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Effectiveness of Rotavirus Vaccine in Preventing Hospitalization due to Rotavirus Gastroenteritis in Young Children in Connecticut, USA

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Abstract

Rotavirus vaccine was recommended for use in US infants to prevent rotavirus gastroenteritis (RGE) in February 2006. This matched case control study assessed the effectiveness of rotavirus vaccine in preventing hospitalization of young. Cases were vaccine-eligible children 8 weeks – 3 years of age, hospitalized due to laboratory-confirmed RGE. Cases (n=42) were matched to 2 control groups: (a) hospitalized controls (n=80): children hospitalized for reasons other than RGE, matched to the cases by age and time of presentation and (b) community controls (n=73): non-hospitalized children matched by age and medical practice. Adjusted vaccine effectiveness against hospitalization with RGE in vaccine eligible children receiving at least one dose of vaccine was 94.3% (95% C.I.: 55.4%–99.3%; p=0.006) for hospitalized controls and 96.9% (95% C.I.: 59.4%–99.8%; p=0.008) for community controls.

Keywords

Rotavirus; Vaccine; Hospitalization

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Introduction

Rotavirus is the number one cause of severe diarrheal illness in children under five years of age [1–3]. In the pre-vaccine era, rotavirus gastroenteritis (RGE) was responsible for almost 40% of diarrhea related hospitalizations [4,5] and was associated with an estimated total annual direct and indirect cost of approximately one billion dollars [6]. Two oral rotavirus vaccines have been licensed and recommended for routine use in infants in the United States: RotaTeq® (RV5), a live-attenuated pentavalent human-bovine reassortant vaccine approved in February 2006, and Rotarix® (RV1), a monovalent live-attenuated human vaccine approved in June 2008. RV1 contains one serotype (G1P[8]) of attenuated human rotavirus, while RV5 contains 5 different serotypes: G1, G2, G3, G4, and P1A[8]. Although efficacy was demonstrated for both vaccines in large clinical trials [7,8], their effectiveness, or efficacy as used in everyday practice, in the general population remains unknown.

The potential public health impact of rotavirus vaccination is considerable. A previous cohort study demonstrated that natural infection protects against reinfection [9]. Subsequent infections were also noted to be less severe. The influence of rotavirus vaccine on the clinical epidemiology of this infection remains to be fully described. Available data from population based immunization system sentinel sites suggest that vaccine uptake is improving in the US [1]. Recent data from active surveillance in the United States revealed a delayed onset of the annual peak rotavirus season in 2007–2008 compared to the 1991–2006 seasons and a >50% decrease in the number of positive rotavirus tests in the 2007–2008 season compared to the 7 preceding seasons [10]. Both active and surveillance data and studies from 8 US sites have shown a 85–95% decline in rotavirus gastroenteritis cases during the 2008 season compared with the 2006 and 2007 seasons [10–15]. Additional post licensure surveillance studies have also shown marked decreases in rotavirus disease in Europe and Australia [16,17].

Ongoing vaccine effectiveness investigations in multiple settings are critical in the post licensure period in order to evaluate how the vaccine will perform against rotavirus disease under routine use. Recently, postlicensure effectiveness trials conducted in the US, Brazil, Nicaragua, Israel, and El Salvador have shown promising results in the effectiveness of rotavirus vaccines used in various settings [18–22]. In other US trials, Wang et al used a national insurance claims database to show that 3 doses of RV5 reduced hospitalizations and ED visits by 100% during the first two seasons after vaccine licensure [21]. Boom et al. found RV5 to be highly effective (85–89%) in the prevention of severe gastroenteritis requiring ED visits or hospitalizations [18]. Our study adds to these findings by evaluating the effectiveness of RV vaccine against hospitalization as its primary outcome.

Methods

Purpose

We conducted a matched case-control study to assess the effectiveness of the rotavirus vaccine as it is used in everyday practice in preventing hospitalization due to rotavirus in children 8 weeks to 3 years of age. The distribution and clinical severity of rotavirus gastroenteritis in this population are also described.

Study Population Eligibility

Case subjects were vaccine eligible children 8 weeks to 3 years of age admitted to Yale New Haven Children's Hospital (YNHCH), a regional tertiary care hospital situated in Southern Connecticut, due to laboratory-confirmed rotavirus gastroenteritis during the period of March 2006 to July 2009. Cases born after November 29, 2005 were eligible for the study since they could have received rotavirus vaccine based on the Advisory Committee on Immunization Practices (ACIP) recommendations. We retrospectively identified potential cases hospitalized from March 1, 2006 – December 31, 2007 of children hospitalized with a documented rotavirus infection from the infection control department and from the hospital's clinical virology laboratory data. In addition, to interviewing caretakers for all consented retrospective subjects, medical record review was also performed to help mitigate the concern of recall bias. Interviews for retrospective subjects took place between the first and second seasons of case enrollment (June to December 2008). Prospectively identified cases were identified from January 1, 2008 – July 31, 2009 via active surveillance using daily lists of pediatric admissions, laboratory surveillance of all stool specimens tested for rotavirus, and infection control monitoring. Potential cases were excluded if the rotavirus infection was nosocomial, defined as a positive rotavirus antigen test >72 hours after admission. Any child for whom this vaccine would not be routinely administered (due to severely immunocompromising illness or medications) was excluded, as were children whose caretakers did not speak English or Spanish. RV5 was available in Connecticut the entire study period, although the state immunization program chose to supply RV1 for children in its state funded program on October 1, 2008.

Selection of Controls

For each case subject, we recruited 4 age-matched controls. There were 2 control groups with 2 controls per case in each group. All eligible controls had to be 8 weeks to 3 years of age, and the same exclusion criteria for cases applied to both control groups.

Control Group #1 consisted of children admitted for reasons other than rotavirus infection who were matched to the case subject's date of birth (± 4 weeks) and date of hospitalization (± 2 weeks). Children with gastroenteritis were included only if they had a negative rotavirus stool antigen test. Because a control could not always be found within the specified time of admission, the criteria for the date of hospitalization were extended to ± 4 weeks for 9 children.

Control Group #2 consisted of children who were not hospitalized. Subjects were identified using lists of patients with birthdates that were ± 4 weeks of the case subject who attended the same medical practice for their routine care as their matched case subject. We chose to include control group #2 to help control for potential confounders (adherence to vaccination recommendations and socioeconomic status) between pediatric care providers. The health of these subjects was confirmed by interview and medical record review portion of this investigation.

The order in which controls on each list were contacted was determined by a random sequence generator. We used risk set sampling such that control subjects were drawn from a

population of children at risk for disease at the time of each case subject's hospitalization [23]. All caretakers of study participants gave written informed consent. This study was approved by the Yale Human Investigations Committee.

Collection of data

Stool specimens of children hospitalized with gastroenteritis were routinely tested for the presence of rotavirus using an enzyme immunoassay (Meridian Premier Rotavirus EIA), which is both sensitive (94%) and specific (100%) [24]. Caretakers of children hospitalized with positive EIA tests were interviewed to ascertain demographic characteristics, medical history, and risk factors for disease (including birthweight <2500g, Medicaid/not insured, living with another child <24 months of age, and daycare attendance). For case subjects and controls hospitalized with non-rotaviral gastroenteritis, severity of illness was assessed with the standardized, validated clinical severity scale used for the large RV5 efficacy trial [25]. Severe gastroenteritis was defined as a score of >16 on this 24-point severity scoring system based on the intensity and duration of fever, vomiting, diarrhea, and changes in behavior. For prospective cases with available stool samples, a rotavirus specific reverse transcription polymerase chain reaction (RT-PCR) assay was used to determine whether the strain of rotavirus was included in the vaccines [26–28]. All PCR studies were performed at Brown University.

Ascertainment of Vaccination

Medical records from all providers involved in the care of enrolled subjects were reviewed for written documentation of receipt of rotavirus vaccine, other vaccines, and chronic medical conditions. All dates of vaccination were verified by review of medical records. Subjects were considered vaccinated if there was written documentation of receipt of at least one dose of rotavirus vaccine. Children vaccinated within 2 weeks of the date of onset of rotavirus gastroenteritis for each case were not counted as vaccinated. We classified course of vaccination as either complete (3 doses of RV5 or 2 doses of RV1) or as incomplete (less than the complete course). If subjects received mixed vaccine types, a total of 3 doses was considered a complete course as defined by the 2009 American Academy of Pediatrics and ACIP schedule.

Statistical Analysis

Differences in demographic characteristics and vaccination status of cases and controls were assessed using chi-squared and Fisher's exact tests as appropriate. Comparisons of illness severity and duration of hospitalization (for control group 1 only) by case/control and vaccination status were made using a Wilcoxon rank sum or Fisher's exact test.

Matched odds ratios were calculated for receipt of rotavirus vaccine and for potential confounders (gender, race, ethnicity, daycare attendance, breastfeeding, prematurity, chronic illness, tobacco exposure, and income) and case/control status. All variables associated with either case/control or vaccination status at $p < 0.2$ were introduced into a multivariate conditional logistic regression model. Only variables that maintained statistical significance at $p < 0.05$ were retained in the final model. This procedure was applied in generating matched adjusted odds ratios and their 95% confidence intervals comparing cases to each

matched control group. Statistical significance of matched odds ratios was assessed by the Mantel-Haenszel chi-square test.

The effectiveness of rotavirus vaccine in preventing hospitalization of young children secondary to RGE was calculated as 1 minus the matched odds ratio. All estimates used a two-tailed critical alpha of 0.05. Analyses were performed using SAS version 9.1.3 (SAS Institute; Cary, NC) for Microsoft.

Results

Recruitment

Data collection took place between January 2008 and August 2009. From January 2006 – August 2009, 45 potentially eligible children were hospitalized at YNHCH due to laboratory-confirmed RGE. Two cases were excluded (a recent transplant patient and a tracheotomy patient living in a hospital facility), and 1 refused to participate. Of the 42 cases enrolled, 22 (52%) were retrospectively enrolled and 20 (48%) were enrolled prospectively (Figure 1).

One hundred and fifty-five control group #1 subjects (hospitalized controls) were identified, of which 66 (42.6%) could not be contacted by phone, 3 (1.9%) were ineligible, 2 (1.3%) declined participation, and 84 (54.2%) enrolled. Medical record review was completed for 80 (95%) of these subjects. Reasons for hospitalization included gastroenteritis with a negative rotavirus test ($n = 6$; 7.1%), respiratory disease ($n = 21$; 25.0%), infections ($n = 24$; 28.6%), planned surgeries ($n = 13$; 15.5%), injuries ($n = 8$; 9.5%), neurologic problems ($n = 6$; 7.1%) and other complaints ($n = 6$; 7.1%). There were 151 control group #2 subjects (community controls) identified of which 57 (37.1%) could not be reached, 4 (2.6%) were ineligible, 6 (4.0%) declined, and 84 (55.6%) enrolled. Medical record review was completed for 73 (87%) subjects. Of all enrolled subjects, 53.5% had public insurance and 46.5% had private insurance.

The only characteristic on which prospectively and retrospectively identified subjects differed significantly was age (14.4 ± 8.7 months vs. 9.3 ± 4.9 months, $p = 0.024$).

Demographic Characteristics

As shown in Table 1, cases vs. matched controls did not differ significantly with respect to most characteristics including receipt of DTaP vaccine, a marker for access to medical care for similar ages to those at which rotavirus vaccine would be administered. Cases were more likely to be Black, and controls from both groups more frequently reported Hispanic ethnicity. Variation was also seen with respect to daycare attendance and tobacco exposure. Cases were similar to hospitalized controls but differed from community controls with regards to prematurity and chronic medical conditions.

Vaccination (Table 2)

There were 5/42 (11.9%) cases, 24/80 (30.0%, $p = 0.026$) hospitalized controls, and 21/73 (28.8%, $p = 0.037$) community controls that received at least 1 dose of rotavirus vaccine at least 14 days prior to the hospitalization date of the case. Of these, 2 (4.8%) cases, 9 (11.3%)

hospitalized controls, and 11 (15.1%) community controls had received a complete course of rotavirus vaccine. Most vaccinated children received RV5 (60.0% of cases, 95.8% of hospitalized controls, and 85.7% of community controls). Age at the time of vaccination was not significantly different between case and control subjects, with the first dose administered to 5 cases between 8 and 10 weeks of age and to 45 controls between 7 and 18 weeks of age.

Serotypes

RT-PCR results for cases identified G1, G2, G3, G4, and G9 serotypes in stool samples. RT-PCR and rotavirus strain typing was performed on 19 samples. Of these specimens, 5 (26.3%) were serotyped as G3, 2 (10.5%) subjects as G1, 2 (10.5%) subjects as G9, 1 (5.3%) subject as G2, and 1 (5.3%) subject G4. One specimen was serotyped as the P6 strain, but no G type was identifiable. The remaining 7 (36.8%) samples were nontypeable. Of the 5 stool samples from cases who had received vaccine, 3 had typeable results. One child who had received 2 doses of the pentavalent RV5 was hospitalized in 2008 with the G3 serotype (included in the vaccine). Another child who received 1 dose of RV5 was hospitalized in 2009 with G9 disease (not included in the vaccine). The third child had received a full course of RV1 and was hospitalized in 2009 with G9 disease (not included in vaccine).

Clinical Severity

Clinical severity was not significantly higher for case subjects than for the subset of controls that were hospitalized for non-rotavirus gastroenteritis (13.9 ± 4.6 vs. 11.5 ± 3.3 , $p=0.107$): 7/42 (16.7%) cases and 2/6 (33.3%) of all controls were mild, 21/42 (50.0%) cases and 4/6 (66.7%) controls were moderate, and 14/42 (33.3%) cases and 0/6 (0%) controls were severe ($p=0.200$). Length of hospital stay did not differ significantly between cases and controls (2.0 ± 1.2 days vs. 2.5 ± 1.4 days, $p=0.382$). Vaccinated vs. non-vaccinated cases also had similar severities and lengths of hospital stay. Comparing cases by season of hospitalization, mean severity scores were similar (13.4 ± 5.7 in 2006–2007, 13.2 ± 4.0 in 2007–2008, and 15.8 ± 1.7 in 2008–2009, $p=0.504$).

Vaccine Effectiveness

The effectiveness of rotavirus vaccine in preventing hospitalization due to RGE is shown in Table 3. The vaccine was 83.5% effective [95% C.I.; 23.7% to 96.4%; $p=0.021$] in preventing hospitalization due to RGE comparing cases to hospitalized controls in an unadjusted model, and 94.3% effective [95% C.I.; 55.7% to 99.0%; $p=0.005$] in a model adjusted for ethnicity, gender, and tobacco exposure. Comparing cases to community controls, the vaccine was 90.7% effective [95% C.I.; 23.7% to 98.9%; $p=0.027$] in an unadjusted model and 96.9% [95% C.I. 59.4% to 99.8%; $p=0.008$] in a model adjusted for race and daycare attendance.

Both partial and complete vaccination courses were successful in preventing hospitalization of young children. Comparing cases to hospitalized controls, an incomplete course of vaccine was 93.2% effective [95% C.I.; 41.4% to 99.2%; $p=0.015$ adjusted as before] and a complete course was 96.3% effective [95% C.I.; 28.9% to 99.8%; $p=0.029$]. Comparing cases to community controls, an incomplete course of vaccine was 93.8% effective [95%

C.I.; 23.0% to 99.5%; $p=0.031$ adjusted as before] and a complete course was 99.1% effective [95% C.I.; 78.1% to 99.9%; $p=0.032$].

Discussion

This study was conducted in the “real world” clinical practice setting, where strict vaccine administration recommendations are not always followed, comorbidities may be present, sociodemographic factors vary, and infective strains may differ. Our results confirm the findings of previous effectiveness studies, and show that rotavirus vaccine demonstrates excellent effectiveness in the prevention of hospitalization of young children (93% to 96%). This was noted for both partial and complete vaccine courses (96% to 99%). We chose to evaluate the effectiveness against hospitalization to capture the most severe cases of rotavirus, which are responsible for the majority of incurred medical costs. The representative, population-based approach and collection of comprehensive interview and medical record data to facilitate adjustment of vaccine effectiveness estimates for confounders strengthen our study.

Strain characterization by PCR was performed in a very limited sample size, and a significant number of our samples were nontypeable. (7/19, 36.8%). The ability of this virus to undergo frequent genetic variation has led to the potential of numerous G/P combinations. Previous epidemiologic surveys have reported rates of 8% to 27% of nontypeable strains even when using PCR and probe hybridization in combination [29]. In our study population, 4 cases were hospitalized within 14 days of receipt of a dose rotavirus vaccine. Whether a positive rotavirus antigen test in these cases was secondary to naturally acquired infection, shedding vaccine virus, or vaccine associated disease is unclear at this point.

Although case-control studies are susceptible to bias, we aimed to minimize it by randomizing lists of control subjects, matching on the main risk factor (age), and using multivariable logistic regression models. To better evaluate selection bias, 2 control groups were recruited. As expected, VE was higher in our community controls (CG2): these children were generally in better health and were less likely to have comorbid conditions. Furthermore, medical record review was performed to confirm receipt of vaccine, removing recall bias with respect to our primary exposure. Although a much higher proportion of controls than cases received the rotavirus vaccine, similar DTaP vaccination between groups suggests that access to care did not differ.

Many potential subjects control subjects could not be contacted as only disconnected telephone numbers and invalid addresses were available. It is possible that the socioeconomic and demographic characteristic of subjects that could not be contacted differed from subjects that enrolled. Also, interviewers were not blinded to case/control status. While this may have served as a potential source of bias in the interview, staff were trained to perform the interview in the same manner regardless of study status. Interviewers had no knowledge of subjects' vaccination status at the time of enrollment.

Rotavirus vaccine was effective in preventing hospitalization in young children. Many questions remain pertaining to vaccine specific effectiveness as well as the long term

effectiveness of the rotavirus vaccine. Continued monitoring and surveillance are necessary to better understand the shifting epidemiology of rotavirus disease in the post vaccination period, the long-term effectiveness of the vaccine, and possible selection of rotaviruses that evade vaccine immunity.

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Figure 1.
Enrollment of Cases and Matched Controls

Table 1
 Characteristics of Children Hospitalized with Rotavirus Gastroenteritis and their Controls

Characteristic	Cases	Control Group 1		Control Group 2	
	N = 42 (%)	N = 80 (%)	P-value	N = 73 (%)	P-value
Age (months)			0.958		0.938
Mean ± SD	11.7 ± 7.4	11.8 ± 7.2		11.8 ± 7.4	
Median	11	11.5		11	
2 – <6	13 (31.0)	23 (28.8)	0.946	22 (30.1)	0.977
6 – <12	10 (23.8)	17 (21.25)		17 (23.3)	
12 – <23	16 (38.1)	35 (43.8)		27 (37.0)	
24 – <36	3 (7.1)	5 (6.3)		7 (9.6)	
Male gender	21 (50.0)	50 (62.5)	0.184	37 (50.7)	0.944
Ethnicity (Hispanic)	6 (14.3)	24 (30.0)	0.056	19 (26.0)	0.142
Race			0.365		0.183
White	22 (52.4)	45 (56.3)		42 (57.5)	
Black	14 (33.3)	18 (22.5)		14 (19.2)	
Other	6 (14.3)	17 (21.3)		17 (23.3)	
Income (USD)					0.657
< 30,000	17 (46.0)	30 (40.0)	0.549	27 (39.7)	
30,000 – 60,000	6 (16.2)	19 (25.3)		16 (23.5)	
> 60,000	14 (37.8)	26 (34.7)		25 (36.8)	
Breastfeeding					0.832
Never	13 (31.0)	21 (26.3)	0.582	24 (32.9)	
Ever	29 (69.1)	59 (73.8)		49 (67.1)	
< 1 month	6 (20.7)	3 (5.1)	0.054	8 (16.3)	0.628
1 month	23 (79.3)	56 (94.9)		41 (83.7)	
Attends daycare	14 (33.3)	16 (20.0)	0.104	13 (17.8)	0.059
Children under 2 years old at home	9 (21.4)	22 (27.5)	0.464	16 (21.9)	0.951
Tobacco exposure	15 (35.7)	16 (20.0)	0.058	12 (16.4)	0.019
Premature	9 (21.4)	16 (20.0)	0.853	6 (8.2)	0.043
Chronic health conditions ¹	17 (40.5)	40 (50.0)	0.317	15 (21.3)	0.027

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Characteristic	Cases N = 42 (%)	Control Group 1 N = 80 (%)	Control Group 2 N = 73 (%)	P-value	P-value
Received DTaP ²	37 (90.2)	71 (89.9)	61 (88.4)	0.949	0.765

¹ Asthma, GERD, eczema, blood disorders, gastrointestinal problems, or other chronic medical conditions by parent report.

² Diphtheria, Tetanus, Acellular Pertussis vaccine. Subjects received at least one dose.

Table 2

Rotavirus Vaccination

<i>Completeness of course of rotavirus vaccine</i>					
	Cases N = 42 (%)	Control Group 1 N = 80 (%)	P-value	Control Group 2 N = 73 (%)	P-value
Not vaccinated	37 (88.1)	56 (70.0)	0.026	52 (71.2)	0.037
Vaccinated	5 (11.9)	24 (30.0)		21 (28.8)	
<i>Incomplete vaccine course</i>	3 (7.1)	15 (18.8)	0.083	10 (13.7)	0.106
<i>Complete vaccine course</i>	2 (4.8)	9 (11.3)		11 (15.1)	
<i>Type of rotavirus vaccine received</i>					
	Cases N = 5 (%)	Control Group 1 N = 24 (%)	P-value	Control Group 2 N = 21 (%)	P-value
Rotateq®	3 (60.0)	23 (95.8)	0.068	18 (85.7)	0.327
Rotarix®	2 (40.0)	1 (4.2)		2 (9.5)	
Mixed	0 (0.0)	0 (0.0)		1 (4.7)	
<i>Percent of subjects that received at least one dose of vaccine by season</i>					
	Cases N (%) ¹	Control Group 1 N (%) ²	P-value	Control Group 2 N (%) ³	P-value
2006 – 2007	1 (4.5)	5 (12.5)	0.409	3 (8.8)	1.000
2007 – 2008	1 (7.1)	12 (42.9)	0.032	11 (44.0)	0.028
2008 – 2009	3 (50.0)	7 (58.3)	1.000	7 (58.3)	1.000

¹For cases, N = 21 for 2006 – 2007, 14 for 2007 – 2008, 6 for 2008 – 2009

²For hospitalized controls, N = 39 for 2006 – 2007, 28 for 2007 – 2008, 12 for 2008 – 2009

³For community controls, N = 36 for 2006 – 2007, 25 for 2007 – 2008, 12 for 2008 – 2009

Table 3 Effectiveness of Rotavirus Vaccine Against Hospitalization¹

	Cases	Controls	
		Hospitalized	Community
Vaccinated	5 (11.9)	24 (30.0)	21 (28.8)
Not vaccinated	37 (88.1)	56 (70.0)	52 (71.2)
Unadjusted			
Matched OR [95% CI]	-	0.165 [0.036 – 0.763] p = 0.021	0.093 [0.011 – 0.763] p = 0.027
Vaccine Effectiveness [95% CI]	-	83.5% [23.7 – 96.4%]	90.7% [23.7 – 98.9%]
Adjusted ²			
Matched OR [95% CI]	-	0.057 [0.007 – 0.446] p = 0.006	0.031 [0.002 – 0.406] p = 0.008
Vaccine Effectiveness [95% CI]	-	94.3% [55.4 – 99.3%]	96.9% [59.4 – 99.8%]

¹Includes only subjects in a matched pair where the case and at least 1 control have complete medical record data available for the applicable control group.

²Adjusted model for cases and hospitalized controls retained ethnicity, tobacco exposure, and gender. Adjusted model for cases and community controls retained race and daycare attendance. Other variables were not statistically significant in the multivariate model (p<0.05) and are not included in the final model presented.