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Sustained Effectiveness of Monovalent and Pentavalent Rotavirus Vaccines in Children

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Abstract

Objective—Using case-control methodology, we measured the vaccine effectiveness (VE) of the 2-dose monovalent rotavirus vaccine (RV1) and 3-dose pentavalent vaccine (RV5) series given in infancy against rotavirus disease resulting in hospital emergency department or inpatient care.

Study design—Children were eligible for enrollment if they presented to 1 of 3 hospitals in Atlanta, Georgia with diarrhea ≤10 days duration during January–June 2013 and were born after RV1 introduction. Stool samples were tested for rotavirus by enzyme immunoassay and immunization records were obtained from providers and the state electronic immunization information system (IIS). Case-subjects (children testing rotavirus antigen-positive) were compared with children testing rotavirus antigen-negative.

Results—Overall, 98 rotavirus-case subjects and 175 rotavirus-negative controls were enrolled. Genotype G12P[8] predominated (n=87, 89%). The VE of 2 RV1 doses was 84% (95% CI 38, 96) among children aged 8–23months and 82% (95% CI 41, 95) among children aged ≥24 months. For the same age groups, the VE of 3 RV5 doses was 80% (95% CI 27, 95) and 87% (95% CI 22, 98), respectively.

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The authors declare no conflicts of interest.

Conclusions—Under routine use, the RV1 and RV5 series were both effective against moderate-to-severe rotavirus disease during a G12P[8] season, and both vaccines demonstrated sustained protection beyond the first two years of life.

Keywords

rotavirus vaccine; vaccine effectiveness; rotavirus; immunization; gastroenteritis; diarrhea

In February 2006, the Advisory Committee on Immunization Practices (ACIP) recommended universal rotavirus vaccination of US infants, with 3 doses of the pentavalent rotavirus vaccine [RV5], RotaTeq (Merck & Co., Inc.) to be given at ages 2, 4 and 6 months.(1) In June 2008, following licensure of the monovalent (RV1) 2-dose vaccine, Rotarix (GlaxoSmithKline Biologicals), ACIP recommendations were updated to include this vaccine with doses recommended at ages 2 and 4 months. Both vaccines are now widely used in the US with no preferential recommendation for either product. In the US, the first dose of rotavirus vaccine (RV) is to be given at age 6 weeks 0 days through 14 weeks 6 days and the last dose by age 8 months 0 days.(1)

Given its later introduction, only limited US data are available on the effectiveness of RV1 (2–4) and no data are available among US children aged ≥24 months. Our objective was to measure the effectiveness of RV1 under routine use through case-control methodology. We performed the evaluation in Georgia, which participates in the Emerging Infections Program Network(5) and where RV1 was available through the Vaccines for Children Program(6) and the private sector. RV5 was also used in the state and therefore effectiveness of RV5 could also be assessed. Evaluating the effectiveness of both RV1 and RV5 in concurrent use with the same methodology is valuable given the differences in the composition and administration schedule of the two products.

METHODS

We conducted active surveillance for children with acute gastroenteritis at 3 hospitals in Atlanta, Georgia (Scottish Rite Children's Hospital, Hughes Spalding Children's Hospital and Egleston Children's Hospital) from January 23, 2013, through June 30, 2013, as previously described(2). Eligible children were those who: (1) presented to the hospital with acute gastroenteritis (≥3 looser-than-normal stools in a 24-hour period during the illness, and onset of diarrhea ≤ 10 days at presentation) as the main or one of the main reasons for the visit and managed as an emergency department (ED) patient, short-stay patient or inpatient; (2) were eligible to have received at least 1 RV1 dose ≥14 days before presentation (born ≥ March 1, 2009, based on timing of RV1 use in the area) and age at evaluation (≥56 days), and (3) resident of Georgia. Children with immune deficiency (eg, malignancy, HIV infection) were not eligible. After written informed consent was obtained, a standardized questionnaire was administered verbally to the parent/guardian and a stool sample from the patient was collected within 14 days of diarrhea onset.

Stool samples were tested at CDC for rotavirus antigen by enzyme immunoassay (EIA) using the Premier™ Rotaclone® kit (Meridian BioScience, Cincinnati, OH, USA). Children were classified as either a rotavirus case-subject or a rotavirus test-negative control based on

the EIA result. Samples that were rotavirus antigen-positive were genotyped as described previously(7).

This project was reviewed for human subjects' protection and approved at CDC and the participating institutions.

Vaccine information

The names of each subject's healthcare providers were obtained from the parent/guardian, the medical record and state IIS electronic immunization information system (IIS), Georgia Registry of Immunization Transactions and Services (GRITS). Providers were contacted by phone or letter and asked to provide written documentation on doses of RV (dates, manufacturer/product name and lot number), DTaP, and PCV that they or any of the child's providers had administered, using sources other than the state IIS. In the unusual circumstance that there was a discrepancy on RV doses, providers were re-contacted to clarify; if records were still discrepant, the provider record was usually accepted over the IIS. In the unusual circumstance that the lot number reported by the provider or in the IIS was not consistent with the reported product name, the product was reclassified based on the lot number. For 17% of the children, providers reported using only the IIS for recording their vaccination information and this was therefore the only source used. For 2 children, a provider record could not be obtained and the IIS record was used as the child's record because it covered the early infancy period (≥3 doses of DTaP, PCV, or full series of RV received through age 8 months) and was therefore considered likely accurate for rotavirus vaccine information.

Statistical analyses

Age (in days) at diarrhea onset and at each vaccine administration was calculated. For analysis, a RV dose was counted if it had been administered ≥14 days before the date of diarrhea onset. Children who had received both RV1 and RV5 or for whom the vaccine type of ≥1 dose was unknown were excluded so that vaccine type-specific VE could be calculated.

The odds ratio and 95% confidence interval for receipt of RV doses for case-subjects compared with controls were determined using unconditional logistic regression; rotavirus VE was calculated as (1 minus odds ratio [OR]) × 100%. Separate models were used to assess the VE of 2 RV1 doses vs no RV doses, and 3 RV5 doses vs no RV doses. In almost all children, rotavirus vaccination status did not change after age 8 months (the maximum age for the last dose of rotavirus vaccine per ACIP recommendations). Therefore, overall VE was calculated for children aged ≥8 months 0 days, which eliminated the need to control for confounding by age. Children aged <8 months were not included in VE analyses.

In all models, we controlled for birth quarter (e.g., Jan–March, April–June) and birth year. To identify other possible confounding variables, all case-subjects and controls that were aged ≥8 months and had an immunization record available for analysis were compared by univariate analysis on factors possibly associated with rotavirus disease(8, 9) (Table I; available at www.jpeds.com); those factors with p-value<0.05 (ie, sex, insurance status, breastfed in the month before illness, attending childcare in the month before illness) were

assessed for confounding in the models by backward elimination, and were retained in the model if the VE point estimate changed by ≥2.5 percentage points. Univariate analysis were repeated for cases that received intravenous fluids vs. controls, and factors assessed for confounding were sex, insurance status, race, and breastfed for ≥4 months. Sub-analyses were planned a priori to assess VE by age (stratified analyses using an interaction term for age group and vaccination status in the model), by type of hospital stay (i.e., ED, inpatient/short-stay) and receipt of intravenous fluids, if case numbers were sufficient. Analyses were performed using Stata 12 (Stata Corp, College Station, TX).

RESULTS

Overall, an adequate stool sample was obtained and tested on 273 (81%) of 339 eligible children, yielding a total of 98 rotavirus antigen-positive and 175 rotavirus antigen-negative children (Table II). The sample was collected ≤ 7 days from diarrhea onset in 93% of children aged ≥8 months. Among the 93 rotavirus case-subjects aged ≥8 months, 14 (15%) had been managed as hospital inpatients, 1 (1%) as short-stay patient, and 78 (84%) as ED patients; overall 37 (40%) had received intravenous fluids. Eighty-seven (89%) of the 98 cases overall (and 88% of cases aged ≥8 months) were genotyped as G12P[8]; the remaining genotypes were G3P[8] (7, 7%), G9P[8] (2, 2%), G1P[8] confirmed by sequencing to be wild-type (1, 1%) and non-type able (1,1%).

Among children aged ≥8 months, an immunization record was available for analysis in 99% of rotavirus case-subjects and 99% of rotavirus negative controls (Table II). Of the 402 RV doses in the vaccination records available for analysis among children aged ≥8 months, a manufacturer-specific lot number was available for 92% of doses, manufacturer/product name was available but without lot number for 7% and neither manufacturer/product name nor lot number was available for 1% of doses. Of the 92 rotavirus-case subjects aged ≥8 months with an analyzable record, 35 (38%) had no RV doses; of the 134 rotavirus negative children, 21 (16%) had no RV doses (Table III; available at www.jpeds.com).

Vaccine Effectiveness of RV1 and RV5

Overall, the effectiveness of 2 RV1 doses vs. 0 doses among children aged ≥8 months was 83% (95% CI 58, 93), with similar results in those aged 8 through 23 months (84%, 95% CI 38, 96) and those aged ≥24 months (82%, 95% CI 41, 95; in this subset, median age (IQR; maximum age) of cases=32.4 (12.5; 47.1) months; of controls=31.4 (10.8; 47.1) months) (Table IV). The 2-dose RV1 effectiveness against the use of intravenous fluids for rotavirus disease was 90% (95% CI 51, 98). There were insufficient case numbers to assess RV1 effectiveness by type of hospital stay.

The effectiveness of 3 RV5 doses vs. 0 doses among children aged ≥8 months was 83% (95%CI 51, 94), with similar results in the two age groups (in group aged ≥24 months, median age (IQR, maximum age) of cases=30.0 (13.0; 47.1) months; of controls=32.2 (10.9; 46.2) months) (Table V). The 3-dose RV5 effectiveness against the use of intravenous fluids for rotavirus disease was 92% (95% CI 53, 99). There were insufficient case numbers to assess RV5 effectiveness by type of hospital stay.

DISCUSSION

RV1 was introduced later than RV5 in the US and hence there are few RV1-specifc vaccine effectiveness assessments from the US, and none among children 2 years and older. Using children enrolled through active surveillance at 3 Atlanta area hospitals, we demonstrated that 2 doses of RV1 and 3 dose of RV5 both provide good protection against rotavirus disease resulting in hospitalization or ED care combined, including among children aged ≥24 months.

Overall, the 2-dose RV1 effectiveness estimate we found for children aged 8 months through 23 months (84%, CI 38, 96) against rotavirus hospitalization or ED care combined in 2013 is between that of our previous estimate (using 5 total hospitals, VE=91 [95% CI 80, 95] using rotavirus-negative controls)(2), and that of the New Vaccine Surveillance Network (NVSN) (70%, CI 39, 86)(3). Our 2013 results are based on smaller case and control numbers and hence our confidence intervals are wider than our previous evaluation. Different from the previous US reports, our 2013 results are based on an almost exclusively G12P[8] season; these data demonstrate further the broad protection from the G1P[8] vaccine. Including children that are older than in our previous evaluation, we again demonstrate high effectiveness of RV1 against rotavirus disease resulting in use of intravenous fluids among those aged ≥ 8 months (90% CI 51,98).

Our results indicate that protection from RV1 against moderate-to-severe rotavirus disease, under routine use, is well sustained beyond age 24 months. To our knowledge, RV1 VE specifically in children this age or older has not previously been reported from the US or another high-income country under real-world conditions. In the extension of the RV1 clinical trial in high-income locations in Singapore, Hong Kong and Taiwan, high efficacy was found for the third year of life (100%, 95% CI 67.5, 100) against severe rotavirus disease defined as that requiring hospitalization or re-hydration therapy in a medical facility and scoring ≥11 on an established clinical severity score (Vesikari scale)(10, 11). Our results of sustained effectiveness of 3 doses of RV5 among children aged ≥24 months are similar to the results reported from NVSN(3), where VE was 83% (95% CI 81, 91) and 79% (95% CI 56, 90) in the third and fourth years of life, respectively, against our similar combined outcome of hospitalization or ED care. In that evaluation, overall effectiveness of 3 doses of RV5 against disease from genotype G12P[8] was 83% (95% CI 57, 93), the same point estimate as our overall result for RV5 during this G12P[8] season. Although our evaluation was not designed to measure differences in effectiveness between the vaccines, the overall effectiveness of the 2-dose RV1 series and the 3-dose RV5 series appear similarly high in this evaluation using the same methodology in the same locations and time period.

The main limitation of our evaluation was the relatively limited number of cases and rotavirus-negative controls, which resulted in wider confidence intervals of our VE estimates and precluded assessment of vaccine type-specific effectiveness by hospital stay setting. As widespread use of highly effective vaccines continues to reduce the incidence of moderate-to-severe rotavirus illness in US children, estimating vaccine type-specific effectiveness (and any permutations, such as partial series or mixed 2-dose series) through case-control evaluations will require a large hospital network. Fortunately, other epidemiological

approaches provide important data to help monitor the overall performance of the US rotavirus vaccine program(4, 12–16).

During a genotype G12P[8] season, the 2-dose RV1 series provided good protection against moderate-to-severe rotavirus gastroenteritis in US children, with sustained protection demonstrated in those aged ≥2 years. The 3-dose RV5 series was also similarly effective in children below and above age 2 years.

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Abbreviations

CI	confidence interval
DTaP	diphtheria-tetanus-acellular pertussis
ED	emergency department
IIS	immunization information system
PCV	pneumococcal conjugate vaccine
OR	odds ratio
PCV	pneumococcal conjugate vaccine
RV	rotavirus vaccine
RV1	monovalent rotavirus vaccine
RV5	pentavalent rotavirus vaccine
VE	vaccine effectiveness

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Online Table 1

Characteristics of children who tested rotavirus positive or rotavirus negative, were aged ≥8 months and had an immunization record available for analysis

Characteristic	Rotavirus positive (n=92)		Rotavirus negative (n=134)		p-value
	Responses 'Yes'/Total	% Yes	Responses 'Yes'/Total	% Yes	
Male	67/92	73	73/134	55	0.0053
Race					0.13
White	31/92	34	32/134	24	
Black	45/92	49	66/134	49	
Other/Unknown	16/92	17	36/134	27	
Hispanic ethnicity	14/92	15	34/134	25	0.067
Insurance					0.011
Private (any)	28/91	31	19/134	14	
Public	60/91	66	110/134	82	
None	3/91	3	5/134	4	
Primary caretaker's age (yrs)	median 29 (IQR 9.5)		median 28 (IQR 9)		
Primary caretaker aged <25 yrs	22/92	24	36/134	27	0.59
Primary caretaker's education < high school graduate or GED	9/91	10	17/133	13	0.51
Other child aged <24 months in household	15/92	16	17/134	13	0.44
Born >4 weeks early	2/92	2	9/134	7	0.12
Birth weight <2500g	4/86	5	16/128	12	0.053
Ever breastfed	69/92	75	98/134	73	0.75
Breastfed 4 or more months	46/92	50	50/134	37	0.058
Breastfed in month before diarrheal illness	4/92	4	16/134	12	0.048
In childcare during month before diarrheal illness	47/92	51	43/134	32	0.0042

Abbreviations: IQR=Interquartile range

Table 2

Number of children who tested rotavirus positive or rotavirus negative by enzyme immunoassay and immunization record status

	All ages	Age ≥8 months		Age 8–23 months		Age ≥24 months	
Test result	**Enrolled and tested**	**Enrolled and tested**	**Immunization record available for analysis No. (%)**	**Enrolled and tested**	**Immunization record available for analysis No. (%)**	**Enrolled and tested**	**Immunization record available for analysis No. (%)**
Rotavirus positive	98	93	92 (99)	42	42 (100)	51	50 (98)
Rotavirus negative	175	136	134 (99)	75	74 (99)	61	60 (98)
TOTAL	273	229		117		112	

Online Table 3

Rotavirus vaccination status among children aged ≥ 8 months with an immunization record available for analysis, by rotavirus EIA result

Number of rotavirus vaccine doses[a]	Subjects with rotavirus n (%)		Rotavirus-negative controls n (%)	
0	35 (38%)		21 (16%)	
1	6 (7%)	3 RV1	6 (4%)	4 RV1
		2 RV5		2 RV5
		1 product unknown		
2	25 (27%)	16 all RV1	59 (44%)	48 all RV1
		3 all RV5		8 all RV5
		6 both products or product unknown for ≥1 dose		3 both products or product unknown for ≥1 dose
3	26 (28%)	0 all RV1	48 (36%)	2 all RV1[b]
		22 all RV5		34 all RV5
		4 both products or product unknown for ≥1 dose		12 both products or product unknown for ≥1 dose
Total	92		134	

[a] A rotavirus vaccine dose was counted if it had been administered ≥14 days before the date of diarrhea onset.

[b] Children with 3 RV1 doses were excluded from analysis of vaccine effectiveness of 2 RV1 doses.

Abbreviations: RV1: monovalent rotavirus vaccine; RV5: pentavalent rotavirus vaccine

Table 4

Vaccine effectiveness of 2 RV1 doses versus 0 RV1 doses

	Cases	No. (%) vaccinated	Controls	No. (%) vaccinated	VE	95% CI
All cases						
Age ≥8 m	51	16 (31)	69	48 (70)	**83**[a]	58–93
Age 8m through 23 m	21	9 (43)	37	30 (81)	**84**[a]	38–96
Age ≥24 m s	30	7 (23)	32	18 (56)	**82**[a,b]	41–95
Cases that received IV fluids						
Age ≥ 8m	22	6 (27)	69	48 (70)	**90**[c]	51–98

[a]Model also included gender

[b]Age median (IQR): cases 32.4m (12.5); controls 31.4m (10.8)

[c]Model also included gender and insurance status (private vs public vs no insurance)

Abbreviations: RV1-monovalent rotavirus vaccine; VE, vaccine effectiveness, CI-confidence interval; m-months; IV-intravenous, IQR-interquartile range

Table 5

Vaccine effectiveness of 3 RV5 doses versus 0 RV5 doses

	Cases	No. (%) vaccinated	Controls	No. (%) vaccinated	VE	95% CI
All cases						
Age ≥8m	57	22 (39)	55	34 (62)	**83**[a]	51–94
Age 8 m through 23m	28	16 (57)	31	24 (77)	**80**[a]	27–95
Age ≥24 m	29	6 (21)	24	10 (42)	**87**[a,b]	22–98
Cases that received IV Fluids						
Age ≥8 m	25	9 (36)	55	34 (62)	**92**[a]	53–99

[a]Model also included insurance status (private vs public vs no insurance)

[b]Age median (IQR): cases 30.0m (13.0); controls 32.2m (10.9)

Abbreviations RV5: pentavalent rotavirus vaccine; VE-vaccine effectiveness; m-month; IV-intravenous; IQR-interquartile range