Effectiveness of Monovalent and Pentavalent Rotavirus Vaccine

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KEY WORDS

rotavirus vaccine, vaccine effectiveness, rotavirus, immunization, gastroenteritis, diarrhea

ABBREVIATIONS

CI—confidence interval
DTaP—diphtheria-tetanus-acellular pertussis
ED—emergency department
EIA—enzyme immunoassay
IIS—immunization information system
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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WHAT'S KNOWN ON THIS SUBJECT: Monovalent rotavirus vaccine was introduced for infants in the United States in 2008. Previous US evaluations have not specifically assessed the performance of this vaccine under routine use.

WHAT THIS STUDY ADDS: Using the same methodology and covering the same time period, high effectiveness (~90%) was demonstrated for the monovalent and the pentavalent rotavirus vaccine series against rotavirus disease resulting in emergency department/inpatient care, in children up to 2 years of age.

abstract

OBJECTIVE: Previous US evaluations have not assessed monovalent rotavirus vaccine (RV1, a G1P[8] human rotavirus strain) effectiveness, because of its later introduction (2008). Using case-control methodology, we measured the vaccine effectiveness (VE) of the 2-dose RV1 and 3-dose pentavalent vaccine (RV5) series against rotavirus disease resulting in hospital emergency department or inpatient care.

METHODS: Children were eligible for enrollment if they presented to 1 of 5 hospitals (3 in Georgia, 2 in Connecticut) with diarrhea of ≤10 days' duration during January through June 2010 or 2011, and were born after RV1 introduction. Stools were collected; immunization records were obtained from providers and state electronic immunization information system (IIS). Case-subjects (children testing rotavirus antigen-positive) were compared with 2 control groups: children testing rotavirus negative and children selected from IIS.

RESULTS: Overall, 165 rotavirus-case subjects and 428 rotavirus-negative controls were enrolled. Using the rotavirus-negative controls, RV1 VE was 91% (95% confidence interval [CI] 80 to 95) and RV5 VE was 92% (CI 75 to 97) among children aged ≥8 months. The RV1 VE against G2P[4] disease was high (94%, CI 78 to 98), as was that against G1P[8] disease (89%, CI 70 to 96). RV1 effectiveness was sustained among children aged 12 through 23 months (VE 91%; CI 75 to 96). VE point estimates using IIS controls were similar to those using rotavirus-negative controls.

CONCLUSIONS: RV1 and RV5 were both highly effective against severe rotavirus disease. RV1 conferred sustained protection during the first 2 years of life and demonstrated high effectiveness against G2P[4] (heterotypic) disease. *Pediatrics* 2013;132:e25–e33

Universal rotavirus vaccination was recommended for US infants by the Advisory Committee on Immunization Practices in February 2006, with 3 doses of the pentavalent rotavirus vaccine [RV5], RotaTeq (Merck & Co., Inc. Whitehouse Station, New Jersey), to be given at ages 2, 4, and 6 months.[1] In June 2008, after licensure of the monovalent (RV1) 2-dose vaccine, Rotarix (GlaxoSmithKline Biologicals Rixensart, Belgium), Advisory Committee on Immunization Practices recommendations were updated to include this vaccine with doses recommended at ages 2 and 4 months. In the United States, the first dose of rotavirus vaccine (RV) is to be given at age 6 weeks through 14 weeks 6 days and the last dose by age 8 months 0 days.[1]

Given differences in strain composition and administration schedule, understanding the effectiveness of both RV1 and RV5 in concurrent use is valuable. Previous evaluations that have measured the field effectiveness of RV among US children were not able to specifically assess the performance of RV1 because they were performed before RV1 was in wide use. Our objective was to measure the effectiveness of RV1 under routine use through case-control methodology. We performed the evaluation in 2 states, Georgia and Connecticut, that were part of the Emerging Infections Program Network[2] and where RV1 was available through the Vaccines for Children Program[3] and the private sector. RV5 was also used in the states and therefore effectiveness of RV5 could be assessed also. These states had a state electronic immunization information system (IIS)[4] and further experience using these systems for assessing vaccine effectiveness (VE) in US children was an additional goal.

METHODS

Children With Gastroenteritis: Rotavirus Case-Subjects and Rotavirus-Negative Controls

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), and 2 hospitals in Connecticut (Yale-New Haven Children's Hospital in New Haven and Connecticut Children's Medical Center in Hartford) from January through June in 2010 and 2011. Eligible children were those who met all the following criteria: (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 1 of the main reasons for the visit and managed as an emergency department (ED) patient, short-stay patient, or inpatient; (2) eligible to have received at least 1 RV1 dose ≥14 days before presentation, by date of birth (based on timing of RV1 use in the area: Georgia, born March 1, 2009 or later; Connecticut, born August 1, 2008 or later) and age at evaluation (≥56 days); and (3) resident of Connecticut or, in Georgia, lived in 1 of 8 metropolitan Atlanta counties or within 40 miles of the treating hospital. Children with a severely immunocompromising condition (eg, malignancy, HIV infection) were not eligible. After written informed consent was obtained, a standardized questionnaire was administered verbally to the parent/guardian that queried demographics, symptoms, household information, and immunization providers, and a stool sample was collected within 14 days of diarrhea onset.

Stool samples were tested at the Centers for Disease Control and Prevention for rotavirus antigen by enzyme immunoassay (EIA) using the Premier Rotaclone kit (Meridian BioScience, Cincinnati, OH). Children were classified as either a rotavirus case-subject or a rotavirus-negative gastroenteritis control based on the EIA result. Samples that were rotavirus antigen–positive were genotyped as described previously.[5]

Enrollment was performed ~40 hours per week and included evening and weekend periods. This project was reviewed for human subjects protection and approved at the Centers for Disease Control and Prevention and the participating institutions.

Vaccine Information

The state public health departments in Georgia and Connecticut maintain an IIS in which most pediatric immunization providers participate. The IISs are populated weekly with data from birth records of infants born in the state. Children born out of state are added to the system when they are provided immunizations by a clinic/provider that participates in the IIS. As of June 2011, 88% and 90% of children aged 4 months to 5 years in the Georgia and Connecticut IIS, respectively, had ≥2 immunizations recorded in the IIS (see Supplemental Information). For this evaluation, IIS staff queried the IIS for each rotavirus case-subject and rotavirus-negative control using the child's name and birthdate. Dates, manufacturer, and lot number (if available) of RV doses and dates of diphtheria-tetanus-acellular pertussis (DTaP) vaccine and 7- or 13-valent pneumococcal conjugate vaccine (PCV) doses administered were obtained.

The names of each subject's health care providers were obtained from the parent/guardian, the medical record, and IIS. 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 (see Supplemental Information).

Second Control Group: IIS Controls

Thirty controls per case-subject were selected from the IIS, matched on birthdate and residence zip code using

a computer program algorithm that selected controls regardless of the child's immunization status. Within the same zip code, controls with the same birthdate as the case-subject were selected first, followed by controls with birthdate within 1 day of case-subject's birthdate (and so on, up to 30 days), until 30 controls were identified. In the unusual circumstance that 30 controls were not identified within the same zip code, a contiguous zip code was used to try to obtain the remaining controls (see Supplemental Information). Cases were not excluded from the total IIS pool.

Analysis

Ages (in days) at diarrhea onset and at each vaccine administration were calculated. For analysis, an RV dose was counted if it had been administered ≥14 days before the date of diarrhea onset or, for IIS controls, ≥14 days before the reference age. The reference age for each IIS control was the age of the matched case-subject at onset of diarrhea. For RV1- or RV5-specific VE analyses, children who had received doses from both manufacturers or for whom manufacturer of ≥1 dose was unknown were excluded.

Rotavirus VE was calculated as (1 − odds ratio [OR]) × 100%. Using the rotavirus-negative controls, ORs for RV dose(s) receipt for case-subjects compared with controls were calculated by unconditional logistic regression, controlling for site (Georgia or Connecticut), season (2010 or 2011), and birth quarter (ie, August 2008–October 2008) in all models. Birth quarter was included because it could be associated with RV receipt (change in uptake over time) and timing of rotavirus disease.[6,7] Other factors assessed for possible confounding in each model were insurance status (private versus public/no insurance), and factors possibly associated with rotavirus disease[8,9] (Supplemental Table 7) for which univariate analysis comparing case-subjects and controls used in the model yielded a $P < .10$. These covariates were assessed by backward elimination and retained if the VE point estimate changed by ≥1.5 percentage points. In almost all children, rotavirus vaccination status did not change after age 8 months, indicating that providers were following age recommendations for the last dose. Therefore, overall VE was calculated for children aged ≥8 months, which eliminated the need to control for confounding by age; children aged <8 months were not included in VE analyses. Subanalyses were planned a priori to assess VE by age (stratified analysis), hospital setting, and rotavirus genotype. VE estimates were calculated by using the number of RV doses from the provider record, and were also calculated by using only the RV information from the IIS.

Using the IIS controls, ORs for RV dose (s) receipt for case-subjects (per IIS record) compared with controls were calculated by conditional logistic regression. VE estimates were calculated once using all case-subjects listed in the IIS and their IIS controls (see Supplemental Information). However, to avoid including children in the analyses who may have received RV but whose providers did not participate in the IIS or whose record had not been entered into the IIS, VE estimates were recalculated using only children who met an IIS record "restriction": ≥1 dose of DTaP, PCV, or RV was listed in the IIS, or there was information in the IIS that parents had refused vaccines.

To help assess whether the VE results could be attributed to bias, a bias-indicator evaluation was performed.[10,11] IIS controls were selected for rotavirus-negative children in the manner described previously for rotavirus case-subjects, and ORs for RV dose(s) receipt for rotavirus-negative children (per IIS record) compared with their IIS controls were calculated using conditional logistic regression. Analyses were performed by using Stata 12 (Stata Corp, College Station, TX).

RESULTS

Overall, a stool sample was obtained and tested on 593 (82%) of 728 enrolled children, yielding a total of 165 rotavirus-positive and 428 rotavirus-negative children. Forty-seven (28%) of the 165 rotavirus case-subjects available for analysis had been managed as hospital inpatients (24% in Georgia and 32% in Connecticut). Only Georgia separately categorized some case-subjects (3%) as short-stay patients. Sixty-eight (41%) of the 165 rotavirus case-subjects had received intravenous fluids.

At least 95% of all rotavirus case-subjects and rotavirus-negative controls had a provider record obtained and ≥94% were located in the IIS; proportions were similar for those aged ≥8 months (Table 1). Of the 597 RV doses in the provider records of children aged ≥8 months, a manufacturer-specific lot number was available for 89% of doses, manufacturer/product name was available but without lot number for 8% and neither manufacturer/product name nor lot number was available for 3% of doses. Of the 123 rotavirus case-subjects aged ≥8 months with a provider record, 73 (59%) had no RV doses; of the 262 rotavirus-negative children, 39 (15%) had no RV doses (Supplemental Table 8).

A total of 3433 IIS controls were available for the rotavirus case-subjects aged ≥8 months. Ninety-one percent of the IIS controls had a birthdate within 14 days of their respective case-subject and 95% resided in the same zip code as the case. Ninety-two percent had ≥1 dose of DTaP, PCV, or RV in the IIS.

VE of RV1

Overall, using rotavirus-negative controls and information from provider

TABLE 1 Number of Children Who Tested Rotavirus Positive or Rotavirus Negative by Season, Site, and Immunization Record Status

	Season 1: January 2010–June 2010				Season 2: January 2011–June 2011				Total			
	All Ages	Age ≥8 mo			All Ages	Age ≥8 mo			All Ages	Age ≥8 mo		
	Enrolled and Tested	Enrolled and Tested	In IIS, *n* (%)	Provider Record Obtained, *n* (%)	Enrolled and Tested	Enrolled and Tested	In IIS, *n* (%)	Provider Record Obtained, *n* (%)	Enrolled and Tested	Enrolled and Tested	In IIS, *n* (%)	Provider Record Obtained, *n* (%)
Georgia												
Rotavirus positive	14	6	6 (100)	6 (100)	98	75	74 (99)	70 (98)	112	81	80 (99)	76 (94)
Rotavirus negative	150	64	63 (98)	63 (98)	140	102	95 (93)	99 (97)	290	166	158 (95)	162 (98)
Connecticut												
Rotavirus positive	2	2	1 (50)	2 (100)	51	45	39 (87)	45 (100)	53	47	40 (85)	47 (100)
Rotavirus negative	40	26	23 (88)	26 (100)	98	76	70 (92)	74 (87)	138	102	93 (91)	100 (98)
Total												
Rotavirus positive	16	8	7 (88)	8 (100)	149	120	113 (94)	115 (96)	165	128	120 (94)	123 (96)
Rotavirus negative	190	90	86 (96)	89 (99)	238	178	165 (93)	173 (97)	428	268	251 (94)	262 (98)

For Georgia, "In IIS" includes children who were listed in IIS and excludes those who were not listed in IIS.
For Connecticut, "In IIS" includes children who were listed in IIS and excludes those who were (1) not listed in IIS, (2) those who were listed in IIS but who were indicated as having opted out of IIS, and (3) those who were listed in IIS but indicated as "moved out of state" and IIS record was not up-to-date for rotavirus vaccines.

records, the effectiveness of 2 RV1 doses versus 0 doses among children aged ≥8 months was 91% (95% confidence interval [CI] 80 to 95) (Table 2). Point estimates were virtually identical using the record from the IIS. Using the IIS controls and the record restriction, the VE was 85% (95% CI 73 to 92) (Table 2).

The 2-dose RV1 effectiveness among subsets of children was examined (Table 3). Using rotavirus-negative controls, the VE of 2 RV1 doses versus 0 doses among children aged ≥8 months against the outcome of hospitalization/short-stay management for rotavirus disease was 98% (95% CI 90 to 100) (Table 3) and against use of intravenous fluids was 95% (95% CI 87 to 98). VE against rotavirus disease managed in the ED was 86% (95% CI 67 to 94). Similar VE results were obtained with the IIS controls and the record restriction (Table 3).

Using rotavirus-negative controls, the VE estimate of 2 RV1 doses versus 0 doses among children aged 12 through 23 months was similar (91%; 95% CI 75 to 96) to that obtained among children aged 8 months through 11 months (85%; 95% CI 35 to 97) (Table 4). The 2 predominant rotavirus genotypes during the evaluation period were G1P[8] and G2P[4] (Table 6). Using rotavirus-negative controls, the 2-dose RV1 effectiveness against G1P[8] rotavirus disease was 89% (95% CI 70 to 96), and against G2P[4] disease was 94% (95% CI 78 to 98) (Table 5).

Few children aged ≥8 months had received only 1 RV1 dose. Of those aged ≥8 months who received 1 RV1 or no RV doses, 8 (10%) of 81 case-subjects and 11 (22%) of 50 rotavirus-negative controls received only 1 RV1 dose, for an overall VE estimate of 53% (95% CI −41 to 84). Of the case-subjects aged ≥8 months who received intravenous fluids and had 1 RV1 or no RV doses, 2 (5%) of 40 had 1 RV1 dose, for a VE estimate of 80% (95% CI −3 to 96).

TABLE 2 Vaccine Effectiveness Among Children Aged ≥8 mo

Evaluation, Control Group and Source of Immunization Data	Cases	No. (%) Vaccinated	Controls	No. (%) Vaccinated	VE	95% CI
a. 2 RV1 doses versus 0 doses						
Controls: rotavirus-negative[a]						
Provider	95	22 (23)	140	101 (72)	91	80 to 95
IIS of above subjects	88	19 (22)	132	92 (70)	92	72 to 96
IIS of above subjects, restricted	84	19 (23)	129	92 (72)	92	82 to 96
IIS (regardless of provider record availability), restricted	85	19 (22)	128	90 (70)	91	80 to 96
Controls: IIS (matched)[a]						
IIS	89	19 (21)	1302	644 (49)	76	58 to 86
IIS, restricted	85	19 (22)	1062	621 (58)	85	73 to 92
b. RV5						
3 RV5 doses vs 0 doses						
Controls: rotavirus-negative[b]						
Provider	79	6 (8)	73	34 (47)	92	75 to 97
Controls: IIS (matched)[c]						
IIS, Georgia only	51	4 (8)	675	253 (37)	87	62 to 95
IIS, Georgia only, restricted	49	4 (8)	522	240 (46)	91	74 to 97
2 RV5 doses versus 0 doses						
Controls: rotavirus-negative						
Provider	75	2 (3)	48	9 (19)	84	1 to 98
c. 2-dose mixed series (1 RV1 plus 1 RV5) vs 0 doses						
Controls: rotavirus-negative						
Provider	76	3 (4)	60	21(35)	95	79 to 99

"Restricted" indicates analysis was restricted to children that had at least 1 dose of DTaP, PCV or RV in IIS record.

[a] Excludes 1 case-subject and 2 rotavirus-negative controls with 3 RV1 doses.

[b] Excludes 1 rotavirus-negative control with 4 RV5 doses.

[c] Analysis performed only with Georgia IIS because IIS in Connecticut could not differentiate RV5 doses from doses with unknown manufacturer.

TABLE 3 Vaccine Effectiveness Among Children aged ≥ 8 months by Hospital Care

Evaluation and Control Group	Source of Immunization Data	Cases	No. (%) Vaccinated	Controls	No. (%) Vaccinated	VE	95% CI
a. 2 RV1 doses versus 0 doses							
Controls: rotavirus-negative							
Inpatient/short-stay cases	Provider	30	2 (7)	140	101 (72)	98	90 to 100
Cases that received IV fluids	Provider	45	6 (13)	140	101 (72)	95	87 to 98
ED cases	Provider	65	20 (31)	140	101 (72)	86[a]	67 to 94
Controls: IIS (matched)							
Inpatient/short-stay cases	IIS	28	2 (7)	440	206 (47)	94	71 to 99
	IIS, restricted	26	2 (8)	360	201 (56)	96	81 to 99
Cases that received IV fluids	IIS	41	6 (15)	634	326 (51)	87	67 to 95
	IIS, restricted	39	6 (15)	533	321 (60)	93	80 to 97
ED cases	IIS	61	17 (28)	862	438 (51)	65	35 to 81
	IIS, restricted	59	17 (29)	702	420 (60)	78	57 to 89
b. 3 RV5 doses versus 0 doses[b]							
Controls: rotavirus-negative							
Inpatient/short-stay cases	Provider	30	2 (7)	73	34 (47)	97[c]	77 to 100
Cases that received IV fluids	Provider	40	1 (2)	73	34 (47)	97	73 to 100
ED cases	Provider	49	4 (8)	73	34 (47)	91	67 to 98

"Restricted" indicates analysis was restricted to children that had at least 1 dose of DTaP, PCV or RV in IIS record.

IV, intravenous.

[a] Model also included insurance status and Hispanic ethnicity (without this adjustment, VE = 85% [95% CI 68 to 93]).

[b] Analysis with IIS controls not performed because IIS in Connecticut could not differentiate RV5 doses from doses with unknown manufacturer and Georgia case numbers were insufficient for Georgia-only analysis.

[c] Model also included insurance status and race (without this adjustment, VE = 90% [95% CI 48 to 98]).

VE of 3 RV5 Doses and 2-Dose Mixed Series (RV1 Plus RV5)

For both sites combined, the effectiveness of 3 RV5 doses versus 0 doses among children aged ≥8 months was 92% (95% CI 75 to 97) and results were similar using the cases and IIS controls from Georgia (Table 2). The VE was ≥91% against rotavirus disease with hospitalization/short-stay management, use of intravenous fluids, or ED care (Table 3). Among children aged 12 through 23 months, the VE for 3 RV5 doses was 90% (95% CI 56 to 98) (Table 4). Three RV5 doses were ≥95%

TABLE 4 Vaccine Effectiveness According to Age

Evaluation and Control Group	Source of Immunization Data	Cases	No. (%) Vaccinated	Controls	No. (%) Vaccinated	VE	95% CI
a. 2 RV1 doses versus 0 doses							
Controls: rotavirus-negative							
Ages 8 mo–11 mo	Provider	14	5 (36)	61	45 (74)	85	35 to 97
Ages 12 mo–23 mo	Provider	66	14 (21)	68	46 (68)	91	75 to 96
Controls: IIS (matched)[a]							
Ages 8 mo–11 mo	IIS	14	4 (29)	196	114 (58)	70	−4 to 91
	IIS, restricted	14	4 (29)	168	114 (68)	89	48 to 98
Ages 12 mo–23 mo	IIS	65	13 (20)	967	462 (48)	76	53 to 87
	IIS, restricted	62	13 (21)	781	452 (58)	84	69 to 92
b. 3 RV5 doses versus 0 doses							
Controls: rotavirus-negative							
Ages 8 mo–11 mo	Provider	10	1 (10)	34	18 (53)	94	37 to 99
Ages 12 mo–23 mo	Provider	55	3 (5)	36	14 (39)	90	56 to 98
Controls: IIS (matched)[a,b]							
Ages 8 mo–11 mo	IIS, Georgia only	10	1 (10)	111	45 (41)	82	(−50 to 98)
	IIS, Georgia only, restricted	10	1 (10)	94	45 (48)	88	(0 to 99)
Ages 12 mo–23 mo	IIS, Georgia only	39	2 (5)	535	198 (37)	92	64 to 98
	IIS, Georgia only, restricted	37	2 (5)	405	185 (46)	94	74 to 99

"Restricted" indicates analysis was restricted to children that had at least 1 dose of DTaP, PCV or RV in IIS record.

[a] Separate model was used for each age group.

[b] Analysis performed only with Georgia IIS because IIS in Connecticut could not differentiate RV5 doses from doses with unknown manufacturer.

TABLE 5 Vaccine Effectiveness among Children aged ≥ 8 months by Genotype

Evaluation and Control Group	Source of Immunization Data	Cases	No. (%) Vaccinated	Controls	No. (%) Vaccinated	VE	95% CI
a. 2 RV1 doses versus 0 doses							
Controls: rotavirus-negative							
G1P[8] cases	Provider	43	9 (21)	140	101 (72)	89	70 to 96
G2P[4] cases	Provider	36	8 (22)	90	64 (71)	94[a,b]	78 to 98
Controls: IIS (matched)							
G1P[8] cases	IIS	43	7 (16)	636	273 (43)	78	48 to 91
	IIS, restricted	42	7 (17)	509	268 (53)	88	68 to 95
G2P[4] cases	IIS	33	7 (21)	455	256 (56)	81[a]	52 to 92
	IIS, restricted	30	7 (23)	358	238 (66)	88[a]	68 to 95
b. 3 RV5 doses versus 0 doses							
Controls: rotavirus-negative							
G1P[8] cases	Provider	37	3 (8)	73	34 (47)	95[c]	74 to 99
G2P[4] cases	Provider	29	1 (3)	50	24 (48)	98[a,d]	74 to 100
Controls: IIS (matched)[e]							
G1P[8] cases	IIS, Georgia only	38	2 (5)	493	174 (35)	91	61 to 98
	IIS, Georgia only, restricted	37	2 (5)	390	172 (44)	94	73 to 99

"Restricted" indicates analysis was restricted to children that had at least 1 dose of DTaP, PCV or RV in IIS record.

[a] Based only on data from season 2 because all G2P[4] cases occurred in season 2.

[b] Model also included insurance status (without this adjustment, VE = 92% [95% CI 76 to 97]).

[c] Model also included insurance status (without this adjustment, VE = 94% [95%CI 69 to 99]).

[d] Model also included race (without this adjustment, VE = 96% [95% CI 59 to 99]).

[e] Analysis performed only with Georgia IIS because IIS in Connecticut could not differentiate RV5 doses from doses with unknown manufacturer. Analysis for G2P[4] cases not performed because of insufficient cases from Georgia alone.

effective against G1P[8] and G2P[4] disease (Table 5). Using rotavirus-negative controls, the VE of a 2-dose mixed series with both RV1 and RV5 was 95% (95% CI 79 to 99) (Table 2).

Bias Indicator

Using all IIS controls selected for the children aged ≥8 months with gastroenteritis who tested negative for rotavirus by EIA and were in the IIS, the VE of ≥2 doses versus 0 doses of any RV product against rotavirus-negative gastroenteritis was –26% (95% CI –77 to 11). Using only children meeting the IIS record restriction, the VE was 5% (95% CI –37 to 34) (of those with ≥2 RV doses or no doses, 185 [82%] of 225 rotavirus negative-children and 4564 [83%] of 5489 IIS controls had ≥2 RV doses).

DISCUSSION

Because RV1 was introduced later than RV5 in the United States, previous product-specific evaluations could assess only the effectiveness of RV5. Using children enrolled through active

TABLE 6 Rotavirus Genotypes Among Enrolled Children Testing Rotavirus-Positive by EIA

	n	(%)
G1P[8][a]	86	52
G2P[4]	50	30
G12P[8]	9	5
G3P[8]	6	4
G4P[8]	4	2
G12P[6]	2	1
G3P[6]	2	1
G2P[8]	1	1
G4/G2 P[8]/P[4]	1	1
Non typeable	4	2
Total	165	

[a] All samples with G1P[8] detected were confirmed by sequencing to contain wild-type G1P[8].

surveillance at 5 hospitals in 2 states, we showed that 2 doses of RV1 and 3 doses of RV5 are both highly effective against rotavirus disease resulting in hospitalization or ED care.

Overall, the 2-dose RV1 effectiveness estimates in these US children are similar to the efficacy results from the prelicensure clinical trial in Europe.[12] In that trial, information on symptoms was available from parent diary cards and severe rotavirus gastroenteritis was defined as a score of ≥11 on an established 20-point severity scoring system (Vesikari scale) on the basis of the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed. The 2-dose efficacy was 90% (95% CI 85 to 94) for severe rotavirus gastroenteritis (Vesikari score ≥11) and 96% (95% CI 84 to 99) for hospitalization for rotavirus (both estimates through the second rotavirus season after enrollment).[12] In our evaluation, using the same methodology in the same locations and time period, the overall effectiveness of the 2-dose RV1 series and the 3-dose RV5 series appear similarly high; the evaluation was not designed to measure differences in effectiveness between the vaccines. Our VE estimates of RV5 are very similar to those found in other US evaluations.[13–18] We also found an overall high VE of a 2-dose mixed series.

We found 2 doses of RV1 to be highly effective against G2P[4] disease and similar to the effectiveness against G1P[8] disease. The effectiveness of RV1 against G2P[4] disease has been a concern given that all 11 genes and protein antigens of G2P[4] are typically distinct from those of G1P[8] strains, such as the RV1 strain, and the other most common circulating strains.[19] In the first large RV1 clinical trial, conducted in Latin America, the efficacy to age 1 year against severe rotavirus gastroenteritis (a clinical definition) caused by genotype G2P[4] was 41% (95% CI −79 to 82) (the clinical definition was diarrhea [3 or more loose or watery stools within 24 hours], with or without vomiting, that required overnight hospitalization or rehydration equivalent to World Health Organization plan B [oral rehydration] or plan C [intravenous rehydration] in a medical facility).[20] Although based on small numbers, this fueled concerns about the vaccine's ability to protect against this genotype. In the later European trial, efficacy against severe G2P[4] disease (Vesikari score ≥11) through the second rotavirus season was 85.5% (95% CI 24.0 to 98.5), but was also based on small numbers.[12] Early reports from Brazil of G2P[4] predominance after RV1 introduction[21] and in areas in Australia using RV1,[22] highlighted the need for postintroduction effectiveness assessments to help address the question of heterotypic protection. Our VE results against G2P[4] are reassuring for high-income settings, where rotavirus vaccines overall have performed better than in middle- and low-income countries. How well RV1 protects against G2P[4] in lower-income settings is still an important issue that requires further monitoring, given that some postintroduction evaluations suggest protection may be only modest in infancy or may not persist.[23–25]

In our evaluation, we found no evidence of waning of protection from RV1 through the second year of life, which is important given that in the United States before RV introduction more than half of RV hospitalizations among children aged <5 years occurred after the first year of life.[1,26] Our results are consistent with those from the European trial in which efficacy during the second season was ≥85% for severe rotavirus disease and disease requiring hospitalization.[12] Additional data on the effectiveness of RV1 in US children beyond age 2 years will be valuable.

Our evaluation adds to the experience of using IIS as a source of immunization records and as a source of controls for evaluations of vaccine effectiveness in US children.[18,27–29] Using the rotavirus-case subjects and the rotavirus-negative controls who had a provider record obtained, the VE estimates for the full series were very similar when only the IIS record was used as compared with using the provider record. This suggests that the additional staff effort to obtain the record directly from the provider may not be required, particularly for mature IIS with high provider participation. As described previously, there are some limitations and assumptions made when using IIS as a source of controls.[14,18] In our current evaluation using IIS controls, the VE estimates that included only children for whom there was indication that child had been active in the registry (which we defined as having ≥1 dose of DTaP, PCV, or RV listed in the IIS [or, in Connecticut, information that vaccines were refused]) were generally similar to those obtained using the rotavirus-negative controls and the provider record, and higher than those that included children in the IIS who had no doses listed. (The VE results with the IIS ≥1 dose restriction were very similar to those obtained with a more stringent IIS restriction[14] [data not shown], used to help ensure the record available covered the early infancy period: ≥3

doses of DTaP, PCV, or full series of RV received through age 8 months). Using the IIS, we found rotavirus vaccine did not protect against rotavirus-negative gastroenteritis, suggesting a lack of major bias in our VE estimates against rotavirus disease.

There are limitations to our evaluation. An adequate stool sample was not obtained on 18% of enrolled children and a provider record was not obtained on 4% of rotavirus case-subjects. These proportions, however, are not greater than those from other US RV evaluations with prospective enrollment and provider records.[13,15] At the time of this evaluation, the Connecticut IIS was unable to distinguish RV5 doses and RV doses of unknown manufacturer and therefore this site was unable to contribute to the RV5 effectiveness using IIS controls. However, both Connecticut and Georgia contributed to the RV5 analyses using the rotavirus-negative controls with the provider records, and we also were able to assess RV5 effectiveness using the Georgia IIS. Finally, VE estimates for children aged ≥8 months who received less than a full series or who received a 2-dose mixed series were based on relatively small numbers of vaccinated children, and longer-term protection could not be assessed. Although substantial effort was made to obtain the most accurate immunization record on all children, the partial series VE reported would overestimate the true VE if some of those vaccinated had truly received additional RV doses.

CONCLUSIONS

This evaluation demonstrates that RV1 is highly effective in US children against severe rotavirus disease during at least the first 2 years of life, and confirms the high effectiveness of RV5.

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