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The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation

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ABSTRACT

Objective: To investigate the risk of intussusception after monovalent rotavirus vaccine (RV1) given to infants aged 2 and 3 months in England.
Methods: Hospital Episode Statistics (HES) were used to identify infants aged 48–183 days admitted between 11/03/2013 and 31/10/2014 with intussusception. Diagnosis was confirmed from medical records and HES procedure codes. Vaccination status was obtained from general practitioners. The risk of admission within 1–7 and 8–21 days of vaccination was analysed using the self-controlled case-series (SCCS) method with age effect adjustment by including historical data before RVI introduction in July 2013.
Results: A total of 119 cases were identified during the study period and intussusception confirmed in 95 of whom 39 were vaccinated 1–21 days before onset. An increased relative incidence (RI) in this period was found, 4.53 (95% confidence interval 2.34–8.58) and 2.60 (1.43–4.81) respectively after the 1st and 2nd doses with an attributable risk of 1.91 and 1.49 per 100,000 doses respectively. The peak risk was 1–7 days after the first dose, RI 13.81 (6.44–28.32), with an estimated 93% of the 15 cases being vaccine-attributable. Mean interval between onset and admission, and clinical features were similar between vaccine-associated and background cases. Despite intussusception being a contraindication to rotavirus vaccination, 10 infants received a further dose; none had a recurrence. The RIs in a meta-analysis combing our results with Australia, Mexico, Brazil and Singapore using RV1, a 2, 4 month schedule and SCCS gave pooled RI estimates of 2.35 (1.45–3.8) and 1.77 (1.29–2.43) in the 21 day period after the 1st and 2nd doses, respectively. The earlier age at the 2nd dose in England did not affect the risk.
Conclusion: We estimate that the RVI programme causes around 21 intussusception admissions annually in England but, since it prevents around 25,000 gastro-intestinal infection admissions, its benefit/risk profile remains strongly positive.

1. Introduction

Rotavirus infects nearly every child by five years of age and is the leading cause of gastroenteritis worldwide [1]. In healthy infants in developed countries the infection results in a mild self-limiting illness with low mortality though it has a high healthcare burden and causes parental anxiety [2]. It is estimated that in England and Wales in the absence of vaccination rotavirus infection is responsible for around 45% of hospitalisations, 20% of accident and emergency attendances and 25% of primary care consultations for acute gastroenteritis in children under five years of age, corresponding to annual incidences per 1000 of 4.5, 9.3 and 28–44 consultations respectively [3].

The first rotavirus vaccine, Rotashield®, was shown to have an attributable risk of intussusception of between 10.5 and 21.4 per 100,000 infants vaccinated [4] and was withdrawn from the market. Subsequently two new rotavirus vaccines were licensed, one containing a monovalent attenuated human rotavirus strain (RV1) and the other a pentavalent human-bovine reassortant vaccine. Although a risk of this magnitude was not seen with these new rotavirus vaccines in randomised controlled trials, they lacked the power to rule out a small risk [5,6]. In post-licensure studies, an increased risk of intussusception after the first dose of these vaccines has been reported in the 1–7 day post-vaccination period with an attributable risk after the first dose of between 1.1 to 4.3 per 100,000 [7–12]. The risk following the second dose appears to

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be smaller, with most studies not finding a significantly increased risk.

In the United Kingdom (UK) the rotavirus vaccine was first added to the routine vaccination programme in July 2013 using the RV1 vaccine, Rotarix® (GlaxoSmithKline). It is given as a 2 dose schedule at 2 and 3 months with the second dose to be given by 24 weeks of age to avoid coinciding with the peak in the background incidence of intussusception around this time [13]. Rotarix® is contraindicated for infants who have had a prior intussusception episode or an uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception. Since its introduction in the UK, the uptake of rotavirus vaccine has been high, with a 77% decline in laboratory-confirmed rotavirus infections and a 26% decline in all-cause acute gastroenteritis-associated hospitalisations compared with the pre-vaccination era [14].

In this study, we investigate whether there is an increased risk of intussusception following either the first or second dose of RV1 vaccine in infants in England. We also examine the timeliness of presentation to hospital which is essential in preventing complications from this rare event.

2. Methods

The Hospital Episode Statistics (HES) [15] database was used to identify cases of intussusception in infants eligible to receive at least one dose of rotavirus vaccine from the start of the national programme until 31/10/2014. The HES database contains details of all admissions to National Health Service hospitals in England. Infants aged 42–183 days old at the start of their admission with an ICD-10 code for intussusception in the primary diagnosis field and born from 11/03/2013 were selected as the vaccine was made available to any babies born up to 15 weeks prior to vaccine introduction on 1st July 2013. Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures version 4 codes attached to each admission were also extracted to investigate any procedures or operations during that admission. An admission for intussusception within 3 days of a previous one was treated as the same admission.

As rotavirus vaccine is delivered in primary care, infants' general practitioners were contacted to ascertain whether the vaccine was given and, if so, the date(s). Each case was categorised according to the Brighton Criteria for intussusception which contain 3 levels of diagnostic certainty [16]; level 1 is the highest level of certainty requiring confirmation by surgical or radiological reduction of the intussusception; level 2 is assigned by the evidence on a number of diagnostic features including intestinal obstruction, intestinal invagination and blood per rectum. Level 3 cases, which comprise those where the diagnostic evidence was less robust, were excluded from the analysis, together with cases for whom clinical information was lacking.

Diagnosis level was assigned without knowledge of vaccination status based on three sources of information; OPCS codes that indicated whether a surgical or radiological procedure was undertaken to reduce the intussusception, any additional information from the GP on treatment and symptoms, validated by a copy of the hospital discharge summary where available, and if no information was available from the HES database or GP, the paediatrician involved in the patient's care was contacted. Information from the GP and the discharge summaries was used to ascertain the date of first symptoms. For the analysis a single event date was determined which was the date of onset identified by the GP or in the hospital letters, or where this information was lacking, the date of hospital admission. Where the onset of symptoms was more than 3 days prior to admission this was only taken as the episode onset if on blinded review the events on this date were clearly part of the intussusception event.

The self-controlled case-series (SCCS) method was used to test the hypothesis of an increased risk of intussusception in three risk periods of 1–7, 8–21 and overall 1–21 days after rotavirus vaccination, where day 0 is the day of vaccination. The SCCS method [17] automatically controls for time-invariant confounding and has been used in previous studies investigating vaccine and intussusception [7,8,10,18]. We used the adaptation of the method developed by Farrington et al. [19] because the standard SCCS approach could not be used as intussusception is a contraindication to vaccination, thus violating the assumption that vaccination is not dependent on the occurrence of the event.

Age adjustment was by 2 weekly intervals, but age had a degree of collinearity with vaccine risk periods due to the lack of control person time around the time of vaccination because the doses were only given a month apart and the risk interval was 3 weeks. To address this, a pre-specified additional analysis was planned where five years of historical HES intussusception data from the period prior to vaccine introduction was included to enable better estimates of age effects. For these cases, hospital admission date was used as the index date.

Sample size calculations based on HES incidence data by age indicated that the expected number of cases from a year of follow-up post-vaccine introduction in the 7 day period after doses one and two was 1.6 and 4.0 respectively. This would enable detection of risks (80% power, 5% significance) of about 5–6 fold after dose 1 and 3–4 fold after dose 2.

The attributable risk was calculated from the relative incidence (RI) estimates. First the attributable fraction (AF) was calculated as (RI-1)/RI for each period after each dose. This was then applied to the cases observed to get an attributable number of cases, and finally this was divided by the estimated number of vaccine doses given to the population from which the cases arose.

To compare cases that were likely to be vaccine-associated with those that were not the features of the cases, including treatment, duration of admission and length of time from symptoms to admission in the 1–7 day risk interval after the first dose were compared to those outside the 1–21 day risk period after either dose. Logistic regression was used to adjust for age when comparing these groups.

A random effects meta-analysis was performed, combining our results with those from four other countries using RV1 and reporting RI estimates by the SCCS method [7,8,10,11]. Estimates for the 8–21 and 1–21 day post-vaccination risk periods were not reported for every country; however, these could be derived from the reported estimates in other risk periods. Pooled estimates were then obtained for the 1–7, 8–21 and 1–21 day post-vaccination periods using the point estimates and 95% confidence intervals (CIs) from each country. Analysis was carried out using Stata version 13 (StataCorp, College Station, TX).

3. Results

A total of 590 admissions in the period 1/07/08 to 31/10/2014 were identified from HES, with age at admission from 42 to 183 days and a K561 ICD-10 code for intussusception in the primary diagnosis field. There were 471 episodes in the 5 years prior to vaccine introduction with a date of birth before 11/03/2013 (age distribution shown in Fig. 1), and 119 with a date of birth after 10/03/2013 and, therefore, eligible for vaccination. Of the 119 episodes in the vaccine-eligible period, 90 were confirmed as Brighton level 1 after review and five as Brighton level 2. Of the remaining 29, one episode was assigned level 3, eight did not fit the criteria for intussusception and, for the remaining 15, the relevant information could not