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Rotavirus Vaccine Is Effective Against Rotavirus Gastroenteritis Resulting in Outpatient Care: Results From the Medically Attended Acute Gastroenteritis (MAAGE) Study

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Abstract

Background.—Rotavirus is a common cause of severe pediatric acute gastroenteritis. Two vaccines are licensed in the United States and have demonstrated high effectiveness against moderate to severe disease. However, fewer data are available on rotavirus vaccine effectiveness (VE) against milder disease.

Methods.—We leveraged active surveillance data from Kaiser Permanente Northwest to calculate rotavirus VE against medically attended rotavirus illness among age-eligible children. We utilized a test-negative case-control design and applied 4 distinct case definitions based on reverse transcription–quantitative real-time PCR (qRT-PCR) assay and enzyme immunoassay (EIA) test results. VE was calculated as 100 × (1 – odds ratio), and models were adjusted for age group.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Results.—The VE analysis population comprised 842 children, 799 (95%) of whom had mild disease requiring at most a clinic visit and 698 (83%) of whom were fully vaccinated against rotavirus. Age-adjusted VE was 70% (95% confidence interval [CI], 37–86%) against disease defined solely by qRT-PCR results, 72% (95% CI, 31–89%) against disease as defined by qRT-PCR with a quantification cycle (C_q) value <27, 73% (95% CI, 32–90%) against disease that was qRT-PCR positive but EIA negative, and 62% (95% CI, −20–88%) against disease defined solely by EIA. Results were similar when restricting to disease resulting in at most an ambulatory clinic or emergency department visit.

Conclusions.—These results support the effectiveness of rotavirus vaccination in protecting US children from mild to moderate and severe disease. Our findings are also useful to show the effectiveness of rotavirus vaccination against qRT-PCR–defined illness.

Keywords

rotavirus; rotavirus vaccine effectiveness; vaccine effectiveness; pediatric gastroenteritis

Rotavirus is a common cause of severe pediatric acute gastroenteritis (AGE). Prior to the introduction of rotavirus vaccine in the United States in 2006, nearly every child was infected by the age of 5, leading to an estimated 400 000 physician office visits, more than 200 000 emergency department (ED) visits, and 55 000–70 000 hospitalizations in the United States annually [1]. Presently, 2 rotavirus vaccines are available and recommended for US infants: RotaTeq (Merck Vaccines), a 3-dose vaccine given at 2, 4, and 6 months of age, and Rotarix (GlaxoSmithKline), a 2-dose vaccine given at 2 and 4 months of age. These vaccines have significantly decreased overall rates of medically attended rotavirus disease in the inpatient, ED, and outpatient settings, and vaccine effectiveness (VE) is high against both inpatient and ED outcomes [2-4]. However, data are lacking on VE against milder disease, such as illness requiring only a physician visit [2]. In the present study, we leveraged data from an active surveillance platform within the Kaiser Permanente Northwest (KPNW) system to calculate rotavirus VE against the full spectrum of medically attended rotavirus illness, among children age-eligible to have received vaccination.

METHODS

Parent Study Design

The present analysis draws from a subset of the population recruited and enrolled in the Medically Attended Acute Gastroenteritis (MAAGE) Study, as previously described [5]. Briefly, all enrolled members of the KPNW integrated healthcare delivery system were surveilled prospectively from 1 April 2014 through 30 September 2016; healthcare encounters related to AGE were identified based on International Classification of Diseases, Clinical Modification, 9th revision (ICD-9-CM; used from 1 April 2014–30 September 2015) or 10th revision (ICD-10-CM; used from 1 October 2015–30 September 2016) codes. Participants were recruited from an age-stratified, representative sample of these encounters and asked to submit a stool sample and complete baseline and follow-up questionnaires; because AGE is common among children younger than 5, this age group was oversampled relative to their population size to enable age-specific incidence to be calculated more

precisely. Participants were also queried about their household members and whether those persons had also experienced recent AGE symptoms. Questionnaire data were supplemented by data from the KPNW electronic health record (EHR).

Laboratory Analyses

Stool samples were initially screened at the Oregon State Public Health Laboratory (OSPHL) for rotavirus, in addition to norovirus, astrovirus, and sapovirus, as described previously [5]. Briefly, nucleic acid was extracted using the MagMax 96 viral RNA extraction kit (Thermo Fisher Scientific, Carlsbad, CA, USA). Rotavirus RNA was detected by TaqMan-based reverse transcription–quantitative real-time polymerase chain reaction (qRT-PCR) targeting the NSP3 gene using the AgPath-ID One-Step RT-PCR Kit (Applied Biosystems, Foster City, CA, USA) on the 7500 Realtime PCR platform (Applied Biosystems). The rotavirus-positive stool samples were then shipped frozen on dry ice to the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. At the CDC, specimens were briefly stored at 4°C prior to RNA extraction and confirmatory testing for rotavirus antigen by enzyme immunoassay (EIA) using Premier Rotaclone (Meridian Diagnostics, Inc, USA) according to the manufacturer's instructions. RNA was extracted from 10% stool suspensions as described previously [6], and all resulting RNA extracts were immediately stored at −80°C until testing. RNA extracts underwent confirmatory testing for rotavirus using a qRT-PCR assay that targeted the rotavirus NSP3 gene to detect amplifiable rotavirus nucleic acid using previously described methods [7]. Rotavirus viral protein 7 (VP7) and viral protein 4 (VP4) genotypes were identified and confirmed by a conventional reverse transcription–PCR (RT-PCR) assay and Sanger sequencing as described previously [6]. Specimens that could not be genotyped and confirmed by RT-PCR amplicon analysis and Sanger sequence analysis underwent additional testing using VP7 and/or VP4 genotype-specific singleplexed qRT-PCR assays as described previously [8].

Analysis Population

From the overall study population, we identified children aged 6 months or older at the time of their MAAGE episode who were age-eligible to have received rotavirus vaccine (birthdate on or after 1 December 2005) and who had at least 6 months of continuous enrollment in the health plan prior to the index encounter. Vaccination data for these children were obtained from the KPNW EHR and cross-checked or supplemented by state immunization registry data where available. To mitigate potential exposure misclassification due to missing records, we excluded children without at least 1 dose of diphtheria-tetanus-pertussis (DTaP) vaccine (since most infants receive these vaccines). The population was further restricted to those children who had provided a stool sample that had been tested for rotavirus by qRT-PCR at the OSPHL; rotavirus-positive samples were additionally restricted to those that underwent confirmatory testing at CDC.

Exposure and Outcome Definitions

Rotavirus vaccination status was defined as follows—fully vaccinated: children receiving 2 doses of Rotarix, 3 doses of RotaTeq, or 3 doses of a mixed series (including unspecified rotavirus vaccine) at least 14 days prior to their first encounter date; partially vaccinated: children receiving 1 dose of Rotarix, 1–2 doses of RotaTeq, or 1–2 doses of a mixed series

and/or unspecified rotavirus vaccine at least 14 days prior to their first encounter date; unvaccinated: children receiving 0 doses of any rotavirus vaccine at least 14 days prior to their first encounter date. Four definitions were used for rotavirus cases: qRT-PCR positive (with no quantification cycle [C_q] value cutoff), qRT-PCR positive with a C_q value less than 27 as measured by the CDC laboratory, qRT-PCR positive (no C_q value cutoff) and EIA negative, and EIA positive. Four corresponding definitions were used for controls: qRT-PCR negative, qRT-PCR negative or qRT-PCR positive with a C_q value of 27 or greater, qRT-PCR negative and nonpositive EIA negative (ie, EIA negative or not performed due to negative qRT-PCR result), and nonpositive EIA (ie, EIA negative or not performed due to negative qRT-PCR). Samples that were qRT-PCR positive at OSPHL but not at CDC were excluded from all analyses. Samples that were qRT-PCR positive but EIA negative were included as EIA-negative samples in analyses of EIA-defined VE. We conducted 2 secondary analyses of VE: (1) using only qRT-PCR− and/or conventional RT-PCR–positive cases from which a G12P[8] genotype was identified using the methods described above, with controls defined as children with qRT-PCR–negative stool; (2) using the qRT-PCR–based definition (no C_q value cutoff) but restricting to unvaccinated children and vaccinated children who had received only Rotarix.

Statistical Analysis

For analysis of VE, we utilized a test-negative case-control design wherein rotavirus-positive children (as defined above) were considered as cases, rotavirus-negative children (as defined above) were considered as controls, and the exposure was rotavirus vaccination status. We compared characteristics, such as age at enrollment, vaccination status, and encounter type (remote [ie, video, phone, or email], ambulatory clinic, ED, or hospitalization), of cases and controls using chi-square tests. Unconditional logistic regression was used to assess the effect of vaccination status on rotavirus positivity, controlling for age group (6–11 months, 12–17 months, 18–23 months, 24–59 months, 5–11 years). Vaccine effectiveness was calculated as (1 – odds ratio) × 100%, and rotavirus-unvaccinated children were used as the referent. The effect of full rotavirus vaccination was presented as the primary analysis, given low numbers of partially vaccinated children. Vaccine effectiveness estimates were also calculated stratified by age and subsetting to outpatient encounters only (ambulatory clinic or ED as the highest level of care for the episode). Vaccine failures, defined as fully vaccinated children who tested positive for rotavirus by qRT-PCR, were further investigated.

As a secondary objective, we estimated household transmission of rotavirus as compared to nonrotavirus AGE. Rotavirus AGE was defined by qRT-PCR results as above. We defined “transmission households” as those reporting at least 1 additional member experiencing AGE with a symptom start date on or after the index-case child’s first medical encounter date.

RESULTS

From the overall parent study population, 4951 children were age-eligible to have received rotavirus vaccination and had at least 6 months of health plan enrollment prior to their index AGE encounter date. Out of these children, 4882 (98.6%) had at least 1 documented dose of

DTaP; 842 (17.2%) of these children were randomly selected and enrolled in the MAAGE study, all of whom contributed a stool sample that was tested for rotavirus by qRT-PCR at OSPHL (Table 1). Age skewed younger among children with a stool sample due to purposeful oversampling of children aged younger than 5 years (Table 1). Rotavirus vaccination status was also higher among children with a stool sample, as compared with children without a stool sample. Supplementary analysis showed that rotavirus vaccination status was highest among younger children, while rotavirus positivity tended to be higher among older children (Supplementary Table 1). Among children with a stool sample who had received at least 1 dose of rotavirus vaccine, 555 (73%) had received only Rotarix, 177 (23%) had received only RotaTeq, and 29 (4%) had received a mixed course.

Fifty-five (6.5%) of the 842 stool samples tested positive for rotavirus, of which 53 were sent to CDC for confirmatory testing, where 49 tested positive by qRT-PCR and 17 also tested positive by EIA; 31 had a C_q value less than 27. Rotavirus cases tended to be older, had more severe encounter types, and were less likely to be vaccinated compared with controls (Table 1). These trends were especially pronounced when using the EIA-based case definition. Among the 49 qRT-PCR–positive cases, 36 (73%) were identified as G12P[8], 7 (14%) were identified as G2P[4], 4 (8%) were of other genotypes, and 2 (4%) could not be genotyped.

Estimates of all-ages rotavirus VE were highly similar across qRT-PCR–based case definitions and ranged from 70% to 73% (Table 2). The point estimate for EIA-defined rotavirus VE was slightly lower, but confidence intervals (CIs) were wide and overlapped those of other definitions. Vaccine effectiveness estimates tended to be substantially higher in the youngest children, but VE could not be calculated for all definitions in all age groups due to the low sample size. All-ages adjusted VE against G12P[8] rotavirus (75%; 95% CI, 38–89%) was similar to VE estimates for other qRT-PCR–based definitions. All-ages adjusted VE for a full series of Rotarix (77%; 95% CI, 47–90%) was also similar to the overall VE estimate.

Of the 34 vaccine failures, 12 (35%) were also EIA positive, while 4 of the 22 EIA-negative vaccine failures (18%) also tested positive for another study virus (norovirus, astrovirus, or sapovirus). The majority of these vaccine failures (25; 74%) occurred in February–May 2015, a known high season for rotavirus [9]. Three of these children had a known immunosuppressive condition.

Children who tested positive for rotavirus by qRT-PCR were significantly more likely to have household members who reported AGE subsequent to the index child’s first AGE-related medical encounter (58% of rotavirus-positive cases vs 21% of rotavirus-negative controls; $P < .0001$) (Supplementary Table 2).

DISCUSSION

We found rotavirus vaccine to be effective against medically attended, qRT-PCR–detected rotavirus illness among children enrolled in an integrated healthcare delivery system in the US Pacific Northwest. To our knowledge, this is one of only a few studies to assess rotavirus

VE against disease requiring only outpatient care and to utilize both qRT-PCR and EIA for testing and definition of rotavirus cases.

Previous estimates of rotavirus VE against outpatient-attended disease in the United States are derived from secondary analysis of insurance claims–based cohorts and vary widely [10, 11], while VE against ED visits has been estimated at 79–81% using case-control data [2]. Although our VE estimates of 62–73% against medically attended rotavirus are lower than many previously reported estimates, this might be expected given that our population was more than 90% ambulatory clinic–only disease, and rotavirus VE tends to be highest against the most severe disease [2]. This distribution of severity also drove the similarities seen in our findings of VE among all medically attended AGE encounters as compared with just ambulatory clinic and ED visits. We also found VE to be notably higher in children aged younger than 2 years as compared with older children, although the limited sample size precluded definitive conclusions. While the sustained effectiveness of rotavirus vaccination has been documented into the second and even the fourth year of life in the United States [12, 13], data from both the United States and Australia suggest that effectiveness may wane with increasing age [13, 14]. Only genotype G12P[8] was detected in sufficient quantities for a genotype-specific analysis of VE; this genotype is known to be in wide circulation in the United States [15]. The moderately high VE against G12P[8] in this study is in alignment with previous research showing good protection against this strain by both vaccines [13, 16]. Similarly, results for Rotarix-specific VE were comparable to that shown in previous research, although somewhat lower as would be expected for milder disease [13, 16]. Our results suggesting that rotavirus may be more likely than other causes of AGE to be transmitted within the household were also consistent with prior research [17], although our study design limits our ability to definitively identify and characterize household outbreaks.

Interestingly, although qRT-PCR assays are typically more sensitive for detection of rotavirus [18], whereas EIA is commonly thought of as more clinically meaningful [19, 20], our estimates of all-ages VE were notably higher in qRT-PCR–based definitions than in our EIA-based definition. This was true even for our definition requiring EIA negativity and qRT-PCR positivity, which we might have expected to capture children who were shedding rotavirus but whose illness was not rotavirus associated; however, the similar VE estimates across definitions suggest that, in our study population, all definitions reliably indicated rotavirus disease. This is in contrast to findings from the US-based New Vaccine Surveillance Network, which showed higher VE estimates for EIA-based case definitions [19]. However, our findings were similar to previous research in that EIA-based cases tended to have higher severity than qRT-PCR–based cases [20]. It seems possible that our findings of lower VE in EIA-defined cases could be related to the older age of these cases as compared with qRT-PCR–defined cases. The point estimates for children younger than 2 years of age were highly similar across both qRT-PCR− and EIA-based case definitions, suggesting a possible comparability of the assays for VE estimation in this age group. However, the present study was not designed to address this question, and there was a relatively low sample size of EIA-defined cases, so definitive conclusions are not possible.

The following limitations should be considered. Although the analytical sample was more than 800, there were low numbers of rotavirus-unvaccinated children and low numbers of

rotavirus-positive children, limiting statistical power for stratified results, as well as the power to detect effectiveness against EIA-positive rotavirus. We were unable to calculate RotaTeq-specific VE estimates or age-stratified VE estimates for Rotarix, but VE has been found to be similar across both vaccines [16] as well as with mixed series [21]. As with any modeling analysis, there remains the possibility of uncontrolled confounding, such as by year of enrollment (which may have affected circulating genotypes and thus possibly vaccine performance, as well as overall rotavirus prevalence and population vaccination coverage). Data were too sparse to include year in all models, but inclusion in the all-ages qRT-PCR model did not change results.

These results confirm the importance of rotavirus vaccination in protecting US children from rotavirus disease requiring outpatient care. The observed effectiveness of rotavirus vaccine against even mild disease supports continued universal rotavirus vaccination in the United States and may provide useful input into future economic analyses of vaccination. Our findings are also useful to show the effectiveness of rotavirus vaccination against qRT-PCR–confirmed illness, as molecular methods are increasingly utilized in the diagnosis of gastroenteritis [22].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Rotavirus Vaccine–Eligible Children With Medically Attended Acute Gastroenteritis, the Subset of These Children Submitting a Stool Sample, and Rotavirus Cases Versus Test-negative Controls

	All Age-eligible Children With MAAGE		Children With MAAGE and Stool Sample		Rotavirus qRT-PCR Negative		Rotavirus qRT-PCR Positive[a]			Rotavirus qRT-PCR Positive[a] with C_q <27			Rotavirus qRT-PCR Positive[b] and EIA Negative			Rotavirus EIA Positive[c]		
	n	%	n	%	n	%	n	%	*P*[d]	n	%	*P*[d]	n	%	*P*[d]	n	%	*P*[d]
Sex																		
Female	2250	46.1	389	46.2	365	46.4	19	38.8	.37	13	41.9	.77	12	37.5	.41	7	41.2	.87
Male	2632	53.9	453	53.8	422	53.6	30	61.2		18	58.1		20	62.5		10	58.8	
Age group																		
6–11 months	678	13.9	163	19.4	158	20.1	3	6.1	.08	3	9.7	.16	3	9.4	.24	0	0.0	.017
12–17 months	693	14.2	148	17.6	141	17.9	7	14.3		2	6.5		7	21.9		0	0.0	
18–23 months	479	9.8	119	14.1	107	13.6	11	22.4		6	19.4		8	25		3	17.6	
24–59 months	1476	30.2	283	33.6	263	33.4	19	38.8		15	48.4		11	34.4		8	47.1	
5–11 years	1556	31.9	129	15.3	118	15.0	9	18.4		5	16.1		3	9.4		6	35.3	
Most severe encounter type																		
Remote	134	2.7	25	3.0	24	3.0	1	2.0	.24	1	3.2	.017	1	3.1	.96	0	0.0	.002
Ambulatory clinic	4520	92.6	774	91.9	725	92.1	43	87.8		25	80.6		30	93.8		13	76.5	
Emergency department	201	4.1	38	4.5	33	4.2	5	10.2		5	16.1		1	3.1		4	23.5	
Inpatient	27	0.6	5	0.6	5	0.6	0	0.0		0	0		0	0		0	0.0	
Rotavirus vaccination status																		
None	794	16.3	80	9.5	68	8.6	12	24.5	.001	8	25.8	.006	7	21.9	.032	5	29.4	.013
Partial	410	8.4	64	7.6	59	7.5	3	6.1		1	3.2		3	9.4		0	0.0	
Full	3678	75.3	698	82.9	660	83.9	34	69.4		22	71		22	68.8		12	70.6	

Abbreviations: CDC, Centers for Disease Control and Prevention; C_q, quantification cycle; EIA, enzyme immunoassay; MAAGE, medically attended acute gastroenteritis; OSPHL, Oregon State Public Health Laboratory; qRT-PCR, reverse transcription–quantitative real-time polymerase chain reaction.

[a]Excludes 2 samples that were rotavirus positive at the OSPHL but not shipped to the CDC and 4 samples that were qRT-PCR-positive at OSPHL but not at CDC.

[b]Excludes 2 samples that were rotavirus positive at OSPHL but not shipped to CDC, 4 samples that were rotavirus qRT-PCR positive at OSPHL but not qRT-PCR positive at CDC, and 17 samples that were qRT-PCR positive and EIA positive at CDC.

[c] Excludes 2 samples that were rotavirus positive at OSPHL but not shipped to CDC and 4 samples that were rotavirus qRT-PCR positive at OSPHL but not qRT-PCR positive at CDC; 32 samples that were qRT-PCR positive but EIA negative are included as EIA-negative samples.

[d] All *P* values are χ^2 tests versus controls (rotavirus-negative children as defined by qRT-PCR and/or EIA).

Table 2.

Age-Stratified Vaccine Effectiveness Estimates for the Effect of Complete-Series Rotavirus Vaccination Against Medically Attended Rotavirus Acute Gastroenteritis (Any Encounter Type) and Acute Gastroenteritis Resulting in Outpatient Care

	qRT-PCR[a]			qRT-PCR With C_q cutoff <27[a]			qRT-PCR + and EIA[b]			EIA[c]		
	VE	**(95% CI)**	***P***	**VE**	**(95% CI)**	***P***	**VE**	**(95% CI)**	***P***	**VE**	**(95% CI)**	***P***
All encounter types												
All age-eligible children[d]	70	(37, 86)	.002	72	(31, 89)	.005	73	(32, 90)	.006	62	(−20, 88)	.10
<2 years of age	90	(71, 96)	<.0001	90	(62, 97)	.0006	90	(69, 96)	<.0001	87	(−51, 99)	.10
2 to <5 years of age	40	(−182, 87)	.51	53	(−127, 90)	.35	Cannot estimate	…		77	(−22, 96)	.084
5–11 years of age	32	(−199, 85)	.61	39	(−283, 90)	.60	59	(−567, 98)	.53	18	(−372, 86)	.83
Ambulatory clinic and emergency department encounters only												
All age-eligible children[d]	70	(37, 86)	.002	73	(33, 89)	.005	74	(33, 90)	.005	61	(−22, 88)	.11
<2 years of age	89	(70, 96)	<.0001	89	(61, 97)	.0007	89	(68, 96)	<.0001	86	(−55, 99)	.11
2 to <5 years of age	45	(−164, 88)	.46	57	(−110, 91)	.29	Cannot estimate	…		77	(−22, 96)	.084
5–11 years of age	31	(−207, 84)	.63	37	(−292, 90)	.62	58	(−585, 97)	.54	15	(−385, 85)	.85

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; C_q, quantification cycle; EIA, enzyme immunoassay; OSHPL, Oregon State Public Health Laboratory; qRT-PCR, reverse transcription–quantitative real-time polymerase chain reaction; VE, vaccine effectiveness.

[a] Excludes 2 samples that were rotavirus positive at OSPHL but not shipped to the CDC and 4 samples that were rotavirus qRT-PCR positive at OSPHL but not qRT-PCR positive at CDC.

[b] Excludes 2 samples that were rotavirus positive at OSPHL but not shipped to CDC, 4 samples that were rotavirus qRT-PCR positive at OSPHL but not qRT-PCR positive at CDC, and 17 samples that were qRT-PCR and EIA positive at CDC.

[c] Excludes 2 samples that were rotavirus positive at OSPHL but not shipped to CDC and 4 samples that were rotavirus qRT-PCR positive at OSPHL but not qRT-PCR positive at CDC; 32 samples that were qRT-PCR positive but EIA negative are included as EIA-negative samples.

[d] Results adjusted for age group.