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Diphtheria, Tetanus, and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures

Recommendations of the Immunization Practices Advisory Committee (ACIP)

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Contents

Definition of Abbreviations

ACIP	Immunization Practices Advisory Committee
CDC	Centers for Disease Control
DT	Diphtheria and Tetanus Toxoids Adsorbed (for pediatric use)
DTP	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed
HbCV	*Haemophilus* b Conjugate Vaccine
IM	Intramuscular(ly)
IPV	Inactivated Poliovirus Vaccine
Lf	Limit of flocculation
MMR	Measles-Mumps-Rubella Vaccine
NCES	National Childhood Encephalopathy Study
OPV	Oral Poliovirus Vaccine
SIDS	Sudden Infant Death Syndrome
Td	Tetanus and Diphtheria Toxoids Adsorbed (for adult use)
TIG	Tetanus Immune Globulin
VAERS	Vaccine Adverse Event Reporting System

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Diphtheria, Tetanus, and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures

Recommendations of the Immunization Practices Advisory Committee (ACIP)

This revision of the Immunization Practices Advisory Committee (ACIP) statement on diphtheria, tetanus, and pertussis updates the statement issued in 1985, and incorporates the 1987 supplementary statement, which addressed two issues: a) the risks and benefits of pertussis vaccine for infants and children with family histories of convulsions; and b) antipyretic use in conjunction with diphtheria and tetanus toxoids and pertussis vaccine absorbed (DTP) vaccination among children with personal or family histories of convulsions (1,2). This document presents new recommendations for epidemiologic investigation and management of contacts of diphtheria patients.

The updated recommendations include a review of the epidemiology of the three diseases and descriptions of the available immunobiologic preparations with appropriate vaccination schedules. Also included are a) new information on and reassessment of the possible relation between receipt of DTP and the occurrence of serious acute neurologic illness and permanent brain damage, b) revisions in the recommendations on precautions for and contraindications to pertussis vaccine use, and c) revisions on recommendations for chemoprophylaxis for household and other close contacts of pertussis patients.

The Committee has reviewed and taken into consideration the recent report by the Institute of Medicine entitled, "Adverse Effects of Pertussis and Rubella Vaccines" in making these recommendations.

INTRODUCTION

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

DIPHTHERIA

At one time, diphtheria was common in the United States. More than 200,000 cases, primarily among children, were reported in 1921. Approximately 5%-10% of cases were fatal; the highest case-fatality ratios were recorded for the very young and the elderly. Reported cases of diphtheria of all types declined from 306 in 1975 to 59 in 1979; most were cutaneous diphtheria reported from a single state (*3*). After 1979, cutaneous diphtheria was no longer notifiable. From 1980 to 1989, only 24 cases of respiratory diphtheria were reported; two cases were fatal, and 18 (75%) occurred among persons $\geq$20 years of age.

Diptheria is currently a rare disease in the United States primarily because of the high level of appropriate vaccination among children (97% of children entering school have received ≥three doses of diphtheria and tetanus toxoids and pertussis vaccine [DTP]) and because of an apparent reduction in the circulation of toxigenic strains of *Corynebacterium diphtheriae*. Most cases occur among unvaccinated or inadequately vaccinated persons. The age distribution of recent cases and the results of serosurveys indicate that many adults in the United States are not protected against diphtheria. Limited serosurveys conducted since 1977 indicate that 22%-62% of adults 18-39 years of age and 41%-84% of those ≥60 years of age may lack protective levels of circulating antitoxin against diphtheria (*4-7*). Thus, it appears that further reductions in the incidence of diphtheria would require more emphasis on adult immunization programs. Both toxigenic and nontoxigenic strains of *C. diphtheriae* can cause disease, but only strains that produce toxin cause myocarditis and neuritis. Furthermore, toxigenic strains are more often associated with severe or fatal illness in noncutaneous (respiratory or other mucosal surface) infections and are more commonly recovered in association with respiratory than from cutaneous infections.

C. diphtheriae can contaminate the skin, usually at the site of a wound. Although a sharply demarcated lesion with a pseudomembranous base often results, the appearance may not be distinctive, and infection can be confirmed only by culture. Usually other bacterial species can also be isolated. Cutaneous diphtheria has most commonly affected indigent adults and certain groups of American Indians.

A complete vaccination series substantially reduces the risk of developing diphtheria, and vaccinated persons who develop disease have milder illnesses. Protection lasts at least 10 years. Vaccination does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.

TETANUS

The occurrence of tetanus in the United States has decreased dramatically from 560 reported cases in 1947, when national reporting began, to a record low of 48 reported cases in 1987 (*8*). The decline has resulted from widespread use of tetanus toxoid and improved wound management, including use of tetanus prophylaxis in emergency rooms.

Tetanus in the United States is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to CDC during 1987 and 1988, 68% were ≥50 years of age, while only six were <20 years of age. No cases of neonatal tetanus were reported. Overall, the case-fatality rate was 21% (*8*). The age distribution of recent cases and the results of serosurveys indicate that many U.S. adults are not protected against tetanus. Serosurveys undertaken since 1977 indicate that 6%-11% of adults 18-39 years of age and 49%-66% of those ≥60 years of age may lack protective levels of circulating tetanus antitoxin (*4-7*). The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain (*8*).

Surveys of emergency rooms suggest that 1%-6% of all persons who receive medical care for injuries that can lead to tetanus receive less than the recommended prophylaxis (*9,10*). In 1987-1988, 58% of tetanus patients with acute injuries did not seek medical care for their injuries; of those who did, 81% did not receive prophylaxis as recommended by ACIP guidelines (*8*).

In 4% of tetanus cases reported during 1987 and 1988, no wound or other condition was implicated. Nonacute skin lesions such as ulcers, or medical conditions such as abscesses were reported in association with 14% of cases.

Neonatal tetanus occurs among infants born under unhygienic conditions to inadequately vaccinated mothers. Vaccinated mothers confer protection to their infants through transplacental transfer of maternal antibody. From 1972 through 1984, 29 cases of neonatal tetanus were reported in the United States (*11*). No cases of neonatal tetanus were reported in the period 1985-1989. Spores of *Clostridium tetani* are ubiquitous. Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary vaccination, with subsequent maintenance of adequate antitoxin levels by means of appropriately timed boosters, is necessary to protect persons among all age-groups. Tetanus toxoid is a highly effective antigen; a completed primary series generally induces protective levels of serum antitoxin that persist for ≥10 years.

PERTUSSIS

Disease caused by *Bordetella pertussis* was once a major cause of infant and childhood morbidity and mortality in the United States (*12,13*). Pertussis became a nationally notifiable disease in 1922, and reports reached a peak of 265,269 cases and 7,518 deaths in 1934. The highest number of reported pertussis deaths (9,269) occurred in 1923. The introduction and widespread use of standardized whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP) in the late 1940s resulted in a substantial decline in pertussis disease, a decline which continued without interruption for nearly 30 years.

By 1970, the annual reported incidence of pertussis had been reduced by 99%. During the 1970s, the annual numbers of reported cases stabilized at an average of approximately 2,300 cases each year. During the 1980s, however, the annual numbers of reported cases gradually increased from 1,730 cases in 1980 to 4,157 cases in 1989. An average of eight pertussis-associated fatalities was reported each year throughout the 1980s. It is not clear whether the increase in reported pertussis reflects a true increase in the incidence of the disease or improvement in the reporting of pertussis. However, these data underestimate the true number of cases, because many are unrecognized or unreported, and diagnostic tests for *B. pertussis*–culture and direct-immunofluorescence assay–may be unavailable, difficult to perform, or incorrectly interpreted. Because direct-fluorescent-antibody testing of nasopharyngeal secretions has been shown in some studies to have low sensitivity and variable specificity, it should not be relied on as a criterion for laboratory confirmation (*14,15*). In addition, reporting criteria have varied widely among the different states. Laboratory diagnosis based on serologic testing is not widely available and is still considered experimental (*16*). In 1990, to improve the accuracy of reporting, the U.S. Council of State and Territorial Epidemiologists adopted uniform case definitions for pertussis (*17*).

Before widespread use of DTP, <20% of cases and 50%-70% of pertussis deaths occurred among children <1 year of age (*13,18*). For the period 1980-1989, 47% of reported illnesses from *B. pertussis* occurred among children <1 year of age, and 72% occurred among children <5 years of age; 61 (77%) of 79 deaths reported to CDC

occurred among children <1 year of age (*19*). Infants <2 months of age were at highest risk of complications, with a case-fatality rate of 1.3%. Although incidence based on reported cases increased among all age-groups during the 1980s, the most striking increases occurred among adolescents and adults (*19*). Whether this represented a true increase or more complete recognition and reporting is not clear.

Pertussis is highly communicable (attack rates of >90% have been reported among unvaccinated household contacts) and can cause severe disease, particularly among very young children. Of 10,749 patients <1 year of age reported nationally as having pertussis nationally during the period 1980-1989, 69% were hospitalized, 22% had pneumonia, 3.0% had ≥one seizure, 0.9% had encephalopathy, and 0.6% died (*19*). The high rate of hospitalization for infants with pertussis has been observed in several population-based studies (*20-22*). Because of the substantial risks of complications of the disease, completion of a primary series of DTP vaccine early in life is essential.

Among older children and adults, including those previously vaccinated, *B. pertussis* infection may result in symptoms of bronchitis or upper-respiratory-tract infection. Pertussis may not be diagnosed because classic signs, especially the inspiratory whoop, may be absent. Older preschool children and school-age siblings who are not fully vaccinated and who develop pertussis can be important sources of infection for infants <1 year of age. Adults also play an important role in the transmission of pertussis to unvaccinated or incompletely vaccinated infants and young children (*23*).

Controversy regarding the safety of pertussis vaccine during the 1970s led to several studies of the benefits and risks of this vaccination during the 1980s. These epidemiologic analyses clearly indicate that the benefits of pertussis vaccination outweigh any risks (*24-28*).

PREPARATIONS USED FOR VACCINATION

Diphtheria and tetanus toxoids are prepared by formaldehyde treatment of the respective toxins and are standardized for potency according to the regulations of the U.S. Food and Drug Administration. The limit of flocculation (Lf) content of each toxoid (quantity of toxoid as assessed by flocculation) may vary among different products. The concentration of diphtheria toxoid in preparations intended for adult use is reduced because adverse reactions to diphtheria toxoid are apparently directly related to the quantity of antigen and to the age or previous vaccination history of the recipient, and because a smaller dosage of diphtheria toxoid produces an adequate immune response among adults.

Pertussis vaccine is a suspension of inactivated *B. pertussis* cells. Potency is assayed by comparison with the U.S. standard pertussis vaccine in the intracerebral mouse protection test. The protective efficacy of pertussis vaccines for humans has been shown to correlate with this measure of vaccine potency.

Diphtheria and tetanus toxoids and pertussis vaccine, as single antigens or various combinations, are available as aluminum-salt-adsorbed preparations. Only tetanus toxoid is available in nonabsorbed (fluid) form. Although the rates of seroconversion are essentially equivalent with either type of tetanus toxoid, the adsorbed toxoid induces a more persistent level of antitoxin antibody. The following preparations are currently available in the United States:

1. Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) and Diphtheria and Tetanus Toxoids Adsorbed (DT) (for pediatric use) are for use among infants and children <7 years of age. Each 0.5-mL dose is formulated to contain 6.7-12.5 Lf units of diphtheria toxoid, 5 Lf units of tetanus toxoid, and ≤16 opacity units of pertussis vaccine. A single human immunizing dose of DTP contains an estimated 4-12 protective units of pertussis vaccine.
2. Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) is for use among persons ≥7 years of age. Each 0.5-mL dose is formulated to contain 2-10 Lf units of tetanus toxoid and ≤2 Lf units of diphtheria toxoid.
3. Pertussis Vaccine Adsorbed (P),* Tetanus Toxoid (fluid), Tetanus Toxoid Adsorbed (T), and Diphtheria Toxoid Adsorbed (D)† (for pediatric use), are single-antigen products for use in special instances when combined antigen preparations are not indicated.

Work is in progress to study the effectiveness of improved acellular pertussis vaccines that have reduced adverse reaction rates. Currently, several candidate vaccines containing at least one of the bacterial components thought to provide protection are undergoing clinical trials. Candidate antigens include filamentous hemagglutinin, lymphocytosis promoting factor (pertussis toxin), a recently identified 69-kiloDalton outer-membrane protein (pertactin), and agglutinogens (*23*). In published studies, some of these vaccines are less prone to cause common adverse reactions than the current whole-cell preparations, and they are immunogenic (*29-36*). Whether their clinical efficacy among infants is equivalent to that of the whole-cell preparations remains to be established.

VACCINE USAGE

The standard, single-dose volume of each of DTP, DT, Td, single-antigen adsorbed preparations of pertussis vaccine, tetanus toxoid, and diphtheria toxoid, and of the fluid tetanus toxoid is 0.5 mL. Adsorbed preparations should be administered intramuscularly (IM). Vaccine administration by jet injection may be associated with more frequent local reactions (*37*).

Primary Vaccination

Children 6 weeks through 6 years old (up to the seventh birthday)

Table 1 details a routine vaccination schedule for children <7 years of age. One dose of DTP should be given IM on four occasions–the first three doses at 4- to 8-week intervals, beginning when the infant is approximately 6 weeks-2 months old; customarily, doses of vaccine are given at 2, 4, and 6 months of age. Individual circumstances may warrant giving the first three doses at 6, 10, and 14 weeks of age to provide protection as early as possible, especially during pertussis outbreaks (*38*). The fourth dose is given approximately 6-12 months after the third dose to maintain

*Distributed by the Division of Biologic Products, Michigan Department of Public Health. Contact Dr. Robert Myers, Chief, Division of Biologic Products, Bureau of Laboratories and Epidemiological Services, Michigan Department of Public Health, Lansing, Michigan 48909 (telephone: 517-335-8120).

†Distributed in the United States by Sclavo, Inc.

adequate immunity during the preschool years. This dose is an integral part of the primary vaccinating course. If a contraindication to pertussis vaccination exists (see Precautions and Contraindications), DT should be substituted for DTP as outlined (see Special Considerations).

Children ≥7 years of age and adults

Table 2 details a routine vaccination schedule for persons ≥7 years of age. Because the severity of pertussis decreases with age, and because the vaccine may cause side effects and adverse reactions, pertussis vaccination has not been recommended for children after their seventh birthday or for adults. For primary vaccination, a series of three doses of Td should be given IM; the second dose is given 4-8 weeks after the first, and the third dose 6-12 months after the second. Td rather than DT is the preparation of choice for vaccination of all persons ≥7 years of age because side effects from higher doses of diphtheria toxoid are more common than they are among younger children.

Interruption of primary vaccination schedule

Interrupting the recommended schedule or delaying subsequent doses does not lead to a reduction in the level of immunity reached on completion of the primary series. Therefore, there is no need to restart a series if more than the recommended time between doses has elapsed.

TABLE 1. Routine diphtheria, tetanus, and pertussis vaccination schedule summary for children <7 years of age—United States, 1991

Dose	Customary age	Age/interval	Product
Primary 1	2 months	6 week old or older	DTP†
Primary 2	4 months	4-8 weeks after first dose*	DTP†
Primary 3	6 months	4-8 weeks after second dose*	DTP†
Primary 4	15 months	6-12 months after third dose*	DTP†
Booster	4-6 years old, before entering kindergarten or elementary school (not necessary if fourth primary vaccinating dose administered after fourth birthday)		DTP†
Additional boosters		Every 10 years after last dose	Td

*Prolonging the interval does not require restarting series.
†Use DT if pertussis vaccine is contraindicated. If the child is ≥1 year of age at the time that primary dose three is due, a third dose 6-12 months after the second completes primary vaccination with DT.

TABLE 2. Routine diphtheria, tetanus, and pertussis vaccination schedule summary for persons ≥7 years of age–United States, 1991

Dose	Age/interval	Product
Primary 1	First dose	Td
Primary 2	4-8 weeks after first dose*	Td
Primary 3	6-12 months after second dose*	Td
Booster	Every 10 years after last dose	Td

*Prolonging the interval does not require restarting series.

Booster Vaccination

Children 4-6 years old (up to the seventh birthday)

Those who received all four primary vaccination doses before their fourth birthday should receive a fifth dose of DTP before entering kindergarten or elementary school. This booster dose is not necessary if the fourth dose in the primary series was given on or after the fourth birthday.

Children ≥7 years of age and adults

Tetanus toxoid should be given with diphtheria toxoid as Td every 10 years. If a dose is given sooner as part of wound management, the next booster is not needed until 10 years thereafter. (See Tetanus Prophylaxis in Wound Management). More frequent boosters are not indicated and can result in an increased occurrence and severity of adverse reactions. One means of ensuring that persons receive boosters every 10 years is to vaccinate them routinely at mid-decade ages, i.e., 15 years old, 25 years old, 35 years old, etc.

Special Considerations

Children with contraindications to pertussis vaccination

For children <7 years of age with a contraindication to pertussis vaccine (see Precautions and Contraindications), DT should be used instead of DTP. To ensure that there will be no interference with the response to DT antigens from maternal antibodies, previously unvaccinated children who receive their first DT dose when <1 year of age should receive a total of four doses of DT as the primary series, the first three doses at 4- to 8-week intervals and the fourth dose 6-12 months later (similar to the recommended DTP schedule) (Table 1). If additional doses of pertussis vaccine become contraindicated after a DTP series is begun in the first year of life, DT should be substituted for each of the remaining scheduled DTP doses.

Unvaccinated children ≥1 year of age for whom pertussis vaccine is contraindicated should receive two doses of DT 4-8 weeks apart, followed by a third dose 6-12 months later to complete the primary series. Children who have already received one or two doses of DT or DTP after their first birthday and for whom further pertussis vaccine is contraindicated should receive a total of three doses of a preparation containing diphtheria and tetanus toxoids appropriate for age, with the third dose administered 6-12 months after the second dose.

Children who complete a primary series of DT before their fourth birthday should receive a fifth dose of DT before entering kindergarten or elementary school. This dose is not necessary if the fourth dose of the primary series was given after the fourth birthday.

Pertussis vaccination for persons ≥7 years of age

Routine vaccination against pertussis is not currently recommended for persons ≥7 years of age. It should be noted, however, that adolescents and adults with waning immunity, whether derived from disease or vaccination, are a major reservoir for transmission of pertussis (*23*). For this reason it is possible that booster doses of acellular pertussis vaccine will be recommended in the future for persons ages ≥7 years of age.

Persons who have recovered from tetanus or diphtheria

Tetanus or diphtheria infection may not confer immunity; therefore, active vaccination should be initiated at the time of recovery from the illness, and arrangements made to ensure that all doses of a primary series are administered on schedule.

Children who have recovered from pertussis

Children who have recovered from satisfactorily documented pertussis do not need pertussis vaccine. Satisfactory documentation includes recovery of *B. pertussis* on culture or typical symptoms and clinical course when epidemiologically linked to a culture-proven case, as may occur during outbreaks. When such confirmation of the diagnosis is lacking, DTP vaccination should be completed, because a presumed pertussis syndrome may have been caused by other *Bordetella* species, *Chlamydia*, or certain viruses.

Prevention of neonatal tetanus

A previously unvaccinated pregnant woman whose child might be born under unhygienic circumstances (without sterile technique) should receive two doses of Td 4-8 weeks apart before delivery, preferably during the last two trimesters. Pregnant women in similar circumstances who have not had a complete vaccination series should complete the three-dose series. Those vaccinated more than 10 years previously should have a booster dose. No evidence exists to indicate that tetanus and diphtheria toxoids administered during pregnancy are teratogenic.

Adult vaccination with Td

The proportions of persons lacking protective levels of circulating antitoxins against diphtheria and tetanus increase with age; at least 40% of those ≥60 years of age may lack protection. Every visit of an adult to a health-care provider should be regarded as an opportunity to assess the person's vaccination status and, if indicated, to provide protection against tetanus and diphtheria. Adults with uncertain histories of a complete primary vaccination series should receive a primary series using the combined Td toxoid. To ensure continued protection, booster doses of Td should be given every 10 years.

Use of Single-Antigen Preparations

A single-antigen adsorbed pertussis vaccine preparation can be used to complete vaccination against pertussis for children <7 years of age who have received fewer than the recommended number of doses of pertussis vaccine but have received the recommended number of doses of diphtheria and tetanus toxoids for their age. Alternately, DTP can be used, although the total number of doses of diphtheria and tetanus toxoids should not exceed six each before the seventh birthday.

Available data do not indicate substantially more adverse reactions following receipt of Td than following receipt of single-antigen, adsorbed tetanus toxoid. Furthermore, adults may be even less likely to have adequate levels of diphtheria antitoxin than of tetanus antitoxin. The routine use of Td in all medical settings, including office practices, clinics, and emergency rooms, for all persons ≥7 years of age who need primary vaccination or booster doses will improve levels of protection against both tetanus and diphtheria, especially among adults.

SIDE EFFECTS AND ADVERSE REACTIONS FOLLOWING DTP VACCINATION

Local reactions (generally erythema and induration with or without tenderness) are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the injection site have been reported rarely (6-10/million doses of DTP). Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia occur frequently. These reactions are substantially more common following the administration of DTP than of DT, but they are self-limited and can be safely managed with symptomatic treatment.

Acetaminophen is frequently given by physicians to lessen fever and irritability associated with DTP vaccination, and it may be useful in preventing seizures among febrile-convulsion-prone children. However, fever that does not begin until ≥24 hours after vaccination or persists for more than 24 hours after vaccination should not be assumed to be due to DTP vaccination. These new or persistent fevers should be evaluated for other causes so that treatment is not delayed for serious conditions such as otitis media or meningitis. Moderate-to-severe systemic events, include high fever (i.e., temperature of ≥40.5 C [105 F]); persistent, inconsolable crying lasting ≥3 hours; collapse (hypotonic-hyporesponsive episode); or short-lived convulsions (usually febrile). These events occur infrequently. These events appear to be without sequelae (*39-41*). Other more severe neurologic events, such as a prolonged convulsion or encephalopathy, although rare, have been reported in temporal association with DTP administration.

Approximate rates for the occurrence of adverse events following receipt of DTP vaccine (regardless of dose number in the series or age of the child) are shown in Table 3 (*42,43*). The frequencies of local reactions and fever are substantially higher with increasing numbers of doses of DTP vaccine, while other mild-to-moderate systemic reactions (e.g., fretfulness, vomiting) are substantially less frequent (*41-43*).

TABLE 3. Adverse events* occurring within 48 hours of DTP vaccinations

Events	Frequency†
Local	
redness	1/3 doses
swelling	2/5 doses
pain	1/2 doses
Systemic	
fever ≥38 C (100.4 F)	1/2 doses
drowsiness	1/3 doses
fretfulness	1/2 doses
vomiting	1/15 doses
anorexia	1/5 doses
persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
fever ≥40.5 C (≥105 F)	1/330 doses
collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
convulsions (with or without fever)	1/1,750 doses

*From Cody CL, Baraff LJ, Cherry JD, et al., 1981 (*42*).
†Rate per total number of doses regardless of dose number in DTP series.

Concern about the possible role of pertussis vaccine in causing neurologic reactions has been present since the earliest days of vaccine use. Rare but serious acute neurologic illnesses, including encephalitis/encephalopathy and prolonged convulsions, have been anecdotally reported following receipt of whole-cell pertussis vaccine given as DTP vaccine (*28,44*). Whether pertussis vaccine causes or is only coincidentally related to such illnesses or reveals an inevitable event has been difficult to determine conclusively for the following reasons: a) serious acute neurologic illnesses often occur or become manifest among children during the first year of life irrespective of vaccination; b) there is no specific clinical sign, pathological finding, or laboratory test which can determine whether the illness is caused by the DTP vaccine; c) it may be difficult to determine with certainty whether infants <6 months of age are neurologically normal, which complicates assessment of whether vaccinees were already neurologically impaired before receiving DTP vaccine; and d) because these events are exceedingly rare, appropriately designed large studies are needed to address the question.

To determine whether DTP vaccine causes serious neurologic illness and brain damage, the National Childhood Encephalopathy Study (NCES) was undertaken during 1976-1979 in Great Britain (*27,45-47*). This large case-control study attempted to identity every patient with serious, acute, childhood, neurologic illness admitted to a hospital in England, Scotland, and Wales. A total of 1,182 young children 2-36 months of age was identified. Excluding those with infantile spasms, an illness shown in a separate analysis not to be attributable to DTP vaccine, 30 of these children (18 with prolonged convulsions and 12 with encephalitis/encephalopathy) had received DTP vaccine within 7 days of the reported onset of their neurologic illness (*48*). Analysis of the data from these patients and from age-matched control children showed a significant association (odds ratio = 3.3; 95% confidence interval 1.7–6.5) between the development of serious acute neurologic illness and receipt of DTP vaccine. Most of these events were prolonged seizures with fever. The attributable risk for all neurologic events was estimated to be 1:140,000 doses of DTP vaccine administered. These 30 children were followed up for at least 12 months to determine whether they had neurologic sequelae. Seven of these children presumed to have been previously normal neurologically had died or had subsequent neurologic impairment. A causal relation between receipt of DTP vaccine and permanent neurologic injury was suggested. The estimated attributable risk for DTP vaccine was 1:330,000 doses with a wide confidence interval.

The methods and results of the NCES have been thoroughly scrutinized since publication of the study. This reassessment by multiple groups has determined that the number of patients was too small and their classification subject to enough uncertainty to preclude drawing valid conclusions about whether a causal relation exists between pertussis vaccine and permanent neurologic damage (*49–54*). Preliminary data from a 10-year follow-up study of some of the children studied in the original NCES study also suggested a relation between symptoms following DTP vaccination and permanent neurologic disability (*55*). However, details are not available to evaluate this study adequately, and the same concerns remain about DTP vaccine precipating initial manifestations of pre-existing neurologic disorders.

Subsequent studies have failed to provide evidence to support a causal relation between DTP vaccination and either serious acute neurologic illness or permanent neurologic injury. These include: a) the 1979 Hospital Activity Analysis of the North West Thames Study in England, in which the hospital records of approximately

17,000 children who each received three doses of DTP vaccine were compared with records of 18,000 children who each received three doses of DT vaccine; b) a 1974-1983 case-cohort study of children in the Group Health Cooperative of Puget Sound who received a total of 106,000 doses of DTP vaccine; and c) a 1974-1984 cohort study of 38,171 Medicaid children in Tennessee who received 107,154 doses of DTP vaccine (*56-58*). An additional study in Denmark of approximately 150,000 children (554 of which had epilepsy) demonstrated no relation between the age at onset of epilepsy and the scheduled age of administration of DTP vaccine (*59*). Although each of these studies individually contained too few subjects to provide definitive conclusions, taken together they stand in contrast to the original NCES findings. A recent study performed in 1987-1988 in Washington and Oregon of neurologic illness among children did not provide evidence of a significantly increased risk of all serious acute neurologic illnesses within 7, 14, or 28 days of DTP vaccination (*60*). However, as a pilot effort, this study had limited power to detect significantly increased risks for individual conditions.

The NCES was the basis of prior ACIP statements suggesting that on rare occasions DTP vaccine could cause brain damage. However, on the basis of a more detailed review of the NCES data as well as data from other studies, the ACIP has revised its earlier view and now concludes:

1. Although DTP may rarely produce symptoms that some have classified as acute encephalopathy, a causal relation between DTP vaccine and permanent brain damage has not been demonstrated. If the vaccine ever causes brain damage, the occurrence of such an event must be exceedingly rare. A similar conclusion has been reached by the Committee on Infectious Diseases of the American Academy of Pediatrics, the Child Neurology Society, the Canadian National Advisory Committee on Immunization, the British Joint Committee on Vaccination and Immunization, the British Pediatric Association, and the Institute of Medicine (*49-54*).
2. The risk estimate from the NCES study of 1:330,000 for brain damage should no longer be considered valid on the basis of continuing analyses of the NCES and other studies.

In addition to these considerations, acute neurologic manifestations related to DTP vaccine are mainly febrile seizures. In an individual case, the role of pertussis vaccine as a cause of serious acute neurologic illness or permanent brain damage is impossible to determine on the basis of clinical or laboratory findings. Anecdotal reports of DTP-induced acute neurologic disorders with or without permanent brain damage can have one of several alternate explanations. Some instances may represent simple coincidence because DTP is administered at a time in infancy when previously unrecognized underlying neurological and developmental disorders first become manifest. Some patients may have short-lived seizures with prompt recovery, and these events represent the first seizure of a child with underlying epilepsy. When epilepsy has its onset in infancy, it is frequently associated with severe mental retardation and developmental delay. These conditions become apparent over a period of several months. The known febrile and other systemic effects of DTP vaccination may stimulate or precipitate inevitable symptoms of underlying central-nervous-system disorders, particularly since DTP may be the first pyrogenic stimulus an infant receives. When children who experience acute, severe central-nervous-system disorders in association with DTP vaccination are studied promptly and carefully, an alternate cause is often found.

Among a subset of NCES children with infantile spasms, both DTP and DT vaccination appeared either to precipitate early manifestations of the condition or to cause its recognition by parents (*48*). This and other studies suggest that neither vaccine causes this illness (*59,61*).

Approximately 5,200 infants succumb to sudden infant death syndrome (SIDS) in the United States each year. Because the peak incidence of SIDS for infants is between 2 and 3 months of age, many instances of a close temporal relation between SIDS and receipt of DTP are to be expected by simple chance. Only one methodologically rigorous study has suggested that DTP vaccine might cause SIDS (*62*). A total of four deaths were reported within 3 days of DTP vaccination, compared with 1.36 expected deaths. However, these deaths were unusual in that three of the four occurred within a 13-month interval during the 12-year study. These four children also tended to be vaccinated at older ages than their controls, suggesting that they might have other unrecognized risk factors for SIDS independent of vaccination. In contrast, DTP vaccination was not associated with SIDS in several larger studies performed in the past decade (*28,63-65*). In addition, none of three studies that examined unexpected deaths among infants not classified as SIDS found an association with DTP vaccination (*62,64,65*).

Claims that DTP may be responsible for transverse myelitis, other more subtle neurologic disorders (such as hyperactivity, learning disorders and infantile autism), and progressive degenerative central-nervous-system conditions have no scientific basis. Furthermore, one study indicated that children who received pertussis vaccine exhibited fewer school problems than those who did not, even after adjustment for socioeconomic status (*66*).

Recent data suggest that infants and young children who have ever had convulsions (febrile or afebrile) or who have immediate family members with such histories are more likely to have seizures following DTP vaccination than those without such histories (*67,68*). For those with a family history of seizures, the increased risks of seizures occurring within 3 days of receipt of DTP or 4-28 days following receipt of DTP are identical, suggesting that these histories are non-specific risk factors and are unrelated to DTP vaccination (*68*).

Rarely, immediate anaphylactic reactions (i.e., swelling of the mouth, breathing difficulty, hypotension, or shock) have been reported after receipt of preparations containing diphtheria, tetanus, and/or pertussis antigens. However, no deaths caused by anaphylaxis following DTP vaccination have been reported to CDC since the inception of vaccine-adverse-events reporting in 1978, a period during which more than 80 million doses of publically purchased DTP vaccine were administered. While substantial underreporting exists in this passive surveillance system, the severity of anaphylaxis and its immediacy following vaccination suggest that such events are likely to be reported. Although no causal relation to any specific component of DTP has been established, the occurrence of true anaphylaxis usually contraindicates further doses of any one of these components. Rashes that are macular, papular, petechial, or urticarial and appear hours or days after a dose of DTP are frequently antigen-antibody reactions of little consequence or are due to other causes such as viral illnesses, and are unlikely to recur following subsequent injections (*69,70*). In addition, there is no evidence for a causal relation between DTP vaccination and hemolytic anemia or thrombocytopenic purpura.

REPORTING OF ADVERSE EVENTS

The U.S. Department of Health and Human Services has established a new Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986 (*71*).The telephone number to call for answers to questions and to obtain VAERS forms is 1-800-822-7967.

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. These requirements took effect March 21, 1988. Reportable events include those listed in the Act for each vaccine and events specified in the manufacturer's vaccine package insert as contraindications to further doses of that vaccine (*72,73*).

REDUCED DOSAGE SCHEDULES OR MULTIPLE SMALL DOSES OF DTP

The ACIP recommends giving only full doses (0.5 mL) of DTP vaccine; if a specific contraindication to DTP exists, the vaccine should not be given.

Concern about adverse events following pertussis vaccine has led some practitioners to reduce the volume of DTP vaccine administered to <0.5mL/dose in an attempt to reduce side effects. No evidence exists to show that this decreases the frequency of uncommon severe adverse events, such as seizures and hypotonic-hyporesponsive episodes. Two studies have reported substantially lower rates of local reactions with the use of one half the recommended dose (0.25mL) compared with a full dose (*43,74*). However, a study among preterm infants showed that the incidence of side effects was unaltered when a reduced dosage of DTP vaccine was used (*75*). Two studies also showed substantially lower pertussis agglutinin responses after the second and third half-doses, although in one of the studies the differences were small (*74,75*). These investigations used pertussis agglutinins as a measure of clinical protection; however, agglutinins are not satisfactory measures of protection against pertussis disease. Further, no evidence exists to show that the low screening dilution used (1:16) indicates protection. Currently, no reliable measures of efficacy other than clinical protection exist. Other evidence against the use of reduced doses comes from earlier studies of DTP vaccine preparations with potencies equivalent to that of half-doses of current vaccine (*76,77*). The risk of pertussis for exposed household members who received these lower potency vaccines was approximately twice as high as the risk of pertussis for those who received vaccines as potent as full doses of current vaccine (29% compared with ≤14%).

The use of an increased number of reduced-volume doses of DTP in order to equal the total volume of the five recommended doses of DTP vaccine is not recommended. Whether this practice reduces the likelihood of vaccine-related adverse events is unknown. In addition, the likelihood of a temporally associated but etiologically unrelated event may be enhanced by increasing the number of vaccinations.

SIMULTANEOUS ADMINISTRATION OF VACCINES

The simultaneous administration of DTP, oral poliovirus vaccine (OPV), and measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately (*78*). Simultaneous vaccination with DTP, MMR, OPV, or inactivated poliovirus vaccine (IPV), and *Haemophilus* b conjugate vaccine (HbCV) is also acceptable (*79*). The ACIP recommends the simultaneous administration of all vaccines appropriate to the age and previous vaccination status of the recipient, including the special circumstance of simultaneous administration of DTP, OPV, HbCV, and MMR at ≥15 months of age.

PRECAUTIONS AND CONTRAINDICATIONS

General Considerations

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 mild upper-respiratory infections with or without low-grade fever are not contraindications. If ongoing medical care cannot be assured, taking every opportunity to provide appropriate vaccinations is particularly important.

Children with moderate or severe illnesses with or without fever can receive DTP as soon as they have recovered. Waiting a short period before administering DTP vaccine avoids superimposing the adverse effects of the vaccination on the underlying illness or mistakenly attributing a manifestation of the underlying illness to vaccination.

Routine physical examinations or temperature measurements are not prerequisites for vaccinating infants and children who appear to be in good health. Appropriate immunization practice includes asking the parent or guardian if the child is ill, postponing DTP vaccination for those with moderate or severe acute illnesses, and vaccinating those without contraindications or precautionary circumstances.

When an infant or child returns for the next dose of DTP, the parent should always be questioned about any adverse events that might have occurred following the previous dose.

A history of prematurity generally is not a reason to defer vaccination (*75,80,81*). Preterm infants should be vaccinated according to their chronological age from birth.

Immunosuppressive therapies–including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses)–may reduce the immune response to vaccines. Short-term (<2-week) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it is reasonable to defer vaccination until the patient has been off therapy for 1 month; otherwise, the patient should be vaccinated while still on therapy (*82*).

Special Considerations for Preparations Containing Pertussis Vaccine

Precautions and contraindications guidelines that were previously published regarding the use of pertussis vaccine were based on three assumptions about the risks of pertussis vaccination that are not supported by available data: a) that the vaccine on rare occasions caused acute encephalopathy resulting in permanent brain damage; b) that pertussis vaccine aggravated preexisting central-nervous-system disease; and c) that certain nonencephalitic reactions are predictive of more severe reactions with subsequent doses (*1*). In addition, children from whom pertussis vaccine was withheld were thought to be well protected by herd immunity, a belief that is no longer valid. The current revised ACIP recommendations reflect better understanding of the risks associated not only with pertussis vaccine but also with pertussis disease.

Contraindications

If any of the following events occur in temporal relationship to the administration of DTP, further vaccination with DTP is contraindicated (see Table 4):

1. An immediate anaphylactic reaction. The rarity of such reactions to DTP is such that they have not been adequately studied. Because of uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of the three 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 and desensitized to tetanus toxoid if specific allergy can be demonstrated (*83,84*).
2. Encephalopathy (not due to another identifiable cause). 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. It may be desirable to delay for months before administering the balance of the doses of DT necessary to complete the primary schedule. Such a delay allows time for the child's neurologic status to clarify.

Precautions (Warnings)

If any of the following events occur in temporal relation to receipt of DTP, the decision to give subsequent doses of vaccine containing the pertussis component

TABLE 4. Contraindications and precautions to further DTP vaccination

Contraindications
An immediate anaphylactic reaction.
Encephalopathy occurring within 7 days following DTP vaccination.
Precautions
Temperature of ≥40.5 C (105 F) within 48 hours not due to another identifiable cause.
Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours.
Convulsions with or without fever occurring within 3 days.

should be carefully considered (Table 4). Although these events were considered absolute contraindications in previous ACIP recommendations, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly because these events are not associated with permanent sequelae (*1*). The following events were previously considered contraindications and are now considered precautions:

1. Temperature of ≥40.5 C (105 F) within 48 hours not due to another identifiable cause. Such a temperature is considered a precaution because of the likelihood that fever following a subsequent dose of DTP vaccine also will be high. Because such febrile reactions are usually attributed to the pertussis component, vaccination with DT should not be discontinued.
2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours. Although these uncommon events have not been recognized to cause death nor to induce permanent neurological sequelae, it is prudent to continue vaccination with DT, omitting the pertussis component (*40,85*).
3. Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours. Follow-up of infants who have cried inconsolably following DTP vaccination has indicated that this reaction, though unpleasant, is without long-term sequelae and not associated with other reactions of greater significance (*41*). Inconsolable crying occurs most frequently following the first dose and is less frequently reported following subsequent doses of DTP vaccine (*42*). However, crying for >30 minutes following DTP vaccination can be a predictor of increased likelihood of recurrence of persistent crying following subsequent doses (*41*). Children with persistent crying have had a higher rate of substantial local reactions than children who had other DTP-associated reactions (including high fever, seizures, and hypotonic-hyporesponsive episodes), suggesting that prolonged crying was really a pain reaction (*85*).
4. Convulsions with or without fever occurring within 3 days. Short-lived convulsions, with or without fever, have not been shown to cause permanent sequelae (*39,86*). Furthermore, the occurrence of prolonged febrile seizures (i.e., status epilepticus*), irrespective of their cause, involving an otherwise normal child does not substantially increase the risk for subsequent febrile (brief or prolonged) or afebrile seizures. The risk is significantly increased ($p = 0.018$) only among those children who are neurologically abnormal before their episode of status epilepticus (*87*). Accordingly, although a convulsion following DTP vaccination has previously been considered a contraindication to further doses, under certain circumstances subsequent doses may be indicated, particularly if the risk of pertussis in the community is high. If a child has a seizure following the first or second dose of DTP, it is desirable to delay subsequent doses until the child's neurologic status is better defined. By the end of the first year of life, the presence of an underlying neurologic disorder has usually been determined, and appropriate treatment instituted. DT vaccine should not be administered before a decision has been made about whether to restart the DTP series. Regardless of which vaccine is given, it is prudent also to administer acetaminophen, 15 mg/kg of body weight, at the time of vaccination and every 4 hours subsequently for 24 hours (*88,89*).

*Any seizure lasting >30 minutes or recurrent seizures lasting a total of 30 minutes without the child fully regaining consciousness.

Vaccination of infants and young children who have underlying neurologic disorders

Infants and children with recognized, possible, or potential underlying neurologic conditions present a unique problem. They seem to be at increased risk for the appearance of manifestations of the underlying neurologic disorder within 2-3 days after vaccination. However, more prolonged manifestations or increased progression of the disorder, or exacerbation of the disorder have not been recognized (*90*). In addition, most neurologic conditions in infancy and young childhood are associated with evolving, changing neurological findings. Functional abnormalities are often unmasked by progressive neurologic development. Thus, confusion over the interpretation of progressive neurologic signs may arise when DTP vaccination or any other therapeutic or preventive measure is carried out.

Protection against diphtheria, tetanus, and pertussis is as important for children with neurologic disabilities as for other children. Such protection may be even more important for neurologically disabled children. They often receive custodial care or attend special schools where the risk of pertussis is greater because DTP vaccination is avoided for fear of adverse reactions. Also, if pertussis affects a neurologically disabled child who has difficulty in handling secretions and in cooperating with symptomatic care, it may aggravate preexisting neurologic problems because of anoxia, intracerebral hemorrhages, and other manifestations of the disease. Whether and when to administer DTP to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. Important considerations include the current local incidence of pertussis, the near absence of diphtheria in the United States, and the low risk of infection with *Clostridium tetani*. On the basis of these considerations and the nature of the child's disorder, the following approaches are recommended:

1. **Infants and children with previous convulsions**. Infants and young children who have had prior seizures, whether febrile or afebrile, appear to be at increased risk for seizures following DTP vaccination than children and infants without these histories (*68*). A convulsion within 3 days of DTP vaccination in a child with a history of convulsions may be initiated by fever caused by the vaccine in a child prone to febrile seizures, may be induced by the pertussis component, or may be unrelated to the vaccination. As noted earlier, current evidence indicates that seizures following DTP vaccination do not cause permanent brain damage. Among infants and children with a history of previous seizures, it is prudent to delay DTP vaccination until the child's status has been fully assessed, a treatment regimen established, and the condition stabilized. It should be noted, however, that delaying DTP vaccination until the second 6 months of life will increase the risk of febrile seizures among persons who are predisposed. When DTP or DT is given, acetaminophen, 15 mg/kg, should also be given at the time of the vaccination and every 4 hours for the ensuing 24 hours (*88,89*).
2. **Infants as yet unvaccinated who are suspected of having underlying neurologic disease**. It is prudent to delay initiation of vaccination with DTP or DT (but not other vaccines) until further observation and study have clarified the child's neurologic status and the effect of treatment. The decision as to whether to begin vaccination with DTP or DT should be made no later than the child's first birthday.

3. **Children who have not received a complete series of vaccine and who have a neurologic event occurring between doses.** Infants and children who have received ≥one dose of DTP and who experience a neurologic disorder (e.g., a seizure, for example) not temporally associated with vaccination, but before the next scheduled dose, present a special management challenge. If the seizure or other disorder occurs before the first birthday and before completion of the first three doses of the primary series of DTP, further doses of DTP or DT (but not other vaccines) should be deferred until the infant's status has been clarified. The decision whether to use DTP or DT to complete the series should be made no later than the child's first birthday, and should take into consideration the nature of the child's problem and the benefits and possible risks of the vaccine. If the seizure or other disorder occurs after the first birthday, the child's neurologic status should be evaluated to ensure that the disorder is stable before a subsequent dose of DTP is given. (See the following #4.)
4. **Infants and children with stable neurologic conditions.** Infants and children with stable neurologic conditions, including well-controlled seizures, may be vaccinated. The occurrence of single seizures (temporally unassociated with DTP) do not contraindicate DTP vaccination, particularly if the seizures can be satisfactorily explained. Parents of infants and children with histories of convulsions should be informed of the increased risk of postvaccination seizures. Acetaminophen, 15 mg/kg, every 4 hours for 24 hours, should be given to children with such histories to reduce the possibility of postvaccination fever (*88,89*).
5. **Children with resolved or corrected neurologic disorders.** DTP vaccination is recommended for infants with certain neurologic problems, such as neonatal hypocalcemic tetany or hydrocephalus (following placement of a shunt and without seizures), that have been corrected or have clearly subsided without residua.

Vaccination of infants and young children who have a family history of convulsion or other central nervous system disorders

A family history of convulsions or other central nervous disorders is not a contraindication to pertussis vaccination (*2*). Acetaminophen should be given at the time of DTP vaccination and every 4 hours for 24 hours to reduce the possibility of postvaccination fever (*88,89*).

Preparations Containing Diphtheria Toxoid and Tetanus Toxoid

The only contraindication to tetanus and diphtheria toxoids is a history of a neurologic or severe hypersensitivity reaction following a previous dose. Vaccination with tetanus and diphtheria toxoids is not known to be associated with an increased risk of convulsions. Local side effects alone do not preclude continued use. If an anaphylactic reaction to a previous dose of tetanus toxoid is suspected, intradermal skin testing with appropriately diluted tetanus toxoid may be useful before a decision is made to discontinue tetanus toxoid vaccination (*83*). In one study, 94 of 95 persons with histories of anaphylactic symptoms following a previous dose of tetanus toxoid were nonreactive following intradermal testing and tolerated further tetanus toxoid challenge without incident (*83*). One person had erythema and induration immediately following skin testing, but tolerated a full IM dose without adverse effects. Mild,

nonspecific skin-test reactivity to tetanus toxoid, particularly if used undiluted, appears to be fairly common. Most vaccinees develop inconsequential cutaneous delayed hypersensitivity to the toxoid.

Persons who experienced Arthus-type hypersensitivity reactions or a temperature of >103 F (39.4 C) following a prior dose of tetanus toxoid usually have high serum tetanus antitoxin levels and should not be given even emergency doses of Td more frequently than every 10 years, even if they have a wound that is neither clean nor minor.

If a contraindication to using tetanus toxoid-containing preparations exists for a person who has not completed a primary series of tetanus toxoid immunization and that person has a wound that is neither clean nor minor, *only* passive immunization should be given using tetanus immune globulin (TIG). (See Tetanus Prophylaxis in Wound Management).

Although no evidence exists that tetanus and diphtheria toxoids are teratogenic, waiting until the second trimester of pregnancy to administer Td is a reasonable precaution for minimizing any concern about the theoretical possibility of such reactions.

Misconceptions Concerning Contraindications to DTP

Some health-care providers inappropriately consider certain conditions or circumstances as contraindications to DTP vaccination. These include the following:

1. Soreness, redness, or swelling at the DTP vaccination site or temperature of <40.5C(105 F).
2. Mild, acute illness with low-grade fever or mild diarrheal illness affecting an otherwise healthy child.
3. Current antimicrobial therapy or the convalescent phase of an acute illness.
4. Recent exposure to an infectious disease.
5. Prematurity. The appropriate age for initiating vaccination among the prematurely born infant is the usual chronological age from birth (*75,80,81*). Full doses (0.5 mL) of vaccine should be used.
6. History of allergies or relatives with allergies.
7. Family history of convulsions.
8. Family history of SIDS.
9. Family history of an adverse event following DTP vaccination.

PREVENTION OF DIPHTHERIA AMONG CONTACTS OF A DIPHTHERIA PATIENT

Identification of Close Contacts

The primary purpose of contact investigation is to prevent secondary transmission of *C. diphtheriae* and the occurrence of additional diphtheria cases. Only close contacts of a patient with culture-confirmed or suspected* diphtheria should be

*For example, a patient for whom the decision has been made to treat with diphtheria antitoxin. Antitoxin can be obtained either from a manufacturer (Connaught Labs, Inc., or Sclavo, Inc.) or the Division of Immunization, CDC (telephone: 404-639-2888).

considered at increased risk for acquiring secondary disease. Such contacts include all household members and other persons with a history of habitual, close contact with the patient, as well as those directly exposed to oral secretions of the patient. Identification of close contacts of a diphtheria patient should be promptly initiated.

Cultures and Antimicrobial Prophylaxis

All close contacts (regardless of their vaccination status) should have samples taken for culture, receive prompt antimicrobial chemoprophylaxis, and be examined daily for 7 days for evidence of disease. Awaiting culture results before administering antimicrobial prophylaxis to close contacts is not warranted. The identification of carriers among close contacts may support the diagnosis of diphtheria for a patient whose cultures are negative either because of prior antimicrobial therapy or because of other reasons. Antimicrobial prophylaxis should consist of either an IM injection of benzathine penicillin (600,000 units for persons <6 years old and 1,200,000 units for those ≥6 years old) or a 7- to 10-day course of oral erythromycin (children: 40 mg/kg/day; adults: 1 g/day). Erythromycin may be slightly more effective, but IM benzathine penicillin may be preferred, because it avoids possible noncompliance with a multi-day oral drug regimen. The efficacy of antimicrobial prophylaxis in preventing secondary disease is presumed but not proven. Identified carriers of *C. diphtheriae* should have follow-up cultures done after they complete antimicrobial therapy. Those who continue to harbor the organism after either penicillin or erythromycin should receive an additional 10-day course of oral erythromycin and follow-up cultures.

Immunization

Active

All household and other close contacts who have received <three doses of diphtheria toxoid or whose vaccination status is unknown should receive an immediate dose of a diphtheria toxoid-containing preparation and should complete the primary series according to schedule (Tables 1 and 2). Close contacts who have completed a primary series of ≥three doses and who have not been vaccinated with diphtheria toxoid within the previous 5 years should receive a booster dose of a diphtheria toxoid-containing preparation appropriate for their age.

Passive

The only preparation available for passive immunization against diphtheria is equine diphtheria antitoxin. Even when close surveillance of unvaccinated close contacts is impossible, use of this preparation is not generally recommended because of the risks of allergic reaction to horse serum. Immediate hypersensitivity reactions occur among approximately 7%, and serum sickness among 5% of adults receiving the recommended prophylactic dose of equine antitoxin. The risk of an adverse reaction to equine antitoxin must be weighed against the small risk that an unvaccinated household contact who receives chemoprophylaxis will contract diphtheria. No evidence exists to support any additional benefit of diphtheria antitoxin use for contacts who have received antimicrobial prophylaxis. If antitoxin is to be used, 5,000-10,000 units IM–after appropriate testing for sensitivity–at a site different from that of the toxoid injection is the dosage usually recommended. Diphtheria antitoxin

is unlikely to impair the immune response to simultaneous administration of diphtheria toxoid, but this has not been adequately studied.

A serum specimen collected from a patient with suspected diphtheria (before antitoxin therapy is initiated) may be helpful in supporting the diagnosis of diphtheria if a level of diphtheria antitoxin below that considered to be protective (i.e., <0.01 IU/mL) can be demonstrated. Such testing may be particularly helpful with a patient for whom antimicrobial therapy had been initiated prior to obtaining diphtheria cultures.

Cutaneous Diphtheria

Cases of cutaneous diphtheria generally are caused by infections with nontoxigenic strains of *C. diphtheriae*. If a toxigenic *C. diphtheriae* strain is isolated from a cutaneous lesion, investigation and prophylaxis of close contacts should be undertaken, as with respiratory diphtheria. If a cutaneous case is known to be due to a nontoxigenic strain, routine investigation or prophylaxis of contacts is not necessary.

TETANUS PROPHYLAXIS IN WOUND MANAGEMENT

Chemoprophylaxis against tetanus is neither practical nor useful in managing wounds. Wound cleaning, debridement when indicated, and proper immunization are important. The need for tetanus toxoid (active immunization), with or without TIG (passive immunization), depends on both the condition of the wound and the patient's vaccination history (Table 5; see also Precautions and Contraindications). Rarely has tetanus occurred among persons with documentation of having received a primary series of toxoid injections.

A thorough attempt must be made to determine whether a patient has completed primary vaccination. Patients with unknown or uncertain previous vaccination histories should be considered to have had no previous tetanus toxoid doses. Persons who had military service since 1941 can be considered to have received at least one dose.

TABLE 5. Summary guide to tetanus prophylaxis in routine wound management, 1991

History of adsorbed tetanus toxoid (doses)	Clean, minor wounds		All other wounds*	
	Td(†)	TIG	Td(†)	TIG
Unknown or < three	Yes	No	Yes	Yes
≥ Three (§)	No(¶)	No	No(**)	No

*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns and frostbite.

†For children <7 years old; DTP (DT, if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons ≥7 years of age, Td is preferred to tetanus toxoid alone.

§If only three doses of *fluid* toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.

¶Yes, if >10 years since last dose.

**Yes, if >5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

Although most people in the military since 1941 may have completed a primary series of tetanus toxoid, this cannot be assumed for each individual. Patients who have not completed a primary series may require tetanus toxoid and passive immunization at the time of wound cleaning and debridement (Table 5).

Available evidence indicates that complete primary vaccination with tetanus toxoid provides long-lasting protection ≥10 years for most recipients. Consequently, after complete primary tetanus vaccination, boosters–even for wound management –need be given only every 10 years when wounds are minor and uncontaminated. For other wounds, a booster is appropriate if the patient has not received tetanus toxoid within the preceding 5 years. Persons who have received at least two doses of tetanus toxoid rapidly develop antitoxin antibodies.

Td is the preferred preparation for active tetanus immunization in wound management of patients ≥7 years of age. Because a large proportion of adults are susceptible, this plan enhances diphtheria protection. Thus, by taking advantage of acute health-care visits, such as for wound management, some patients can be protected who otherwise would remain susceptible. For routine wound management among children <7 years of age who are not adequately vaccinated, DTP should be used instead of single-antigen tetanus toxoid. DT may be used if pertussis vaccine is contraindicated or individual circumstances are such that potential febrile reactions following DTP might confound the management of the patient. For inadequately vaccinated patients of all ages, completion of primary vaccination at the time of discharge or at follow-up visits should be ensured (Tables 1 and 2).

If passive immunization is needed, human TIG is the product of choice. It provides protection longer than antitoxin of animal origin and causes few adverse reactions. The TIG prophylactic dose that is currently recommended for wounds of average severity is 250 units IM. When tetanus toxoid and TIG are given concurrently, separate syringes and separate sites should be used. The ACIP recommends the use of only adsorbed toxoid in this situation.

PROPHYLAXIS FOR CONTACTS OF PERTUSSIS PATIENTS

Spread of pertussis can be limited by decreasing the infectivity of the patient and by protecting close contacts. To reduce infectivity as quickly as possible, a course of oral erythromycin (children: 40 mg/kg/day; adults: 1g/day) or trimethoprim-sulfamethoxazole (children: trimethoprim 8 mg/kg/day, sulfamethoxazole 40 mg/kg/day; adults: trimethoprim 320mg/day, sulfamethoxazole 1,600mg/day) is recommended for patients with clinical pertussis. Antimicrobial therapy should be continued for 14 days to minimize any chance of treatment failure. It is generally accepted that symptoms may be ameliorated when effective therapy is initiated during the catarrhal stage of disease (*91*). Some evidence suggests erythromycin therapy can alter the clinical course of pertussis when initiated early in the paroxysmal stage (*19,92,93*).

Erythromycin or trimethoprim-sulfamethoxazole prophylaxis should be administered for 14 days to all household and other close contacts of persons with pertussis, regardless of age and vaccination status. Although data from controlled clinical trials are lacking, prophylaxis of all household members and other close contacts may prevent or minimize transmission (*92,94-96*). All close contacts <7 years of age who

have not completed the four-dose primary series should complete the series with the minimal intervals (Table 1). Those who have completed a primary series but have not received a dose of DTP vaccine within 3 years of exposure should be given a booster dose.

Prophylactic postexposure passive immunization is not recommended. The use of human pertussis immune globulin neither prevents illness nor reduces its severity. This product is no longer available in the United States.

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