

# CLINICAL CAPSULES

## More Miss Day Care With Rotavirus

Rotavirus is a common cause of gastroenteritis that, in a review of 284 cases, was significantly more likely to keep children younger than 3 years of age away from day care, compared with nonrotavirus gastroenteritis.

A total of 115 cases (40%) were confirmed rotavirus infections. Overall, 70% of children with rotavirus gastroenteritis missed at least 1 day of day care, compared with 55% of children with nonrotavirus gastroenteritis, reported Dr. Susan E. Coffin of the University of Pennsylvania, Philadelphia, and her colleagues (Pediatr. Infect. Dis. J. 2006;25:584-9).

Children aged 7-12 months were the hardest hit; 54% of both the 7- to 9-month-olds and the 10- to 12-month-olds had rotavirus infections. By contrast, nonrotavirus infections peaked in children aged 4-6 months (72%).

The researchers collected stool samples from children with acute gastroenteritis at five urban and suburban pediatric practices during the winter-to-spring seasons of 2002-2003 and 2003-2004. The study was supported by Merck and Co.

Children with rotavirus infections were significantly more likely than those with nonrotavirus infections to exhibit vomiting (83% vs. 66%), a combination of diarrhea and vomiting (75% vs. 50%), or fever (60% vs. 43%).

Rotavirus had a significant impact on parents, too. Parents or guardians of the children with rotavirus were significantly more likely to miss at least 1 day of work than parents of children with nonrotavirus infections (62% vs. 40%).

The proportion of children who needed additional medical care, including hospitalization, was similar among both rotavirus and nonrotavirus cases.

## Extreme Fevers May Merit Antibiotics

Children with very high fevers are at increased risk for both bacterial and viral illness, and clinical features don't reliably distinguish between the two conditions.

Dr. Barbara W. Trautner of Baylor College of Medicine, Houston, and her colleagues identified 103 cases of hyperpyrexia—defined as a rectal temperature of 106 ° F or higher—in a review of 130,828 patient visits (1 case per 1,270 visits).

The researchers found that 20 of these children (19%) had serious bacterial infections and 22 (21.4%) had laboratory-confirmed viral illness (Pediatrics 2006;118:34-40).

About a third of the children (35%) had fevers that lasted longer than 48 hours, and the cause of the fever was unknown in 60 children (58%).

The incidence of serious bacterial infection in children with underlying illnesses was more than double that in children without underlying illness (37% vs. 16%). But no other factors, including age and maximum temperature, were significantly predictive of serious bacterial infection compared with viral infection. Notably, the differences in white blood cell counts were not significant enough to be helpful in distinguishing bacterial vs. viral illness, although the median WBC was insignificantly higher in cases of viral illness.

The increased use of rapid testing continues to raise awareness of bacterial and viral coinfection, but only one child of 103 had a coinfection, which suggests that a positive rapid viral test alone may not be sufficient to rule out treatment with antibiotics.

## Bocavirus and Respiratory Illness

Human bocavirus DNA was identified in 82 (5.6%) of 1,474 nasal specimens from children with upper and lower respiratory tract infections collected over a 20-month period in a San Diego children's hospital.

The prevalence of the human bocavirus (HBoV) infections peaked at 14% between March and May in both 2004 and 2005, although the reason for the spring peak was unclear, reported Dr. John C. Arnold of Children's Hospital, San Diego, and his colleagues. The study included children up to age 18 years, but most (63%) were less than 1 year old (Clin. Infect. Dis. 2006;43:283-8).

The researchers reviewed the records of 68 (83%) of the 82 patients with HBoV to discover the clinical characteristics associated with the infection in children. They found underlying illnesses in 21 (31%) children including 11 patients with asthma and 7 patients with neuromuscular disorders.

Cough was the most common symptom, based on data from 54 patients with no obvious coinfections or detectable viral antigens. Cough occurred in 46 (85%) of these children, and 10 (19%) had coughs described as "paroxysmal." A total of 33 patients (62%) showed clinical signs of lower respiratory tract infections, and bronchiolitis was the most common diagnosis (26%). Difficulty breathing, nasal congestion, fever, and diarrhea were also common in patients with HBoV, and five patients had a rash.

—Heidi Splette

## 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.<sup>1</sup>

**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.<sup>2</sup>

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

- 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.<sup>1,3</sup> However, children with moderate or severe illness should not be immunized until recovered.<sup>4</sup>

Elective immunization procedures should be deferred during an outbreak of poliomyelitis because of the risk of provoking paralysis.<sup>5,6,7</sup>

**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:<sup>2</sup>

- 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.<sup>4</sup>

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.<sup>8</sup> 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.<sup>1,3,4</sup>

For infants or children at higher risk for seizures than the general population, an appropriate antipyretic 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.<sup>2,9</sup>

Whether to administer DAPTACEL® to children with preexisting 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.<sup>10</sup>

**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.<sup>1,11</sup>

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.<sup>4</sup> Pertussis-containing vaccines are not contraindicated in persons with HIV infection.<sup>7</sup>

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 (I.M.) 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 discontinued, it seems reasonable to defer immunization until the patient has been on therapy for one month; otherwise, the patient should be vaccinated while still on therapy.<sup>4</sup>

If DAPTACEL® is administered to persons with an immunodeficiency disorder, an 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.<sup>2</sup>

**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 and 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 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.<sup>12</sup>

**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
<b>Local</b>									
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
<b>Systemic</b>									
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<0.005: 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 3 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 5 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.<sup>12,13</sup>

Rates of serious adverse events that are less common than those reported in the Sweden 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 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 2<sup>13,16</sup>**  
**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
<b>Local</b>								
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
<b>Systemic</b>								
Fever††								
Any	12.0*	43.7	7.7*	50.0	14.8*	53.2	14.5*	67.9
≥38°C (100.4°F)	0.7	19.9	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‡								
Moderate + Severe	16.0	22.2	9.0*	26.0	11.6*	23.1	17.6*	41.2
Severe	1.5	3.7	0.9	2.8	1.3	2.0	3.0*	13.4
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*	8.2
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/scrolling 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% - 19.7%, 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 2 immunization (n = 321).<sup>13</sup>

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.<sup>4,19</sup>

- 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.<sup>4</sup>

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.<sup>20</sup>

A review by the Institute of Medicine (IOM) found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré syndrome.<sup>21</sup> The following illnesses have been reported as temporally associated with some vaccines containing tetanus toxoid: neurological complications<sup>22,23</sup> including cochlear lesion, brachial plexus neuropathies,<sup>24</sup> paralysis of the radial nerve,<sup>25</sup> paralysis of the recurrent nerve, accommodation paresis and EEG disturbances with encephalopathy (with or without permanent intellectual or motor function impairment).<sup>25-28</sup> In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.<sup>28</sup>

**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 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 I.M. injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.<sup>1</sup>

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 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 DTP 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®.<sup>27</sup> 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.<sup>2</sup>

**PERSONS 7 YEARS OF AGE AND OLDER SHOULD NOT BE IMMUNIZED WITH DAPTACEL® OR ANY OTHER PERTUSSIS-CONTAINING VACCINES.<sup>2</sup> 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.<sup>1</sup>**

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;17:1-35,51-53,54,65,68,440-445,759-765. 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):1-36. 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. W