Complete Summary

GUIDELINE TITLE

(1) Pertussis vaccination: use of acellular pertussis vaccines among infants and young children.
(2) Use of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine as a five-dose series. (Addendum)

BIBLIOGRAPHIC SOURCE(S)

Notice to readers: FDA approval of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, (INFANRIX) for fifth consecutive DTaP vaccine dose. MMWR Recomm Rep 2003 Sep 26;52(38):921. [4 references]

Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. MMWR Recomm Rep 1997 Mar 28;46(RR-7):1-25. [50 references]

Use of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine as a five-dose series. Supplemental recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 2000 Nov 17;49(RR13):1-8. [17 references]

GUIDELINE STATUS

The guideline titled "Use of Diphtheria Toxoid-tetanus Toxoid-acellular Pertussis Vaccine as a Five-dose Series" (MMWR Morb Mortal Wkly Rep 2000 Nov 17;49(RR-13):1-8) supplements the previous recommendations published in the guideline titled "Pertussis Vaccination: Use of Acellular Pertussis Vaccines Among Infants and Young Children" (MMWR Morb Mortal Wkly Rep 1997 Mar 28;46(RR-7):1-25) regarding use of DTaP and summarizes new Advisory Committee on Immunization Practices (ACIP) recommendations regarding DTaP vaccines as a five-consecutive--dose series.

Please note that a published erratum has been published for the guideline: "Use of Diphtheria Toxoid-Tetanus Toxoid-Acellular Pertussis Vaccine as a Five-Dose Series", MMWR Morb Mortal Wkly Rep 2000 Dec 1;49(47):1074.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

On April 7, 2005, after concluding that the overall risk versus benefit profile is unfavorable, the FDA requested that Pfizer, Inc voluntarily withdraw Bextra (valdecoxib) from the market. The FDA also asked manufacturers of all marketed prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including Celebrex (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. Finally, FDA asked manufacturers of non-prescription (over the counter [OTC]) NSAIDs to revise their labeling to include more specific information about the potential gastrointestinal (GI) and cardiovascular (CV) risks, and information to assist consumers in the safe use of the drug. See the FDA Web site for more information.

Subsequently, on June 15, 2005, the FDA requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products. FDA recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health concern. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Pertussis disease (infection due to *Bordetella pertussis*; whooping cough)

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Family Practice
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

1997 Guideline

- To provide general information regarding whole-cell pertussis vaccines currently licensed in the United States
- To summarize results of recent studies of the immunogenicity, efficacy, and safety of *acellular* pertussis vaccines administered to infants and young children
- To present recommendations for the use of Tripedia®, TriHIBit™, ACEL-IMUNE®, and Infanrix™ vaccines
- To supplement previous recommendations on pertussis vaccination

2000 Supplement

- To supplement previous recommendations regarding the use of diphtheria and tetanus toxoids and acellular pertussis vaccines as a five-consecutive-dose series
- To summarize data regarding reactogenicity of acellular pertussis vaccines when administered as the fourth and fifth consecutive doses

2003 supplement

To supplement previous recommendations regarding the U.S. Food and Drug Administration (FDA) approved use of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) (INFANRIX®, SmithKline Beecham Biologicals, Rixensart, Belgium) as a fifth dose for children aged 4 to 6 years after 4 previous doses of INFANRIX®.

TARGET POPULATION

Children younger than 7 years

INTERVENTIONS AND PRACTICES CONSIDERED

1. Diphtheria and tetanus toxoids and acellular pertussis vaccines (DTaP): (Tripedia®, ACEL-IMUNE®, Infanrix®, Certiva™)
2. Diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP)

MAJOR OUTCOMES CONSIDERED

- Vaccine efficacy
- Serum antibody levels following vaccination
- Incidence of pertussis
- Incidence of adverse events related to the administration of acellular pertussis vaccine

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): Supplemental guidelines for the use of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) as a five dose series are included in these recommendations (MMWR Morbid Mortal Wkly Rep 2000 Nov 17; 49[RR-13]: 1-8).

The most current supplemental guidelines for the Food and Drug Administration (FDA) approved use of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, (INFANRIX®) as a fifth consecutive DTaP vaccine dose are **also** included in these recommendations (MMWR Morbid Mortal Wkly Rep 2003 Sept 26; 52 [38]; 921-921).

Recommended Childhood Vaccination Schedule

The routine diphtheria, tetanus, and pertussis vaccination schedule for children aged <7 years comprises five doses of vaccine containing diphtheria, tetanus, and pertussis antigens. Three (primary) doses should be administered during the first year of life, generally at ages 2, 4, and 6 months. To maintain adequate immunity during preschool years, the fourth (first booster) dose is recommended for children aged 15 to 18 months. The fourth dose should be administered greater than or equal to 6 months after the third. If the interval between the third and fourth doses is greater than or equal to 6 months and the child is not likely to return for a visit at the recommended age, the fourth dose of either diphtheria, tetanus and acellular pertussis or whole-cell diphtheria, tetanus, and pertussis may be administered as early as age 12 months. The fifth (second booster) dose is recommended for children aged 4 to 6 years to confer continued protection against disease during the early years of schooling. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.

See Special Notices below

Vaccine Preference

Diphtheria, tetanus, and acellular pertussis vaccines are efficacious when administered to infants as the primary series (i.e., doses 1-3). In addition, local reactions, fever, and other systemic events occur substantially less often after diphtheria, tetanus, and acellular pertussis administration than after administration of whole-cell diphtheria, tetanus, and pertussis. Therefore, diphtheria, tetanus, and acellular pertussis vaccines are recommended for all five doses in the vaccination schedule. For children who have started the vaccination

series with one, two, three, or four doses of whole-cell diphtheria, tetanus, and pertussis, diphtheria, tetanus, and acellular pertussis is also recommended for all remaining doses in the schedule. During the period of transition from use of whole-cell diphtheria, tetanus, and pertussis to diphtheria, tetanus, and acellular pertussis, whole-cell diphtheria, tetanus, and pertussis is an acceptable alternative to diphtheria, tetanus, and acellular pertussis for any of the five doses. For the first four doses, whole-cell diphtheria, tetanus, and pertussis combined with Haemophilus influenza type B (Hib) vaccine (diphtheria, tetanus, and pertussis-Haemophilus influenza type B vaccine) is an acceptable alternative to diphtheria, tetanus, and acellular pertussis and Haemophilus influenza type B vaccine administered at separate sites.

Licensed Products

Three acellular pertussis vaccines (Tripedia® and Infanrix™ for the first four doses and ACEL-IMUNE® for all five doses) are licensed for the diphtheria, tetanus, and pertussis vaccination series. The Food and Drug Administration (FDA) has not approved Tripedia® or Infanrix™ as the fifth dose among persons who have received only Tripedia® or only Infanrix™ for the first four doses in the vaccination series, because data are insufficient to evaluate their safety in this situation. However, such data should be available before infants vaccinated with four doses of these vaccines require a fifth dose at age 4 to 6 years. TriHIBit™ (ActHIB® reconstituted with Tripedia®) is licensed only for the fourth dose of the vaccination series, and is not licensed for the first three doses. TriHIBit™ can be used for the fourth dose following three doses of either diphtheria, tetanus, and acellular pertussis or whole-cell diphtheria, tetanus, and pertussis and a primary series of any Haemophilus influenza type B vaccine.

New Information from the 2000 Supplement

Four vaccines containing diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) are licensed for use among infants in the United States; two of these, ACEL-IMUNE® (a product of Lederle Laboratories) and Tripedia® (Aventis Pasteur, Inc.) are licensed for use as the complete five-dose series (see Table in the 2000 supplement). The other two licensed vaccines, Infanrix® and Certiva™, are approved for use for the first four doses of the five-dose series, beginning at ages 2, 4, and 6 months. Licensure of other diphtheria, tetanus and acellular pertussis vaccines as a five-dose series is anticipated.

New Information from the 2003 Supplement

On July 8, 2003, the U.S. Food and Drug Administration (FDA) approved the use of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Infanrix®, SmithKline Beecham Biologicals, Rixensart, Belgium) as a fifth dose for children aged 4 to 6 years after 4 previous doses of Infanrix®.

****See Special Notices below***

Dosage and Administration

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

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

- Cleanse the rubber stoppers of both vials with a suitable germicide.
- Thoroughly agitate the vial of Tripedia®. Insert the needle of a syringe through the vial's rubber stopper and withdraw **0.6** mL of Tripedia®.
- Inject Tripedia® into the vial of lyophilized ActHIB®. Agitate vial thoroughly; the combined reconstituted vaccines should appear whitish in color.
- Withdraw **0.5** mL dose of the combined vaccines; administer intramuscularly within 30 minutes of reconstitution.

Interchangeable Use of Acellular Pertussis Vaccines

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

See Special Notices below.

Simultaneous Administration of Vaccines

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

Special Considerations

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

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

Among infants and children with a history of previous seizures, it is prudent to delay pertussis vaccination until the child's neurologic status has been assessed. Infants and children with a stable neurologic condition, including well-controlled seizures, may be vaccinated with diphtheria, tetanus, and acellular pertussis. Infants with evolving neurologic conditions should not be vaccinated until a treatment regimen has been established and the condition has stabilized. Acetaminophen or ibuprofen may be administered to these children at the time of diphtheria, tetanus, and acellular pertussis vaccination and every 4 hours for 24 hours thereafter to reduce the possibility of postvaccination fever.

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

Children Who Have Had Pertussis Disease

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

Pertussis Vaccination for Persons Aged Greater than or Equal to 7 Years

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

Adverse Reactions

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

Moderate-to-severe systemic events (e.g., temperature of greater than or equal to 105°F [greater than or equal to 40.5°C]; febrile seizures; persistent, crying lasting greater than or equal to 3 hours; and hypotonic hyporesponsive episodes) have been reported rarely after administration of diphtheria, tetanus, and acellular pertussis, and occur less frequently among children administered diphtheria, tetanus, and acellular pertussis than among children administered whole-cell diphtheria, tetanus, and pertussis.

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

See Special Notices below.

Contraindications

If either of the following events occurs after administration of diphtheria, tetanus, and acellular pertussis or whole-cell diphtheria, tetanus, and pertussis, subsequent vaccination with diphtheria, tetanus, and acellular pertussis or whole-cell diphtheria, tetanus, and pertussis is contraindicated:

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

Precautions

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

- Temperature of greater than or equal to 105°F (greater than or equal to 40.5°C) within 48 hours, not attributable to another identifiable cause
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours
- Persistent crying lasting greater than or equal to 3 hours, occurring within 48 hours
- Convulsions with or without fever, occurring within 3 days

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

Reporting of Adverse Events After Vaccination

As with any newly licensed vaccine, surveillance for rare adverse events potentially associated with administration of diphtheria, tetanus, and acellular pertussis is important for assessing its safety in large-scale use. The National Childhood Vaccine Injury Act of 1986 requires health-care providers to report serious adverse events that follow pertussis vaccination. The events that must be reported are detailed in the Reportable Events Table within this Act, and include anaphylaxis or anaphylactic shock, encephalopathy (or encephalitis), shock collapse or hypotonic hyporesponsive collapse, and any acute complication or

sequela (including death) of these events. Adverse reactions should be reported to VAERS. VAERS reporting forms and information are available 24 hours a day by calling (800) 822-7967.

Vaccine Injury Compensation

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

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

Special Notice: *On November 17, 2000 the CDC issued supplemental recommendations on the use of diphtheria and tetanus toxoids and acellular pertussis vaccine (MMWR Morbid Mortal Wkly Rep 2000 Nov 17;49(RR-13):1-8)*.

Supplemental Advisory Committee on Immunization Practices recommendations for using diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines

Data are limited regarding differences in reactogenicity among currently licensed acellular pertussis vaccines. Increases in frequency and magnitude of substantial local reactions at the injection site with increasing dose number have been reported for all currently licensed diphtheria, tetanus, and acellular pertussis vaccines. Swelling of the thigh or entire upper arm after receipt of fourth and fifth doses of acellular pertussis vaccines has been documented for multiple products from different manufacturers. However, because reports of these reactions have generally not been solicited during safety studies, the frequency is unknown, and the absence of reports does not establish a lack of reaction after receipt of particular diphtheria, tetanus, and acellular pertussis vaccines. Additionally, in the majority of studies of adverse events after receipt of the fourth and fifth doses of diphtheria, tetanus, and acellular pertussis, participants represent a subset (a substantially limited subset in certain studies) of children who received the first three doses. Therefore, the observed frequencies of substantial swelling reactions might have been influenced by selection biases of unknown direction and magnitude. Data are insufficient to establish that mixed sequences of diphtheria, tetanus, and acellular pertussis vaccines from different manufacturers are associated with higher or lower frequencies of these reactions than receipt of a single product for the entire diphtheria, tetanus, and acellular pertussis series. Additional data regarding the reactogenicity of diphtheria, tetanus, and acellular pertussis vaccines when administered as a five-dose series are needed.

Whether children who experience entire limb swelling after a fourth dose of diphtheria, tetanus, and acellular pertussis are at increased risk for this reaction after the fifth dose is unknown. Because reports to date indicate that the reactions are self-limited and in recognition of the benefits of the preschool dose of diphtheria, tetanus, and acellular pertussis, a history of extensive swelling after the fourth dose should not be considered a contraindication for receipt of the fifth dose of the diphtheria, tetanus, and acellular pertussis series.

Parents or caregivers of children receiving the fourth and fifth doses of the diphtheria, tetanus, and acellular pertussis series should be informed of the increases in reactogenicity that have been observed. Although available data demonstrate that these reactions are self-limited and resolve without sequelae, they might be clinically indistinguishable from other conditions (e.g., cellulitis) that require treatment. Therefore, providers must make decisions regarding evaluation and management of children with suspected reactions after diphtheria, tetanus, and acellular pertussis vaccination on a case-by-case basis.

Interchangeable Use of Acellular Pertussis Vaccines

Children who began the series with diphtheria, tetanus, and acellular pertussis at age 2 months began eligibility to receive a fifth dose of diphtheria, tetanus, and acellular pertussis during mid-2000. A child who began the series late and was vaccinated on an accelerated schedule might have become eligible for the fifth dose before then. Data are insufficient to document the safety, immunogenicity, and efficacy of using diphtheria, tetanus, and acellular pertussis vaccines from different manufacturers in a mixed sequence. For this reason, the ACIP recommends that whenever feasible, the same brand of diphtheria, tetanus, and acellular pertussis vaccine should be used for all doses of the vaccination series. However, the vaccine provider might not know or have available the type of diphtheria, tetanus, and acellular pertussis vaccine previously administered to a child. Neither circumstance should present a barrier to administration of diphtheria, tetanus, and acellular pertussis vaccine, and any of the available licensed diphtheria, tetanus, and acellular pertussis vaccines can be used to complete the vaccination series.

Special Notice: *On September 26, 2003 the CDC issued supplemental recommendations on the use of diphtheria and tetanus toxoids and acellular pertussis vaccine (MMWR Morbid Mortal Wkly Rep 2003 Sep 26; 52(38); 921-921)*.

Sufficient data are now available to establish the frequency of adverse events after a fifth dose of INFANRIX® at age 4 to 6 years in children who have received 4 previous doses of INFANRIX®. The frequency of local injection site reactions (erythema and swelling) increases with successive doses of INFANRIX®. In two German studies, 93 and 390 children, respectively, received a fifth dose of INFANRIX® at age 4 to 6 years after 4 previous doses of INFANRIX®. Among solicited adverse events, swelling $\geq$5 cm (2 inches) in the injected limb within the 3 days after vaccination was reported in 15% and 20% of the vaccinees, respectively. Extensive swelling of the injected limb was reported spontaneously by parents of nine (9.7%) and 25 (6.4%) vaccinees, respectively, in these two studies.

The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians recommend that children routinely receive a series of 5 doses of vaccine against diphtheria, tetanus, and pertussis before age 7 years. ACIP recommends that the first 4 doses be administered at ages 2, 4, 6, and 15 to 18 months and the fifth dose at age 4 to 6 years.

Data are limited on the safety, immunogenicity, and efficacy of using DTaP vaccines from different manufacturers for successive doses of the DTaP series. ACIP recommends that, whenever feasible, the same brand of DTaP should be used for all doses of the series but that vaccination should not be deferred because the type of DTaP used for previous doses is not available or is unknown. In such situations, any of the available licensed DTaP vaccines can be used to continue or complete the series.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Seven field studies (three randomized controlled studies and four observational studies) evaluating the efficacy of diphtheria and tetanus toxoids and acellular vaccine (DTaP) and whole-cell DTP were cited, in addition to the Multicenter Acellular Pertussis Trial evaluating the safety of the vaccines.

Data from the Vaccine Adverse Event Reporting System (VAERS) were used to compare rates of fever, seizures, and hospitalizations among children who, having had >3 previous doses of whole-cell DTP, were administered either DTaP or whole-cell DTP vaccines for the fourth or fifth doses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Elimination of pertussis disease
- Decreased incidence of adverse events following pertussis vaccination

POTENTIAL HARMS

1997 Guideline

- Mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia may occur after both whole-cell diphtheria, tetanus, and pertussis (DTP) vaccination and diphtheria, tetanus and acellular pertussis vaccination.

However, data concerning adverse reactions following the first four doses indicate that mild reactions are less common among children who receive diphtheria, tetanus, and acellular pertussis vaccine. These reactions are self-limited and can be managed safely with symptomatic treatment.
- Moderate-to-severe systemic events (e.g., temperature of greater than or equal to 105°F, febrile seizures; persistent, crying lasting greater than or equal to 3 hours; and hypotonic hyporesponsive episodes) have been reported rarely after administration of diphtheria, tetanus, and acellular pertussis, and occur less frequently among children administered diphtheria, tetanus, and acellular pertussis than among children administered whole-cell DTP.

2000 Supplement

- Local increases in erythema, swelling, and pain at the injection site and increases in fever have been reported with the fourth dose as compared with the first dose for each of the currently licensed diphtheria, tetanus, and acellular pertussis vaccines. These reactions typically have onset within 2 days of vaccination and resolve completely without sequelae. Data regarding the reactogenicity of a fifth dose of diphtheria, tetanus, and acellular pertussis administered after four doses of the diphtheria, tetanus, and acellular pertussis vaccine are limited, but suggest further increases in the local reactogenicity of the fifth dose compared with the fourth dose.
- Swelling involving the entire thigh or upper arm has been reported after booster doses of different acellular pertussis vaccines.

2003 Supplement

- Sufficient data are now available to establish the frequency of adverse events after a fifth dose of INFANRIX® at age 4 to 6 years in children who have received 4 previous doses of INFANRIX®.
- The frequency of local injection site reactions (erythema and swelling) increases with successive doses of INFANRIX®.

CONTRAINDICATIONS

CONTRAINDICATIONS

If either of the following events occurs after administration of diphtheria, tetanus, and acellular pertussis or whole-cell diphtheria, tetanus, and pertussis, subsequent vaccination with diphtheria, tetanus, and acellular pertussis or whole-cell diphtheria, tetanus, and pertussis is contraindicated:

- *An immediate anaphylactic reaction*. Further vaccination with any of the three components of diphtheria, tetanus, and acellular pertussis or whole-cell diphtheria, tetanus, and pertussis should be deferred because of uncertainty as to which component of the vaccine might be responsible. Because of the importance of tetanus vaccination, persons who experience anaphylactic reactions may be referred to an allergist for evaluation and (if specific allergy can be demonstrated) desensitized to tetanus toxoid.

- *Encephalopathy not attributable to another identifiable cause* (e.g., an acute, severe central nervous system disorder occurring within 7 days after vaccination and generally consisting of major alterations in consciousness, unresponsiveness, or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours.) In such cases, diphtheria and tetanus vaccine should be administered for the remaining doses in the vaccination schedule to ensure protection against diphtheria and tetanus.

QUALIFYING STATEMENTS

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- In the future, booster doses of adult formulations of acellular pertussis vaccines may be recommended to prevent the occurrence and spread of the disease among older persons.
- Vaccine Adverse Event Reporting System (VAERS) is a passive surveillance system and these data should be interpreted with caution because the events reported may be linked to vaccine administration only by temporal coincidence.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Notice to readers: FDA approval of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, (INFANRIX) for fifth consecutive DTaP vaccine dose. MMWR Recomm Rep 2003 Sep 26;52(38):921. [4 references]

Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. MMWR Recomm Rep 1997 Mar 28;46(RR-7):1-25. [50 references]

Use of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine as a five-dose series. Supplemental recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep 2000 Nov 17;49(RR13):1-8. [17 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Mar 28 (revised 2000 Nov; addendum released 2003 Sep 26)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Advisory Committee on Immunization Practices (ACIP)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Advisory Committee on Immunization Practices (ACIP) Membership List, February 2000: John F. Modlin, MD (Chairman); Dixie E. Snider, Jr., MD, MPH (Executive Secretary); Dennis A. Brooks, MD, MPH; David W. Fleming, MD; Fernando A. Guerra, MD; Charles M. Helms, MD, PhD; David R. Johnson, MD, MPH; Chinh T. Le, MD; Paul A. Offit, MD; Margaret B. Rennels, MD; Lucy S. Tompkins, MD, PhD; Bonnie M. Word, MD

Ex-Officio Members: William Egan, PhD; Geoffrey S. Evans, MD; Michael A. Gerber, MD; T. Randolph Graydon; Martin G. Myers, MD; Kristin Lee Nichol, MD, MPH; Douglas A. Thoroughman, PhD; David H. Trump, MD, MPH

Liaison Representatives: American Academy of Family Physicians-Richard Zimmerman, MD; American Academy of Pediatrics-Larry Pickering, MD and Jon Abramson, MD; American Association of Health Plans-Eric K. France, MD; American College of Obstetricians and Gynecologists-Stanley A. Gall, MD; American College of Physicians-Pierce Gardner, MD; American Hospital Association-William Schaffner, MD; American Medical Association-H. David Wilson, MD; Association of Teachers of Preventive Medicine-W. Paul McKinney, MD; Biotechnology Industry Organization-Yvonne E. McHugh, PhD; Canadian National Advisory Committee on Immunization-Victor Marchessault, MD; Hospital Infection Control Practices Advisory Committee-Jane D. Siegel, MD; Infectious Diseases Society of America-Samuel L. Katz, MD; National Immunization Council and Child Health Program, Mexico-Jose Ignacio Santos, MD; National Medical Association-

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Epidemiology and Surveillance Division National Immunization Program in collaboration with the Advisory Committee on Immunization Practices Acellular Pertussis Vaccine Working Group: Margaret B. Rennels, M.D.; John F. Modlin, M.D.; Karen M. Farizo, M.D.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

The guideline titled "Use of Diphtheria Toxoid-tetanus Toxoid-acellular Pertussis Vaccine as a Five-dose Series" (MMWR Morb Mortal Wkly Rep 2000 Nov 17;49(RR-13):1-8) supplements the previous recommendations published in the guideline titled "Pertussis Vaccination: Use of Acellular Pertussis Vaccines Among Infants and Young Children" (MMWR Morb Mortal Wkly Rep 1997 Mar 28;46(RR-7):1-25) regarding use of DTaP and summarizes new Advisory Committee on Immunization Practices (ACIP) recommendations regarding DTaP vaccines as a five-consecutive--dose series.

Please note that a published erratum has been published for the guideline: "Use of Diphtheria Toxoid-Tetanus Toxoid-Acellular Pertussis Vaccine as a Five-Dose Series", MMWR Morb Mortal Wkly Rep 2000 Dec 1;49(47):1074.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

November 2000 Guideline

- HTML Format
- Portable Document Format (PDF)

September 2003 Addendum

HTML Format

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 30, 1998. It was updated on November 28, 2000 and April 2, 2004. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs).

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