

ACEL-IMUNE PI
Infant Indication
Multi -Dose
1800-31
12/27/96

DIPHTHERIA and TETANUS TOXOIDS and
ACELLULAR PERTUSSIS VACCINE ADSORBED

ACEL-IMUNE®

DESCRIPTION

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), ACEL-IMUNE, is a sterile combination of PUROGENATED® Diphtheria Toxoid, PUROGENATED® Tetanus Toxoid, and Acellular Pertussis Vaccine which is adsorbed to an aluminum adjuvant. 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. The bulk vaccine is prepared by Lederle Laboratories. ACEL-IMUNE is filled, labeled, packaged, and released by Lederle Laboratories. ACEL-IMUNE is for intramuscular use only. After shaking, the vaccine is a homogeneous white suspension.

The diphtheria and tetanus toxoids are derived from *Corynebacterium diphtheriae* and *Clostridium tetani*, respectively, which are grown in media according to the method of Mueller and Miller.^{1,2} *C. diphtheriae* is grown in a defined medium containing casamino acids and *C. tetani* in a medium containing beef heart infusion. They are detoxified by use of formaldehyde.

The toxoids are refined by the Pillemer alcohol fractionation method³ and are diluted with a solution containing sodium phosphate monobasic, sodium phosphate dibasic, glycine, and thimerosal (mercury derivative) as a preservative. The acellular pertussis vaccine component is prepared by growing Phase I *Bordetella pertussis* in Stainer-Scholte defined medium and harvesting the culture fluid. Purification of the acellular pertussis vaccine component is accomplished by ammonium sulfate fractionation steps and a final sucrose density gradient centrifugation. The acellular pertussis vaccine component is detoxified with formaldehyde and thimerosal (mercury derivative) is added as a preservative.

The diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine are combined, diluted in phosphate buffered saline (PBS), and adsorbed to aluminum adjuvant. The aluminum adjuvant is formulated to contain 0.23 mg aluminum per 0.5 mL dose as aluminum hydroxide and aluminum phosphate. The residual free formaldehyde content by assay is $\leq 0.02\%$. Thimerosal (mercury derivative) is present in a final concentration of 1:10,000. The final product may also contain gelatin and polysorbate 80 which are used in early stages of the manufacture of the pertussis component.

Each single dose of 0.5 mL of ACEL-IMUNE is formulated to contain 9 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid (both toxoids induce not less than 2 units of antitoxin per mL in the guinea pig potency test) and 300 hemagglutinating (HA) units of acellular pertussis vaccine. A hemagglutination unit is that amount of material which completely agglutinates chicken red blood cells as measured by the HA assay.⁴ The acellular pertussis vaccine component contains

approximately 40 µg (but not more than 60 µg) of pertussis antigen protein per 0.5 mL dose with approximately 86% filamentous hemagglutinin (FHA), approximately 8% inactivated pertussis toxin (PT, also known as lymphocytosis promoting factor), approximately 4% per dose of 69-kilodalton outer membrane protein (pertactin), and approximately 2% type 2 fimbriae (pertussis-specific agglutinin).

The potency of the pertussis component is evaluated by measurement of antibodies to FHA, PT, pertactin, and fimbriae in immunized mice by ELISA.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis (whooping cough) during infancy and childhood has been a routine practice in the United States since the late 1940s. It has played a major role in markedly reducing the incidence of cases and deaths from each of these diseases.

Diphtheria is primarily a localized and generalized intoxication caused by diphtheria toxin, an extracellular protein metabolite of toxinogenic strains of *C. diphtheriae*. While the incidence of diphtheria in the US has decreased from over 200,000 cases reported in 1921, before the general use of diphtheria toxoid, to only 15 cases reported from 1990 to 1994,⁵ the case fatality rate has remained constant at about 5% to 10%. The highest case fatality rates are in the very young and

in the elderly. Diphtheria remains a serious disease in some areas of the world as demonstrated by the recent epidemic in the former Soviet Union.⁶

Following adequate immunization with diphtheria toxoid it is thought that protection lasts for at least 10 years.⁷ Antitoxin levels of at least 0.01 antitoxin units/mL are generally regarded as protective.⁸ This significantly reduces both the risk of developing diphtheria and the severity of clinical illness. It does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or on the skin.⁷

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *C. tetani*. The incidence of tetanus in the US has dropped dramatically with the routine use of tetanus toxoid, with an average of 57 cases reported annually from 1985-1994.⁹ Spores of *C. tetani* are ubiquitous, and there is essentially no natural immunity to tetanus toxin.

Thus, universal primary immunization with tetanus toxoid with subsequent maintenance of adequate antitoxin levels, by means of timed boosters, is recommended to protect all age groups.⁷ Tetanus toxoid is a highly effective antigen and a completed primary series generally induces serum antitoxin levels of at least 0.01 antitoxin units, a level which has been reported to be protective.⁹ It is thought that protection persists for at least 10 years.⁷

The toxoids of tetanus and diphtheria induce neutralizing antibodies to the toxins produced by the infecting organisms. In two clinical studies with ACEL-IMUNE, serum antitoxin levels to diphtheria and tetanus toxins were shown to be greater than 0.01 antitoxin units/mL in 100% of 140 infants following three doses.¹⁰ These levels are generally regarded to be protective.^{9, 11}

Pertussis (whooping cough) is a highly communicable disease of the respiratory tract. Attack rates of over 90% have been reported in unimmunized household contacts.^{9, 12} Since immunization against pertussis (whooping cough) became widespread, the number of reported cases and associated mortality in the US has declined from about 120,000 cases and 1100 deaths in 1950,¹³ to a historical low of 1010 cases in 1976. However, since the early 1980's, reported pertussis incidence has increased with peaks occurring in 1983, 1986, 1990, and 1993. Following the peak in reported cases in 1993, the numbers declined during 1994 and the first 2 quarters of 1995 - a pattern consistent with the previously observed 3-4 year periodicity in pertussis incidence.¹⁴ An average of 4515 cases were reported annually from 1990-1994.⁹ Precise data do not exist, since bacteriological confirmation of pertussis can be obtained in less than half of the suspected cases. In the US, most reported illness from *B. pertussis* occurs in infants and young children; approximately 80% of reported deaths occur in children less than 1 year old.⁷ Older children and adults, in whom classic signs are often absent, may go undiagnosed and serve as reservoirs of disease.^{7, 15}

Pertussis disease (whooping cough) is caused by a gram-negative coccobacillus, *B. pertussis*. Several antigens that are thought to play a role in protective immunity have been isolated from cultures of *B. pertussis*. These include FHA, PT, pertactin, and fimbriae.¹⁶⁻¹⁸ Another biologically active component, endotoxin, may contribute to reactogenicity of pertussis vaccines.¹⁹ The Takeda acellular pertussis vaccine component used in ACEL-IMUNE contains inactivated FHA, PT, pertactin, and type 2 fimbriae, with minimal endotoxin compared to that in whole-cell pertussis vaccine. The pertussis component induces immunity against pertussis disease in humans.

Efficacy of ACEL-IMUNE was assessed in infants in a prospective study conducted in Germany at 227 investigator sites. A total of 8532 infants were randomized to receive ACEL-IMUNE (n=4273) or Lederle whole-cell DTP (n=4259) at mean ages of 3, 5 and 7 months followed by a fourth dose of ACEL-IMUNE (n=3991) or DTP (n=3925) at a mean age of 17 months. By parental choice, 1739 additional infants received German-manufactured Diphtheria and Tetanus Toxoids (DT) at mean ages of 3 and 5 months followed by a third dose at a mean age of 17 months. In order to adjust for potential confounding, several variables were examined to determine which ones differed between the randomized and non-randomized groups and affected the risk of developing pertussis. Telephone calls were performed every 14 days by investigator personnel to ensure close surveillance of pertussis disease among study subjects and household members. Evaluation of a 7-day cough which was not improving included a nasopharyngeal specimen for culture and blood sample for acute serology. Subjects with greater than 14 days of cough were evaluated by central investigators and convalescent serology was scheduled for 6-8 weeks after cough onset. Completeness of surveillance to ascertain the presence and duration of

cough illness was not directly assessed; however, study sites were monitored for compliance with the protocol.

A total of 154 cases were identified using a case definition of 21 days or more of cough with paroxysms, whoop or post-tussive vomiting plus confirmation by positive culture for *B. pertussis*, or household contact with a person with positive culture for *B. pertussis*, or by serologic confirmation (significant rise in PT IgG between acute and convalescent samples or PT IgA value significantly elevated above the normal limits). Case rates per 100 person-years of follow-up for each vaccine were: DTaP, 0.48; DTP, 0.22; and DT, 2.98. Adjusting for single adult households and households in which all siblings were unimmunized, the vaccine efficacy after 3 doses and before receipt of the fourth dose of ACEL-IMUNE or until 19 months of age was 73% (95% CI 51 to 86) and after 4 doses 85% (95% CI 76 to 90). DTP efficacy after 3 doses was 83% (95% CI 65 to 92) and after 4 doses was 94% (95% CI 89 to 97). For ACEL-IMUNE, there is no significant difference in efficacy between 3 and 4 doses ($p=0.16$).

Considering all observation time, i.e., including from after the third dose until the fourth dose (approximately 40% of follow-up time) and from after the fourth dose until the end of the study (approximately 60% of follow-up time), the adjusted efficacy estimated for ACEL-IMUNE was 81% (95% CI 73 to 87) compared to 91% for DTP (95% CI 85 to 95). The relative risk for pertussis in the ACEL-IMUNE group compared to the DTP group was 1.5 (95% CI 0.7 to 3.4) after 3 doses and 2.8 (95% CI 1.3 to 5.9) after 4 doses.

Some subjects with 21 days or more of cough with paroxysms, whoop or post-tussive vomiting did not have complete laboratory tests. Of those subjects whose available tests were negative (DT, 113 subjects; DTaP, 241 subjects; and DTP, 239 subjects), 68% in the DT group, 69% in the ACEL-IMUNE group, and 68% in the Lederle whole-cell DTP group had at least one missing laboratory test. In the efficacy analysis these subjects were classified as non-cases. The effect of this classification was evaluated by applying missing value imputation procedures in which it was assumed that the probability of being a pertussis case was the same among subjects with and without all laboratory results; missing values were found to have minimal effect on vaccine efficacy.¹⁰ It is possible, however, that the misclassification of such subjects due to missing laboratory values may have resulted in overestimates of ACEL-IMUNE and whole-cell DTP efficacy.

Vaccine efficacy was also estimated in a household contact analysis within the prospective German study. A primary case of pertussis was defined as cough for 21 or more days with paroxysms, whoop, or post-tussive vomiting plus laboratory confirmation. A total of 167 households had a member other than a study infant who met this definition. A secondary case of pertussis was defined as cough for 21 or more days with paroxysms, whoop, or post-tussive vomiting plus laboratory confirmation, with an onset within 7-28 days after onset of pertussis in a primary case in the household. Thirteen secondary cases were identified among study infants, resulting in secondary attack rates of 9.5% (ACEL-IMUNE), 2.0% (DTP), and 32% (DT). Based on this analysis, the vaccine efficacy for ACEL-IMUNE was 70% (95% CI 11 to 90).

Analysis of potentially confounding variables revealed none that were associated with both vaccine group and pertussis case status.¹⁰

Following primary immunization, US children (n=126) had antibody titers to pertussis antigens which were similar to those achieved in German children who participated in a pilot study (n=52) and a subset of children in the efficacy trial (n=52) where vaccine efficacy was demonstrated.¹⁰

In a clinical study conducted in the US, 77 infants received ACEL-IMUNE, HibTITER and Hepatitis B vaccine simultaneously at 2, 4 and 6 months of age. Ninety-four percent of the children demonstrated anti-PRP antibodies $\geq 1 \mu\text{g/mL}$. All of the 74 infants evaluated for HBs responses had anti-HBs titers of $>10 \text{ m IU/mL}$.¹⁰

Sera from 30 infants who received OPV simultaneously with ACEL-IMUNE at 2 and 4 months showed that at 6 months, 90-100% had protective neutralizing antibody to all three poliovirus types (comparable to results seen with simultaneous DTP administration with OPV).¹⁰

Ninety-two to 100% of 15-18 month old children (n=48) who received MMR simultaneously with ACEL-IMUNE had protective titers to measles, mumps, and rubella; similar results were seen for children who received DTP and MMR simultaneously.²⁰

INDICATIONS AND USAGE

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, ACEL-IMUNE, is indicated for active immunization of children from 6 weeks of age up to age 7 years (prior to seventh birthday) for protection against diphtheria, tetanus, and pertussis.

This product is not recommended for immunizing persons on or after their seventh birthday (see **DOSAGE AND ADMINISTRATION**).

Children who have recovered from culture-confirmed pertussis need not receive further doses of a pertussis-containing vaccine⁷, but should complete the recommended series with Diphtheria and Tetanus Toxoids Adsorbed for pediatric use (DT).

ACEL-IMUNE is intended for active immunization against diphtheria, tetanus, and pertussis, and is not to be used for treatment of actual infection.

If a contraindicating event to the pertussis vaccine component occurs, Diphtheria and Tetanus Toxoids, Adsorbed for pediatric use (DT) should be substituted for each of the remaining doses. The Advisory Committee on Immunization Practices (ACIP) recommends that if an immediate anaphylactic reaction occurs, no further vaccination with any of the three antigens in DTP should be carried out.⁷

As with any vaccine, ACEL-IMUNE may not protect 100% of individuals receiving the vaccine.

If passive immunization is required, Tetanus Immune Globulin (TIG) or Diphtheria Antitoxin are recommended.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THIMEROSAL, A MERCURY DERIVATIVE, IS A CONTRAINDICATION.

THE DECISION TO ADMINISTER OR DELAY DTP VACCINATION BECAUSE OF A CURRENT OR RECENT FEBRILE ILLNESS DEPENDS LARGELY ON THE SEVERITY OF THE SYMPTOMS AND THEIR ETIOLOGY. ALTHOUGH A MODERATE OR SEVERE FEBRILE ILLNESS IS SUFFICIENT REASON TO POSTPONE VACCINATION, MINOR ILLNESSES SUCH AS A MILD UPPER RESPIRATORY INFECTION WITH OR WITHOUT LOW GRADE FEVER ARE NOT CONTRAINDICATIONS.^{7, 21, 22}

ROUTINE IMMUNIZATION SHOULD BE DEFERRED DURING AN OUTBREAK OF POLIOMYELITIS PROVIDING THE PATIENT HAS NOT SUSTAINED AN INJURY THAT INCREASES THE RISK OF TETANUS AND PROVIDING AN OUTBREAK OF DIPHTHERIA OR PERTUSSIS DOES NOT OCCUR SIMULTANEOUSLY.²³

DATA ON THE USE OF ACEL-IMUNE IN CHILDREN FOR WHOM WHOLE-CELL PERTUSSIS VACCINE IS CONTRAINDICATED ARE NOT AVAILABLE. UNTIL SUCH DATA ARE AVAILABLE, IT WOULD BE PRUDENT TO CONSIDER THE ACIP AND AMERICAN ACADEMY OF PEDIATRICS (AAP) CONTRAINDICATIONS TO WHOLE-CELL PERTUSSIS VACCINE AS CONTRAINDICATIONS TO ACEL-IMUNE.

IMMUNIZATION WITH ACEL-IMUNE IS CONTRAINDICATED IF THE CHILD HAS EXPERIENCED ANY EVENT FOLLOWING PREVIOUS IMMUNIZATION WITH ANY VACCINE CONTAINING A PERTUSSIS COMPONENT, WHICH IS CONSIDERED BY THE AAP OR ACIP TO BE A CONTRAINDICATION TO FURTHER DOSES OF PERTUSSIS VACCINE. THESE EVENTS ARE.

AN IMMEDIATE ANAPHYLACTIC REACTION. BECAUSE OF THE UNCERTAINTY AS TO WHICH COMPONENT OF THE VACCINE MIGHT BE RESPONSIBLE, NO FURTHER VACCINATION WITH ANY OF THE ANTIGENS IN DTP SHOULD BE CARRIED OUT. ALTERNATIVELY, BECAUSE OF THE IMPORTANCE OF TETANUS VACCINATION, SUCH INDIVIDUALS MAY BE REFERRED FOR EVALUATION BY AN ALLERGIST.^{7, 21, 22}

ENCEPHALOPATHY (NOT DUE TO ANOTHER IDENTIFIABLE CAUSE) OCCURRING WITHIN 7 DAYS FOLLOWING VACCINATION THIS IS

DEFINED AS AN ACUTE, SEVERE CENTRAL NERVOUS SYSTEM DISORDER OCCURRING WITHIN 7 DAYS FOLLOWING VACCINATION, AND GENERALLY CONSISTING OF MAJOR ALTERATIONS IN CONSCIOUSNESS, UNRESPONSIVENESS, GENERALIZED OR FOCAL SEIZURES THAT PERSIST MORE THAN A FEW HOURS, WITH FAILURE TO RECOVER WITHIN 24 HOURS. EVEN THOUGH CAUSATION BY DTP CANNOT BE ESTABLISHED, NO SUBSEQUENT DOSES OF PERTUSSIS VACCINE SHOULD BE GIVEN.^{7, 21, 22}

THE CLINICAL JUDGMENT OF THE ATTENDING PHYSICIAN SHOULD PREVAIL AT ALL TIMES.

WARNINGS

THE ACIP AND THE AAP STATE THAT IF ANY OF THE FOLLOWING EVENTS OCCUR IN TEMPORAL RELATION TO RECEIPT OF DTP OR DTaP, THE DECISION TO GIVE SUBSEQUENT DOSES OF VACCINE CONTAINING THE PERTUSSIS COMPONENT SHOULD BE CAREFULLY CONSIDERED. ALTHOUGH THESE EVENTS WERE ONCE CONSIDERED CONTRAINDICATIONS TO WHOLE-CELL DTP, THERE MAY BE CIRCUMSTANCES, SUCH AS A HIGH INCIDENCE OF PERTUSSIS, IN WHICH THE POTENTIAL BENEFITS OUTWEIGH THE POSSIBLE RISKS, PARTICULARLY BECAUSE THESE EVENTS HAVE NOT BEEN SHOWN TO CAUSE PERMANENT SEQUELAE.^{7, 21, 22}

1. TEMPERATURE OF $\geq 40.5^{\circ}\text{C}$ (105°F) WITHIN 48 HOURS NOT DUE TO IDENTIFIABLE CAUSE.
2. COLLAPSE OR SHOCK-LIKE STATE (HYPOTONIC-HYPORESPONSIVE EPISODE) WITHIN 48 HOURS.
3. PERSISTENT, INCONSOLABLE CRYING LASTING ≥ 3 HOURS, OCCURRING WITHIN 48 HOURS.
4. CONVULSIONS WITH OR WITHOUT FEVER OCCURRING WITHIN 3 DAYS.^{7, 21, 22, 24}

Data on the use of ACEL-IMUNE in children with a personal history of convulsion or an evolving or changing disorder of the central nervous system are not available. In the opinion of the manufacturer, the presence of a personal history of convulsion or an evolving disorder affecting the central nervous system is considered a warning against further immunization with this vaccine.

The ACIP and the AAP recommend considering deferral of immunization against pertussis in children with progressive neurologic disorders, personal history of convulsion, and known or suspected neurologic conditions which predispose to seizures or neurologic deterioration until the child's status has been fully assessed, a treatment regimen established, and the condition stabilized.^{7, 21, 22, 25}

Children with a personal or family history of convulsion may have an increased risk for seizures following DTP vaccination compared with children without such histories^{26, 27} However, the

ACIP states that children with stable central nervous system disorders, including well-controlled seizures or satisfactorily explained single seizures may receive pertussis vaccination. The ACIP and AAP do not consider a family history of seizures to be a contraindication to pertussis vaccination.^{7, 21, 22} Data on the use of ACEL-IMUNE in such persons are not available.

Although there are no data on whether the prophylactic use of antipyretics can decrease the risk of febrile convulsions, data suggest that acetaminophen will reduce the incidence of postvaccination fever.²⁸ The ACIP and AAP recommend administering acetaminophen at age-appropriate doses at the time of vaccination and every 4 hours for 24 hours to children at higher risk for seizures than the general population.^{7, 22, 29} The decision to administer a pertussis-containing vaccine to such children must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. The physician should review the full text of ACIP and AAP guidelines prior to considering vaccination for such children.^{7, 22, 29} The parent or guardian should be advised of the potential increased risk.

A detailed follow-up of the National Childhood Encephalopathy Study (NCES) indicated that children who had had a serious acute neurologic illness were significantly more likely than children in a control group without acute neurologic illness to have chronic nervous system dysfunction 10 years later.³⁰ These children with chronic nervous system dysfunction were more likely than children in the control group to have received DTP within 7 days of onset of the original serious acute neurologic illness (i.e., 12 [3.3%] of 367 children vs. six [0.8%] of 723

children).^{21,30} After reviewing the follow-up data, a committee of the Institute of Medicine (IOM) concluded that the NCES provided evidence of an association between DTP and chronic nervous system dysfunction in children who had had a serious acute neurologic illness after vaccination with DTP.³¹ However, IOM also concluded that the results were insufficient to determine whether DTP increases the overall risk for chronic nervous system dysfunction in children.³¹ The ACIP indicated that the results of the NCES were insufficient to determine whether DTP administration before the acute neurological event influenced the potential for neurologic dysfunction 10 years later.²¹ Acute encephalopathy or permanent neurological injury have not been reported in clinical trials after administration of ACEL-IMUNE, but the experience with this vaccine is insufficient to rule this out (see **ADVERSE REACTIONS**).

ACEL-IMUNE should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer ACEL-IMUNE to children with coagulation disorders, it should be given with caution. (see **Drug Interactions**).

PRECAUTIONS

General

CARE IS TO BE TAKEN BY THE HEALTH PROVIDER FOR SAFE AND EFFECTIVE USE OF THIS PRODUCT.

1. PRIOR TO ADMINISTRATION OF ANY DOSE OF ACEL-IMUNE, THE PARENT OR GUARDIAN SHOULD BE ASKED ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS OF THE VACCINE RECIPIENT. THE PHYSICIAN SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE EVENT AFTER PREVIOUS IMMUNIZATIONS IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH ACEL-IMUNE AND TO ALLOW AN ASSESSMENT OF BENEFITS AND RISKS.
2. BEFORE THE INJECTION OF ANY BIOLOGICAL, THE PHYSICIAN SHOULD TAKE ALL PRECAUTIONS KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER SIDE REACTIONS. This should include a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.
3. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunization procedures.^{7, 22, 32, 33} Deferral of administration of vaccine may be considered in individuals receiving immunosuppressive therapy.⁷ Other groups should receive this vaccine according to the usual recommended schedule.^{7, 22, 33, 34} (See Drug Interactions).

4. This product is not contraindicated for use in individuals with human immunodeficiency virus (HIV) infection.³⁵
5. *Since this product is a suspension containing an adjuvant, shake vigorously to obtain a uniform suspension prior to withdrawing each dose from the multiple dose vial.*
6. A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.
7. Special care should be taken to prevent injection into a blood vessel.

Information For Patient

PRIOR TO ADMINISTRATION OF ACEL-IMUNE, HEALTH CARE PERSONNEL SHOULD INFORM THE PARENT, GUARDIAN, OR OTHER RESPONSIBLE ADULT OF THE RECOMMENDED IMMUNIZATION SCHEDULE FOR PROTECTION AGAINST DIPHTHERIA, TETANUS, AND PERTUSSIS AND THE BENEFITS AND RISKS TO THE CHILD RECEIVING THIS VACCINE CONTAINING AN ACELLULAR PERTUSSIS COMPONENT. GUIDANCE SHOULD BE PROVIDED ON MEASURES TO BE TAKEN SHOULD ADVERSE EVENTS OCCUR, SUCH AS ANTIPYRETIC MEASURES FOR ELEVATED TEMPERATURES AND THE NEED TO REPORT ADVERSE EVENTS TO THE HEALTH CARE PROVIDER. PARENTS SHOULD BE PROVIDED WITH VACCINE INFORMATION MATERIALS AT THE TIME OF EACH VACCINATION, AS STATED IN THE NATIONAL CHILDHOOD VACCINE INJURY ACT³⁶

THE HEALTH CARE PROVIDER SHOULD INFORM THE PATIENT, PARENT, OR GUARDIAN OF THE IMPORTANCE OF COMPLETING THE IMMUNIZATION SERIES UNLESS CONTRAINDICATED.

PATIENTS, PARENTS, OR GUARDIANS SHOULD BE INSTRUCTED TO REPORT ANY SERIOUS ADVERSE REACTIONS TO THEIR HEALTH CARE PROVIDER

Drug Interactions

Children receiving immunosuppressive therapy may have a reduced response to active immunization procedures.^{7, 22, 32, 33} Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.³²

As with other intramuscular injections, ACEL-IMUNE should be given with caution to children on anticoagulant therapy.

Tetanus Immune Globulin or Diphtheria Antitoxin, if used, should be given in a separate site with a separate needle and syringe if used at the same time as ACEL-IMUNE.

Please see **DOSAGE AND ADMINISTRATION** for information regarding simultaneous administration with other vaccines.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

ACEL-IMUNE has not been evaluated for its carcinogenic, mutagenic potential, or impairment of fertility.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with ACEL-IMUNE. It is not known whether ACEL-IMUNE vaccine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. ACEL-IMUNE vaccine is **NOT** recommended for use in a pregnant woman.

THIS PRODUCT IS NOT RECOMMENDED FOR USE IN INDIVIDUALS 7 YEARS OF AGE OR OLDER.

Pediatric Use

The safety and effectiveness of ACEL-IMUNE in children below the age of 6 weeks have not been established (see **DOSAGE AND ADMINISTRATION**).

For immunization of children 7 years of age and older, Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) is recommended^{7, 22}

Protection against the indicated diseases (tetanus, diphtheria, pertussis) is based on a full course of immunization.

ADVERSE REACTIONS

Adverse reactions associated with ACEL-IMUNE have been evaluated in a total of 6941 US and German infants administered a total of 20,390 doses for the first three doses in the series. A total of 5152 of these infants received ACEL-IMUNE for the fourth dose in a 4-dose DTaP series as toddlers and a total of 357 of these toddlers also received ACEL-IMUNE for the fifth dose in a 5-dose DTaP series at 4 to 6 years of age. Adverse event data were actively collected using parent diary cards, phone call follow-up and/or by questioning the parents at clinic visits.

In the German efficacy study where 8,532 infants were randomized to receive DTaP or DTP, a total of 16,642 doses of ACEL-IMUNE were given. When compared to Lederle whole-cell pertussis DTP vaccine, ACEL-IMUNE produced significantly fewer local reactions and systemic events (see Table 1 below).

Table 1
Adverse Events Occurring Within 72 Hours
Following DTaP and DTP

EVENT	% OF CHILDREN							
	ACEL-IMUNE				Lederle-Whole Cell DTP			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
Number of Children^a	4273	4223	4155	3991	4259	4149	4087	3925
Local								
Erythema >23 mm ^b	2	3	5	10	15	11	11	13
Induration >23mm ^b	2	4	6	9	17	13	11	13
Systemic								
Fever ^c ≥38.0°C ^b	7	12	16	26	44	35	40	50
Fever ^c >39.0°C ^b	0.3	1	1	2	1	2	3	4
Fretfulness ^b	18	18	16	15	47	33	28	31
Drowsiness ^b	23	16	12	11	40	25	19	21
Decreased Appetite ^b	10	9	7	9	21	14	12	17

- ^a For each adverse event, information was not available for a small number of subjects; 2/3 of all subjects received vaccinations in the thigh, 1/3 in the buttocks
- ^b p < 0.001 - when compared to whole-cell DTP for all doses.
- ^c Rectal temperature

In other clinical studies of ACEL-IMUNE conducted in the US, 2593 children received 8601 doses for doses 1 through 4. In general, rates of local reactions and systemic events were comparable to those reported in the German efficacy study and lower than for whole-cell DTP. Rates of local reactions increased over the first 4 doses of ACEL-IMUNE: erythema >20mm from 1% (dose 1) to 8% (dose 4), induration >20mm from 1% (dose 1) to 6% (dose 4), and tenderness from 4% (dose 2) to 16% (dose 4). Rates of temperature ≥38.0°C increased over the 4-dose series from 2% (dose 1) to 18% (dose 4). With the exception of drowsiness which decreased over the 4-dose series from 20% (dose 1) to 5% (dose 4), similar rates for doses 1 through 4 were reported for other systemic events: fretfulness from 18% (dose 4) to 23% (doses 1 and 2), and loss of appetite from 9% (dose 1) to 12% (dose 4).¹⁰

In four clinical studies conducted in Germany and the US, a total of 357 children received a fifth dose of ACEL-IMUNE in a 5-dose DTaP series at 4 to 6 years of age. Two hundred seventy-eight subjects received vaccine formulated to contain 0.15 mg aluminum per dose and 79 subjects received vaccine formulated to contain 0.23 mg aluminum per dose. While there were no comparative DTP groups in these study segments, the reactogenicity of ACEL-IMUNE was no greater than that described for historical controls who received a fifth dose of whole-cell DTP after 4 previous doses of whole-cell DTP.^{10, 37, 38}

Table 2
Percent of Adverse Events Occurring within 72 Hours
Following the Fifth Dose of ACEL-IMUNE
in Children Who Received Four Previous Consecutive Doses
of ACEL-IMUNE

Symptom	DTaP ¹ N= 357
Erythema	
Any	35
Significant ²	20
Induration	
Any	30
Significant ²	14
Tenderness	38
Fever $\geq 38.0^{\circ}\text{C}$	9
$>39.0^{\circ}\text{C}$	3
Fretfulness	9
Drowsiness	10
Decreased appetite	8
Vomiting	3

¹ For some adverse events, information was not available for a small number of subjects

² Significant varied by protocol from $>20\text{mm}$ - $>24\text{mm}$

In the large German efficacy trial, 4273 subjects received 16,642 doses of ACEL-IMUNE and 4259 subjects received 16,420 doses of DTP. Adverse events (rates per 1000 doses) meeting

AAP and ACIP criteria as absolute contraindications or precautions to further pertussis immunization and occurring within 72 hours following the immunizations were: persistent or unusual cry (1.14 for DTaP, 4.75 for DTP), fever $\geq 40.5^{\circ}\text{C}$ (0.06 for DTaP, 0.18 for DTP), seizures, all of which were febrile (0.06 for DTaP, 0.18 for DTP) and hypotonic-hyporesponsive episode (0 for DTaP and 0.06 for DTP). When the total clinical trial experience with ACEL-IMUNE is considered (25,899 immunizations), rates per 1000 doses of ACEL-IMUNE were: persistent or unusual cry (1.27), fever $\geq 40.5^{\circ}\text{C}$ (0.08), seizure (0.04), possible seizure (0.04), and hypotonic-hyporesponsive episode (0.04).¹⁰

Adverse reactions associated with ACEL-IMUNE have been evaluated in clinical trials in 911 children receiving this vaccine as the fourth or fifth dose in the DTP series when they had previously received 3 or 4 doses of whole-cell DTP. The percent of children experiencing common symptoms at any time within 72 hours following immunization is summarized in Table 3.

Table 3
Percent of Children with Symptoms Following a
Fourth or Fifth Dose of ACEL-IMUNE
After 3 or 4 Doses of Whole-Cell DTP

Symptom	% of Children ¹ Reporting Symptoms within 72 Hours of Immunization n = 911
Tenderness	26
Erythema (>2 cm)	10
Induration (>2 cm)	7
Increased injection site temperature	17
Fever ² ≥38°C (100.4°F)	19
>39°C (102.2°F)	1.5
Drowsiness	6
Fretfulness	17
Vomiting	2

¹ Children 17 to 24 months of age (fourth dose) and 4 to 6 years of age (fifth dose).

² Rectal temperature for 17-24 month olds
Oral temperature for 4-6 year olds

In a large, post-marketing surveillance study, 28,095 doses of ACEL-IMUNE were administered to children as a fourth or fifth dose following previous doses with whole-cell DTP. The rates of local and systemic events reported in a subset of approximately 4400 subjects who were evaluated by telephone interview within 48 to 72 hours postimmunization were: tenderness, 31%; erythema ≥ 1 inch, 4%; induration ≥ 1 inch, 3.5%; perceived fever, 15%; irritability, 25%; and vomiting, 2%.¹⁰

As with other aluminum-containing vaccines, a nodule may occasionally be palpable at the injection site for several weeks. Sterile abscess formation or subcutaneous atrophy at the injection site may occur rarely.³⁹

Urticaria, erythema multiforme or other rash, arthralgias,⁴⁰ and, more rarely, a severe anaphylactic reaction⁷ (e.g., urticaria with swelling of the mouth, difficulty breathing, hypotension, or shock) have been reported following administration of preparations containing diphtheria, tetanus, and/or pertussis antigens.

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection) may follow receipt of tetanus toxoid.

Whole-cell pertussis DTP has been associated with acute encephalopathy.³¹ A detailed follow-up of the National Childhood Encephalopathy Study (NCES) indicated that children who had had a serious acute neurologic illness were significantly more likely than children in a control group without acute neurologic illness to have chronic nervous system dysfunction 10 years later.³⁰ These children with chronic nervous system dysfunction were more likely than children in the control group to have received DTP within 7 days of onset of the original serious acute neurologic illness (i.e., 12 [3.3%] of 367 children vs. six [0.8%] of 723 children).^{21,30} After reviewing the follow-up data, a committee of the Institute of Medicine (IOM) concluded that the NCES provided evidence of an association between DTP and chronic nervous system dysfunction in children who had had a serious acute neurologic illness after vaccination with DTP.³¹ However, IOM also concluded that the results were insufficient to determine whether DTP increases the overall risk for chronic nervous system dysfunction in children.³¹ The ACIP indicated that the results of the NCES were insufficient to determine whether DTP administration

before the acute neurological event influenced the potential for neurologic dysfunction 10 years later.²¹

Onset of infantile spasms has occurred in infants who have recently received DTP and DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or DTP was not causally related to infantile spasms.^{31, 41} The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.^{7, 31}

A bulging fontanelle associated with increased intracranial pressure which occurred within 24 hours following DTP immunization has been reported, although a causal relationship has not been established.^{31, 42-44}

The above findings regarding possible association of unusual neurologic events relate only to DTP vaccine containing whole-cell pertussis. At this time there are insufficient data to determine their relevance to ACEL-IMUNE.

Sudden Infant Death Syndrome (SIDS) has occurred in infants following administration of whole-cell pertussis DTP and DTaP. Large case-control studies of SIDS in the US have shown that receipt of whole-cell DTP was not causally related to SIDS.⁴⁵⁻⁴⁷ A review by a committee of the IOM concluded that available evidence did not indicate a causal relation

between DTP vaccine and SIDS.³¹ The rate of SIDS in the German efficacy trial was 0.2 per thousand infants and in US safety studies was 0.8 per thousand infants vaccinated with ACEL-IMUNE.¹⁰ The reported rate of SIDS in the US from 1985 through 1991 was 1.5 per thousand live births.⁴⁸ Since SIDS occurs most commonly at the age when DTP primary immunizations are recommended, by chance alone, some cases of SIDS can be expected to follow receipt of whole-cell pertussis DTP and DTaP.

Neurological complications,⁴⁹ such as convulsions,⁴⁰ encephalopathy^{40, 50} and various mono- and polyneuropathies,⁵⁰⁻⁵⁶ including Guillain-Barré syndrome,^{57, 58} have been reported following administration of preparations containing diphtheria, tetanus, and/or pertussis antigens. A review by the IOM found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.⁵⁹ Permanent neurological disability and death have been reported rarely in temporal relation to immunization with vaccines containing pertussis antigens; however, a causal relationship has not been established.

As with any vaccine, there is the possibility that broad use of ACEL-IMUNE could reveal adverse reactions not observed in clinical trials.

In clinical trials involving 25,899 immunizations with ACEL-IMUNE, there were no occurrences of anaphylaxis or encephalopathy. Six deaths were reported to study investigators. Causes of death included three SIDS and three accidental deaths. None of these events was determined to be vaccine-related and all occurred more than 4 weeks

postimmunization. No deaths from invasive bacterial infections were reported in studies with ACEL-IMUNE.

Adverse Event Reporting

Any adverse reactions following immunization should be reported by the health care provider to the US Department of Health and Human Services (DHHS). The **National Childhood Vaccine Injury Act** requires that the manufacturer and lot number of the vaccine administered be recorded by the health care provider in the vaccine recipient's permanent medical record (or in a permanent office log or file), along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.

The Act further requires the health care provider to report to the Secretary of the Department of Health and Human Services, the occurrence following immunization of any event set forth in the Vaccine Injury Table, including anaphylaxis or anaphylactic shock within 24 hours; encephalopathy or encephalitis within 7 days, shock-collapse or hypotonic-hyporesponsive collapse within 7 days, residual seizure disorder, any acute complication or sequelae (including death) of above events, or any event that would contraindicate further doses of vaccine, according to this ACEL-IMUNE package insert.³⁶

The US Department of Health and Human Services has established VAERS to accept all reports of suspected adverse events after the administration of any vaccine including, but not limited to, the reporting of events required by the National Childhood Vaccine Injury Act of 1986.³⁶ The VAERS toll-free number for VAERS forms and information is 800-822-7967.

DOSAGE AND ADMINISTRATION

For intramuscular use only

The dose is 0.5 mL to be given intramuscularly.

Primary Immunization

For infants, the primary immunization series of ACEL-IMUNE consists of three doses of 0.5 mL each. The customary age for the first dose is 2 months of age but can be given as young as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. It is also recommended that ACEL-IMUNE be given for all three doses since no interchangeability data on DTaP vaccines exist for the primary series.

ACEL-IMUNE may be used to complete the primary series in infants who have received one or two doses of whole-cell pertussis DTP. However, the safety and efficacy of ACEL-IMUNE in such infants has not been evaluated.

Booster Immunization

When ACEL-IMUNE or DTP is given for the primary series, a fourth dose of ACEL-IMUNE is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. A fifth dose of 0.5 mL is recommended at 4 to 6 years of age, preferably prior to entrance into kindergarten or elementary school. If the fourth dose was administered on or after the fourth birthday, a fifth dose prior to school entry is not considered necessary.⁷

Preterm infants should be vaccinated according to their chronological age, calculated from date of birth.⁷

Interruption of the recommended schedules with a delay between doses does not interfere with the final immunity achieved; nor does it necessitate starting the series over again, regardless of the length of time elapsed between doses.⁷

In the case of anaphylaxis, no further vaccination with any of the three antigens in DTaP should be carried out. Alternatively, because of the importance of tetanus vaccination, such individuals may be referred for evaluation by an allergist.⁷ If a contraindication to the pertussis vaccine component occurs, Diphtheria and Tetanus Toxoids Adsorbed, for pediatric use (DT), should be substituted for each of the remaining doses.

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

Shake vigorously to obtain a uniform suspension prior to withdrawing each dose from the multiple dose vial. The vaccine should not be used if it cannot be resuspended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration (see **DESCRIPTION**).

The vaccine should be injected intramuscularly. The preferred sites are the anterolateral aspect of the thigh or the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Before injection, the skin at the injection site should be cleansed and prepared with a suitable germicide.

After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel.

For booster immunization against tetanus and diphtheria of individuals 7 years of age or older, the use of Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) is recommended.

Routine simultaneous administration of DTaP, OPV (or IPV), Hib vaccine, MMR and Hepatitis B vaccine may be given to children who are the recommended age to receive these vaccines and for whom no specific contraindications exist at the time of the visit.⁷

HOW SUPPLIED

NDC 0005-1800-31 5.0 mL Vial

STORAGE

DO NOT FREEZE. STORE REFRIGERATED, AWAY FROM FREEZER COMPARTMENT, AT 2°C TO 8°C (36°F TO 46°F).



Manufactured by:

LEDERLE LABORATORIES
Division American Cyanamid Company
Pearl River, NY 10965

Marketed by:
WYETH-LEDERLE VACCINES AND PEDIATRICS
Wyeth-Ayerst Laboratories
Philadelphia, PA 19101



REFERENCES

1. Mueller JH, Miller PA. Production of diphtheria toxin of high potency (100 Lf) on a reproducible medium. *J Immunol.* 1941;40:21-32.
2. Mueller JH, Miller PA. Factors influencing the production of tetanus toxin. *J Immunol.* 1947;56:143-147.
3. Pillemer L, Grossberg DB, Wittler RG. The immunochemistry of toxins and toxoids. II. The preparation of immunologic evaluation of purified tetanal toxoid. *J Immunol.* 1946;54:213-224.
4. Arai H, Sato Y. Separation and characterization of two distinct hemagglutinins contained in purified leukocytosis promoter factor from *Bordetella pertussis*. *Biochimica et Biophysica Acta.* 1976;444:765-782.
5. CDC. Summary of Notifiable Diseases, United States, 1994. *MMWR.* 1995; 43(53):70-71.
6. Diphtheria Epidemic-New Independent States of the Former Soviet Union, 1990-1994. *MMWR.* 1995;44(10):177-181.
7. Diphtheria, tetanus and pertussis: Recommendations for vaccine use and other preventive measures -- recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR.* 1991;40 (RR-10).
8. Ipsen J. Immunization of adults against diphtheria and tetanus. *NEJM.* 1954;251:459-466.
9. *Federal Register Notice*, Friday, December 13, 1985, Vol. 50, No. 240.
10. Unpublished data available from Lederle Laboratories.
11. Pappenheimer AM Jr. Diphtheria. In: Germanier R, ed. *Bacterial Vaccines*. New York, NY: Academic Press Inc; 1984:1-36.
12. Kendrick PL. Secondary familial attack rates from pertussis in vaccinated and unvaccinated children. *Am J Hygiene.* 1940;32:89-91.
13. Reported incidence of notifiable diseases in the United States. *MMWR.* 1970;19(53):44.
14. Pertussis surveillance - United States. January 1992-June 1995. *MMWR* 1995;44(28):525-529.

15. Mortimer JD Jr. Pertussis and its prevention: a family affair. *J Infect Dis.* 1990;161:473-479.
16. Cowell JL, Oda M, Burstyn DG, et al. Prospective protective antigens and animal models for pertussis. In: Leive L, Schlessinger D, eds. *Microbiology - 1984.* Washington, DC: American Society for Microbiology; 1984:172-175.
17. Shahin RD, Brennan MJ, Li ZM, et al. Characterization of the protective capacity and immunogenicity of the 69-kd outer membrane protein of *Bordetella pertussis*. *J Exper Med.* 1990;171(1):63-73.
18. Novotny P, Kobisch M, Cownley K, et al. Evaluation of *Bordetella bronchiseptica* vaccines in specific-pathogen-free piglets with bacterial cell surface antigens in enzyme linked immunosorbent assay. *Infect Immun.* 1985;50:190-198.
19. Manclark CR, Cowell JL. Pertussis vaccine. In: Germanier R, ed. *Bacterial Vaccines.* New York, NY: Academic Press, Inc; 1984:69-106.
20. Rothstein EP, Bernstein HH, Glode MP, et al. Simultaneous administration of a diphtheria and tetanus toxoids and acellular pertussis vaccine with measles-mumps-rubella and oral poliovirus vaccines. *AJDC.* 1993;(147):854-857.
21. Update: Vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR.* 1996;45 (RR-12):22-31.
22. American Academy of Pediatrics. *Report of the Committee on Infectious Diseases.* 23rd ed. Elk Grove Village, Ill: American Academy of Pediatrics; 1994.
23. Sutter RW, Patriarca PA, Suleiman AJM, et al. Attributable risk of DTP (Diphtheria and Tetanus Toxoids and Pertussis Vaccine) injection in provoking paralytic poliomyelitis during a large outbreak in Omar. *J Infect Dis.* 1992;165:444-449.
24. Pertussis vaccination: acellular pertussis vaccine for reinforcing and booster use-supplementary ACIP statement. *MMWR.* 1992;41(RR-1):1-10.
25. Livingstone S. *Comprehensive management of epilepsy in infancy.* Springfield, IL: Charles C. Thomas; 1972;159-66.
26. Livengood JR, Mullen JR, White JW, et al. Family history of convulsions and use of pertussis vaccine. *J Pediatr.* 1989;115:527-531.
27. Stetler HC, Orenstein WA, Bart KJ, et al. History of convulsion and use of pertussis vaccine. *J Pediatr.* 1985;107:175-9.

28. Ipp MM, Gold R, Greenberg S, et al. Acetaminophen prophylaxis of adverse reactions following vaccination of infants with diphtheria-pertussis-tetanus toxoids-polio vaccine. *Pediatr Infect Dis J.* 1987;6:721-725.
29. Pertussis immunization: family history of convulsions and use of antipyretics - supplementary ACIP statement. *MMWR.* 1987;36(18):281-282.
30. Miller D, Madge N, Diamond J, et al. Pertussis immunization and serious acute neurological illnesses in children. *BMJ.* 1993;307:1171-6.
31. Howson CP, Howe CJ, Fineberg HV. Adverse effects of pertussis and rubella vaccines, pertussis vaccines and CNS disorders. Institute of Medicine (IOM). Washington, DC: National Academy Press; 1991.
32. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Use of Vaccines and Immuno Globulins in Persons with Altered Immunocompetence. *MMWR.* 1993;42(RR-4).
33. Immunization of children infected with human immunodeficiency virus - supplementary ACIP statement. *MMWR.* 1988;37(12):181-183.
34. Recommendation of the ACIP: immunization of children infected with human T-lymphotropic virus type III/lymphadenopathy-associated virus. *MMWR.* 1986;35(38):595-606.
35. General Recommendations on Immunization--Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR.* 1989;38(13):221.
36. CDC. Vaccine Adverse Event Reporting System--United States. *MMWR.* 1990;39:730-733.
37. Morgan CM, Blumberg DA, Cherry JD, et al. Comparison of acellular and whole-cell pertussis-component DTP vaccines. *AJDC.* 1990;144:41-45.
38. Cody CL, Baraff LJ, Cherry JP, et al. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics.* 1981;68(5):650-660.
39. Fawcett HA, Smith NP. Injection-site granuloma due to aluminum. *Arch Dermatol.* 1984;120:1318-1322.
40. Adverse events following immunization. *MMWR.* 1985;34(3):43-47.
41. Bellman MH, Ross EM, Miller DL. Infantile spasms and pertussis immunization. *Lancet.* 1983; 1:1031-1034.

42. Jacob J, Mannino F. Increased intracranial pressure after diphtheria, tetanus and pertussis immunization. *AJDC*. 1979;(133):217-218.
43. Mathur R, Kumari S. Bulging fontanel following triple vaccine. *Indian Pediatr*. 1981;18 (6):417-418.
44. Shendurnikar N, Gandhi DJ, Patel J, et al. Bulging fontanel following DTP vaccine. *Indian Pediatr*. 1986;23(11):960.
45. Griffin MR, Ray Wa, Livengood JR, et al. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. *N Engl J Med*. 1988; 319(10):618-623.
46. Hoffman HJ, Hunter JC, Damus K, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological study of sudden infant death syndrome risk factors. *Pediatrics*. 1987;79:598-611
47. Walker AM, Jick H, Perera DR, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome. *Am J of Pub Health*. 1987; 77:945-951.
48. Willinger M, Hoffman HJ, Hartford RB. Infant sleep position and risk for sudden infant death syndrome: report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, MD. *Pediatrics*. 1994; 93(5):814-819.
49. Rutledge SL, Snead OC. Neurological complications of immunizations. *J Pediatr*. 1986;109:917-924.
50. Schlenska GK. Unusual neurological complications following tetanus toxoid administration. *J Neurol*. 1977;215:299-302.
51. Blumstein GI, Kreithen H. Peripheral neuropathy following tetanus toxoid administration. *JAMA*. 1966;198:1030-1031.
52. Reinstein L, Pargament JM, Goodman JS. Peripheral neuropathy after multiple tetanus toxoid injections. *Arch Phys Med Rehabil*. 1982;63:332-334.
53. Tsairis P, Dyck PJ, Mulder DW. Natural history of brachial plexus neuropathy. *Arch Neurol*. 1972;27:109-117.
54. Quast U, Hennessen W, Widmark RM. Mono- and polyneuritis after tetanus vaccination. *Dev Biol Stand*. 1979;43:25-32.

55. Holliday PL, Bauer RB. Polyradiculoneuritis secondary to immunization with tetanus and diphtheria toxoids. *Arch Neurol.* 1983;40:56-57.
56. Fenichel GM. Neurological complications of tetanus toxoid. *Arch Neurol.* 1983;40:390.
57. Pollard JD, Selby G. Relapsing neuropathy due to tetanus toxoid. *J Neurol Sci.* 1978;37:113-125.
58. Newton N, Janati A. Guillain-Barré syndrome after vaccination with purified tetanus toxoid. *S Med J.* 1987;80:1053-1054.
59. Stratton KR, Howe CJ, Johnston RB. Adverse events associated with childhood vaccines. Evidence bearing on causality. Institute of Medicine. Washington, DC: National Academy Press; 1994.