



BY WILLIAM G. WILKOFF, M.D.

LETTERS FROM MAINE

What's Your Recipe?

Practicing pediatrics is a lot like baking brownies. I've been to enough picnics and to enough potluck suppers to know that everyone likes brownies. And it is clear that every parent wants

quality health care for their children. The problem is that there are lots of ways to make a brownie. Do you like yours more like cake or more like fudge? From scratch or a mix? Nuts? On top or mixed in? Is store-bought in a cellophane bag good enough? Likewise, everyone seems to have his or her own definition of quality health care. Of course you want your child's condition accurately diagnosed and treated with the

most appropriate remedy. Just as chocolate, flour, and sugar are to a brownie, those are the essential ingredients of quality health care. But the ratios between the ingredients and the special additions to the recipe are what make one provider's approach to health care delivery more or less appealing to the appetite of the patients and their families. In our group of four pediatricians, each of us has his or her particular style of de-

livering quality health care. We talk frequently among ourselves and see each other's charts many times during a typical day. We use the same rationale for choosing antibiotics and asthma medications. And, although we try to speak with one voice, we each have our own distinct accent that can put a different spin on the same message.

As the senior member of the group, I tend to rely on my age and an aura of experience to convince the patient's family that I have chosen the diagnosis and treatment wisely. Instead of ordering much lab work or x-rays, I use the unstated "because-I-said-so" rationale. While it's a defense that may not stand up in court, it works more often than not with most families who have chosen me as their primary care provider. I'm sure I don't spend as much time as my partners do explaining anatomy and physiology in great detail... but I do draw a lot of pictures.

But, there are some families for whom lab work and x-rays are part of their definition of quality health care. Just as there are some parents who prefer their medical care with a liberal dose of worry sprinkled on top. They will tend to choose one of my partners who shares their preference for looking at worst-case scenarios.

Please don't hear this as a judgmental observation. I completely understand why some people are comforted by hearing about all the ugly and unlikely possibilities that have been ruled out. It's just not the way I like to bake my brownies.

My usual health care delivery style is the pop-in-the-microwave-ready-to-serve version. I contend that in a blindfolded taste test the consumer couldn't tell the difference between mine and the baked-from-scratch version. It's got the essential ingredients of the correct diagnosis and treatment. And, surprisingly, many working parents with busy lives and overscheduled children like the quick turnaround time in the office. But, not surprisingly, other parents feel more comfortable when they know a diagnosis and treatment plan has baked in the oven for 15 or 20 minutes.

With four pediatricians in our group, the families who choose us can select a primary care provider whose style best fits their preferences.

But occasionally families will ask to see someone other than their primary care provider because on a particular day or with a particular complaint, they feel that a different style would be a better fit for their schedule or their emotional needs.

The challenge for physicians comes when we are on call and the only package on the shelf. Obviously, if there is time, I would like all families to receive the style of care they are most comfortable with. I can still bake them from scratch, add nuts, or make them sweet and fudgy, and I will. The challenge is figuring out just how each family likes its brownies.

DR. WILKOFF practices general pediatrics in a multispecialty group practice in Brunswick, Maine. Write to Dr. Wilkoff at our editorial offices (pdnews@elsevier.com).

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed DAPTACEL®

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 this 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 ACIP, 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.^{1,2} 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.^{5,6,7}

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 DTap vaccine, providers and parents should evaluate the risks and benefits of subsequent doses of whole-cell pertussis DTP or DTap vaccines:²

- Temperature of >40.5°C (105°F) 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.⁸ However, ACIP 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 DTap vaccines according to the recommended schedule.^{1,3,4}

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.^{2,9}

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 ACIP has issued guidelines for such children.¹⁰

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 non-hospital settings, including proper airway management.^{1,11}

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.⁴ Pertussis-containing vaccines are not contraindicated in persons with HIV infection.⁷

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 DOSAGE 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 DOSAGE 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, 3,694 children received a total of 3 doses and 476 children received 4 doses of DAPTACEL®.^{12,13,14,15,16,17,18}

In the Sweden I Efficacy Trial, information on systemic and local reactions were recorded on 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. 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.¹²

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<0.0001; DAPTACEL® versus DT ††Rectal temperature

†† Statistical comparisons were not made for this variable DT: Swedish National Biologics Laboratories DTP: Aventis Pasteur Inc.

In patients who received DAPTACEL®, the incidence rates per 1,000 doses of rectal temperature >40°C (104°F) within 48 hours of vaccination was 0.39 following dose 1 and dose 2 and the incidence of persistent crying >3 hours within 24 hours of vaccination was 1.16 and 0.39 following dose 1 and 2, respectively.

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.^{12,13}

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®. Local and systemic adverse events were consistently less common in DAPTACEL® recipients at 2, 4, 6 and 17-18 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 2^{13,18} 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								
Any	12.7*	44.4	20.6*	57.5	22.2*	51.9	36.5*	55.7
>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								
Any	4.3*	23.1	4.3*	32.1	4.7*	25.0	18.6*	28.9
>10 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								
Any	10.2*	37.0	7.5*	51.9	8.8*	48.1	23.9*	86.6
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 [†]								
Any ≥37.5°C (99.5°F)	12.0*	43.7	7.7*	50.0	14.8*	53.2	14.5*	67.9
>38°C (100.4°F)	0.7	1.9	0*	7.8	1.2*	11.7	1.9*	17.9
>40°C (104°F)	0.3	0	0	1.0	0	1.1	0	0
Irritability ^{††}								
Any	41.0*	65.7	41.4*	68.9	40.9*	67.3	36.9*	79.4
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 [‡]								
Any	16.0	22.2	9.0*	16.0	11.6*	23.1	17.6*	41.2
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 [§]								
Any	43.2	52.8	21.8*	33.0	14.4*	32.7	13.3*	29.9
Moderate + Severe	7.7	8.3	2.8*	7.5	1.3	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 (Aventis 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/screaming and inability to console †‡ Moderate = missed one or two feeds; Severe = little or no intake for more than two feeds § Moderate = sleeping much 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). The incidence of redness, swelling, pain or tenderness at the injection site after each dose was 12.5% - 18.7%, 14.3% - 17.8%, and 15.9% - 30.5% respectively. Fever >38°C (100.4°F) was observed in 9.9% - 11.9% of subjects. One afebrile seizure occurred within 24 hours post dose immunization (n = 321).¹³

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

Anaphylaxis-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.²⁰

A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.²¹ The following illnesses have been reported as temporally associated with some vaccines containing tetanus toxoid: neurological complications^{22,23} including cochlear lesion, brachial plexus neuropathies,²⁴ paralysis of the radial nerve,²⁰ paralysis of the recurrent nerve, accommodation paresis and EEG disturbances with encephalopathy (with or without permanent intellectual or motor function impairment).^{25,26} In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanospasmodin should be considered as a possible etiology.²⁵

DOSAGE AND ADMINISTRATION: JUST BEFORE USE, SHAKE THE VIAL WELL, until a uniform cloudy suspension results. WITHDRAW AND INJECT A 0.5 mL DOSE. Administer the vaccine intramuscularly (I.M.). In the infant, 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 I.M. injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

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 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 DTap 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®.²⁷ 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.²

PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL® OR ANY OTHER PERTUSSIS-CONTAINING VACCINES.³ 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.

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.

REFERENCES:

1. American Academy of Pediatrics. In: Pickering LK, ed. 2000 Red Book: Report on the Committee of Infectious Diseases. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2001:17-31, 35-51, 53-54, 65-68, 440-445, 759-765. 2. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children. MMWR 1997;46(RR-7):1-25. 3. Recommendations of the Advisory Committee on Immunization Practices (ACIP). General recommendations on immunization. MMWR 1994;43(RR-1):1-38. 4. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Diphtheria, Tetanus, and Pertussis: Recommendations for vaccine use and other preventive measures. MMWR 1991;40(RR-10):1-28. 5. Expanded programme on immunization, injection and paralytic poliomyelitis. Wkly Epidemiol Rec 1980;5:38-40. 6. Sutter RW, et al. Attributable risk of DTP (diphtheria and tetanus toxoids and pertussis vaccine) injection in provoking paralytic poliomyelitis during a large outbreak in Oman. J Infect Dis 1992;165:444-449. 7. Christie AB. Infectious diseases: Epidemiology and Clinical Practice. 4th ed. Edinburgh, Churchill Livingstone; 1987:2:817-825. 8. Livenwood JR, et al. Family history of convulsion and use of pertussis vaccine. J Pediatr 1989;115(4):527-531. 9. ACIP General Recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002; 51 (RR-02): 1-36. 10. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Update: Vaccine side effects, adverse reactions, contraindications, and precautions. MMWR 1996;45(RR-12):1-35. 11. National Advisory Committee on Immunization (NACI). Canadian Immunization Guide, 5th ed. Minister of Public Works and Government Services Canada; 1998: 9-13,133-139. 12. Gustafsson L