

Diagnostic Wrinkles Anticipated in Pandemic Flu

BY BRUCE JANCIN

VAIL, COLO. — Recent anecdotal reports suggest that the diagnosis of novel influenza A(H1N1) should not be ruled out by a negative upper respiratory tract specimen in a patient with pneumonia.

There have been two patients at Albany (N.Y.) Medical Center and one in Denver who were hospitalized with se-

vere lower respiratory tract infections whose nasopharyngeal swabs were negative for influenza A by rapid tests—but who had endotracheal aspirates positive for the novel H1N1 virus by culture and polymerase chain reaction.

“That’s something to watch for. It would be consistent with findings in animal models showing the virus replicates very well in the lower respiratory tract,” said Dr. Adriana Weinberg, who report-

ed on the cases at a conference on pediatric infectious diseases sponsored by the Children’s Hospital, Denver.

“As the pandemic evolves, perhaps we may see more cases with florid infection in the lower respiratory tract and not so much virus in the upper respiratory tract,” said Dr. Weinberg, professor of medicine, pediatrics, and pathology and medical director of the clinical virology laboratory at the Uni-

versity of Colorado Hospital, Aurora.

At present, the preferred specimens for making the diagnosis of novel H1N1 are the same as for seasonal influenza: nasal washings in children and nasopharyngeal aspirates or swabs in adults. That being said, negative results on those upper respiratory tract specimens do not necessarily rule out novel H1N1 in patients with lower respiratory tract infections.

“In these patients, you may want to proceed with obtaining an induced sputum, an endotracheal aspirate, or a bronchoalveolar lavage specimen to rule out the pandemic strain,” according to Dr. Weinberg.

Most diagnostic tests for seasonal influenza A or A plus B will also pick up the pandemic strain. A caveat is that the rapid tests, which in general are not ter-

RotaTaq® [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 RotaTaq should not receive further doses of RotaTaq.

WARNINGS AND PRECAUTIONS

Immunocompromised Populations: No safety or efficacy data are available for the administration of RotaTaq 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); RotaTaq 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 RotaTaq 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 RotaTaq 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 RotaTaq 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 RotaTaq when compared to placebo. In post-marketing experience, cases of intussusception have been reported in temporal association with RotaTaq. 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. RotaTaq 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 [0.0%, 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 RotaTaq to individuals with immunodeficient close contacts such as: Individuals with malignancies or who are otherwise immunocompromised; or Individuals receiving immunosuppressive therapy. RotaTaq 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 RotaTaq 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 RotaTaq.

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

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

Post-Exposure Prophylaxis: No clinical data are available for RotaTaq 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 RotaTaq 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 (RotaTaq 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 RotaTaq when compared to 2.6% of placebo recipients within the 42-day period of a dose in the phase 3 clinical studies of RotaTaq. The most frequently reported serious adverse events for RotaTaq compared to placebo were: bronchiolitis (0.6% RotaTaq vs. 0.7% placebo), gastroenteritis (0.2% RotaTaq vs. 0.3% placebo), pneumonia (0.2% RotaTaq vs. 0.2% placebo), fever (0.1% RotaTaq vs. 0.1% placebo), and urinary tract infection (0.1% RotaTaq vs. 0.1% placebo).

Deaths: Across the clinical studies, 52 deaths were reported. There were 25 deaths in the RotaTaq 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 RotaTaq 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 RotaTaq recipients and 5 cases among placebo recipients (see Table 1). The data did not suggest an increased risk of intussusception relative to placebo.

	RotaTaq (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	
	RotaTaq	Placebo	RotaTaq	Placebo	RotaTaq	Placebo	RotaTaq	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 RotaTaq 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 RotaTaq (by vaccination group and interval after dose) for RotaTaq 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 RotaTaq) 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	
	RotaTaq	Placebo	RotaTaq	Placebo	RotaTaq	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°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 RotaTaq (N=6,138) as compared with placebo (N=5,573) recipients, respectively, were: 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: RotaTaq 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	
	RotaTaq	Placebo	RotaTaq	Placebo	RotaTaq	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°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 RotaTaq 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 RotaTaq: *Gastrointestinal disorders*—Intussusception (including death), 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, RotaTaq 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. The safety data available are in the ADVERSE REACTIONS section.

There was no evidence for reduced antibody responses to the vaccines that were concomitantly administered with RotaTaq.

USE IN SPECIAL POPULATIONS

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 RotaTaq 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 RotaTaq in infants with controlled gastroesophageal reflux disease.

NONCLINICAL TOXICOLOGY

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

PATIENT COUNSELING INFORMATION

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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Physicians can expect to see lots more patients with a prominent gastrointestinal presentation.

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ribly sensitive for the diagnosis of seasonal influenza viruses, appear to be even less sensitive for novel H1N1.

“A positive rapid test indicates you may be dealing with the pandemic strain, but a negative test does not rule out pandemic influenza. However, culture and PCR [polymerase chain reaction] are extremely sensitive for this strain,” she continued.

The Centers for Disease Control and Prevention has acted quickly in preparing tools for the diagnosis of novel H1N1. Regular PCR and culture cannot differentiate between seasonal influenza A and the novel H1N1 strain. But just 2 weeks after the first U.S. case of novel H1N1 disease was diagnosed in April, the CDC began sending out to U.S. sentinel laboratories PCR kits that are highly specific for the virus. Less than 2 months later, those kits were on-site at 233 U.S. laboratories, including all state health department laboratories, and at 386 international laboratories.

In addition to many more patients with novel H1N1 presenting with lower respiratory tract infection than physicians are accustomed to encountering with seasonal influenza, physicians can also expect to see lots more patients with a prominent gastrointestinal presentation, she said. Animal studies suggest that the pandemic strain replicates much better in the GI tract than do seasonal influenza viruses, and that has been borne out in the first 400 U.S. cases of novel H1N1.

More than 90% of those patients presented with fever and cough, and two-thirds had a sore throat—all typical of seasonal influenza—but in addition, 25% presented with diarrhea and 25% had vomiting.

*Rotavirus Efficacy and Safety Trial