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Impact of rotavirus vaccine on acute gastroenteritis emergency department visits and hospitalizations in a highly-vaccinated urban cohort

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ABSTRACT

Background: Rotavirus vaccines (RVV) have significantly reduced rotavirus disease in children over the past 4 years in the United States. In this study, we describe the impact of RVV in preventing acute gastroenteritis (AGE) hospital encounters in a highly-vaccinated urban pediatric network during the 2007 and 2008 rotavirus seasons. Methods: We used 5 urban practices from a practice-based network to conduct a retrospective cohort study comparing the numbers of AGE emergency department (ED) visits and hospitalizations in RVV-immunized (exposed) and non-immunized (unexposed) children during the first 2 full seasons following RVV introduction. We determined incident rate ratios (IRR), using Poisson regression, and vaccine effectiveness for each outcome. Results: The 2007 and 2008 cohorts were analyzed separately. 62% of the 2007 cohort was vaccinated and 88% of the 2008 cohort. AGE hospitalizations were significantly reduced among RVV-immunized children from the 2007 cohort in the 2008 season with vaccine effectiveness of 67%. Sub-analysis of this cohort by age revealed that RVV was most protective against hospitalizations in the youngest age group (IRR = 0.21, 95% CI (0.06, 0.82). A trend toward protection against hospitalization was detected for both cohorts in the first season following immunization that did not reach a statistically significant level. For AGE ED visits, no significant difference was seen between RVV-immunized and non-immunized children in either cohort, although there was a trend toward protection (IRR's: 0.67 - 0.7). Conclusions: RVV was highly effective in preventing AGE hospitalizations for a subset of our cohort in 2008. Given reports of RVV effectiveness, we hypothesize that herd immunity is responsible for the inability to detect a significant difference between RVV-immunized and non-immunized children in our highly-vaccinated cohort.

Keywords: Rotavirus; Pediatrics; Acute Gastroenteritis

1. INTRODUCTION

Prior to the introduction of rotavirus vaccine (RVV) in 2006, rotavirus (RV) was the most common cause of acute gastroenteritis (AGE) among children under 5 years of age in the United States [1]. Recent surveillance data and several post-licensure studies have shown significant reductions in RV disease activity and RV-related healthcare encounters [2,3]. In this report, we examine the effectiveness of RVV in preventing hospital-related AGE outcomes in a highly vaccinated urban cohort of children enrolled in a pediatric practice-based research network.

2. MATERIALS AND METHODS

2.1. Study Design

A retrospective cohort study was performed evaluating the effectiveness of RVV in preventing AGE emergency department (ED) visits and hospitalizations during the first two full RV seasons after RVV introduction.

2.2. Study Setting

The CHOP network includes 33 ambulatory pediatric practices, of which 5 are located within 2 miles of CHOP's main hospital. These practices refer >90% of children to CHOP's main hospital for emergency care and hospitalization [4] and use the EpicCare (Verona, WI) electronic health record (EHR). The CHOP main hospital

is a tertiary care pediatric hospital with over 24,000 inpatient admissions and 70,000 ED visits annually. All CHOP ED visits and hospitalizations are captured in the EHR.

2.3. Study Populations

The study population included any child born between February 22, 2006 (RotaTeq® licensure date; RotaTeq® was the only RVV available in the US during the study period) and February 29, 2008, who had at least one visit at one of the 5 selected sites prior to 2 months of age. Children were divided into 2 distinct cohorts: 1) the 2007 cohort included children eligible for AGE outcomes in both the 2007 and 2008 seasons and 2) the 2008 cohort included children eligible for AGE outcomes in the 2008 season only.

2.4. Exposures and Outcomes

The exposure was receipt of any number of doses of RVV (1, 2 or 3); unexposed patients received zero RVV doses. The primary outcomes were AGE-related ED visits and hospitalizations, defined as any ED or hospital encounter with a diagnosis code for a diarrheal illness using the AGE ICD-9-CM codes: 001 - 005, 006 - 007, 008 - 008.5, 008.6, 008.61, 008.8, 009 - 009.3, 558.9, 787 - 787.03, 787.91 [5]. Outcomes were not assessed until the child was 6 weeks of age (earliest recommended age for RVV administration).

2.5. Data Collection

The EHR was queried to identify total numbers of AGE ED visits and hospitalizations, subject demographics, other immunizations received, complex chronic conditions (CCC) [6], and numbers of primary care sick and preventative visits.

2.6. Statistical Methods

We characterized cohort subjects by all potential risk factors. We compared demographic variables and healthcare utilization between RVV-immunized and non-immunized groups using chi-square analysis for categorical variables and student's t test for continuous variables. We conducted univariable analyses using Poisson regression to determine associations between potential risk factors and outcomes.

For the multivariable analysis, we estimated the association between RVV exposure and the outcomes for each season using Poisson regression. All potential confounders and risk factors with a p value < 0.2 on univariable analysis were included in the multivariable model. We used a stratified analysis to assess effect modification.

Vaccine effectiveness (VE) in preventing AGE outcomes was calculated using the formula: VE = (1-Incident Rate Ratio (IRR)) × 100, where IRR is the adjusted ratio for each AGE outcome among vaccinated versus unvaccinated subjects [7].

3. RESULTS

3.1. Characteristics of the Study Population

The study population included 2 cohorts: 3278 children in the 2007 cohort and 2705 children in the 2008 cohort. Among the 2007 cohort, 62% received at least 1 RVV dose and 43% were fully vaccinated with 3 doses. For the 2008 cohort, 88% received at least 1 dose and 63% received 3 doses. Demographic characteristics of children in the 2 cohorts were similar except non-vaccinated children in the 2008 cohort were more likely to be black (70.6% vs. 80%, p = 0.003). Non-vaccinated children had lower rates of healthcare utilization than their vaccinated peers; this disparity was more pronounced in the 2008 cohort. In 2007 and 2008, respectively 60% and 44% of RVV-immunized children were up-to-date with recommended preventative care visits, whereas 39% and 6% of non-immunized children were up-to-date (p values < 0.0001).

3.2. AGE ED Visits and Hospitalizations

For both cohorts, there was a trend toward protection for RVV-immunized children against AGE ED visits and hospitalizations. However, the only statistically significant protective effect was seen for the 2007 cohort in the 2008 season against hospitalizations (IRR 0.33, 95% CI (0.11, 0.96)) with a VE of 67% (**Table 1**).

Sub-analyses demonstrated that the 3-dose regimen was most protective against AGE hospitalizations in the youngest age group (those 6 weeks of age at entry into the first RV season) for the 2007 cohort in season 2008 (IRR = 0.21, 95% CI (0.06, 0.82), VE 79%) compared with 1 (IRR = 0.48, 95% CI (0.05, 4.29)) or 2 doses (IRR = 0.42, 95% CI (0.09, 1.95)). There was no significant protective vaccination effect in the older age groups regardless of RVV dose number for either outcome.

4. DISCUSSION

In this cohort study of an urban pediatric healthcare network with high rates of vaccination, we found a significant reduction in AGE hospitalizations among RVV-immunized children in the 2008 season. We demonstrated by age and dose-stratified analysis that the 3-dose RVV regimen was most effective in preventing AGE hospitalizations among the youngest children in the 2007 cohort during the second RV season.

For AGE hospitalizations, RVV-immunized children from the 2007 cohort were protected in the 2008 season with VE of 67%. This finding is similar to other cohort studies which demonstrated VE ranging from 59% -

Table 1. IRR for AGE-related ED visits and hospitalizations.

	2007 Cohort				2008 Cohort	
	2007 Season		2008 Season		2008 Season	
	RVV Immunized N = 2031	RVV Non-Immunized N = 1247	RVV Immunized N = 2031	RVV Non-Immunized N = 1247	RVV Immunized N = 2395	RVV Non-Immunized N = 310
AGE ED Visits[a]	88 (4.3%)	71 (5.7%)	151 (7.4%)	65 (5.2%)	184 (7.7%)	22 (7.1%)
AGE ED Visit IRR (95% CI)[b]	0.69 (0.27, 1.76)		0.67 (0.41, 1.11)		0.70 (0.25, 1.99)	
AGE Hospitalizations[a]	32 (1.6%)	19 (1.5%)	18 (0.9%)	8 (0.6%)	48 (2%)	8 (2.6%)
AGE Hospitalization IRR (95% CI)[b]	0.41 (0.15, 1.11)		0.33* (0.11, 0.96)		0.46 (0.10, 2.13)	

[a]Percentage following number is the percent of AGE ED visits or hospitalizations for total N of each column; [b]IRR's adjusted for age at start of 1st season, race, presence of a chronic condition, preventative visits up-to-date at 14months, non-rota immunizations up-to-date by 7 months, total sick visits, time in cohort, and include a term for interaction between RV immunization and age; *Value statistically significant.

66% [8,9]. The reason for greater VE among younger infants in the 2007 cohort in the 2008 season is unclear and has not been previously described. Those infants received their RVV doses more recently so may have had higher titers of anti-RV antibodies and, therefore, increased protection during the 2008 season as compared with older children from the 2007 cohort. The smaller number of unvaccinated patients in the 2008 cohort may have affected our ability to detect a statistical difference between RVV-immunized and non-immunized patients in that cohort. In the context of findings by Clark *et al.*, which describe a 77% reduction in hospitalizations for community-acquired RV disease at CHOP for the 2008 season compared with the mean from 13 prior seasons [10], we believe indirect protection by herd immunity is a likely possibility for our inability to detect a significant vaccine effect in this highly vaccinated population.

There were several limitations for this study. By using AGE as an outcome, we cannot truly assess the reduction in RV disease due to RVV. However, viral stool pathogen testing was not uniformly conducted so we could not capture RV-specific disease as a retrospective outcome. Despite previous validation, identifying AGE outcomes using ICD-9-CM codes, may introduce bias due to error in both physician diagnosis and the recording of codes. Also, we used retrospective data and only captured ED visits and hospitalizations at CHOP's main hospital. If parents sought care for their children elsewhere, our data capture may be incomplete.

This study demonstrates that RVV is effective in preventing severe AGE requiring hospitalization among immunized children and adds to the growing evidence that RVV has had a significant impact on childhood AGE in areas where it has been routinely implemented. More work is needed to determine if a differential in protection based on a child's age, as seen in the youngest children in the 2007 cohort, truly exists.

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