

DTaP-HepB-IBV Can Be Given With Hib, PCV-7

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Coadministering the seven-valent pneumococcal conjugate vaccine and a *Haemophilus influenzae* type b conjugate vaccine with the pentavalent diphtheria, tetanus, acellular pertussis, hepatitis B, and polio combination vaccine in infants does not compromise the safety and immunogenicity of the latter vaccine, a study has shown.

Previous studies have demonstrated comparable safety and immunogenicity of both the pentavalent vaccine containing diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, and inactivated poliovirus vaccines (DTaP-HepB-IPV) and the separate administration of the component vaccines when the *H. influenzae* type b vaccine (Hib) is administered to both groups. However, the coadministration of the seven-valent pneumococcal conjugate vaccine (PCV-7) with separate DTaP, Hib, HepB,

and IBV vaccines has been linked with inconsistencies in immunologic responses, Dr. Michael E. Pichichero of the University of Rochester (N.Y.) and his colleagues said (J. Pediatr. 2007;151:43-9).

To compare the immunogenic impact of coadministration of the PCV-7 and Hib vaccines with the combined DTaP-HepB-IPV vaccine to that achieved via separate administration of all component vaccines, the investigators enrolled a total of 575 healthy infants from 22 U.S. sites into the

current study and randomly assigned them to one of three conditions: Combination Vaccine Group (DTaP-HepB-IPV plus PCV-7 and Hib), Separate Vaccine Group, or Staggered Vaccine Group (DTaP-HepB-IPV plus Hib, with PCV-7 administered 2 weeks later). The vaccines were administered at each of the three primary immunization visits at 2, 4, and 6 months of age.

With respect to diphtheria, tetanus, pertussis, and poliovirus antibody responses, the immunogenicity of the combination vaccine

RotaTeq® [Rotavirus Vaccine, Live, Oral, Pentavalent]

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS

A demonstrated history of hypersensitivity to any component of the vaccine. Infants who develop symptoms suggestive of hypersensitivity after receiving a dose of RotaTeq should not receive further doses of RotaTeq.

PRECAUTIONS

General: Prior to administration of RotaTeq, the health care provider should determine the current health status and previous vaccination history of the infant, including whether there has been a reaction to a previous dose of RotaTeq or other rotavirus vaccine. Febrile illness may be reason for delaying use of RotaTeq except when, in the opinion of the physician, withholding the vaccine entails a greater risk. Low-grade fever (<100.5°F [38.1°C]) itself and mild upper respiratory infection do not preclude vaccination with RotaTeq. The level of protection provided by only one or two doses of RotaTeq was not studied in clinical trials. As with any vaccine, vaccination with RotaTeq may not result in complete protection in all recipients. Regarding post-exposure prophylaxis, no clinical data are available for RotaTeq when administered after exposure to rotavirus.

Intussusception: Following administration of a previously licensed live rhesus rotavirus-based vaccine, an increased risk of intussusception was observed. In REST (n=69,625), the data did not show an increased risk of intussusception for RotaTeq when compared to placebo. In post-marketing experience, cases of intussusception have been reported in temporal association with RotaTeq. See ADVERSE REACTIONS, Intussusception and Post-marketing Reports.

Immunocompromised Populations: No safety or efficacy data are available for the administration of RotaTeq to infants who are potentially immunocompromised including: Infants with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; Infants on immunosuppressive therapy (including high-dose systemic corticosteroids). RotaTeq may be administered to infants who are being treated with topical corticosteroids or inhaled steroids; Infants with primary and acquired immunodeficiency states, including HIV/AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. There are insufficient data from the clinical trials to support administration of RotaTeq to infants with indeterminate HIV status who are born to mothers with HIV/AIDS; Infants who have received a blood transfusion or blood products, including immunoglobulins within 42 days. No safety or efficacy data are available for administration of RotaTeq to infants with a history of gastrointestinal disorders including infants with active acute gastrointestinal illness, infants with chronic diarrhea and failure to thrive, and infants with a history of congenital abdominal disorders, abdominal surgery, and intussusception. Therefore, caution is advised when considering administration of RotaTeq to these infants.

Shedding and Transmission: Shedding was evaluated among a subset of subjects in REST 4 to 6 days after each dose and among all subjects who submitted a stool antigen rotavirus positive sample at any time. RotaTeq was shed in the stools of 32 of 360 (8.9%, 95% CI (6.2%, 12.3%)) vaccine recipients tested after dose 1; 0 of 249 (0.0%, 95% CI (0.0%, 1.5%)) vaccine recipients tested after dose 2; and in 1 of 385 (0.3%, 95% CI (<0.1%, 1.4%)) vaccine recipients after dose 3. In phase 3 studies, shedding was observed as early as 1 day and as late as 15 days after a dose. Transmission was not evaluated. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient close contacts such as: Individuals with malignancies or who are otherwise immunocompromised; or Individuals receiving immunosuppressive therapy. There is a theoretical risk that the live virus vaccine can be transmitted to non-vaccinated contacts. The potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus.

Information for Parents/Guardians: Parents or guardians should be given a copy of the required vaccine information and be given the "Patient Information" appended to the Prescribing Information. Parents and/or guardians should be encouraged to read the patient information that describes the benefits and risks associated with the vaccine and ask any questions they may have during the visit. See PRECAUTIONS and Patient Information.

Drug Interactions: Immunosuppressive therapies including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. For administration of RotaTeq with other vaccines, see DOSAGE AND ADMINISTRATION, Use with Other Vaccines in the Prescribing Information.

Carcinogenesis, Mutagenesis, Impairment of Fertility: RotaTeq has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

Pediatric Use: Safety and efficacy have not been established in infants less than 6 weeks of age or greater than 32 weeks of age. Data are available from clinical studies to support the use of RotaTeq in pre-term infants according to their age in weeks since birth. (See ADVERSE REACTIONS, Safety in Pre-Term Infants.) Data are available from clinical studies to support the use of RotaTeq in infants with controlled gastroesophageal reflux disease.

ADVERSE REACTIONS

71,725 infants were evaluated in 3 placebo-controlled clinical trials including 36,165 infants in the group that received RotaTeq and 35,560 infants in the group that received placebo. Parents/guardians were contacted on days 7, 14, and 42 after each dose regarding intussusception and any other serious adverse events. The racial distribution was as follows: White (69% in both groups); Hispanic-American (14% in both groups); Black (8% in both groups); Multiracial (5% in both groups); Asian (2% in both groups); Native American (RotaTeq 2%, placebo 1%), and Other (<1% in both groups). The gender distribution was 51% male and 49% female in both vaccination groups. Because clinical trials are conducted under conditions that may not be typical of those observed in clinical practice, the adverse reaction rates presented below may not be reflective of those observed in clinical practice.

Serious Adverse Events: Serious adverse events occurred in 2.4% of recipients of RotaTeq when compared to 2.6% of placebo recipients within the 42-day period of a dose in the phase 3 clinical studies of RotaTeq. The most frequently reported serious adverse events for RotaTeq compared to placebo were: bronchiolitis (0.6% RotaTeq vs. 0.7% Placebo), gastroenteritis (0.2% RotaTeq vs. 0.3% Placebo), pneumonia (0.2% RotaTeq vs. 0.2% Placebo), fever (0.1% RotaTeq vs. 0.1% Placebo), and urinary tract infection (0.1% RotaTeq vs. 0.1% Placebo).

Deaths: Across the clinical studies, 52 deaths were reported. There were 25 deaths in the RotaTeq recipients compared to 27 deaths in the placebo recipients. The most commonly reported cause of death was sudden infant death syndrome, which was observed in 8 recipients of RotaTeq and 9 placebo recipients.

Intussusception: In REST, 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of intussusception at 7, 14, and 42 days after each dose, and every 6 weeks thereafter for 1 year after the first dose. For the primary safety outcome, cases of intussusception occurring within 42 days of any dose, there were 6 cases among RotaTeq recipients and 5 cases among placebo recipients (see Table 1). The data did not suggest an increased risk of intussusception relative to placebo.

	RotaTeq (n=34,837)	Placebo (n=34,788)
Confirmed intussusception cases within 42 days of any dose	6	5
Relative risk (95% CI) [†]	1.6 (0.4, 6.4)	
Confirmed intussusception cases within 365 days of dose 1	13	15
Relative risk (95% CI)	0.9 (0.4, 1.9)	

[†]Relative risk and 95% confidence interval based upon group sequential design stopping criteria employed in REST.

Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period after the first dose, which was the period of highest risk for the rhesus rotavirus-based product (see Table 2).

Day Range	Dose 1		Dose 2		Dose 3		Any Dose	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
1-7	0	0	1	0	0	0	1	0
1-14	0	0	1	0	0	1	1	1
1-21	0	0	3	0	0	1	3	1
1-42	0	1	4	1	2	3	6	5

All of the children who developed intussusception recovered without sequelae with the exception of a 9-month-old male who developed intussusception 98 days after dose 3 and died of post-operative sepsis. There was a single case of intussusception among 2,470 recipients of RotaTeq in a 7-month-old male in the phase 1 and 2 studies (716 placebo recipients).

Hematochezia: Hematochezia reported as an adverse experience occurred in 0.6% (39/6,130) of vaccine and 0.6% (34/5,560) of placebo recipients within 42 days of any dose. Hematochezia reported as a serious adverse experience occurred in <0.1% (4/36,150) of vaccine and <0.1% (7/35,536) of placebo recipients within 42 days of any dose.

Seizures: All seizures reported in the phase 3 trials of RotaTeq (by vaccination group and interval after dose) for RotaTeq compared to placebo, respectively, were: days 1-7 (10 vs. 5), days 1-14 (15 vs. 8), and days 1-42 (33 vs. 24). Seizures reported as serious adverse experiences occurred in <0.1% (27/36,150) of vaccine and <0.1% (18/35,536) of placebo recipients (not significant). Ten febrile seizures were reported as serious adverse experiences, 5 were observed in vaccine recipients and 5 in placebo recipients.

Most Common Adverse Events

Solicited Adverse Events: Detailed safety information was collected from 11,711 infants (6,138 recipients of RotaTeq) which included a subset of subjects in REST and all subjects from Studies 007 and 009 (Detailed Safety Cohort). A Vaccination Report Card was used by parents/guardians to record the child's temperature and any episodes of diarrhea and vomiting on a daily basis during the first week following each vaccination. Table 3 summarizes the frequencies of these adverse events and irritability.

Adverse experience	Dose 1		Dose 2		Dose 3	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
Elevated temperature*	17.1% n=6,130	16.2% n=5,077	20.0% n=5,215	19.4% n=4,725	18.2% n=4,865	17.6% n=4,382
Vomiting	6.7%	5.4%	5.0%	4.4%	3.6%	3.2%
Diarrhea	10.4%	9.1%	8.6%	6.4%	6.1%	5.4%
Irritability	7.1%	7.1%	6.0%	6.5%	4.3%	4.5%

*Temperature $\geq 100.5^\circ\text{F}$ [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures

Other Adverse Events: Parents/guardians of the 11,711 infants were also asked to report the presence of other events on the Vaccination Report Card for 42 days after each dose. Fever was observed at similar rates in vaccine (N=6,138) and placebo (N=5,573) recipients (42.6% vs. 42.8%). Adverse events that occurred at a statistically higher incidence (ie, 2-sided p-value <0.05) within the 42 days of any dose among recipients of RotaTeq (N=6,138) as compared with placebo (N=5,573) recipients, respectively, include: diarrhea (24.1% [n=1,479] vs. 21.3% [n=1,186]), vomiting (15.2% [n=929] vs. 13.6% [n=758]), otitis media (14.5% [n=887] vs. 13.0% [n=724]), nasopharyngitis (6.9% [n=422] vs. 5.8% [n=325]), and bronchospasm (1.1% [n=66] vs. 0.7% [n=40]).

Safety in Pre-Term Infants: RotaTeq or placebo was administered to 2,070 pre-term infants (25 to 36 weeks gestational age, median 34 weeks) according to their age in weeks since birth in REST. All pre-term infants were followed for serious adverse experiences; a subset of 308 infants was monitored for all adverse experiences. There were 4 deaths throughout the study, 2 among vaccine recipients (1 SIDS and 1 motor vehicle accident) and 2 among placebo recipients (1 SIDS and 1 unknown cause). No cases of intussusception were reported. Serious adverse experiences occurred in 5.5% of vaccine and 5.8% of placebo recipients. The most common serious adverse experience was bronchiolitis, which occurred in 1.4% of vaccine and 2.0% of placebo recipients. Parents/guardians were asked to record the child's temperature and any episodes of vomiting and diarrhea daily for the first week following vaccination. The frequencies of these adverse experiences and irritability within the week after dose 1 are summarized in Table 4.

Adverse event	Dose 1		Dose 2		Dose 3	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
Elevated temperature*	18.1% N=127	17.3% N=133	25.0% N=124	28.1% N=121	14.8% N=115	20.4% N=108
Vomiting	5.8%	7.8%	2.9%	2.2%	4.4%	4.7%
Diarrhea	6.5%	5.8%	7.3%	7.3%	3.7%	3.9%
Irritability	3.9%	5.2%	2.9%	4.4%	8.1%	5.4%

*Temperature $\geq 100.5^\circ\text{F}$ [38.1°C] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures

Post-marketing Reports: The following adverse events have been identified during post-approval use of RotaTeq from reports to the Vaccine Adverse Event Reporting System (VAERS). Reporting of adverse events following immunization to VAERS is voluntary, and the number of doses of vaccine administered is not known; therefore, it is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to vaccine exposure using VAERS data. In post-marketing experience, the following adverse events have been reported in infants who have received RotaTeq: **Gastrointestinal** – Intussusception, Hematochezia.

Reporting Adverse Events: Parents or guardians should be instructed to report any adverse events to their health care provider. Health care providers should report all adverse events to the US Department of Health and Human Services' Vaccine Adverse Events Reporting System (VAERS). VAERS accepts all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report on line to www.vaers.hhs.gov.

For more detailed information, please read the Prescribing Information. RotaTeq is a registered trademark of Merck & Co., Inc.

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Immunogenicity of the combination vaccine was at least as good as that achieved with separate vaccines.

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coadministered with Hib and PCV-7 "was at least as good as" that achieved with the separate and staggered vaccine schemes, the investigators reported. Additionally, the three groups achieved similar rates of seroprotection for HepB and Hib, and seropositivity for PCV-7 was high in all groups.

Although there were significantly higher rates of fever observed in the combination group, compared with both other groups, "there were no significant differences in rates of fever at or above 102.2° F [39.0° C], and the fevers were short in duration," the authors said. Additionally, while the rates of irritability and some local swelling were higher with the combination vaccine, there were no group differences in the rates of symptoms for which parents sought medical advice, they said.

Chlamydia Screening Guides Closer to Agreement

Updated U.S. Preventive Services Task Force guidelines on chlamydial infection detection recommend screening all sexually active, nonpregnant women aged 24 years and younger, as well as older women at increased risk and all pregnant women aged 24 years and younger.

The guidelines, which were last published in 2001, do not recommend screening older women, regardless of pregnancy, if they are not at increased risk. The task force stated that there is not enough evidence to make a recommendation regarding the screening of men.

The updated recommendations are similar to those of the American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, and the Centers for Disease Control and Prevention, with the difference that these organizations recommend screening for women aged 25 years and younger.

The updated document can be found at www.ahrq.gov/clinic/uspstf07/chlamydia/chlamydiars.htm.

—Leanne Sullivan