

Exclusivity Program Has Mixed Economic Results

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As an incentive for pharmaceutical companies to conduct clinical trials in children, the Pediatric Exclusivity Program yields variable results, ranging from a generous economic net gain to a net loss, according to a study by Dr. Jennifer Li of Duke Clinical Research Institute, Durham, N.C., and colleagues (JAMA 2007;297:480-8).

Most drugs receive marketing approval in the United States based on clinical trials performed only in an adult population, although the drugs are often used to treat children. The Pediatric Exclusivity Program was designed to encourage pharmaceutical companies to obtain data concerning dosing, safety, and efficacy of marketed drugs in children. Written requests from the Food and Drug Administration specify the number of studies, the indication, sample sizes, and trial designs.

In exchange for performing the requested pediatric studies, the pharmaceutical company receives an additional 6 months of marketing exclusivity.

The Best Pharmaceuticals for Children Act of 2002, which created the Pediatric Exclusivity Program, is due for renewal this year. However, despite its success in generating much-needed data on safety and efficacy of drugs given to children, the program has been criticized for providing "windfall" profits to the pharmaceutical

industry. Dr. Li and her colleagues evaluated the economic return from marketing exclusivity in a subset of nine drugs that were granted pediatric exclusivity.

During 2002-2004, a total of 59 products received pediatric exclusivity. Of these, 13 (22%) were considered "blockbuster" drugs, with annual sales in the United States in excess of \$1 billion. Median annual sales revenue from the 59 products was considerably lower, at \$181.3 million, and 23 products had annual sales revenue under \$150 million.

The investigators classified the 59 products into nine therapeutic areas and selected one drug from each category for evaluation.

The indications for the nine selected drugs were asthma, tumors, attention-deficit/hyperactivity disorder, diabetes mellitus, gastroesophageal reflux, bacterial infection, and bone mineralization. The selection was heavily weighted toward products that were expected to yield a high economic return, with five "blockbusters" among the nine drugs.

Costs to the pharmaceutical companies in coordinating the clinical trials were estimated from information culled from the final clinical study reports. The estimated costs did not include costs of regulatory filings, costs of juvenile preclinical studies, or costs associated with development of special formulations for pediatric use.

Estimates of after-tax cash inflow over a 6-month period of extended patent protection were extrapolated from market sales data from the previous 3 years. For each of the nine drugs, the investigators calculated the net economic return by subtracting the estimated after-tax cash outflow resulting from the requested pediatric trials from the after-tax cash inflow projected over a 6-month period of extended patent protection.

In the group of nine drugs, 16 efficacy studies, 10 pharmacokinetic studies, and 1 safety study were performed in response to written requests. Median cost per written request was estimated to be \$12.3 million (range, \$5.1 million-\$43.8 million).

Eight of the nine drugs underwent a labeling change as a result of the clinical trials conducted under pediatric exclusivity. "Importantly, several were associated with substantial safety concerns and lack of effectiveness in the pediatric population," wrote Dr. Li and colleagues.

For 6 months' market exclusivity, the median net economic benefit for the nine drugs was estimated to be \$134,265,456, ranging from a loss of \$8,946,033 to a gain of \$507,899,374, with a net return:cost ratio ranging from -0.68 to 73.63. With a 3-month market exclusivity, the median net economic return decreased to \$64,041,833, ranging from a loss of \$11,088,214 to a gain of \$250,500,635. The net return:cost ratio decreased to a range of -0.84 to 36.31.

The investigators predicted that the reduction of marketing protection from 6 to 3 months would likely dissuade pharmaceutical companies from requesting pediatric exclusivity for products that were unlikely to generate a high economic return.

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.

Table 1

Confirmed cases of intussusception in recipients of RotaTeq as compared with placebo recipients during REST

	RotaTeq (n=34,837)	Placebo (n=34,788)
Confirmed intussusception cases within 42 days of any dose	6	5
Relative risk (95% CI) ¹	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)	

¹Relative 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).

Table 2
Intussusception cases by day range in relation to dose in REST

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.

Table 3

Solicited adverse experiences within the first week after doses 1, 2, and 3 (Detailed Safety Cohort)

Adverse experience	Dose 1		Dose 2		Dose 3	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
Elevated temperature*	17.1%	16.2%	20.0%	19.4%	18.2%	17.6%
	n=6,130	n=5,560	n=5,703	n=5,173	n=5,496	n=4,989
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.

Table 4

Solicited adverse experiences within the first week of doses 1, 2, and 3 among pre-term infants

Adverse event	Dose 1		Dose 2		Dose 3	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
Elevated temperature*	18.1%	17.3%	25.0%	28.1%	14.8%	20.4%
	N=154	N=154	N=137	N=137	N=135	N=129
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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