HHS Public Access

Author manuscript

J Infect Dis. Author manuscript; available in PMC 2016 October 24.

Published in final edited form as:

J Infect Dis. 2016 September 1; 214(5): 732–738. doi:10.1093/infdis/jiw233.

Rotavirus Strain Trends During the Postlicensure Vaccine Era: United States, 2008–2013

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Abstract

Background—Group A rotaviruses (RVA) are a significant cause of pediatric gastroenteritis worldwide. The New Vaccine Surveillance Network (NVSN) has conducted active surveillance for RVA at pediatric hospitals and emergency departments at 3–7 geographically diverse sites in the United States since 2006.

Methods—Over 6 consecutive years, from 2008 to 2013, 1523 samples from NVSN sites that were tested positive by a Rotaclone enzyme immunoassay were submitted to the Centers for Disease Control and Prevention for genotyping.

Results—In the 2009, 2010, and 2011 seasons, genotype G3P[8] was the predominant genotype throughout the network, with a 46%–84% prevalence. In the 2012 season, G12P[8] replaced G3P[8] as the most common genotype, with a 70% prevalence, and this trend persisted in 2013 (68.0% prevalence). Vaccine (RotaTeq; Rotarix) strains were detected in 0.6%–3.4% of genotyped samples each season. Uncommon and unusual strains (eg, G8P[4], G3P[24], G2P[8], G3P[4],

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Potential conflicts of interest. D. I. B. has a patent and received royalties for what is now Rotarix vaccine. M. M. M. has laboratory service agreements with GlaxoSmithKline and Merck. All other authors report no potential 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.

G3P[6], G24P[14], G4P[6], and G9P[4]) were detected sporadically over the study period. Year, study site, and race were found to be significant predictors of genotype.

Conclusions—Continued active surveillance is needed to monitor RVA genotypes in the United States and to detect potential changes since vaccine licensure.

Keywords

rotavirus; genotype; prevalence; surveillance; vaccine

Group A rotaviruses (RVA) commonly cause acute gastroenteritis (AGE) and are estimated to account for approximately 200 000 deaths annually in children <5 years of age worldwide [1]. RVA are nonenveloped, spherical viruses with a capsid composed of 3 concentric protein layers. Traditionally, RVA have been classified by a binomial typing system, GxP[x], based on serological or genetic characterization of the 2 proteins that compose the outer capsid layer of the virion: VP7, the G-type determinant; and VP4, which determines the P type [2]. In the United States, vaccination against RVA was reinitiated after licensure of 2 live-attenuated vaccines by the Food and Drug Administration: RotaTeq (Merck, Whitehouse Station, New Jersey), which was licensed in 2006; and Rotarix (GlaxoSmithKline, Research Triangle Park, North Carolina), which was licensed in 2008 [3]. RotaTeq is a pentavalent vaccine that expresses the G1, G2, G3, G4, and P[8] antigens of human RVA strains on a bovine RVA backbone [4]. Rotarix is a monovalent vaccine derived from a human G1P[8] RVA strain [5]. Since the reinitiation of the RVA immunization program, the incidence of RVA-associated AGE and diarrheal disease requiring medical intervention has declined dramatically in young children in the United States, and the typical winter or early spring peak seasonality pattern of RVA has changed [6–9].

The New Vaccine Surveillance Network (NVSN) has been conducting active AGE surveillance throughout the postlicensure RVA vaccine era [10]. Three sites, the University of Rochester School of Medicine and Dentistry (Rochester, New York), Vanderbilt University Medical Center (Nashville, Tennessee), and Cincinnati Children's Hospital Medical Center (Cincinnati, Ohio) began surveillance in 2006, and additional sites (Texas Children's Hospital, [Houston, Texas], Children's Mercy Hospitals and Clinics [Kansas City, Missouri], and Seattle Children's Hospital [Seattle, Washington]) were added in 2009. A seventh site, Children's Hospital Research Center (Oakland, California), participated during the 2011 and 2013 seasons. The diversity in study sites across the United States is a strength of the network. Samples from enrolled cases are tested for RVA at surveillance site laboratories and then forwarded to the Rotavirus Surveillance Laboratory at the Centers for Disease Control and Prevention (CDC; Atlanta, Georgia) for strain characterization.

To continue monitoring circulating RVA strains for changes that may influence vaccine performance, continued surveillance is necessary. This report provides RVA strain surveillance data for the entire NVSN from 2008 through 2013.

METHODS

The study was conducted over 5 seasons: 1 October 2008 through 31 October 2009 (hereafter referred to as 2009), 1 November 2009 through 30 June 2010 (hereafter, 2010), 1 July 2010 through 30 June 2011 (hereafter, 2011), 1 December 2011 through 30 November 2012 (hereafter, 2012), and 1 December 2012 through 30 November 2013 (hereafter, 2013). Enrollment periods varied from season to season owing to differences in the funding periods of cooperative agreements between the CDC and study site institutions.

Children were enrolled in the NVSN study by using criteria described previously [11, 12]. Briefly, children who were hospitalized or presented to emergency departments or outpatient clinics (Nashville only) with AGE were enrolled if they had at least 3 loose stools and/or 1 episode of vomiting within the previous 24 hours, had onset of AGE symptoms within 10 days of presentation, and were not immunocompromised [13]. Medical chart abstractions and epidemiologic information, including verified RVA immunization data, were obtained. The institutional review boards from each study site and the CDC approved the study. Written consent was obtained from the parent or guardian of each child at the time of enrollment.

Stool specimens or elutions of fecal material from diapers were collected up to 10–14 days after AGE onset. Specimens were tested at surveillance site laboratories for RVA antigen by using the Premier Rotaclone RVA Detection Kit (Meridian Diagnostics, Cincinnati). RVA-positive stool specimens were sent to the CDC for genotyping analysis and sequencing.

Ten percent stool suspensions were prepared using phosphate-buffered saline, and RVA double-stranded RNA was extracted as described previously [14] or by using the using the MagNA Pure Compact or MagNA Pure-96 automated extraction systems (Roche Applied Science, Indianapolis, Indiana). Reverse transcription–polymerase chain reaction (RT-PCR)–based genotyping and sequencing of VP4 and VP7 genes were performed as described previously [14], except that, starting in 2011, PCR products were visualized using a LabChip GX instrument (PerkinElmer, Waltham, Massachusetts). Samples that could not be amplified by RT-PCR were tested by an NSP3 real-time RT-PCR (qRT-PCR) assay to determine whether they contained amplifiable nucleic acid [15]. Genotypes were assigned by agarose gel analysis or by comparison of sequences determined in the study with RVA sequences in GenBank, using the BLASTN program (available at: http://blast.ncbi.nlm.nih.gov/Blast.cgi) or by RotaC v2.0 analysis (available at: http://rotac.regatools.be/) [16]. To examine the data for an association between genotype and study site, year, vaccination status, race, ethnicity, or age group, stepwise conditional logistic regression analysis was performed using SAS, version 9.3.

RESULTS

Over the 5 seasons, 1523 RVA antigen test–positive samples from NVSN sites were submitted to the CDC. Thirty-nine samples submitted as RVA-positive specimens had enzyme immunoassay–based OD values at or below the assay cutoff (0.15) but had visible color changes when compared to the negative control. These samples were classified as

"visual positives" and were included in the positive samples to be genotyped. Of the 1523 samples, 1299 (85.3%) contained amplifiable RVA RNA by genotyping RT-PCR or qRT-PCR assays. Samples that could be amplified by RT-PCR and/or qRT-PCR but could not be genotyped were designated as nontypeable (NT).

The complete genotyping results are shown in Table 1 and Figure 1. For the 2009 season, when 3 sites performed surveillance and 143 samples were submitted, genotype G3P[8] was the most common genotype (Figure 1), and it predominated at the Cincinnati and Nashville sites (61%–63% prevalence; Table 1). Genotype G9[8], detected in 52% of the samples at the Rochester site (Table 1), was the second most common genotype detected that season (Figure 1). G1P[8], G2P[4], and G12P[8] were detected at lower frequencies at all 3 sites, and G2P[4] comprised one third of the samples from the Cincinnati site (Table 1). One vaccine strain detection (RotaTeq) occurred at the Nashville site (Table 1). In 2008–2009, 2 uncommon genotypes, 3 G8P[4] strains, and 1 G3P[24] strain were detected at the Rochester site (Figure 1 and Table 1).

For the 2010 season, when 6 sites performed surveillance and 141 samples were submitted, the majority of samples were collected by the Houston site (Table 1). The predominant genotype was G3P[8] (Figure 1), and this genotype was most frequently found at both the Houston and Kansas City sites (88%–94% prevalence; Table 1). G1P[8] was the predominant genotype at the Seattle site (79%; Table 1). The other sites (Cincinnati, Nashville, and Rochester) submitted fewer samples for the 2010 season. Five vaccine strains (4 RotaTeq and 1 Rotarix) were detected in samples from Houston (Table 1 and Figure 1), composing 3.5% of all samples typed in 2010.

In the 2011 season, there was a large increase in the number of samples submitted (351), owing to a higher incidence of AGE, compared with the 2010 season, and again the majority of samples were submitted by the Houston site. G3P[8] was again the predominant genotype (46%), followed by G2P[4] and G12P[8], with 30% and 12% prevalence, respectively (Figure 1). RotaTeq vaccine strain was detected in 7 surveillance samples during the 2011 season (Figure 1). At 4 sites, Cincinnati, Kansas City, Nashville, and Rochester, G3P[8] was the predominant genotype (45%–92% prevalence; Table 1). G12 P[8] was most common at the West Coast sites of Oakland and Seattle (49%–59%; 1). In Houston, G2P[4] was the predominant Table genotype (51%; Table 1). In 2011, a small number of mixed infections (G1G2P[8], G2P[4]P[8], G3G12P[8], and G2G3P[4]P [8]) were detected, as were 6 NT genotypes (2 GNTP[8] and 4 GNTP[NT]; Table 1). Uncommon strains G2P[8], G3P[4], G3P [6], and G9P[4] were detected in samples from Houston, and 5 G12P[6] strains were detected in Rochester, along with a G3P [6] strain (Figure 1 and Table 1).

In the 2012 season, the number of samples genotyped declined to 118. Genotype G12P[8] displaced G3P[8] as the predominant genotype with 70% of the strains identified as the G12P[8] genotype (Figure 1). The proportion of genotype G3P[8] fell to 12% (Figure 1). G12P[8] was the dominant genotype at all sites except Rochester, which submitted only 3 G2P[4] samples (Table 1). G2P[4] was the second most common genotype overall, accounting for 12% (Figure 1). There was 1 RotaTeq detection in Houston (Table 1).

Uncommon strains G4P[6] and G24P[14] were detected in samples from Houston, and there was a single detection of G8P[4] in Seattle (Figure 1 and Table 1).

For the 2013 season, the number of samples genotyped rose to 546, along with 13 partially or totally NT strains. As observed for the 2012 season, G12P[8] was the dominant genotype, accounting for 68% of strains (Figure 1), and it was the most commonly detected genotype at all sites, except Rochester, where G3P[8] made up 72% of strains (Table 1). G3P[8] also was the second most commonly detected genotype overall during 2013 (17%; Figure 1). Three vaccine strains (2 RotaTeq and 1 Rotarix) were detected in 2013 (Figure 1 and Table 1). Two mixed genotype specimens (G3G12P[8] and G9G12P[8]) were detected in Houston (Figure 1 and Table 1).

Stepwise conditional logistic regression analysis revealed that year ($P < .0001$), study site ($P < .0001$), and race ($P = .0055$) were statistically significant predictors of genotype (Table 2). Associations between genotype and other effects, including vaccination status, were not significant (Table 2).

DISCUSSION

We report here RVA genotyping data for the NVSN from 2008 through 2013. In this robust, active network with diverse geographic representation, we found over a 5-season period that there was a change of RVA strains after vaccine introduction, from G1P[8] to G3P[8] and then to G12P[8]. Prior surveillance data from the 3 original NVSN sites for the 2006 and 2007 seasons revealed a predominance of RVA genotype G1P[8] at all 3 sites in 2006 and 2 of 3 sites in 2007 [10]. The NVSN study site in Nashville reported a predominance of G1P[8] strains in the 2008 season and G3P[8] predominance in the 2009 season [17]. The National Rotavirus Strain Surveillance System, a passive surveillance network in the United States, previously had reported G3P [8] predominance for the 2008 season [14]. Our results showed a predominance of genotype G3P[8] in 2009 through 2011. In the 2012 season, however, genotype G12P[8] prevalence rose sharply, to 70%, displacing G3P[8] as the dominant genotype, and G12P [8] remained dominant in the 2013 season. G12 RVA are considered emerging human RVA strains, and the lineage III G12 allele has spread worldwide rapidly [18, 19]. Strain G12P[8] was associated with a large outbreak of pediatric gastroenteritis in Rochester in 2007 (an outbreak detected through the NSVN) [13], and this genotype has been reported recently in Niger [20], Spain [21], Nicaragua [22], Haiti [23], and Australia [24]. It appears that G12P[8] strains now are established in the United States. In addition to G12P[8], genotype G12P[6] was also present, albeit at low levels, in 2010 and 2011.

Following RVA vaccine introduction in some countries, there have been reports of shifts in RVA genotype prevalence that have been speculated to be result of immune pressure from a vaccinated population [25]. Trends toward G3P[8] predominance were observed in countries and regions using RotaTeq in national immunization programs and toward G2P[4] predominance in countries using Rotarix [25]. In 2007, several states in Australia started using RotaTeq vaccine, and a change in G1P[8] to G3P [8] predominance subsequently was observed in these regions [18]. By 2008, however, G1P[8] dominance was reestablished in

RotaTeq states, changed to G2P[4] in 2011 [26, 27], reverted to G1P[8] in 2012 [28], and then changed to G12P[8] predominance in 2013 [24]. RVA vaccine coverage in the United States was estimated to be 43.9% in 2009 and rose to 72.6% by 2013 [29,30], with RotaTeq being the more widely used vaccine. Somewhat analogous to the situation in RotaTeq states in Australia, G3P[8] was the predominant genotype in the United States during 2008–2011 following vaccine introduction and has since been replaced by G12P[8]. We cannot exclude the possibility that RotaTeq selects for genotype G3P[8], but, if this is true, the shift to this genotype appears to be short-lived following vaccine introduction. In Nicaragua, a country with high RotaTeq coverage, a switch to G3P[8] predominance did not occur after vaccine introduction [31], but in 2012–2013 a very high prevalence of G12P[8] strains was documented [22]. The emergence of G12P[8] in the United States and other countries may reflect a new trend in RVA genotype prevalence that is not driven by vaccine pressure. It has been postulated that in Nicaragua the emergence and persistence of G12 strains was due to the presence of a susceptible population that was immunologically naive to this globally emerging genotype [22], and the same may be true for the United States. It should be noted that an estimate of RotaTeq vaccine effectiveness against G12P[8] strains in the United States (83%) was slightly lower than that for other common RVA genotypes (87%–89%), although genotype-specific vaccine protection against G12P[8] remained statistically significant [11].

RVA vaccine strains were detected in diarrheal stools each year of this study in 1%–3% of AGE surveillance samples from the NVSN. The first detection of a vaccine-derived RVA strain in 2009 occurred in a child infected by a vaccine-derived G1P[8] RotaTeq reassortant (vdG1P[8]), likely through an immunized younger sibling [32]. Subsequently, AGE cases associated with vdG1P[8] have been described in Australia and Finland [33–35]. In 2010, 5 vaccine strain–associated AGE cases (4 RotaTeq and 1 Rotarix) were identified in samples collected at the Houston NVSN site [36]. In these 4 RotaTeq cases, 3 were vaccinated with RotaTeq and 2 were associated with vdG1P[8], with 1 apparent sibling transmission. The Rotarix case represented a case of possible community transmission, since the patient had not been vaccinated and there was no immunization history in the family [36]. Since RotaTeq and Rotarix vaccine strains likely will continue to be detected in AGE surveillance samples, we have developed real time RT-PCR assays for detecting both vaccine strains [37] and now use them in regular surveillance testing. In Australia, RotaTeq vaccine components were detected in 1%–6% of surveillance samples from 2012–2013 [24, 28]; it is likely that vaccine strains will be detected in other RVA surveillance programs worldwide in countries where RVA vaccines have been introduced. Despite the fact that use of live-attenuated vaccines poses the risk of vaccine strain–associated AGE, significant reductions in RVA-associated morbidity and mortality continue to be observed in most countries following vaccine introduction. Even in regions with reduced vaccine efficacy (ie, Africa and Southeast Asia), significant reductions in severe disease have been observed, and the well-documented benefits of immunization greatly outweigh the small increase in vaccine-associated RVA cases [33].

Unusual strains identified during the study included several genotypes not previously reported from the United States. A G3P[24] strain from Rochester was detected during the 2009 season that appears to be a reassortant between human, equine, simian, and bovine

RVAs [38, 39]. G8P[4] strains were detected in specimens from Rochester in 2009 [40] and were found to be very similar genetically to a G8P[4] strain from Germany [41]. A G8P[4] strain was discovered again in 2012, in Seattle. Also in 2012, a G24P[14] strain was detected in Houston that is currently being characterized. In 2011, A G9P[4] strain was found in a sample from Houston. G9P[4] strains had been reported from California and Latin America [42, 43]. It is likely that as postvaccine surveillance continues, more uncommon or unusual RVA strains associated with AGE will be detected. The impact of these unusual strains on the epidemiology of RVA at the study sites has yet to be determined.

Logistic regression analysis found significant associations between genotype and year, study site, and race. The significance of geotemporal variation is not surprising given the observed variability of genotypes by location and year. The association between genotype and race is somewhat surprising and may be a result of different allelic frequencies of histo-blood group antigens (eg, FUT2 and Lewis antigens) in racial groups [12, 44, 45]. It is also possible that race/ethnicity confounds these results owing to the geographic differences in their distribution. Some sites skewed more heavily black (Cincinnati) or other/mixed race (Oakland), reinforcing the idea that race and geography are confounding variables. It is very important to note that vaccination status was not significant, suggesting that these trends did not relate to vaccination and possible immune pressure [25]. An average of 62.3% (range, 57.5%–68.2%) of enrolled children age eligible for vaccination at the 7 study sites during the study period received a complete RVA vaccination series, which is between the estimates of 43.9% and 72.6% for the United States in 2009 and 2013 [29, 30], respectively.

In conclusion, this report describes RVA genotype surveillance data from the NVSN for 2008–2013. During the study period, a major shift in predominant genotype prevalence was observed (from G3P[8] to G12P[8]), and vaccine strains were detected in surveillance samples each year. These trends indicate that ongoing surveillance studies are needed to monitor the dynamics of RVA genotype circulation in the United States. Additionally, it will be important to define the potential impact of RVA vaccines on viral evolution toward design of vaccine updates for continued effectiveness.

Acknowledgments

We thank Jon R. Gentsch, for scientific guidance; Freda C. Lyde, for technical assistance; and Azadeh Tasslimi, for epidemiological support.

Financial support. This work was supported by the CDC.

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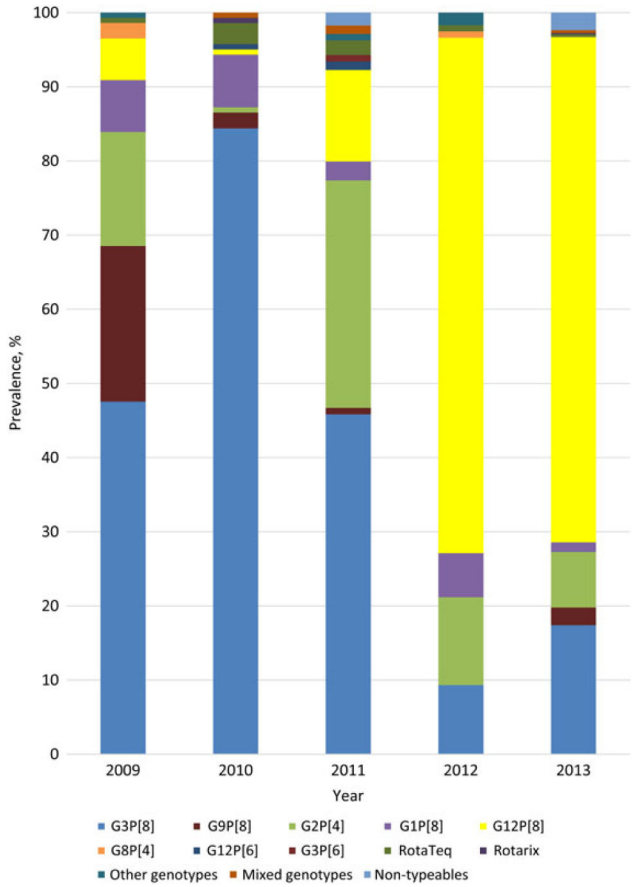

Figure 1.

Genotype prevalence, by season. Other genotypes include G2P[8], G3P [4], G3P[24], G4P[6], G9P[4], and G24P[14]. Mixed genotypes in include G1G2P[8], G2G3P[4]P[8], G2P[4]P[8], G2G9P[4]P[8], G3G12P[8], and G9G12P[8]. Nontypeable (NT) genotypes include G2P[NT], GNTP[NT], and GNTP[8].

Table 1

Genotypes Identified During the 5 Rotavirus Seasons Monitored by the New Vaccine Surveillance Network, By Site

		Strains Classified, No. (%)[a]									
Season, Study Site	**Samples Genotyped, No.**	**G1P[8]**	**G2P[4]**	**G3P[8]**	**G9P[8]**	**G12P[8]**	**RotaTeq**	**Rotarix**	**Other Genotypes[b]**	**Mixed[c]**	**NT[d]**
2009											
Cincinnati	51	1 (2)	17 (33)	31 (61)	…	2 (4)	…	…	…	…	…
Nashville	38	5 (13)	4 (11)	24 (63)	2 (5)	2 (5)	1 (3)	…	…	…	…
Rochester	54	4 (7)	1 (2)	13 (24)	28 (52)	4 (7)	…	…	4 (7)	…	…
2010											
Cincinnati	2	…[e]	…	…	2 (100)	…	…	…	…	…	…
Houston	106	…	…	100 (94)	1 (1)	…	4 (4)	1 (1)	…	…	…
Kansas City	17	…	…	15 (88)	…	1 (6)	…	…	1 (6)	…	…
Nashville	1	…	…	1 (100)	…	…	…	…	…	…	…
Rochester	1	…	…	…	…	…	…	…	…	1 (100)	…
Seattle	14	11 (79)	…	3 (21)	…	…	…	…	…	…	…
2011											
Cincinnati	48	…	3 (6)	44 (92)	…	…	…	…	…	…	1 (2)
Houston	152	3 (2)	77 (51)	50 (33)	2 (1)	10 (7)	2 (1)	…	4 (3)	1 (<1)	3 (2)
Kansas City	45	…	9 (20)	31 (69)	…	…	3 (7)	…	…	2 (4)	…
Nashville	33	…	12 (36)	17 (52)	1 (3)	1 (3)	…	…	1 (3)	…	1 (3)
Oakland	45	2 (4)	4 (9)	12 (27)	…	22 (49)	2 (4)	…	1 (2)	2 (4)	…
Rochester	11	1 (10)	1 (10)	5 (45)	…	…	…	…	4 (36)	…	…
Seattle	17	3 (18)	1 (6)	1 (6)	…	10 (59)	…	…	…	1 (6)	1 (6)
2012											
Cincinnati	24	…	3 (13)	…	…	21 (88)	…	…	…	…	…
Houston	55	4 (7)	7 (13)	8 (15)	…	33 (60)	1 (2)	…	2 (4)	…	…
Kansas City	5	…	…	2 (40)	…	3 (60)	…	…	…	…	…
Nashville	16	…	…	1 (6)	…	15 (94)	…	…	…	…	…
Rochester	3	…	3 (100)	…	…	…	…	…	…	…	…

Season, Study Site	Samples Genotyped, No.	Strains Classified, No. (%)[a]									
		G1P[8]	G2P[4]	G3P[8]	G9P[8]	G12P[8]	RotaTeq	Rotarix	Other Genotypes[b]	Mixed[c]	NT[d]
Seattle	15	3 (20)	1 (7)	…	…	10 (67)	…	…	1 (7)	…	…
2013											
Cincinnati	32	…	3 (9)	3 (9)	…	24 (75)	…	1 (3)	…	…	1 (3)
Houston	114	…	5 (5)	28 (25)	4 (3)	74 (65)	…	…	…	2 (2)	1 (<1)
Kansas City	89	…	12 (13)	28 (31)	2 (2)	40 (45)	…	…	…	…	7 (8)
Nashville	138	1 (1)	5 (4)	…	2 (1)	126 (91)	1 (1)	…	…	…	3 (2)
Oakland	85	3 (4)	12 (14)	9 (11)	1 (1)	60 (71)	…	…	…	…	…
Rochester	32	1 (3)	2 (6)	23 (72)	…	6 (19)	…	…	…	…	…
Seattle	56	2 (4)	2 (4)	4 (7)	4 (7)	42 (7)	1 (2)	…	…	…	1 (2)
Overall	1299	44 (3)	184 (14)	453 (35)	49 (4)	506 (39)	15 (<1)	2 (<1)	18 (1)	9 (<1)	19 (1)

Abbreviation: NT, nontypeable.

[a] Percentages may not add to 100 due to rounding in individual cells.

[b] Includes G2P[8], G3P[4], G3P[6], G3P[24], G4P[6], G8P[4], G9P[4], G12P[6], and G24P[14].

[c] Includes G1G2P[8], G2G3P[4]P[8], G2P[4]P[8], G2G9P[4]P[8], G3G12P[8], and G9G12P[8].

[d] Includes G2P[NT], GNTP[NT], and GNTP[8].

[e] No samples were identified as this genotype.

Table 2

Logistic Regression Analysis of Rotavirus Genotype as Predicted by Study Site, Year, Vaccination Status (Any Dose), Race, Hispanic Ethnicity, and Age Group

Variable, Parameter	Odds Ratio (95% CI)	*P* Value
Study site		
Nashville	Reference	<.0001
Rochester	0.051 (.029–.088)	
Cincinnati	0.475 (.301–.751)	
Seattle	0.480 (.280–.821)	
Houston	0.428 (.285–.645)	
Kansas City	0.246 (.154–.392)	
Oakland	1.043 (.614–1.771)	
Year		
2009	Reference	<.0001
2010	0.642 (.357–1.152)	
2011	2.890 (1.788–4.671)	
2012	23.410 (12.866–42.593)	
2013	20.758 (12.916–33.364)	
Race		
White	Reference	.0055
Black	0.723 (.539–.970)	
Other/mixed	0.580 (.411–.820)	
Age		
<1 y	Reference	.8691
1 y	…	
2 y	…	
3–4 y	…	
>4 y	…	
Ethnicity		
Hispanic	Reference	.1154
Non-Hispanic	…	
Vaccination status		
Vaccinated (any dose)	…	.1379
Unvaccinated	Reference	

Abbreviation: CI, confidence interval.