Lack of impact of rotavirus vaccination on childhood seizure hospitalizations in England – An Interrupted Time Series Analysis.

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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 – 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 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.

METHODS

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 less than 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), likely 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.

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 the negative binomial distribution. We corrected for multiple testing using the Holm method. Data analysis was performed using R 3.4.1.(19)

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 (Figure 1). There

was a decreasing trend in admissions with febrile convulsions, pre-dating the introduction of the rotavirus vaccine (Table 1). This trend is particularly well demonstrated for those aged 1-2 years (Figure 1), in whom we see the peak of presentation with febrile convulsions.

Our primary outcome model did not detect a statistically significant reduction in annual admissions of under 3 year olds with either febrile, afebrile or all seizures in association with vaccine introduction and use (Table 2). Sub-analysis by age groups failed to show any significant relationship with vaccine use when adjusted for multiple testing in those aged 0-2 years old. A *p* value of 0.01 (Table 2) was noted in those aged 2-3 when examining annual all-cause childhood seizure admissions in association with rotavirus vaccination. However in this subgroup, our ITS analysis is limited to only one year of post-vaccine data to compare to 9 years of pre-vaccine data and may not be truly significant. When the model was restricted to rates of admission in March, the peak of the rotavirus season in England, a reported *p* value of 0.01 was noted in relation to vaccine use and reduction of febrile seizures in those aged 2-3 years (Figure 2), alongside a *p* value of 0.002 in this age group for all-cause seizures (Table 2). As noted before, this age group is limited to only one year of post vaccine data and though corrected for multiple testing - is an analysis of a subset (by age group) in a subset (March only admissions). A planned secondary analysis looking at the primary research question but analysing all admissions with seizures, as opposed to first admission, had the same findings (data not shown).

CONCLUSIONS

Our study assessed the age-specific incidence rates of paediatric admissions with febrile and afebrile seizures for all English NHS Trusts across a 10-year period. Using ITS analysis, we did not detect a reduction in the rate of seizure admissions of <3 year olds associated with the mid-study introduction of rotavirus vaccine. We observed a reduction in the number of admissions with febrile seizures that pre-dated vaccine introduction and is likely to be due to evolving patterns of admission from pressures on hospital bed availability. This is consistent with the study from South East Spain

where rotavirus vaccination initially appeared negatively correlated with childhood seizure admissions, and all cause hospitalisation but accounting for confounders such as total hospitalisation rate there was no vaccine specific effect on seizures (14). They too attributed the decreasing trend in seizure hospitalisations to changes in admission policies from financial constraints following the economic crisis. When examining admissions in the peak of rotavirus season, we found a potential signal suggesting reduction in febrile seizures in children aged 2-3 years old. However with only one year of post-vaccine data in this age group we feel this is statistical artefact. The peak age of febrile seizures is 18 months and in this age cohort we did not detect any effect despite younger children with seizure being more likely to be admitted.

The strength of our study is its robust ecological size, comparing trends over a decade across the whole of the English paediatric population. Although an alternative study design, we analysed 80 to 100-fold more seizures requiring medical attention than the aforementioned three cohort studies (8-9, 14). These found varying strengths of direct protective association, with the lowest reported as a 20% risk reduction in risk of seizures. Despite the inherent flaws of an ecological study design, if such a significant effect existed in England we believe our much larger study would have detected a signal, given that our vaccine uptake is also higher. Thus we argue that this is an important negative finding; if a protective association of the monovalent vaccine cannot be detected at such this population level then the effect is unlikely to be clinically, or economically, significant.

A major limitation of our study is that our data source only recorded paediatric hospital admissions and did not capture ED attendances. We were not able to examine whether vaccine effect can be found in presentations of convulsions to the ED where more minor attendances may be discharged after a period of observation. Current national emergency datasets in England do not consistently record discharge diagnoses and so do not allow the same analyses. Reassuringly both of the cohort

studies (8,11) that examined this still reported a significant finding for their sub-analyses of only admitted patients.

As the HES dataset is centrally anonymised, a further limitation of our study is that we were unable to independently assess the accuracy of ICD-10 coding. However a seizure is a significant clinical event and is likely to be well recorded. Given that hospitals are paid based on these records they are financially incentivised to maintain the accuracy of them, as such they are the standard inpatient dataset for the UK.

Our study is unique by investigating this protective association in England, where the monovalent vaccine Rotarix® is used. Existing studies have been performed in domains and countries predominately using the pentavalent vaccine (RotaTeq®, *Merck & Co.*), excepting Spain where both have been used, though combined coverage only reaches 29-41% and Rotarix® was unavailable for several years. One intriguing hypothesis for our findings is that the effect on seizures is specific to the pentavalent vaccine.

Other explanations for our contrary findings could include a different underlying epidemiology of rotavirus infection. Incidence of RAGE-associated childhood seizures has not been well documented in England and perhaps compared to other countries we see less CNS involvement. We were also unable to consider differing patterns of other seizure-inducing infections, such as influenza. Of note, this may have affected previous studies and may explain why the reducing trend in seizure hospitalisation in those under five years of age, noted by Pringle et al in the US (12), did not reflect the biennial pattern of RAGE which has emerged, as would be expected if it was the result of direct vaccine benefit.

To extend this work we are planning to collect data to perform a time series analysis of presentations to the ED with childhood seizures in England over the same period, obtaining ICD-10 discharge diagnoses from individual hospital trusts through the PERUKI network (20). We aim to

capture whether a protective association of the monovalent vaccine can be found against less severe forms of childhood seizures, which do not require hospitalisation. With a well-defined introduction of this vaccine and high uptake levels, ecological changes in England remain important in attempting to define any putative protective effect of the rotavirus vaccine, where further scientific evidence is needed.

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Authors' contributions:

RM developed the idea and design of the study. RB analysed the data, interpreted the results and drafted and edited the manuscript. RM and AF critically revised the manuscript. All authors read and approved the final manuscript.

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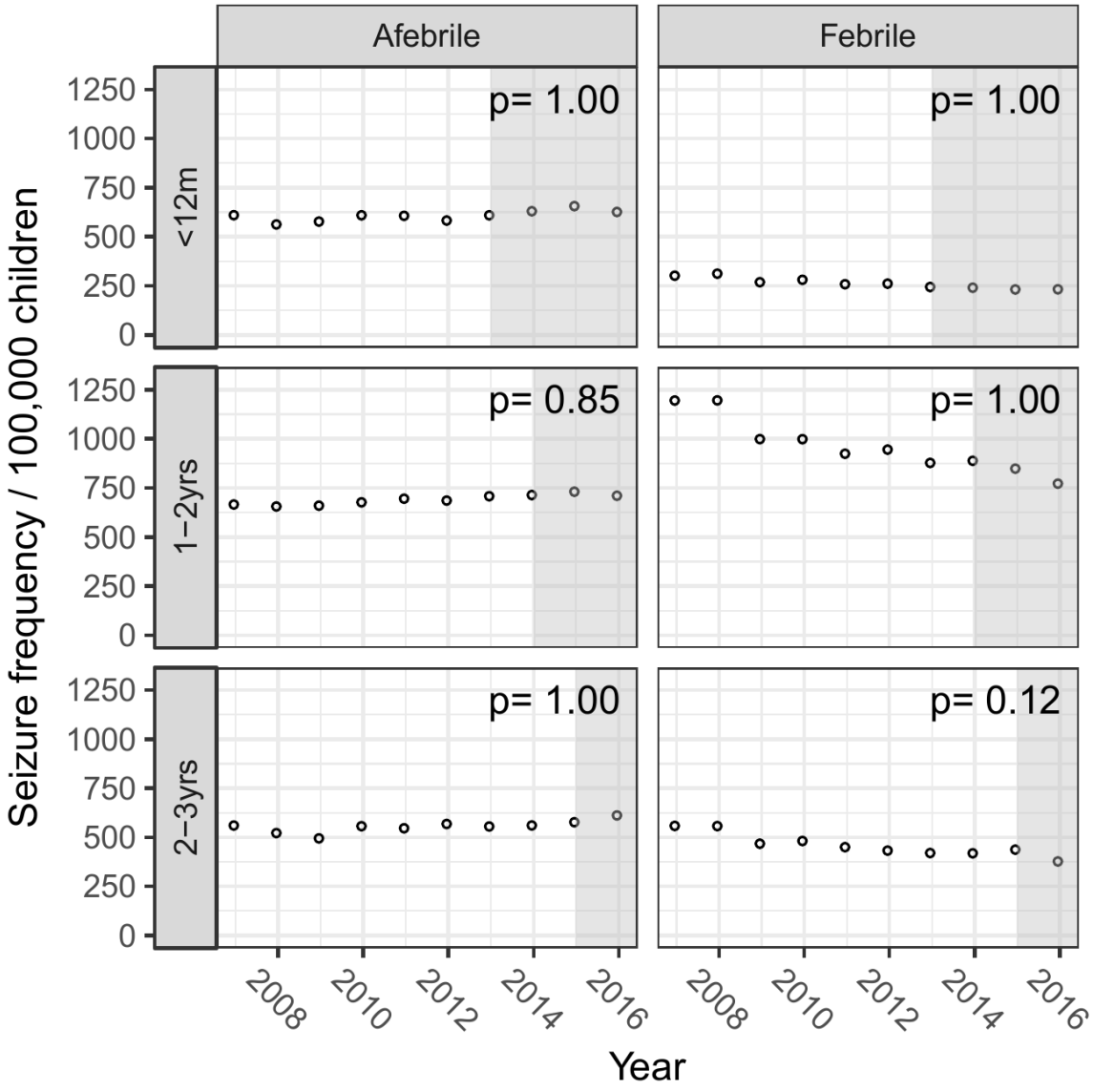
Figure Legends:



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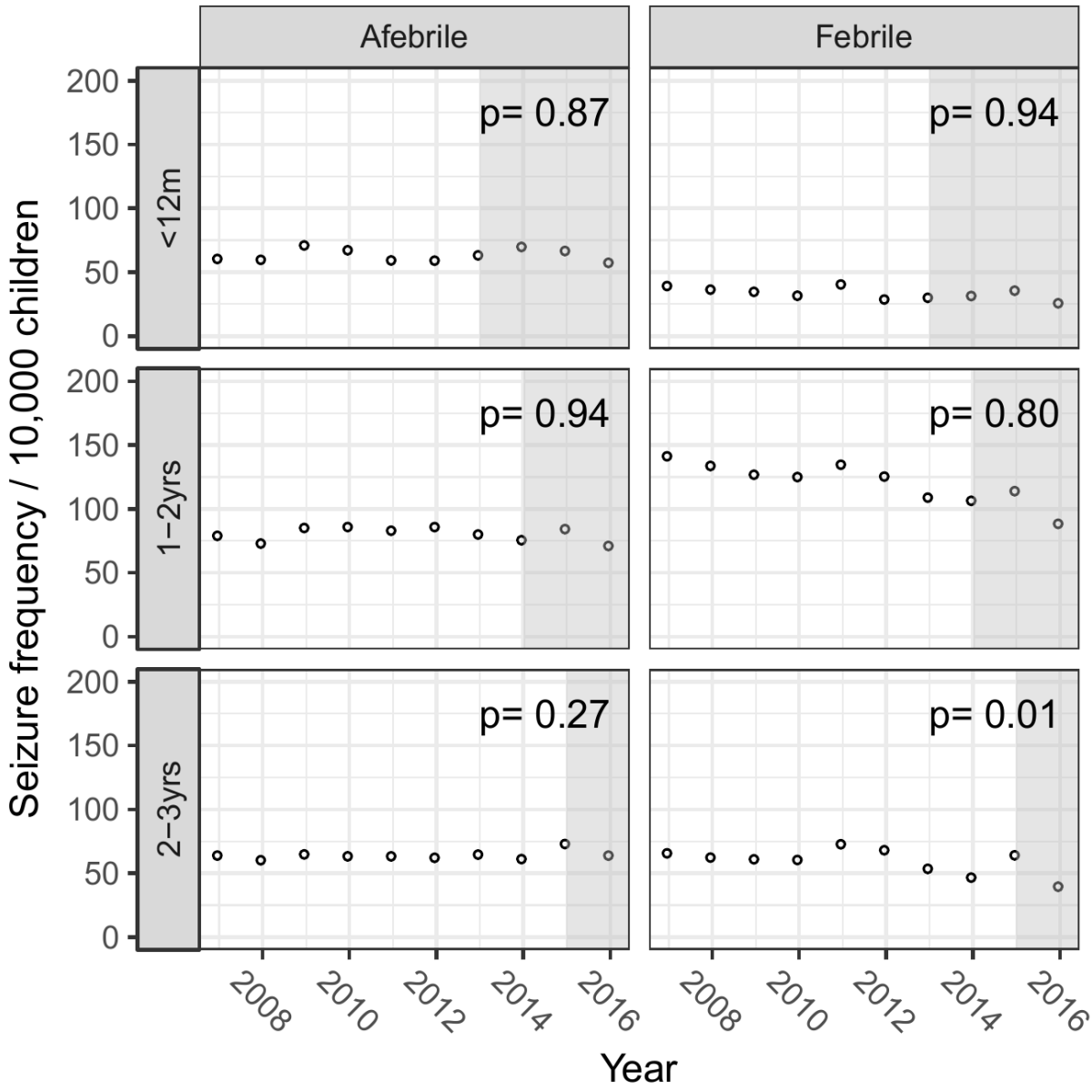
241 Figure 1: Afebrile and febrile annual first-time seizure admission rates by age.

242 Shaded area represents period vaccine available for age cohort. P value denotes effect of vaccine

243 introduction on model.



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245 Figure 2: Afebrile and febrile first-time seizure admission rates in March of each year by age.

246 Shaded area represents period vaccine available for age cohort. P value denotes effect of vaccine

247 introduction on model.

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	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

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.

		Whole Year			**March only sub-analysis**		
		Febrile	Afebrile	All Seizures	Febrile	Afebrile	All Seizures
Children Aged <3		***0.84***	***0.83***	***0.93***	1	1	0.65
	Aged <12m	1.0	1.0	0.94	0.94	0.87	1
	Aged 1-2	1.0	0.85	0.8	0.80	0.94	1
	Aged 2-3	0.12	1.0	0.01	0.01	0.27	0.002

Table 2 P values of evidence for statistical association of mid-study introduction of vaccine use and trends of childhood seizure hospitalizations in England from 2007-2017. P values are from separate regression model outputs analyzed in R. The primary model outcome is highlighted in italics. All subsequent sub-analyses have been corrected for multiple testing. The shaded table represents model outputs using admission data only collected in March, the peak of rotavirus seasonality.

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