



BY WILLIAM G. WILKOFF, M.D.

switch allegiances based on my gut response to a candidate's stated position, his

## LETTERS FROM MAINE

# A Vote for a Vaccine Czar

**N**o one who knows me well would ever describe me as a political animal. As a registered Independent, I

voting record... and, of course, his or her hairstyle and sartorial choices. When forced to choose based solely on the issues, I tend to side with those who claim that less government is better. However, from time to time, this attitude of "just leave us alone and we'll sort it out ourselves" just doesn't work. A frightening example in which market forces and communal altruism have failed us is the current shambles we have made

of our national vaccine program.

I had already begun to write this letter when Dr. Michael Pichichero's I.D. Consult column appeared in the February issue of PEDIATRIC NEWS ("Feds Should Help Bring Vaccines to U.S. Market"). He knows far more than I do about the details of how the system works and fails. And, he offers some rational solutions to at least some of the problems. But I can't resist the temptation to add my less knowledgeable

and more emotional 2 cents' worth to his observations.

First, let me restate his frustration and concern about the current state of our vaccine supplies. While I admit that when it comes to remembering PIN numbers and passwords, age has taken its toll on my memory, I think I still qualify for a "pretty sharp" rating in most categories. But I have thrown in the towel when it comes to keeping up to date with the latest recommended vaccine schedule and its many addenda.

I now rely totally on our nurses to compare the patient's immunization records with the newest guidelines and our fluctuating vaccine supply and then come up with the best fit. The process is so time consuming for our clinical staff that I routinely room more than 50% of my patients. The patients and their parents may at times be flattered when the doctor summons them from the waiting room himself. And it does add a bit more of a homey quality to our medical home. But clearly it is not the most efficient way of providing medical care.

Vaccine costs and the inscrutable, unscrupulous, and variable reimbursement practices of the third-party payers has left us gun-shy when it comes to adding new vaccines to our offerings. We stay clear of the cutting edge of vaccine technology to avoid being shredded to ribbons and left holding a very expensive bag of immunizations. As someone who remembers when *Haemophilus influenzae* meningitis sat at the top of the rule-out diagnoses for a young child with fever, the Hib vaccine shortage makes me very nervous.

It is clear to even the less-government-is-better folks like myself that the federal government must step into the arena and ensure that vaccines are not only safe, but available. It must also create and maintain sufficient financial incentives to keep the private sector enthusiastic about vaccine research and development.

Regardless of whom we elect this November, the year 2009 should provide an excellent opportunity for change. Dr. Pichichero's recommendations take advantage of the current system, but I think we need to think bigger. Let's raise vaccine supply and safety issues to the cabinet level.

It's time for a Vaccine Czar, a Godfather (or Godmother) of Immunization. Someone who has the president's ear every day. Someone armed with a sharp knife that cuts red tape like warm butter. Someone who carries a big stick to whack the kneecaps of the insurance companies. And someone with an ample supply of carrots to keep the pharmaceutical companies drooling for the profits of newly developed vaccines.

I fell under the spell of Obama Charisma many months ago, but I think any of the top candidates can be convinced that vaccine supply is a critical issue. We just need to start yelling louder and they'll hear us.

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### 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.

#### WARNINGS AND PRECAUTIONS

**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 data are available regarding potential vaccine virus transmission from vaccine recipient to nonvaccinated household or other contacts [See Shedding and Transmission].

**Gastrointestinal Illness:** 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. Caution is advised when considering administration of RotaTeq to these infants.

**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, Clinical Studies Experience and Post-Marketing Experience.

**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. RotaTeq is a solution of live reassortant rotaviruses and can potentially be transmitted to persons who have contact with the vaccine. The potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus.

**Febrile Illness:** 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.

**Incomplete Regimen:** The clinical studies were not designed to assess the level of protection provided by only one or two doses of RotaTeq.

**Limitations of Vaccine Effectiveness:** RotaTeq may not protect all vaccine recipients against rotavirus.

**Post-Exposure Prophylaxis:** No clinical data are available for RotaTeq when administered after exposure to rotavirus.

#### ADVERSE REACTIONS

**Clinical Studies Experience:** 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) <sup>†</sup>		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)

<sup>†</sup>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).

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).

\*Rotavirus Efficacy and Safety Trial

**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.

**Kawasaki Disease:** In the phase 3 clinical trials, infants were followed for up to 42 days of vaccine dose. Kawasaki disease was reported in 5 of 36,150 vaccine recipients and in 1 of 35,536 placebo recipients with unadjusted relative risk 4.9 (95% CI 0.6, 239.1).

#### 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*	n=5,616 17.1%	n=5,077 16.2%	n=5,215 20.0%	n=4,725 19.4%	n=4,865 18.2%	n=4,382 17.6%
Vomiting	n=6,130 6.7%	n=5,560 5.4%	n=5,703 5.0%	n=5,173 4.4%	n=5,496 3.6%	n=4,989 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  $\geq 100.5^\circ\text{F}$  [ $38.1^\circ\text{C}$ ] 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*	N=127 18.1%	N=133 17.3%	N=124 25.0%	N=121 28.1%	N=115 14.8%	N=108 20.4%
Vomiting	N=154 5.8%	N=154 7.8%	N=137 2.9%	N=137 2.2%	N=135 4.4%	N=129 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  $\geq 100.5^\circ\text{F}$  [ $38.1^\circ\text{C}$ ] rectal equivalent obtained by adding 1 degree F to otic and oral temperatures and 2 degrees F to axillary temperatures

**Post-Marketing Experience:** 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 disorders*—Intussusception, Hematochezia. *Skin and subcutaneous tissue disorders*—Urticaria. *Infections and infestations*—Kawasaki disease.

**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.

#### 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.

**Concomitant Vaccine Administration:** In clinical trials, RotaTeq was administered concomitantly with diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus vaccine (IPV), H. influenzae type b conjugate (Hib), hepatitis B vaccine, and pneumococcal conjugate vaccine [see CLINICAL STUDIES]. The safety data available are in the ADVERSE REACTIONS section [see Clinical Studies Experience].

There was no evidence for reduced antibody responses to the diphtheria or tetanus toxoid components of DTaP or to the other vaccines that were concomitantly administered with RotaTeq. However, insufficient immunogenicity data are available to confirm lack of interference of immune responses when RotaTeq is concomitantly administered with childhood vaccines to prevent pertussis.

**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, Clinical Studies Experience.) Data are available from clinical studies to support the use of RotaTeq in infants with controlled gastroesophageal reflux disease.

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

**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.

For more detailed information, please read the Prescribing Information.

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