

VERBATIM

'I think it's especially important for pediatricians to remind parents that they are modeling safety to their children. Do they buckle up? Wear a bicycle helmet? Drink and drive? The closer the age of the child is to the potential behavior (riding a bike, driving, dating), the more direct is the connection between parental behavior and the child's likely actions.'

Dr. Michael S. Jellinek, p.28

Kawasaki Cases Lead to RotaTeq Label Changes

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Several postmarketing reports of Kawasaki disease in recipients of the RotaTeq vaccine have prompted changes in the vaccine's label, but to date there is no known cause-and-effect relationship between the vaccine and these re-

ports, according to the Food and Drug Administration.

Last month, the FDA approved the labeling changes, which add information to the adverse reactions and postmarketing sections of the vaccine's label. The information added includes six cases of Kawasaki disease that were observed in the phase III clinical trial of RotaTeq—five cases among 36,150 infants who received RotaTeq and one case among 35,536 infants who received the placebo.

There have been three additional cases of Kawasaki disease reported to the Vaccine Adverse Event Reporting System (VAERS) since

The three reports of Kawasaki disease to VAERS do not exceed the number of cases that would normally be expected in children.

RotaTeq was approved in February 2006 for preventing rotavirus infection—information that has also been added to the postmarketing section of the label. The three cases were identified through routine monitoring of

VAERS and were reported in children receiving routine pediatric vaccines, including RotaTeq, according to an FDA statement on the Center for Biologics Evaluation and Research Web site.

The three reports to VAERS do not exceed the number of cases that would normally be expected in children, and there is “not a known cause-and-effect relationship between receiving RotaTeq, or any other vaccine, and the occurrence of Kawasaki disease,” the statement said. No changes to the indication for RotaTeq have been made, and no new warnings or precautions have been issued, and “health-care practitioners and parents should remain confident in using RotaTeq.” As of June 8, about 6 million RotaTeq doses had been distributed in the United States, according to the FDA.

The FDA and the Centers for Disease Control and Prevention are continuing to monitor the safety of all vaccines, and encourage health care providers to report to VAERS any cases of Kawasaki disease and other serious adverse events in recipients of RotaTeq and other vaccines.

The CDC's Vaccine Safety Datalink (VSD) project also is monitoring for Kawasaki disease in RotaTeq vaccinees. In early June, the VSD project reported one case of Kawasaki disease that occurred within 30 days of RotaTeq vaccination, which was not confirmed.

This case is among 65,000 RotaTeq doses administered to children under age 1 year who are enrolled in the project, which is monitoring the safety of vaccines among patients enrolled in eight managed care organizations.

Kawasaki disease affects about 4,000 children annually in the United States; 80% are younger than age 5. RotaTeq is manufactured by Merck.

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed DAPTACEL®

R only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE: DAPTACEL® is indicated for active immunization against diphtheria, tetanus and pertussis in infants and children 6 weeks through 6 years of age (prior to seventh birthday). Children who have had well-documented pertussis (culture positive for *B. pertussis* or epidemiologic linkage to a culture positive case) should complete the vaccination series with DT; some experts recommend including acellular pertussis vaccine as well. Although well-documented pertussis disease is likely to confer immunity, the duration of protection is unknown.¹

CONTRAINDICATIONS: This vaccine is contraindicated in children and adults seven years of age and older. Hypersensitivity to any component of the vaccine is a contraindication to further administration.²

The following events after receipt of DAPTACEL® are contraindications to further administration of any pertussis-containing vaccine:²

- An immediate anaphylactic reaction. Because of uncertainty as to which component of the vaccine may be responsible, no further vaccination with diphtheria, tetanus or pertussis components should be carried out. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.

- Encephalopathy not attributable to another identifiable cause (e.g., an acute, severe central nervous system disorder occurring within 7 days after vaccination and 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, DT vaccine should be administered for the remaining doses in the vaccination schedule.

The decision to administer or delay vaccination because of a current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. According to the ACP, all vaccines can be administered to persons with mild illness such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness.¹³ However, children with moderate or serious illness should not be immunized until recovered.⁴

Elective immunization procedures should be deferred during an outbreak of poliomyelitis because of the risk of provoking paralysis.^{14,17}

WARNINGS: The stopper to the vial of this product contains dry natural latex rubber that may cause allergic reactions. If any of the following events occur within the specified period after administration of a whole-cell pertussis DTP or DTPa vaccine, providers and parents should evaluate the risks and benefits of subsequent doses of whole-cell pertussis DTP or DTPa vaccines:²

- Temperature of 104.0°F (40.0°C) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent crying lasting 3 hours within 48 hours.
- Convulsions with or without fever within 3 days.

When a decision is made to withhold pertussis vaccine, immunization with DT vaccine should be continued.⁴ Because of the risk of hemorrhage, DAPTACEL® should not be given to children with any coagulation disorder, including thrombocytopenia, which would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

Studies suggest that, when given whole-cell pertussis DTP vaccine, infants and children with a history of convulsions in first-degree family members have a 2.4-fold increased risk for neurologic events.¹⁸ However, ACP has concluded that a history of convulsions or other central nervous system disorders in parents or siblings is not a contraindication to pertussis vaccination and that children with such family histories should receive DTPa vaccines according to the recommended schedule.^{13,14}

For infants or children at higher risk for seizures than the general population, an appropriate antiepileptic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing an acellular pertussis component (including DAPTACEL®) and for the following 24 hours, to reduce the possibility of post-vaccination fever.^{2,3}

Whether to administer DAPTACEL® to children with proven or suspected underlying neurologic disorders must be decided on an individual basis. An important consideration includes the current local incidence of pertussis. The ACP has issued guidelines for such children.¹⁹

PRECAUTIONS: General: Care is to be taken by the health-care provider for the safe and effective use of this vaccine.

Epinephrine Hydrochloride Solution (1:1,000), other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers must be familiar with current recommendations for the initial management of anaphylaxis in the hospital setting, including proper airway management.^{1,21}

Before an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. The expected immune response to DAPTACEL® may not be obtained in immunosuppressed persons.² Pertussis-containing vaccines are not contraindicated in persons with HIV infection.¹

IT IS EXTREMELY IMPORTANT WHEN A CHILD RETURNS FOR THE NEXT DOSE IN THE SERIES THAT THE PARENT OR GUARDIAN SHOULD BE QUESTIONED CONCERNING ANY SYMPTOMS AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE OF VACCINE. (See **CONTRAINDICATIONS AND ADVERSE REACTIONS**.)

Drug Interactions: As with other intramuscular (IM) injections, use with caution in patients on anticoagulant therapy. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy is to be soon discontinued, it seems reasonable to defer immunization until the patient has been off therapy for one month; otherwise, the patient should be vaccinated while still on therapy.⁴

If DAPTACEL® is administered to persons with an immunodeficiency disorder, on immunosuppressive therapy or after a recent injection of immune globulin, an adequate immunologic response may not occur.

For information regarding simultaneous administration with other vaccines refer to **DOSEAGE AND ADMINISTRATION**. If passive immunization is needed for tetanus or diphtheria prophylaxis, Tetanus Immune Globulin (Human) (TIG), or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate needle and syringe.³

Carcinogenesis, Mutagenesis, Impairment of Fertility: DAPTACEL® has not been evaluated for its carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy Category C: Animal reproduction studies have not been conducted with DAPTACEL®. It is not known whether DAPTACEL® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. DAPTACEL® is NOT recommended for use in a pregnant woman.

Geriatric Use: This product is NOT recommended for use in adult populations.

Pediatric Use: SAFETY AND EFFECTIVENESS OF DAPTACEL® IN INFANTS BELOW 6 WEEKS OF AGE HAVE NOT BEEN ESTABLISHED. (See **DOSEAGE AND ADMINISTRATION**.)

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE OR OLDER. Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) is to be used in individuals 7 years of age or older.

ADVERSE REACTIONS: Over 11,400 doses of DAPTACEL® have been administered to infants and toddlers in 6 clinical studies. In all, 6,894 children received a total of 3 doses and 476 children received 4 doses of DAPTACEL®.^{19, 22, 23, 24, 25, 26, 27, 28}

In the Sweden I Efficacy Trial, DAPTACEL® was compared with DT and a whole-cell pertussis DTP vaccine. A standard diary card kept for 14 days after each dose and follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls were made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2 months after the last injection. There were fewer of the common local and systemic reactions following DAPTACEL® than following the whole-cell pertussis DTP vaccine. As shown in Table 1, the 2,587 infants who enrolled to receive DAPTACEL® at 2, 4 and 6 months of age had similar rates of reactions within 24 hours as recipients of DT and significantly lower rates than infants receiving whole-cell pertussis DTP.²²

TABLE 1²²

PERCENTAGE OF INFANTS FROM SWEDEN I EFFICACY TRIAL WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 24 HOURS POST-DOSE 1, 2 AND 3 OF DAPTACEL® COMPARED WITH DT AND WHOLE-CELL PERTUSSIS DTP VACCINES

EVENT	Dose 1 (2 MONTHS)			Dose 2 (4 MONTHS)			Dose 3 (6 MONTHS)		
	DAPTACEL® N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL® N = 2,563	DT N = 2,555	DTP N = 2,040	DAPTACEL® N = 2,549	DT N = 2,538	DTP N = 2,001
Local									
Tenderness (Any)	8.0*	8.4	59.5	10.1*	10.3	60.2	10.8*	10.0	50.0
Redness ≥2 cm	0.3*	0.3	6.0	1.0*	0.8	5.1	3.7*	2.4	6.4
Swelling ≥2 cm	0.9*	0.7	10.6	1.6*	2.0	10.0	6.3*	3.9	10.5
Systemic									
Fever [†] ≥38°C (100.4°F)	7.8*	7.6	72.3	19.1*	18.4	74.3	23.6*	22.1	65.1
Fretfulness [‡]	32.3	33.0	82.1	39.6	39.8	85.4	35.9	37.7	73.0
Anorexia	11.2*	10.3	39.2	9.1*	8.1	25.6	8.4*	7.7	17.5
Drowsiness	32.7*	32.0	56.9	25.9*	25.6	50.6	18.9*	20.6	37.6
Crying ≥1 hour	1.7*	1.6	11.8	2.5*	2.7	9.3	1.2*	1.0	3.3
Vomiting	6.9*	6.3	9.5	5.2**	5.8	7.4	4.3	5.2	5.5

N = Number of evaluable subjects *p<0.001: DAPTACEL® versus whole-cell pertussis DTP **p<0.003: DAPTACEL® versus whole-cell pertussis DTP †p<0.0001: DAPTACEL® versus DT ‡Rectal temperature ††Statistical comparisons were not made for this variable DT: Swedish National Biologics Laboratories DT: Sanofi Pasteur Inc.

One case of whole limb swelling and generalized symptoms, with resolution within 24 hours, was observed following dose 2 of DAPTACEL®. No episodes of anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of vaccination with DAPTACEL®. Over the entire study period, 6 seizures were reported in the DAPTACEL® group, 9 in the DT group and 3 in the whole-cell pertussis DTP group, for overall rates of 2.3, 3.5 and 1.4 per 1,000 vaccines, respectively. One case of infantile spasms was reported in the DAPTACEL® group. There were no instances of invasive bacterial infection or death.^{19,23}

Rates of serious adverse events that are less common than those reported in the Sweden I Efficacy Trial are not known at this time.

Table 2 summarizes the safety results from the Phase II Study in Canada in children who were immunized at 2, 4, 6 and 17-18 months of age with DAPTACEL®. For adverse events, parents recorded information for 72 hours post-immunization in a diary card. Local reaction of redness and swelling were assessed and measured by the parents using a template with graded size markings. Study staff collected the information from the parents during a structured telephone interview at 2-6, 8-12, 24, 48 and 72 hours and 7 days post-immunization and recorded the information in the case report form. Local and systemic adverse events were consistently less common in DAPTACEL® recipients at 2, 4 and 6 months of age than in those who received whole-cell pertussis DTP vaccine. Following the fourth dose, the same trends were observed, except for rates of severe redness and swelling which did not differ between the 2 vaccine groups. Rates of local reactions of redness and swelling were increased following the fourth dose compared with the first 3 doses as was mild tenderness but there was no increase in severe tenderness.

TABLE 2²³

PERCENTAGE OF CHILDREN FROM PHASE II STUDY IN CANADA WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 72 HOURS OF VACCINATION WITH DAPTACEL® AND WHOLE-CELL PERTUSSIS DTP VACCINE AT 2, 4, 6 AND 17-18 MONTHS OF AGE

EVENT	Dose 1 (2 MONTHS)		Dose 2 (4 MONTHS)		Dose 3 (6 MONTHS)		Dose 4 (18 MONTHS)	
	DAPTACEL® N = 324	DTP N = 108	DAPTACEL® N = 321	DTP N = 106	DAPTACEL® N = 320	DTP N = 104	DAPTACEL® N = 301	DTP N = 97
Local								
Redness	12.7*	44.4	20.6*	57.5	22.2*	51.9	36.5*	55.7
Any ≥10 mm	1.2*	13.9	7.8*	22.6	10.0*	17.3	27.9	36.1
≥35 mm	0.3*	3.7	0.3*	5.7	1.6	1.9	21.9	20.6
Swelling	4.3*	23.1	4.3*	32.1	4.7*	25.0	18.6*	28.9
Any ≥1 mm	1.9*	15.7	2.2*	21.7	3.8*	14.4	15.9*	25.8
≥35 mm	0.3*	6.5	0*	5.7	0.9*	4.8	11.3	15.5
Tenderness†	10.2*	37.0	7.5*	51.9	8.8*	48.1	23.9*	86.6
Any Moderate + Severe	0.9*	13.0	1.2*	20.8	1.3*	17.3	3.0*	53.6
Severe	0*	4.6	0.3*	7.5	0*	4.8	0.3*	12.4
Systemic								
Fever [‡]	12.0*	43.7	7.7*	50.0	14.8*	53.2	14.5*	67.9
Any ≥37.5°C (99.5°F)	0.7	1.9	0*	7.8	1.2*	11.7	1.9*	17.9
≥38°C (100.4°F)	0.3	0	0	1.0	0	1.1	0	0
≥40°C (104°F)								
Irritability	41.0*	65.7	41.4*	68.9	40.9*	67.3	36.9*	79.4
Any Moderate + Severe	9.0*	18.5	6.9*	22.6	5.0*	22.1	5.0*	24.7
Severe	0	1.9	0.3	0	0	1.0	0	2.1
Anorexia [§]	16.0	22.2	9.0*	16.0	11.6*	23.1	17.6*	41.2
Any Moderate + Severe	1.5	3.7	0.9	2.8	1.3	1.9	2.0*	13.4
Severe	0	0	0.3	0	0	0	0	2.1
Drowsiness [¶]	43.2	52.8	21.8*	33.0	14.4*	32.7	13.3*	29.9
Any Moderate + Severe	7.7	13.3	2.8*	7.5	3.3	11.0*	1.0*	6.2
Severe	0.3	0	0	0	0	0	0	0
Crying ≥3 hours	0.6	0.9	0.3	0.9	0	1.0	0	1.0

N = Number of evaluable subjects * DTP: whole-cell pertussis DTP vaccine (Sanofi Pasteur Limited) † Significantly less reactogenic than whole-cell DTP vaccine, p<0.05 ‡ Moderate = sustained cry with gentle pressure at injection site; Severe = cries when leg is moved

§ Temperature measurements were axillary ¶ Number of evaluable subjects for DAPTACEL®/DTP = 301/103, 298/102, 257/94 and 207/78 at 2, 4, 6 and 18 months, respectively

• Moderate = more difficulty with settling, even with cuddling; Severe = persistent crying/screeching and inability to console † Moderate = missed one or two feeds; Severe = little or no intake for more than two feeds ‡ Moderate = sleeping more than normal; Severe = sleeping most of the time with difficulty arousing

The US Bridging Study was designed, in part, to assess the safety of DAPTACEL® in infants at 2, 4 and 6 months of age, with routinely recommended, concurrently given childhood vaccines (*Haemophilus influenzae* type b vaccine, OPV and hepatitis B). Fever ≥38°C (100.4°F) was observed in 9.9% - 11.9% of subjects. One febrile seizure occurred within 24 hours post dose 2 immunization (n = 321).²³

Additional adverse reactions evaluated in conjunction with pertussis, diphtheria and tetanus vaccination are as follows:

- As with other aluminum-containing vaccines, a nodule may be palpable at the injection sites for several weeks. Sterile abscess formation at the site of injection has been reported.^{4,19}

Rarely, anaphylactic reactions (i.e., hives, swelling of the mouth, difficulty breathing, hypotension or shock) have been reported after receiving preparations containing diphtheria, tetanus and/or pertussis antigens.⁴

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2-8 hours after an injection), may follow receipt of tetanus toxoid. A few cases of peripheral neuropathy have been reported following tetanus toxoid administration, although the evidence is inadequate to accept or reject a causal relation.²⁴

A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.²⁵ The following illnesses have been temporally associated with some vaccines containing tetanus toxoid: neurological complications²⁶⁻²⁹ including cochlear lesion, brachial plexus neuropathies,³⁰ paralysis of the radial nerve,³¹ paralysis of the recurrent nerve, accommodation paresis and EEG disturbances with encephalopathy (with or without permanent intellectual or motor function impairment).^{32,33} In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.²⁸

DOSEAGE AND ADMINISTRATION: JUST BEFORE USE, SHAKE THE VIAL WELL, until a uniform, cloudy suspension results. WITHDRAW AND INJECT 0.5 mL DOSE. Administer the vaccine intramuscularly (IM), in children younger than 1 year (i.e., infants), the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for IM injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.³

DO NOT administer this product intravenously or subcutaneously.

Immunization Series: A 0.5 mL dose of DAPTACEL® is approved for administration as a 4 dose series at 2, 4 and 6 months of age, at intervals of 6-8 weeks and at 17-20 months of age. The customary age for the first dose is 2 months of age, but it may be given as early as 6 weeks of age and up to the seventh birthday. The interval between the third and fourth dose should be at least 6 months. It is recommended that DAPTACEL® be given for all doses in the series because no data on the interchangeability of DAPTACEL® with other DTPa vaccines exist. At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of DAPTACEL® in children who have previously received 4 doses of DAPTACEL®. DAPTACEL® may be used to complete the immunization series in infants who have received 1 or more doses of whole-cell pertussis DTP. However, the safety and efficacy of DAPTACEL® in such infants have not been fully demonstrated.³

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL® OR ANY OTHER PERTUSSIS-CONTAINING VACCINES. DAPTACEL® should not be combined through reconstitution or mixed with any other vaccine. If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series. Pre-term infants should be vaccinated according to their chronological age from birth.³

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with DAPTACEL®. There is no need to start the series over again, regardless of the time between doses.

STORAGE: DAPTACEL® should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has been exposed to freezing should not be used. Do not use after expiration date.²

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