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Short communication

Lack of impact of rotavirus vaccination on childhood seizure hospitalizations in England – An interrupted time series analysis

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ABSTRACT

Observational studies have linked a reduction in childhood seizures (CS) to the introduction of rotavirus vaccination (RV). England is opportunely placed to explore this due to well-defined introduction, high uptake of RV and centralised Hospital Episodes Statistics recording all admissions. We investigated the association between seizures and vaccine use through interrupted time-series analysis of all CS admissions in children <3 years old (ICD-10 codes; G40*-G41*, R56.0*) during 2007–2017. We did not detect a statistically significant association between the introduction of RV and admission with febrile ($p = 0.84$), afebrile ($p = 0.83$) or all CS ($p = 0.93$), even when limited to peak rotavirus seasonality (March). This is the first ecological study in a country that exclusively uses the monovalent vaccine. Although a negative finding, we would argue that if an effect cannot be detected at this population level then it is unlikely to be clinically or economically significant but generates hypotheses of potential non-specific effects.

1. Background

The introduction of a live attenuated Rotavirus vaccine (Rotarix®, *GlaxoSmithKline Biologicals*), to the UK's child immunisation schedule in July 2013 has resulted in significant improvements in morbidity and healthcare usage by preventing rotavirus acute gastroenteritis (RAGE). In the UK 93% of eligible children complete their vaccination course with evidence of substantial herd protection [1].

Although the main symptoms of rotavirus infection are gastrointestinal, it is also linked to central nervous system (CNS) pathology. Studies from the United States (US) reported that up to 7% of infected children experience convulsions [2]. These may be febrile convulsions secondary to the pyrexia frequently associated with rotavirus, or alternatively a direct effect of infection as rotavirus has been detected both in blood [3] and cerebrospinal fluid [4]. Other putative mechanisms are indirect neurotoxicity, mediated through NSP4 enterotoxin [5] or nitric oxide [6]. With rotavirus infection frequently gastro-intestinally asymptomatic [7], it may potentially be an under-recognised cause of CNS morbidity.

In the US, Payne et al. [8] performed a large retrospective cohort analysis of over 250,000 children from the CDC Vaccine Safety Datalink database and found an 18–21% risk reduction in rates of Emergency Department (ED) attendance or admission to hospital with childhood seizures in the year after rotavirus vaccination. A second study from the US using an insurance claim database of 1.8 million children showed a 24% risk reduction of seizure hospitalisations persisting up to five years after vaccination [9]. Both studies used Cox regression to analyse time to event, despite this technique assuming that the factors investigated have a constant impact on the hazard – or risk – over time [10]. In Australia, Sheridan [11] used the screening method to compare the vaccination status of 2211 children attending the ED with febrile seizures to the general population and found vaccine effectiveness of 35–38% for preventing presentation to the ED in the two years after vaccination. However ecological studies examining population-level benefit have found more variable strengths of association against seizure hospitalisation, ranging from 1 to 8% in an interrupted time series analysis (ITS) in the USA [12], a non-significant 16–34% trend in an uncontrolled before/after study design in North West Spain [13], to no association at all in South East Spain [14].

With such striking but inconsistent findings on one of the conditions most feared by parents [15], we felt it important to assess if the same effect could be detected in the UK. We chose to examine population-level trends of childhood seizures regardless of

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individual characteristics, both before and after vaccine introduction, using an ITS analysis [16] to examine the vaccine's effect on pooled aggregate risk of seizure.

2. Methods

2.1. Data sources

Hospital Episodes Statistics (HES) is a centralised records system capturing all admissions and associated International Classification of Diseases (ICD-10) disease codes across National Health Service (NHS) Trusts in England. As all acute paediatric inpatient care occurs in NHS Trusts, with a financial incentive for accurately recorded admissions, these records can be effective in monitoring public health trends.

We used HES to identify all admissions of children <3 years old with their first diagnosis of febrile or afebrile seizures (ICD-10 codes; G40*, epilepsy and recurrent seizures, G41*, status epilepticus, R56.0*, febrile convulsions) between April 2007 and March 2017. The previous studies have established a protective vaccine association in this age group, with some the largest impact in these infants [13], probably because they have the highest burden of rotavirus infection. As an analysis of non-identifiable routinely collected data, following HRA guidance [17], our study did not require ethical review.

2.2. Data analysis

We fitted separate regression models for febrile and afebrile seizure counts; offset for English population changes using Office for National Statistics (ONS) mid-year estimates. Due to the immediate nature of vaccine introduction we tested for both a step and slope change in the rate of admissions before and after vaccine introduction. Age and year of admission were included in the model as predictor co-variates. To avoid autocorrelation we analysed by whole year periods and assessed this using the Durbin-Watson test. In our secondary analyses we fitted separate models by age group to assess the effects of vaccination on both afebrile and febrile seizures, both of which could both be aetiologically relevant to rotavirus but have different age admission patterns. We also performed a further separate sub-analysis examining annual admissions in March – the height of rotavirus season in England. As model residuals showed evidence of over-dispersion using the Poisson distribution, in the final analysis we used negative binomial distribution. We corrected for multiple testing using the Holm method. Data analysis was performed using R 3.4.1 [19].

3. Results

During the 10-year study, the English population under 3 years old encompassed approximately 20 million children (ONS). We identified 125,096 and 113,775 first-time admissions with afebrile and febrile seizures, respectively, across all hospitals in England, resulting in overall mean incidence rates of 623 and 568/100,000 population. Rates of completed vaccine use in English eligible children remain consistently high, averaging 90% since introduction [18]. England's birth rate was also stable, with a mean of 672,216 ± SD 13,166 children born per year (ONS).

The absolute numbers and rates of admission with non-febrile seizures remained broadly comparable (Table 1), even when analysis was restricted to different age groups (Fig. 1). There was a decreasing trend in admissions with febrile convulsions, predating the introduction of the rotavirus vaccine (Table 1). This trend is particularly well demonstrated for those aged 1–2 years (Fig. 1), in whom we see the peak of presentation with febrile convulsions.

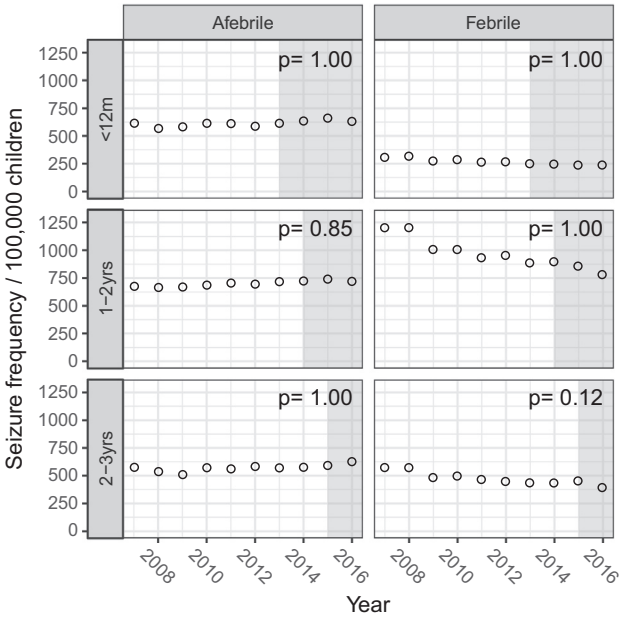

Fig. 1. Afebrile and febrile annual first-time seizure admission rates by age. Shaded area represents period vaccine available for age cohort. P value denotes effect of vaccine introduction on model.

Table 1
Changes in birth rate & seizure admissions to inpatient English NHS Trusts over the period April 2007-March 2017 for children aged 0 to <3 years. Each year follows the English tax year, beginning in April and finishing the following March. The birth rate is as reported from ONS mid-year estimates. Shaded area represents period vaccine available.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
England Birth Rate	655357	672809	671058	687007	688120	694241	664517	661496	664399	663157
Afebrile convulsions (n)	11778	11514	11672	12595	12738	12788	12906	12923	13147	13035
Rate / 100,000	619	586	584	620	623	618	631	640	661	655
Febrile convulsions (n)	13111	13597	11705	11987	11267	11409	10725	10519	10174	9281
Rate / 100,000	689	692	585	590	551	551	524	521	511	467

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