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Early impact of rotavirus vaccination in a large paediatric hospital in the United Kingdom

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Running title: Impact of rotavirus vaccine on hospitalisations

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Summary

The impact of routine rotavirus vaccination on community-acquired (CA)- and healthcare-associated (HA)-rotavirus gastroenteritis (RVGE) at a large paediatric hospital, UK, was investigated over a 13 year period. A total of 1644 hospitalised children aged 0-15 years tested positive for rotavirus between July 2002 and June 2015. Interrupted time-series analysis demonstrated that post vaccine introduction (July 2013-June 2015), CA- and HA-RVGE hospitalisations were 83% (95% CI: 72-90%) and 83% (95% CI: 66-92%) lower than expected, respectively. Rotavirus vaccination has rapidly reduced the hospital rotavirus disease burden among both CA- and HA-RVGE cases.

Keywords: Rotavirus, Healthcare-associated infection; Epidemiology; Vaccination

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Background

Prior to the introduction of routine vaccination, rotavirus was the most common cause of severe gastroenteritis in children under five years of age worldwide.[1] In the UK, rotavirus gastroenteritis (RVGE) was estimated to be responsible for 45% and 20% of acute gastroenteritis hospitalisations and emergency department attendances in children under five years of age, respectively.[2] Rotavirus is also an important cause of healthcare-associated (HA) gastroenteritis; among children at a large paediatric hospital, UK, rotavirus was detected by reverse transcription-polymerase chain reaction (RT-PCR) in 43% of community-acquired (CA) and in 31% of HA-gastroenteritis cases.[3]

Several European countries have introduced rotavirus vaccine into their childhood immunization programmes, with effectiveness against RVGE hospitalisations estimated at over 80%.[4] In July 2013 the UK introduced the live-attenuated, two-dose oral monovalent rotavirus vaccine (Rotarix™, GlaxoSmithKline Biologicals SA, Belgium) with doses given at two and three months of age.[5] Vaccine uptake for a completed course reached 89% by June 2015.[6] Early impact studies in the UK suggested a large reduction (77%) in laboratory-confirmed rotavirus infections in vaccine age-eligible infants.[7] However, no impact on HA-infection has yet been described. Understanding the impact of rotavirus vaccination on both CA- and HA-RVGE cases may have implications for both hospital infection control and bed management policies, and will help inform the evidence base for continued immunization in the UK.

This retrospective investigation aimed to quantify the impact of rotavirus vaccination on HA- and CA-RVGE cases at the same children's hospital as our prospectively conducted study from the pre-vaccine period.[3]

Methods

Study Setting

The study was conducted at Alder Hey Children's NHS Foundation Trust, Liverpool, UK (Alder Hey). Alder Hey provides primary, secondary, and tertiary care facilities for >200,000 children each year and has approximately 240 inpatient beds. General medicine, general surgery, and a range of specialist services including critical care, oncology, cardiac, and neurosurgery are provided; there is also a large emergency department.

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Case definition

Children aged between 0 and 15 years who were admitted with RVGE between July 2002 and June 2015, or those in whom RVGE developed after hospitalisation, were eligible for inclusion. Testing for rotavirus was conducted on clinician request throughout the study period with no age restriction. RVGE was defined as rotavirus antigen detected by immunochromatographic test or by enzyme immunoassay in a faecal specimen of a child with acute gastroenteritis. RVGE was considered HA if gastroenteritis developed ≥48 hours after admission and there was no record of diarrhoea or vomiting on admission. Clinical and anonymised demographic data were collected for each participant, and included information on specimen date, admission date, age and symptoms on admission. The pre-vaccine period was defined as July 2002 to June 2013 and the vaccine period was defined as July 2013 to June 2015.

Statistical analysis

To assess the impact of rotavirus vaccination on hospitalisations for CA- and HA-RVGE, an interrupted time-series methodology was used. Firstly, monthly expected incidence of rotavirus hospitalisations was estimated by fitting a negative binomial regression model to pre-vaccine monthly incidence data, offset for total monthly admissions and adjusting for seasonality and secular trends using calendar month and rotavirus year (July to June), respectively.[8] This model was used to predict the counter-factual numbers of RVGE hospitalisations (in the absence of vaccination) for the vaccine period, where the impact of vaccination is expressed by the difference between the counter-factual expectation and observed number of hospitalisations. To quantify change in the number of RVGE hospitalisations by the introduction of the vaccine, a second model included a derived binary indicator variable for the post-vaccine period, enabling the computation of risk ratios (RR) and associated 95% confidence interval (CI). This second model offset for total monthly admissions and adjusted for month and rotavirus year. Percentage change in incidence was calculated as **100 X (1 – *RR*)**. The analysis was undertaken separately for CA- and HA-RVGE hospitalisations. To investigate the impact of routine vaccination on different age groups the analysis stratified overall RVGE hospitalisations by age group (<2 years old and 2-4 years).

Demographic and clinical characteristics were compared between RVGE cases from the pre and post-vaccine periods and between CA- and HA-RVGE cases. For continuous variables we used a t-test or Wilcoxon rank-sum test if not normally distributed and χ^2 or Fisher's exact test for categorical variables. All data handling and statistical analyses were performed using R Version 3.1.2 (R Development Core Team, Vienna, Austria).

Ethical approval

Ethical approval was provided by NHS Research Ethics Committee, South Central-Berkshire (Reference: 14/SC/1140).

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Results

A total of 1644 hospitalised cases of RVGE were documented between July 2002 and June 2015. CA-cases accounted for 74.2% (n=1220) of all RVGE cases, 25.4% (n=418) cases were HA-RVGE and 0.4% (n=6) did not meet the case definition for either HA or CA. In the pre-vaccine period there was a mean of 145 RVGE hospitalisations per year (range: 109-191), comprising 108 (83-150) CA- and 37 (18-58) HA cases (Table 1). In the first post-vaccine year (July 2013-June 2014) there were a total of 22 RVGE cases and in the subsequent year (July 2014 – June 2015) there were 30 RVGE cases. In the pre-vaccine period 25% (range: 15-35%) of RVGE cases were classified as HA compared with 29% (18% in 2013/14; 37% in 2014/15) in the vaccine period (p=0.6).

There was an estimated 82% reduction in RVGE hospitalisations (95% CI 70-89%) in the vaccine period, compared with what would have been expected in the absence of vaccination (Table 1; Figure 1). Most of the decline occurred in vaccine age-eligible children <2 years old (84%: 95% CI 74-90%). A reduction of 69% (95% CI 38-86%) was observed in children age 2-4 years who were too old to have been vaccinated. There was an insufficient number of RVGE hospitalisations in children aged over 5 years in the pre-vaccine era (mean per year=12; range 6-20) to enable fitting of the regression model (Table 1). The magnitude of reduction in hospitalisations in the vaccine period was similar in both CA-RVGE (83%: 95% CI 72-90%) and HA-RVGE (83%: 95% CI 66-92%) cases (Table 1; Figure 1).

The median age of pre-vaccine CA-RVGE cases (12 months, Interquartile Range [IQR] 7-23), was lower than the age of CA-RVGE cases from the vaccine period (23 months, IQR 14-26; p<0.001). The median age of -HA-RVGE cases that occurred in the pre-vaccine period (9 months, IQR 4-22), was non-significantly higher than that of HA-RVGE cases in the vaccine period (5 months, IQR 4-14; p=0.131). The median age of CA-RVGE cases in the pre-vaccine period was significantly higher than that of HA-RVGE cases (p<0.001), with this age difference even greater in the vaccine period (p<0.001).

Discussion

Since the introduction in 2013 of routine rotavirus vaccination in the UK there has been a significant decline in hospitalisations for RVGE in this large paediatric hospital. The magnitude of reduction was similar for both CA- and HA-RVGE cases. Age stratified analysis provided further evidence that the reduction in hospitalisations is highly likely to be due to the impact of vaccination as the largest reduction was observed in vaccine eligible infants <2 years of age. Furthermore, as shown in other settings, there was an increase in age of RVGE cases post vaccine introduction.[7,9] The observed reduction in vaccine ineligible older age groups (2-4 years) is similar to that observed through national laboratory surveillance and may be indicative of an indirect effect of vaccination.[7]

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We established that HA-RVGE cases were significantly younger than CA-RVGE cases. Furthermore, an increase in age in the vaccine period was observed among CA-RVGE cases but this was not observed among HA-RVGE cases. Similar age profiles were also observed at a paediatric hospital in Greece following vaccine introduction.[10] These data suggest that hospitalised infants aged <1 year remain at risk of developing HA-RVGE even among highly vaccinated populations, possibly through direct or indirect exposure to rotavirus from older children and adults.

Our study relied upon rotavirus antigen testing in stool, which is known to be a better predictor of symptomatic rotavirus disease than PCR-based methods; interpretation of a positive PCR result is rendered difficult because of the high frequency of asymptomatic rotavirus shedding in young children, necessitating the development of a real-time PCR cut-off to define symptomatic infection.[11] Therefore, it is likely that the cases in this study represent clinical disease. Although rotavirus vaccination cannot be definitively established as the cause of the observed reduction in RVGE hospitalisations due to the ecological nature of this study, there are additional factors which suggest vaccine impact. The reduction in CA- and HA-RVGE cases in the vaccine period has not been mirrored by a similar decline in respiratory syncytial virus (RSV) infection, another viral pathogen that predominately affects young children in winter; indeed, the incidence of HA-RSV infection has remained stable whilst RSV infection has increased in the community (data not shown). There were also no major changes in hospital infection prevention and control policies during the period of study. Finally, our study examined two post-vaccine seasons and took into account long-term seasonal and annual trends.

This study has demonstrated that since the introduction of routine rotavirus vaccination in the UK, in addition to a marked decline of CA-RVGE cases, there has been a similar fall in HA-RVGE hospitalisations. The reduction in RVGE cases is expected to save bed days and reduce the burden on infection control teams with potential for both clinical and economic benefit.

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Conflicts of interest

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Table I. RVGE hospitalisations at Alder Hey among children 0-15 years of age, pre- and post-rotavirus vaccine introduction

	Yearly mean number of hospitalisations (range) pre-vaccine introduction, July 2002-June 2013*	Number of hospitalisations post-vaccine introduction. July 2013-June 2015		Risk Ratio (95% CI)	Percent decline in hospitalisations (95% CI)†	p-value
		Year 1	Year 2			
Overall	145 (109-191)	22	30	0.18 (0.11-0.30)	82 (70-89)	<0.001
Age						
<2 years	111 (88-145)	17	16	0.16 (0.10-0.26)	84 (74-90)	<0.001
2-4 years	22 (15-32)	2	13	0.31 (0.14-0.62)	69 (38-86)	0.017
5-15 years	12 (6-20)	2	1	-	-	-
CA-RVGE	108 (83-150)	18	19	0.17 (0.10-0.28)	83 (72-90)	<0.001
HA-RVGE	37 (18-58)	4	11	0.17 (0.08-0.34)	83 (66-92)	<0.001

*yearly means are based on a rotavirus year running July to June

†Calculated as 1-risk ratio. Risk ratio was calculated using a negative binomial model adjusting for calendar month and rotavirus year.

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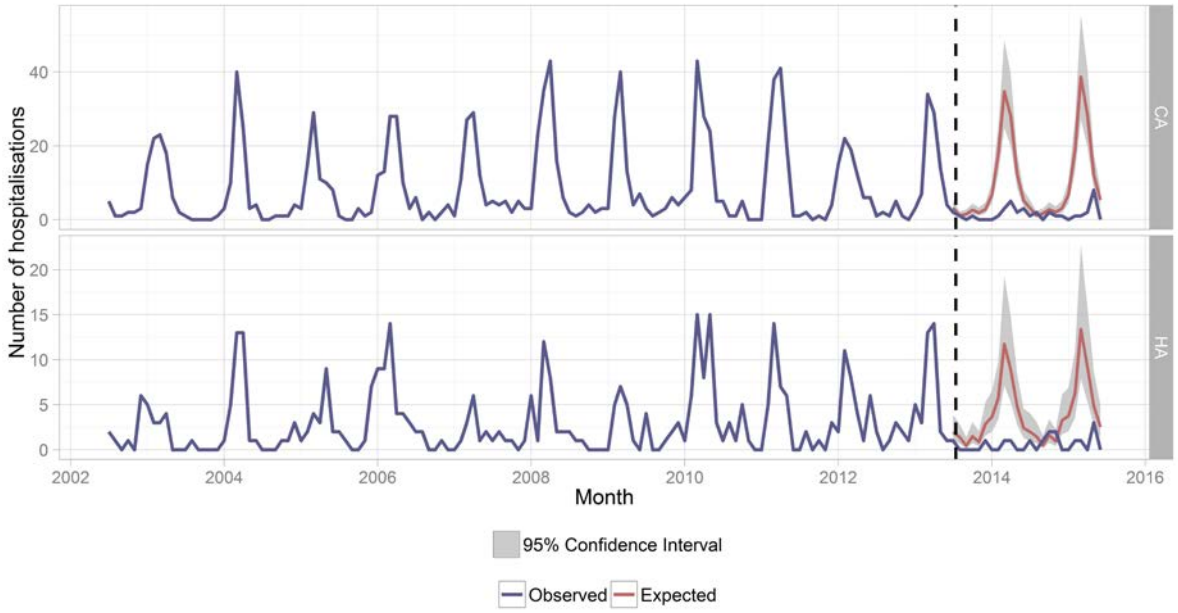

Figure 1. CA- and HA-RVGE hospitalisations at Alder Hey, July 2002 to June 2015. The blue line is the observed incidence of RVGE; the red line is the *expected* incidence and the grey shading the 95% confidence intervals for the *expected* incidence. The black hashed line represents the introduction of rotavirus vaccine in the UK in July 2013.