Pertussis, Pertussis Vaccine, and Care of Exposed Persons

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Background: **Pertussis is a highly contagious bacterial infection caused by *Bordetella pertussis*. Before routine vaccination against pertussis was available, most persons were infected during childhood. After widespread vaccination, however, the incidence of pertussis in the United States dropped by more than 95 percent, though localized outbreaks continue to occur.**

Methods: **A multidisciplinary team developed a set of review articles as part of continuing medical education modules in the Teaching Immunization in Medical Education (TIME) Project. The team developed the materials using expert judgment and selected materials from the literature and the Centers for Disease Control and Prevention (CDC). The first step was the creation of specific learning objectives that used the spectrum of Bloom's taxonomy, when possible. After the materials were developed, they were pilot-tested and revised. Subsequently they underwent summative evaluation by field-testing the materials with 24 other primary care physicians. Then the materials were reviewed by the CDC and national vaccine experts and revised based on their comments.**

Results and Conclusions: **The efficacy of whole-cell pertussis vaccine is about 70 to 90 percent, though local adverse events are common. Since 1990 several purified, acellular pertussis vaccines have been developed that have one quarter to one half of the common adverse events associated with whole-cell vaccine and have similar efficacy rates. The incidence of pertussis can be further reduced by increasing age-appropriate vaccination rates. (J Am Board Fam Pract 1996;9:422-34.)**

Historically pertussis (whooping cough) has caused considerable morbidity and mortality in the United States, and before routine vaccination became available, most children were eventually infected by *Bordetella pertussis*. Periodic peaks in incidence occurred approximately every 3 to 4 years. Between 1925 and 1930, 36,013 persons died in the United States of complications from pertussis. More than 1 million cases of pertussis were reported in the United States from 1940 through 1945.[1] After pertussis vaccination became widely used in the mid-1940s, the incidence of pertussis dropped by more than 95 percent. Despite this success, however, an epidemic of 6586 cases occurred in 1993 (Figure 1).

Methods

The Centers for Disease Control and Prevention (CDC) and the Association of Teachers of Preventive Medicine (ATPM) initiated the Teaching Immunization in Medical Education (TIME) Project to survey current teaching about immunization and to develop guidelines and educational materials to address any deficiencies found. A multidisciplinary team at the University of Pittsburgh developed a set of review articles as part of continuing medical education modules in the TIME project. The team developed these

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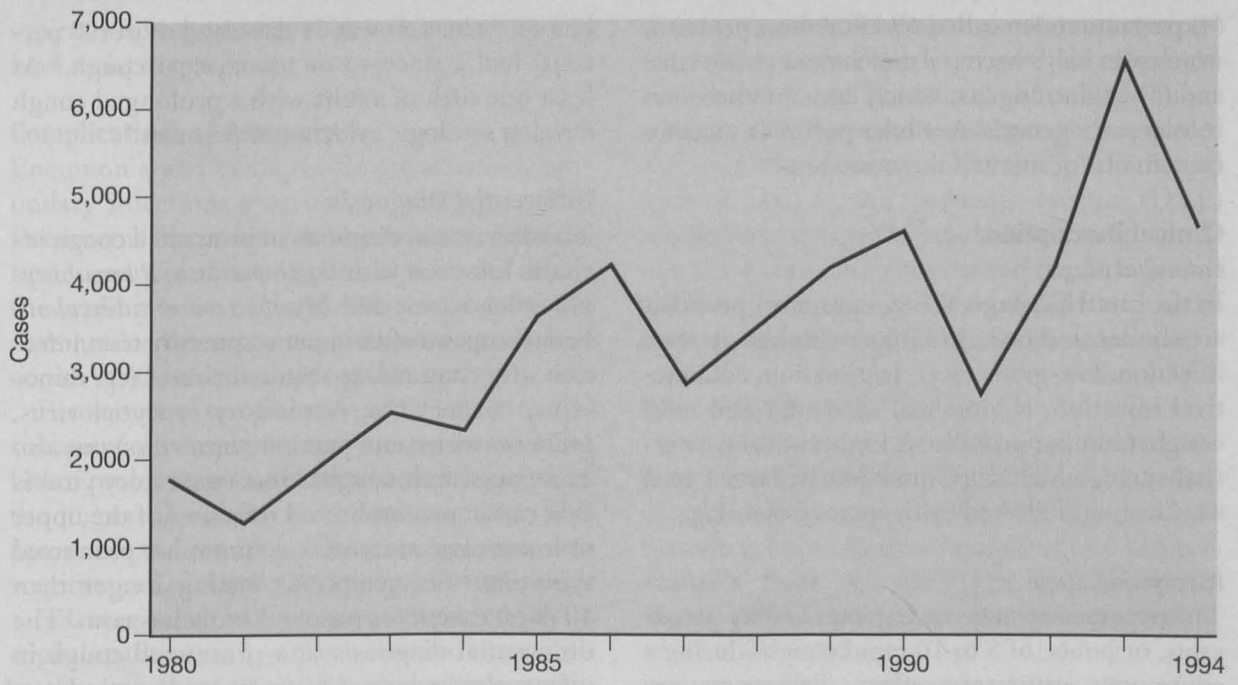

Figure 1. Annual number of cases of pertussis.
Source: Centers for Disease Control and Prevention

materials using expert judgment, selected materials from the medical literature, and publications from the CDC, including the Recommendations of the Advisory Committee on Immunization Practices. The first step in developing the modules was creating specific learning objectives that used the spectrum of Bloom's taxonomy, when possible. The modules were pilot-tested with 10 primary care physicians and revised based on this evaluation. An independent, primary care, summative evaluation was conducted by field-testing the materials with 24 primary care physicians not affiliated with the University of Pittsburgh. The materials were then reviewed by CDC experts and revised based on their comments, and subsequently reviewed by 2 national vaccine experts and revised based on their comments.

Transmission, Communicability, and Incubation Period of Pertussis

Transmission of pertussis occurs by respiratory droplets and occasionally by contact with freshly contaminated objects. Pertussis is highly contagious. From 70 to 100 percent of susceptible household members[1] and 50 to 80 percent of susceptible school contacts will become infected following exposure to an acute case. Transmission within medical settings has been documented.[2] Infected persons are contagious from 7 days after exposure to 3 weeks after the onset of the paroxysmal stage. Adults and adolescents are the primary source of pertussis infection for infants;[3] 47 percent of reported cases occur in infants, and most (72 percent) occur in children before the age of 5 years.[4] Female patients are somewhat more likely than male patients to have clinical symptoms of pertussis. The incubation period ranges from 5 to 21 days and is typically 7 to 10 days. Immunity acquired from pertussis disease lasts for many years and is possibly lifelong. Transplacental immunity wanes rapidly.

Bacteriology

The cause of pertussis is *Bordetella pertussis*, an aerobic gram-negative rod. Components (antigens) that are important in the organism's ability to cause disease include (1) a tracheal cytotoxin that destroys cilia, making it difficult to clear the thick mucus; (2) a pertussis toxin (also called lymphocytosis-promoting factor) that causes lymphocytosis, contributes to damage of the cilia, and helps attachment to the respiratory epithelium; (3) filamentous hemagglutinin, which helps the bacteria attach to cilia of the respiratory tract;

(4) pertactin (also called 69 kilodalton protein), which also helps bacterial attachment to the cilia; and (5) agglutinogens, which have an uncertain role in pathogenesis. Acellular pertussis vaccines contain one or more of these antigens.

Clinical Description

Catarrhal Stage

In the catarrhal stage, the symptoms of pertussis are similar to those of an upper respiratory tract infection: low-grade fever, lacrimation, conjunctival injection, rhinorrhea, sneezing, and mild cough. Communicability is highest in the catarrhal stage, which starts insidiously, lasts 1 to 2 weeks, and is followed by the paroxysmal stage.

Paroxysmal Stage

The paroxysmal stage is characterized by paroxysms, or bouts, of 5 to 10 rapid coughs during a continuous expiratory effort. Paroxysms are caused by difficulty in expelling thick mucus from the bronchi. Following the paroxysm, an exaggerated inspiratory effort can occur through the narrowed glottis, resulting in the characteristic high-pitched whoop. Many infected individuals, particularly infants and adults, do not have the inspiratory whoop. During the paroxysm, cyanosis, bulging eyes, lacrimation, epistaxis, salivation, and distention of neck veins commonly occur. Following the episode, the patient might vomit, appear apathetic and dazed, and be exhausted. On examination, subconjunctival hemorrhages and petechiae on the head and neck might be found. The paroxysms are worse at night and occur periodically at a frequency of about 15 bouts per 24 hours. Between episodes children can appear well. A common laboratory finding during the paroxysmal stage is a lymphocytosis of 11,000/μL or higher. This stage lasts 2 to 6 weeks and is followed by the convalescent stage.

Convalescent Stage

During this gradual recovery stage, the inspiratory whooping and vomiting occur less frequently. This stage lasts for 1 to 3 weeks, although the cough itself can persist for months, and paroxysms can recur with subsequent respiratory infections.

Adults and adolescents usually have a mild disease characterized by a prolonged cough that is often paroxysmal. For instance, in a study of university students, the median duration of cough before evaluation was 21 days, and most (90 percent) had a staccato or paroxysmal cough.[5] At least one fifth of adults with a prolonged cough develop serologic evidence of pertussis.[6]

Differential Diagnosis

The differential diagnosis of protracted cough includes infection with *B parapertussis*, *B bronchiseptica*, adenovirus, and *Mycobacterium tuberculosis*. Bronchospasm after upper respiratory tract infection with community-acquired viruses (eg, rhinovirus, coronavirus, respiratory syncytial virus, influenza virus, and parainfluenza virus) can also cause persistent cough. Most respiratory viruses that cause uncomplicated infection of the upper or lower respiratory tract do not cause protracted symptoms (ie, symptoms lasting longer than 10 days) except for postviral bronchospasm. The differential diagnosis of a protracted cough in infants also includes *Chlamydia trachomatis*, *Ureaplasma urealyticum*, cytomegalovirus, and *Pneumocystis carinii*. Cystic fibrosis, smoking, and gastroesophageal reflux are noninfectious causes of protracted cough.

Diagnosis

A diagnosis of pertussis is often suspected during the paroxysmal stage. The clinical definition of pertussis is a cough illness lasting at least 2 weeks with one of the following: paroxysms of cough, inspiratory whoop, or post-tussive vomiting without other apparent cause (as reported by a health professional).[7] Pertussis can be confirmed by laboratory studies or linked epidemiologically to a laboratory-confirmed case. A probable case of pertussis meets the same clinical definition but is not laboratory confirmed or epidemiologically linked to a laboratory-confirmed case.[7] Suspected cases of pertussis should be reported promptly to state or local health departments.

The diagnosis is confirmed by growing *B pertussis* on special agar, such as Bordet-Gengou or Regan-Lowe; the organism does not grow well on more common agars or transport media. A calcium alginate or Dacron (not cotton) swab should be used to collect specimens, which should be obtained from the posterior nasopharynx rather than the throat. If the local laboratory is not equipped to isolate *B pertussis*, then Regan-Lowe media can be used for transport to a reference laboratory. Direct fluorescent antibody tests on nasopharyngeal

aspirates, although available, lack sensitivity and have variable specificity.

Complications of Pertussis

Pneumonia and otitis media are common secondary infections that occur during pertussis. Pneumonia, the most common serious complication, occurs in about 15 percent of cases[4] and is the leading cause of death. Generally, pertussis does not lead to permanent lung damage. Apnea occurs in 40 percent of reported cases.[4]

Paroxysms of cough can lead to interstitial or subcutaneous emphysema and to pneumothorax. Other problems include epistaxis, hernia, ulcer of the lingual frenulum, and rectal prolapse. The paroxysms and resulting exhaustion, anorexia, and vomiting can lead to dehydration and weight loss.

Seizures occur in 2.2 percent of cases and encephalopathy in 0.7 percent of cases.[4] Approximately one third of the patients with encephalopathy die; another one third have permanent brain damage; the remaining one third recover. Encephalopathy is caused by hypoxia or minute cerebral hemorrhages. The hospitalization rate is 43 percent for reported cases of all ages and 69 percent for infants younger than 12 months of age.[4] The case fatality rate is 0.6 percent for infants younger than 12 months of age.

Treatment

Antibiotic therapy can abort or diminish the severity of illness if given in the catarrhal phase, when pertussis is often not suspected. Unfortunately antibiotics have little clinical effect on the paroxysmal phase, although the period of communicability is shortened. Erythromycin, 50 mg/kg/d for 14 days, is the drug of choice. Erythromycin eliminates the organism from the nasopharynx within 4 days; hence, health care workers can return to work after 5 days of treatment. Trimethoprim-sulfamethoxazole is recommended as an alternative for those who cannot take erythromycin, although it is of unproved efficacy.

Supportive therapy with supplemental oxygen, intravenous hydration, and proper nutrition might be needed. The use of an oximeter or an apnea monitor is often appropriate.

Prophylaxis of Household and Close Contacts

All household members and those in close contact with persons with pertussis should receive erythromycin (or trimethoprim-sulfamethoxazole) for 14 days as prophylaxis, regardless of age and vaccination status. Those in close contact who are younger than 7 years and who have not completed the four-dose primary series of diphtheria and tetanus toxoids and pertussis vaccine (DTP) should be vaccinated using the accelerated schedule; those who have not received the fifth dose of DTP and have not had a dose of DTP within the previous 3 years should be given a booster dose.

Whole-Cell Pertussis Vaccine

Whole-cell pertussis vaccine is made from a suspension of killed *B pertussis*. Generally, it is produced in combination with diphtheria and tetanus toxoids as DTP. Monovalent pertussis vaccine is available from the Michigan Department of Health (517-335-8120) for the rare situations in which it is needed.

Vaccine efficacy, that is, protection from pertussis disease, varies depending upon the vaccine, the study design, and how pertussis is defined.[8] Estimates of efficacy in the United States are generally 70 to 90 percent.[1,4] Multiple doses are required for optimal immunogenicity.[8] For instance, efficacy, based on a case definition of a cough of a least 14 days with paroxysms, whoop, or vomiting, is 36 percent after one dose, 49 percent after two doses, and 83 percent after three doses.[9] Efficacy wanes with time from vaccination; there is almost no residual protection 12 years after the last dose.

Adverse Events Following Whole-Cell Pertussis Vaccine

Whole-cell pertussis vaccine causes the following adverse events, most of which are minor: localized edema at the injection site (41 percent of recipients), fever, drowsiness, and fretfulness. Uncommon adverse events are persistent crying for 1 or more hours following DTP vaccination, an unusual high-pitched cry, seizures, and hypotonic-hyporesponsive episodes.[10] Most seizures that occur after DTP vaccination are simple febrile seizures and do not have any permanent sequelae. Acetaminophen, when taken after vaccination, reduces the likelihood of fever and is particularly recommended for those with a personal or family history of seizures. Rates of systemic adverse events following DTP vaccination are shown in Table 1.

Table 1. Systemic Adverse Events Following DTP Vaccination.

Event	Frequency per Number of Doses
Fever ≥ 38°C (100.4°F)	1/2
Fretfulness	1/2
Drowsiness	1/3
Anorexia	1/5
Vomiting	1/15
Persistent inconsolable crying	1/100
Fever ≥ 40.5°C (105°F)	1/330
Unusual, high-pitched cry	1/1000
Hypotonic-hyporesponsive episode	1/1750
Convulsions	1/1750

From Cody et al, with permission.[10]
DTP = diphtheria and tetanus toxoids and pertussis vaccine.

The possibility of permanent or severe adverse events following whole-cell pertussis vaccination is a subject of intense debate. It is generally accepted that on rare occasions a few children have anaphylactic reactions to DTP that contraindicate further doses. The possibility of other allegedly permanent or serious adverse events is less well-accepted. The controversy stems from the limitations of the available scientific data, negative publicity from the media, the frequency of minor adverse events following whole-cell pertussis vaccine, and the frequency of vaccinations. Many of the reports of adverse events are uncontrolled case reports or case series, and they could have resulted from temporal coincidence. In the first year of life, DTP is given 3 times. If a child has an illness or injury in the first year of life, there is a 3 in 52 chance, or an approximately 1 in 17 chance, that it will occur within 1 week of the administration of a dose of DTP. Thus, temporal associations that are due to chance alone are quite common. Pertussis vaccination dramatically decreases both the number of hospitalizations and deaths caused by pertussis; furthermore, it has a cost-to-benefit ratio of 1 to 11.1.[11]

The best-known study of neurologic adverse events after DTP is the 1981 National Childhood Encephalopathy Study (NCES) in Britain. The NCES, which is the largest and longest study in the field, concluded that the risk of permanent brain damage following pertussis vaccination was 1 in 330,000 doses and the risk of encephalopathy was 1 in 140,000 doses.[12] Griffith,[13] in a scientific and legal reevaluation of the NCES data, challenged that conclusion, noting that cases of documented viral meningitis were attributed to DTP vaccine. Accordingly, the 1 in 330,000 figure that was previously cited should no longer be considered reliable.[14] In a recent follow-up study of the NCES data, Miller et al[15] found an association between acute encephalopathy and chronic neurologic damage, regardless of the cause of acute encephalopathy. As the NCES found an association between DTP and acute encephalopathy, Miller et al also found an association between DTP vaccination and chronic neurologic damage in those who had acute encephalopathy. The findings of this follow-up study have been subject to controversy.

In response to controversy about vaccine safety and the need to protect the country from vaccine-preventable diseases, the United States Congress passed the National Childhood Injury Act in 1986 and the Vaccine Compensation Amendments in 1987. These laws created a federal no-fault compensation program, developed an excise tax on vaccines to fund the program, and requested a scientific review of possible adverse events from common childhood vaccines. The Institute of Medicine (IOM), an independent scientific organization, conducted the reviews ordered by the National Childhood Injury Act,

Table 2. Summary of Institute of Medicine Conclusions About Alleged Adverse Events Following DTP Vaccination.

Evidence Favors Rejection of Causal Relation	Evidence Favors Acceptance of Causal Relation	Evidence Established a Causal Relation
Infantile spasms	Acute encephalopathy	Anaphylaxis
Hypsarrhythmia	Shock and "unusual shock-like state"	Protracted, inconsolable crying
Reye syndrome	Chronic neurologic damage in those with an acute neurologic reaction after DTP	
Sudden infant death syndrome		

Modified from Table 1-2 in Howson et al.[16]
DTP = Diphtheria and tetanus toxoids and pertussis vaccine.

Table 3. Study Sites, Vaccines, Vaccination Schedules, and Efficacy Estimates Used in the Evaluation of the Efficacy of Acellular Pertussis Vaccine When Administered in Infancy.

Site of Study	Acellular Pertussis Vaccine	Vaccine Composition					Trial Type	Schedule Studied (months)	Vaccine Efficacy	
		PT Inactivation							DTaP % (95% CI)	DTP* % (95% CI)
		Chemical	Genetic	FHA	Pn	Fim				
Stockholm, Sweden	CLL-4F$_2$	X		X	X	X	Randomized double-blind	2,4,6	85 (81-89)	48 (37-58)
Stockholm, Sweden	SKB-2	X		X			Randomized double-blind	2,4,6	59 (51-66)	48 (37-58)
Italy	Bsc-3P		X	X	X		Randomized double-blind	2,4,6	84 (76-90)	36 (14-52)
Italy	SKB-3P	X		X	X		Randomized double-blind	2,4,6	84 (76-90)	36 (14-52)
Mainz, Germany	SKB-3P	X		X	X		Household contact with passive surveillance	3,4,5	89 (77-95)	97 (83-99)
Göteborg, Sweden	NAV-aP	X					Randomized double-blind	3,5,12	71 (63-78)	None
Erlangen, Germany	LPT-4F$_1$ (ACEL-IMUNE)	X		X	X	X	Randomized open DT control	2,4,6, 15-18	81 (73-87)†	91 (85-95)†
Niakhar, Senegal	PM-2	X		X			Household contact with active surveillance	2,4,6	86 (71-93)	96 (87-99)
Munich, Germany	CB-2 (Tripedia)	X		X			Case-control study with passive surveillance	2,4,6	94 (65-99)	97 (73-99)

Modified from Centers for Disease Control and Prevention.[29]
PT = pertussis toxin; FHA = filamentous hemagglutinin; Pn = pertactin; Fim = fimbrial agglutinogen;
DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; DTP = diphtheria and tetanus toxoids and pertussis vaccine;
DT = diphtheria and tetanus toxoids vaccine.
*The whole-cell pertussis vaccines differed; some are not available in the United States.
†Efficacy after 3 or 4 doses.

leading to the publication of *Adverse Effects of Pertussis and Rubella Vaccines*[16] in 1991. In evaluating possible associations between vaccines and alleged adverse outcomes, the IOM committee looked at biological plausibility, reviewed published studies, and evaluated the results of those studies in terms of the strength of the evidence offered. The results of the IOM reports are summarized in Table 2.

The IOM offered three possible interpretations of the finding that DTP was associated with chronic neurologic damage in those with acute encephalopathy after DTP vaccination[17]: (1) DTP might cause serious acute neurologic illnesses followed by chronic nervous system dysfunction; (2) DTP might trigger such events in those with underlying brain or metabolic illnesses; or (3) DTP might cause an acute neurologic illness in a child with an underlying brain or metabolic illness that would itself have led to chronic neurologic dysfunction even if the DTP were not given. The IOM findings on chronic neurologic damage were reviewed by the National Vaccine Advisory Committee and the Advisory Committee on Immunization Practices. Both of these groups of scientists concluded that the data are insufficient to know whether DTP causes chronic neurologic damage in those who experienced a temporal association between DTP and an acute neurologic event.

Acellular Pertussis Vaccine

Acellular pertussis vaccines were developed as a result of adverse events associated with whole-cell

Table 4. Percentage of Infants With Mild or Local Reactions by the Third Evening After Pertussis Vaccination at Ages 2, 4, and 6 Months.

Vaccine	Temperature ≥ 37.8°C	Swelling > 20 mm	Severe Fussiness*
DTaP	25	4.2	4.7
DTP	60	22.4	12.4

Adapted from data in Decker et al.[30]
DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; DTP = diphtheria and tetanus toxoids and pertussis vaccine.
*Fussiness was classified as severe when the infant cried persistently and could not be comforted.

pertussis vaccine. Licensure of acellular vaccines occurred in two stages in the United States: (1) in 1991, acellular vaccines were licensed for use as the fourth and fifth doses; (2) in 1996, after further efficacy studies were conducted, acellular vaccines were licensed for use as the primary series for use in infancy.

The first acellular pertussis vaccines licensed in the United States were the Lederle/Takeda (ACEL-IMUNE) and Connaught/BIKEN (Tripedia) vaccines, which differ both in the number and relative proportions of the component antigens. The major component (86 percent) of the Lederle/Takeda vaccine is filamentous hemagglutinin; however, it also contains pertussis toxin, fimbrial agglutinogen, and the pertactin (outer membrane protein). The Connaught/BIKEN vaccine contains pertussis toxin and filamentous hemagglutinin in equal proportions. These acellular vaccines are combined with diphtheria and tetanus toxoids to form the diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). The immunogenicity of these vaccines appears to equal that of the whole-cell vaccines.[18-25] Efficacy rates for the fourth and fifth doses are similar for the Lederle/Takeda and Connaught/ BIKEN vaccines and were estimated at 82 percent in one study.[21] Acellular vaccines have approximately one quarter to one half of the common adverse events associated with whole-cell vaccine.[18,19,25]

Results from trials conducted in Sweden, Italy, Germany, and Senegal of the acellular pertussis vaccines given as the primary series have recently been released. Most of these trials were sponsored by the National Institute for Allergy and Infectious Diseases or the National Institute of Child Health and Human Development, and several were published recently.[26-28] The acellular vaccines vary in several respects: (1) the method of inactivating pertussis toxin, (2) the number of different antigens, (3) the amount of each of these antigens, (4) the amount of diphtheria and tetanus toxoids, and (5) the amount of adjuvant. Pertussis toxin can be inactivated by genetic means or one of several different chemical methods. All of the acellular vaccines have pertussis toxin, but they vary in the presence or absence of filamentous hemagglutinin, pertactin (outer membrane protein), and fimbrial agglutinogen (Table 3).

The studies differed in their methods as well as in the vaccines tested. Hence, it was difficult to compare the various trials with regard to safety and efficacy rates. Differences in study methods included (1) design type, (2) degree of blinding, (3) case definition of pertussis, (4) criteria for confirmation of pertussis infection, (5) ethnicity of study population, (6) number of children studied, (7) timing of the vaccine schedule, and (8) manufacturer of whole-cell vaccine used for comparison. Efficacy rates for the acellular vaccines ranged

Table 5. Incidence of Moderate-to-Severe Adverse Reactions per 1000 Doses of Acellular and Whole-Cell Pertussis Vaccines Within 48 to 72 Hours of Inoculation at Ages 2, 4, and 6 Months

Vaccine	Temperature ≥ 40°C	Hypotonic-Hyporesponsive Episodes	Persistent Crying ≥ 3 Hours	Convulsions	Cyanosis
DTaP	0.1*–1.4	0.0–0.4	0.3–1.1†	0.0–0.3	0
DTP	0.2*–4.6	0.1–0.8	3.7–5.5	0.1–0.2	0.0–0.6
DT	0.4–0.9	0.0–0.4	0.0–0.1	0.0–0.3	0

DTaP = diphtheria and tetanus toxoids and acelluar pertussis vaccine; DTP = diphtheria and tetanus toxoids and pertussis vaccine; DT = diphtheria and tetanus toxoids vaccine.
*Temperature ≥ 40.5°C in one study.
† One study used steady or severe crying or screaming as a criterion.

Table 6. Comparison of Responses to Connaught/BIKEN, DTaP, and Whole-Cell DTP Vaccines Given at Ages 2, 4, and 6 Months.

Assay	Connaught/BIKEN DTaP Vaccine		Whole-Cell DTP Vaccine*	
	Seroconversion Percent†	Postvaccination GMT	Seroconversion Percent†	Postvaccination GMT
PT-ELISA	99.2	127‡	83.8	67
FHA-ELISA	85.6	84‡	10.7	3
Agglutinogens	4.2§	9	67.5	83
CHO cell assay	93.3	841	61.5	260

Modified from Centers for Disease Control and Prevention.[29]
DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; DTP = diphtheria and tetanus toxins and pertussis vaccine; PT = pertussis toxin; ELISA = enzyme-linked immunoassay; FHA = filamentous hemagglutinin; GMT = geometric mean titer; CHO = Chinese hamster ovary.
*Whole-cell vaccine, manufactured by Lederle Laboratories.
†Proportion who achieved a postimmunization (one month after third dose) value that was at least fourfold greater than both the preimmunization value and the minimum detectable level.
‡Postvaccination GMTs differ significantly ($P < 0.05$).
§Agglutinogens are not contained in the Connaught/BIKEN vaccine.

from about 59 to 94 percent. Efficacy rates for the whole-cell vaccines varied according to the differences among the various whole-cell vaccines used as well as differences in the methods used to conduct the study. Some of the whole-cell vaccines studied are not available in the United States.

Seizures, persistent crying, and hypotonic-hyporesponsive episodes have been reported after acellular pertussis vaccination. The rates of both mild and moderate-to-severe adverse events are much lower, however, after administration of DTaP than after whole-cell DTP; furthermore, the rates of adverse events are similar for DTaP and pediatric diphtheria and tetanus toxoids (DT) (Tables 4 and 5).

The Connaught/BIKEN, also called CB-2, acellular pertussis vaccine was licensed in the United States on 31 July 1996 for the first four doses of the routine series to be given at 2, 4, 6, and 15 to 20 months. Seroconversion rates to pertussis toxin and filamentous hemagglutinin are higher (Table 6) and adverse event rates are lower for Connaught/BIKEN than for whole-cell vaccine.

If readily available, DTaP is recommended because of the reduced risk of adverse events when compared with DTP. DTaP instead of DTP is strongly recommended for children with a family history of seizures.

Schedule and Administration

The schedule for DTP is provided in Table 7. Premature infants should be vaccinated with full doses at the appropriate chronological age. Full doses should be used because fractional doses are not as immunogenic as full doses and might not lessen the risk of adverse events. Although five doses of DTP are recommended, persons who receive their fourth dose on or after their fourth birthday do not need the fifth dose. DTP is administered intramuscularly.

Persons 7 years of age and older should not receive whole-cell pertussis vaccine because of the higher incidence of adverse events and the low morbidity of pertussis in older children and adults. One half of older children and adults who receive monovalent whole-cell pertussis vaccine or DTP develop induration at the injection site.[31,32] Tetanus and diphtheria toxoids, adult type (Td) should be used for the primary series in persons 7 years of age and older (three doses) and for routine booster doses every 10 years. Adult Td vaccine contains the same quantity of tetanus toxoid as DTP, but only one third as much diphtheria toxoid. Acellular pertussis vaccines have not been licensed for use in adults. Acellular vaccines for children contain a higher dose of diphtheria toxoid than is recommended for adults; hence, a new formulation would need to be developed.

Contraindications and Precautions to Pertussis Vaccine

Contraindications and precautions to whole-cell and acellular pertussis vaccines are shown in Table 8. Precautions are situations in which the

Table 7. Routine DTP Vaccination Schedule for Children Less than 7 Years of Age—United States.

Dose	Customary Age	Age and Interval	Vaccine
1	2 months	6 weeks or older	DTaP*†
2	4 months	4-8 weeks after 1st dose‡	DTaP*†
3	6 months	4-8 weeks after 2nd dose‡	DTaP*†
Reinforcing	15-18 months‡	6-12 months after 3rd dose‡	DTaP*†§
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth dose administered after 4th birthday)		DTaP*†§
Additional boosters	Every 10 years after last dose; the first booster may be given at age 11-12 (or 14-16) years, provided that ≥ 5 years have passed since previous Td or DTP		Td

Modified from Centers for Disease Control and Prevention.[29]
DTaP = diphtheria and tetanus toxins and acellular pertussis vaccine; Td = tetanus and diphtheria toxoids, adult type; DTP = diphtheria and tetanus toxoids and pertussis vaccine.
*Whole-cell DTP is an acceptable alternative to DTaP.
†Unless the patient has had an anaphylactic reaction after a previous dose, use DT if pertussis vaccine is contraindicated.
‡Prolonging the interval does not require restarting series.
§*Connaught/BIKEN (Tripedia) and Lederle/Takeda (ACEL-IMUNE) can be used interchangeably for the fourth and fifth doses.*

pertussis vaccine is generally withheld but the decision is made on an individual basis with the parent. The risk of acquiring pertussis needs to be weighed against the risks of another adverse event. If the pertussis component is withheld because of a contraindication or precaution, then pediatric DT is administered instead, except in the case of true anaphylaxis, in which the diphtheria and pertussis components are contraindicated. In such cases, skin testing may be done to assess whether tetanus toxoid can be given. Contraindications and precautions apply to acellular pertussis vaccines as well as whole-cell vaccine.

Many health care providers are overly cautious when interpreting vaccine contraindications.[33,34] Local vaccine adverse events, low-to-moderate fevers following previous doses, and a family history of severe DTP adverse events, mental retardation, seizures, or allergies are not valid contraindications.

DTP vaccination should be postponed for infants that have an evolving neurologic disorder, unevaluated seizures, or a neurologic event between doses of pertussis vaccine. Vaccination should be resumed after evaluation and treatment of the condition.

Vaccine Liability and Informing Patients about Vaccination

Patients should receive information that is easy to understand about the benefits and risks of vaccination. The old, lengthy Vaccine Information Pamphlets have been replaced with new, shorter Vaccine Information Statements. Since 1 October 1994, all vaccine providers have been required by law to use the Vaccine Information Statements developed by the CDC.

The Vaccine Injury Compensation Program (VICP) was established to award no-fault compensation for specified injuries that are temporally related to vaccine administration. The VICP is funded by the vaccine excise tax and has greatly reduced the risk of litigation to both providers and vaccine manufacturers; at one time liability concerns were so great that some manufacturers were unwilling to continue production of certain vaccines. Since enactment of the VICP, lawsuits have declined dramatically.

Successful litigation has occurred, however, for failure to vaccinate. Two cases have successfully been brought against providers for failure to administer hepatitis vaccine or hepatitis B immune globulin; other cases are pending for failure to vaccinate against hepatitis B, measles, and *Haemophilus influenzae* type b.[35]

Causes of Pertussis Outbreaks

Outbreaks of pertussis continue to occur in the United States despite the availability of pertussis vaccine. Factors leading to outbreaks include high communicability, unrecognized pertussis in adults and adolescents whose immunity has waned, the need for multiple doses to achieve good immunity, and undervaccination. Pertussis is highly communicable, as shown by secondary household attack rates of 70 to 100 percent.[36,37]

Table 8. Contraindications and Precautions to DTP and DTaP Vaccines.

Contraindication or Precaution	Clinical Condition
Contraindications based on adverse events following DTP or DTaP	Anaphylaxis
	Encephalopathy within 7 days—give DT subsequently
Precautions based on adverse events following DTP or DTaP (individualize decision in consultation with parents regarding administration of DTP versus DT)	Fever ≥ 40.5°C (105°F) within 48 hours
	Shock-like state or collapse (hypotonic-hyporesponsive episode) within 48 hours
	Persistent, inconsolable crying within 48 hours
	Convulsions within 72 hours; if administering another dose, use DTaP and give acetaminophen
General vaccine contraindications	Moderate or severe acute illness—delay until recovery from acute phase

DTP = diphtheria and tetanus toxins and pertussis vaccine; DTaP = diphtheria and tetanus toxins and acellular pertussis vaccine; DT = diphtheria and tetanus toxins vaccine.

Pertussis is frequently undiagnosed in adolescents and adults, because their disease symptoms are subclinical[38,39] and they typically do not have the characteristic inspiratory whoop. The typical symptom in adults is prolonged cough.[5] Pertussis can occur in adults because vaccine-induced immunity wanes with time,[40] leaving many persons unprotected by the time they reach adolescence.[38,39] Because pertussis is often undiagnosed in adults, they are a common source of infection for infants[3] and contribute to disease transmission during outbreaks that occur in medical facilities.[2,32]

Most preschool-aged children who develop pertussis are not age-appropriately vaccinated.[3] One study of selected urban areas found the vaccination status of most (58 to 90 percent) 2-year-old children was not up to date.[41] Undervaccination results in decreased protection. For instance, during a pertussis outbreak, the attack rates were 30 percent, 50 percent, and 82 percent, respectively, for those who had received 3 to 5, 1 to 2, and 0 doses of vaccine.[37] Health care providers can have a major role in addressing the problem of undervaccination by preventing missed opportunities for vaccine administration, giving simultaneous vaccinations, and interpreting contraindications correctly.

Missed opportunities to vaccinate occur when a child is seen by a provider for a reason other than well-child care or vaccinations and the child's vaccination status is not addressed. In Rochester, NY, 422 of 515 children (82 percent) had a missed vaccination opportunity; most (64 percent) occurred when vaccines were mistakenly withheld because of mild acute illnesses.[42] Simultaneous vaccine administration is also important in maximizing vaccination opportunities.

Many providers are overly cautious in interpreting vaccine contraindications.[33,43-45] For instance, in Minnesota many physicians (36 percent) would not administer a DTP vaccination to a child who had a febrile reaction of 39.4°C (102.9°F) after the last dose even though fever at this level is not considered to be a valid contraindication.[33] Because of the high morbidity from pertussis in infancy and the need to complete the entire primary series to achieve optimal efficacy, vaccinations should not be delayed unless there is a genuine precaution or contraindication. Using a screening checklist might help.

Office Procedures To Improve Vaccination Compliance

The most important procedures to improve vaccination rates are (1) evaluating the practice's current vaccination rates, (2) recognizing problem areas and planning strategies, (3) setting goals, (4) implementing the plan, and (5) providing ongoing feedback to the individual providers about vaccination rates in their own patients.

The first step in developing a plan, a step that is frequently overlooked, is evaluating the current vaccination rates of the practice; evaluation is a central tenet of continuous quality improvement. This exercise might uncover vaccination barriers within the clinic. For instance, in one clinic audit the vaccination barriers, in descending order, consisted of gaps in patient attendance at the clinic, missed opportunities to vaccinate, and overly cautious interpretations of contraindications.[46]

The second step is problem solving and planning. Physicians and staff can choose from the following strategies to design interventions that are suited for them and their patients.

1. During office visits the staff can routinely check the vaccination status of patients before the physician sees the patient, either during registration (perhaps using a computer) or while the nurse checks the patient's temperature, blood pressure, and heart rate. Colored stickers, checklists, or inked rubber stamps are practical ways to communicate the need for vaccinations.
2. The office can send reminder postcards to inform parents about needed vaccinations.
3. The physician can write standing orders to allow nurses to administer routine vaccines without requiring a new order for each patient.[47]
4. Nurses, not physicians, can administer the vaccines.
5. The office can provide parents with Personal Health Guides, or well-child care booklets or records, that explain the importance of preventive measures and contain recording forms. The Personal Health Guide is part of the Put Prevention into Practice Program for physicians. The program kit includes stickers to communicate the need for vaccine, prevention flow sheets, and reminder postcards. It can be ordered from the Superintendent of Documents, PO Box 371954, Pittsburgh, PA 15250-7954; or by fax (202-512-2250).
6. Staff can use combination vaccines when available to reduce the number of injections that children receive, thereby decreasing discomfort.

The third step to improve vaccination rates is setting a goal, including a numerical objective. For instance, 90 percent of 2-year-olds will be fully vaccinated by a specified date.

The fourth step is implementation of the plan. Many different strategies will work if vaccination rates are monitored before and after the intervention.

The final step is monitoring vaccination rates and providing feedback to providers. For instance, the percentage of fully vaccinated 2-year-olds can be graphed and displayed, allowing physicians and teams to compare their records. The physician or team that vaccinates the highest percentage of patients can be awarded a prize. The impact of evaluation, competition, and feedback should not be underestimated — they are among the most important changes a practice can make to improve vaccination rates.

The Teaching Immunization in Medical Education (TIME) Project

This article was written as a component of the Teaching Immunization in Medical Education (TIME) Project, a multiyear project guided by a national advisory committee of experts in the fields of immunization and medical education. The project is a collaborative effort of the CDC, ATPM, and the University of Pittsburgh School of Medicine. The goal of the project is to enhance the educational preparation of physicians through an innovative curriculum on immunization and vaccine-preventable diseases, thereby influencing the immunization practices of physicians in an effort to increase vaccination levels. Information about continuing medical education (CME) materials to support this article, CME modules on other vaccine-preventable diseases, and case-based materials designed for medical students and residents can be obtained by directly contacting ATPM, Suite 204, 1511 South Ritchie Highway, Arnold, Md 21012; telephone 800-789-6737, fax 800-678-7102. Some CME modules will also be available at the ATPM World Wide Web site: http://www.atpm.org/cme/cme.htm.

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