Vaccine 34 (2016) 3684–3689

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

*Article history:*
Received 27 January 2016
Received in revised form 13 April 2016
Accepted 18 April 2016
Available online 7 June 2016

*Keywords:*
Intussusception
Rotavirus
Vaccine safety
Self-controlled case-series

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.

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## 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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http://dx.doi.org/10.1016/j.vaccine.2016.04.050
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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

**Table 1**
Description of the 95 Brighton level 1 and 2 intussusception cases included in the risk analysis, that are in the risk period 1–21 days after dose 1 or 2 of rotavirus vaccine.

| Variable | Level | Count of cases in risk period | Count of cases outside the risk period | Total count (%) |
|---|---|---|---|---|
| Sex | Male | 29 | 37 | 66 (69%) |
| | Female | 10 | 19 | 29 (31%) |
| Radiological reduction | No | 17 | 26 | 43 (45%) |
| | Yes | 22 | 30 | 52 (55%) |
| Surgery | No | 23 | 34 | 57 (60%) |
| | Yes | 16 | 22 | 38 (40%) |
| Brighton | 1 | 38 | 52 | 90 (95%) |
| | 2 | 1 | 4 | 5 (5%) |
| Vaccine doses | 0 | 0 | 13 | 13 (14%) |
| | 1 | 12 | 7 | 19[a] (20%) |
| | 2 | 27 | 36 | 63[b] (66%) |
| Age | 6w–9w/6d | 10 | 4 | 14 (15%) |
| | 10w–13w/6d | 11 | 8 | 19 (20%) |
| | 14w–17w/6d | 15 | 12 | 27 (28%) |
| | 18w–21w/6d | 2 | 16 | 18 (19%) |
| | 22w–26w/1d | 1 | 16 | 17 (18%) |

[a] 1 individual had onset before vaccination.
[b] 12 individuals had onset before vaccination (2 before first dose, 10 between doses).

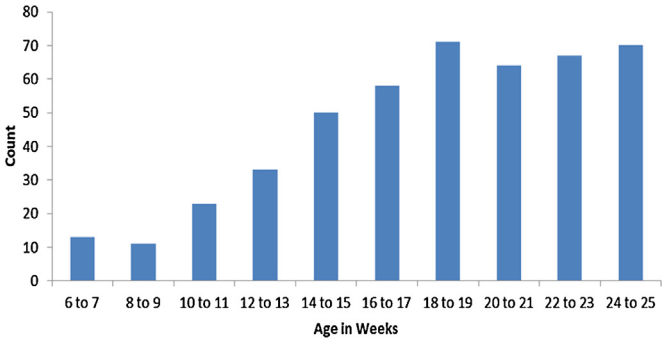


**Fig. 1.** Age distribution of the historic cases.

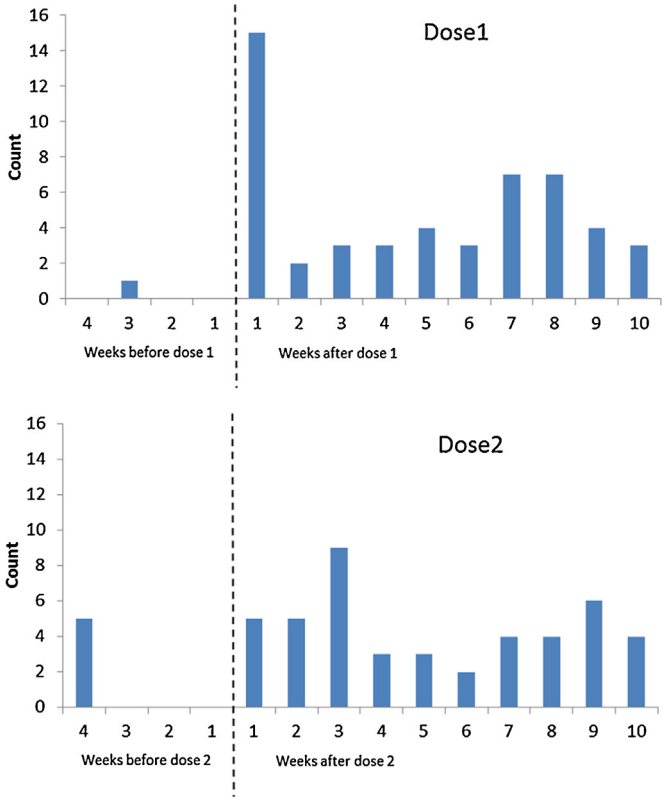


**Fig. 2.** Distribution of intussusception events 4 weeks before to 10 weeks after monovalent rotavirus vaccine doses 1 and 2.

be traced. Copies of medical discharge summaries and letters were available for 72 of the 95 level 1 and 2 cases (76%). Of the 95 cases, 66 (69%) were in males with an age range of 6–26 weeks (Table 1).

Overall there were 20 intussusception events 1–21 days after dose one and 19 events in the same period after dose two (Table 2 and Fig. 2). After the first dose, 15 of the 20 cases occurred in the 1–7 day period, with the interval between vaccination and onset of symptoms ranging from 4 to 6 days. After the second dose, there were 5 cases in the 1–7 day post-vaccination risk period and 14 in the 8–21 day risk period. A significantly increased risk was seen in the overall 1–21 day period post-vaccination for both the first and second dose of rotavirus vaccine (RI, 4.53; 95% CI, 2.34–8.58, and RI, 2.60; 95% CI, 1.43–4.81, respectively) (Table 2). When this post-vaccination risk period was spilt into 1–7 days and 8–21 days, the RI in the period 1–7 days after the first dose and 8–21 days after the second dose remained significantly elevated (Table 2). When the cases born before 11/03/2013 were included, the age effects were better specified which improved precision of the vaccine risks. The model incorporating the historic data also happened to give a lower background incidence in the younger age groups than the model without these data which led to higher relative incidence estimates for the vaccine risk periods (Table 2).

Using the model with the historical age data, the attributable fractions for days 1–7 and 8–21 after doses one and two were 93%, 37%, 55% and 64%, respectively, and the estimated number of vaccine-attributable cases 13.91, 1.86, 2.73 and 8.94 respectively. Based on dose one and two national vaccine coverage of 93.3% and 88.3% [20] and an England population estimate for infants under 1 year of age of 664,517 [21] and 1 year 4 months follow-up, the number of first and second doses given were around 826,659 and 782,358, respectively. The attributable risk in the 1–21 day period after dose one was, therefore, 15.77/826,659 (1.91 per 100,000 doses) and 11.67/782,358 (1.49 per 100,000 doses) after dose two. For the 1–7 day period after dose one only, the attributable risk is 1.68 per 100,000 doses.

Fifty-two (55%) of the 95 cases had their intussusception reduced radiologically, 38 (40%) underwent surgery and 5 had no intervention. In the 15 infants with intussusception in the 1–7 days after the first dose, 8 (53%) had radiological reduction and 7 (47%)

**Table 2**
Relative incidence of intussusception in risk periods after first and second monovalent rotavirus vaccine doses.

| Historical cases for age effect | Dose | Risk period (days) | Cases in risk period | RI (95% CI[a]) |
|---|---|---|---|---|
| Yes | 1 | 1–7 | 15 | 13.81 (6.44–28.32) |
| | | 8–21 | 5 | 1.59 (0.34–3.75) |
| | | 1–21 | 20 | 4.53 (2.34–8.58) |
| | 2 | 1–7 | 5 | 2.20 (0.50–5.02) |
| | | 8–21 | 14 | 2.77 (1.36–5.32) |
| | | 1–21 | 19 | 2.60 (1.43–4.81) |
| No | 1 | 1–7 | 15 | 8.50 (3.27–28.75) |
| | | 8–21 | 5 | 1.18 (0.28–3.99) |
| | | 1–21 | 20 | 3.13 (1.34–7.57) |
| | 2 | 1–7 | 5 | 1.74 (0.37–5.16) |
| | | 8–21 | 14 | 2.74 (1.22–5.89) |
| | | 1–21 | 19 | 2.41 (1.15–5.59) |

[a] Percentile bootstrap ($n = 1000$) 95% confidence intervals.

**Table 3**
Features of the intussusception admissions in infants in the 1–7 day post first dose risk period compared to those outside vaccine risk periods.

| Feature | 1–7 days post first dose $n/N$ (%) | Out of risk period-baseline[b] $n/N$ (%) | Odds ratio (95%CI)[a] |
|---|---|---|---|
| *Treatment* | | | |
| Radiological | 8/15 (53.3%) | 30/56 (53.6%) | 0.96 (0.24–3.91) |
| Surgical | 7/15 (46.7%) | 22/56 (39.3%) | 1.58 (0.38–6.59) |
| *Days from onset to admission* | | | |
| Same day | 5/15 (33.3%) | 29/56 (51.8%) | 1.04 (0.24–4.60) |
| Mean (range) in days | 0.71 (0–4) | 0.77 (0–4) | |
| *Duration of admission* | | | |
| 0–1 days | 9/15 (60.0%) | 32/56 (57.1%) | 0.44 (0.11–1.85) |
| Mean (range) in days | 0.33 (0–8) | 0.50 (0–12) | |
| *Gender* | | | |
| Male | 10/15 (66.7%) | 37/56 (66.1%) | 0.54 (0.11–2.58) |

[a] Odds ratio adjusted for in age in days.
[b] Not within 1–21 days of dose 1 or 2.

**Table 4**
Meta-analysis of results from four countries using monovalent rotavirus vaccine: relative incidence and 95% confidence intervals.

| Country | Period post dose 1 | | | Period post dose 2 | | |
|---|---|---|---|---|---|---|
| | 1–7 days | 8–21 days | 1–21 days | 1–7 days | 8–21 days | 1–21 days |
| Australia | 6.76 (2.40–19.01) | 3.45 (1.33–8.94) | 4.55 (2.21–9.38)[a] | 2.84 (1.10–7.34) | 2.11 (0.97–4.62) | 2.35 (1.28–4.33)[a] |
| Mexico | 5.30 (3.00–9.30) | 0.99 (0.52–1.91)[b] | 2.43 (1.51–3.90)[a] | 1.80 (0.90–3.80) | 2.20 (1.40–3.45)[b] | 2.07 (1.41–3.04)[a] |
| Singapore | 8.36 (2.42–28.96) | 0.10 (0.01–10.0)[c] | 2.85 (1.13–7.19)[a] | 3.09 (0.41–12.37) | 1.54 (0.20–11.69) | 2.06 (0.47–8.94)[a] |
| Brazil | 1.10 (0.30–3.30) | 0.51 (0.20–1.33)[b] | 0.71 (0.33–1.50)[a] | 2.60 (1.30–5.20) | 1.12 (0.65–1.93)[b] | 1.61 (1.05–2.48)[a] |
| Mexico (2) | 6.49 (4.17–10.09)[d] | 1.08 (0.90–1.30)[d] | 1.75 (1.24–2.48)[d] | 1.29 (0.80–2.11)[d] | 1.00 (0.84–1.20)[d] | 1.06 (0.75–1.48)[d] |
| England | 13.81 (6.44–28.32) | 1.59 (0.34–3.75) | 4.53 (2.34–8.58) | 2.20 (0.50–5.02) | 2.77 (1.36–5.32) | 2.60 (1.43–4.81) |
| Pooled[e] | 6.03 (3.61–10.07) | 1.13 (0.71–1.79) | 2.35 (1.45–3.80) | 1.83 (1.35–2.50) | 1.61 (1.04–2.47) | 1.77 (1.29–2.43) |

[a] Estimated from combining published 1–7 and 8–21 day period risks.
[b] Estimated from combining published 8–14 and 15–21 day period risks.
[c] Actually zero events in this period, RI of 0.1 with wide 95% CI used.
[d] Estimates are for 0–6, 7–30 and 0–30 days with 7–30 estimated by subtraction of 0–6 from 0 to 30 estimates.
[e] Pooled using random effects method of DerSimonian and Laird (Metan command in stata) due to heterogeneity between countries for some periods.

needed surgical intervention, which was similar to the management of cases outside the vaccine risk periods (Table 3). In the period the vaccine was given and in the 5 years prior to the vaccine's introduction there were no intussusception admissions in which an infant died.

The interval from onset of symptoms to admission ranged from 0 to 4 days. Five of the 15 (33.3%) infants with onset in the 1–7 day risk window after the first dose were admitted on the same day as their symptoms started compared to 29 of the 56 (51.8%) of those outside the vaccine risk periods, although this difference was not statistically significant (Table 3), and not different when adjusting for age. The duration of the admission ranged from 0 to 12 days and was similar in infants with onset shortly after the first dose and those outside the vaccine risk periods (Table 3), and non-significantly lower when adjusting for age.

Although rotavirus vaccine is contraindicated for children with a previous intussusception, 3 infants had an admission for intussusception in the 2 months before receiving their first dose of rotavirus vaccine and 10 children went on to have their second dose after confirmed intussusception following the first dose. No repeat episodes of intussusception were recorded in the HES data.

The pooled results for the meta-analysis showed a significantly increased RI after dose one and dose two 21 days after vaccination (Table 4). A significantly increased RI was also seen following dose one and two in the 1–7 day post-vaccination period and also post dose two in the 8–21 day period.

## 4. Discussion

This is the first study of the risk of intussusception after rotavirus vaccine to be reported from the European region and the first using a schedule in which the second dose is given at 3 months of age. Our relative risk estimate of 13.81 (6.44–28.32) for the 1–7 day period after the first dose of RV1 is somewhat higher than those obtained for RVI using the SCCS method in Mexico, Australia and Singapore (Table 4). This may reflect the use of symptom onset in our analysis rather than the later admission date as used by others; had admission date been used instead of onset date for the 15 cases in the 1–7 day period after the first dose, 5 would have been assigned to the 8–21 day risk period, thus decreasing the RI in this earlier interval. Our RI estimate for the 1–7 day period after dose two was within the range reported by the other three countries, indicating that the earlier age at administration of the second dose in England, which is closer to that in countries using the Expanded Programme on Immunisation schedule recommended by the World Health Organisation, is unlikely to influence the vaccine-associated risk of intussusception. When pooling results across the six studies there was an approximate three-fold increased risk 1–21 days after the first dose and two-fold increased risk after the second dose. The characteristics of the cases in the 1–7 day period after the first dose in our study (where we estimated that 93% were vaccine-attributable) were similar to those outside the vaccine risk period, confirming the findings from Singapore [10].

We also found a significantly elevated risk in the 8–21 day period after the second dose but not after the first. The results of the other three SCCS studies for this post-vaccination period were mixed, although the pooled estimate was consistent with our findings. The RI for this period will be affected by whether symptom onset or hospital admission date is used in the analysis, as with the 1–7 day period, though in the opposite direction. Using the overall RI for the 1–21 period should capture all vaccine-attributable cases and, in the meta-analysis, significantly elevated RI estimates for the 1–21 day period were found after both the first and second doses; in our study in England this gave AR estimates of 1.91 and 1.49 per 100,000 doses respectively.

In the UK, the risk of intussusception after rotavirus vaccine is explicit in written guidance provided to healthcare professionals administering the vaccine and parents are told to be aware of abdominal pain, vomiting and redcurrant jelly stools and to contact a doctor immediately to ensure rapid treatment [22]. In April 2015, two deaths from intussusception temporally related to rotavirus vaccination were reported in France in infants who did not receive timely medical care [23]. This led the World Health Organisation Global Advisory Committee on Vaccine Safety to publish a statement underlining the importance of close monitoring of infants after vaccination and the need for prompt medical care for infants with suspected intussusception at any time [24]. In our study, the interval between symptom onset and admission was short (mean <1 day) and similar in cases with a close temporal association with vaccination and those outside the post-vaccination risk period. However, the causal association with vaccination may not be recognised as there was absence of any mention of the vaccination in the medical records in all but one case. This case was one of 10 infants who received a second dose despite confirmed intussusception episode after their first dose. Although none of these infants had a repeat episode following their second dose, greater awareness of the contraindications to vaccination and of the vaccine-associated risk is needed.

This study uses routinely collected hospital data which has the potential for inaccuracy in the diagnostic coding. While we minimised misdiagnoses by excluding cases with insufficient information to confirm the diagnosis according to the Brighton Collaboration criteria, this may have resulted in exclusion of true cases. Furthermore, a recent study found that only 86% of intussusception cases reported to the British Paediatric Surveillance Unit had a HES admission with an intussusception code [25]. Both of these factors would lead to an underestimate of the attributable risk though not the RI estimates, assuming that missed cases were randomly distributed in relation to the timing of vaccination.

The 2–3 fold elevated risk of intussusception after a first and second dose of RV1 demonstrated by our study, would result in an estimated 21 additional intussusception cases each year in England. This number needs to be compared with the 25,000 annual admissions for an acute gastrointestinal infection that the rotavirus vaccine programme has prevented [14]. The benefit/risk profile of the programme is therefore still strongly positive [26]. It is however unclear whether the increased risk of intussusception in the post-vaccination period translates into a sustained increase in the absolute risk of an intussusception episode in the first year of life or whether, as suggested by ecological studies, this overall risk remains unchanged [27]. If so this would suggest that the vaccine acts as a trigger for an event that would anyway occur albeit later. Surveillance of intussusception in infants eligible to receive rotavirus vaccine in England will be continued in order to evaluate the overall ecological impact of the vaccination programme on this rare event.

*Conflict of interest*: None declared.

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