

# AMERICAN ACADEMY OF PEDIATRICS

Committee on Infectious Diseases

## Acellular Pertussis Vaccine: Recommendations for Use as the Initial Series in Infants and Children

**ABSTRACT.** In 1991 and 1992, the US Food and Drug Administration approved two acellular pertussis vaccines combined with diphtheria and tetanus toxoids for use as the fourth and fifth doses after the initial three-dose primary series with the standard whole-cell pertussis vaccine administered at 2, 4, and 6 months of age. Recently completed trials of acellular pertussis vaccines conducted in Europe have documented the efficacy of these vaccines when administered as a primary series in infancy. Based on these studies, two acellular pertussis vaccines, Tripedia (Connaught Laboratories, Swiftwater, PA) and ACEL-IMUNE (Wyeth-Lederle Laboratories, Pearl River, NY), were licensed by the Food and Drug Administration for the initial three-dose series. Additional acellular pertussis vaccines are likely to be licensed for use in infants in the future. The recommendations in this statement supplement previous American Academy of Pediatrics guidelines for the use of acellular pertussis vaccines.<sup>1-4</sup>

### BACKGROUND

Although whole-cell pertussis (DTwP) vaccines are effective in prevention of pertussis disease, concerns about local and systemic reactions have stimulated efforts to produce less reactogenic vaccines.

DTwP vaccines are prepared from inactivated cells of *Bordetella pertussis* and contain multiple defined and undefined antigens. In contrast, acellular pertussis vaccines (Table 1) contain one or more of five purified antigens derived from *B pertussis* organisms. All acellular pertussis vaccines contain inactivated pertussis toxoid (PT) in different concentrations (Table 2) but vary in the inclusion and concentration of four other antigens. These four pertussis antigens are filamentous hemagglutinin (FHA), pertactin (PRN), a nonfimbrial protein formerly called 69-kd outer membrane protein, and two fimbrial proteins (fimbria [FIM] types 2 and 3), formerly called agglutinogens (Tables 2 and 3).

### RECENT TRIALS OF PERTUSSIS VACCINES

In National Institutes of Health (NIH)-sponsored phase 1 and 2 trials conducted in 1991 and 1992, safety and immunogenicity of 13 acellular pertussis vaccines were evaluated. In these studies, the adverse events after administration of acellular pertussis vaccines were significantly less frequent and less severe than those associated with the DTwP refer-

ence group,<sup>1</sup> and the acellular pertussis vaccines were immunogenic.<sup>2</sup> These and other data formed the basis for selection of vaccines for inclusion in the two NIH-sponsored efficacy trials conducted in Stockholm, Sweden, and Italy. Efficacy trials also were conducted by the NIH in Göteborg, Sweden, and by various pharmaceutical manufacturers in Munich, Erlangen, and Mainz, Germany, and Senegal (Table 3).

These seven trials evaluating the efficacy of three or four doses of different acellular pertussis vaccines in infancy were completed or reported in 1995<sup>3-7</sup> (Table 3). The NIH-sponsored trials in Stockholm and Italy are the only two of the seven trials that compared the safety and efficacy of more than one acellular pertussis vaccine per trial.<sup>4,5</sup> These two trials compared acellular pertussis vaccines with a placebo (diphtheria-tetanus [DT]) and with a US DTwP vaccine<sup>4,5</sup> given at the US infant immunization schedule of 2, 4, and 6 months of age. In the NIH-sponsored trial in Göteborg,<sup>3</sup> a monovalent (PT alone) acellular pertussis vaccine was administered subcutaneously using a schedule of 3, 5, and 12 months. The fourth dose at 12 to 18 months of age was not given in these three trials. All three of these studies (Stockholm, Italy, and Göteborg) included a group randomized to receive DT, enabling calculation of an absolute vaccine efficacy. Another study of more than 80 000 infants is underway in Stockholm to evaluate three different acellular pertussis vaccines in addition to a whole-cell vaccine.

The trials not sponsored by the NIH used different study designs and different immunization schedules. The study conducted in Munich, Germany, forms the basis for approval of Tripedia (Connaught Laboratories, Swiftwater, PA) for use in infants (see "Efficacy"). The trial conducted in Erlangen formed the basis for approval of the four-component acellular pertussis vaccine (PT, FHA, PRN, and FIM) (ACEL-IMUNE; Wyeth-Lederle Laboratories, Pearl River, NY). In the study in Mainz, a three-component investigational acellular pertussis vaccine<sup>6</sup> containing PT, FHA, and PRN was administered at 3, 4, and 5 months of age; efficacy was determined by attack rates of pertussis in household contacts.<sup>6,7</sup> In the study in Senegal, a two-component acellular pertussis vaccine containing PT and FHA was administered at 2, 4, and 6 months of age.<sup>7</sup>

In aggregate, the efficacy trials demonstrated that acellular pertussis vaccines, when administered beginning at 2 or 3 months of age, caused lower rates of fever and local adverse reactions, including ery-

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**TABLE 1.** Licensed Acellular Pertussis-containing Vaccines as of December 1996

Manufacturer	Antigens*	Trade Name	Licensed by FDA†	Year Approved
Connaught Laboratories	PT	Tripedia	First 3 doses	1996
	FHA		Fourth and fifth doses	1992
Wyeth-Lederle Laboratories	PT	ACEL-IMUNE	Fourth and fifth doses	1991
	FHA		First 3 doses	1996
	Fimbria 2			
	Pertactin			

\* PT indicates pertussis toxoid; and FHA, filamentous hemagglutinin.

† FDA indicates US Food and Drug Administration.

thema, induration, and pain or tenderness, than the widely used DTwP vaccines<sup>1</sup> and reduced rates of more serious adverse events, including hypotonic-hyproresponsive episodes (HHEs), persistent crying, temperature higher than 40°C (104.9°F), and seizures. In the NIH-sponsored trials in Stockholm and Italy, the acellular pertussis vaccines were more effective than DTwP vaccines given in these field trials<sup>4,5</sup>; in the trials in Erlangen, Mainz, and Senegal<sup>6,7</sup> in which different DTwP vaccines were used, efficacy was somewhat higher in the DTwP vaccine groups.

The US Food and Drug Administration (FDA) recently approved Tripedia and ACEL-IMUNE, the first two of several acellular pertussis vaccines likely to be approved for use as the primary series. Vaccines licensed in the future may vary in formulation, inactivation process and adjuvant and antigen content, as well as in study design and case definitions used for evaluation, making direct comparison of preparations evaluated in different studies difficult.

#### EFFICACY

In most of the recent studies of various acellular products, the World Health Organization (WHO) definition or a similar definition of pertussis was used. The WHO definition is paroxysmal cough for 21 or more days and at least one of the following additional criteria: (1) positive nasopharyngeal culture in the study child or a family member, (2) seroconversion or a significant rise in immunoglobulin G or A antibody against PT and FHA antigens, and (3) contact with a culture-confirmed infected household member.

#### VACCINE PRODUCTS

As noted, two acellular pertussis vaccines have been licensed for use in infancy. Information on the safety, immunogenicity, and efficacy of the acellular pertussis vaccine produced by Connaught Laboratories (Tripedia) in infants has been derived from its use in an efficacy trial in 1986 in Sweden<sup>8,9</sup> and the recently completed prospective, case-control trial in Munich.<sup>7</sup> Additional data on immunogenicity and safety also are available from studies in the United States.<sup>10,11</sup>

In the 1986 NIH-sponsored trial in Sweden, two groups receiving acellular pertussis vaccines, one containing PT and FHA and the other containing only PT, were compared with a control group that received DT, all given at approximately 6 and 8 months of age, which differs from the US schedule.<sup>8</sup>

The bivalent vaccine had a protective efficacy of 69% (95% confidence interval [CI], 47 to 82) for all cases of culture-confirmed pertussis with any cough for 1 day or longer, and in the monovalent group, protective efficacy was 54% (95% CI, 26 to 72) in preventing culture-confirmed pertussis using a non-WHO case definition. Because a DTwP group was not included, these results were compared with historical data in which the DTwP vaccine was believed to be 80% to 85% effective. Therefore, the acellular pertussis vaccines were not approved for routine use at that time. In the recently completed trial in Munich, 16 780 children enrolled in a prospective study received DTaP, DTwP, DT, or no vaccine at 2, 4, and 6 months of age (Table 3). A case of pertussis was defined as an illness with cough of 21 days' duration or longer and confirmed by positive culture for *B pertussis* or exposure to a household contact with a culture-proven case. The clinical efficacy of three doses of the bivalent (PT and FHA) acellular pertussis vaccine compared with DT was 80% (95% CI, 59 to 90), and the efficacy of three doses of DTwP vaccine manufactured in Germany was 87% (95% CI, 33 to 97). Because of differences in enrollment of infants in the study, the efficacy estimates for DTaP and DTwP are not directly comparable. Additional information about the immunogenicity and safety of a fifth dose after four doses of the acellular vaccine is being collected and is expected to be available before infants who have completed the initial four-dose acellular pertussis vaccine combined with diphtheria and tetanus toxoids (DTaP) series are 4 to 6 years of age and require a fifth dose. In a trial in Erlangen, Germany, the acellular pertussis vaccine produced by Wyeth-Lederle (ACEL-IMUNE) was 81% efficacious in infants who had received the vaccine at 2, 4, and 15 to 18 months of age; and the whole cell vaccine produced in the United States by the same company was 91% efficacious. Infants whose parents refused pertussis vaccines received DT and other infants were randomized to receive DTaP or DTwP.

#### OTHER VACCINES

In the recently completed NIH-sponsored trial in Stockholm,<sup>5</sup> in which the WHO definition was applied, infants were immunized with three doses of acellular pertussis vaccine or a standard US-prepared DTwP vaccine beginning at 2 months of age. The efficacy was 85% for the five-component acellular pertussis vaccine (PT, FHA, PRN, and FIM 2 and 3), 59% for a two-component acellular pertussis vaccine (PT and FHA), and 48% for the DTwP vaccine

**TABLE 2.** Vaccine Manufacturer, Pertussis Inactivation Process, and Antigen Content of Acellular Pertussis Combined With Diphtheria and Tetanus Toxoid Vaccines Evaluated in Clinical Trials

Vaccine Manufacturer	Pertussis Toxoid Inactivation Process	Pertussis Toxoid, µg/dose	Filamentous Hemagglutinin, µg/dose	Pertactin, µg/dose	Fimbria, µg/dose	Diphtheria Toxoid, Lf*	Tetanus Toxoid, Lf*
Connaught Laboratories (Tripedia)	Formaldehyde	23.4	23.4	...	...	6.7	5
Wyeth-Lederle Laboratories (ACEL-IMUNE)	Formaldehyde	3.2	34.4	1.6	0.8†	9	5
Connaught, Ltd, (Canada)	Glutaraldehyde	10	5	3	5‡	15	5
SmithKline Beecham	Formaldehyde and glutaraldehyde	25	25	...	...	17	10
Chiron-Biocine	Genetic and formaldehyde	5	2.5	2.5	...	25	10
SmithKline Beecham§	Formaldehyde and glutaraldehyde	25	25	8	...	25	10
North American Vaccine	Hydrogen peroxide	40	...	...	...	25	7
Pasteur-Mérieux	Glutaraldehyde	25	25	...	...	15	5

\* Lf indicates limit of flocculation units per dose.

† Fimbria type 2.

‡ Fimbria types 2 and 3.

§ Same vaccine tested in trials in Italy and Mainz, Germany.

**Table 3. International Efficacy Trials in Infants of Acellular Pertussis Vaccines Combined With Diphtheria and Tetanus Toxoids**

Site of trial	Trade name and approval status	Vaccine manufacturer	Vaccine composition†				Schedule studied (mos)	Vaccine efficacy (95% CI)					
			PT	FHA	PRN	FIM		DTaP†			DTwP†		
								0	50	100	0	50	100
Munich, Germany* [1]	Tripedia®, all doses	Connaught, Inc, (U.S.A.)					2, 4, 6	—+			—+		
Erlangen, Germany [2]	ACEL-IMUNE®, all doses	Wyeth-Lederle					2, 4, 6, 15–18	+			+		
Stockholm, Sweden [3]	Not approved#	Connaught, Ltd. (Canada)					2, 4, 6	+			+		
Stockholm, Sweden [3]	Withdrawn	SmithKline Beecham					2, 4, 6	+			+		
Italy [3]	Not approved#	Chiron/Biocine					2, 4, 6	+			—		
Italy [3]	Not approved#	SmithKline Beecham					2, 4, 6	+			—		
Göteborg, Sweden [3]	Not approved#	North American Vaccine					3, 5, 12	+			None		
Mainz, Germany [4]	Not approved#	SmithKline Beecham					3, 4, 5	+			+		
Senegal, West Africa [5]	Not approved#	Pasteur/Merieux					2, 4, 6	—			+		

† PT = pertussis toxoid; FHA = filamentous hemagglutinin; PRN = pertactin; FIM = fimbria; DTaP = acellular pertussis vaccine; DTwP = whole-cell vaccine

\* Efficacy data included cases of pertussis 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. Efficacy results for DTaP preparations should only be compared in studies using direct side-by-side study design as occurred in the trials in Stockholm and Italy.

# Not approved as of date of this publication

[1] Prospective case-control study with passive surveillance [ref 7]; trial not designed to permit comparison of efficacy data between DTaP and DTwP groups

[2] Randomized, double-blind cohort study with an open non-randomized DT cohort [ref 7]

[3] Prospective, randomized, double-blind placebo-controlled cohort [ref 3–5]

[4] Prospective, blinded, household case contact study (surveillance in catchment area of an earlier DTaP immunogenicity study) [ref 6]

[5] Prospective, randomized, double-blind cohort study with a parallel DT non-study group [ref 7]

(Table 3). In the Italian trial,<sup>4</sup> efficacy was 84% for both of the three-component acellular pertussis vaccines (PT, FHA, and PRN) and 36% for the whole-cell vaccine. The efficacy of the whole-cell vaccine was

85% when evaluated shortly after completion of the three-dose series in children 6 to 9 months of age. The efficacy of the DTwP vaccine waned faster than that of the acellular products because of a rapid

decline in efficacy during the second year.<sup>5</sup> The lower efficacy of whole-cell vaccine in both trials was not anticipated and is an underestimate of the effectiveness of the DTwP vaccine in the United States, where four rather than three doses are given by 15 to 18 months of age.<sup>12-14</sup>

Surveillance statistics in the United States do not permit calculation of vaccine-specific attack rates, but the efficacy of whole-cell vaccines used in the United States has been assessed in household contact studies.<sup>18</sup> Depending on the case definition used, the efficacy of whole-cell pertussis vaccine was 95% to 98% for children with positive results on cultures and 77% to 95% for children with positive results on cultures or serologic testing, depending on disease severity. This study demonstrated that DTwP was highly effective in preventing pertussis in preschool children exposed to infection within their households,<sup>15</sup> supporting the observation that DTwP vaccines used in the United States successfully have controlled disease.

Results of manufacturer-supported studies and the NIH-supported study in Göteborg are more difficult to compare than the other two NIH-supported studies involving multiple acellular pertussis vaccines, because of differences in immunization schedules, study designs, and comparison vaccines. In addition, each study evaluated only one acellular product. In the Göteborg trial, the monovalent PT vaccine had an efficacy of 71%.<sup>1</sup> In the trial in Mainz,<sup>4</sup> the efficacy of trivalent acellular pertussis vaccine was 89% compared with 98% for the DTwP vaccine manufactured in Germany, as calculated from attack rates of pertussis in household contacts classified by pertussis immunization status. In the trial in Senegal, efficacy was 85% for a bivalent (PT and FHA) vaccine and 96% for a whole-cell vaccine manufactured in France.<sup>7</sup> These efficacy rates may change as additional data from longer follow-up periods are analyzed.

### IMMUNOGENICITY

When used for the primary series in infants, the immunogenicity of the various antigens constituting the DTaP vaccines (Table 3) generally was similar or higher<sup>4,5</sup> than that of the same antigens of the DTwP vaccines when concentrations of serum antibody to PT, FHA, PRN, and FIM were measured by enzyme immunoassay.<sup>2-6,10,11</sup> However, in none of the trials

could antibody responses be correlated with protection against disease, indicating that currently measured antibody responses to the various vaccine antigens cannot be used to predict efficacy.<sup>9</sup> A correlate of protection is difficult to determine when the mechanism of immunity is complex and has not been well defined.<sup>8</sup>

### ADVERSE REACTIONS

After primary immunization with the acellular pertussis vaccines, rates of local reactions (erythema, induration, and tenderness at the injection site), drowsiness, irritability, anorexia, and fever have been reported to occur at significantly lower rates than reactions occurring in age-matched children after immunization with DTwP vaccines.<sup>1,4,5</sup> Each of these minor side effects occurred significantly less in US infants who received Tripedia than in infants who received DTwP vaccines after the first, second, and third immunizations at 2, 4, and 6 months of age (Table 4). Similar low rates of adverse reactions have been reported following ACEL-IMUNE in studies conducted in the United States and Europe. Although differences were observed in reactions in a study that compared two whole-cell and 13 acellular pertussis vaccine candidates, none of the acellular pertussis vaccines were found to be consistently the most or least reactogenic,<sup>1</sup> and no association was found between the number of vaccine components and reactogenicity.

Certain serious adverse events, such as HHEs, persistent, inconsolable crying for 3 or more hours, temperature of 40°C and higher, and seizures, occur less frequently after acellular pertussis vaccine (Table 5). In the Munich trial, data on these adverse events after administration of DTwP were not collected in a manner that permits comparison. Data collected in the Stockholm, Erlangen, and Italian trials permit comparison between DTaP and DTwP groups with regard to these side effects. In the Italian trial, HHEs and persistent crying for 3 or more hours were significantly ( $P < .01$  and  $.001$ , respectively) less frequent in the acellular pertussis groups than in the group that received DTwP.<sup>4</sup> In the trial in Stockholm, protracted crying for 3 or more hours occurred in recipients of the two DTaP vaccines and the DT vaccine at a significantly ( $P < .001$ ) lower rate than in recipients of DTwP vaccines.<sup>5</sup> Surveillance after licensure in the United States has shown that rates of

**TABLE 4.** Minor Side Effects Reported Within 72 Hours of Immunization in 672 US Infants Receiving Tripedia DTaP or Connaught Whole-cell Pertussis Vaccine DTwP at 2, 4, and 6 Months of Age\*

Event	Dose 1†		Dose 2†		Dose 3†	
	DTaP, % (n = 505)	DWwP, % (n = 167)	DTaP, % (n = 499)	DTwP, % (n = 159)	DTaP, % (n = 490)	DTwP, % (n = 152)
Erythema (>1 inches)	1	8	2	8	2	7
Induration (>1 inches)	1	13	1	11	1	11
Pain or tenderness	12	51	7	44	7	43
Drowsiness	39	60	18	45	16	26
Irritability	35	73	30	72	27	56
Anorexia	6	27	5	20	6	19
Temperature >101°F and <104°F	0.5	4	2	8	4	11

\* Vaccines supplied by Connaught, Inc (Swiftwater, PA) and Connaught Ltd (Canada). Data are from package inserts.

† DTaP compared with DTwP, all significant,  $P < .01$ . n indicates number of infants in each category.



**TABLE 5.** Incidence of Moderate to Severe Reactions Within 48 to 72 Hours of Administration of Acellular and Whole Cell Pertussis Vaccines at 2, 4, and 6 Months of Age

Study Site and Vaccine	HHE†		Persistent Crying >3 h		Temperature >40°C		Seizures	
	No.	Incidence/ 100 000 Doses	No.	Incidence/ 100 000 Doses	No.	Incidence/ 100 000 Doses	No.	Incidence/ 100 000 Doses
United States								
DTaP (Tripedia)*	1	14	4	56	2	28	0	0
Erlangen								
DTaP (ACEL-IMUNE)	0	0	13	103	1	8	1	8
DTwP	1	8	69	552	3	24	1	8
Italy <sup>8</sup>								
DTaP (CB)	1	7	9	66	4	29	0	0
DTaP (SKB)	0	0	6	44	5	36	1	7
DTwP	9	67	54	400	32	240	3	22
Stockholm <sup>9</sup>								
DTaP (CN)	1	13	4	52	2	26	0	0
DTaP (SKB)	0	0	2	26	4	52	2	26
DTwP	5	81	23	374	28	456	1	16

\* Data are from an open-label, noncontrolled clinical study of 2457 infants (7102 doses). DTaP indicates diphtheria and tetanus toxoids, acellular pertussis; CB, Chiron/Biocine, CN, Connaught, SKB, SmithKline Beecham; and DTwP, diphtheria and tetanus toxoids, whole-cell pertussis.

† HHE, indicates hypotonic-hyporesponsive episode, persistent, inconsolable crying for 3 or more hours, temperature higher than 40°C, and seizures within 48 hours of immunization in children.

seizures and hospitalization are reduced by 60% to 70% with the use of DTaP for the fourth and fifth doses of the diphtheria-tetanus-pertussis (DTP) immunization series.<sup>16</sup>

None of the efficacy trials enrolled adequate numbers of children to evaluate the role of acellular pertussis vaccines in the category of the rare, serious adverse events, such as encephalopathy occurring within 7 days, or immediate anaphylaxis. Only extensive evaluation after licensure can determine whether serious adverse events that occur at a rate of 1 in 100 000 immunizations or less are reduced with acellular pertussis vaccines. Because many studies have failed to show an association between these rare events and immunization with DTwP vaccines,<sup>17</sup> it is unlikely that acellular pertussis vaccines will affect the rate at which permanent neurologic disease develops in children after immunization. The reduced number of reactions, especially febrile responses, after immunization with various DTaP preparations should make these vaccines desirable for use in infants and children.

The Vaccine Adverse Event Reporting System is designed to accept reports of all serious adverse events that occur after receipt of any immunization including DTaP. Additional information about the program or questions about reporting requirements or completion of the report form or requests for reporting forms can be directed to (800) 822-7967.

### RECOMMENDATIONS

The following recommendations pertain to the use of acellular pertussis vaccines in children. Other aspects of pertussis are addressed in the current edition of the *Red Book*<sup>13</sup> and in previous American Academy of Pediatrics Guidelines.<sup>12,18,19</sup>

1. All infants routinely should be immunized with five doses of diphtheria-, tetanus-, and pertussis-containing vaccine beginning at 6 to 8 weeks of age or as soon as possible thereafter, unless con-

traindicated. If the fourth dose was administered after the fourth birthday because of delays in completing the immunization schedule, the fifth dose can be omitted. In the United States, DTaP is preferred for all doses in the immunization schedule. During the transition period from the use of DTP to DTaP, DTP is an acceptable alternative for any of the five doses. For the first four doses, DTP combined with *H influenzae* type b conjugate vaccine (DTP-Hib) is an acceptable alternative to DTaP and Hib vaccines administered at separate sites.

2. In children who have begun their primary immunization schedule with DTwP, an approved DTaP vaccine can be used to complete the pertussis immunization schedule.
3. For children who have had adverse reactions to DTwP resulting in a precaution for administration of the pertussis immunization (ie, HHE within 48 hours, inconsolable crying for  $\geq 3$  hours within 48 hours, temperature  $>40.5^{\circ}\text{C}$  [ $104.9^{\circ}\text{F}$ ] within 48 hours, or febrile seizure within 72 hours), DTaP is recommended if the antipertussis immunization schedule is to be completed. The risks and benefits of giving additional doses need to be evaluated on an individual basis.
4. Children who have a true contraindication to pertussis immunization (ie, encephalopathy not caused by another identifiable cause occurring within 7 days, or an immediate anaphylactic reaction after DTwP or DTaP immunization) should receive no further doses of DTwP or DTaP. In children with encephalopathy, DT should be substituted for each of the remaining DTwP or DTaP doses. In children with an immediate anaphylactic reaction, further immunization with any of the three antigens in DTaP or DTP should be deferred because of the uncertainty as to which component of the vaccine might be responsible. Persons who experience anaphylactic reactions may be referred

to an allergist for evaluation and desensitization to tetanus toxoid if specific allergy can be demonstrated.

5. Simultaneous administration of DTaP and other recommended vaccines is acceptable. Vaccines should not be mixed in the same syringe unless approved by the FDA. On September 27, 1996, the FDA approved reconstituting Tripedia with ActHIB vaccine and administering the combination as a single injection for the booster (fourth) dose of the DTP immunization series in those 15 months and older. Mixing these two vaccines in the same syringe for doses 1 through 3 or 5 is not yet FDA approved. Note: ActHIB (distributed by Connaught Laboratories) is identical to OmniHIB (distributed by SmithKline Beecham Pharmaceuticals).

### FUTURE DIRECTIONS

Other acellular pertussis vaccines may be approved soon by the FDA for use in children for the primary series beginning at 2 months of age. Evaluation of these vaccines necessitates consideration that each product will vary in the number of pertussis antigens, how antigens are prepared and combined, the quantity of antigens in the final product (Table 3), and the study designs used for evaluation. These differences may make comparisons of efficacy, immunogenicity, and adverse events among the clinical trials difficult.

Development of recommendations about the interchangeability of these products for primary or booster immunization will be complicated by the absence of serologic correlates of immunity. When feasible, the same DTaP vaccine should be used for the first three doses of the pertussis immunization series. No data exist on the safety, immunogenicity, or efficacy of different DTaP vaccines when administered interchangeably in the primary immunization series of a child. However, in those circumstances in which the DTaP product(s) received previously is not known, or the previously administered product is not available, any of the licensed DTaP vaccines may be used to complete the primary immunization schedule. These recommendations may change as data become available regarding the response to different DTaP vaccines administered interchangeably in a primary series.

Additional surveillance will be needed to determine the frequency of rare adverse reactions and to possibly generate product-specific estimates of vaccine efficacy. Such data are necessary to guide the process of selection when several acellular pertussis vaccines become available and for development of more effective vaccines in the future. In addition, vaccines that combine a DTaP vaccine with other antigens are being evaluated. Additional evaluation of the use of DTaP vaccines in children with precautions or contraindications to DTP immunization, including evolving neurologic disorders and adverse events associated with prior pertussis immunization, should be considered.

Additional studies of the safety of acellular pertussis vaccines in adolescents and adults also are in

progress.<sup>20</sup> The use of these vaccines in persons 7 years and older to reduce further the reservoir and circulation of *B pertussis* is not recommended currently but may be effective in the future in controlling pertussis, including reduction in disease in infants too young to benefit from immunization.<sup>21</sup>

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### REFERENCES

1. Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. *Pediatrics*. 1995; 96(suppl):557-566
2. Edwards DM, Meade BD, Decker MD, et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. *Pediatrics*. 1995; 96(suppl):548-557
3. Trollfors B, Taranger J, Lagergard T, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. *N Engl J Med*. 1995;333:1045-1050
4. 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;334:341-348
5. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med*. 1996;334:349-355
6. Schmitt HJ, Wirsing von König CH, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *JAMA*. 1996;275:37-41
7. International Symposium on Pertussis Vaccine Trials, Rome; October 30-November 1, 1995. In: *Trial Synopses*. Rome: Institute Superiore di Sanità; 1995
8. Ad Hoc Group for the Study of Pertussis Vaccines. Placebo-controlled trial of two acellular pertussis vaccines in Sweden: protective efficacy and adverse events. *Lancet*. 1988;1:955-960. Published erratum appears in *Lancet*. 1988;1:1238
9. Storsaeter J, Blackwelder WC, Hollander HO. Pertussis antibodies, protection, and vaccine efficacy after household exposure. *Am J Dis Child*. 1992;146:167-172
10. Blumberg DA, Mink CM, Cherry JD, et al. Comparison of acellular and

- whole-cell pertussis component diphtheria-tetanus-pertussis vaccines in infants. *J Pediatr*. 1991;119:194–204
11. Kimura M, Kuno-Sakai H, Sato Y, et al. A comparative trial of the reactogenicity and immunogenicity of Takeda acellular pertussis vaccine combined with tetanus and diphtheria toxoids: outcomes in 3- to 8-month old infants, 9- to 23-month old infants and children, and 24- to 30-month old children. *Am J Dis Child*. 1991;145:734–741
  12. American Academy of Pediatrics, Committee on Infectious Diseases. Acellular pertussis vaccines: recommendations for use as the fourth and fifth doses. *Pediatrics*. 1992;90:121–123
  13. American Academy of Pediatrics. Pertussis. In: Peter G, ed. 1994 *Red Book. Report of the Committee on Infectious Diseases*. 23rd ed. Elk Grove Village, Ill: American Academy of Pediatrics; 1994:355–367
  14. Centers for Disease Control and Prevention. Update: childhood vaccine preventable diseases—United States, 1994. *MMWR*. 1995;43:718–719
  15. Onorato IM, Wassilak SG, Meade B. Efficacy of whole-cell pertussis vaccine in pre-school children in the United States. *JAMA*. 1992;267:2745–2749
  16. Rosenthal S, Chen R, Hadler SC. The safety of acellular pertussis vs. whole-cell pertussis vaccine: a post marketing assessment. *Arch Pediatr Adolesc Med*. 1996;150:457–460
  17. Committee on Infectious Diseases, American Academy of Pediatrics. The relationship between pertussis vaccine and brain damage: reassessment. *Pediatrics*. 1991;88:397–400
  18. American Academy of Pediatrics, Committee on Infectious Diseases. The status of acellular pertussis vaccine: current perspectives. *Pediatrics*. 1991;88:401–405
  19. Halsey NA, Peter G. New developments with pertussis vaccines. *Pediatrics*. 1995;96:970–971
  20. Edwards KM, Decker MD, Graham BS, et al. Adult immunization with acellular pertussis vaccine. *JAMA*. 1993;269:53–56
  21. Nennig ME, Shinefield HR, Edwards KM, et al. Prevalence and incidence of adult pertussis in an urban population. *JAMA*. 1996;275:1672–1674

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