Febrile Seizures in the Era of Rotavirus Vaccine

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A protective association between rotavirus vaccination and childhood seizures in the year after vaccination was recently reported from the United States. In the state of Queensland, Australia, the authors found that rotavirus vaccine was 35.8% and 38.0% effective at preventing emergency department presentation and subsequent hospitalization, respectively, for febrile seizures among children up to two years following vaccination.

Key words. febrile seizures; rotavirus vaccine.

Rotaviruses are the most common cause of severe childhood gastroenteritis worldwide and result in approximately 450,000 deaths in children <5 years of age [1, 2]. In addition, rotavirus-related illnesses are associated with both febrile and afebrile seizures [3].

Recently, a retrospective analysis of a cohort of US children found a protective association between full rotavirus vaccination and childhood seizures resulting in emergency department (ED) presentation or hospital admission in the year after vaccination [4]. Using a preexisting linked data set containing febrile, but not afebrile, seizure outcome data, we sought evidence of a similar effect in children in Queensland, Australia, after introduction of the publicly funded rotavirus vaccine, RotaTeq (RV5) (Merck & Co, Inc/CSL Biotherapies), in mid-2007 into the state’s immunization schedule [5].

METHODS

Using routinely collected health data, we calculated the vaccine effectiveness (VE) of rotavirus vaccine in preventing ED presentation and subsequent hospitalization for febrile seizures using the screening method described here. Our method involved comparing the proportion of children with febrile seizures who were vaccinated (proportion of cases vaccinated [PCV]) with the proportion of the target population vaccinated (PPV) [6]. PPV values were obtained from the population-based Australian Childhood Immunisation Register (ACIR). The ACIR receives positive immunization notifications from the Queensland vaccination register (Vaccination Information and Vaccination Administration System [VIVAS]), to which Queensland vaccine service providers report immunizations.

We investigated VE among three 12-month cohorts of children born between May 2007 and April 2008 (VE calculated for 2009/2010/2011), between May 2008 and April 2009 (VE calculated for 2010/2011), and between May 2009 and April 2010 (VE calculated for 2011) (Table 1). The birth cohorts were constructed to ensure that children were age eligible for rotavirus vaccination [5] and had the opportunity to receive the full 3-dose course of RV5, with all doses due before 33 weeks of age, before the calendar year in which VE was assessed. As part of a larger rotavirus-based linkage study, we had data specific for febrile seizures (International Statistical Classification of Diseases and Related Health Problems [ICD], 10th Revision, code R56.0) from ED records of 25 Queensland public hospitals. In 2010/2011, these 25 hospitals were responsible for 80% of all nonadmitted hospital presentations, (including ED presentations and outpatient visits) for any cause, in Queensland public hospitals.

To determine the PCV, the Queensland Health Data Linkage Unit linked vaccination (VIVAS) and ED presentation data using LinkageWiz data-matching software, version 5.3 (LinkageWiz, Inc, Adelaide, South Australia) to probabilistically identify potentially matching records. Weighting scores were assigned to matching variables, including surname, first name, date of birth, and address. Middle- and lower-weighted pairs were individually assessed, and higher-weighted pairs were checked for false matching related to multiple births.
As VE was assessed over an observation period of 1 year for 12-month birth cohorts, the age range of the children within each observational period was 2 years. We obtained VE estimates and 95% confidence intervals (CIs) by fitting logistic regression models with the outcome variable as the incidence of both rotavirus infection and febrile seizures, resulting in ED presentation and hospitalization for febrile seizures in children up to 4 years after rotavirus vaccination. We found 3 doses of RV5 to have a protective association with an afebrile illness [7]. It is interesting to note that in our population, the protective effect seemed to endure with the highest point VE estimate in children aged between 2 years 8 months and 4 years 7 months (2 to 4 years after vaccination). Nevertheless, the largest absolute impact would be expected to occur in younger children because of their higher incidence of both rotavirus infection and febrile seizures.

**RESULTS**

There were 2211 ED presentations for febrile seizure, 635 (28.7%) of which led to hospital admissions, included in the analysis. Among the youngest children aged between 8 months and 2 years 7 months, the VE estimates of the full 3-dose rotavirus vaccine course against any febrile seizures leading to ED presentation and subsequent hospitalization were 35.8% (95% CI, 26.0%–44.2%) and 38.0% (95% CI, 20.1%–51.9%), respectively (Table 1). We found that the protective association against any febrile seizure resulting in ED presentation and hospitalization remained substantial in older children, up to 4 years after rotavirus vaccination. VE against any ED presentation was significantly associated with age group (P = .003), but VE against any hospitalization was not (P = .210). VE remained statistically significant when restricting the analysis to the first febrile seizure occurring during the period of analysis.

**DISCUSSION**

We found 3 doses of RV5 to have a protective association for febrile seizures in children up to 4 years after rotavirus vaccination. The VE estimate against any febrile seizure resulting in ED presentation for the youngest age group, 35.8%, is broadly consistent with the US finding of a reduction of 21.0% (95% CI, 12.5%–28.6%) of all childhood seizures requiring ED care or hospitalization in the first year after rotavirus vaccination [4].

We investigated the association specifically between rotavirus vaccination and febrile seizures by using a preexisting linked data set that did not contain afebrile seizure-associated diagnostic codes. Because many rotavirus-associated seizure events are afebrile [3], restricting our analysis to febrile seizures will have excluded some rotavirus-associated events. Our higher point estimates for VE compared with the findings in US children may result from febrile seizures being more specific for rotavirus than for all seizures. Conversely, a 2010 study of young children presenting to a US hospital with a first-time seizure identified rotavirus in 8% of children with febrile seizures and 21% of children with an afebrile illness [7].
with the peak incidence of febrile seizures occurring at 18 months of age [8].

Our study had several limitations. The analysis was stratified according to age group; however, it is possible that other factors related to both receiving rotavirus vaccination and experiencing febrile seizures and/or seeking ED care for febrile seizures biased the results. The validity of our analysis depends on the accuracy of data linkages. Incomplete data linkage of the original vaccination or ED-presentation data sets, in which pairs of records failed to link because of incorrect or missing information, is more likely to have occurred than false-positive links. Incomplete data linkage would have led to an underestimation of the proportions of cases vaccinated and an overestimation of VE. The completeness of linkages may have varied with the children’s ages because of changes in address over time. However, because the linkages were also based on variables that were unlikely to change, including date of birth, gender, and name, we do not think that the linkage rates differed excessively according to age. Accuracy of the data linkages may have also varied with the weighting of the linkage pairs, but we were unable to investigate this potential bias because of the complex linking of 5 data sets in this study. Our study benefited from obtaining accurate PPV estimates from the ACIR, which is estimated to capture data on 99% of the eligible population [9]. We do not have information on the specificity of ICD coding for febrile convulsions in Queensland EDs. A lack of specificity may have biased the results, with the inclusion of seizures unrelated to infectious agents likely to have biased VE toward the null.

Our findings may have also been confounded by differential receipt of influenza vaccine. It is more likely that children vaccinated with rotavirus vaccine would have also been vaccinated against influenza, a common cause of febrile seizures, and a confounding effect caused by this would lead to an overestimation of VE. However, influenza vaccination is not publicly funded for children in Australia, and uptake is likely to have been modest within the target age group [10]. Moreover, accurate coverage data are not available from which to estimate any potential confounding effect.

Although the prognosis for children with either afebrile or febrile seizures with mild rotavirus gastroenteritis is good [3, 7], a reduction in seizures from rotavirus vaccination may result in substantial benefits to children, their parents, and the health system more broadly. A Canadian study of 1359 children hospitalized with rotavirus, before vaccine introduction, found that 7% had seizures at presentation [11], and a study in Korea found that 7.8% of 755 children hospitalized with mild rotavirus experienced seizures (afebrile, 5.6%; febrile, 2.2%) [3]. Martin et al [7], in their study of first-time seizures among young children, found that 7 of 13 children in whom rotavirus was detected had afebrile seizures, and the other 6 children had febrile seizures. The incidence of febrile seizures [8] and the proportion of seizures caused by rotavirus also vary according to region, with a study in Hong Kong finding that only 1.3% of children hospitalized with febrile seizures, before rotavirus vaccine introduction, were rotavirus positive according to an enzyme immunoassay [12]. This number compares to 8% of children presenting with a first-time febrile seizure in the United States, some of whom had been born shortly before or since the introduction of rotavirus vaccination and were therefore eligible to have received rotavirus vaccination [7].

Our results support the recent US finding that there is substantial benefit to be gained from the reduction of childhood febrile seizures through rotavirus vaccination. The benefits of early childhood rotavirus vaccination, some of which were not obvious before introduction, continue to accumulate.

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Potential conflicts of interest. K.G. was previously a member of an advisory board to GlaxoSmithKline (GSK) on pneumococcal conjugate vaccines. S.B.L. has been an investigator on clinical studies sponsored by GSK, Merck, and bioCSL, he has served on a GSK advisory board for pneumococcal vaccine, and his institute has received consultancy fees from Merck for him to deliver presentations on rotavirus epidemiology in South Africa, Taiwan, and Vietnam, and to participate in an MMRV expert forum. R.S.W. and S.L.S report no conflicts.

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