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Protective Association Between Rotavirus Vaccination and Childhood Seizures in the Year Following Vaccination in US Children

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Abstract

Background—Rotavirus illness has been linked to childhood seizures. We investigated whether a protective association exists between receipt of rotavirus vaccine and being hospitalized or visiting the emergency department for seizures in the year after vaccination.

Methods—We retrospectively analyzed a cohort of children born after 28 February 2006 (when rotavirus vaccine was licensed in the United States) and enrolled in the Vaccine Safety Datalink (VSD) through November 2009. Seizure rates from 4 to 55 weeks following last rotavirus vaccination were compared by vaccine exposure status (fully vaccinated and unvaccinated). A

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time-to-event analysis using a Cox proportional hazards model was performed, accounting for time-varying covariates. We calculated the relative incidence of seizure compared by vaccine exposure status during the postexposure interval.

Results—Our cohort contained VSD data on 250 601 infants, including 186 502 children fully vaccinated (74.4%) and 64 099 (25.6%) not vaccinated with rotavirus vaccine. Rates of seizures were associated with rotavirus vaccination status. After adjusting for covariates (VSD site, age at last dose, sex, and calendar month of the index date), a statistically significant protective association was observed between a full course of rotavirus vaccination vs no vaccination for both first-ever seizures (risk ratio [RR] = 0.82; 95% confidence interval [CI], .73–.91) and all seizures (RR = 0.79; 95% CI, .71–.88).

Conclusions—A full course of rotavirus vaccination was statistically associated with an 18%–21% reduction in risk of seizure requiring hospitalization or emergency department care in the year following vaccination, compared with unvaccinated children. This reduction in childhood seizures complements the well-documented vaccine-related benefit of preventing US diarrhea hospitalizations.

Keywords

rotavirus; vaccine; seizures; surveillance; vaccine safety

Since the introduction of rotavirus vaccines for universal vaccination of infants in the United States (RotaTeq [RV5], Merck Vaccines, Whitehouse Station, New Jersey; Rotarix [RV1], GlaxoSmithKline Biologicals, Rixensart, Belgium), vaccination against rotavirus has resulted in substantial declines in severe gastroenteritis among US children [1–5].

Rotavirus infection is not limited to the intestine and is associated with antigenemia in approximately one-half of children hospitalized with rotavirus gastroenteritis [6–9]. Furthermore, rotavirus has been isolated in cell culture from the sera of infected children, thus confirming that the existence of viremia and the potential for systemic illness exists [6]. Wild-type rotavirus has been detected in cerebrospinal fluid by polymerase chain reaction and electron microscopy in cases of seizure occurring with diarrhea [10–13]. Clinical neurologic illness has been linked to rotavirus infection in numerous studies and case reports [14–19]. One of the largest, a multicenter study of 1359 patients hospitalized with laboratory-confirmed rotavirus in Canada from 2005 to 2007, reported that 7% of these subjects experienced a seizure [20]. A retrospective cohort analysis at a single US hospital from 2002 to 2006 reported that 6 of 34 children (18%) hospitalized with rotavirus-associated seizures spent at least 1 day in an intensive care unit, and a lumbar puncture was performed on 20 of these 34 children (59%) [21].

Gastroenteritis-associated seizures often occur in clusters (>1 seizure in 24 hours) and while the child is afebrile [22]. These events may be more likely than febrile seizures to prompt emergent care, invasive diagnostic procedures, and follow-up medical care and/or medication, and are not included in guidelines addressing the management of children with simple febrile seizures [23–25].

With the clinically observed relationship between natural rotavirus infections and seizures, we studied a retrospective cohort of children enrolled in the Vaccine Safety Datalink (VSD) to investigate whether a protective association exists between receipt of rotavirus vaccination and being hospitalized or receiving care at an emergency department (ED) for seizure the year following vaccination.

METHODS

We retrospectively analyzed a cohort of children born from March 2006 through November 2009 enrolled in the VSD to estimate the relative risk of seizures recorded in inpatient and ED settings by rotavirus vaccination status.

Vaccine Safety Datalink

VSD is a collaborative project between the Centers for Disease Control and Prevention (CDC) and managed care organizations (MCOs) throughout the United States. Participating MCOs capture epidemiological, clinical, and vaccination data on approximately 3% of the US population (8.8 million persons) annually for the purpose of vaccine safety research [26, 27]. Eight VSD MCOs contributed data to this study, including Group Health Cooperative of Puget Sound (Seattle, Washington), Kaiser Permanente Northwest (Portland, Oregon), Kaiser Permanente Medical Care Program of Northern California (Oakland, California), Southern California Kaiser Permanente Health Care Program (Los Angeles, California), Harvard Pilgrim Health Care (Boston, Massachusetts), Health Partners Research Foundation (Minneapolis, Minnesota), Marshfield Clinic Research Foundation (Marshfield, Wisconsin), and Kaiser Permanente Colorado (Denver, Colorado). This study was approved by institutional review boards at the CDC and at each participating VSD institution.

Definition of Rotavirus Vaccination Exposure

We used VSD records to identify the dates of rotavirus vaccination for subjects born after 28 February 2006, when RV5 was licensed. Subjects having 3 recorded RV5 vaccinations and 2 recorded RV1 vaccinations were considered fully vaccinated, and subjects receiving no doses were considered unvaccinated. For this time period, our database included mostly RV5 vaccinations (>99%), although we did include children receiving RV1 and classified them according to Advisory Committee on Immunization Practices (ACIP) recommendations.

Definition of Seizures

Seizure cases were identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 780.3* (convulsions), 779.0* (convulsions in newborn), 333.2* (myoclonus), or 345* (epilepsy) occurring in the VSD hospitalization or ED automated files. Results from a separate study suggested that the positive predictive value (PPV) of VSD inpatient and ED *ICD-9-CM* data for seizures is relatively high. In that VSD data quality assessment, 859 VSD-recorded seizures (identified using the same *ICD-9-CM* codes as our study) among children 6 weeks to 23 months of age were compared with medical chart review findings. These codes were demonstrated to have a PPV of 97% and 64% for the hospital and ED clinical settings, respectively [28].

Study Interval Definitions

Diagnoses of seizures were obtained from hospital and ED visit discharge codes occurring 29–388 days (approximately 4–55 weeks) following last rotavirus vaccination, which allowed sufficient time for rotavirus vaccine–mediated immunity to be established. Censoring occurred for subjects having no diagnoses of these conditions at the end of the postexposure interval. Analyses focused on the aggregate risk for this postexposure interval, with 6 successive 59-day subsets analyzed to indicate whether trends in risk were apparent over time.

Sample Selection

Children born after 28 February 2006 were selected and characterized by vaccination status (fully vaccinated and unvaccinated). The date of last rotavirus vaccination served as the index date for those vaccinated. For unvaccinated children, an index date was randomly selected by a computer program to fall within the age recommended by ACIP [29] for receiving rotavirus vaccination. Study subjects with VSD records for at least 1 year were retained in the sample.

Statistical Analyses

A time-to-event analysis using a Cox proportional hazards model was performed, accounting for time-varying covariates. The retrospective cohort method calculated the relative incidence of seizure compared by vaccine exposure status during the postexposure interval.

We compared the characteristics of children whose complete vaccination records indicated that they received some vaccines but not rotavirus vaccine, with those children having received recommended vaccines including rotavirus vaccine. Additional analyses compared children who received partial courses of rotavirus vaccine and, although our results for partially vaccinated children were comparable to those from fully vaccinated children, these were not statistically significant and are not shown. Subjects having no ACIP-recommended childhood vaccinations were excluded from analysis, as they likely differed from those who received these vaccinations.

We estimated the postexposure interval hazard (risk) of seizure using a model comparing fully vaccinated children to those receiving no rotavirus vaccination. We calculated risks for the full risk period following last rotavirus dose, as well as risks for 6 equal time periods (29–88 days, 89–148 days, 149–208 days, 209–268 days, 269–328 days, and 329–388 days). For each model, we controlled for the VSD site, age at last dose, sex, index month, and year.

RESULTS

In our original VSD cohort of 260 666 children, 186 513 were fully immunized with rotavirus vaccines and 74 153 were not immunized with any rotavirus vaccine. More than 99% of those fully immunized received at least 1 other recommended vaccine, whereas 86% of those not immunized with rotavirus vaccine received at least 1 other recommended vaccine (96.8% of total). We limited our analysis to those children having at least 1 other

recommended vaccine to avoid potential bias coassociated with vaccination status and healthcare utilization. Therefore, our final analysis cohort contained VSD data on 250 601 children, including 186 502 children fully immunized with rotavirus vaccines (74.4%) and 64 099 (25.6%) not immunized with rotavirus vaccine.

Fully immunized children ranged from 38% to 64% of the cohort total by VSD site. All but 1 site had >50% of children fully immunized. The proportion not immunized against rotavirus at all ranged from 15% to 45%. Those who were fully vaccinated were older than unvaccinated children ($P < .001$; Table 1).

We identified 2244 first-time cases of seizures following the index date (1575 fully vaccinated and 669 unvaccinated). Of subjects with seizures, 1713 (68%) were evaluated in the ED and 74% of these ED patients received at least 1 rotavirus vaccination, compared with 72% of those hospitalized receiving an immunization ($P = .209$). Among unvaccinated children, 55% of all seizures occurred during the traditional rotavirus season (January–June), whereas 48%–49% of seizures occurred during these months among vaccinated children ($P = .023$). Seizure rates were statistically related to vaccination status. Among fully vaccinated and unvaccinated children, first-time seizures occurred at a rate of 1145 and 1212 per 100 000 person-years, respectively, and all seizures occurred at a rate of 1383 and 1502 per 100 000 person-years, respectively (Table 2).

After adjusting for covariates, a statistically significant protective association was observed between a full course of rotavirus vaccination and first-ever seizures (risk ratio [RR] = 0.816; 95% confidence interval [CI], .729–.914), and for all seizures (RR = 0.790; 95% CI, .714–.875) Table 2).

DISCUSSION

We observed that rotavirus vaccination was statistically associated with an approximate 18%–21% reduction in risk of seizures requiring hospitalization or ED care in the year following vaccination, compared with unvaccinated children. This additional, and somewhat unanticipated, potential benefit of rotavirus vaccination complements the well-documented vaccine-related benefit of preventing US diarrhea hospitalizations.

Overall, seizures are estimated to contribute to 1%–2% of the annual burden in pediatric hospitalizations and ED visits in the United States [30–32]. Based on these published estimates, our observed reduction in risk could potentially translate to the prevention of approximately 1000 hospitalizations and 5000 ED visits for seizures per year among young children. Seizure-related hospitalizations and ED visits each cost approximately \$4553 (2006) [30] and \$498 (2007), respectively [31]; therefore, this finding could amount to >\$7 million in prevented healthcare costs per year, should our reported association be fully and causally related. Additionally, the averted emotional toll to family members, the avoidance of potentially painful procedures to the young child, and obviated antiseizure medication regimens would accrue further benefits.

A previous analysis of the VSD dataset using a sequential analysis method from May 2006 through May 2008 explored the relationship between seizures and RV5 vaccination during

only the first 30 days after receipt of vaccine and found a relative risk of 0.67, although the null hypothesis was not rejected in that analysis [33]. Our longer-term and statistically significant results support this short-term indication, as do the many published clinical reports that strongly indicate a biological plausibility of this association [14–20]. Several mechanisms may explain this protective association between rotavirus vaccination and seizures, with the most probable mechanism being that vaccination directly prevents systemic rotavirus infection, including extraintestinal complications involving the central nervous system [34]. Vaccination may also prevent secondary effects of rotavirus infection, including a rotavirus-related elevation of nitric oxide in cerebrospinal fluid inducing neurotoxicity [35, 36], and/or calcium channel fluctuations resulting in neurotransmitter dysregulation [37–39].

Although the majority of our subjects were between 8 and 18 months of age, the peak occurrence of febrile seizures is between 18–24 months and the peak age for nonfebrile seizures is <12 months of age [40–42]. Therefore, our results may disproportionately capture the effect of vaccination upon nonfebrile seizures. However, these nonfebrile seizures may be etiologically most relevant to acute gastroenteritis infections and less genetically influenced than febrile seizures. Retrospective studies of first-time seizures occurring with mild acute illness found that diarrhea or gastroenteritis was a common feature of illness in children with first-time seizures, and was more common in children with nonfebrile seizures compared to children with febrile seizures (38%–52% vs 11%–16%, $P < .001$) [22, 43, 44].

Some limitations should be considered. First, >99% of our studied rotavirus vaccination events consisted of RV5 vaccine, so our results are not generalizable to RV1 vaccine. Second, our study does not differentiate between clinical subgroups of seizure types. Third, we were unable to control for underlying conditions that could be associated both with getting vaccinated and with seizure, such as gestational prematurity, or for some other seizure-causing pathogen having similar seasonality among the same age groups. Fourth, children in the VSD population are enrolled in MCOs and are not necessarily representative of all US children, and these possible differences may include factors related to immunization. Results for partially vaccinated children were comparable to those from fully vaccinated children, but were not statistically significant. Last, we assessed the level of potential bias in using *ICD-9-CM* codes for seizures in the VSD database, applying our risk ratio of 0.79 and the high PPV of 0.81 published by Shui et al [28]. We calculated that any such bias in our study would be directed towards the null and would be relatively small.

In conclusion, we found that a full course of rotavirus vaccination was associated with statistically significant reductions in the risk of childhood seizures during the year following last rotavirus vaccination. This reduction in childhood seizures complements the well-documented vaccine-related benefit of preventing US diarrhea hospitalizations.

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Table 1

Characterization of Subjects in the Analytical Cohort by Rotavirus Vaccination Status

Variable	Not Vaccinated (n = 64 099), No.	Full Vaccination (n = 186 502), No.	P Value
Age			
6–11 wk	0	4 (<1%)	<.001 ^a
12–19 wk	1018 (2%)	1651 (1%)	
20–34 wk	5839 (9%)	3434 (2%)	
35–48 wk	57 242 (89%)	181 413 (97%)	
Sex			
Female	30 958 (48%)	91 241 (49%)	.006 ^a
Male	33 141 (52%)	95 261 (51%)	
Seizure			
Yes	669 (1%)	1575 (1%)	<.001 ^a
No	63 429 (99%)	184 920 (99%)	
Seasonality of seizure event			
January–June	369 (55%)	774 (49%)	.010 ^a
July–December	300 (45%)	801 (51%)	
Days since vaccination that seizure occurred ^b			
29–88 d	99 (15%)	249 (16%)	.581
89–148 d	114 (17%)	246 (16%)	
149–208 d	114 (17%)	297 (19%)	
209–268 d	140 (21%)	345 (22%)	
269–328 d	139 (21%)	285 (18%)	
329–388 d	63 (9%)	153 (10%)	

For unvaccinated children, an index date was randomly selected by a computer program to fall within the age recommended by the Advisory Committee on Immunization Practices for receiving rotavirus vaccination.

^aStatistically significant.

^bThe date of last rotavirus vaccination serves as the index date for those vaccinated.

Table 2

Cox Proportional Hazards Model Results for Risk of Seizure Following Rotavirus Vaccination

Vaccination Exposure	(First) Seizure Rate (per 100 000 PY)	Strata	Risk Ratio (95% CI) ^a
None	1212		1.000
Full course	1145	First-ever seizure	0.816 (.729-.914) ^b
		All seizures	0.790 (.714-.875) ^b

Abbreviations: CI, confidence interval; PY, person-years.

^aModels were adjusted for sex, age at last vaccine dose, Vaccine Safety Datalink site, index month, and year.^bStatistically significant finding.

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