</sup>	0.23	Thimerosal	9.0	5.0	Chemical

\*Adapted from Edwards KM, Meade BD, Decker MD, et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. *Pediatrics* 1995; 96(suppl):548-57.

<sup>†</sup>PT=inactivated pertussis toxin; FHA=filamentous hemagglutinin; Pn=pertactin; Fim=fimbriae.

<sup>§</sup>Measured in limit of flocculation units (Lf) per dose.

<sup>¶</sup>Formaldehyde stabilized.

\*\*Fim 2 and 3.

<sup>††</sup>Fim 2.

**TABLE 2. Absolute efficacy of DTaP and whole-cell DTP\* vaccines when administered to infants: results from seven field studies**

Type of study		Vaccine composition <sup>†</sup>				Age at vaccination (mos)	Case definition	Vaccine efficacy % (95% CI)	
Site of study	DTaP vaccines	PT	FHA	Pn	Fim			DTaP	DTP
<b>Randomized controlled studies</b>									
Stockholm, Sweden (14)	CLL-4F <sub>2</sub>	+	+	+	+	2, 4, 6	≥21 days of paroxysmal cough <sup>§</sup>	85 (81–89)	48 (37–58) <sup>¶</sup>
	SKB-2	+	+			2, 4, 6	≥21 days of paroxysmal cough <sup>§</sup>	59 (51–66)	48 (37–58) <sup>¶</sup>
Italy (15)	BSc-3P	+	+	+		2, 4, 6	≥21 days of paroxysmal cough <sup>§</sup>	84 (76–90)	36 (14–52) <sup>¶</sup>
	SKB-3P (Infanrix™)	+	+	+		2, 4, 6	≥21 days of paroxysmal cough <sup>§</sup>	84 (76–89)	36 (14–52) <sup>¶</sup>
Göteborg, Sweden (24)	NAV-1	+				3, 5, 12	≥21 days of paroxysmal cough <sup>§</sup>	71 (63–78)	Not studied
<b>Observational studies**</b>									
Erlangen, Germany †† (Manufacturer data)	LPT-4F <sub>1</sub> (ACEL-IMUNE®)	+	+	+	+	3, 5, 7, 17	≥21 days cough and paroxysms or whoop or vomiting and confirmation by culture or serology or link to culture-positive household contact	73 (51–86) <sup>§§</sup> 85 (76–90) <sup>¶¶</sup>	83 (65–92) <sup>§§</sup> 94 (89–97) <sup>¶¶</sup>
Six areas, Germany (23)	SKB-3P (Infanrix™)	+	+	+		3, 4, 5	≥21 days of paroxysmal cough <sup>§</sup>	89 (77–95)	98 (83–100) <sup>***</sup>
Senegal †† (Manufacturer data)	PM-2	+	+			2, 4, 6	≥21 days of paroxysmal cough <sup>§</sup>	85 (66–93)	96 (86–99) <sup>***</sup>
Munich, Germany (Manufacturer data), (25)	CB-2 (Tripedia®)	+	+			3, 5, 7	≥21 days any cough and confirmation by culture or link to culture; positive household contact	80 (59–90)	95 (81–99) <sup>***†††</sup>

\*Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP); diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP).

† PT=pertussis toxin; FHA=filamentous hemagglutinin; Pn=pertactin; Fim=fimbriae; + indicates that vaccine contains antigen.

§ With culture or serologic confirmation. In Stockholm and Göteborg, cases linked to a culture-confirmed household contact were also considered confirmed; in Senegal, cases identified as positive by polymerase chain reaction (PCR) and linked to a culture-confirmed case were also considered confirmed.

¶ DTP distributed by Connaught Laboratories, Inc. and licensed for use in the United States.

\*\* LPT-4F<sub>1</sub> was tested in a prospective cohort study, SKB-3P and PM-2 in household contact studies, and CB-2 in a case-control study.

†† In Erlangen and Senegal, children were randomly administered DTaP or whole-cell DTP; however, recruitment of DT recipients was not randomized.

§§ Efficacy after three doses; whole-cell DTP distributed by Wyeth-Lederle Vaccines and Pediatrics and licensed for use in the United States.

¶¶ Efficacy after four doses; whole-cell DTP distributed by Wyeth-Lederle Vaccines and Pediatrics and licensed for use in the United States.

\*\*\* Whole-cell DTP used in six areas and Munich studies in Germany was manufactured by Behringwerke A.G.; whole-cell DTP used in Senegal was manufactured by Pasteur Mérieux.

††† DTaP and whole-cell DTP vaccine efficacy estimates are not directly comparable because of differences in recruitment of children in the study.

combined to obtain a 1:1 ratio and are treated with formaldehyde to inactivate PT. Each dose of Tripedia<sup>®</sup> contains approximately 23.4 µg protein of inactivated PT (toxoid) and 23.4 µg protein of FHA, as well as 6.7 limit of flocculation units (Lf) of diphtheria toxoid and 5.0 Lf of tetanus toxoid. The combined components are adsorbed using aluminum potassium sulfate and preserved with 1:10,000 thimerosal (Table 1).

## Immunogenicity

The Multicenter Acellular Pertussis Trial, an immunogenicity and safety study conducted in six centers in the United States and sponsored by the National Institutes of Health (NIH), compared antibody responses of infants vaccinated at ages 2, 4, and 6 months with whole-cell DTP or with one of 13 different acellular pertussis vaccines, including Tripedia<sup>®</sup>. Antibody to pertussis antigens was measured in serum samples taken before administration of the first dose and 1 month after administration of the third dose of Tripedia<sup>®</sup>; 99% and 86% of children had fourfold or greater increases in titers of antibody to PT and FHA, respectively. More than 90% of children administered Tripedia<sup>®</sup> developed diphtheria and tetanus antibody levels indicative of immunity to these diseases (i.e., >0.1 antitoxin units [u] per mL and >0.01 u/mL, respectively), as did ≥90% of those administered whole-cell DTP (26). The immunogenicity of Tripedia<sup>®</sup> when administered as a fourth dose to children aged 12–14 months has not been studied.

## Clinical Efficacy

Two studies conducted in Sweden and Germany provide data concerning the clinical efficacy of Tripedia<sup>®</sup>. During 1985–1987, a randomized, placebo-controlled clinical trial in Sweden examined the efficacy of two doses of two acellular pertussis vaccines. The acellular pertussis component of one vaccine was comparable to the acellular pertussis component of Tripedia<sup>®</sup> (17,18). The first dose was administered at age 5–11 months, the second dose 8–12 weeks later. For culture-confirmed disease with cough of any duration, the vaccine's efficacy after two doses was 69% (95% confidence interval [CI]=47%–82%) (18). Using a more stringent case definition (i.e., ≥21 days paroxysmal cough and confirmation by culture) resulted in an efficacy estimate of 81% (95% CI=61%–90%) (27). A non-blinded follow-up study conducted during the 42-month period following the clinical trial yielded similar results (28).

A case-control study in Germany evaluated the efficacy of three doses of Tripedia<sup>®</sup> administered to children aged approximately 3, 5, and 7 months (Connaught Laboratories, Inc., Tripedia<sup>®</sup> package insert). Comparison groups received whole-cell DTP (manufactured by Behringwerke, A.G.), DT, or no vaccine. A case of pertussis was defined as an illness with cough of ≥21 days duration and confirmation by positive culture for *B. pertussis* or household contact with a culture-proven case. The estimated clinical efficacy of three doses of Tripedia<sup>®</sup> compared with DT was 80% (95% CI=59%–90%). For infants who received three doses of whole-cell DTP, the vaccine efficacy estimate was 95% (95% CI=81%–99%) (25). However, the two efficacy estimates are not directly comparable because of differences in the way infants were enrolled in the two groups.

## Safety

The safety of Tripedia<sup>®</sup> was assessed in studies conducted in the United States and Germany. Local reactions (e.g., erythema, swelling, or pain), fever, and other common systemic symptoms (e.g., anorexia, vomiting, drowsiness, or fussiness) occurred less frequently among infants administered Tripedia<sup>®</sup> than among those who received whole-cell DTP (Connaught Laboratories, Inc., Tripedia<sup>®</sup> package insert). In the Multicenter Acellular Pertussis Trial, local and common systemic events occurred less frequently among Tripedia<sup>®</sup> recipients than among recipients of whole-cell DTP (Table 3) (29). Among recipients of 41,615 doses of Tripedia<sup>®</sup> in the trial in Germany, few moderate to severe adverse events occurred within 7 days after vaccination (Connaught Laboratories, Inc., Tripedia<sup>®</sup> package insert). The following events and rates of occurrence (per 1,000 doses administered) were reported: persistent crying for  $\geq 3$  hours, 0.12; febrile seizures, 0.05; afebrile seizures, 0.02; and hypotonic hyporeponsive episodes, 0.05. Rates of invasive bacterial infections, hospitalizations, and deaths among infants vaccinated with Tripedia<sup>®</sup> were similar to those observed among recipients of DT. None of the deaths or invasive bacterial infections was vaccine related.

In a study conducted in the United States, children aged 15–20 months who had received Tripedia<sup>®</sup> (n=109) or whole-cell DTP (n=30) for the first three doses were administered Tripedia<sup>®</sup> as the fourth dose (30). Although the differences were not statistically significant, the percentages of children who had local adverse events (e.g., erythema, swelling, or pain) or certain systemic adverse events (i.e., temperature  $>101$  F [ $>38.3$  C] or irritability) within 72 hours after administration of the fourth dose was higher among children who had received Tripedia<sup>®</sup> for the first three doses. However, the frequency of adverse events was lower than that observed in previous studies in which a fourth dose of whole-cell DTP followed three previous doses of whole-cell DTP.

Limited data are available to evaluate the safety of Tripedia<sup>®</sup> when administered as a fifth dose to children aged 4–6 years who have received four previous doses of Tripedia<sup>®</sup>. The frequency of local and mild systemic reactions after the last of five doses was no greater among children administered Tripedia<sup>®</sup> (n=18) than among children in the same study who were administered five doses of whole-cell DTP (n=10) (M.E. Pichichero, unpublished data). More data concerning the safety of Tripedia<sup>®</sup> in such circumstances are being collected and will be available before infants who receive Tripedia<sup>®</sup> for the first four doses require a fifth dose at age 4–6 years. Data are insufficient to assess the safety of Tripedia<sup>®</sup> administered to persons aged  $\geq 7$  years.

## Simultaneous Administration

Data concerning the immunogenicity of Tripedia<sup>®</sup> administered simultaneously with other childhood vaccines are limited. In a clinical study, infants received Tripedia<sup>®</sup>, *Haemophilus influenzae* type b (Hib) conjugate vaccine (tetanus toxoid conjugate) (ActHIB<sup>®</sup>), oral poliovirus vaccine (OPV), and hepatitis B vaccine simultaneously (Connaught Laboratories, Inc., Tripedia<sup>®</sup> package insert). In one of the study groups, infants were administered Tripedia<sup>®</sup>, ActHIB<sup>®</sup>, and OPV at ages 2, 4, and 6 months, and hepatitis B vaccine at ages 2 and 4 months. After three doses, all of the 69 children who received ActHIB<sup>®</sup> simultaneously with Tripedia<sup>®</sup> vaccine had serum

**TABLE 3. Percentage of infants reported to have had the indicated reaction by the third evening after any dose of pertussis vaccine administered at ages 2, 4, and 6 months (Multicenter Acellular Pertussis Trial)\***

Vaccine	N	Erythema	Swelling	Pain <sup>†</sup>	Fever <sup>§</sup> >101F (>38.3C)	Anorexia	Vomiting	Drowsiness	Fussiness <sup>¶</sup>
Tripedia®	135	32.6**	20.0**	9.6**	5.2**	22.2**	7.4	41.5**	19.3**
ACEL-IMUNE®	217	26.3**	15.6**	3.7**	3.2**	24.9	13.4	40.6**	14.3**
Infanix™	120	39.2**	30.0**	10.8**	3.3**	19.2**	12.5	46.7**	15.0**
DTP <sup>††</sup>	371	72.7	60.9	40.2	15.9	35.0	13.7	62.0	41.5

\* Source: Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995;96(suppl):557-66.

<sup>†</sup> Moderate or severe: cried or protested to touch or when leg moved.

<sup>§</sup> Rectal temperatures.

<sup>¶</sup> Moderate or severe: prolonged or persistent crying, child could not be comforted and refused to play.

\*\* p<0.01 when compared with DTP.

<sup>††</sup> Diphtheria and tetanus toxoids and whole cell pertussis vaccines manufactured by Lederle Laboratories.

Hib capsular polysaccharide antibody (anti-PRP) levels indicative of clinical protection ( $\geq 1 \mu\text{g/mL}$ ). Testing of sera from a group of 12 infants administered hepatitis B vaccine simultaneously with the other two vaccines at ages 2 and 4 months documented a protective antibody response in 11 of the infants (93%) (i.e., anti-hepatitis B surface antigen [anti-HBs] levels of  $>10 \text{ mIU/mL}$ ). Testing of sera from another subset of 20 infants who were administered OPV simultaneously with the other vaccines at ages 2, 4, and 6 months demonstrated that 100% had protective neutralizing antibody to all three poliovirus types. Children ( $n=9$ ) to whom Tripedia<sup>®</sup>, ActHIB<sup>®</sup>, and measles, mumps, and rubella (MMR) vaccine were administered simultaneously at separate sites developed antibody to measles, mumps, and rubella. Simultaneous administration of Tripedia<sup>®</sup> and inactivated poliovirus vaccine (IPV) or varicella vaccine has not been studied.

### TRIHIBIT<sup>™</sup>

On September 27, 1996, FDA licensed TriHIBit<sup>™</sup> (ActHIB<sup>®</sup> vaccine reconstituted with Tripedia<sup>®</sup> vaccine) for the **fourth doses** of the diphtheria, tetanus, and pertussis vaccine series and the Hib vaccine series. When ActHIB<sup>®</sup> is combined with Tripedia<sup>®</sup> by reconstitution, each dose contains 10  $\mu\text{g}$  of purified Hib capsular polysaccharide conjugated to 24  $\mu\text{g}$  of inactivated tetanus toxoid and 8.5% of sucrose, in addition to the content of Tripedia<sup>®</sup>.

### Immunogenicity

In a randomized clinical trial, children aged 15–20 months were administered either Tripedia<sup>®</sup> and ActHIB<sup>®</sup> vaccines at separate sites ( $n=98$ ) or combined as a single dose ( $n=93$ ) (Connaught Laboratories, Inc., Tripedia<sup>®</sup> package insert). Before the study began, these children all had received three doses of a Hib conjugate vaccine and three doses of whole-cell DTP at approximately ages 2, 4, and 6 months. One month after administration of the fourth dose, 100% of the children in both groups had anti-PRP antibody concentrations  $\geq 1 \mu\text{g/mL}$ , an indication of long-term protection against invasive *H. influenzae* type b disease. The proportions of children with protective antibody responses to diphtheria and tetanus toxoids were also high and similar in the two groups. The proportions of children who had fourfold or greater serum antibody responses to PT (measured by enzyme-linked immunosorbent assay [ELISA] or Chinese hamster ovary [CHO] cell assay) were  $>85\%$  in both groups. Among children who received TriHIBit<sup>™</sup>, the proportion with fourfold or greater antibody responses to FHA was slightly lower. The clinical importance of this difference is not known.

### Clinical Efficacy

TriHIBit<sup>™</sup> has been licensed for use as the fourth dose of the two vaccination series on the basis of immunogenicity and safety data. Its protective efficacy when used for this purpose has not been evaluated.



## Safety

The safety of TriHIBit™ was evaluated in two studies involving a total of 960 children who had each received three doses of a Hib vaccine and three doses of whole-cell DTP vaccine at approximately ages 2, 4, and 6 months (Connaught Laboratories, Inc., Tripedia® package insert). At age 15–20 months, these children were administered the fourth dose of Tripedia® and ActHIB® vaccines either combined by reconstitution as a single injection or as two injections at separate sites. Rates of local and systemic reactions were similar in the two groups. Local reactions were mild and resolved within 48 hours following vaccination. The most common local reaction was pain at the injection site.

## Simultaneous Administration

When TriHIBit™ was administered to children aged 15–20 months (n=47) simultaneously with MMR vaccine, >95% developed serum antibody to measles, mumps, and rubella at levels indicative of protection against these diseases (Connaught Laboratories, Inc., Tripedia® package insert). Immune responses to OPV or IPV and hepatitis B vaccine when administered simultaneously with TriHIBit™ have not been studied.

## ACEL-IMUNE®

On December 30, 1996, FDA licensed ACEL-IMUNE® for all five doses of the recommended diphtheria, tetanus, and pertussis vaccination series among children aged 6 weeks–6 years. Each dose of the acellular pertussis component of ACEL-IMUNE® contains approximately 34.4 µg of FHA, 3.2 µg of inactivated PT, 1.6 µg of Pn, and 0.8 µg of Fim type 2. The acellular pertussis vaccine components are purified by ammonium sulfate fractionation and sucrose density gradient centrifugation. PT is detoxified by treatment with formaldehyde. Each dose of ACEL-IMUNE® contains 9.0 Lf units of diphtheria toxoid, 5.0 Lf units of tetanus toxoid, and 300 hemagglutinating units of acellular pertussis vaccine. The FHA and PT components both exhibit hemagglutinating activity. The combined components are adsorbed to aluminum hydroxide and aluminum phosphate and preserved with 1:10,000 thimerosal (Table 1).

## Immunogenicity

Data from the Multicenter Acellular Pertussis Trial provide evidence of the immunogenicity of ACEL-IMUNE® (26). Investigators measured levels of serum antibody to each of the four vaccine antigens after administration of three doses. The percentages of vaccinees with fourfold or greater increases in antibody titer (compared with pre-vaccination levels) were: PT, 67%; FHA, 80%; Pn, 71%; and Fim, 59%. The percentages of these children who developed diphtheria antibody levels of  $\geq 0.1$  u/mL and tetanus antibody levels of  $\geq 0.01$  u/mL (i.e., indications of immunity against these diseases) were 86% and 100%, respectively. Antibody responses observed among children in the United States were similar to those observed among children in the study in Germany that demonstrated the efficacy of ACEL-IMUNE®.

Antibody response to ACEL-IMUNE® when administered to children aged 12–14 months was evaluated in a clinical trial (Wyeth-Lederle Vaccines and Pediatrics,

unpublished data). ACEL-IMUNE<sup>®</sup> was administered as a fourth dose to children aged 12–14 months (n=58) or 15–18 months (n=50) who had previously received three doses of whole-cell DTP. In both age groups, >85% of the children had twofold or greater antibody responses to PT, FHA, Pn, and Fim.

## Clinical Efficacy

Efficacy of ACEL-IMUNE<sup>®</sup> was assessed in a prospective study in Erlangen, Germany (Wyeth-Lederle Vaccines and Pediatrics, ACEL-IMUNE<sup>®</sup> package insert). Infants were randomly assigned to groups that were administered either ACEL-IMUNE<sup>®</sup> or whole-cell DTP (distributed by Wyeth-Lederle Vaccines and Pediatrics) at a mean age of 3, 5, 7, and 17 months. A third group of infants (not selected randomly) received DT at ages 3, 5, and 17 months. In this study, pertussis was defined as cough illness lasting  $\geq 21$  days with at least one pertussis-associated symptom (paroxysms, whoop, or post-tussive vomiting) confirmed by culture, serology, or epidemiologic link to a culture-positive household contact. Between the third and fourth doses, the efficacy of ACEL-IMUNE<sup>®</sup> (compared with DT) was 73% (95% CI=51%–86%) and the efficacy of whole-cell DTP 83% (95% CI=65%–92%). After four doses, the efficacy of ACEL-IMUNE<sup>®</sup> was 85% (95% CI=76%–90%), and that of whole-cell DTP was 94% (95% CI=89%–97%). Considering the full observation period after the third and fourth doses, the adjusted efficacy of ACEL-IMUNE<sup>®</sup> was 81% (95% CI=73%–87%) compared with 91% (95% CI=85%–95%) for whole-cell DTP.

## Safety

Studies from the United States and Germany provide data concerning the frequency and nature of adverse events that occur after administration of ACEL-IMUNE<sup>®</sup>. In the Multicenter Acellular Pertussis Trial, children who were administered ACEL-IMUNE<sup>®</sup> experienced fewer local adverse events (e.g., pain, redness, or swelling at the injection site) and systemic adverse events (e.g., temperature  $>101$  F [ $>38.3$  C], or fussiness) after any of the first three doses than children who were administered whole-cell DTP (Table 3) (29). Similarly, in other studies conducted in the United States and Germany, adverse events (local and systemic) after any of the initial four doses occurred less frequently among children who received ACEL-IMUNE<sup>®</sup> than among children administered whole-cell DTP (Wyeth-Lederle Vaccines and Pediatrics, ACEL-IMUNE<sup>®</sup> package insert). Rates of adverse events increased with the number of previous doses of ACEL-IMUNE<sup>®</sup> administered, but were lower than rates for children who received the same number of doses of whole-cell DTP. Among 357 children who were administered five doses of ACEL-IMUNE<sup>®</sup>, adverse events occurred no more frequently than among children in previous studies (historical controls) who received five doses of whole-cell DTP (Wyeth-Lederle Vaccines and Pediatrics, ACEL-IMUNE<sup>®</sup> package insert).

In the efficacy trial in Germany (n=16,642 doses of ACEL-IMUNE<sup>®</sup>), the following rates of moderate to severe adverse events (per 1,000 doses administered) were observed within 72 hours after administration of the vaccine: persistent or unusual cry, 1.14; temperature  $\geq 105$  F ( $\geq 40.5$  C), 0.06; febrile seizures (no other type of seizure occurred), 0.06; and hypotonic hyporesponsive episodes, 0 (Wyeth-Lederle Vaccines

and Pediatrics, ACEL-IMUNE<sup>®</sup> package insert). Rates of all these adverse events were higher among children who received whole-cell DTP.

A clinical trial examined the frequency of local reactions (e.g., erythema, induration, or tenderness) and systemic reactions (e.g., fever, fussiness, drowsiness, or anorexia) among children aged 12–14 months or 15–18 months, all of whom had previously received three doses of whole-cell DTP. Differences in the frequency of adverse reactions in the two age groups were not statistically significant (Wyeth-Lederle Vaccines and Pediatrics, unpublished data).

Neither anaphylaxis nor encephalopathy occurred during clinical trials that involved administration of 25,899 doses of ACEL-IMUNE<sup>®</sup>. Six deaths of infants or young children who participated in these trials were reported to study investigators; none was vaccine-related and all occurred >4 weeks after vaccination (Wyeth-Lederle Vaccines and Pediatrics, ACEL-IMUNE<sup>®</sup> package insert). The reactogenicity of ACEL-IMUNE<sup>®</sup> among persons aged ≥7 years has not been evaluated.

## Simultaneous Administration

The immunogenicity of ACEL-IMUNE<sup>®</sup> when administered simultaneously with other recommended childhood vaccines was evaluated in three studies. ACEL-IMUNE<sup>®</sup>, Hib vaccine, and hepatitis B vaccine were administered simultaneously to 77 infants at ages 2, 4, and 6 months. After administration of the third dose, serum samples from 94% of the infants demonstrated anti-PRP antibodies indicative of clinical protection (≥1 µg/mL), and all of the infants evaluated (n=74) had antibody levels indicative of protection against hepatitis B (i.e., anti-HBs titers of >10 mIU/mL) (Wyeth-Lederle Vaccines and Pediatrics, ACEL-IMUNE<sup>®</sup> package insert). In another clinical study, 30 infants were administered OPV simultaneously with ACEL-IMUNE<sup>®</sup> at ages 2 and 4 months; ≥90% had protective neutralizing antibody to all three poliovirus types at age 6 months. When MMR vaccine was administered simultaneously with ACEL-IMUNE<sup>®</sup> to children aged 15–18 months (n=48), ≥92% developed serum antibody titers indicative of protection against measles, mumps, and rubella. Similar results were obtained when whole-cell DTP was administered simultaneously with OPV or MMR vaccine (31). Simultaneous administration of ACEL-IMUNE<sup>®</sup> and IPV or varicella vaccine has not been evaluated.

## INFANRIX<sup>™</sup>

On January 29, 1997, FDA licensed Infanrix<sup>™</sup> for use as the initial four doses of the recommended diphtheria, tetanus, and pertussis vaccination series among children aged 6 weeks–6 years. Infanrix<sup>™</sup> is also licensed for all remaining doses in the schedule for children who have received one or more doses of whole-cell DTP vaccine. Each dose of Infanrix<sup>™</sup> contains 25 µg PT, 25 µg FHA, 8 µg Pn, 25 Lf of diphtheria toxoid, and 10 Lf of tetanus toxoid (Table 1). The three antigens in the acellular pertussis vaccine component are separately purified in successive chromatographic steps (hydrophobic, affinity, ion exchange, and size exclusion processes). Formalin and glutaraldehyde are used to detoxify PT; FHA and Pn are treated with formalin. The combined components are adsorbed onto ≤0.625 mg of aluminum (as aluminum hydroxide) and preserved with 2-phenoxyethanol.

## Immunogenicity

In the Multicenter Acellular Pertussis Trial, three doses of Infanrix™ were administered to children at ages 2, 4, and 6 months. One month after the third dose, investigators measured fourfold or greater antibody responses to PT, FHA, and Pn in ≥83% of children who received Infanrix™, a higher proportion than observed among recipients of whole-cell DTP (26). All the children who were administered Infanrix™ developed diphtheria antibody titers of ≥0.1 u/mL and tetanus antibody titers of ≥0.01 u/mL (i.e., indications of immunity against these diseases). Whether their primary vaccination was with Infanrix™ or whole-cell DTP, >86% of children aged 15–20 months had a fourfold or greater rise in serum antibody to each of the pertussis antigens in the vaccine after administration of Infanrix™ as the fourth dose (M. E. Pichichero, unpublished data). The immunogenicity of Infanrix™ administered as a fourth dose to children aged 12–14 months has not been studied.

## Efficacy

The efficacy of Infanrix™ was evaluated in two separate studies (Table 2). In Italy, researchers compared the efficacy of Infanrix™, DTaP manufactured by Chiron Biocine, whole-cell DTP manufactured by Connaught Laboratories, and DT in a randomized controlled trial that enrolled more than 15,000 children (15). Participants received three doses of one of the vaccines at ages 2, 4, and 6 months. The efficacy of Infanrix™ in preventing pertussis disease (defined as paroxysmal cough ≥21 days duration, with culture or serologic confirmation of infection with *B. pertussis*) was 84% (95% CI=76%–89%). The efficacy of whole-cell DTP was 36% (95% CI=14%–52%). After the trial, children were followed in an observational study to an average age of 33 months (range: 20–39 months); the efficacy of Infanrix™ remained high throughout this followup period (78%, 95% CI=62%–87%) (SmithKline Beecham Pharmaceuticals, Infanrix™ package insert).

The second study, conducted in six areas in Germany, was a household contact study. In preparation for this study, three doses of Infanrix™ were administered at ages 3, 4, and 5 months to more than 22,000 infants as part of a large immunogenicity and safety study (23). Infants who did not participate in this study could have received whole-cell DTP vaccine (manufactured by Behringwerke, A.G.) or DT vaccine. The efficacy study included 453 households with confirmed cases of pertussis in which 360 contact children aged 6–47 months were eligible for inclusion in the vaccine efficacy calculations. A case of pertussis was defined as ≥21 days of paroxysmal cough illness plus confirmation of *B. pertussis* infection by culture and/or serologic testing. The efficacy of Infanrix™ was 89% (95% CI=77%–95%); the efficacy of whole-cell DTP was 98% (95% CI=83%–100%).

## Safety

The occurrence of adverse events following vaccination with Infanrix™ was evaluated in clinical studies involving approximately 30,000 children. In these studies, 28,749 infants received Infanrix™ as a three dose primary series, 5,830 children received Infanrix™ as a fourth dose following three doses of Infanrix™, and 22 children received Infanrix™ as a fifth dose following four doses of Infanrix™. In addition,

439 children and 169 children received Infanrix™ as a fourth or fifth dose following three or four doses of whole-cell DTP vaccine, respectively. In comparative studies, administration of Infanrix™ was followed by fewer of the local and systemic adverse reactions commonly associated with whole-cell DTP vaccination (15,29,32–34). However, results of these studies demonstrated that the rates of erythema, swelling, and fever increased with each successive dose of Infanrix™ (SmithKline Beecham Pharmaceuticals, Infanrix™ package insert). In the Multicenter Acellular Pertussis Trial, local and common systemic adverse events occurred less frequently following any dose of Infanrix™ in the primary series than following any dose of whole-cell DTP (Table 3) (29).

The efficacy study conducted in Italy monitored the frequency of moderate to severe adverse events occurring after administration of any of the primary doses of Infanrix™. Rates (per 1,000 doses administered) of adverse events occurring ≤48 hours after administration were: persistent crying ≥3 hours duration, 0.44; seizures, 0.07; and temperature ≥104 F (≥40.0 C), 0.36. These rates were similar to or slightly higher than the rates reported among children who were administered DT, but lower than those for children who received whole-cell DTP. In this trial, no hypotonic hyporesponsive episodes occurred among children to whom Infanrix™ was administered.

In the safety study in Germany, data were available regarding 1,809 children who received three doses of Infanrix™ at ages 3, 4, and 5 months and a fourth dose at a mean age of 20 months. The percentages of children who experienced each of the adverse events ≤3 days after administration of the fourth dose were: redness, 46%; swelling, 35%; pain, 26%; fever ≥100.4 F (≥38 C), 26%; and restlessness, 16%. In this study the rates of redness, swelling, pain, and fever increased with successive doses of Infanrix™ (SmithKline Beecham Pharmaceuticals, Inc., Infanrix™ package insert).

Additional safety data are available from another study conducted in Germany (SmithKline Beecham Pharmaceuticals, Inc., Infanrix™ package insert). Children aged 13–27 months received Infanrix™ or whole-cell DTP (manufactured by Behringwerke, A.G.) as a fourth dose. These children had previously received three doses of the same vaccine. Among children administered Infanrix™ as the fourth dose, the incidence of redness, swelling, pain, fever, and restlessness was lower than among children administered whole-cell DTP as the fourth dose.

Infanrix™ has not been licensed previously for administration of the fourth or fifth dose to children who have received three or four doses of whole-cell DTP. Two studies conducted in the United States examined the frequency of adverse events among children who had previously received three or four doses of whole-cell DTP vaccine at approximately ages 2, 4, 6, and 15–18 months (Table 4). Children aged 15–20 months received Infanrix™ or whole-cell DTP vaccine as the fourth dose; children aged 4–6 years were administered Infanrix™ or whole-cell DTP as the fifth dose (33,34). Significantly fewer local and systemic adverse events were reported following administration of Infanrix™ than following whole-cell DTP vaccine.

In the safety study in Germany, edematous swelling of the entire thigh into which the vaccine was injected was reported spontaneously by parents or care-givers of 62 of 5,361 vaccinees (1.2%) after administration of the fourth dose. The swelling generally began within 48 hours of vaccination and resolved spontaneously without sequelae during an average of 4 days. In other countries where Infanrix™ has been

**TABLE 4. Adverse events (%) occurring <3 days after administration of Infanrix™ to children aged 15–20 months and 4–6 years\*†**

Event	15–20 months		4–6 years	
	Infanrix™ (N=110)	Whole-cell DTP vaccine (N=55)	Infanrix™ (N=115)	Whole-cell DTP vaccine (N= 57)
<b>Local</b>				
Redness	23 <sup>§</sup>	45 <sup>§</sup>	19 <sup>§</sup>	40 <sup>§</sup>
Swelling	14	24	15 <sup>§</sup>	33 <sup>§</sup>
Pain†	5 <sup>§</sup>	38 <sup>§</sup>	12 <sup>§</sup>	40 <sup>§</sup>
<b>Systemic</b>				
Fever >100.5 F**	2 <sup>§</sup>	20 <sup>§</sup>	1 <sup>§</sup>	12 <sup>§</sup>
Fussiness	34 <sup>§</sup>	69 <sup>§</sup>	20	30
Drowsiness	9 <sup>§</sup>	24 <sup>§</sup>	11	18
Poor appetite	9 <sup>§</sup>	20 <sup>§</sup>	6 <sup>§</sup>	16 <sup>§</sup>
Vomiting	2	0	1	4

\* All children had previously been administered diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine: children aged 15–20 months had received three doses; children aged 4–6 years had received four doses.

† Sources: 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;93:656–9 and Annunziato PW, Rothstein EP, Bernstein HH, Blatter MM, Reisinger KS, Pichichero ME. 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;148:503–7.

§ p<0.05.

†Moderate or severe=cried or protested to touch or cried when arm moved.

\*\* Oral temperatures.

licensed, this type swelling has been reported rarely following administration of Infanrix™ for any dose, including the primary series (SmithKline Beecham Pharmaceuticals, Infanrix™ package insert). Edematous swelling has also been reported following administration of other DTaP vaccines, acellular pertussis vaccine alone (without DT), whole-cell DTP vaccine and other vaccines (19,35–37). However, the precise frequency of these reactions among vaccinated children is unknown.

Data are insufficient to evaluate the safety of administration of a fifth dose of Infanrix™ to children aged 4–6 years who have received Infanrix™ for the previous four doses. Additional information regarding the immunogenicity and safety of a fifth dose of Infanrix™ administered to children who have received four prior doses of the same vaccine is being collected. This information is expected to be available before infants who receive Infanrix™ for the first four doses require a fifth dose at age 4–6 years. The safety of Infanrix™ when administered to persons aged ≥7 years has not been assessed.

## Simultaneous Administration

In a clinical trial in the United States, Infanrix™ was administered simultaneously, at separate sites, with hepatitis B vaccine, Hib vaccine, and OPV to children aged 2, 4, and 6 months. One month after the third dose, 100% of infants (n=64) administered hepatitis B vaccine simultaneously with Infanrix™ demonstrated anti-HBs antibodies

≥10 mIU/mL and 90% of infants (n=72) who received Hib vaccine simultaneously with Infanrix™ achieved anti-PRP antibodies ≥1 µg/mL (i.e., antibody levels indicative of protection against these diseases). The percentage of infants who were administered OPV simultaneously with Infanrix™ (n=60–61) who developed protective neutralizing antibody to poliovirus types 1, 2, and 3 ranged from 96% to 100% (38). No data are available regarding antibody responses to MMR vaccine, varicella vaccine, or IPV when administered simultaneously with Infanrix™.

## VACCINE USE

### Recommended Childhood Vaccination Schedule

The routine diphtheria, tetanus, and pertussis vaccination schedule for children aged <7 years comprises five doses of vaccine containing diphtheria, tetanus, and pertussis antigens (Table 5). Three (primary) doses should be administered during the first year of life, generally at ages 2, 4, and 6 months. To maintain adequate immunity during preschool years, the fourth (first booster) dose is recommended for children

**TABLE 5. Routine diphtheria, tetanus, and pertussis vaccination schedule for children aged <7 years—United States, 1997**

Dose	Age	Customary age/ interval	Product*†§
Primary 1	2 months	Age ≥6 weeks	DTaP
Primary 2	4 months	4–8 weeks after first dose¶	DTaP
Primary 3	6 months	4–8 weeks after second dose¶	DTaP
First Booster	15–18 months**	6–12 months after third dose¶	DTaP††
Second Booster	Age 4–6 years, before entering kindergarten or elementary school (not necessary if fourth dose [first booster] is administered after fourth birthday)		DTaP
Additional booster	Every 10 years after last dose		Td§§

\* Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP); diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP) is an acceptable alternative to DTaP for any of the five doses.

† Use diphtheria and tetanus toxoids, adsorbed (DT) if encephalopathy has occurred after administration of a previous dose of pertussis-containing vaccine. If the child is age ≥1 year at the time the first dose of DT is administered, a third dose administered 6–12 months after the second dose completes primary vaccination with DT.

§ Whenever possible, the same DTaP product should be used for all doses. If the same product is not available, Tripedia®, ACEL-IMUNE®, and Infanrix™ can be used interchangeably.

¶ Prolonging the interval does not require restarting the series.

\*\* If the interval between the third and fourth doses is ≥6 months and the child is not likely to return for a visit at the recommended age, the fourth dose of either DTaP or DTP may be administered as early as age 12 months.

†† TriHIBit™ can be administered as the fourth dose following a primary series with either DTaP or whole-cell DTP and a primary series with any *Haemophilus influenzae* type b conjugate vaccine.

§§ Tetanus-diphtheria toxoids absorbed (Td) (for adult use).

aged 15–18 months. The fourth dose should be administered  $\geq 6$  months after the third. If the interval between the third and fourth doses is  $\geq 6$  months and the child is not likely to return for a visit at the recommended age, the fourth dose of either DTaP or whole-cell DTP may be administered as early as age 12 months. The fifth (second booster) dose is recommended for children aged 4–6 years to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.

## Vaccine Preference

DTaP vaccines are efficacious when administered to infants as the primary series (i.e., doses 1–3). In addition, local reactions, fever, and other systemic events occur substantially less often after DTaP administration than after administration of whole-cell DTP. Therefore, DTaP vaccines are recommended for all five doses in the vaccination schedule. For children who have started the vaccination series with one, two, three, or four doses of whole-cell DTP, DTaP is also recommended for all remaining doses in the schedule. During the period of transition from use of whole-cell DTP to DTaP, whole-cell DTP is an acceptable alternative to DTaP for any of the five doses. For the first four doses, whole-cell DTP combined with Hib vaccine (DTP-Hib vaccine) is an acceptable alternative to DTaP and Hib vaccine administered at separate sites.

## Licensed Products

Three acellular pertussis vaccines (Tripedia<sup>®</sup> and Infanrix<sup>™</sup> for the first four doses and ACEL-IMUNE<sup>®</sup> for all five doses) are licensed for the diphtheria, tetanus, and pertussis vaccination series. FDA has not approved Tripedia<sup>®</sup> or Infanrix<sup>™</sup> as the fifth dose among persons who have received only Tripedia<sup>®</sup> or only Infanrix<sup>™</sup> for the first four doses in the vaccination series, because data are insufficient to evaluate their safety in this situation. However, such data should be available before infants vaccinated with four doses of these vaccines require a fifth dose at age 4–6 years.

TriHIBit<sup>™</sup> (ActHIB<sup>®</sup> reconstituted with Tripedia<sup>®</sup>) is licensed only for the fourth dose of the vaccination series, and is not licensed for the first three doses. TriHIBit<sup>™</sup> can be used for the fourth dose following three doses of either DTaP or whole-cell DTP and a primary series of any Hib vaccine.

## Dosage and Administration

The dose of all four vaccines—Tripedia<sup>®</sup>, TriHIBit<sup>™</sup>, ACEL-IMUNE<sup>®</sup>, and Infanrix<sup>™</sup>—is 0.5 mL, administered intramuscularly. Fractional doses (<0.5 mL) should not be administered. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm (39).

To administer TriHIBit<sup>™</sup> (ActHIB<sup>®</sup> reconstituted with Tripedia<sup>®</sup>) (Connaught Laboratories, Inc., ActHIB<sup>®</sup> package insert):

- Cleanse the rubber stoppers of both vials with a suitable germicide.
- Thoroughly agitate the vial of Tripedia<sup>®</sup>. Insert the needle of a syringe through the vial's rubber stopper and withdraw **0.6 mL** of Tripedia<sup>®</sup>.



- Inject Tripedia<sup>®</sup> into the vial of lyophilized ActHIB<sup>®</sup>. Agitate vial thoroughly; the combined reconstituted vaccines should appear whitish in color.
- Withdraw **0.5** mL dose of the combined vaccines; administer intramuscularly within 30 minutes of reconstitution.

## **Interchangeable Use of Acellular Pertussis Vaccines**

Whenever feasible, the same brand of DTaP vaccine should be used for all doses of the vaccination series. Data do not exist regarding the safety, immunogenicity, and efficacy of using DTaP vaccines from different manufacturers for successive doses of the primary or booster vaccination series. However, the vaccine provider may not know or may not have available the type of DTaP vaccine previously administered to a child. Neither circumstance should present a barrier to administration of the vaccine and any of the licensed DTaP vaccines may be used to complete the vaccination series.

## **Simultaneous Administration of Vaccines**

Limited data regarding simultaneous administration of the first three doses of DTaP with other childhood vaccines indicate no interference with response to any of these other antigens. Data are available regarding administration of DTaP with the other vaccines recommended at the same time as the fourth and fifth doses of the diphtheria, tetanus, and pertussis series (i.e., Hib vaccine, OPV, MMR vaccine, and varicella vaccine), and regarding administration of whole-cell DTP (all doses in the series) with these vaccines (40). On the basis of this experience, DTaP may be administered simultaneously with hepatitis B vaccine, Hib vaccine, and IPV or OPV to infants at ages 2, 4, or 6 months as indicated in the recommended childhood vaccination schedule (41). All vaccines appropriate to the age and previous vaccination status of the child should be administered simultaneously including DTaP, Hib vaccine, IPV or OPV, hepatitis B vaccine, MMR vaccine, and varicella vaccine.

## **Special Considerations**

### ***Vaccination of Infants and Young Children Who Have a Personal or Family History of Seizures***

Infants and young children who have had previous seizures (whether febrile or nonfebrile) are at greater risk for seizures after administration of whole-cell pertussis vaccination than are infants who do not have such a history (42). Because these reactions may be caused by the fever induced by whole-cell DTP and because DTaP is less frequently associated with moderate to high fever, DTaP is the vaccine of choice when pertussis vaccination is considered for these children.

Among infants and children with a history of previous seizures, it is prudent to delay pertussis vaccination until the child's neurologic status has been assessed. Infants and children with a stable neurologic condition, including well-controlled seizures, may be vaccinated with DTaP. Infants with evolving neurologic conditions should not be vaccinated until a treatment regimen has been established and the condition has stabilized. Acetaminophen or ibuprofen may be administered to these

children at the time of DTaP vaccination and every 4 hours for 24 hours thereafter to reduce the possibility of postvaccination fever.

Data from one study indicate that infants and young children who have a parent or sibling with a history of convulsions are more likely to have seizures following whole-cell DTP vaccination than those without such histories (43). However, seizures occur infrequently after administration of whole-cell DTP, are usually febrile in nature, and generally have a benign outcome (44). An estimated 5%–7% of children have parents or siblings with a history of convulsions (43). If these children were exempted from pertussis vaccination, unvaccinated persons and the general population might face an increased risk for pertussis. Therefore, a family history of convulsions or other central nervous system disorders is **not** a contraindication to pertussis vaccination. Acetaminophen or ibuprofen may be administered to these children at the time of DTaP vaccination and every 4 hours for 24 hours thereafter to reduce the possibility of postvaccination fever.

### ***Children Who Have Had Pertussis Disease***

Although pertussis disease is likely to confer immunity against pertussis, the duration of such immunity is unknown. Children with well-documented pertussis disease (i.e., positive culture for *B. pertussis* or epidemiologic linkage to a culture-positive case) should be administered DT vaccine for the remaining doses of the vaccination series to ensure that they are protected against diphtheria and tetanus. Some experts recommend including the pertussis component for subsequent vaccination of infants who have had culture-proven pertussis because infants may have a suboptimal immune response following *B. pertussis* infection (45).

### ***Pertussis Vaccination for Persons Aged $\geq 7$ Years***

Pertussis vaccines are presently licensed for use only among children aged 6 weeks–6 years. In the United States, adolescents and adults whose immunity has waned are an important reservoir for *B. pertussis* and may infect unvaccinated young children. In the future, booster doses of adult formulations of acellular pertussis vaccines may be recommended to prevent the occurrence and spread of the disease among these older persons. However, acellular pertussis vaccines combined with diphtheria and tetanus toxoids will need to be reformulated for use in adults because all infant formulations contain more diphtheria toxoid than is recommended for persons aged  $\geq 7$  years. Recommendations regarding routine vaccination of adults will require additional research (e.g., studies of the incidence, severity, and cost of pertussis among adolescents and adults; studies of the effectiveness and safety of adult formulations of DTaP; and studies of the cost-effectiveness of a strategy of adult vaccination).

## **ADVERSE REACTIONS**

Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia may occur after both whole-cell DTP vaccination and DTaP vaccination. However, data concerning adverse reactions following the first four doses indicate that mild reactions are less common among children who receive DTaP. These reactions are self-limited and can be managed safely with symptomatic treatment.\*

\*For a complete discussion, see the general ACIP statement on diphtheria, tetanus, and pertussis and the supplementary statements on DTaP (16,17,42).

Moderate-to-severe systemic events (e.g., temperature of  $\geq 105$  F [ $\geq 40.5$  C]; febrile seizures; persistent, crying lasting  $\geq 3$  hours; and hypotonic hyporesponsive episodes) have been reported rarely after administration of DTaP, and occur less frequently among children administered DTaP than among children administered whole-cell DTP.

Data from the Vaccine Adverse Event Reporting System (VAERS)\* were used to compare rates of fever, seizures, and hospitalizations among children who, having had  $\geq 3$  previous doses of whole-cell DTP, were administered either DTaP or whole-cell DTP vaccines for the fourth or fifth doses (46). During 1991–1993, approximately 5 million doses of DTaP (distributed by Connaught Laboratories, Inc., or Wyeth-Lederle Vaccines and Pediatrics) and 27 million doses of whole-cell DTP were distributed for use among children aged 15 months–6 years. Adverse events were reported significantly less commonly among the children who received DTaP. VAERS is a passive surveillance system and these data should be interpreted with caution because the events reported may be linked to vaccine administration only by temporal coincidence.

## CONTRAINDICATIONS

If either of the following events occurs after administration of DTaP or whole-cell DTP, subsequent vaccination with DTaP or whole-cell DTP is contraindicated:

- *An immediate anaphylactic reaction.* Further vaccination with any of the three components of DTaP or whole-cell DTP should be deferred because of uncertainty as to which component of the vaccine might be responsible. Because of the importance of tetanus vaccination, persons who experience anaphylactic reactions may be referred to an allergist for evaluation and (if specific allergy can be demonstrated) desensitized to tetanus toxoid.
- *Encephalopathy not attributable to another identifiable cause* (e.g., an acute, severe central nervous system disorder occurring within 7 days after vaccination and generally consisting of major alterations in consciousness, unresponsiveness, or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours.) In such cases, DT vaccine should be administered for the remaining doses in the vaccination schedule to ensure protection against diphtheria and tetanus.

## PRECAUTIONS

If any of the following events occurs within the specified period after administration of either whole-cell DTP or DTaP, vaccine providers and parents should evaluate the risks and benefits of administering subsequent doses of a pertussis-containing vaccine:

- Temperature of  $\geq 105$  F ( $\geq 40.5$  C) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours.

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\*VAERS is a passive surveillance system for reporting of adverse events temporally associated with administration of vaccines.

- Persistent crying lasting  $\geq 3$  hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

In circumstances in which the benefits of further pertussis vaccination outweigh the possible risks (e.g., during an outbreak of pertussis), DTaP should be administered for the subsequent doses.

## REPORTING OF ADVERSE EVENTS AFTER VACCINATION

As with any newly licensed vaccine, surveillance for rare adverse events potentially associated with administration of DTaP is important for assessing its safety in large-scale use. The National Childhood Vaccine Injury Act of 1986 requires health-care providers to report serious adverse events that follow pertussis vaccination (47). The events that must be reported are detailed in the Reportable Events Table within this Act, and include anaphylaxis or anaphylactic shock, encephalopathy (or encephalitis), shock collapse or hypotonic hyporesponsive collapse, and any acute complication or sequela (including death) of these events. Adverse reactions should be reported to VAERS (48). VAERS reporting forms and information are available 24 hours a day by calling (800) 822-7967.

## VACCINE INJURY COMPENSATION

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, provides a mechanism through which compensation can be paid on behalf of a person thought to have been injured or to have died as a result of receiving a vaccine covered by the program (49,50).

A Vaccine Injury Compensation Table in the Act lists the vaccines covered by the program and the injuries, disabilities, and conditions (including death) for which compensation may be paid. Development or onset of anaphylaxis or anaphylactic shock  $\leq 4$  hours or encephalopathy with onset  $\leq 72$  hours after administration of pertussis vaccine (or sequelae of these conditions) are potentially compensable under this law. Persons may be compensated for an injury listed in the established table or one that can be demonstrated to result from administration of a listed vaccine. Additional information about the program is available.\*

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\*National Vaccine Injury Compensation Program  
Health Resources and Services Administration  
Parklawn Building, Room 8-05  
5600 Fishers Lane  
Rockville, MD 20857  
Telephone: (800) 338-2382 (24-hour recording)

Persons wishing to file a claim for vaccine injury should call or write to:  
U.S. Court of Federal Claims  
717 Madison Place, NW  
Washington, DC 20005  
Telephone: (202) 219-9657

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