HHS Public Access

Author manuscript

*J Infect Dis*. Author manuscript; available in PMC 2015 October 24.

Published in final edited form as:

*J Infect Dis*. 2012 October ; 206(8): 1275–1279. doi:10.1093/infdis/jis490.

# Symptomatic Infection and Detection of Vaccine and Vaccine-Reassortant Rotavirus Strains in 5 Children: A Case Series

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## Abstract

Vaccine or vaccine-reassortant rotavirus strains were detected in fecal specimens from 5 of 106 (4.7%) immunocompetent children who required treatment for rotavirus gastroenteritis at a large pediatric hospital in Texas in 2009–2010. Four strains were related to pentavalent rotavirus vaccine, whereas one was related to monovalent rotavirus vaccine. The contribution of these strains to each patient's illness was unclear given that 2 patients had prominent respiratory symptoms and 2 were concurrently infected with another pathogen (group F adenovirus and norovirus). Continued monitoring is necessary to assess the role of vaccine strains and vaccine-reassortant strains in pediatric rotavirus infections.

Rotavirus is a nonenveloped, RNA virus belonging to the *Reoviridae* family [1]. Group A rotaviruses, the primary source of human infection, have been genotyped conventionally through characterization of the 2 outer capsid proteins, *VP7* (G-type) and *VP4* (P-type). These capsid proteins contribute to regional and temporal diversity of circulating strains [2, 3].

Two live, attenuated, orally administered vaccines are currently licensed and recommended for use in infants: 3-dose pentavalent vaccine (RotaTeq [RV5]; Merck Vaccines), which contains 5 G1-G4, and P[8] human-bovine reassortant strains, and 2-dose monovalent

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***Disclaimer.*** The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC).

***Potential conflicts of interest.*** All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

vaccine (Rotarix [RV1]; GlaxoSmith-Kline Biologicals), which contains a single human G1P[8] strain.

Following vaccination, rotavirus vaccine strains replicate in the gastrointestinal tract and may be shed in the stool. In prelicensure trials and 1 postlicensure assessment, viral shedding was observed 7 days after the first dose in 25.6%–26.5% of RV1 recipients and in 8.9%–21.4% of RV5 recipients 1–15 days after any dose [4–6]. Likely transmission of vaccine virus from infants given RV1 to their unvaccinated twins was observed in a randomized clinical trial [7]. Transmission of RV5 virus through fecal shedding has not been formally assessed; however, 1 instance of horizontal transmission of vaccinederived virus to an unvaccinated sibling resulting in acute gastroenteritis (AGE) requiring medical attention has been described [8].

Rotavirus has the ability to undergo reassortment with wild-type or vaccine-derived strains because of its segmented genome [9]. Little is known about the frequency with which reassortment occurs or the resulting clinical outcome. This report describes 5 children with AGE who were found to be shedding rotavirus vaccine strains and/or vaccine-reassortant strains during routine surveillance.

## METHODS

Active surveillance for AGE was conducted at Texas Children's Hospital from November 2009 through June 2010. Children aged 15 days–4 years with AGE (≥3 episodes of diarrhea and/or ≥1 episode of vomiting) requiring emergency department treatment or hospitalization were offered enrollment. A questionnaire assessing disease symptoms and epidemiologic factors was administered, and fecal specimens were collected within 14 days of illness onset.

Institutional review board approval was obtained from Baylor College of Medicine and Texas Department of State Health Services. Informed consent was obtained from participants' parents/guardians.

Fecal specimens were tested for rotavirus antigen using the Premier Rotaclone kit (Meridian Bioscience, Inc). RNA was extracted from 10% stool suspensions using the MagNA Pure Compact instrument with the MagNA Pure Compact RNA isolation kit (Roche Applied Science). *VP4* and *VP7* genotyping and amplicon sequencing were performed [10], and identification of RV5 and RV1 strains was carried out through comparison with vaccine strain sequences deposited in GenBank [8]. Identification of RV1 was accomplished also by alignment of *NSP2* sequence with that obtained by genomic sequencing of RV1 vaccine itself (unpublished data). Examination of stool samples by electron microscopy (EM) and testing for other agents of gastroenteritis by reverse-transcription polymerase chain reaction (RT-PCR), polymerase chain reaction (PCR), and culture were performed as previously described [8].

## RESULTS

A total of 1133 patients with AGE were enrolled. Fecal specimens were obtained from 997 subjects (88.0%); 106 of these (10.6%) were rotavirus-positive by RT-PCR. Subsequent

genomic sequencing of the 106 rotavirus-positive fecal specimens identified 5 (4.7%) patients with vaccine-reassortant and/or vaccine strains. The epidemiologic and clinical characteristics of these 5 patients and their virus characterization findings are described below.

### Patient 1

A previously healthy 22-month-old boy presented with a history of 11 episodes of nonbloody, nonbilious emesis occurring over a 2-hour period (Table 1). He was treated with oral ondansetron, orally rehydrated, and discharged. The patient returned 8 hours later with persistent vomiting. Because he was tachycardic and dehydrated, he received intravenous fluids overnight and was discharged the next day. Although the patient had received no doses of rotavirus vaccine, his infant sibling received a second dose of RV5 7 days prior to the patient's illness onset.

The *VP7* G1 gene of RV5 component strain WI79-9 (G1P [5]) (99.9% identity in 839 bases sequenced) and the *VP4* P[8] (100% identity in 835 bases) and *VP6* I2 (100% identity in 338 bases) genes from RV5 strain WI79-4 (G6P[8]) (Table 2) were detected in a fecal specimen obtained 2 days after illness onset. The *VP3* M2 gene matched the sequence of strains WI79-4 (G6P[8]), WI78-8 (G3P[5]), and BrB-9 (G4P[5]) (100% identity in 500 bases). The strain appears to be a reassortant derived by insertion of the WI79-9 (G1P[5]) G1 gene onto a WI79-4 (G6P[8]) backbone. Rotaviruses and unidentified particles 30–40 nm in diameter were observed by EM. All other tests were negative.

### Patient 2

A 4-month-old boy presented with a 4-day history of rhinorrhea and nonbloody diarrhea, and 3 days of fever. The patient was wheezing and tachypneic with an oxygen saturation of 95%. He was diagnosed with bronchiolitis, treated with levalbuterol and vaponephrine, and observed overnight. The patient received his first dose of RV5 11 days before illness onset.

Genetic analysis of a fecal specimen obtained 9 days after illness onset detected the *VP7* G1 gene of RV5 strain WI79-9 (G1P[5]) (100% identity in 854 bases) and the *VP4* P[8] gene from RV5 strain WI79-4 (G6P[8]) (100% identity in 835 bases) (Table 2). The *VP6* I2 gene detected matched that of RV5 component strains WI79-9 (G1P[5]), SC2-9 (G2P[5]), WI78-8 (G3P[5]), and BrB-9 (G4P[5]) (100% identity in 342 bases). The *VP3* M2 gene matched the sequence of strains WI79-4 (G6P[8]), WI78-8 (G3P[5]), and BrB-9 (G4P[5]) (100% identity in 500 bases). This strain appears to be a double reassortant with either the WI79-9 (G1P[5]) *VP7* and *VP6* genes inserted onto a WI79-4 (G6P[8]) backbone or the VP4 of WI79-4 (G6P[8]) and VP3 of WI79-4 (G6P[8]), BrB-9 (G4P[5]), or WI78-8 (G3P[5]) inserted onto a WI79-9 (G1P [5]) backbone. Rotaviruses and adenoviruses were observed by EM. Real-time PCR was positive for adenovirus group F; all other tests were negative.

### Patient 3

A previously healthy 2-month-old girl presented with 4 days of vomiting and 2 days of fever, cough, and conjunctivitis without diarrhea. On physical exam, she was fussy but consolable with mild conjunctival injection and nasal discharge. Laboratory evaluation

revealed an elevated white blood cell count (19 700/μL) with 12% bandemia. Urinalysis and urine culture were negative. The patient was treated with intravenous ceftriaxone and discharged. She received her first dose of RV5 1 day before illness onset.

A fecal specimen was obtained 5 days after illness onset and appeared to contain nonreassortant RV5 component strain BrB-9 (G4P[5]) alone. The *VP7* G4 gene of BrB-9 (G4P[5]) was detected (100% identity in 363 bases) along with *VP4* P [5] (100% identity in 416 bases), *VP6* I2 (100% identity in 342 bases), and *VP3* M2 genes (100% identity in 500 bases) consistent with BrB-9 (G4P[5]). By EM, a few unidentified 30-nm particles were observed; all other tests were negative.

### Patient 4

A previously healthy 2-month-old boy presented with 3 days of nonbloody diarrhea and 2 days of fever and irritability. On physical exam, he was fussy but consolable with a slightly distended abdomen and hyperactive bowel sounds. Negative laboratory examinations included complete blood count with differential, urinalysis, and urine culture (catheterized). The patient was orally rehydrated and discharged. He received his first dose of RV5 2 days before illness onset.

Four distinct *VP7* genotypes were detected in a specimen obtained 3 days after illness onset: the G1 gene of RV5 component strain WI79-9 (G1P[5]) (100% identity in 116 bases); the G2 gene of strain SC2-9 (G2P[5]) (100% identity in 202 bases); the G4 gene of strain BrB-9 (G4P[5]) (100% identity in 363 bases); and the G6 gene of strain WI79-4 (G6P[8]) (99.8% identity in 421 bases) (Table 2). The *VP4* P[8] gene (99.9% identity in 835 bases) and *VP6* I2 (100% identity in 342 bases) genes from RV5 strain WI79-4 (G6P[8]) were detected. The *VP3* M2 gene matched the sequence of strains WI79-4 (G6P [8]), WI78-8 (G3P[5]), and BrB-9 (G4P[5]) (100% identity in 500 bases). This specimen appears to contain 4 strains, the WI79-4 (G6P[8]) component strain itself and 3 potential reassortant strains each composed of strain WI79-4 (G6P[8]) but expressing G1, G2, and G4 individually. Rotaviruses were observed by EM, and real-time RT-PCR was positive for norovirus genogroup II. All other tests were negative.

### Patient 5

A 6-month-old boy presented with a 1-day history of nonbloody, nonbilious vomiting with diarrhea, lethargy, and fever. His past medical history was notable for failure-to-thrive and gastroesophageal reflux. The patient's 2.5-year-old sister also had been ill with vomiting. On physical exam, he was tachycardic and had generalized pallor. The patient failed oral rehydration and was subsequently treated with intravenous ondansetron and fiuids and was observed overnight. Neither the patient nor his sister had received any doses of either rotavirus vaccine.

Analyses of a fecal specimen obtained 8 days after illness onset identified what appears to be an RV1-derived strain. Sequences of the *VP7* (850 bases), *VP4* (803 bases), and NSP2 (991 bases) genes each shared 99.8% identity with cognate RV1 vaccine strain sequences.

Rotaviruses and unidentified particles 40–45 nm in diameter were observed by EM. All other tests were negative.

## DISCUSSION

These patients illustrate a spectrum of potential clinical and virologic outcomes associated with routine use of live, attenuated rotavirus vaccines. The diversity of these occurrences include apparent transmission of an RV5 vaccine-reassortant strain from a vaccinated infant to an unvaccinated sibling ( patient 1); detection of an RV5 vaccine-reassortant strain in a recently vaccinated child ( patient 2); detection of a nonreassortant RV5 vaccine strain in a recently vaccinated child ( patient 3); detection of an RV5 vaccine strain and 3 potential vaccine-reassortant strains in a recently vaccinated child ( patient 4); and detection of an RV1 vaccine strain in an unvaccinated child residing in an area with low RV1 coverage ( patient 5).

Although these findings suggest potentially unusual transmission or vaccine replication processes, the contribution of the vaccine or vaccine-reassortant strain to each patient's illness is unclear. Patient 1's illness was clinically consistent with rotavirus AGE and occurred after exposure to a younger sibling who had recently received RV5. This patient's history of exposure and subsequent illness is similar to a prior report of sibling transmission of the same vaccine-derived G1P[8] strain [8], supporting the likely linkage between this vaccine-reassortant strain and patient 1's illness. Patients 2 and 3 had upper respiratory symptoms accompanied by vomiting or diarrhea, and their illnesses were less typical of rotavirus disease alone. Additionally, detection of adenovirus group F in patient 2's specimen provides a plausible alternate etiology. Similarly, although patient 4 had diarrhea without respiratory symptoms, the presence of norovirus genogroup II in his fecal specimen along with the potential vaccine-reassortant strains makes it impossible to discern the cause of his illness. The presence of multiple reassortant RV5 strains in patient 4's stool is very unusual, and these findings will be confirmed using an advanced genetic characterization method such as microarray analysis and/or deep sequencing. Both patient 5 and his 2.5-year-old sister presented with symptoms consistent with rotavirus disease. The RV1 strain detected in this unvaccinated patient's stool is suggestive of an environmental exposure to a vaccine strain that is not widely present in the patient's community. Although RV1 uptake rates in the Houston area during this surveillance period are not known, no enrolled patient received any doses of RV1, thus confirming its rare use. However, because a full epidemiologic investigation was not conducted, it is impossible to determine how this patient's exposure to RV1 occurred or the role of RV1 in the patient's illness. These outcomes highlight the difficulty in establishing clear causative relationships between vaccine-derived strains and clinical illness, despite exhaustive laboratory testing.

The detection of rotavirus vaccine or vaccine-derived reassortant strains in fecal specimens from 5 of 106 (4.7%) immunocompetent, rotavirus-positive children hospitalized or visiting the emergency department with AGE symptoms was surprising. Although the population rate of severe AGE related to vaccine or vaccine-reassortant strains is likely to be low given the large number of vaccinated children and their contacts residing in the catchment area of our surveillance hospital, such events may not be as uncommon as previously suspected.

Continued monitoring is necessary to assess the rate of occurrence and clinical relevance of vaccine strains and vaccine-reassortant strains in symptomatic and asymptomatic pediatric rotavirus infections.

## Acknowledgments

We thank Yahaira Colorado, M. Helena Espinosa, Karla Romero, Daiquiri Saenz, Deyanira Verdejo, and Rose Mata for their capable work in recruiting participants and collecting data; Charles Humphrey and Maureen Metcalfe for EM; Nicole Gregoricus and Jan Vinje for norovirus, adenovirus, sapovirus, and astrovirus testing; Nancy Garrett and Cheryl Bopp for bacterial culture attempts; Shannon Rogers, Allan Nix, and Steve Oberste for enterovirus and parechovirus testing; and Virginia Moyer, MD, and Hoonmo Koo, MD, for editorial comments.

***Financial support.*** This work was funded by a contract between the Texas Department of State Health Services and Texas Children's Hospital. Texas Department of State Health Services received funding from the Centers for Disease Control and Prevention (funding opportunity number CDC-RFA-CI07-70405ARRA09: Strengthening the Evidence Base: Epidemiology and Laboratory Capacity for Infectious Diseases [ELC] Rotavirus Vaccine Effectiveness) and subsequently contracted with Texas Children's Hospital. Drs Boom and Baker and Ms Sahni report having received institutional support for aspects of the work contained in this manuscript.

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*J Infect Dis*. Author manuscript; available in PMC 2015 October 24.

**Table 1**

Demographic Characteristics, Clinical Symptoms, and Fecal Testing Results of the 5 Patients Described in This Study

| Characteristic | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| Age at presentation in months | 22.5 | 4.6 | 2.9 | 2.3 | 6.2 |
| Symptoms | | | | | |
| Diarrhea | | | | | |
| Duration; maximum episodes in 24 h | None | 5 d; 4 episodes | 3 d; 18 episodes | None | 1 d; 5 episodes |
| Vomiting | | | | | |
| Duration; maximum episodes in 24 h | 1 d; 11 episodes | None | None | 4 d; 3 episodes | 1 d; 12 episodes |
| Fever | | | | | |
| Duration; maximum | 1 d; 38.8°C (rectal) | 5 d; 38.6°C (rectal) | 1 d; 38.3°C (rectal) | 2 d; 39.4°C (axillary) | 1 d; 38.6°C (rectal) |
| Intravenous rehydration | Yes | None | None | None | Yes |
| Hospitalization for AGE episode | Yes; 23-hour stay | Yes; 23-hour stay | None | None | Yes; 23-hour stay |
| Race/ethnicity | White, non-Hispanic | White, Hispanic | White, Hispanic | Middle Eastern, non-Hispanic | White, non-Hispanic |
| Birth history | | | | | |
| Gestation, birth weight | Term, 7 lb 3 oz | Term, 7 lb 13 oz | Term, 9 lb 8 oz | Term, 7 lb 12 oz | Term, 6 lb 9 oz |
| History of breastfeeding | | | | | |
| Duration | Yes; 7–12 mo | Yes; <1 mo | Yes; 1–3 mo | Yes; <1 mo | Yes; 1–3 mo |
| Other children in the home | 1 sibling aged <6 mo | 2 siblings, both aged ≥5 y | 2 siblings, both aged ≥5 y | None | 1 sibling, aged 2.5 y |
| Daycare attendance | None | None | None | None | None |

| Characteristic | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| Rotavirus vaccination history | | | | | |
| Patient | No doses RV1 or RV5 | 1st dose RV5 11 d prior to illness onset | 1st dose RV5 2 d prior to illness onset | 1st dose RV5 1 d prior to illness onset | No doses RV5 or RV1 |
| Other children aged <5 y in the home | 2nd dose RV5 7 d before patient's illness onset | NA[a] | NA[a] | NA[a] | No doses RV5 or RV1 |
| Timing of fecal specimen collection | 2 d after illness onset | 9 d after illness onset | 5 d after illness onset | 3 d after illness onset | 8 d after illness onset |
| Rotavirus strain detected | 1 RV5 vaccine-reassortant strain | 1 RV5 double vaccine-reassortant strain | 1 RV5 vaccine strain | 1 RV5 vaccine strain & 3 RV5 vaccine-reassortant strains | RV1 vaccine strain |
| AGE coinfections[b] | Unidentified particles 30–40 nm in diameter | Adenovirus group F | Unidentified particles 30 nm in diameter | Norovirus genogroup II | Unidentified particles 40–45 nm in diameter |

Abbreviations: AGE, acute gastroenteritis; NA, not applicable; RV1, Rotarix vaccine; RV5, RotaTeq vaccine.

[a]Other children in the home were ≥5 years at the time of the patient's illness, and, therefore, were born before rotavirus vaccine was licensed in the United States.

[b]Specimens were tested for norovirus genogroups I and II, astroviruses, sapoviruses, enteroviruses, parechoviruses [11–14], adenovirus, *Salmonella*, *Shigella*, *Campylobacter*, *diarrheagenic Escherichia coli*, and *Vibrios*.

**Table 2**

Genes of the 5 RotaTeq Vaccine (RV5) Strains and 4 RV5 Vaccine Strains and Reassortant Case Strains Detected and Sequenced in This Study[a]

| | RV5 Component Strains[b] | | | | | Case Strains | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Gene** | **WI79-9** | **SC2-9** | **WI78-8** | **BrB-9** | **WI79-4** | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** |
| *VP7* | G1 (GU565057)[c] | G2 (GU565068) | G3 (GU565079) | G4 (GU565090) | G6 (GU565046) | G1 (GU565057) | G1 (GU565057) | G4 (GU565090) | GKGU565057) G2(GU565068) G4(GU565090) G6(GU565046)[d] |
| *VP4* | P[5] (GU565055) | P[5] (GU565066) | P[5] (GU565077) | P[5] (GU565088) | P[8] (GU565044) | P[8] (GU565044) | P[8] (GU565044) | P[5][e] | P[8] (GU565044) |
| *VP6*[f] | I2 (GU565056) | I2 (GU565067) | I2 (GU565078) | I2 (GU565089) | I2 (GU565045) | I2 (GU565045) | I2 (GU565056 or GU565067 or GU565078 or GU565089) | I2 (GU565056 or GU565067 or GU565078 or GU565089) | I2 (GU565045) |
| *VP3* | M1 (GU565054) | M1 (GU565065) | M2 (GU565075) | M2 (GU565087) | M2 (GU565043) | M2[g] | M2[g] | M2[g] | M2[g] |

[a] A Rotarix vaccine (RV1)–derived strain was identified in the specimen obtained from patient 5 and is not included in this table.

[b] Within the RV5 component strains, the *VP1, VP2, VP6, NSP1, NSP2, NSP3, NSP4,* and *NSP5/6* of all 5 strains are identical or nearly identical. The *VP3* genes of WI79-9 and SC2-9 are identical. The *VP3* genes of WI78-8, BrB-9, and WI79-4 are identical or nearly identical. The *VP4* genes of WI79-9, SC2-9, WI78-8, and BrB-9 are identical or nearly identical.

[c] GenBank accession number for reference sequence (RV5 component strains) or closest sequence match (case strains).

[d] Four distinct *VP7* genotypes detected.

[e] One *VP4* P[5] genotype detected, but 4 sequences (GU565055, GU565066, GU565077, GU565088) are identical in the region sequenced (416 bases) and could not be distinguished.

[f] Within the region of the VP6 gene sequenced (342 bases), GU565056, GU565067, GU565078, and GU565089 are identical, and a single base substitution distinguishes GU565045 from the other 4 strains.

[g] One *VP3* M2 genotype detected, but all 3 M2 sequences (GU565075, GU565087, GU565043) are identical in the region sequenced (500 bases) and could not be distinguished.