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Impact of high coverage of monovalent human rotavirus vaccine on Emergency Department presentations for rotavirus gastroenteritis

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ABSTRACT

Introduction: Australia was one of the first countries to introduce nationally funded rotavirus vaccination. The program has had a substantial impact on both rotavirus and all-cause acute gastroenteritis (AGE) hospitalisations and rotavirus laboratory tests. Evidence for an impact on Emergency Department (ED) presentations is limited. This study assessed changes in ED presentations for rotavirus in children aged <5 years in New South Wales, Australia, following introduction of monovalent human rotavirus vaccine (RV1, Rotarix®, GlaxoSmithKline Australia Pty Ltd., Victoria, Australia).
Method: A time series analysis to examine trends in total non-admitted ED presentations for all-cause AGE and in the rotavirus-attributable fraction using data on rotavirus positive laboratory tests.
Results: A decline in the rate of non-admitted ED presentations for AGE was observed for all ages, being most notable in 1 year old children. Compared with the pre-immunisation period, we estimated the average weekly rate was lower across the first 4.5 years of the program for both all-cause AGE (18.3%; 70.5 versus 57.5 per 100,000 population) and rotavirus attributable (55.4%; 17.3 versus 7.7 per 100,000 population) presentations. In the fourth year of the program, estimated annual rotavirus attributable presentations were 77% lower than the pre-vaccination annual mean (996 versus 4300 per year).
Conclusion: The program was associated with a substantial decline in rotavirus attributable non-admitted AGE presentations to ED among children aged <5 years.

1. Introduction

Worldwide, rotavirus is the leading cause of acute gastroenteritis in children aged <5 years, with almost all children in this age group infected at least once [1]. The World Health Organisation estimated that 453,000 children aged <5 years died from rotavirus in 2008 [2], with deaths mostly confined to developing and middle income countries [2]. Before rotavirus vaccines were included in the Australian National Immunisation Program, rotavirus was estimated to account annually for 10,000 hospitalisations, 22,000 Emergency Department (ED) presentations (excluding children subsequently admitted to hospital), and 115,000 presentations to primary care providers in <5 years of age, at a cost to the Australian health care system of $30 million ($AUD) [3,4]. This estimate excluded societal costs such as income lost by carers, which add considerably to the overall cost of disease [5,6].

Australia was one of the first countries to introduce a nationally funded vaccination program for rotavirus, commencing for all infants on 1 July 2007 [7]. Both RV5 (RotaTeq® CSL Biotherapies/Merck & Co.) and RV1 (Rotarix® GlaxoSmithKline Biologicals [GSK]) are funded under the program, with the state of New South Wales (NSW) exclusively using RV1. RV1 is an oral monovalent live attenuated human rotavirus vaccine, given in a two dose course at approximately 2 and 4 months of age, with upper age limits imposed on delivery of both doses [8]. High 2-dose vaccine coverage (86.9% in non-Indigenous infants and 76.1% in indigenous children) was obtained early following program introduction [9].

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Hospitalisations for rotavirus and all-cause acute gastroenteritis (AGE) have declined in Australia since rotavirus vaccination commenced [10–13], consistent with international findings [14,15]. However, the decline has not been as marked or consistent in Australian indigenous children [13,16,17]. Rotavirus activity, reflected in laboratory notifications, also declined in NSW [18] and Queensland [19] after program introduction. Only one previous study has assessed ED presentations, reporting a decline in all-cause AGE in NSW in the first year after program introduction [18].

In this study we aimed to estimate (1) the incidence of non-admitted AGE ED presentations due to rotavirus in children age <5 years in NSW and (2) the impact of the vaccination program on the incidence of non-admitted ED presentations for rotavirus attributable and all-cause AGE in this age group.

2. Materials and methods

2.1. Data

The study population was all children aged <5 years in NSW, Australia for 2003–2011, inclusive. Weekly population estimates were calculated by linear interpolation of midyear estimated resident populations [20,21]. In 2011, the NSW population aged <5 years was approximately 481,000 and there were approximately 99,000 births.

Data on ED presentations were obtained from the NSW ED data collection. Only those public hospital EDs that provided data across the whole study period were included in the study ($n = 50$). These EDs accounted for approximately 72% of all ED presentations in the study period and included almost all urban and all larger regional hospitals in NSW.

Aggregate weekly counts of non-admitted ED presentations for all-cause AGE were extracted by year of age. An ED presentation was defined as being for AGE if the primary diagnosis was recorded using codes for gastroenteritis or gastroenteritis symptoms (nausea, vomiting and/or diarrhoea). We included presentations selected using AGE codes from any of the three different diagnosis classification systems used in ED information systems reporting to the ED data collection; International Classification of Diseases, 9th Revision, the International Classification of Diseases, 10th Revision, Australian Modification and the Systemised Nomenclature of Medicine – Clinical Terms. The specific codes used are reported in Supplementary File 1.

Of 13 public and 2 private diagnostic laboratories that provide services across NSW, 10 public laboratories provided either the aggregate weekly counts of rotavirus positive tests in children aged <5 years, or the date of specimen collection and age, from which the authors calculated aggregate weekly counts. Results were included regardless of whether the specimen was collected at an ED, hospital or primary care site as the purpose of collecting the laboratory data was to provide a measure of the circulation of rotavirus within the community. This was then used to estimate the rotavirus attributable fraction of non-admitted ED visits for all-cause AGE.

2.2. Analysis

Analyses were carried out by epidemiological weeks in three steps using SAS software version 9.3® [22]: model equations are provided in the Supplementary File.

(1) Weekly rates of non-admitted ED presentations for all-cause AGE and of rotavirus positive laboratory tests were calculated by dividing each weekly count by the interpolated weekly population.

(2) Weekly rates of rotavirus-attributable, non-admitted ED presentations for all-cause AGE were estimated using time series analysis. A generalised additive model (GAM) [23] was used to assess the relationship between the weekly rate of all-cause AGE presentations (the dependent variable) and the weekly rate of rotavirus positive laboratory results and calendar time (explanatory variables). To account for the varied seasonality of infectious causes of AGE, the influence of time in weeks was modelled using a non-parametric cubic spline with six turning points (or "knots") per year plus a linear term for week. Normally distributed model residuals were assumed for the parametric component of the model and checked using quantile–quantile plots. Independence of the residuals over time was checked using autocorrelation plots. Weekly rates of rotavirus-attributable AGE presentations were estimated by multiplying the estimate of the co-efficient for the rate of laboratory positive results from the model (the adjusted ratio of rotavirus ED presentations to positive rotavirus laboratory test results) by the weekly rate of laboratory positive results.

(3) Separate ordinary linear regression models were used to estimate the vaccine program-associated change in the mean weekly incidence rate of observed all-cause AGE presentations, and of estimated (from Step 2) rotavirus attributable and non-rotavirus attributable AGE presentations. The vaccine period was included in each model using a binary indicator variable assigned the value 0 in the pre-vaccination program period (5 January 2003 to 30 June 2007), and 1 in the vaccination program period (1 July 2007 to 31 December 2011). The model coefficient for the indicator variable was interpreted as an estimate of the absolute change in the mean weekly rate associated with the vaccine program period. The model intercept provided the estimate of the mean weekly incidence rate during the pre-vaccination program period. The sum of these two estimates provided an estimate of the mean weekly incidence rate during the vaccination program period.

In order to aid interpretation and comparison with other studies, we also present annualised calendar year estimates, obtained by summing the 52 weekly values in the weekly analysis described above, including pre- and post-vaccination comparisons. Unlike the regression analysis, these comparisons exclude the year 2007, when the vaccination program commenced mid-year.

2.3. Ethics approval

The study was approved by the NSW Population and Health Services Research Ethics Committee (LNR 2012/05/018) and The University of New South Wales Human Research Ethics Committee (HC12349).

3. Results

There was a decline in the weekly rates of non-admitted ED presentations for all-cause AGE and rotavirus positive laboratory tests following introduction of the vaccine program (Fig. 1). The observed reductions were most evident for the youngest children (Fig. 2).

Comparison of the rate of all-cause AGE presentations predicted by the model with the observed rate of all-cause AGE presentations showed a good fit (Fig. 3). Quantile–quantile plots showed the assumption of normally distributed model residuals was reasonable, but there was minor autocorrelation in the residuals (Figs. S1 and S2 in Supplementary File 2). The model estimated that 4.7 (95% CI: 4.6–4.9) additional rotavirus attributable ED presentations per 100,000 population occurred per week for a concurrent increase

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