DIPHTHERIA & TETANUS TOXOIDS WITH ACELLULAR PERTUSSIS ADSORBED, HEPATITIS B (RECOMBINANT) & INACTIVATED POLIOVIRUS VACCINES

COMBINED BACTERIAL & VIRAL VACCINES

Names:
Pediarix

Manufacturers:
Diphtheria and tetanus toxoids manufactured by Chiron Behring (Marburg, Germany).
Pertussis antigens, HbsAg, poliovirus antigens manufactured by SmithKline Beecham Biologicals (Rixensart, Belgium).
Distributed by GlaxoSmithKline

Synonyms: DTaP-HBV-IPV

Comparison: Therapeutically equivalent to various combinations of constituent vaccines. The diphtheria toxoid, tetanus toxoid, and pertussis antigens are the same as those in *Infanrix*-brand DTaP vaccine. The various acellular DTaP products are generically equivalent, given their differences in contents and methods of standardization. The ACIP considers available data regarding safety and clinical efficacy to be insufficient to express a preference between the various formulations of DTaP available in the US. Using the same brand of DTaP for a child's vaccination series is generally preferred, but any licensed DTaP vaccine may be used to complete the vaccination series. The hepatitis B surface antigen is the same as that in *Engerix-B*-brand hepatitis B vaccine.

Note: Vaccines containing diphtheria, tetanus, and pertussis antigens are the preferred immunizing agents for most children. Tetanus and diphtheria toxoids for adult use (Td) is the preferred immunizing agent for adults and older children.

Specific information about the individual components of this drug appear in the individual monographs on diphtheria and tetanus toxoids with acellular pertussis vaccine, hepatitis B vaccine, and inactivated poliovirus vaccine.

IMMUNOLOGIC CHARACTERISTICS

Microorganism: Bacteria, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*. Viruses, hepatitis B virus, polioviruses type 1, 2, and 3.

Viability: Inactivated

Antigenic Form: Mixture of two toxoids with three acellular pertussis antigens (inactivated pertussis toxin [PT], filamentous hemagglutinin [FHA], and pertactin [69-kilodalton outer membrane protein]), hepatitis B surface antigen (HBsAg), and three types of poliovirus vaccine

Antigenic Type: Proteins

Strains: Toxigenic strains of *Corynebacterium diphtheriae* and *Clostridium tetani*. Unspecified strain of *Bordetella pertussis*. Hepatitis B adw_2 subtype. Poliovirus type 1 (Mahoney strain), type 2 (MEF-1 strain), and type 3 (Saukett strain).

USE CHARACTERISTICS

Indications: For active immunization against diphtheria, tetanus, pertussis, all known subtypes of hepatitis B virus, and three types of poliomyelitis, as a 3-dose primary series in infants born of HBsAg-negative mothers, beginning as early as 6 weeks of age.

Reduced risk of hepatocellular carcinoma: Hepatitis B vaccine is recognized as the first anti-cancer vaccine, because it can prevent primary liver cancer. A clear link has been demonstrated between chronic hepatitis B infection and the occurrence of hepatocellular carcinoma.

As hepatitis D (caused by the delta virus) does not occur in the absence of hepatitis B infection, vaccination with *Pediarix* will also prevent hepatitis D.

Refer to the CDC's wound-management guidelines in the DTP Overview.

Limitations: *Pediarix* is not indicated for use as a booster dose after a 3-dose primary series of *Pediarix*. Give children who receive a 3-dose primary series of *Pediarix* a fourth dose of DTaP vaccine

at 15 to 18 months of age and a fourth dose of IPV at 4 to 6 years of age. Because the pertussis antigen components of *Infanrix* are the same as in *Pediarix*, give these children *Infanrix* as their fourth dose of DTaP.

Give infants born of HBsAg-positive mothers HBIG and monovalent hepatitis B vaccine within 12 hours of birth and complete the hepatitis B vaccination series.

Give infants born of mothers of unknown HBsAg status monovalent hepatitis B vaccine within 12 hours of birth and complete the hepatitis B vaccination series.

Pediarix will not prevent hepatitis caused by other agents, such as hepatitis A, C, and E viruses, or other pathogens known to infect the liver. Hepatitis B has a long incubation period. Vaccination with *Pediarix* may not prevent hepatitis B infection in people who had an unrecognized hepatitis B infection during vaccine administration.

Diphtheria toxoid immunization decreases, but does not eliminate, carriage of *C. diphtheriae* in the pharynx, nose, or on the skin. Do not use diphtheria toxoid for the treatment of actual diphtheria infections. Select appropriate antibiotics (eg, erythromycin, penicillin) to treat active infections. Give diphtheria antitoxin if the patient is unlikely to have adequate active immunity to diphtheria toxin.

Tetanus toxoid is not intended for the treatment of that disease. For treatment of tetanus infection and for passive prophylaxis, consider use of tetanus immune globulin and appropriate antibiotics (eg, a penicillin, a tetracycline).

Pertussis vaccine does not stimulate local secretory antibody production to prevent attachment of the microorganism to the respiratory epithelium. Pertussis vaccine is not intended for the treatment of the disease. Select appropriate antibiotics (eg, erythromycin) to treat active infections.

Outmoded Practices: Do not use reduced volumes (fractional doses) of vaccines. The effect of such practices on the frequency of serious adverse events and protection against disease has not been determined.

Contraindications:

Absolute: Do not give further doses of a vaccine containing pertussis antigens to children who have recovered from culture-confirmed pertussis. This vaccine is also contraindicated in people with a hypersensitivity to any component of the vaccine, including yeast, neomycin, and polymyxin B.

The following events are contraindications to administration of any pertussis-containing vaccine, including *Pediarix*:

Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine not attributable to another identifiable cause.

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy. Do not administer pertussis vaccine to people with such conditions until a treatment regimen has been established and the condition has stabilized.

Relative: Defer vaccination during the course of a moderate or severe illness with or without fever. Vaccinate such children as soon as they have recovered from the acute phase of the illness.

If any of these events occur in temporal relation to receipt of a vaccine containing a pertussis component, base the decision to give subsequent doses of a vaccine containing a pertussis component on careful consideration of potential benefits and possible risks:

- Temperature 40.5°C (105°F) and higher within 48 hours not caused by another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting 3 hours or more, occurring within 48 hours;
- Seizures with or without fever, occurring within 3 days.

There may be circumstances, such as a high local incidence of pertussis, in which the potential benefits outweigh possible risks. Particularly because these events are not associated with permanent sequelae.

The occurrence of any type of neurological symptoms or signs, including 1 or more convulsion following DTaP administration, is generally a contraindication to further use. The presence of any evolving or changing disorder affecting the CNS contraindicates administration of pertussis vaccine regardless of whether the suspected neurological disorder is associated with occurrence of any type of seizure activity.

When a decision is made to withhold pertussis vaccine, continue immunization with DT vaccine, hepatitis B vaccine, and IPV. If Guillain-Barré syndrome occurs within 6 weeks of receipt of tetanus toxoid, base the decision to give subsequent doses of any vaccine containing tetanus toxoid on careful consideration of potential benefits and possible risks.

The decision to administer a pertussis-containing vaccine to children with stable CNS disorders must be made by the physician on an individual basis, considering all relevant factors, and assessing potential risks and benefits for that individual. The ACIP and AAP have issued guidelines for such children.

Immunodeficiency: Patients receiving immunosuppressive therapy or who have other immune-deficiencies may have a diminished antibody response to active immunization. Consider deferral of vaccine administration. Nonetheless, routine immunization of symptomatic and asymptomatic HIV-infected patients is recommended.

Elderly: DTaP is generally contraindicated after 7 years of age.

Adults: DTaP is generally contraindicated after 7 years of age. Tetanus and diphtheria toxoids for adult use (Td) is the preferred immunizing agent for adults and older children.

Carcinogenicity: *Pediarix* has not been evaluated for carcinogenic potential.

Mutagenicity: *Pediarix* has not been evaluated for mutagenic potential.

Fertility Impairment: *Pediarix* has not been evaluated for the potential for impairment of fertility.

Pregnancy: Category C. DTaP is generally contraindicated after 7 years of age. It is not known if *Pediarix* antigens or corresponding antibodies cross the placenta. Generally, most IgG passage across the placenta occurs during the third trimester. Problems in humans have not been documented and are unlikely.

Lactation: DTaP is generally contraindicated after 7 years of age. It is not known if *Pediarix* antigens or corresponding antibodies cross into human breast milk. Problems in humans have not been documented and are unlikely.

Children: Do not reduce or divide the DTaP dose for preterm infants or other children. Safety and efficacy of *Pediarix* in infants younger than 6 weeks of age have not been evaluated. *Pediarix* is not recommended for people 7 years of age and older. Use Td, IPV, and hepatitis B vaccine for people 7 years of age and older. Children who have recovered from culture-confirmed pertussis do not need further doses of a pertussis-containing vaccine.

Adverse Reactions: *Pediarix* is associated with higher rates of fever, compared with separately administered vaccines. In one study that evaluated medically attended fever after the first dose of *Pediarix* or separately administered vaccines, infants who received *Pediarix* had a higher rate of medical encounters for fever within the first 4 days after vaccination.

A total of 20,739 doses of *Pediarix* have been administered to 7028 infants as a 3-dose primary series. The most common adverse reactions observed in clinical trials were local injection-site reactions (eg, pain, redness, swelling), fever, and fussiness. In comparative studies, administration of *Pediarix* was associated with higher rates of fever relative to separately administered vaccines. The prevalence of fever was highest on day of vaccination and the following day. More than 98% of fever episodes resolved within the 4-day period after vaccination (ie, vaccination day and the next 3 days).

Rates of most other solicited adverse events after *Pediarix* were comparable with rates observed after separately administered vaccines.

In a German study, data were collected for 4666 infants who received *Pediarix* concomitantly at separate sites with 1 of 4 Hib vaccines and for 768 infants in the control group that received separate *Infanrix*, Hib, and OPV vaccines. Unlike the *Pediarix* group, infants in the separate-administration group did not receive hepatitis B vaccine. Data on adverse events were collected by parents using standardized diary cards for 4 consecutive days after each vaccine dose (ie, vaccination day and next 3 days). The primary end-point was any Grade 3 solicited symptom (ie, redness or swelling more than 20 mm, fever higher than 103.1°F, or crying, pain, vomiting, diarrhea, loss of appetite, or restlessness that prevented normal daily activities) over the 3-dose primary series. Of 3773 infants for whom safety data were available, 16.2% (95% CI: 14.9% to 17.5%) of 3029 infants who received *Pediarix* and Hib vaccine compared with 20.3% (95% CI: 17.5% to 23.4%) of 744 infants who received separate vaccines were reported to have had at least one Grade 3 solicited symptom within 4 days of vaccination. The difference between groups in the rate of Grade 3 symptoms was 4.1% (90% CI: 1.4% to 7.1%).

In this study, infants also were monitored for unsolicited adverse events that occurred within 30 days after vaccination using diaries, supplemented by spontaneous reports and a medical history as reported by parents. Over the entire study period, 6 subjects in the group that received *Pediarix* reported seizures. Two of these subjects had a febrile seizure, 1 of whom also developed afebrile seizures. The remaining 4 subjects had afebrile seizures, including 2 with infantile spasms. Two subjects reported seizures within 7 days after vaccination (1 subject had febrile and afebrile seizures, and 1 subject had afebrile seizures), corresponding to a rate of 0.22 seizures per 1000 doses (febrile seizures, 0.07 per 1000 doses; afebrile seizures, 0.14 per 1000 doses). No subject who received concomitant *Infanrix*, Hib, and OPV reported seizures. No cases of hypotonic-hyporesponsiveness, encephalopathy, or anaphylaxis were reported.

In a separate German study that evaluated the safety of *Infanrix* in 22,505 infants who received 66,867 doses of *Infanrix* administered as a 3-dose primary series, the rate of seizures within 7 days of vaccination with *Infanrix* was 0.13 per 1000 doses (febrile seizures, 0.0 per 1000 doses; afebrile seizures, 0.13 per 1000 doses).

Post-dose 1 safety data are available from a US study initiated in December 2001, designed to assess *Pediarix* administered concomitantly with Hib and pneumococcal conjugate vaccines, relative to separately administered *Infanrix*, *Engerix-B*, IPV, Hib, and pneumococcal conjugate vaccines at 2, 4, and 6 months of age. The study was powered to evaluate fever higher than 101.3°F. Enrollment for this study is complete, with 673 infants in the group that received *Pediarix* and 335 infants in the separate vaccines group. Safety data after the second and third doses are expected in 2003. Data for fever within 4 days after dose 1 (ie, vaccination day and next 3 days) are presented in the following table.

Infants in a US Study with Fever within 4 Days of Dose 1* at 2 Months of Age with *Pediarix* Administered Concomitantly with Hib Vaccine and Pneumococcal Conjugate Vaccine or with Separate Coadministration of *Infanrix, Engerix-B*, IPV, Hib Vaccine, and Pneumococcal Conjugate Vaccine

	Pediarix, Hib, and Pneumococcal Conjugate (N = 667)	*Infanrix*, *Engerix-B*, IPV, Hib, and Pneumococcal Conjugate (N = 333)	Separate Vaccine Group Minus Combination Vaccine Group
Fever[t]	%	%	Difference (95% CI)
≥ 100.4°F ~	27.9	19.8	-8.07 (-13.54, -2.60)
> 101.3°F	7.0	4.5	-2.54 (-5.50, 0.41)
> 102.2°F ~	2.2	0.3	-1.95 (-3.22, -0.68)
> 103.1°F	0.4	0.0	-0.45 (-0.96, 0.06)
M.A. ~	1.2	0.0	-1.20 (-2.03, -0.37)

N number of infants for whom at least one symptom sheet was completed, excluding 3 infants for whom temperature was not measured and 3 infants whose temperature was measured by the tympanic method.
* Within 4 days of dose 1 defined as day of vaccination and the next 3 days.
t Rectal temperatures.
~ The group that received *Pediarix* compared with separate vaccine group, $P < 0.05$ (2-sided Fisher Exact test) or the 95% confidence interval on the difference between groups does not include 0.
M.A. Medically attended (a visit to or from medical personnel).

In this study, medical attention for fever within 4 days after vaccination was sought for 8 infants who received *Pediarix* (1.2%) and no infants who received separately administered vaccines. Four infants were seen by medical personnel in an office setting; no diagnostic tests were performed in 2 infants and a complete blood count (CBC) was done in the other 2 infants. Of 3 infants who were seen in an emergency room, all had a CBC and a blood and urine culture performed; chest x-rays were done in 2 infants and a nasopharyngeal specimen was tested for RSV in 1 infant. One infant was hospitalized for a workup that included a CBC, blood and urine cultures, a lumbar puncture, and a chest x-ray. All episodes of medically attended fever resolved within 4 days post-vaccination.

In 12 clinical trials, 5 deaths were reported in 7028 (0.07%) recipients of *Pediarix* and 1 death was reported in 1764 (0.06%) recipients of comparator vaccines. Causes of death in the group that received *Pediarix* included 2 cases of sudden infant death syndrome (SIDS) and one case of each of the following: convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma. One case of SIDS was reported in the comparator group. The rate of SIDS among all recipients of *Pediarix* across the 12 trials was 0.3/1000. The rate of SIDS observed for recipients of *Pediarix* in the German safety study was 0.2/1000 infants (reported rate of SIDS in Germany in the latter part of the 1990s was 0.7/1000 newborns). The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1000 live births. By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.

Limited data are available on the safety of administering *Pediarix* after a birth dose of hepatitis B vaccine. In a study conducted in Moldova, 160 infants received a dose of hepatitis B vaccine within 48 hours of birth followed by 3 doses of *Pediarix* at 6, 10, and 14 weeks of age. No information was collected on the HBsAg status of mothers of enrolled infants. Although there was no comparator group who received *Pediarix* without a birth dose of hepatitis B vaccine, available data suggest that some local adverse events may occur at a higher rate when *Pediarix* is administered after a birth dose of hepatitis B vaccine.

Rarely, an anaphylactic reaction (ie, hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertus-

sis antigens. Arthus-type hypersensitivity reactions, characterized by severe local reactions, may follow receipt of tetanus toxoid. A review by the Institute of Medicine (IOM) found evidence for a causal relationship between receipt of tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. A few cases of demyelinating diseases of the CNS have been reported after some tetanus toxoid-containing vaccines or tetanus and diphtheria toxoid-containing vaccines, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship. A few cases of peripheral mononeuropathy and of cranial mononeuropathy have been reported after tetanus toxoid administration, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.

Worldwide voluntary reports of adverse events received for *Infanrix* and *Engerix-B* in children younger than 7 years of age since market introduction of these US-licensed vaccines are listed below. This list includes adverse events for which 20 or more reports were received, except for intussusception, idiopathic thrombocytopenic purpura, thrombocytopenia, anaphylactic reaction, angioedema, encephalopathy, hypotonic-hyporesponsive episode, and alopecia for which less than 20 reports were received. These latter events are included either because of the seriousness of the event or the strength of causal connection to components of this or other vaccines or drugs.

An expert panel assembled by the IOM concluded that no causal association exists between pertussis vaccination and autism, infantile spasms, hypsarrhythmia, Reye syndrome, SIDS, aseptic meningitis, chronic neurologic damage, erythema multiforme or other rash, Guillain-Barré syndrome, hemolytic anemia, juvenile diabetes, learning disabilities, attention deficit disorder, peripheral mononeuropathy, or thrombocytopenia.

The panel found evidence consistent with a causal association between DTwP and acute encephalopathy, shock and "unusual shock-like state," anaphylaxis, and protracted, inconsolable crying.

When a child returns for the next dose in a series of either pertussis or DTaP vaccinations, question the adult accompanying the child about possible side effects following the prior dose. If any of the effects that contraindicate additional pertussis vaccine doses occur, continue childhood immunization with bivalent DT toxoids, rather than DTaP.

In the following list, abbreviations were used to note the vaccines associated with adverse reactions. After *Infanrix* (a). After *Engerix-B* (b). After either *Infanrix* or *Engerix-B* (a+b).

Body as a whole: Asthenia (b), fever (a+b), lethargy (b), malaise (b), SIDS (a+b).

Cardiovascular: Cyanosis (a+b), edema (b), pallor (b).

CNS: Convulsions (a+b), encephalopathy (a), headache (b), hypotonia (a+b), hypotonic-hyporesponsive episode (a), somnolence (a+b).

Dermatologic: Alopecia (b), erythema (a+b), erythema multiforme (b), petechiae (b), pruritis (a+b), rash (a+b), urticaria (a+b).

GI: Abdominal pain (b), anorexia (b), diarrhea (a+b), intussusception (a+b), nausea (b), vomiting (a+b).

Hematologic/Lymphatic: Idiopathic thrombocytopenic purpura (a+b), lymphadenopathy (a), thrombocytopenia (a+b).

Hepatic: Jaundice (b), liver function tests abnormal (b).

Hypersensitivity: Anaphylactic reaction (a+b), angioedema (b), hypersensitivity (a).

Immunologic: Cellulitis (a).

Local: Injection-site reactions (a+b).

Musculoskeletal: Arthralgia (b), limb swelling (a+b).

Psychiatric: Crying (a+b), irritability (a+b).

Respiratory: Respiratory tract infection (a).

Special Senses: Ear pain (a).

DIPHTHERIA & TETANUS TOXOIDS WITH ACELLULAR PERTUSSIS ADSORBED, HEPATITIS B (RECOMBINANT) & INACTIVATED POLIOVIRUS VACCINES

PHARMACOLOGIC & DOSING CHARACTERISTICS

Dosage: Three 0.5 mL doses, at 6- to 8-week intervals (preferably 8 weeks).

The customary age for the first dose is 2 months of age, but it may be given starting at 6 weeks of age. Only monovalent hepatitis B vaccine can be used for the birth dose.

Infants born of HBsAg-positive mothers should receive HBIG and hepatitis B vaccine within 12 hours of birth at separate sites and complete the hepatitis B vaccination series. Infants born of mothers of unknown HBsAg status should receive hepatitis B vaccine within 12 hours of birth and complete the hepatitis B vaccination series.

Vaccinate preterm infants according to their chronological age from birth.

Children previously vaccinated with one or more doses of hepatitis B vaccine: Infants born of HBsAg-negative mothers and who received a dose of hepatitis B vaccine at or shortly after birth may be administered 3 doses of *Pediarix* according to the recommended schedule. There are no data to support the use of a 3-dose series of *Pediarix* in infants who have previously received more than one dose of hepatitis B vaccine. *Pediarix* may be used to complete a hepatitis B vaccination series in infants who received 1 or more doses of hepatitis B vaccine and who are also scheduled to receive the other vaccine components of *Pediarix*.

Children previously vaccinated with one or more doses of Infanrix: *Pediarix* may be used to complete the first 3 doses of the DTaP series in infants who have received 1 or 2 doses of *Infanrix* and are also scheduled to receive the other vaccine components of *Pediarix*.

Children previously vaccinated with one or more doses of IPV: Pediarix may be used to complete the first 3 doses of the IPV series in infants who have received 1 or 2 doses of IPV and are also scheduled to receive the other vaccine components of *Pediarix*.

Interchangeability of Pediarix and licensed DTaP, IPV, or hepatitis B vaccines: Pediarix can be given for all 3 doses because data are limited regarding the safety and efficacy of using acellular pertussis vaccines from different manufacturers for successive doses of the pertussis vaccination series. *Pediarix* is not recommended for completion of the first 3 doses of the DTaP vaccination series initiated with a DTaP vaccine from a different manufacturer because no data are available regarding the safety or efficacy of using such a regimen.

Pediarix may be used to complete a hepatitis B vaccination series initiated with a hepatitis B vaccine from a different manufacturer.

Pediarix may be used to complete the first 3 doses of the IPV vaccination series initiated with IPV from a different manufacturer.

If any recommended dose of pertussis vaccine cannot be given, give DT, hepatitis B, and inactivated poliovirus vaccines as needed to complete the series.

Route & Site: IM injection. Do not administer SC or IV. Preferred sites are anterolateral aspects of thigh or deltoid muscle of upper arm. Do not inject in gluteal area or areas where there may be a major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response.

Documentation Requirements: Federal law requires that (1) the manufacturer and lot number of this vaccine, (2) the dates of its administration, and (3) the name, address, and title of the person administering the vaccine be documented in the recipient's permanent medical record or in a permanent office log.

Certain adverse events must be reported to VAERS (800-822-7967). Refer to Immunization Documents in the Resources section for complete information.

Overdosage: No specific data are available. Larger-than-recommended volume of vaccine may increase the risk of injection-site reactions, but are unlikely to have other consequences.

Booster Doses: Complete the diphtheria, tetanus, pertussis, hepatitis B, and poliovirus vaccination series with other vaccines, as necessary.

DIPHTHERIA & TETANUS TOXOIDS WITH ACELLULAR PERTUSSIS ADSORBED, HEPATITIS B (RECOMBINANT) & INACTIVATED POLIOVIRUS VACCINES

Missed Doses: Interrupting the recommended schedule or delaying subsequent doses does not require restarting the series. Use Td, rather than DTaP, for doses after 7 years of age. Interrupting the recommended schedule with a delay between doses should not interfere with the final immunity achieved with *Pediarix*, but waiting does delay achieving adequate protection from infection. There is no need to start the series over, regardless of time elapsed between doses.

Related Interventions: For children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at time of vaccination with an acellular pertussis component and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

Efficacy: *Pediarix* efficacy is based on immunogenicity of individual antigens compared to licensed vaccines. Efficacy of the pertussis component, which does not have a well-established correlate of protection, was determined in clinical trials of *Infanrix*. Efficacy of HBsAg was determined in clinical studies of *Engerix-B*. Serological correlates of protection exist for the diphtheria, tetanus, hepatitis B, and poliovirus components.

Efficacy of a 3-dose primary series of *Infanrix* has been assessed in two clinical studies, one in Italy and one in Germany. A double-blind, randomized, DT-controlled trial conducted in Italy, assessed *Infanrix* when administered at 2, 4, and 6 months of age. After 3 doses, the absolute protective efficacy of *Infanrix* against WHO-defined typical pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76% to 89%). When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of *Infanrix* was 71% (95% CI: 60% to 78%) against longer than 7 days of any cough and 73% (95% CI: 63% to 80%) against 14 or more days of any cough. A second follow-up period to a mean age of 33 months was conducted in a partially unblinded cohort, showing that after 3 doses and with no booster dose in the second year of life, the efficacy of *Infanrix* against WHO-defined pertussis was 86% (95% CI: 79% to 91%) among children followed to 6 years of age.

A prospective efficacy trial was conducted in Germany, employing a household-contact study design. In preparation for this study, 3 doses of *Infanrix* were administered at 3, 4, and 5 months of age to more than 22,000 children living in 6 areas of Germany. Infants who did not participate in the safety and immunogenicity study could have received a whole-cell DTP vaccine or DT vaccine. Index cases were identified by spontaneous presentation to a physician. Households with at least one other member aged 6 through 47 months were enrolled. Household contacts of index cases were monitored for incidence of pertussis by a physician who was blinded to the vaccination status of the household. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 household contacts who had not received a pertussis vaccine, 96 developed WHO-defined pertussis, as compared to 7 of 112 contacts vaccinated with *Infanrix*. The protective efficacy of *Infanrix* was 89% (95% CI: 77% to 95%), with no indication of waning of protection up until the time of the booster vaccination. When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of *Infanrix* against 7 or more days of any cough was 67% (95% CI: 52% to 78%) and against 7 or more days of paroxysmal cough was 81% (95% CI: 68% to 89%). The corresponding efficacy rates of *Infanrix* against 14 or more days of any cough or paroxysmal cough were 73% (95% CI: 59% to 82%) and 84% (95% CI: 71% to 91%), respectively.

Protective efficacy with *Engerix-B* was demonstrated in a clinical trial in neonates at high risk of hepatitis B infection. Fifty-eight neonates born of mothers who were both HBsAg-negative and HBsAg-positive were given *Engerix-B* (10 mcg at 0, 1, and 2 months) without concomitant HBIG. Two infants became chronic carriers in the 12-month follow-up period after initial inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the chronic carrier state during the first 12 months of life was 95%.

Pediarix Formulation: In a US study, immune responses to each antigen in *Pediarix* 1 month after the third vaccination were compared to those after administration of US-licensed vaccines (*Infanrix*, *Engerix-B*, and OPV [*Orimune*, Lederle]). Both groups received *Haemophilus influenzae* type b (Hib) vaccine (Aventis Pasteur) concomitantly. One month after the third dose of *Pediarix*, vaccine response rates for each of the pertussis antigens (except FHA), geometric mean antibody concentrations for each pertussis antigen, and seroprotection rates for diphtheria, tetanus, hepatitis B, and the polioviruses, were noninferior to those achieved after separately administered vaccines. The vaccine response to FHA marginally exceeded the 10% limit for noninferiority.

Antibody Responses to Antigens in *Pediarix* Compared with *Infanrix, Engerix-B*, and OPV in US Infants Vaccinated at 2, 4, and 6 Months of Age

	Pediarix (N = 86 to 91)	*Infanrix*, *Engerix-B*, OPV (N = 73 to 78)
Anti-Diphtheria		
% ≥ 0.1 IU/mL*	98.9	100
Anti-Tetanus		
% ≥ 0.1 IU/mL*	100	100
Anti-PT		
% VR*	98.9	98.7
GMCt	97.1	47.5
Anti-FHA		
% VR	95.6	100
GMCt	119.1	153.2
Anti-Pertactin		
% VR*	95.6	91.0
GMCt	150.4	108.6
Anti-HBsAg		
% ≥ l0 mIU/mL*	100	100
GMCt	1661.2	804.9
Anti-Polio 1		
% ≥ 1:8* ~	100	98.6
Anti-Polio 2		
% ≥ 1:8* ~	98.8	100
Anti-Polio 3		
% ≥ 1:8* ~	100	100

VR Vaccine response: In initially seronegative infants, appearance of antibodies (concentration greater than or equal to 5 ELU/mL); in initially seropositive infants, at least maintenance of pre-vaccination concentration.
GMC Geometric mean antibody concentration.
* Seroprotection rate or vaccine response rate to *Pediarix* not inferior to separately administered vaccines (upper limit of 90% CI on the difference for separate administration minus *Pediarix* less than 10%).
t GMC in the group that received *Pediarix* not inferior to separately administered vaccines (upper limit of 90% CI on the ratio of GMC for separate administration/*Pediarix* less than 1.5 for anti-PT, anti-FHA, and anti-pertactin, and less than 2.0 for anti-HBsAg).
~ Poliovirus neutralizing antibody titer.

Onset: Escalating protection with each sequential dose.

Duration: After adequate immunization against diphtheria and tetanus, protection persists for 10 or more years. After immunization against pertussis, protection persists for approximately 4 to 6 years. After immunization against hepatitis B and poliovirus, protection persists for many years.

Protective Level:

Diphtheria: Serum antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels at least 0.1 IU/mL are regarded as protective.

Tetanus: A serum tetanus antitoxin level of 0.01 IU/mL is considered the minimum protective level. More recently, a level at least 0.1 to 0.2 IU/mL has been considered as protective.

Pertussis: Efficacy of the pertussis component does not have a well-established correlate of protection.

Hepatitis B: People who develop anti-HBs antibodies after active infection are usually protected against subsequent infection. Antibody concentrations at least 10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B.

Poliovirus: Any detectable neutralizing antibody, in practice a titer greater than 1:4.

Mechanism: *Corynebacterium diphtheriae* may cause a localized or generalized disease. Diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*, causes systemic intoxication. Complete immunization induces protective antitoxin antibodies against diphtheria toxin and significantly reduces the risk of developing diphtheria. Immunized patients who develop disease have milder illnesses.

Tetanus toxoid induces specific protective antibodies against the exotoxin excreted by *Clostridium tetani*.

Pertussis vaccine exerts an adjuvant effect on the diphtheria and tetanus toxoids. The role of circulating pertussis antibodies is not clear at present.

Hepatitis B vaccine induces specific antibodies against the surface antigen of hepatitis B virus.

Poliovirus vaccine induces neutralizing antibodies, reducing pharyngeal excretion of poliovirus through a mucosal secretory-IgA response at that site. This helps block respiratory transmission. Some immunity in the mucosa of the GI tract develops, but it is inferior to that induced by OPV. If patients vaccinated with IPV swallow viable polioviruses, the viruses can be shed in their stools.

Drug Interactions: Do not mix *Pediarix* with any other vaccine or immune globulin in the same syringe or vial. When coadministration of other vaccines is required, give with separate syringes and at different injection sites.

Concomitant vaccine administration: In clinical trials, *Pediarix* was routinely administered, at separate sites, concomitantly with Hib vaccine. Safety data are available after the first dose of *Pediarix* administered concomitantly, at separate sites, with Hib and pneumococcal conjugate vaccines.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (in greater than physiologic doses), may reduce the immune response to vaccines. Recipients may remain susceptible despite immunization. Although no specific *Pediarix* data are available, if immunosuppressive therapy will be discontinued shortly, defer immunization until off-therapy for 3 months; otherwise, vaccinate while still on therapy.

Inactivated vaccines are not generally affected by circulating antibodies or administration of exogenous antibodies. Vaccination may occur at any time before or after antibody administration.

As with other IM injections, do not give *Pediarix* to children on anticoagulant therapy, unless the potential benefit clearly outweighs the risk of administration.

PHARMACEUTICAL CHARACTERISTICS

Concentration: Each 0.5 mL dose contains 25 Lf U of diphtheria toxoid, 10 Lf U of tetanus toxoid, 25 mcg of inactivated PT, 25 mcg of FHA, 8 mcg of pertactin, 10 mcg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus, 8 DU of Type 2 poliovirus, and 32 DU of Type 3 poliovirus.

Quality Assay: Diphtheria and tetanus toxoid potency is determined by measuring neutralizing antitoxin in previously immunized guinea pigs. The potency of PT, FHA, and pertactin is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice. Hepatitis B potency is established by HBsAg ELISA. Poliovirus potency is determined by D-antigen ELISA and by a poliovirus-neutralizing cell-culture assay on sera from previously immunized rats.

DIPHTHERIA & TETANUS TOXOIDS WITH ACELLULAR PERTUSSIS ADSORBED, HEPATITIS B (RECOMBINANT) & INACTIVATED POLIOVIRUS VACCINES

Packaging: Package of 10 single-dose vials (NDC #: 58160-0841-11), Package of 5 single-dose prefilled *Tip-Lok* syringes without needles (58160-0841-46), package of 25 single-dose prefilled *Tip-Lok* syringes without needles (58160-0841-50), package of 25 single-dose prefilled *Tip-Lok* syringes with 1-inch 25-gauge BD *SafetyGlide* needles (58160-0841-56), package of 25 single-dose prefilled *Tip-Lok* syringes with ⅝-inch 25-gauge BD *SafetyGlide* needles (58160-0841-57)

Doseform: Suspension

Appearance: Turbid white suspension after shaking.

Solvent: Saline

Adjuvant: Aluminum, not more than 0.85 mg aluminum per 0.5 mL by assay

Preservative: 2.5 mg of 2-phenoxyethanol per 0.5 mL

Allergens: The vial stopper is latex-free. The tip cap and the rubber plunger of needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex-sensitive people.

Excipients: 4.5 mg of NaCl per 0.5 mL. Each dose also contains up to 100 mcg of residual formaldehyde and up to 100 mcg of polysorbate 80 (Tween 80). Thimerosal is used in early stages of manufacture and is removed by subsequent purification steps to below the analytical limit of detection (less than 25 ng of mercury/20 mcg HbsAg or less than 12.5 ng mercury per 0.5 mL dose). Neomycin sulfate and polymyxin B are used in poliovirus manufacturing and may be present at up to 0.05 ng neomycin and up to 0.01 ng polymyxin B per 0.5 mL dose. Procedures in HbsAg manufacture result in a product that contains up to 5% yeast protein.

pH: 5.8 to 6.8

Shelf Life: 24 months when stored between 2° to 8°C (36° to 46°F).

Storage/Stability: Store at 2° to 8°C (36° to 46°F). Discard frozen vaccine. *Pediarix* has been shown to be stable when held at temperatures between 68° and 77°F (20° to 25°C) for up to 24 hours. If accidently left at temperatures between 47° and 77°F, return the vaccine as soon as possible. Shipping data not provided.

Handling: Vaccine must be well shaken before administration. Do not use if resuspension does not occur with vigorous shaking.

Production Process: Diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* in modified Latham medium derived from bovine casein. Bovine materials used in these extracts are sourced from countries USDA determined neither have nor are at risk of bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The three acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from fermentation broth; pertactin is extracted from cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

Hepatitis B surface antigen (HBsAg) is obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of hepatitis B virus, in synthetic medium. The surface antigen expressed in *S. cerevisiae* cells is purified by several physiochemical steps, including precipitation, ion-exchange chromatography, and ultrafiltration. Purified HBsAg undergoes dialysis with cysteine to remove residual thimerosal.

To yield enhanced-potency inactivated poliovirus components, each of the three strains of poliovirus is individually grown in Vero cells, a continuous line of monkey kidney cells cultivated on microcarriers. Calf serum and lactalbumin hydrolysate are used during Vero cell culture and/or virus culture. Calf serum is sourced from countries USDA determined neither have nor are at risk of BSE.

After clarification, each viral suspension is purified by ultrafiltration, diafiltration, and successive chromatographic steps, and inactivated with formaldehyde. Each purified viral strain is then pooled to form a trivalent concentrate.

Diphtheria, tetanus, and pertussis antigens are individually adsorbed onto aluminum hydroxide. Hepatitis B component is adsorbed onto aluminum phosphate. All five antigens are then diluted and combined to produce the final formulated vaccine.

DISEASE EPIDEMIOLOGY

See monographs for individual vaccine components.

OTHER INFORMATION

Perspective: See monographs for individual vaccine components.

First Licensed: December 13, 2002

National Policy: See recommended childhood vaccination schedule, revised each January.